Investigational candidates for snakebite envenoming

Biologics

Immunoglobulin products – animal plasma/serum derived

Chicken anti-neurotoxin IgY (ANT- IgY) (egg yolk derived) (against cobra and krait)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 2111

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: cobra and krait

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgY antibodies are whole immunoglobulins derived from the egg yolks of chickens immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including chickens.

Chicken anti-neurotoxin IgY (ANT- IgY) (egg yolk derived) against cobras and kraits was developed as follows: pure anti-neurotoxin (ANT- IgY) were developed by immunizing White Leghorn hens with Cobra and Krait venoms for demonstrating antigen-antibody binding in vitro/in vivo. The purified IgY from immunized egg-yolk showed immunoprecipitation in Ouchterlony's Double Diffusion (ODD) experiment. For characterizing ANT-IgY distribution and clearance pattern, the study utilized an enzyme-linked immunosorbent assay (ELISA) in serum at different intervals following intravenous (IV) administration. The Kinetica 5.1 software estimated pharmacokinetic parameters, including half-life. The IgY showed a time-dependent elimination through the intestinal route in fecal matter. After conjugating with a fluorochrome-Vivotag-750S, injected the purified ANT-IgY intravenously into the healthy mice. Subsequently, captured live-animal images to demonstrate the distribution and elimination profile of the molecule. Intramuscular injection of fluorochrome-tagged venom created the envenomed mice model. The live-animal images demonstrated the quick mobilization of venom into vital tissues. Intravenous administration of tagged ANT-IgY in the envenomed model showed the movement of ASV to the tissues venom traffics. The observed pharmacological benefit promise scope of ASV-IgY for therapeutic use. (https://pubmed.ncbi.nlm.nih.gov/35196538/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Sree Chitra Tirunal Institute for Medical Sciences and Technology

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/35196538/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Naja naja (Indian cobra); Bungarus caeruleus (Common krait)
Snake family	Elapidae
Risk category	Both Category 1 & 2
Countries	India
Regions	South Asia

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Chicken immunization with crude venom, IgY extracted from egg yolk

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja naja (Indian cobra); Bungarus caeruleus (Common krait)	Naja naja (Indian cobra); Bungarus caeruleus (Common krait)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Neurotoxic (paralysis)

Chicken IgY (egg yolk derived) (against Bitis arietans and Crotalus durissus terrificus)

Alternative name(s): Whole immunoglobulin antibodies; chicken antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1700

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Bitis arietans (Puff adder) and Crotalus durissus terrificus (Amaru, Asakamio, Cascabel, Cascavel, Ma ára, Maracá, Maracabóia, Palla, Sak-kah-sak, Saka sneki, South American rattlesnake); Crotoxin from Crotalus durissus terrificus (Amaru, Asakamio, Cascabel, Cascavel, Ma ára, Maracá, Maracabóia, Palla, Sak-kah-sak, Saka sneki, South American rattlesnake)

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgY antibodies are whole immunoglobulins derived from the egg yolks of chickens immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including chickens.

Chicken IgY (egg yolk derived) candidate against B. arietans or C. d. terrificus was developed as follows: adult hens were immunized nine times with 20µg of B. arietans or C. d. terrificus venoms at three-week intervals between immunizations. Developing antibodies presented increasing avidity and affinity to antigenic toxin epitopes along immunization, attaining a plateau after the seventh immunization. Pooled egg yolk-purified IgY antivenom antibodies, subjected to in vitro-in vivo lethality assay using Swiss adult mice, exhibited potent venom lethal neutralizing activity. (https://pubmed.ncbi.nlm.nih.gov/28595875/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Universidade Estadual do Norte Fluminense Darcy Ribeiro (UENF) (State University of Northern Rio de Janeiro)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/28595875/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Bitis arietans (Puff adder); Crotalus durissus terrificus (Amaru, Asakamio, Cascabel, Cascavel, Ma ára, Maracá, Maracabóia, Palla, Sak-kah-sak, Saka sneki, South American rattlesnake)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Brazil
Regions	South America; Southern Africa

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Chicken immunization with crude venom, IgY extracted from egg yolk

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bitis arietans (Puff adder); Crotalus durissus terrificus (Amaru, Asakamio, Cascabel, Cascavel, Ma ára, Maracá, Maracabóia, Palla, Sak-kah-sak, Saka sneki, South American rattlesnake)	Bitis arietans (Puff adder); Crotalus durissus terrificus (Amaru, Asakamio, Cascabel, Cascavel, Ma ára, Maracá, Maracabóia, Palla, Sak-kah-sak, Saka sneki, South American rattlesnake)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Chicken IgY (egg yolk derived) (against Bothrops alternatus)

Alternative name(s): Whole immunoglobulin antibodies; chicken antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1865

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Bothrops alternatus

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgY antibodies are whole immunoglobulins derived from the egg yolks of chickens immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including chickens.

Chicken IgY (egg yolk derived) candidate against Bothrops alternatus was developed as follows: An IgY-based antivenom against B. alternatus venom was developed by immunization of chickens. After the 3rd immunization, levels of specific IgY reached a maximum that was maintained throughout the observation period. Furthermore, IgY against B. alternatus recognized protein complexes of the venom with high (>40 kDa), medium (20-40 kDa) and low (<20 kDa) molecular weights. IgY antivenoms obtained after 8 immunizations neutralized 35.65 µg of B. alternatus venom per mg of antivenom, while specific activities values ranged from 0.28 to 0.42. (https://pubmed.ncbi.nlm.nih.gov/30914282/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Argentinean National Agricultural Technology Institute (INTA)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/30914282/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Bothrops alternatus (Jararaca de agosto)
Snake family	Viperidae
Risk category	Category 1 (Highest Medical Importance)
Countries	Argentina
Regions	South America

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Chicken immunization with crude venom, IgY extracted from egg yolk

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops alternatus (Jararaca de agosto)	Bothrops alternatus (Jararaca de agosto)
Snake family		Viperidae
Risk category		Category 1 (Highest Medical Importance)

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

Chicken IgY (egg yolk derived) (against Bungarus multicinctus)

Alternative name(s): Whole immunoglobulin antibodies; chicken antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1713

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Bungarus multicinctus (Many-banded krait) venom proteins

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgY antibodies are whole immunoglobulins derived from the egg yolks of chickens immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including chickens.

Chicken IgY (egg yolk derived) candidate against B. multicinctus was developed as follows: Chickens were immunized with B. multicinctus proteins, and polyclonal immunoglobulin Y (IgY) antibodies were purified from eggs. IgY showed a binding activity to B. multicinctus proteins that was similar to horse antivenin, and its titer in chickens lasted for at least 6 months. We constructed two antibody libraries by phage display antibody technology, which contain 1.0 × 107 and 2.9 × 108 transformants, respectively (see candidate 'Chicken svFv (egg yolk derived) (against Bungarus multicinctus)'). Polyclonal IgY demonstrated a similar neutralization efficiency as did horse-derived antivenin in mice that were injected with a minimum lethal dosage (MLD) of venom proteins. A mixture of several monoclonal anti-B. multicinctus scFv antibodies was also able to partially inhibit the lethal effect on mice. (https://pubmed.ncbi.nlm.nih.gov/27663029/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Taipei Medical University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/27663029/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Bungarus multicinctus (Many-banded krait)
Snake family	Elapidae
Risk category	Category 1 (Highest Medical Importance)
Countries	Taiwan
Regions	East Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Chicken immunization with crude venom, IgY extracted from egg yolk

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bungarus multicinctus (Many-banded krait)	Bungarus multicinctus (Many-banded krait)
Snake family		Elapidae
Risk category		Category 1 (Highest Medical Importance)

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Chicken IgY (egg yolk derived) (against Cobra, Krait, Russells Viper and Saw-scaled Viper)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1467

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Cobra, Krait, Russells Viper and Saw-scaled Viper

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgY antibodies are whole immunoglobulins derived from the egg yolks of chickens immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including chickens.

Chicken IgY (egg yolk derived) antivenom against Cobra, Krait, Russells Viper and Saw-scaled Viper is being developed by SASTRA University in India as part of a grant funded by Indian BIRAC. The grant description is: Generation, Characterization and Pre-clinical Evaluation of Chicken Egg Yolk sourced Anti-Snake Venom IgY against venoms of Cobra, Krait, Russells Viper and Saw-scaled Viper. No other information is available.

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Shanmugha Arts, Science, Technology & Research Academy (SASTRA University)

Key funders: Biotechnology Industry Research Assistance Council (BIRAC)

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Naja naja (Indian cobra); Daboia russelii (Russel's viper); Common krait (Bungarus caeruleus); Echis carinatus (Indian saw-scaled viper)
Snake family	Viperidae,Elapidae
Risk category	Both Category 1 & 2
Countries	India
Regions	South Asia

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Chicken immunization with crude venom, IgY extracted from egg yolk

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Unknown	Unknown
Snake family		
Risk category		Unknown

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Chicken IgY (egg yolk derived) (against D. acutus, China)

Alternative name(s): Whole immunoglobulin antibodies; chicken antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1709

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Deinagkistrodon acutus

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgY antibodies are whole immunoglobulins derived from the egg yolks of chickens immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including chickens.

Chicken IgY (egg yolk derived) candidate against D. acutus in China was developed as follows: IgY from the egg yolk of white leghorn chickens previously immunized intramuscularly with D. acutus venom was extracted by water, precipitated by ammonium sulfate and purified by affinity chromatographic system. y three steps, including caprylic acid extraction, ammonium sulfate precipitation and affinity chromatography, IgY antibodies were isolated and purified from egg yolk, which exhibited a single protein band on SDS-PAGE and two bands (about 65 kDa and 35 kDa, respectively) under reducing conditions, and presented a high titer (1:40,000) tested by ELISA. Immunoblot analysis confirmed that these IgY were polyclonal antibodies since they bound to components of D. acutus venom. Furthermore, immunodiffusion assay showed that anti-D. acutus venom IgY cross-reacted with the venoms of Trimeresurus albolabris and D. saxatilis Emelianov, but did not react to the venoms of Bungarus multicinctus and Naja atra. In the neutralizing lethal assay, the median effective dose of anti-D. acutus venom IgY was 14.14 mg/kg of mouse body weight under the challenge dose (3 LD50 of D. acutus venom). In neutralizing the haemorrhagic, edema-forming and myotoxic activities of D. acutus venom, IgY showed the characteristic dose-dependent neutralization effects against all these toxic activities of D. acutus venom. (https://pubmed.ncbi.nlm.nih.gov/28396683/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: College of Life Science, Chongqing

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/28396683/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Deinagkistrodon acutus (Chinese copperhead)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	China
Regions	East Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Chicken immunization with crude venom, IgY extracted from egg yolk

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Deinagkistrodon acutus (Chinese copperhead); Trimeresurus albolabris (White-lipped pit viper); Deinagkistrodon saxatilis (Central asian pit-viper); Bungarus multicinctus (Many-banded krait); Naja atra (Chinese cobra)	Deinagkistrodon acutus (Chinese copperhead); Cross-reactivity with Trimeresurus albolabris (White-lipped pit viper) and Deinagkistrodon saxatilis (Central asian pit-viper), but did not react to the venoms of Bungarus multicinctus (Many-banded krait) and Naja atra (Chinese cobra)
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Haemorrhagic (bleeding)

Chicken IgY (egg yolk derived) (against D. acutus, Taiwan)

Alternative name(s): Whole immunoglobulin antibodies; chicken antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1880

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Deinagkistrodon acutus (DA) venom proteins

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgY antibodies are whole immunoglobulins derived from the egg yolks of chickens immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including chickens.

Chicken IgY (egg yolk derived) candidate against D. acutus in Taiwan was developed as follows: yolk immunoglobulin (IgY) was purified from eggs, and DA protein was recognized using Western blotting and an enzyme-linked immunosorbent assay (ELISA), similar to therapeutic horse antivenin. The ELISA also indicated that specific IgY antibodies were elicited after the fifth booster, plateaued, and lasted for at least 3 months. To generate monoclonal single-chain variable fragment (scFv) antibodies, we used phage display technology to construct two libraries with short or long linkers, containing 6.24 × 10(8) and 5.28 × 10(8) transformants, respectively (see candidate 'Chicken scFv (egg yolk derived) (against D. acutus, Taiwan)'). Both IgY and mixed scFv inhibited the lethal effect in mice injected with the minimum lethal dosage of the DA protein. (https://pubmed.ncbi.nlm.nih.gov/26475102/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Taipei Medical University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/26475102/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Deinagkistrodon acutus (Chinese copperhead)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Taiwan
Regions	East Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Chicken immunization with crude venom, IgY extracted from egg yolk

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Deinagkistrodon acutus (Chinese copperhead)	Deinagkistrodon acutus (Chinese copperhead)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Chicken IgY (egg yolk derived) (against Daboia russelii formosensis)

Alternative name(s): Whole immunoglobulin antibodies; chicken antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1787

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Daboia russelii formosensis (DRF) venom proteins

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgY antibodies are whole immunoglobulins derived from the egg yolks of chickens immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including chickens.

Chicken IgY (egg yolk derived) candidate against Daboia russelii formonsensis was developed as follows: Glutaraldehyde-attenuated Daboia russelii formosensis (DRF) venom proteins were used to immunize chickens. Polyclonal yolk-immunoglobulin (IgY) antibodies were generated and showed a specific binding affinity. Phage display technology was used to generate two antibody libraries of single-chain variable fragments (scFvs) containing 3.4×10^7 and 5.5×10^7 transformants, respectively (see candidate 'Chicken scFv (egg yolk derived) (against Daboia russelii formonsensis)'). In vivo studies showed that anti-DRF IgY exhibited complete protective effects and mixed scFv antibodies increased the survival rate and time of mice challenged with a lethal dose of DRF proteins. (https://pubmed.ncbi.nlm.nih.gov/29076991/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Taipei Medical University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/29076991/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Daboia russelii formosensis (Russel's viper)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Taiwan
Regions	East Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Chicken immunization with crude venom, IgY extracted from egg yolk

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russelii formosensis (Russel's viper)	Daboia russelii formosensis (Russel's viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Chicken IgY (egg yolk derived) (against Naja naja atra)

Alternative name(s): Whole immunoglobulin antibodies; chicken antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1705

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Naja naja atra (NNA) (Chinese cobra) venom proteins

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgY antibodies are whole immunoglobulins derived from the egg yolks of chickens immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including chickens.

Chicken IgY (egg yolk derived) candidate against Naja naja atra (NNA) was developed as follows: Hens were immunized with inactivated NNA venom proteins from the cobra Naja naja atra (NNA). Purified yolk IgY antibodies showed specific anti-NNA binding activity comparable to that of the equine-derived antivenin. Phage display technology was used to generate two antibody libraries containing 9.0 × 10^8 and 8.4 × 10^8 clones with a short or long linker, respectively (see candidate 'Chicken svFv (egg yolk derived) (against Naja naja atra)'). Animal model studies showed that anti-NNA IgY antibodies exhibited complete protective effects, while a combination of scFv antibodies raised the survival rates and times of mice challenged with lethal doses of NNA venom proteins.(https://pubmed.ncbi.nlm.nih.gov/30248928/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Taipei Medical University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/30248928/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Naja naja atra (Chinese cobra)
Snake family	Elapidae
Risk category	Category 1 (Highest Medical Importance)
Countries	Taiwan
Regions	East Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Chicken immunization with crude venom, IgY extracted from egg yolk

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja naja atra (Chinese cobra)	Naja naja atra (Chinese cobra)
Snake family		Elapidae
Risk category		Category 1 (Highest Medical Importance)

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Chicken IgY (egg yolk derived) (against Oxyuranus scutellatus)

Alternative name(s): Chicken-derived antivenom (ChDAv) towards taipan snake (Oxyuranus scutellatus); Whole immunoglobulin antibodies; chicken antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1935

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Oxyuranus scutellatus venom

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgY antibodies are whole immunoglobulins derived from the egg yolks of chickens immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including chickens.

Chicken IgY (egg yolk derived) candidate (ChDAv) against Oxyuranus scutellatus was developed as follows: hens were immunized in the breast area by the subcutaneous injection of 50 µg O. scutellatus venom, and anti-taipan venom IgY was purified from egg yolks. During antivenomic assessment, ChDAv showed lower ability to immunocapture the α subunit of taipoxin, the most important neurotoxin in the venom. ChDAv showed a lower ability to neutralize the coagulant and lethal activities of taipan venom. ChDAv was more immunogenic in rabbits than EDAv, probably due to the fact that chickens are phylogenetically more distant to rabbits than horses. In conclusion, the production of anti-taipan antivenom was less effective when chicken egg yolks were used as source of immunoglobulins instead of horses. (https://pubmed.ncbi.nlm.nih.gov/27373994/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: University of Costa Rica (including the Clodomiro Picado Institute)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/27373994/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Oxyuranus scutellatus (Coastal taipan)
Snake family	Elapidae
Risk category	Both Category 1 & 2
Countries	Papua New Guinea
Regions	Australia-Papua (incl Pacific)

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Chicken immunization with crude venom, IgY extracted from egg yolk

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Oxyuranus scutellatus (Coastal taipan)	Oxyuranus scutellatus (Coastal taipan)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Procoagulant (blood clotting)

Chicken IgY (egg yolk derived) (against Trimeresurus albolabris)

Alternative name(s): Whole immunoglobulin antibodies; chicken antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1715

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Trimeresurus albolabris (white-lipped green pit viper) venom

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgY antibodies are whole immunoglobulins derived from the egg yolks of chickens immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including chickens.

Chicken IgY (egg yolk derived) candidate against Trimeresurus albolabris was developed as follows: IgY in egg yolk from white leghorn chicken previously injected with T. albolabris venom was extracted by water, precipitated by ammonium sulfate and purified by affinity chromatographic system. IgY was identified by SDS-PAGE, ELISA and Western blot, and its neutralizing assay was conducted on mice. Chickens injected multiple times with T. albolabris venom elicited strong antibody responses, and from their egg yolk IgY was isolated and purified, which exhibited a single protein band on SDS-PAGE and two bands (about 65 and 35 kDa, respectively) under reduced conditions. Immunoblot analysis revealed that these IgY are polyclonal antibodies since they bind with most venom components. In the neutralizing assay, all mice survived while the ratios of IgY/venom reached up to 3.79 (50.0 mg/13.2 mg). (https://pubmed.ncbi.nlm.nih.gov/27563307/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Chongqing Normal University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/27563307/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Trimeresurus albolabris (white-lipped green pit viper)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	China
Regions	East Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Chicken immunization with crude venom, IgY extracted from egg yolk

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Trimeresurus albolabris (white-lipped green pit viper)	Trimeresurus albolabris (white-lipped green pit viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Chicken IgY (egg yolk derived) (against Trimeresurus mucrosquamatus)

Alternative name(s): Whole immunoglobulin antibodies; chicken antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 2015

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Trimeresurus mucrosquamatus (brown-spotted pit viper, Taiwanese habu and pointed-scaled pit viper)

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgY antibodies are whole immunoglobulins derived from the egg yolks of chickens immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including chickens.

Chicken IgY (egg yolk derived) candidate against Trimeresurus mucrosquamatus was developed as follows: TM venom powders was dissolved in 1 PBS for chicken immunization. Their identity was analyzed on SDS-PAGE using Coomassie blue staining. The protein pattern showed a complex of components containing one major band with molecular weight of 30 kD. By Western blotting, the polyclonal anti-TM IgY antibodies recognized a panel of proteins which were also identified by polyclonal anti-TM IgG antibodies purified from horse sera. The results indicated that immunization with TM venom elicited similar humoral antibody responses in chickens and horses. Using phage display technology to process four rounds of panning, selected single chain variable fragments (scFv) could specifically recognize TM venom proteins, which were later identified as a group of homogeneous venom serine protease (see candidate 'Chicken scFv (egg yolk derived) (against Trimeresurus mucrosquamatus). Treatment using bivalent anti-TM/TS polyclonal IgY prevented 2/3 of the mice from dying of envenomation. In addition, the anti-TM polyclonal IgY antibodies offered partial protective effect, delaying the mice death (https://pubmed.ncbi.nlm.nih.gov/25769957/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Taipei Medical University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/25769957/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Trimeresurus mucrosquamatus (brown-spotted pit viper, Taiwanese habu and pointed-scaled pit viper)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Taiwan
Regions	East Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Chicken immunization with crude venom, IgY extracted from egg yolk

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Trimeresurus mucrosquamatus (brown-spotted pit viper, Taiwanese habu and pointed-scaled pit viper)	Trimeresurus mucrosquamatus (brown-spotted pit viper, Taiwanese habu and pointed-scaled pit viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Chicken IgY (egg yolk derived) (against Trimeresurus stejnegeri)

Alternative name(s): Whole immunoglobulin antibodies; chicken antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1893

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: T. stejnegeri venom proteins

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgY antibodies are whole immunoglobulins derived from the egg yolks of chickens immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including chickens.

Chicken IgY (egg yolk derived) candidate against Trimeresurus stejnegeri was developed as follows: T. stejnegeri venom proteins were inactivated by glutaraldehyde in order to immunize hens for polyclonal immunoglobulin (IgY) antibodies production. After IgY binding assays, two antibody libraries were constructed expressing single-chain variable fragment (scFv) antibodies joined by the short or long linker for use in phage display antibody technology (see candidate 'Chicken scFv (egg yolk derived) (against Trimeresurus stejnegeri)'). In in vivo studies, the data demonstrated that anti-TS IgY provided 100% protective effects, while combined scFvs augmented partial survival time of mice injected with a lethal amount of TS proteins. (https://pubmed.ncbi.nlm.nih.gov/33281887/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Taipei Medical University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33281887/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Trimeresurus stejnegeri (Bamboo viper, Chinese green tree pit viper)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Taiwan
Regions	East Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Chicken immunization with crude venom, IgY extracted from egg yolk

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Trimeresurus stejnegeri (Bamboo viper); Trimeresurus mucrosquamatus (Taiwanese habu)	Trimeresurus stejnegeri (Bamboo viper); Trimeresurus mucrosquamatus (Taiwanese habu)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Combined Bothrops AV + synthetic SVSP peptides pepB and pepC

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1834

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Bothrops jararaca; SVSP (batroxobin): Bothrops jararaca

Route of administration: Not yet determined

Ig format: F(ab')2 immunoglobulin molecule fragments

Ig final product type/preparation: Liquid final product

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals AND/OR peptides and proteins (synthetic or naturally derived) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes; peptides

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). Therapeutic peptides are short chains of amino acids linked by peptide bonds. Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other approaches are being investigated for novel therapeutics (natural or synthetic) that are cheaper, capable of rapid production, and have higher specificity and lower immunogenicity - such as peptides. The present treatment in Brazil for Bothrops spp envenoming consists of intravenous administration of bothropic antivenom (Bothrops AV), which is capable of reversing most of the systemic symptoms, while presenting limitations to treat the local effects, such as hemorrhage and to neutralize the snake venom serine protease (SVSP).

The combined Bothrops AV + synthetic SVSP peptides pepB and pepC candidate, in this context, was developed to evaluate the activity of selective serine protease inhibitors (pepC and pepB) in combination with the bothropic antivenom in vivo. Further, their possible synergistic effects were investigated in the treatment of coagulopathy and hemorrhage induced by Bothrops jararaca venom. The in vivo activity in mouse models of local hemorrhage and a series of in vitro hemostasis assays was evaluated. Results showed that pepC and pepB, when combined with the antivenom, increase its protective activity in vivo and decrease the hemostatic disturbances in vitro with high selectivity, possibly by inhibiting botropic proteases. These data suggest that the addition of serine protease inhibitor to the antivenom can improve its overall potential. (https://pubmed.ncbi.nlm.nih.gov/34126124/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Butantan Institute, Fundacao Butantan

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/34126124/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Bothrops jararaca (Jararaca)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Brazil
Regions	South America

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent equine immunization; Peptide synthesis

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops jararaca (Jararaca)	Bothrops jararaca (Jararaca)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: SVSPs

Syndromic profiles: Haemorrhagic (bleeding),Procoagulant (blood clotting)

Inoserp Europe polyvalent antivenom (against European vipers)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1334

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment for snakebite envenoming

Target: Crude snake venom; European snakes

Route of administration: Intravenous

Ig format: F(ab')2 immunoglobulin molecule fragments

Ig final product type/preparation: Lyophilized (freeze-dried)

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Lyophilized Inoserp Europe antivenom is a F(ab')2 polyvalent antivenom, designed to cover envenoming caused by medically important snakes of the Eurasian region. It is a sterile lyophilized white powder formulated to be reconstituted with 10 mL of sterile water for injection. Horse hyperimmune plasmas were produced by immunization with a mixture of lyophilized pools of venoms of the following European species: Vipera ammodytes, Vipera aspis, Vipera berus, Vipera latastei, Montivipera xanthina, Macrovipera schweizeri, Macrovipera lebetina obtuse, Macrovipera lebetina cernovi, and Macrovipera lebetina turanica. The venom-neutralizing efficacy of the antivenom was evaluated in mice and the results showed it had appropriate neutralizing potency against the venoms of several species of Vipera, Montivipera, and Macrovipera. Paraspecificity of the antivenom was demonstrated as well, since it neutralized venoms of species not included in the immunization schemes and contains satisfactory levels of total proteins and $F(ab')_2$ fragment concentration. Therefore, this new polyvalent antivenom could be effective in the treatment of snake envenoming in Europe, including Western Russia and Turkey (https://pubmed.ncbi.nlm.nih.gov/30841582/).

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: INOSAN Biopharma SA

Preclinical sources: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6468668/pdf/toxins-11-00149.pdf

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Vipera ammodytes (horned viper); Vipera aspis (European viper); Vipera berus (common European adder); Vipera latastei (snub-nosed viper); Montivipera xanthina (rock viper); Macrovipera schweizeri (Milos viper); Macrovipera lebetina obtuse (West-Asian blunt-nosed viper); Macrovipera lebetina cernovi (Chernov Blunt-nosed Viper); Macrovipera lebetina turanica (Turan blunt-nosed viper)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	France; Albania; Greece; Italy; Turkey; Spain; Azerbaijan; Russia
Regions	Western Europe; Eastern Europe

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Venom dependent equine immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Vipera ammodytes (horned viper); Vipera ammodytes meridionalis (eastern sand viper); Vipera ammodytes ruffoi; Vipera aspis francisciredi (Central Italian asper); Vipera aspis (European viper); Vipera berus (common European adder); Vipera bornmuelleri (Lebanon viper); Vipera latastei (snub-nosed viper); Vipera latifii (Latifi's viper); Vipera transcaucasiana (Transcaucasian sand viper); Vipera renardi renardi; Montivipera raddei raddei (Armenian viper); Montivipera xanthina (Rock viper); Macrovipera lebetina cernovi (Chernov Blunt-nosed Viper); Macrovipera lebetina obtuse (West-Asian blunt-nosed viper); Macrovipera lebetina turanica (Turan blunt-nosed viper); Macrovipera schweizeri (Milos viper)	Montivipera raddei raddei (Armenian viper); Vipera xanthina (rock viper); Vipera renardi renardi; Vipera transcaucasiana (Transcaucasian sand viper); Vipera latifii (Latifi's viper); Vipera bornmuelleri (Lebanon viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Murine monoclonal 3FTx-specific IgGs (against Naja ashei)

Alternative name(s): Anti-Naja ashei Three-Finger Toxins (3FTxs)-Specific Monoclonal Antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1896

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: 3FTx: Naja ashei

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized with snake venom. Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives. In addition, novel immunization techniques are being explored to overcome challenges with snake venom production, namely limited quantity, high cost, specificity and challenges with animal captivity, as well as in the search for pan-specific or broad spectrum antivenoms, which would be more convenient and cost effective than current mono- or poly-specific antivenoms. Thus, advances in toxin-specific antibodies production hold much promise in future therapeutic strategies of snakebite envenoming. (https://pubmed.ncbi.nlm.nih.gov/35448894/)

Three-finger toxin (3FTx)-specific monoclonal murine IgGs against Naka ashei venom were developed as follows: anti-3FTxs monoclonal antibodies were developed against N. ashei venom in mice. All the three test mAbs (P4G6a, P6D9a, and P6D9b) were found to be IgG antibodies, isotyped as IgG1. SDS-PAGE analysis of the test mAbs showed two major bands at approximately 55 and 29 kDa, suggestive of immunoglobulin heavy and light chain composition, respectively. The immunoaffinity-purified test mAbs demonstrated higher binding efficacy to the target antigen compared to negative control. Similarly, a cocktail of the test mAbs was found to induce a significantly higher inhibition (p-value < 0.0001) compared to two leading commercial brands of antivenoms on the Kenyan market, implying a higher specificity for the target antigen. Both the test mAbs and 3FTxs polyclonal antibodies induced comparable inhibition (p-value = 0.9029). The inhibition induced by the 3FTxs polyclonal antibodies was significantly different from the two antivenoms (p-value < 0.0001). Our results demonstrate the prospects of developing toxin-specific monoclonal-based antivenoms for snakebite immunotherapy. (https://pubmed.ncbi.nlm.nih.gov/35448894/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Pan African University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/35448894/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Naja ashei (Ashe's spitting cobra)
Snake family	Elapidae
Risk category	Category 1 (Highest Medical Importance)
Countries	Kenya
Regions	East Africa

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent murine immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja ashei (Ashe's spitting cobra)	Naja ashei (Ashe's spitting cobra)
Snake family		Elapidae
Risk category		Category 1 (Highest Medical Importance)

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: 3FTxs

Syndromic profiles: Not specified

Novel anti-Crotalus mictlantecuhtli rabbit antiserum (against C. mictlantecuhtli)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1901

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: C. mictlantecuhtli

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives. In addition, novel immunization techniques are being explored to overcome challenges with snake venom production, namely limited quantity, high cost, specificity and challenges with animal captivity, as well as in the search for pan-specific or broad spectrum antivenoms, which would be more convenient and cost effective than current mono- or poly-specific antivenoms.

Novel anti-Crotalus mictlantecuhtli rabbit antiserum candidate against C. mictlantecuhtli was developed as follows: The aim was to evaluate the immunogenic properties of C. mictlantecuhtli venom and its potential to generate polyclonal antibodies capable of neutralizing other pitviper venoms. An experimental anti-Crotalus mictlantecuhtli serum, using the rabbit model, was generated to test recognition and neutralizing capacity against the homologous venom as well as venoms from C. atrox, C.basiliscus, C. durissus terrificus, C. scutulatus salvini, C. tzabcan and Ophryacus sphenophrys. Pre-incubation neutralization experiments using our experimental serum showed positive results against venoms containing crotoxin, while venoms from two non-neurotoxic pit-vipers were not neutralized. Rescue experiments in mice showed that, when intravenously injected (i.v.), C. mictlantecuhtli venom is not neutralized by a maximum dose of Antivipmyn and the experimental serum after 5 min of envenomation, albeit mice envenomated intraperitoneally (i.p.) and rescued i.v. with Antivipmyn survived even at 50 min after envenomation. Our results highlight the importance of using the highly neurotoxic C. mictlantecuhtli venom to increase antivenom effectiveness against Mexican neurotoxic pitvipers. (https://pubmed.ncbi.nlm.nih.gov/32891663/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Instituto de Biotecnología, UNAM

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/32891663/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	C. mictlantecuhtli (Veracruz Rattlesnake)
Snake family	Viperidae
Risk category	Category 1 (Highest Medical Importance)
Countries	Mexico
Regions	North America

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotalus mictlantecuhtli (Veracruz neotropical rattlesnake); Crotalus atrox (Western diamondback rattlesnake); Crotalus basiliscus (Mexican west coast rattlesnake); Crotalus durissus terrificus (South American rattlesnake); Crotalus scutulatus salvini (Huamantlan Rattlesnake); Crotalus tzabcan (Yucatan neotropical rattlesnake); Ophryacus sphenophrys (Broad-horned pitviper)	Crotalus mictlantecuhtli (Veracruz neotropical rattlesnake); Crotalus basiliscus (Mexican west coast rattlesnake); Crotalus durissus terrificus (South American rattlesnake); Crotalus scutulatus salvini (Huamantlan Rattlesnake); Ophryacus sphenophrys (Broad-horned pitviper)
Snake family		Viperidae

Tested in	Effective against (any efficacy data)
Risk category	Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Novel anti-crotamine polyclonal antibodies (against Crotalus molossus nigrescens)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 2528

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crotamine; plus crude snake venom: Crotalus molossus nigrescens

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals (here rabbits) immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including rabbits. In addition, novel immunization techniques are being explored to overcome challenges with snake venom production, namely limited quantity, high cost, and challenges with animal captivity, as well as in the search for pan-specific or broad spectrum antivenoms, which would be more convenient and cost effective than current mono- or poly-specific antivenoms.

Three novel anti-crotamine polyclonal antibody candidates against Crotalus spp were developed either via fusion protein immunization (see candidate 'Novel anti-crotamine polyclonal antibodies via recombinant fusion protein immunization (against Crotalus spp)') or crude venom (see also candidate 'Novel anti-crotamine polyclonal antibodies (against C. oreganus helleri)') as follows: Mexican pit viper antivenoms have shown low immunoreactivity against crotamine, which is an urgent quality to be improved. The objective was to evaluate the ability of a novel recombinant fusion protein composed of sphingomyelinase D and crotamine (called rSMD-crotamine), and two whole venoms from Crotalus molossus nigrescens and C. oreganus helleri to produce neutralizing antibodies against crotamine. These immunogens were separately used for immunization procedures in rabbits. Three experimental antivenoms were generated to test their cross-reactivity via western-blot against crotamine from 7 species (C. m. nigrescens, C. o. helleri, C. durissus terrificus, C. scutulatus salvini, C. basiliscus, C. culminatus and C. tzabcan). We also performed pre-incubation neutralization experiments in mice to measure the neutralizing potency of each antivenom against crotamine induced hind limb paralysis. The antivenoms showed broad recognition across crotamine from most of the tested species. Also, neutralization against crotamine paralysis symptom was successfully achieved by the three antivenoms, albeit with different efficiencies. The results highlight the use of crotamine enriched

venoms and the novel recombinant fusion protein as promising immunogens to improve the neutralizing potency against crotamine for the improvement of Mexican antivenoms. (https://pubmed.ncbi.nlm.nih.gov/33894246/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Texas A&M University; National Autonomous University of Mexico (UNAM)

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Crotalus molossus nigrescens (Black-tailed rattlesnake)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Mexico
Regions	North America

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Crude venom immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	C. m. nigrescens (Black-tailed rattlesnake); C. o. helleri (Southern Pacific rattlesnake); C. durissus terrificus (South American rattlesnake); C. scutulatus salvini (Mojave green); C. basiliscus (Mexican west coast rattlesnake); C. culminatus (Northwestern Neotropical Rattlesnake); C. tzabcan (Tzabcan Rattlesnake)	C. m. nigrescens (Black-tailed rattlesnake); C. o. helleri (Southern Pacific rattlesnake); C. durissus terrificus (South American rattlesnake); C. scutulatus salvini (Mojave green); C. basiliscus (Mexican west coast rattlesnake); C. culminatus (Northwestern Neotropical Rattlesnake); C. tzabcan (Tzabcan Rattlesnake)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Neurotoxic (paralysis)

Novel anti-crotamine polyclonal antibodies (against Crotalus oreganus helleri)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 2531

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crotamine; plus crude snake venom: Crotalus oreganus helleri

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals (here rabbits) immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including rabbits. In addition, novel immunization techniques are being explored to overcome challenges with snake venom production, namely limited quantity, high cost, and challenges with animal captivity, as well as in the search for pan-specific or broad spectrum antivenoms, which would be more convenient and cost effective than current mono- or poly-specific antivenoms.

Three novel anti-crotamine polyclonal antibody candidates against Crotalus spp were developed either via fusion protein immunization (see candidate 'Novel anti-crotamine polyclonal antibodies via recombinant fusion protein immunization (against Crotalus spp)') or crude venom (see also candidate 'Novel anti-crotamine polyclonal antibodies (against Crotalus molossus nigrescens)') as follows: Mexican pit viper antivenoms have shown low immunoreactivity against crotamine, which is an urgent quality to be improved. The objective was to evaluate the ability of a novel recombinant fusion protein composed of sphingomyelinase D and crotamine (called rSMD-crotamine), and two whole venoms from Crotalus molossus nigrescens and C. oreganus helleri to produce neutralizing antibodies against crotamine. These immunogens were separately used for immunization procedures in rabbits. Three experimental antivenoms were generated to test their cross-reactivity via western-blot against crotamine from 7 species (C. m. nigrescens, C. o. helleri, C. durissus terrificus, C. scutulatus salvini, C. basiliscus, C. culminatus and C. tzabcan). We also performed pre-incubation neutralization experiments in mice to measure the neutralizing potency of each antivenom against crotamine induced hind limb paralysis. The antivenoms showed broad recognition across crotamine from most of the tested species. Also, neutralization against crotamine paralysis symptom was successfully achieved by the three antivenoms, albeit with different efficiencies. The results highlight the use of

crotamine enriched venoms and the novel recombinant fusion protein as promising immunogens to improve the neutralizing potency against crotamine for the improvement of Mexican antivenoms. (https://pubmed.ncbi.nlm.nih.gov/33894246/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Texas A&M University; National Autonomous University of Mexico (UNAM)

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Crotalus oreganus helleri (Southern Pacific rattlesnake)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	United States of America
Regions	North America

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Crude venom immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	C. m. nigrescens (Black-tailed rattlesnake); C. o. helleri (Southern Pacific rattlesnake); C. durissus terrificus (South American rattlesnake); C. scutulatus salvini (Mojave green); C. basiliscus (Mexican west coast rattlesnake); C. culminatus (Northwestern Neotropical Rattlesnake); C. tzabcan (Tzabcan Rattlesnake)	C. m. nigrescens (Black-tailed rattlesnake); C. o. helleri (Southern Pacific rattlesnake); C. durissus terrificus (South American rattlesnake); C. scutulatus salvini (Mojave green); C. basiliscus (Mexican west coast rattlesnake); C. culminatus (Northwestern Neotropical Rattlesnake); C. tzabcan (Tzabcan Rattlesnake)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Neurotoxic (paralysis)

Novel anti-crotamine polyclonal antibodies via recombinant fusion protein immunization (against Crotalus spp)

Alternative name(s): Polyclonal antibodies via rSMD-crotamine immunization

Chemical name: N/A

CAS number: N/A

PCR ID: 2030

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crotamine

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals (here rabbits) immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including rabbits. In addition, novel immunization techniques are being explored to overcome challenges with snake venom production, namely limited quantity, high cost, and challenges with animal captivity, as well as in the search for pan-specific or broad spectrum antivenoms, which would be more convenient and cost effective than current mono- or poly-specific antivenoms.

Three novel anti-crotamine polyclonal antibody candidates against Crotalus spp were developed either via fusion protein immunization or crude venom (see candidates 'Novel anti-crotamine polyclonal antibodies (against Crotalus molossus nigrescens)' and 'Novel anti-crotamine polyclonal antibodies (against C. oreganus helleri)') as follows: Mexican pit viper antivenoms have shown low immunoreactivity against crotamine, which is an urgent quality to be improved. The objective was to evaluate the ability of a novel recombinant fusion protein composed of sphingomyelinase D and crotamine (called rSMD-crotamine), and two whole venoms from Crotalus molossus nigrescens and C. oreganus helleri to produce neutralizing antibodies against crotamine. These immunogens were separately used for immunization procedures in rabbits. Three experimental antivenoms were generated to test their cross-reactivity via western-blot against crotamine from 7 species (C. m. nigrescens, C. o. helleri, C. durissus terrificus, C. scutulatus salvini, C. basiliscus, C. culminatus and C. tzabcan). We also performed pre-incubation neutralization experiments in mice to measure the neutralizing potency of each antivenom against crotamine induced hind limb paralysis. The antivenoms showed broad recognition across crotamine from most of the tested species. Also, neutralization against crotamine paralysis symptom was successfully achieved by the three antivenoms, albeit with different efficiencies. The results highlight the use of crotamine enriched

venoms and the novel recombinant fusion protein as promising immunogens to improve the neutralizing potency against crotamine for the improvement of Mexican antivenoms. (https://pubmed.ncbi.nlm.nih.gov/33894246/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: National Autonomous University of Mexico (UNAM); Texas A&M University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33894246/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Crotalus molossus nigrescens (Black-tailed rattlesnake)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Mexico; United States of America
Regions	North America

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Fusion protein immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	C. m. nigrescens (Black-tailed rattlesnake); C. o. helleri (Southern Pacific rattlesnake); C. durissus terrificus (South American rattlesnake); C. scutulatus salvini (Mojave green); C. basiliscus (Mexican west coast rattlesnake); C. culminatus (Northwestern Neotropical Rattlesnake); C. tzabcan (Tzabcan Rattlesnake)	C. m. nigrescens (Black-tailed rattlesnake); C. o. helleri (Southern Pacific rattlesnake); C. durissus terrificus (South American rattlesnake); C. scutulatus salvini (Mojave green); C. basiliscus (Mexican west coast rattlesnake); C. culminatus (Northwestern Neotropical Rattlesnake); C. tzabcan (Tzabcan Rattlesnake)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Neurotoxic (paralysis)

Novel anti-short-chain α-neurotoxin (ScNtx) antivenom via toxin immunization (against elapids)

Alternative name(s): Anti-ScNtx (toxin) antibodies (against elapids); anti-ScNtx experimental antivenom (EAV)

Chemical name: N/A

CAS number: N/A

PCR ID: 1871

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Short-chain consensus α-neurotoxin: elapids (Acanthophis, Oxyuranus, Walterinnesia, Naja, Dendroaspis and Micrurus)

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives. In addition, novel immunization techniques are being explored to overcome challenges with snake venom production, namely limited quantity, high cost, specificity and challenges with animal captivity, as well as in the search for pan-specific or broad spectrum antivenoms, which would be more convenient and cost effective than current mono- or poly-specific antivenoms.

A novel equine anti-short-chain α-neurotoxin antivenom against elapids was developed using toxin-mediated immunization as follows: A recombinant consensus short-chain α-neurotoxin (ScNtx) was developed based on sequences from the most lethal elapid venoms from America, Africa, Asia, and Oceania (https://pubmed.ncbi.nlm.nih.gov/29626299/). An antivenom was generated by immunizing horses with ScNtx. and showed that it can successfully neutralize the lethality of pure recombinant and native short-chain α-neurotoxins, as well as whole neurotoxic elapid venoms from diverse genera such as Micrurus, Dendroaspis, Naja, Walterinnesia, Ophiophagus and Hydrophis. These results provide a proof-of-principle for using recombinant proteins with rationally designed consensus sequences as universal immunogens for developing next-generation antivenoms with higher effectiveness and broader neutralizing capacity. (https://pubmed.ncbi.nlm.nih.gov/31409779/). The approach and resulting anti-ScNtx antibodies was then combined with antibodies from traditional crude venom (Micrurus tener) immunization in a blended antivenom (see candidate 'Novel equine blended anti-Micrurus tener and anti-ScNtx antibodies (against elapids)'

(https://pubmed.ncbi.nlm.nih.gov/33423840/).

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Instituto de Biotecnología, UNAM

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/29626299/
https://pubmed.ncbi.nlm.nih.gov/33423840/
https://pubmed.ncbi.nlm.nih.gov/31409779/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Acanthophis, Oxyuranus, Walterinnesia, Naja, Dendroaspis and Micrurus spp
Snake family	Elapidae
Risk category	Both Category 1 & 2
Countries	
Regions	Central America; North America; East Asia; Australia-Papua (incl Pacific)

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Immunization with recombinant toxin

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Micrurus fulvius; M. tener; M. browni; M. distans; M. laticollaris; M. diastema; Micrurus nigrocinctus; M. surinamensis; Dendroaspis angusticeps; Dendroaspis polylepis; Dendroaspis viridis; Naja atra; N. haje; Naja kaouthia; N. katiensis; Naja oxiana; N. nigricollis, N. pallida, and N. mossambica; N. nubiae; N. melanoleuca; N. naja;Naja nivea; Ophiophagus hannah; Hydrophis platura; Walterinnesia aegyptia; Oxyuranus scutellatus; Pseudechis australis; Pseudechis colleti	M. laticollaris; M. diastema; Micrurus nigrocinctus; M. surinamensis; N. nubiae; N. haje; N. melanoleuca; N. naja
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: 3FTxs

Syndromic profiles: Neurotoxic (paralysis)

Novel anti-short-chain α-neurotoxin D.H. rabbit antiera via toxin immunization (against Micrurus diastema)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1872

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Short-chain α-neurotoxin: Micrurus diastema

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives. In addition, novel immunization techniques are being explored to overcome challenges with snake venom production, namely limited quantity, high cost, specificity and challenges with animal captivity, as well as in the search for pan-specific or broad spectrum antivenoms, which would be more convenient and cost effective than current mono- or poly-specific antivenoms.

A novel anti-short-chain α-neurotoxin rabbit antiera candidate against Micrurus diastema was developed via recombinant toxin-mediated immunization as follows: An isoform of the D.H α-neurotoxin transcript was identified in the venom of M. diastema. The mature α-neurotoxin coded in the D.H transcript was heterologously expressed, and it was found soluble (4.2 mg/l) in the cytoplasm of a bacterial system. The recombinant D.H (rD.H) had an IC50 value of 31.5 ± 4.4 nM on nicotinic acetylcholine receptors of the muscular type expressed in rhabdomyosarcoma cells (TE671). The rDH also had an LD50 of 0.15 mg/kg mice, and it was evaluated as a potential immunogen in New Zealand rabbits. The protective capacity of rabbit sera was tested against two native coral snake α-neurotoxins, and against rD.H. One of the anti-rD.H rabbit sera was able to neutralize the lethality of all three neurotoxins when tested in groups of CD1 mice. This work contributes to the increasing understanding of the high diversity of 3FTxs, and shows that recombinant coral snake α-neurotoxins are promising supplements for hyperimmunization protocols for coral snake antivenom production. (https://pubmed.ncbi.nlm.nih.gov/29391193/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Instituto de Biotecnología, UNAM

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/29391193/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Micrurus diastema (Variable coral snake)
Snake family	Elapidae
Risk category	Category 2 (Secondary Medical Importance)
Countries	Mexico
Regions	North America

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Immunization via recombinant toxin

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Micrurus diastema (Variable coral snake)	Micrurus diastema (Variable coral snake)
Snake family		Elapidae
Risk category		Category 2 (Secondary Medical Importance)

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: 3FTxs

Syndromic profiles: Neurotoxic (paralysis)

Novel anti-SVSP antivenom via toxin immunization (against Bothrops jararaca)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 2109

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: SVSPs: Bothrops jararaca

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives. In addition, novel immunization techniques are being explored to overcome challenges with snake venom production (namely limited quantity, high cost, specificity and challenges with animal captivity, as well as in the search for pan-specific or broad spectrum antivenoms, which would be more convenient and cost effective than current mono- or poly-specific antivenoms. In Brazil, although the antibothropic serum produced by the Butantan Institute is effective, studies show that some symptoms observed in cases of envenoming are not efficiently neutralized. Moreover, it has been shown that the commercial antivenom (Bothrops AV) does not fully neutralize in vitro some serine proteases present in the Bothrops jararaca venom. (https://pubmed.ncbi.nlm.nih.gov/31494207/)

Novel anti-SVSP antivenom via toxin immunization (against Bothrops jararaca) was developed via a new method in the production of specific immunoglobulins capable of neutralizing the activities of SVSPs as follows: A pool of serine proteases that was not inhibited by the commercial antivenom, made up of four enzymes (KN-BJ2, BjSP, HS112 and BPA) from the B. jararaca venom was obtained through two chromatographic steps (DEAE-HPLC and C8-RP-HPLC). The identities of these proteases were confirmed by SDS-PAGE, followed by tryptic digestion and mass spectrometry analysis. This pool was inoculated into BALB/c and C57BL/6 mice, using SBA-15 as adjuvant, and the produced IgGs were purified by affinity chromatography. The sera were characterized by ELISA, avidity and proteolytic neutralization assays. Both animal models responded to the immunization, producing higher IgGs titers when compared to the commercial antivenom. The experimental serum from BALB/c mice presented a better hydrolysis inhibition of the selective fluorescent substrate for serine proteases (~80%) when compared to C57BL/6 (~25%) and the commercial antivenom (<1%)

at the dose of 500:1 (weight of antivenom:weight of venom). These results show that a different immunization method using isolated serine proteases improves the toxins neutralizing efficacy and could lead to a better end product to be used as a supplemental medicine to the currently used immunotherapy. (https://pubmed.ncbi.nlm.nih.gov/31494207/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Rural Federal University of Rio de Janeiro, Universidade Federal Rural do Rio de Janeiro (UFRRJ)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/31494207/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Bothrops jararaca (Jararaca)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Brazil
Regions	South America

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Toxin-mediated immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops jararaca (Jararaca)	Bothrops jararaca (Jararaca)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVSPs

Syndromic profiles: Not specified

Novel bivalent snake antivenom (IgG) (against Daboia russelii & Echis carinatus) (Pakistan)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 2033

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Daboia russelii and Echis carinatus

Route of administration: Intravenous

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Novel bivalent snake antivenom (IgG) candidate against Daboia russelii & Echis carinatus was tested in a Phase II clinical trial in Pakistan through the Antisnake Venom and Antirabies Serology laboratory, funded by Department of health, Government of Sindh, Pakistan in 2014/2015. (https://en.irct.ir/trial/16643). Results were published in 2017, with all patients recovering from coagulopathy after receiving IV infusion of 10 mL investigational ASV diluted in 100 mL normal saline tested by 20-minute WBCT. (https://www.researchgate.net/publication/318431274_Phase_II_Clinical_Trial_to_Establish_Efficacy_of_a_Locally_Appropriate_Bivalent_Anti_Snake_Venom_in_Pakistan)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Phase II

Highest R&D stage (any condition): Phase II (SBE)

Development status: Active

Developers/investigators: Antisnake Venom and Antirabies Serology Laboratory, Sindh

Evidence of clinical trials? Yes

Phase II/Phase III(Status: , October 2014-): *Clinical Trial of a new snake antivenom for the treatment of viper snake bites in Sindh.* (CT number: IRCT2014070218314N1, CT source:

http://en.irct.ir/trial/16643)

Production/source

	Derived from
Snake species	Daboia russelii (Indian Russell's viper); Echis carinatus (Saw-scaled viper)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	
Regions	South Asia

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent immunization, details unclear

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russelii (Indian Russell's viper); Echis carinatus (Saw-scaled viper)	Unknown
Snake family		
Risk category		

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Novel camelid IgG antivenom (against Echis sochureki)

Alternative name(s): Camelid immunoglobulins against Echis sochureki venom

Chemical name: N/A

CAS number: N/A

PCR ID: 1708

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Echis sochureki

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals (here rabbits) immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including camels.

A novel camelid IgG antivenom candidate against Echis sochureki was developed as follows: dromedaries (Camelus dromedarius) were successfully immunized against the venom of Indian saw-scaled Viper- Echis carinatus sochureki. The specificity was assessed and potential of camels immunised with venom of medically most important snake of Western India, the saw-scaled viper (Echis c. sochureki). Using WHO standard pre-clinical in vivo tests the neutralisation of the venom responsible for the lethal, haemorrhagic, coagulant and local necrotizing activities were measured, since these are the most significant effects that characterize envenoming by this species. The anti-venom was found significantly effective in the neutralisation of all these effects tested and thus, revealed further an immunological perspective, that camel IgG anti-venom (monospecific) would be as efficacious as specific equine anti-venoms. (https://pubmed.ncbi.nlm.nih.gov/28528176/).

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: S P Medical College & Hospital, Bikaner

Key funders: Biotechnology Industry Research Assistance Council (BIRAC)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/28528176/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Echis carinatus sochureki (Indian saw-scaled viper)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	India
Regions	South Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Crude venom immunization of camels

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Echis carinatus sochureki (Indian saw-scaled viper)	Echis carinatus sochureki (Indian saw-scaled viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage),Procoagulant (blood clotting)

Novel equine anti-Bitis antivenom (against B. arietans)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1877

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: B. arietans

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). The African continent suffers from a severe antivenom crisis and current antivenom production is only sufficient to treat 25% of snakebite cases. (https://pubmed.ncbi.nlm.nih.gov/26730709/)

A novel equine anti-Bitis antivenom candidate against B. arietans is part of five experimental antivenoms investigated against the main snake species found in Mozambique. Development was as follows: Adult horses primed with the indicated venoms were divided into 5 groups (B. arietans; B. nasicornis + B. rhinoceros (see candidate 'Novel equine anti-Bitis antivenom (against B. nasicornis + B. rhinoceros)'); N. melanoleuca (see candidate 'Novel equine anti-Naja antivenom (against N. melanoleuca)'); N. mossambica (see candidate 'Novel equine anti-Naja antivenom (against N. mossambica)'); N. annulifera + D. polylepis + D. angusticeps (see candidate 'Novel equine anti-Naja antivenom (against N. annulifera + D. polylepis + D. angusticeps)') and reimmunized two times for antivenom production. Blood was collected, and plasma was separated and subjected to antibody purification using caprylic acid. Plasmas and antivenoms were subject to titration, affinity determination, cross-recognition assays and in vivo venom lethality neutralization. A commercial anti-Crotalic antivenom was used for comparison. The purified antivenoms exhibited high titers against B. arietans, B. nasicornis and B. rhinoceros (5.18 x 106, 3.60 x 106 and 3.50 x 106 U-E/mL, respectively) and N. melanoleuca, N. mossambica and N. annulifera (7.41 x 106, 3.07 x 106 and 2.60 x 106 U-E/mL, respectively), but lower titers against the D. angusticeps and D. polylepis (1.87 x 106 and 1.67 x 106 U-E/mL). All the groups, except anti-N. melanoleuca, showed significant differences from the anti-Crotalic antivenom (7.55 x 106 U-E/mL). The affinity index of all the groups was high, ranging from 31% to 45%. Cross-recognition assays showed the recognition of proteins with similar molecular weight in the venoms and may indicate the possibility of paraspecific neutralization. The three monospecific antivenoms were able to provide in vivo protection. The results indicate that the anti-Bitis and anti-Naja antivenoms developed would be useful for treating snakebite envenomations in Mozambique, although their effectiveness should to be increased. The authors propose instead the development of monospecific antivenoms, which would serve as the basis for two polyvalent

antivenoms, the anti-Bitis and anti-Elapidae. Polyvalent antivenoms represent an increase in treatment quality, as they have a wider range of application and are easier to distribute and administer to snake envenoming victims. (https://pubmed.ncbi.nlm.nih.gov/26730709/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Butantan Institute, Fundacao Butantan

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/26730709/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	B. arietans (Puff adder)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Mozambique
Regions	Southern Africa

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent equine immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	B. arietans (Puff adder)	B. arietans (Puff adder)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Novel equine anti-Bitis antivenom (against B. nasicornis and B. rhinoceros)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 2035

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: B. nasicornis, B. rhinoceros

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). The African continent suffers from a severe antivenom crisis and current antivenom production is only sufficient to treat 25% of snakebite cases. (https://pubmed.ncbi.nlm.nih.gov/26730709/)

A novel equine anti-Bitis antivenom candidate against B. nasicornis + B. rhinoceros is part of five experimental antivenoms investigated against the main snake species found in Mozambique. Development was as follows: Adult horses primed with the indicated venoms were divided into 5 groups (B. arietans (see candidate 'Novel equine anti-Bitis antivenom (against B. arietans)'); B. nasicornis + B. rhinoceros; N. melanoleuca (see candidate 'Novel equine anti-Naja antivenom (against N. melanoleuca)'); N. mossambica (see candidate 'Novel equine anti-Naja antivenom (against N. mossambica)'); N. annulifera + D. polylepis + D. angusticeps (see candidate 'Novel equine anti-Naja antivenom (against N. annulifera + D. polylepis + D. angusticeps)') and reimmunized two times for antivenom production. Blood was collected, and plasma was separated and subjected to antibody purification using caprylic acid. Plasmas and antivenoms were subject to titration, affinity determination, cross-recognition assays and in vivo venom lethality neutralization. A commercial anti-Crotalic antivenom was used for comparison. The purified antivenoms exhibited high titers against B. arietans, B. nasicornis and B. rhinoceros (5.18 x 106, 3.60 x 106 and 3.50 x 106 U-E/mL, respectively) and N. melanoleuca, N. mossambica and N. annulifera (7.41 x 106, 3.07 x 106 and 2.60 x 106 U-E/mL, respectively), but lower titers against the D. angusticeps and D. polylepis (1.87 x 106 and 1.67 x 106 U-E/mL). All the groups, except anti-N. melanoleuca, showed significant differences from the anti-Crotalic antivenom (7.55 x 106 U-E/mL). The affinity index of all the groups was high, ranging from 31% to 45%. Cross-recognition assays showed the recognition of proteins with similar molecular weight in the venoms and may indicate the possibility of paraspecific neutralization. The three monospecific antivenoms were able to provide in vivo protection.The results indicate that the anti-Bitis and anti-Naja antivenoms developed would be useful for treating snakebite envenomations

in Mozambique, although their effectiveness should to be increased. The authors propose instead the development of monospecific antivenoms, which would serve as the basis for two polyvalent antivenoms, the anti-Bitis and anti-Elapidae. Polyvalent antivenoms represent an increase in treatment quality, as they have a wider range of application and are easier to distribute and administer to snake envenoming victims. (https://pubmed.ncbi.nlm.nih.gov/26730709/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Butantan Institute, Fundacao Butantan

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/26730709/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Bitis nasicornis (Rhinoceros viper); Bitis rhinoceros (West African Gaboon viper)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Mozambique
Regions	Southern Africa

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent equine immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bitis nasicornis (Rhinoceros viper); Bitis rhinoceros (West African Gaboon viper)	Bitis nasicornis (Rhinoceros viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Novel equine anti-elapid antivenom (against N. annulifera, D. polylepis, D. angusticeps)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 2037

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: N. annulifera, D. polylepis, D. angusticeps

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). The African continent suffers from a severe antivenom crisis and current antivenom production is only sufficient to treat 25% of snakebite cases. (https://pubmed.ncbi.nlm.nih.gov/26730709/)

A novel equine anti-Naja antivenom candidate against N. annulifera, D. polylepis, D. angusticeps is part of five experimental antivenoms investigated against the main snake species found in Mozambique. Development was as follows: Adult horses primed with the indicated venoms were divided into 5 groups (B. arietans (see candidate 'Novel equine anti-Bitis antivenom (against B. arietans)'); B. nasicornis + B. rhinoceros (see candidate 'Novel equine anti-Bitis antivenom (against B. nasicornis + B. rhinoceros)'); N. melanoleuca (see candidate 'Novel equine anti-Naja antivenom (against N. melanoleuca)'); N. mossambica (see candidate 'Novel equine anti-Naja antivenom (against N. mossambica)'); and N. annulifera + D. polylepis + D. angusticeps and reimmunized two times for antivenom production. Blood was collected, and plasma was separated and subjected to antibody purification using caprylic acid. Plasmas and antivenoms were subject to titration, affinity determination, cross-recognition assays and in vivo venom lethality neutralization. A commercial anti-Crotalic antivenom was used for comparison. The purified antivenoms exhibited high titers against B. arietans, B. nasicornis and B. rhinoceros (5.18 x 106, 3.60 x 106 and 3.50 x 106 U-E/mL, respectively) and N. melanoleuca, N. mossambica and N. annulifera (7.41 x 106, 3.07 x 106 and 2.60 x 106 U-E/mL, respectively), but lower titers against the D. angusticeps and D. polylepis (1.87 x 106 and 1.67 x 106 U-E/mL). All the groups, except anti-N. melanoleuca, showed significant differences from the anti-Crotalic antivenom (7.55 x 106 U-E/mL). The affinity index of all the groups was high, ranging from 31% to 45%. Cross-recognition assays showed the recognition of proteins with similar molecular weight in the venoms and may indicate the possibility of paraspecific neutralization. The three monospecific antivenoms were able to provide in vivo protection. The results indicate that the anti-Bitis and anti-Naja antivenoms developed would be useful for treating snakebite envenomations

in Mozambique, although their effectiveness should to be increased. The authors propose instead the development of monospecific antivenoms, which would serve as the basis for two polyvalent antivenoms, the anti-Bitis and anti-Elapidae. Polyvalent antivenoms represent an increase in treatment quality, as they have a wider range of application and are easier to distribute and administer to snake envenoming victims. (https://pubmed.ncbi.nlm.nih.gov/26730709/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Butantan Institute, Fundacao Butantan

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/26730709/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Naja annulifera (Snouted cobra); Dendroaspis polylepis (Black mamba); Dendroaspis angusticeps (Eastern green mamba)
Snake family	Elapidae
Risk category	Both Category 1 & 2
Countries	Mozambique
Regions	Southern Africa

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent equine immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja annulifera (Snouted cobra); Dendroaspis polylepis (Black mamba); Dendroaspis angusticeps (Eastern green mamba)	N/A
Snake family		
Risk category		N/A

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Novel equine anti-Naja antivenom (against N. melanoleuca)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1878

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: N. melanoleuca

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). The African continent suffers from a severe antivenom crisis and current antivenom production is only sufficient to treat 25% of snakebite cases. (https://pubmed.ncbi.nlm.nih.gov/26730709/)

A novel equine anti-Naja antivenom candidate against N. melanoleuca is part of five experimental antivenoms investigated against the main snake species found in Mozambique. Development was as follows: Adult horses primed with the indicated venoms were divided into 5 groups (B. arietans (see candidate 'Novel equine anti-Bitis antivenom (against B. arietans)'); B. nasicornis + B. rhinoceros (see candidate 'Novel equine anti-Bitis antivenom (against B. nasicornis + B. rhinoceros)'); N. melanoleuca; N. mossambica (see candidate 'Novel equine anti-Naja antivenom (against N. mossambica)'); N. annulifera + D. polylepis + D. angusticeps (see candidate 'Novel equine anti-Naja antivenom (against N. annulifera + D. polylepis + D. angusticeps)') and reimmunized two times for antivenom production. Blood was collected, and plasma was separated and subjected to antibody purification using caprylic acid. Plasmas and antivenoms were subject to titration, affinity determination, cross-recognition assays and in vivo venom lethality neutralization. A commercial anti-Crotalic antivenom was used for comparison. The purified antivenoms exhibited high titers against B. arietans, B. nasicornis and B. rhinoceros (5.18 x 106, 3.60 x 106 and 3.50 x 106 U-E/mL, respectively) and N. melanoleuca, N. mossambica and N. annulifera (7.41 x 106, 3.07 x 106 and 2.60 x 106 U-E/mL, respectively), but lower titers against the D. angusticeps and D. polylepis (1.87 x 106 and 1.67 x 106 U-E/mL). All the groups, except anti-N. melanoleuca, showed significant differences from the anti-Crotalic antivenom (7.55 x 106 U-E/mL). The affinity index of all the groups was high, ranging from 31% to 45%. Cross-recognition assays showed the recognition of proteins with similar molecular weight in the venoms and may indicate the possibility of paraspecific neutralization. The three monospecific antivenoms were able to provide in vivo protection.The results indicate that the anti-Bitis and anti-Naja antivenoms developed would be useful for treating snakebite envenomations in Mozambique, although their effectiveness should to be increased. The authors propose instead the development of monospecific antivenoms, which would serve as the basis for two polyvalent

antivenoms, the anti-Bitis and anti-Elapidae. Polyvalent antivenoms represent an increase in treatment quality, as they have a wider range of application and are easier to distribute and administer to snake envenoming victims. (https://pubmed.ncbi.nlm.nih.gov/26730709/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Butantan Institute, Fundacao Butantan

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/26730709/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Naja melanoleuca (Black and white cobra)
Snake family	Elapidae
Risk category	Both Category 1 & 2
Countries	Mozambique
Regions	Southern Africa

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent equine immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja melanoleuca (Black and white cobra)	Naja melanoleuca (Black and white cobra)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Novel equine anti-Naja antivenom (against N. mossambica)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 2036

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Naja mossambica

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). The African continent suffers from a severe antivenom crisis and current antivenom production is only sufficient to treat 25% of snakebite cases. (https://pubmed.ncbi.nlm.nih.gov/26730709/)

A novel equine anti-Naja antivenom candidate against N. mossambica is part of five experimental antivenoms investigated against the main snake species found in Mozambique. Development was as follows: Adult horses primed with the indicated venoms were divided into 5 groups (B. arietans (see candidate 'Novel equine anti-Bitis antivenom (against B. arietans)'); B. nasicornis + B. rhinoceros (see candidate 'Novel equine anti-Bitis antivenom (against B. nasicornis + B. rhinoceros)'); N. melanoleuca (see candidate 'Novel equine anti-Naja antivenom (against N. melanoleuca)'); N. mossambica; N. annulifera + D. polylepis + D. angusticeps (see candidate 'Novel equine anti-Naja antivenom (against N. annulifera + D. polylepis + D. angusticeps)') and reimmunized two times for antivenom production. Blood was collected, and plasma was separated and subjected to antibody purification using caprylic acid. Plasmas and antivenoms were subject to titration, affinity determination, cross-recognition assays and in vivo venom lethality neutralization. A commercial anti-Crotalic antivenom was used for comparison. The purified antivenoms exhibited high titers against B. arietans, B. nasicornis and B. rhinoceros (5.18 x 106, 3.60 x 106 and 3.50 x 106 U-E/mL, respectively) and N. melanoleuca, N. mossambica and N. annulifera (7.41 x 106, 3.07 x 106 and 2.60 x 106 U-E/mL, respectively), but lower titers against the D. angusticeps and D. polylepis (1.87 x 106 and 1.67 x 106 U-E/mL). All the groups, except anti-N. melanoleuca, showed significant differences from the anti-Crotalic antivenom (7.55 x 106 U-E/mL). The affinity index of all the groups was high, ranging from 31% to 45%. Cross-recognition assays showed the recognition of proteins with similar molecular weight in the venoms and may indicate the possibility of paraspecific neutralization. The three monospecific antivenoms were able to provide in vivo protection. The results indicate that the anti-Bitis and anti-Naja antivenoms developed would be useful for treating snakebite envenomations in Mozambique, although their effectiveness should to be increased. The authors propose instead the development of monospecific antivenoms, which would serve as the basis for two polyvalent antivenoms, the anti-Bitis

and anti-Elapidae. Polyvalent antivenoms represent an increase in treatment quality, as they have a wider range of application and are easier to distribute and administer to snake envenoming victims. (https://pubmed.ncbi.nlm.nih.gov/26730709/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Butantan Institute, Fundacao Butantan

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/26730709/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Naja mossambica (Mozambique spitting cobra)
Snake family	Elapidae
Risk category	Both Category 1 & 2
Countries	Mozambique
Regions	Southern Africa

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent equine immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja mossambica (Mozambique spitting cobra)	Naja mossambica (Mozambique spitting cobra)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Novel equine blended anti-Micrurus tener and anti-ScNtx antibodies (against elapids)

Alternative name(s): Ab-blend

Chemical name: N/A

CAS number: N/A

PCR ID: 2029

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Short-chain consensus α-neurotoxin (ScNtx): elapids (Acanthophis, Oxyuranus, Walterinnesia, Naja, Dendroaspis and Micrurus); and crude snake venom: Micrurus tener

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives. In addition, novel immunization techniques are being explored to overcome challenges with snake venom production, namely limited quantity, high cost, specificity and challenges with animal captivity, as well as in the search for pan-specific or broad spectrum antivenoms, which would be more convenient and cost effective than current mono- or poly-specific antivenoms.

A novel equine blended anti-Micrurus tener and anti-ScNtx antibody antivenom candidate against elapids was developed using toxin-mediated immunization combined with traditional crude venom immunization as follows: A recombinant consensus short-chain α-neurotoxin (ScNtx) was developed based on sequences from the most lethal elapid venoms from America, Africa, Asia, and Oceania (https://pubmed.ncbi.nlm.nih.gov/29626299/). An antivenom was generated by immunizing horses with ScNtx. and showed that it can successfully neutralize the lethality of pure recombinant and native short-chain α-neurotoxins, as well as whole neurotoxic elapid venoms from diverse genera such as Micrurus, Dendroaspis, Naja, Walterinnesia, Ophiophagus and Hydrophis (see candidate 'Novel anti-short-chain α-neurotoxin antivenom via toxin immunization (against elapids)') (https://pubmed.ncbi.nlm.nih.gov/31409779/). The approach and resulting anti-ScNtx antibodies was then combined with antibodies from traditional crude venom (Micrurus tener) immunization in a blended antivenom. Horses were hyperimmunized with either the venom of M. tener (PLA2-predominant) or a recombinant short-chain consensus α-neurotoxin (ScNtx). Then, the combination of the two monospecific horse antibodies (anti-M. tener and anti-ScNtx) was used to test their efficacy against eleven Micrurus venoms. The blend of anti-M. tener and anti-ScNtx antibodies had a better

capacity to neutralize the lethality of diverse species from North, Central and South American Micrurus venoms. The antibodies combination neutralized both the ScNtx and ten out of eleven Micrurus venom tested, and particularly, it neutralized the venoms of M. distans and M. laticollaris that were neither neutralized by monospecific anti-M. tener nor anti-ScNtx. (https://pubmed.ncbi.nlm.nih.gov/33423840/).

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Instituto de Biotecnología, UNAM

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/29626299/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6692343/ https://pubmed.ncbi.nlm.nih.gov/33423840/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Acanthophis spp; Oxyuranus spp; Walterinnesia spp; Naja spp; Dendroaspis spp; Micrurus spp; Micrurus tener (Texas coral snake)
Snake family	Elapidae
Risk category	Both Category 1 & 2
Countries	
Regions	North America; Australia-Papua (incl Pacific); East Asia; Central America

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Separate immunization with crude venom PLUS immunization with toxin, with resulting antibodies blended

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Micrurus fulvius; M. tener; M. browni; M. distans; M. laticollaris; M. diastema; Micrurus nigrocinctus; M. surinamensis; M. mosquitensis; M. dumerilii; M. mipartitus	Micrurus fulvius; M. tener; M. browni; M. distans; M. laticollaris; M. diastema; Micrurus nigrocinctus; M. surinamensis; M. mosquitensis; M. dumerilii;
Snake family		Elapidae
Risk category		Category 2 (Secondary Medical Importance)

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: 3FTxs

Syndromic profiles: Neurotoxic (paralysis)

Novel equine F(ab')2 antivenom via streamlined processing (against Vipera ammodytes)

Alternative name(s): Novel equine F(ab')2 antivenom (against Vipera ammodytes ammodytes) via streamlined plasma downstream processing

Chemical name: N/A

CAS number: N/A

PCR ID: 1679

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Vipera ammodytes (Nose-horned viper, Sand viper)

Route of administration: Not yet determined

Ig format: F(ab')2 immunoglobulin molecule fragments

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments (including F(ab)2) derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

F(ab')2 fragment antibodies are generated by pepsin digestion of whole IgG antibodies to remove most of the Fc region, leaving some of the hinge region. F(ab')2 fragments have two antigen-binding F(ab) portions linked together by disulfide bonds, so are divalent with a molecular weight of about 110 kDa. Traditional antivenoms are made from IgG antibodies (either whole or as fragments) derived from the plasma of horses immunized with snake venom. Although antivenoms are the only validated treatment against snakebite envenoming, traditional plasma derived antivenom from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock. Other animal models and more sustainable, cost-effective and higher purity production techniques have been investigated as alternatives for antibody production.

A novel equine F(ab')2 antivenom against Vipera ammodytes ammodytes was developed via streamlined plasma downstream processing, to test compact, feasible and economically viable platform for preparation. The antivenom was developed as follows: The principle of simultaneous caprylic acid precipitation and pepsin digestion has been implemented into plasma downstream processing. Balance between incomplete IgG breakdown, F(ab')2 over-digestion and loss of the active drug's protective efficacy was achieved by adjusting pepsin to a 1:30 substrate ratio (w/w) and setting pH at 3.2. Precipitation and digestion co-performance required 2 h-long incubation at 21 °C. Final polishing was accomplished by a combination of diafiltration and flow-through chromatography. In vivo neutralization potency of the F(ab')2 product against the venom's lethal toxicity was determined. Only three consecutive steps, performed under finely tuned conditions, were sufficient for preservation of the highest process recovery with the overall yield of 74%, comparing favorably to others. At the same time, regulatory requirements were met. Final product was aggregate- and pepsin-free. Its composition profile was analyzed by mass spectrometry as a quality control check.

Impurities, present in minor traces, were identified mostly as IgG/IgM fragments, contributing to active drug. Specific activity of the F(ab')2 preparation with respect to the plasma was increased 3.9-fold. (https://pubmed.ncbi.nlm.nih.gov/32760431/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: University of Zagreb

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/32760431/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Vipera ammodytes ammodytes (Nose horned viper)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Croatia
Regions	Eastern Europe

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent immunization of horse, followed by a highly streamlined mode for production of equine F(ab')2 antivenom engineered using the principle of simultaneous caprylic acid precipitation and pepsin digestion implemented into plasma downstream processing

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Vipera ammodytes ammodytes (Nose horned viper)	Vipera ammodytes ammodytes (Nose horned viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Novel equine pan-specific antiserum via diverse-toxin immunization (against elapids)

Alternative name(s): Novel pan-specific neurotoxic antiserum via diverse-toxin-repertoire immunization (against elapids)

Chemical name: N/A

CAS number: N/A

PCR ID: 1685

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Toxin fractions (TFs) of venom and crude snake venom ('diverse toxin repertoire'): Naja kaouthia (Monocellate cobra, Thai cobra); Naja sputatrix (Southern Indonesian spitting cobra); Naja atra (Chinese cobra); Naja philippinensis (Northern Philippine cobra); Bungarus fasciatus (Banded krait); Bungarus candidus (Blue krait, Malayan krait), (4 Naja spp. and 2 Bungarus spp.)

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives. In addition, novel immunization techniques are being explored to overcome challenges with snake venom production, namely limited quantity, high cost, and challenges with animal captivity, as well as in the search for pan-specific, broad spectrum, or pathology-specific antivenoms, which would be more convenient and cost effective than current mono- or poly-specific antivenoms.

A novel equine pan-specific antiserum candidate against medically important elapids of Asia was developed using a novel 'diverse-toxin-repertoire' immunization approach as follows: The strategy was to use toxin fractions (TFs) of the venoms in place of crude venoms in order to reduce the number of antigens the horses were exposed to. Twelve venom samples from six medically important elapid snakes (4 Naja spp. and 2 Bungarus spp.) were collected from 12 regions/countries in Asia. Nine of these 12 venoms were ultra-filtered to remove high molecular weight, non-toxic and highly immunogenic proteins. The remaining 3 venoms were not ultra-filtered due to limited amounts available. The 9 toxin fractions (TFs) together with the 3 crude venoms were emulsified in complete Freund's adjuvant and used to immunize 3 horses using a low dose, low volume, multisite immunization protocol. The horse antisera were assayed by ELISA and by in vivo lethality neutralization in mice.

The findings were: a) The 9 TFs were shown to contain all of the venom toxins but were devoid of high MW proteins. When these TFs, together with the 3 crude venoms, were used as the immunogen, satisfactory ELISA antibody titers against homologous/heterologous venoms were obtained. b) The horse antiserum immunologically reacted with and neutralized the lethal effects of both the homologous and the 16 heterologous Asian/African elapid venoms tested. Thus, the use of TFs in place of crude venoms and the inclusion of a variety of elapid venoms in the immunogen mix resulted in antiserum with wide paraspecificity against elapid venoms from distant geographic areas. (https://pubmed.ncbi.nlm.nih.gov/27058956/).

A follow up study showed that the antiserum can neutralize 9 out of 10 additional neurotoxic venoms. Altogether, 36 snake venoms belonging to 10 genera from 4 continents were neutralized by the antiserum. Toxin profiles previously generated using proteomic techniques of these 36 venoms identified α-neurotoxins, β-neurotoxins, and cytotoxins as predominant toxins presumably neutralized by the antiserum. (https://pubmed.ncbi.nlm.nih.gov/32647261/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Chulabhorn Research Institute; Mahidol University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/32647261/ https://pubmed.ncbi.nlm.nih.gov/27058956/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Naja kaouthia (Monocellate cobra, Thai cobra); Naja sputatrix (Southern Indonesian spitting cobra); Naja atra (Chinese cobra); Naja philippinensis (Northern Philippine cobra); Bungarus fasciatus (Banded krait); Bungarus candidus (Blue krait, Malayan krait)
Snake family	Elapidae
Risk category	Both Category 1 & 2
Countries	Thailand; Malaysia; Vietnam; Philippines; Indonesia; China; Taiwan
Regions	East Asia; South East Asia

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Immunization of horses using 'diverse-toxin-repertoire' for pan-specific antibody/antisera development

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja kaouthia (Monocellate cobra, Thai cobra); Naja sputatrix (Southern Indonesian spitting cobra); Naja atra (Chinese cobra); Naja philippinensis (Northern Philippine cobra); Bungarus fasciatus (Banded krait); Bungarus candidus (Blue krait, Malayan krait); Ophiophagus hannah (Hamadryad, King cobra); Naja sumatrana (Equatorial spitting cobra); Naja siamensis (Indochinese spitting cobra, Siamese spitting cobra); Naja oxiana (Central Asian cobra, Transcaspian cobra); Naja naja (Indian cobra, Spectacled cobra); Naja haje (Egyptian cobra); Naja nigricollis (Black-necked spitting cobra); Bungarus caeruleus (Indian krait); Bungarus sindanus (Sind krait); Bungarus fasciatus (Banded krait); Naja melanoleuca (Black & white cobra, Forest cobra); Naja nubiae (Nubian spitting cobra); Laticauda colubrine; Hydrophis schistosus (Common Seasnake); Notechis scutatus (Tiger snake); Oxyuranus scutellatus (Coastal Taipan, Papuan taipan); Pseudechis australis (King brown snake, Mulga snake); Naja senegalensis (Senegalese cobra); Dendroaspis viridis (Western green mamba); Dendroaspis polylepis (Black mamba); Dendroaspis angusticeps (Eastern green mamba); Micrurus nigrocinctus (Babaspul, Central American coralsnake, Coral, Coral centroamericana, Coral macho, Corallilo, Gargantilla, Limlim, Silviara)	Naja kaouthia (Monocellate cobra, Thai cobra); Naja sputatrix (Southern Indonesian spitting cobra); Naja atra (Chinese cobra); Naja philippinensis (Northern Philippine cobra); Bungarus fasciatus (Banded krait); Bungarus candidus (Blue krait, Malayan krait); Ophiophagus hannah (Hamadryad, King cobra); Naja sumatrana (Equatorial spitting cobra); Naja siamensis (Indochinese spitting cobra, Siamese spitting cobra); Naja oxiana (Central Asian cobra, Transcaspian cobra); Naja naja (Indian cobra, Spectacled cobra); Naja haje (Egyptian cobra); Naja nigricollis (Black-necked spitting cobra); Bungarus caeruleus (Indian krait); Bungarus sindanus (Sind krait); Bungarus fasciatus (Banded krait); Naja melanoleuca (Black & white cobra, Forest cobra); Naja nubiae (Nubian spitting cobra); Laticauda colubrine; Hydrophis schistosus (Common Seasnake); Notechis scutatus (Tiger snake); Oxyuranus scutellatus (Coastal Taipan, Papuan taipan); Pseudechis australis (King brown snake, Mulga snake); Naja senegalensis (Senegalese cobra); Dendroaspis viridis (Western green mamba); Dendroaspis polylepis (Black mamba); Micrurus nigrocinctus (Babaspul, Central American coralsnake, Coral, Coral centroamericana, Coral macho, Corallilo, Gargantilla, Limlim, Silviara)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: PLA2s,3FTxs

Syndromic profiles: Neurotoxic (paralysis)

Novel equine/rabbit broad-spectrum antiserum via r3FTX toxin immunization (against cobra spp)

Alternative name(s): Broad-Spectrum Antiserum against Cobra Venoms Using Recombinant Three-Finger Toxins

Chemical name: N/A

CAS number: N/A

PCR ID: 1829

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: α-neurotoxins, short-chain α-neurotoxins (α-cobratoxins) and cardiotoxin A3: Naja species

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives. In addition, novel immunization techniques are being explored to overcome challenges with snake venom production (namely limited quantity, high cost, specificity and challenges with animal captivity, as well as in the search for pan-specific or broad spectrum antivenoms, which would be more convenient and cost effective than current mono- or poly-specific antivenoms.

Novel equine/rabbit broad-spectrum antiserum candidate against Cobra species was developed using recombinant 3FTX toxin immunization strategy as follows: recombinant type long-chain α-neurotoxins (P01391), short-chain α-neurotoxins (P60770), and cardiotoxin A3 (P60301) were used to generate a new immunogen formulation. The study investigated potency of the resulting antiserum against the venom lethality of three medially important cobras in Asia, including the Thai monocled cobra (Naja kaouthia), the Taiwan cobra (Naja atra), and the Thai spitting cobra (Naja Siamensis) snake species. With the fusion of protein disulfide isomerase and the low-temperature settings, the correct disulfide bonds were built on these recombinant 3FTXs (r3FTXs), which were confirmed by the circular dichroism spectra and tandem mass spectrometry. Immunization with r3FTX was able to induce the specific antibody response to the native 3FTXs in cobra venoms. Furthermore, the horse and rabbit antiserum raised by the r3FTX mixture is able to neutralize the venom lethality of the selected three medically important cobras. Thus, the study demonstrated that the r3FTXs are potential immunogens in the development of novel antivenom with broad neutralization activity for the therapeutic treatment of victims involving cobra snakes in countries. (https://pubmed.ncbi.nlm.nih.gov/34437427/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: National Health Research Institute, Taiwan

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/34437427/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Naja kaouthia (Thai monocled cobra); Naja atra (the Taiwan cobra)
Snake family	Elapidae
Risk category	Both Category 1 & 2
Countries	Taiwan; Thailand
Regions	East Asia; South East Asia

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Immunization of horse and rabbits with recombinant Three-Finger Toxins.

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja kaouthia (Thai monocled cobra); Naja atra (the Taiwan cobra); Naja Siamensis (Thai spitting cobra)	Naja kaouthia (Thai monocled cobra); Naja atra (the Taiwan cobra); Naja Siamensis (Thai spitting cobra)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: 3FTxs

Syndromic profiles: Neurotoxic (paralysis)

Novel F(ab')2 antivenom (against Daboia russelii siamensis) (China)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1812

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Daboia russelii siamensis (Siamese Russell's viper)

Route of administration: Intravenous

Ig format: F(ab')2 immunoglobulin molecule fragments

Ig final product type/preparation: Liquid final product

Thermostability: Stable at room temperature and 2–8◦C for up to 10 days. In long-term stability experiments, stable at 20 deg c for 88 days, and at 80 deg C for 89 days

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Traditional antivenoms are made from IgG antibodies (either whole or as fragments) derived from the plasma of horses immunized with snake venom. F(ab')2 fragment antibodies are generated by pepsin digestion of whole IgG antibodies to remove most of the Fc region, leaving some of the hinge region. F(ab')2 fragments have two antigen-binding F(ab) portions linked together by disulfide bonds, so are divalent with a molecular weight of about 110 kDa.

Although antivenoms against Bungarus multicinctus, Agkistrodon and Cobra have been applied in clinical practices, the antivenom against Daboia russelii siamensis is not available in China. To satisfy the urgent clinical need, the antivenom against Daboia russelii siamensis has been manufactured by immunization of the horse with venom. To minimize immunogenicity and clinical adverse reactions, purified immunoglobulin G (IgG) of the antivenom of Daboia russelii siamensis is digested by pepsin to yield the V-shaped F(ab')2. Since the understanding of in-vivo dynamics of the F(ab')2 antivenom of Daboia russelii siamensis is incomplete, a phase I clinical study evaluating its safety, tolerability and pharmacokinetics is conducted in Shanghai Xuhui Central Hospital (Registration No. CTR20202621). (https://www.wuxuwang.com/linchuang/f645cbbc-4a8f-11eb-830e-b8599fb47a0c)

The study aims to develop and optimize a sensitive, specific, and quantitative LBA method for the determination of F(ab')2 antivenom of Daboia russelii siamensis in human serum. The full validation is performed according to the regulatory guidelines. The validated method is successfully applied to the phase I clinical study in Chinese healthy volunteers. (https://pubmed.ncbi.nlm.nih.gov/35149421/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Phase I

Highest R&D stage (any condition): Phase I (SBE)

Development status: Active

Developers/investigators: Shanghai Serum Biotechnology Co Ltd

Evidence of clinical trials? Yes

Phase I(Status: , December 2020-): *A single-center, randomized, double-blind, placebo-controlled, dose-escalating phase I clinical study to evaluate the safety, tolerability and pharmacokinetics of a single dose of anti-viper venom in healthy Chinese subjects feature* (CT number: CTR20202621, CT source: http://www.chinadrugtrials.org.cn/clinicaltrials.searchlistdetail.dhtml)

Production/source

	Derived from
Snake species	Daboia russelii siamensis (Siamese Russell's viper)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	China
Regions	East Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent immunization of horses

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russelii siamensis (Siamese Russell's viper)	Daboia russelii siamensis (Siamese Russell's viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Novel freeze-dried trivalent antivenom (FDTAV) (against Bothrops, Lachesis, Crotalus)

Alternative name(s): FDAV

Chemical name: N/A

CAS number: N/A

PCR ID: 1456

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Bothrops, Lachesis and Crotalus spp

Route of administration: Intravenous

Ig format: F(ab')2 immunoglobulin molecule fragments

Ig final product type/preparation: Lyophilized (freeze-dried)

Thermostability: Room temperature stable; thermostable over one year at 56°C

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Traditional antivenoms are derived from the plasma/serum of mammals – usually horses – hyperimmunized with selected snake venom(s). The plasma, which contains snake venom-specific immunoglobulins, is then isolated and purified, with immunoglobulins either left intact as whole Ig (IgG) format, or cleaved into F(ab')2 or F(ab) antibody fragments. F(ab')2 fragment antibodies are generated by pepsin digestion of whole IgG antibodies to remove most of the Fc region, leaving some of the hinge region. F(ab')2 fragments have two antigen-binding F(ab) portions linked together by disulfide bonds, so are divalent with a molecular weight of about 110 kDa. In Brazil, antivenoms for snakebite against Bothrops, Lachesis and Crotalus snakebites exist, but are currently formulated in liquid form and require storage at 4 °C. A major concern regarding snakebites treatment effectiveness relates to the failure in liquid antivenom (AV) distribution due to the lack of an adequate cold chain in remote areas. To minimize this problem, freeze-drying has been suggested to improve AV stability. (https://pubmed.ncbi.nlm.nih.gov/29176824/)

A novel, freeze-dried trivalent antivenom (FDTAV) against Bothrops, Lachesis and Crotalus has been defveloped by Butantan in Brazil. The antivenom would enable cold-chain free storage. Clinical studies have shown neutralising efficacy comparing the safety and efficacy of a freeze-dried trivalent antivenom (FDTAV) and the standard liquid AV provided by the Brazilian Ministry of Health (SLAV) to treat Bothrops, Lachesis and Crotalus snakebites. A prospective, randomized, open, phase IIb trial, carried out from June 2005 to May 2008 in the Brazilian Amazon was undertaken (but retrospectively registered in 2017). Primary efficacy endpoints were the suppression of clinical manifestations and return of hemostasis and renal function markers to normal ranges within the first 24 hours of follow-up. Primary safety endpoint was the presence of early adverse reactions (EAR) in the first 24 hours after treatment. FDTAV thermal stability was determined by estimating AV potency over one year at 56°C. Of the patients recruited, 65 and 51 were assigned to FDTAV and SLAV groups, respectively. Only mild EARs were reported, and they were not different between groups. There were no differences in fibrinogen (p = 0.911) and clotting time (p = 0.982) recovery between FDTAV and SLAV

treated groups for Bothrops snakebites. For Lachesis and Crotalus snakebites, coagulation parameters and creatine phosphokinase presented normal values 24 hours after AV therapy for both antivenoms. These promising results pregarding efficacy, safety and thermal stability indicate that FDTAV is suitable for a larger phase III trial. (https://pubmed.ncbi.nlm.nih.gov/29176824/; https://www.isrctn.com/ISRCTN12845255)

FDTAV has also been determined to have efficacy in neutralizing the biological activities of Bothrops atrox venoms from Manaus (Brazil) and Leticia (Colombia), exhibiting an efficacy similar to those of currently available liquid Bothrops antivenoms. These results indicate that freeze-dried trivalent antivenom may be beneficial for applications in the Brazilian and Colombian Amazon regions. (https://pubmed.ncbi.nlm.nih.gov/34214579/)

Each vial of FDTAV contains heterologous horse F(ab')2, neutralizing at least 100 mg, 60 mg and 30 mg of the reference venoms of Bothrops jararaca, Lachesis muta and Crotalus durissus terrificus, respectively, in mice, sucrose (1 g), NaCl (0.17 g) and phenol (35 mg maximum). Each vial is accompanied by an ampoule containing 20 mL of sterile saline solution (0.9%)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Phase II

Highest R&D stage (any condition): Phase II (SBE)

Development status: Active

Developers/investigators: Butantan Institute, Fundacao Butantan

Evidence of clinical trials? Yes

Phase IIb(Status: , July 2017-): *Freeze-dried trivalent antivenom for snakebites in the Brazilian Amazon: A study about safety and ef* (CT number: ISRCTN12845255, CT source: http://isrctn.com/ISRCTN12845255)

Production/source

	Derived from
Snake species	Bothrops jararaca; B. alternatus; B. jararacuçu; B. moojeni; B. neuweidi; Lachesis muta; Crotalus durissus terrificus; C. d. collilineatus
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Brazil
Regions	South America

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent equine immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops (including B. atrox) spp; Lacheis spp; Crotalus spp	Bothrops (including B. atrox) spp; Lacheis spp; Crotalus spp
Snake family		Viperidae
Risk category		N/A

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Novel ICP-AVRI-UOP Sri Lankan polyspecific antivenom

Alternative name(s): ICP-AVRI-UOP Sri Lankan polyspecific antivenom

Chemical name: N/A

CAS number: N/A

PCR ID: 1440

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Daboia russelii, Echis carinatus, Hypnale hypnale, Naja naja

Route of administration: Intravenous

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Lyophilized (freeze-dried)

Thermostability: Room temperature stable

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

While Indian polyvalent antivenoms (PAV) - raised against the 'big four' venomous snakes of India (D. russelii, N. naja, E. carinatus, and B. caeruleus) - are used across the South Asian continent for treating snakebite, due to geographical variation in venom composition the Indian PAV shows poor efficacy in neutralizing the lethality and toxicity of venom from the same species of snakes in other countries, including Sri Lanka. Supply is also an issue. There is therefore a need for country-specific traditional antivenom production (in lieu of other more progressive, universal toxin-specific approaches that are as yet out of reach).

ICP-AVRI-UOP Sri Lankan polyspecific antivenom is a new whole IgG, freeze-dried, polyspecific antivenom prepared from the plasma of horses immunized with the venoms of the snakes Daboia russelii, Echis carinatus, Hypnale hypnale, and Naja naja from Sri Lanka. It is a collaboration between ICP (Costa Rica), University of Peradeniya (Sri Lanka) and Animal Venom Research International (USA). The preclinical neutralizing ability of this antivenom against several toxic and enzymatic activities of these four venoms was analysed, and compared with that of a batch of VINS antivenom (India) being currently used in Sri Lanka. The activities tested were: lethality, haemorrhagic, in vitro coagulant, proteinase and phospholipase A2. Both antivenoms neutralized, to a different extent, these activities of the venom of D. russelii, E. carinatus, and N. naja. In general, the polyspecific Sri Lankan antivenom was more effective than the Indian antivenom in the neutralization of the venoms of D. russelii and E. carinatus, whereas the Indian antivenom showed a higher efficacy against the venom of N. naja. Regarding H. hypnale, the new Sri Lankan antivenom was effective in the neutralization of all activities tested, whereas the Indian antivenom neutralized lethality but not haemorrhagic, coagulant, proteinase and PLA2 activities, in agreement with the fact that this venom is not included in the immunization mixture for this antivenom. Results suggest that the new polyspecific Sri Lankan antivenom has a satisfactory preclinical neutralizing profile and compares favourably with the Indian antivenom. (https://pubmed.ncbi.nlm.nih.gov/27720977/)

The product is now being tested in a clinical trials to evaluate its efficacy and safety in human victims of snakebite envenomings by D. russelii, E. carinatus and H. hypnale in Sri Lanka. (https://slctr.lk/trials/slctr-2016-012; https://slctr.lk/trials/slctr-2016-015)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Phase II

Highest R&D stage (any condition): Phase II (SBE)

Development status: Active

Developers/investigators: University of Costa Rica (including the Clodomiro Picado Institute); University of Peradeniya; Animal Venom Research International (AVRI)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/27720977/

Evidence of clinical trials? Yes

Phase II(Status: , June 2016-): *A dose finding study in Hump-nosed pit viper bites with new antivenom* (CT number: SLCTR/2016/015, CT source: https://slctr.lk/trials/slctr-2016-015)

Phase II/Phase III(Status: , June 2016-): *A study of the safety of a Sri Lankan antivenom compared to Indian antivenom in patients with snakeb* (CT number: SLCTR/2016/012, CT source: https://slctr.lk/trials/slctr-2016-012)

Production/source

	Derived from
Snake species	Daboia russelii (Russel's viper); Echis carinatus (Saw-scaled viper); Hypnale hypnale (Hump-nosed pitviper); Naja naja (Spectacled cobra)
Snake family	Viperidae,Elapidae
Risk category	Both Category 1 & 2
Countries	Sri Lanka
Regions	South Asia

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent equine immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russelii (Russel's viper); Echis carinatus (Saw-scaled viper); Hypnale hypnale (Hump-nosed pitviper); Naja naja (Spectacled cobra)	Daboia russelii (Russel's viper); Echis carinatus (Saw-scaled viper); Hypnale hypnale (Hump-nosed pitviper); Naja naja (Spectacled cobra)
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Haemorrhagic (bleeding),Procoagulant (blood clotting)

Novel murine anti-haemorrhagic antivenom via DNA immunization (against Echis ocellatus)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1870

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Disintegrin/SVMP: Echis ocellatus (West African carpet viper)

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives. In addition, novel immunization techniques are being explored to overcome challenges with snake venom production, namely limited quantity, high cost, specificity and challenges with animal captivity, as well as in the search for pan-specific or broad spectrum antivenoms, which would be more convenient and cost effective than current mono- or poly-specific antivenoms.

A novel murine anti-haemorrhagic antivenom against Echis ocellatus was developed using a novel DNA immunization approach as follows: The objective was to explore whether a DNA immunization approach targeting the major haemorrhage molecule of a prothrombin activator-like metalloproteinase from E. ocellatus venom could be conceived to inspire antibodies with more prominent specificity and equal adequacy to current conventional antivenoms systems. The notably T helper 2-type polarized immune response accomplished by GeneGun DNA delivery technique over intramuscular injection of DNA was exploited to advance antibody initiation against a toxin present in the venom of E. ocellatus. The study utilized DNA encoding the carboxyldisintegrin and cysteine-rich (DC) domains (EoDC-2) of EoMP-6 (GenBank accession number: AY261531), a prothrombin activator-like metalloproteinase in the venom of E. ocellatus for the DNA immunization. Results suggest that the generated anti-EoDC-2 showed a remarkable efficacy by (a) interfering with the interaction of the recombinant disintigrin “EoDC-2” isolated from the E. ocellatus as well as other viper species to the α2β1-integrins on platelets; (b) complete inhibition of the catalytic site of the metalloproteinase molecules in vitro. Furthermore, it has a polyspecific potential and constitutively expressed significant inhibition by cross-reaction and neutralised venom-induced local haemorrhage exerted by different viper species in vivo. (https://www.sciencedirect.com/science/article/pii/S2221169116311662#)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Sultan Qaboos University

Key funders: Wellcome

Preclinical sources: https://doi.org/10.1016/j.apjtb.2016.12.015
https://www.sciencedirect.com/science/article/pii/S2221169116311662#!

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Echis ocellatus (West African carpet viper)
Snake family	Viperidae
Risk category	Category 1 (Highest Medical Importance)
Countries	
Regions	West Africa

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Immunization via DNA (GeneGun delivery tecnique)

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Echis ocellatus (West African carpet viper); Crotalus atrox (Western diamondback rattlesnake); Bitis arietans (Puff adder)	Echis ocellatus (West African carpet viper); Crotalus atrox (Western diamondback rattlesnake); Bitis arietans (Puff adder)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: SVMPs,Disintegrins

Syndromic profiles: Haemorrhagic (bleeding)

Novel murine antiserum via DNA+ protein boost immunization (against Micrurus corallinus)

Alternative name(s): Antiserum against Micrurus corallinus (Coral Snake) Venom via heterologous Multiepitope DNA Prime/Recombinant Protein Boost Immunisation Strategy

Chemical name: N/A

CAS number: N/A

PCR ID: 1690

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: 3FTXs and PLA2: Micrurus corallinus venom

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives. In addition, novel immunization techniques are being explored to overcome challenges with snake venom production, namely limited quantity, high cost, specificity and challenges with animal captivity, as well as in the search for pan-specific or broad spectrum antivenoms, which would be more convenient and cost effective than current mono- or poly-specific antivenoms.

A novel murine antiserum against Micrurus corallinus was developed using DNA plus protein boost immunization strategy as follows: First mapping, by the SPOT-synthesis technique, was conducted of potential B-cell epitopes from five putative toxins from M. corallinus - four 3FTXs and one PLA2 - which were used to design two multiepitope DNA strings for the genetic immunisation of female BALB/c mice. Results demonstrate that sera obtained from animals that were genetically immunised with these multiepitope constructs, followed by booster doses of recombinant proteins lead to a 60% survival in a lethal dose neutralisation assay. As such, genetic immunisation with a synthetic multiepitope gene followed by booster doses with recombinant protein is a promising approach to develop an alternative antielapidic serum against M. corallinus venom without the need of collection and the very challenging maintenance of these snakes in captivity. (https://pubmed.ncbi.nlm.nih.gov/26938217/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Butantan Institute, Fundacao Butantan

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/26938217/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Micrurus corallinus (Coral Snake)
Snake family	Elapidae
Risk category	Category 2 (Secondary Medical Importance)
Countries	Brazil
Regions	South America

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Genetic immunisation with a synthetic multiepitope gene (DNA prime) followed by recombinant protein boost.

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Micrurus corallinus (Coral Snake)	Micrurus corallinus (Coral Snake)
Snake family		Elapidae
Risk category		Category 2 (Secondary Medical Importance)

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s,3FTxs

Syndromic profiles: Not specified

Novel murine antivenom via toxin/peptide immunization (against Deinagkistrodon acutus)

Alternative name(s): Novel antivenom against the Deinagkistrodon (D.) acutus snake venom using B-cell linear epitopes of three primary toxins (serine protease, metalloprotease, and phospholipase A2)

Chemical name: N/A

CAS number: N/A

PCR ID: 1868

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Serine protease, metalloprotease, and phospholipase A2: Deinagkistrodon acutus (Chinese copperhead, sharp-nosed pitviper) venom

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives. In addition, novel immunization techniques are being explored to overcome challenges with snake venom production (namely limited quantity, high cost, specificity and challenges with animal captivity, as well as in the search for pan-specific or broad spectrum antivenoms, which would be more convenient and cost effective than current mono- or poly-specific antivenoms.

Novel murine antivenom candidate against Deinagkistrodon acutus was developed using recombinant toxin/peptide immunization as follows: cDNA sequences of three toxins of D. acutus venom were retrieved from the NCBI database. B-cell linear epitopes were predicted using DNAStar and the website server software provided by IEDB. Then, the sequences of the predicted epitopes were artificially synthesized and inserted into the vector pET-32a-c(+). Recombinant antigen peptide was expressed and purified. BALB/c mice were immunized with the recombinant antigen peptide. The immunoprotective effect of this novel antivenom was measured by neutralization of venom haemorrhagic activity. Six epitopes were obtained by bioinformatics analysis. ELISA analysis showed that antibody titre was >8,000 against snake venom and >64,000 against the recombinant peptide. Neutralization assays confirmed that the developed antivenom could effectively reduce the haemorrhagic activity of snake venom. (https://pubmed.ncbi.nlm.nih.gov/26957285/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Third Military Medical University, Chongqing

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/26957285/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Deinagkistrodon acutus (Chinese copperhead, sharp-nosed pitviper)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	China
Regions	East Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Immunization with recombinant antigen peptides (B-cell linear epitopes of three primary toxins serine protease, metalloprotease, and phospholipase A2)

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Deinagkistrodon acutus (Chinese copperhead, sharp-nosed pitviper)	Deinagkistrodon acutus (Chinese copperhead, sharp-nosed pitviper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs,PLA2s,SVSPs

Syndromic profiles: Haemorrhagic (bleeding)

Novel ovine pathology-specific experimental antivenom (EAV) 1 (against VICC/haemotoxic)

Alternative name(s): Pathology-specific experimental antivenoms for haemotoxic snakebite; EAV 1; Novel ovine haemotoxic experimental antivenom (EAV) 1 (against venom-induced consumption coagulapathy)

Chemical name: N/A

CAS number: N/A

PCR ID: 1785

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: 7 haemotoxic snake species (Viperae; Crotalinae and Colubrinae families)

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives. In addition, novel immunization techniques are being explored to overcome challenges with snake venom production, namely limited quantity, high cost, and challenges with animal captivity, as well as in the search for pan-specific, broad spectrum or pathology-specific antivenoms, which would be more convenient and cost effective than current mono- or poly-specific antivenoms.

Novel ovine pathology-specific experimental antivenom (EAV) 1 against venom-induced consumption coagulopathy (VICC) from haemotoxic snakebite is one of two experimental pathology-specific antivenoms being explored through a project under the Liverpool School of Tropical Medicine, funded by Wellcome. The antivenoms were developed as follows: Two different immunogen mixtures, consisting of seven and twelve haemotoxic venoms sourced from geographically diverse and/or medically important snakes, were used to raise ovine polyclonal antibodies, prior to characterisation of their immunological binding characteristics and in vitro neutralisation profiles against each of the venoms. Despite variability of the immunogen mixtures, both experimental antivenoms - EAV 1 and EAV 2 (see candidate 'Novel ovine pathology-specific experimental antivenom (EAV) 2 (against VICC/haemotoxic)') - exhibited broadly comparable in vitro venom binding and neutralisation profiles against the individual venom immunogens in immunological and functional assays. However, in vivo assessments using a murine preclinical model of antivenom efficacy revealed substantial differences in venom neutralisation. The experimental antivenom generated from the seven venom immunogen

mixture outperformed the comparator, by providing protective effects against venom lethality caused by seven of the eight geographically diverse venoms tested, including three distinct venoms that were not used as immunogens to generate this antivenom. These findings suggest that a core set of venom immunogens may be sufficient to stimulate antibodies capable of broadly neutralising a geographically diverse array of haemotoxic snake venoms, and that adding additional venom immunogens may impact negatively on the dose efficacy of the resulting antivenom. (https://pubmed.ncbi.nlm.nih.gov/34407084/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Liverpool School of Tropical Medicine (LSTM)

Key funders: Wellcome

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/34407084/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Bothrops asper (Barba amarilla, Cascabelle, Fer-de-lance); Bothrops jararaca (Caiçaca, Jararaca, Yarara, Yararaca); Echis ocellatus (West African carpet viper, Ocellated carpet viper); Calloselasma rhodostoma (Malayan pit viper); Dispholidus typus (Boomslang); Deinagkistrodon acutus (Deinagkistrodon); Daboia russelii (Russell's viper)
Snake family	Viperidae,Colubridae
Risk category	Both Category 1 & 2
Countries	Costa Rica; Brazil; Nigeria; South Africa; Sri Lanka
Regions	Central America; South America; West Africa; Southern Africa; South Asia; South East Asia; East Asia

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Multi-venom immunogen mixtures for immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops asper (Barba amarilla, Cascabelle, Fer-de-lance); Calloselasma rhodostoma (Malayan pit viper); Echis ocellatus (West African carpet viper, Ocellated carpet viper); Daboia russelii (Russell's viper); Bitis arietans (Puff adder); Echis carinatus (Saw scaled viper); Vipera ammodytes (Horned viper, Long-nosed viper, Nose-horned viper, Sand viper); Lachesis muta (Southern American bushmaster, Atlantic bushmaster)	Bothrops asper (Barba amarilla, Cascabelle, Fer-de-lance); Echis ocellatus (West African carpet viper, Ocellated carpet viper); Daboia russelii (Russell's viper); Bitis arietans (Puff adder); Vipera ammodytes (Horned viper, Long-nosed viper, Nose-horned viper, Sand viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: SVMPs,SVSPs

Syndromic profiles: Procoagulant (blood clotting)

Novel ovine pathology-specific experimental antivenom (EAV) 2 (against VICC/haemotoxic)

Alternative name(s): Pathology-specific experimental antivenoms for haemotoxic snakebite; EAV 2; Novel ovine haemotoxic experimental antivenom (EAV) 2 (against venom-induced consumption coagulapathy)

Chemical name: N/A

CAS number: N/A

PCR ID: 1786

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: 12 haemotoxic snake species (Viperae; Crotalinae and Colubrinae families)

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives. In addition, novel immunization techniques are being explored to overcome challenges with snake venom production, namely limited quantity, high cost, and challenges with animal captivity, as well as in the search for pan-specific, broad spectrum or pathology-specific antivenoms, which would be more convenient and cost effective than current mono- or poly-specific antivenoms.

Novel ovine pathology-specific experimental antivenom (EAV) 1 against venom-induced consumption coagulopathy (VICC) from haemotoxic snakebite is one of two experimental pathology-specific antivenoms being explored through a project under the Liverpool School of Tropical Medicine, funded by Wellcome. The antivenoms were developed as follows: Two different immunogen mixtures, consisting of seven and twelve haemotoxic venoms sourced from geographically diverse and/or medically important snakes, were used to raise ovine polyclonal antibodies, prior to characterisation of their immunological binding characteristics and in vitro neutralisation profiles against each of the venoms. Despite variability of the immunogen mixtures, both experimental antivenoms - EAV 1 (see candidate 'Novel ovine pathology-specific experimental antivenom (EAV) 1 (against VICC/haemotoxic)') and EAV 2 - exhibited broadly comparable in vitro venom binding and neutralisation profiles against the individual venom immunogens in immunological and functional assays. However, in vivo assessments using a murine preclinical model of antivenom efficacy revealed substantial differences in venom neutralisation. The experimental antivenom generated from

the seven venom immunogen mixture outperformed the comparator, by providing protective effects against venom lethality caused by seven of the eight geographically diverse venoms tested, including three distinct venoms that were not used as immunogens to generate this antivenom. These findings suggest that a core set of venom immunogens may be sufficient to stimulate antibodies capable of broadly neutralising a geographically diverse array of haemotoxic snake venoms, and that adding additional venom immunogens may impact negatively on the dose efficacy of the resulting antivenom. (https://pubmed.ncbi.nlm.nih.gov/34407084/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Liverpool School of Tropical Medicine (LSTM)

Key funders: Wellcome

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/34407084/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Bothrops asper (Barba amarilla); Bothrops jararaca (Caiçaca, Jararaca); Echis ocellatus (West African carpet viper); Calloselasma rhodostoma (Malayan pit viper); Dispholidus typus (Boomslang); Deinagkistrodon acutus (Deinagkistrodon); Daboia russelii (Russell's viper); Bitis arietans (Puff adder); Echis carinatus (Saw scaled viper); Rhabdophis subminiatus (Red-necked keelback snake);Trimeresurus albolabris (White-lipped pit viper); Crotalus atrox (The western diamondback rattlesnake)
Snake family	Viperidae,Colubridae
Risk category	Both Category 1 & 2
Countries	Costa Rica; Brazil; Nigeria; South Africa; Sri Lanka; India; Hong Kong; United States of America
Regions	Central America; South America; West Africa; South East Asia; Southern Africa; East Asia; South Asia; Middle East; North America

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Multi-venom immunogen mixtures for immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops asper (Barba amarilla, Cascabelle, Fer-de-lance); Calloselasma rhodostoma (Malayan pit viper); Echis ocellatus (West African carpet viper, Ocellated carpet viper); Daboia russelii (Russell's viper); Bitis arietans (Puff adder); Echis ocellatus (West African carpet viper, Ocellated carpet viper); Vipera ammodytes (Horned viper, Long-nosed viper, Nose-horned viper, Sand viper); Lachesis muta (Southern American bushmaster, Atlantic bushmaster)	Unclear
Snake family		
Risk category		Unknown

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: SVMPs,SVSPs

Syndromic profiles: Procoagulant (blood clotting)

Novel pan-specific antivenom (against medically significant snakes of India) (Project)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1464

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Unclear

Route of administration: Not yet determined

Ig format: Unknown

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Grant funding to Indriyam Biologics from Indian BIRAC in 2018 for discovery and preclinical stage snakebite biologics R&D indicates the development of novel biological therapeutics. This is supported by the grant title: 'A Pan-specific Antiserum against major medically significant Snakes of India - A simple, effective and novel approach'. https://www.indriyambiologics.com/overview

No other information is available.

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: Indriyam Biologics

Key funders: Biotechnology Industry Research Assistance Council (BIRAC)

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Unknown
Snake family	
Risk category	Unknown
Countries	India
Regions	South Asia

Immunizing venom protocol/strategy:

Production technique and/or immunization strategy: Unknown

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Unknown	Unknown
Snake family		
Risk category		Unknown

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Novel PNG taipan antivenom (against Oxyuranus scutellatus)

Alternative name(s): ICP monovalent Papuan taipan antivenom

Chemical name: N/A

CAS number: N/A

PCR ID: 1866

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Oxyuranus scutellatus

Route of administration: Intravenous

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Liquid final product

Thermostability: 2-8 degrees

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Treatment for taipan envenoming in Papua New Guinea (PNG) is via Seqirus taipan (monovalent) antivenom, which is available in PNG at a cost of ~US$1,270/vial. Given the cost, a new, truly monospecific taipan antivenom has been prepared at Instituto Clodomiro Picado (ICP) at the University of Costa Rica (San José, Costa Rica) against the venom of O. scutellatus from PNG. It is a whole-IgG preparation generated by caprylic acid fractionation of the plasma of horses immunized with this venom. It is estimated to cost less than 25% of the current Seqirus AV at approximately US$300/vial. A comparative pre-clinical assessment of the ability of ICP and bioCSL antivenoms to neutralize the venom of PNG taipan revealed a similar potency for the neutralization of lethality and myotoxicity in mouse tests and phospholipase A2 (PLA2) activity, although the ICP whole-IgG antivenom showed a higher efficacy in the neutralization of in vitro coagulant activity. (https://pubmed.ncbi.nlm.nih.gov/25157124/). The antivenom was tested in Phase I (2014) and II (2016) randomized trials to assess their safety and efficacy in the clinical setting. (https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=361999&isReview=true). Other efficacy and cross-reactivity tests have been conducted, for example against brown snake (Pseudonaja sp) envenoming: (https://pubmed.ncbi.nlm.nih.gov/30910521/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Phase II

Highest R&D stage (any condition): Phase II (SBE)

Development status: Active

Developers/investigators: University of Costa Rica (including the Clodomiro Picado Institute); University of Melbourne (including the Australian Venom Research Unit, AVRU)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/30910521/ https://pubmed.ncbi.nlm.nih.gov/21610854/

Evidence of clinical trials? Yes

Phase I/Phase II(Status: , October 2012-): *A Phase I/Phase II randomized controlled trial (RCT) of a new antivenom, compared to the currently used CSL taipan antivenom, for the treatment of the effects of Papuan taipan bite* (CT number: ACTRN12612001062819, CT source: https://anzctr.org.au/ACTRN12612001062819.aspx)

Production/source

	Derived from
Snake species	Oxyuranus scutellatus (PNG taipan)
Snake family	Elapidae
Risk category	Both Category 1 & 2
Countries	Papua New Guinea
Regions	Australia-Papua (incl Pacific)

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent equine immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Oxyuranus scutellatus (PNG taipan); Pseudonaja spp (brown snakes)	Oxyuranus scutellatus (PNG taipan)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Procoagulant (blood clotting)

Novel polyvalent equine antivenom (against Micrurus spp, Argentina)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 2040

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Micrurus fulvius, M. nigrocinctus and M. surinamensi

Route of administration: Not yet determined

Ig format: Unknown

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). Producing an antivenom to treat coral snake envenomings has been challenging since coral snakes are difficult to catch, produce small amounts of venom, and the antivenoms produced have shown limited cross neutralization. Novel production techniques and approaches are being explored to investigate possible pan-specific coral snake antivenoms.

Novel equine polyvalent antivenom candidate against Micrurus spp were developed as follows: experimental equine polyvalent and monovalent antivenoms against the venoms of Micrurus (M.) fulvius, M. nigrocinctus and M. surinamensis were generated and studied for their immunochemical reactivity on the venoms used as immunogens and on M. pyrrhocryptus, M altirostris and M. balyocoriphus venoms. Assessment of the neutralizing capacity of the polyvalent experimental antivenom was based on inhibition of lethality (preincubation and rescue assay experiments in mice) and indirect haemolytic and phospholipase activities. The immunochemical reactivity and neutralizing capacity were compared with those of two therapeutic antivenoms used for the treatment of coral snake envenomation in North America and in Argentina. In general, the experimental antivenom conferred a comparable level of neutralization against the venoms used as immunogens when compared to the therapeutic antivenoms and a certain level of cross-neutralization against the other venoms. The results suggest the need for additional venoms in the immunogenic mixture used, in order to obtain a broad spectrum anti-Micrurus antivenom with a good neutralizing potency. Paraspecific neutralization of South American coral snake venoms, although present at a higher level than the neutralization conferred by available nonspecific Micrurus therapeutic antivenoms, was rather low in relation to the specific neutralizing capacity. (https://pubmed.ncbi.nlm.nih.gov/34303716/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: University of Buenos Aires (Universidad de Buenos Aires)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/34303716/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Micrurus fulvius (Eastern coral snake); Micrurus nigrocinctus (Central American coral snake); Micrurus surinamensis (Aquatic Coral Snake)
Snake family	Elapidae
Risk category	Category 2 (Secondary Medical Importance)
Countries	Argentina
Regions	South America

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent immunization of horses to obtain monospecific antisera, then combined to form polyvalent antivenom

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Micrurus fulvius (Eastern coral snake); Micrurus nigrocinctus (Central American coral snake); Micrurus surinamensis (Aquatic Coral Snake); Micrurus pyrrhocryptus (Argentinian coral snake); Micrurus altirostris (Uruguayan coral snake); Micrurus balyocoriphus (Mesopotamian coral snake)	Micrurus fulvius (Eastern coral snake); Micrurus nigrocinctus (Central American coral snake); Micrurus surinamensis (Aquatic Coral Snake) To some extent: Micrurus pyrrhocryptus (Argentinian coral snake); Micrurus altirostris (Uruguayan coral snake); Micrurus balyocoriphus (Mesopotamian coral snake)
Snake family		Elapidae
Risk category		Category 2 (Secondary Medical Importance)

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Novel polyvalent equine antivenom (against Micrurus spp, Colombia)

Alternative name(s): Novel coral snake antivenom; Antiveneno Anticoral Polivalente

Chemical name: N/A

CAS number: N/A

PCR ID: 2039

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: M. dumerilii, M. isozonus, M. mipartitus and M. surinamensis

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: 2-8 degrees celsius

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). Producing an antivenom to treat coral snake envenomings has been challenging since coral snakes are difficult to catch, produce small amounts of venom, and the antivenoms produced have shown limited cross neutralization. Novel production techniques and approaches are being explored to investigate possible pan-specific coral snake antivenoms.

Novel polyvalent antivenom candidate against Micrurus species was developed as follows: Here we present data of cross neutralization among monovalent antivenoms raised in horses against M. dumerilii, M. isozonus, M. mipartitus and M. surinamensis and the development of a new polyvalent coral snake antivenom, resulting from the mix of monovalent antivenoms. The results, show that this coral snake antivenom has high neutralizing potency and wide taxonomic coverage, constituting a possible alternative for a long sought Pan-American coral snake antivenom. (https://pubmed.ncbi.nlm.nih.gov/30856180/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Colombian National Institute of Health, Instituto Nacional de Salud (INS)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/30856180/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	M. dumerilii (Capuchin coral snake); M. isozonus (Equal-banded Coral Snake); M. mipartitus (Red-tailed coral snake); M. surinamensis (aquatic coral snake)
Snake family	Elapidae
Risk category	Category 2 (Secondary Medical Importance)
Countries	Colombia
Regions	South America

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent immunization of horses to obtain monospecific antisera, then combined to form polyvalent antivenom

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	M. dumerilii (Capuchin coral snake); M. mipartitus (Red-tailed coral snake); M. isozonus (Equal-banded Coral Snake); M. surinamensis (aquatic coral snake); M. medemi; M. lemniscatus (South American coral snake); M. spixii (Amazonian Coral Snake)	M. dumerilii (Capuchin coral snake); M. mipartitus (Red-tailed coral snake); M. isozonus (Equal-banded Coral Snake); M. surinamensis (aquatic coral snake); M. medemi; M. lemniscatus (South American coral snake); M. spixii (Amazonian Coral Snake)
Snake family		Elapidae
Risk category		Category 2 (Secondary Medical Importance)

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Novel polyvalent murine, equine and rabbit antisera (against Micrurus spp, Brazil)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 2028

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: M. spixii; M. frontalis; M. corallinus; M. altirostris; M. lemniscatus

Route of administration: Not yet determined

Ig format: F(ab')2 immunoglobulin molecule fragments

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized (with snake venom). Producing an antivenom to treat coral snake envenomings has been challenging since coral snakes are difficult to catch, produce small amounts of venom, and the antivenoms produced have shown limited cross neutralization. Novel production techniques and approaches are being explored to investigate possible pan-specific coral snake antivenoms.

Novel murine, equine and rabbit antisera candidates against Micrurus spp were developed as follows: EIn the present study, we investigated the immunogenic potential of the Micrurus venoms in three different animal species (mouse, rabbit and horse), as well as the antigenic cross-reactivity of mono- and polyvalent experimental antisera. These analyses were performed in order to establish a possible new antigenic mixture for the production of a polyvalent antivenom with higher neutralization potential than the one used in Brazil for human therapy. The data showed that Micrurus venoms exhibited the same immunogenicity pattern in the three utilized animal species and that the specific antisera presented a large cross-reactivity when analyzed with ELISA and Western blot assays. Nonetheless, these positive results were not well correlated with the neutralizing potential of the antisera. Thus, the establishment of a new antigenic mixture to produce novel more efficient therapeutic Micrurus antivenom is not a simple task. Further studies, particularly with the Micrurus lemniscatus, Micrurus altirostris and Micrurus surinamensis venoms, are necessary to establish new strategies for the production of antivenoms with broad neutralizing activity for the treatment of accidents involving coral snakes throughout the country. (https://pubmed.ncbi.nlm.nih.gov/27045363/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Butantan Institute, Fundacao Butantan

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/27045363/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	M. spixii; M. frontalis; M. corallinus; M. altirostris; M. lemniscatus
Snake family	Elapidae
Risk category	Category 2 (Secondary Medical Importance)
Countries	Brazil
Regions	South America

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent immunization to obtain monospecific antisera, then combined to form polyvalent antivenom

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	M. spixii; M. frontalis; M. corallinus; M. altirostris; M. lemniscatus	M. spixii, M. frontalis and M. corallinus
Snake family		Elapidae
Risk category		Category 2 (Secondary Medical Importance)

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Novel rabbit antivenom via venom plus toxin immunization (against Micrurus spp)

Alternative name(s): Coral antivenom against Micrurus spp; Novel rabbit antivenom via combined venom plus toxin immunization protocol (against Micrurus spp)

Chemical name: N/A

CAS number: N/A

PCR ID: 1680

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Micrurus frontalis; and 3FTXs and PLA2 from Micrurus corallinus

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals (here rabbits) immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including rabbits. In addition, novel immunization techniques are being explored to overcome challenges with snake venom production (namely limited quantity, high cost, and challenges with animal captivity).

A novel rabbit antivenom candidate via venom plus toxin immunization against Micrurus spp was developed as follows: a combined immunization protocol, using priming doses of M. frontalis venom and booster doses of synthetic B-cell epitopes derived from M. corallinus toxins (four three-finger toxins-3FTX; and one phospholipase A2-PLA2) were used to obtain coral antivenom in a rabbit model. Immunized animals elicited a humoral response against both M. frontalis and M. corallinus venoms, as detected by sera reactivity in ELISA and Western Blot. Relevant cross-reactivity of the obtained sera with other Micrurus species (Micrurus altirostris, Micrurus lemniscatus, Micrurus spixii, Micrurus surinamensis) venoms was also observed. The elicited antibodies were able to neutralize PLA2 activity of both M. frontalis and M. corallinus venoms. In vivo, immunized rabbit sera completely protected mice from a challenge with 1.5 median lethal dose (LD50) of M. corallinus venom and 50% of mice challenged with 1.5 LD50 of M. frontalis venom. These results show that this combined protocol may be a suitable alternative to reduce the amount of venom used in coral antivenom production in Brazil. (https://pubmed.ncbi.nlm.nih.gov/31695693/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: University of Texas Medical Branch, Galveston

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/31695692/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Micrurus frontalis (coralsnake); Micrurus corallinus (Cobra coral)
Snake family	Elapidae
Risk category	Category 2 (Secondary Medical Importance)
Countries	Brazil
Regions	South America

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Combined immunization protocol, using priming doses of Micrurus frontalis venom and booster doses of synthetic B-cell epitopes derived from Micrurus corallinus toxins (four three-finger toxins-3FTX; and one phospholipase A2-PLA2) to obtain coral antivenom in a rabbit model.

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Micrurus frontalis; Micrurus corallinus; Micrurus altirostris; Micrurus lemniscatus; Micrurus spixii; Micrurus surinamensis	Micrurus frontalis; Micrurus corallinus; Micrurus altirostris; Micrurus lemniscatus; Micrurus spixii; Micrurus surinamensis
Snake family		Elapidae
Risk category		Category 2 (Secondary Medical Importance)

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: PLA2s,3FTxs

Syndromic profiles: Not specified

Novel Sri Lankan Polyvalent Antivenom (SL PAV)

Alternative name(s): SL PAV

Chemical name: N/A

CAS number: N/A

PCR ID: 2179

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Daboia russelii, Echis carinatus, Hypnale hypnale, Naja naja, Bungarus caeruleus

Route of administration: Not yet determined

Ig format: F(ab')2 immunoglobulin molecule fragments

Ig final product type/preparation: Lyophilized (freeze-dried)

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized with snake venom. F(ab')2 fragment antibodies are generated by pepsin digestion of whole IgG antibodies to remove most of the Fc region, leaving some of the hinge region. F(ab')2 fragments have two antigen-binding F(ab) portions linked together by disulphide bonds, so are divalent with a molecular weight of about 110 kDa. (https://www.abcam.com/secondary-antibodies/advantages-of-immunoglobulin-fab-and-fab2-fragments).

While Indian polyvalent antivenoms (PAV) - raised against the 'big four' venomous snakes of India (D. russelii, N. naja, E. carinatus, and B. caeruleus) - are used across the South Asian continent for treating snakebite, due to geographical variation in venom composition the Indian PAV shows poor efficacy in neutralizing the lethality and toxicity of venom from the same species of snakes in other countries, including Sri Lanka. Supply is also an issue. There is therefore a need for country-specific traditional antivenom production (in lieu of other more progressive, universal toxin-specific approaches that are as yet out of reach).

A novel Sri Lankan polyvalent antivenom - SL PAV - has been developed against Daboia russelii, Echis carinatus, Hypnale hypnale, Naja naja and Bungarus caeruleus. This is similar to the ICP-AVRI-UOP SL antivenom (SL snake venom-specific PAV by Instituto Clodomiro Picado (ICP), Costa-Rica (see candidate 'Novel ICP-AVRI-UOP Sri Lankan polyvalent antivenom') but with the addition of B. caeruleus venom. The quality and in vivo venom neutralization potency of the country-specific PAV produced against the venom of the five most medically important snakes of SL (Daboia russelii, Echis carinatus, Hypnale hypnale, Naja naja, Bungarus caeruleus) was assessed. LC-MS/MS analysis of two batches of PAV showed the presence of 88.7–97.2% IgG and traces of other plasma proteins. The tested PAVs contained minor amounts of undigested IgG and F(ab')2 aggregates, showed complement activation, were devoid of IgE, endotoxin, and content of preservative was below the threshold level. Immunological cross-reactivity and in vitro neutralization of enzymatic activities,

pharmacological properties demonstrated superior efficacy of SL PAV compared to Indian PAV against SL snake venoms. The in vivo neutralization study showed that the tested PAVs are potent to neutralize the lethality and venom-induced toxicity of SL snake venoms. The suggests that introduction of SL-specific PAV will improve snakebite management in SL. (https://pubmed.ncbi.nlm.nih.gov/34521877/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Tezpur University; Premium Serums and Vaccines; University of Peradeniya

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/34521877/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Daboia russelii (Russel's viper); Echis carinatus (Saw-scaled viper); Hypnale hypnale (Hump-nosed pitviper); Naja naja (Spectacled cobra); Bungarus caeruleus (Common krait)
Snake family	Viperidae,Elapidae
Risk category	Both Category 1 & 2
Countries	Sri Lanka
Regions	South Asia

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent equine immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russelii (Russel's viper); Echis carinatus (Saw-scaled viper); Hypnale hypnale (Hump-nosed pitviper); Naja naja (Spectacled cobra); Bungarus caeruleus (Common krait)	Daboia russelii (Russel's viper); Echis carinatus (Saw-scaled viper); Hypnale hypnale (Hump-nosed pitviper); Naja naja (Spectacled cobra); Bungarus caeruleus (Common krait)
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: SVMPs,LAAO,Hyaluronidase

Syndromic profiles: Not specified

Rabbit anti-rDisintegrin polyclonal antibodies (ARDPAs) via recombinant toxin immunization (against Crotulus spp)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1920

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Disintegrins/SVMPs: Crotalus scutulatus venom toxins

Route of administration: Not yet determined

Ig format: Intact Ig immunoglobulin molecule (whole)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Whole IgG antibodies are immunoglobulins derived from mammals (here rabbits) immunized (with snake venom). Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other animal models have been investigated as alternatives for antibody production which are less expensive, easier to handle, and more productive, including rabbits.

Rabbit anti-rDisintegrin polyclonal antibodies (ARDPAs) candidate against Crotulus species (rattlesnakes) was developed as follows: r-Mojastin 1 was purified from baterial cells, cloned from the venom gland of a type B Mohave rattlesnake (Crotalus scutulatus scutulatus). An anti-recombinant disintegrin polyclonal antibody (ARDPA) was developed by immunizing rabbits with r-Mojastin 1, and extracting antibodies from animal plasma. The anti-recombinant disintegrin polyclonal antibody (ARDPA) was tested for the detection of disintegrins and ADAMs (a disintegrin and metalloproteases) in individual crude snake venoms of Mohave rattlesnakes (Crotalus scutulatus scutulatus) of varying geographical locations (and determined that the antibody allows for a quick and cost-efficient identification of venom types). (https://pubmed.ncbi.nlm.nih.gov/27989783/). This was followed by an examination of the efficacy and cross-reactivity of the novel polyclonal antibody targeting the disintegrin domain in SVMPs to neutralize isolated disintegrins, P-II/P-III SVMPs, and crude venoms. The results showed disintegrin activity on platelet aggregation in whole blood and the migration of the SK-Mel-28 cells that can be neutralized with anti-disintegrin polyclonal antibody. An SNMP was characterized and found that anti-disintegrin was also able to inhibit its activity in an in vitro proteolytic assay. The study also found that anti-disintegrin could neutralize the proteolytic and hemorrhagic activities from crude Crotalus atrox venom. Results suggest that anti-disintegrin polyclonal antibodies have the potential for a targeted approach to neutralize SVMPs in the treatment of snakebite envenomations. (https://pubmed.ncbi.nlm.nih.gov/33807363/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Texas A&M University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/27989783/ https://pubmed.ncbi.nlm.nih.gov/33807363/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Crotalus scutulatus scutulatus (Mohave rattlesnake)
Snake family	Viperidae
Risk category	Category 1 (Highest Medical Importance)
Countries	United States of America
Regions	North America

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Immunization with recombinant toxin, plasma-derived antibodies

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotalus scutulatus scutulatus (Mohave rattlesnake); Crotalus atrox (Western diamondback rattlesnake); Crotalus helleri (Southern pacific rattlesnake)	Crotalus scutulatus scutulatus (Mohave rattlesnake); Crotalus atrox (Western diamondback rattlesnake); Crotalus helleri (Southern pacific rattlesnake)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: SVMPs,Disintegrins

Syndromic profiles: Haemorrhagic (bleeding)

Snake (Micrurus) North American immune F(ab')2 Equine

Alternative name(s): Micrurus spp; Novel polyvalent equine antivenom F(ab')2 (against North American Coral snakes)

Chemical name: N/A

CAS number: N/A

PCR ID: 2005

Technical profile

Biologics > Immunoglobulin products - animal plasma/serum derived > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Micrurus fulvius (Eastern coralsnake, Florida coralsnake, Harlequin coralsnake)

Route of administration: Intravenous

Ig format: F(ab')2 immunoglobulin molecule fragments

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments derived from the plasma of immunized animals bind specific components/toxins (antigens) within snake venom to neutralize its effects.

MeSH headings / pharmacological class: Antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

IgG antibodies are whole immunoglobulins derived from the plasma of mammals immunized with snake venom. F(ab')2 fragment antibodies are generated by pepsin digestion of whole IgG antibodies to remove most of the Fc region, leaving some of the hinge region. F(ab')2 fragments have two antigen-binding F(ab) portions linked together by disulfide bonds, so are divalent with a molecular weight of about 110 kDa. (https://www.abcam.com/secondary-antibodies/advantages-of-immunoglobulin-fab-and-fab2-fragments). Since Wyeth's NASCA coral snake antivenom has been discontinued, there are other efforts for Micrurus spp effective antivenoms for the North American market.

To address the past shortage of coral snake antivenom in the United States, a novel, equine F(ab')2 antivenom has been produced against M. fulvius venom and has been tested in 20 cases in Florida, USA as part of a phase III clinical trial through the University of Arizona (https://clinicaltrials.gov/ct2/show/NCT01337245). The patients were mostly male (18/20; 90 percent), adult (mean age 36 years; range 11 to 61), and presented for care with a mean delay of 5.7 hours (range 1.6 to 16). All patients received five vials of antivenom, and one patient received a second dose. Venom was detectable at baseline in nine (45 percent) patients and became undetectable in all cases within two hours of antivenom administration. No patients experienced respiratory failure, and all survived. Adverse effects (immune reactions) occurred in six patients. Equine F(ab')2 antivenom is currently restricted to experimental protocols and is not available for general clinical use. (https://www.acep.org/toxicology/newsroom/Oct2020/coral-snake-envenomations-just-keep-breathing/). No clinical results have been published officially. Some PK studies have been undertaken with this AV (https://pubmed.ncbi.nlm.nih.gov/30773936/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Phase III

Highest R&D stage (any condition): Phase III (SBE)

Development status: Active

Developers/investigators: University of Arizona

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/30773936/

Evidence of clinical trials? Yes

Phase III(Status: , April 2011-): *Emergency Treatment of Coral Snake Envenomation With Antivenom* (CT number: NCT01337245, CT source: https://clinicaltrials.gov/show/NCT01337245)

Production/source

	Derived from
Snake species	Micrurus fulvius (Florida coral snake); Micrurus spp
Snake family	Elapidae
Risk category	Category 2 (Secondary Medical Importance)
Countries	United States of America
Regions	North America

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Venom-dependent equine immunization

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Micrurus fulvius (Florida coral snake)	Micrurus fulvius (Florida coral snake)
Snake family		Elapidae
Risk category		Category 2 (Secondary Medical Importance)

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Immunoglobulin products – recombinant

Broadly neutralizing antibodies (against Indian and African snakes) (Project)

Alternative name(s): bNAbs

Chemical name: N/A

CAS number: N/A

PCR ID: 1477

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Unspecified low molecular weight snake venom toxins

Route of administration: Not yet determined

Ig format: Ig

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Broadly neutralizing antibodies (bNAbs), originally identified and isolated for HIV, are unique in targeting highly conserved epitopes, offering potential in the discovery of a universal antivenom. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Broadly neutralizing antibody candidates against Indian and African snakes is part of a research programme under IAVI, funded by Wellcome. The project aims to reduce global levels of morbidity and mortality from snakebite envenoming by discovering and developing antibodies that can neutralise the low molecular weight snake venom toxins. These non-immunogenic toxins are poorly neutralised by currently available antivenoms, produced by animal derived immunisations. The project will discover neutralising antibodies through immunisation experiments, using rationally designed immunogens, and select for high-affinity antibodies via synthetic libraries using recombinant toxins. (https://wellcome.org/grant-funding/people-and-projects/grants-awarded/antibody-discovery-and-development-against-non)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: International AIDS Vaccine Initiative (IAVI)

Key funders: Wellcome; UK Foreign, Commonwealth & Development Office (FCDO, formerly DFID)

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Unknown
Snake family	
Risk category	Unknown
Countries	
Regions	

Immunizing venom protocol/strategy:

Production technique and/or immunization strategy: Immunisation using rationally designed immunogens, selection via synthetic libraries using recombinant toxins.

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Unknown	Unknown
Snake family		
Risk category		Unknown

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Broadly Neutralizing svMP-specific Human mAbs (against North American vipers) (Project)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 2024

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: SVMP

Route of administration: Not yet determined

Ig format: Other Camelid inspired humanised mAbs (type unspecified)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Fully human broadly neutralizing antibodies have very low immunogenicity and are easy to engineer recombinantly, so can be highly specific. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Broadly Neutralizing svMP-specific Human mAb candidates is being developed as part of a project through Texas A&M funded by the US NIH. The project's long-term goal is to develop novel, effective humanized antivenom therapeutics for Viperidae envenomation. The objective of this project is to test the hypothesis that camelid-inspired inhibitory paratope synthetic human antibodies targeted to the active site of medically-relevant viperid venom metalloproteinases (svMPs) can provide broad antivenom protection without cross-reaction with human metalloproteinases and without the risk of hypersensitivity. This objective will be addressed through an established collaboration of complementary expertise between the snake venom toxinology team at National Natural Toxins Research Center (NNTRC) and the antibody discovery team at University of California Riverside (UCR). To test our hypothesis, the project will address the following three Specific Aims. Aim 1: Qualitative and Quantitative Characterization of the hemorrhagic activity of viperid svMPs, Aim 2: Discovery of Broadly Neutralizing svMP-Specific Human mAbs. Aim 3: Evaluation of the antivenom efficacy of svMP inhibitory mAbs in vitro and in vivo. The proposed research is significant because it will advance understanding of the hemorrhagic aspects caused by snake envenomation at biochemical/cellular levels and develop effective humanized mAb antivenoms, which will be directly translatable for therapeutic use. The novelties of our project are (1) development and application of a novel Hemorrhage Score system to characterize svMPs; (2) isolation of humanized svMP-specific antivenom mAbs from libraries carrying novel convex paratopes; (3) development groundbreaking

functional (rather than binding-based) HTS for facile discovery of mAbs inhibiting hemorrhagic snake toxins; and (4) potentially shifting the conventional antivenom production into specific neutralizing humanized mAb therapeutics. (https://reporter.nih.gov/project-details/10310508).

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: Texas A&M University

Key funders: US National Institutes of Health (NIH)

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Unknown
Snake family	
Risk category	Unknown
Countries	
Regions	North America

Immunizing venom protocol/strategy:

Production technique and/or immunization strategy: Isolation of humanized svMP-specific antivenom mAbs from libraries carrying novel convex paratopes

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Unknown	Unknown
Snake family		
Risk category		Unknown

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding)

Camelid nanobodies (VHH and VHH-Fc) (plant expressed) (against Naja kaouthia/α-cobratoxin)

Alternative name(s): Recombinant single-domain antigen-binding fragments from camelid heavy chain-only antibodies; anti-α-cobratoxin nanobodies; VHH clones C2 and C21; VHH2-Fc; ; cobra toxin antibody; anti-α-cobratoxin single domain antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1722

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: α-cobratoxin (α-Cbtx): Naja kaouthia (Thai cobra) venom

Route of administration: Not yet determined

Ig format: VHH-Fc

Ig final product type/preparation: Unknown

Thermostability: Tm values of 86 and 75 °C

Mechanism of action: Antibodies or antibody fragments (including VHHs) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

VHH antibodies (or nanobodies) are the antigen binding fragments of heavy chain only antibodies. Camelids naturally produce antibodies composed only of heavy chains in which the target recognition module is composed of a single variable domain (VHH or Nb). Advantageous features of nanobodies include their small size, high solubility, high stability, and excellent tissue penetration in vivo (https://pubmed.ncbi.nlm.nih.gov/29213270/). Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Camelid nanobodies (VHH) candidate against Naja kaouthia/α-cobratoxin was developed as follows: First (in 2013), four llama VHHs were isolated from an immune VHH-displayed phage library and were shown to have high affinity, in the low nM range, for α-cobratoxin (α-Cbtx), the most lethal component of Naja kaouthia venom. The highest affinity VHH (C2) was fused to a human Fc fragment to create a VHH2-Fc antibody that would offer prolonged serum persistence. After in planta (Nicotiana benthamiana) expression and purification, the VHH2-Fc antibody retained high affinity binding to α-Cbtx. Mouse α-Cbtx challenge studies showed that the highest affinity VHHs (C2 and C20) and the VHH2-Fc antibody effectively neutralized lethality induced by α-Cbtx. (https://pubmed.ncbi.nlm.nih.gov/23894495/).

In a follow up study (2017), to thermal stabilize C2 and C20, changes were made to their frame work 1 region that was previously identified to be stabilizing, as well as reverted to the hallmark amino acids highly conserved in VHH domains; these changes improved their melting temperature (Tm) by 2

and 6 °C respectively. The further addition of a non-canonical disulfide bond raised the Tm an additional 13 and 9 °C respectively; giving final Tm values of 86 and 75 °C. Testing these mutants at 1 mg/mL at a range of elevated temperatures for an hour; at 65 °C the wild type C2 and C20 had lost 35 and 95% of their binding activity respectively, while the mutants with the added disulfide bond retained nearly 100% of their initial binding activity. (https://pubmed.ncbi.nlm.nih.gov/28209480/)

In March 2013, the University of Guelph granted PlantForm Corporation an exclusive license for technology (vivoXPRESS®) that drives high levels of protein expression in plants. PlantForm Corporation has patent protection in the US (patent number 8 465 742 and 8 883 152, titled "Anti-cobra toxin antibody fragments and method of producing a VHH library") and in the European Union (patent number 2 355 849, titled "Methods of improving the therapeutic efficacy of antibody fragments") . PlantForm Corporation has patent pending in Canada (application number 2 745 473) and India. (https://adis.springer.com/drugs/800053981)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: PlantForm; University of Guelph; US Naval Research Laboratory (NRL)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/23894495/ https://pubmed.ncbi.nlm.nih.gov/28209480/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Naja kaouthia (Thai cobra)
Snake family	Elapidae
Risk category	Both Category 1 & 2
Countries	United States of America
Regions	North America

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display, and plant expressed

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja kaouthia (Thai cobra)	Naja kaouthia (Thai cobra)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: 3FTxs

Syndromic profiles: Not specified

Camelid nanobodies (VHH) (against Bothrops atrox)

Alternative name(s): Recombinant single-domain antigen-binding fragments from camelid heavy chain-only antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1678

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Hemorrhagic and myotoxic proteins: B. atrox venom

Route of administration: Not yet determined

Ig format: VHH

Ig final product type/preparation:

Thermostability: Thermostable properties, temperature unknown

Mechanism of action: Antibodies or antibody fragments (including VHHs) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

VHH antibodies (or nanobodies) are the antigen binding fragments of heavy chain only antibodies. Camelids naturally produce antibodies composed only of heavy chains in which the target recognition module is composed of a single variable domain (VHH or Nb). Advantageous features of nanobodies include their small size, high solubility, high stability, and excellent tissue penetration in vivo (https://pubmed.ncbi.nlm.nih.gov/29213270/). Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Camelid nanobodies (VHHs) candidate/s against B. atrox snake venom haemorrhagic and myotoxic components were developed as follows: An immune library was constructed after immunizing a Lama glama with whole venom of B. atrox, from which nanobodies were selected by phage display using partially purified haemorrhagic and myotoxic proteins. Biopanning selections retrieved 18 and eight different nanobodies against the haemorrhagic and the myotoxic proteins, respectively. In vivo assays in mice showed that five nanobodies inhibited the haemorrhagic activity of the proteins; three neutralized the haemorrhagic activity of whole B. atrox venom, while four nanobodies inhibited the myotoxic protein. A mixture of the anti-haemorrhagic and anti-myotoxic nanobodies neutralized the local tissue haemorrhage and myonecrosis induced by the whole venom, although the nanobody mixture failed to prevent the venom lethality. (https://pubmed.ncbi.nlm.nih.gov/32457735/).

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Instituto Nacional de Salud, Peru

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/32457735/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Bothrops atrox (fer-de-lance)
Snake family	Viperidae
Risk category	Category 1 (Highest Medical Importance)
Countries	Peru
Regions	South America

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops atrox (fer-de-lance)	Bothrops atrox (fer-de-lance)
Snake family		Viperidae
Risk category		Category 1 (Highest Medical Importance)

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Haemorrhagic (bleeding)

Camelid nanobodies (VHH) (against Bothrops jararacussu)

Alternative name(s): Recombinant single-domain antigen-binding fragments from camelid heavy chain-only antibodies; VHH clones KF498607, KF498608, and KC329718

Chemical name: N/A

CAS number: N/A

PCR ID: 1692

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Bothropstoxin I and II (BthTX-I and BthTX-II): myotoxic phospholipases from Bothrops jararacussu venom

Route of administration: Not yet determined

Ig format: VHH

Ig final product type/preparation:

Thermostability: Thermostable properties, temperature unknown

Mechanism of action: Antibodies or antibody fragments (including VHHs) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

VHH antibodies (or nanobodies) are the antigen binding fragments of heavy chain only antibodies. Camelids naturally produce antibodies composed only of heavy chains in which the target recognition module is composed of a single variable domain (VHH or Nb). Advantageous features of nanobodies include their small size, high solubility, high stability, and excellent tissue penetration in vivo (https://pubmed.ncbi.nlm.nih.gov/29213270/). Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Camelid nanobodies (VHHs) candidate/s against Bothrops jaracussu were developed as follows: VHHs with specificity to Bothropstoxin I and II (BthTX-I and BthTX-II), two myotoxic phospholipases from Bothrops jararacussu venom, were selected from an immune VHH phage display library. After biopanning, 28 and 6 clones recognized BthTX-I and BthTX-II by ELISA, respectively. Complementarity determining regions (CDRs) and immunoglobulin frameworks (FRs) of 13 VHH-deduced amino acid sequences were identified, as well as the camelid hallmark amino acid substitutions in FR2. Three VHH clones (KF498607, KF498608, and KC329718) were capable of recognizing BthTX-I by Western blot and showed affinity constants in the nanomolar range against both toxins. VHHs inhibited the BthTX-II phospholipase A2 activity, and when tested for cross-reactivity, presented specificity to the Bothrops genus in ELISA (but not Crotulus). Furthermore, two clones (KC329718 and KF498607) neutralized the myotoxic effects induced by B. jararacussu venom, BthTX-I, BthTX-II, and by a myotoxin from Bothrops brazili venom (MTX-I) in mice. Molecular docking revealed that VHH CDRs are expected to bind the C-terminal of both toxins, essential for myotoxic activity, and to epitopes in the BthTX-II enzymatic cleft. (https://pubmed.ncbi.nlm.nih.gov/27028872/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Oswaldo Cruz Foundation (FIOCRUZ), Fundação Oswaldo Cruz

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/27028872/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Bothrops jararacussu (Jararacussu)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Brazil
Regions	South America

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops jararacussu (Jararacussu) Cross-reactivity to Bothrops alternatus (Urutu); Bothrops atrox (Common lancehead); Bothrops bilineata (Two-striped forest-pitviper); Bothrops brazili (Brazil's lancehead); Bothrops diporus (Painted Lancehead); Bothrops insularis (Golden lancehead); Bothrops jararaca (Jararaca); Bothrops leucurus (Bahia lancehead); Bothrops marajoensis (Marajó lancehead); Bothrops matogrossensis (Boca-de-Sapo); Bothrops moojeni (Brazilian lancehead); Bothrops pauloensis (Boca-de-Sapo); Bothrops pirajai (Piraja's Lancehead); Bothrops urutu (Urutu)	Bothrops jararacussu (Jararacussu) Cross-reactivity to Bothrops alternatus (Urutu); Bothrops atrox (Common lancehead); Bothrops bilineata (Two-striped forest-pitviper); Bothrops brazili (Brazil's lancehead); Bothrops diporus (Painted Lancehead); Bothrops insularis (Golden lancehead); Bothrops jararaca (Jararaca); Bothrops leucurus (Bahia lancehead); Bothrops marajoensis (Marajó lancehead); Bothrops matogrossensis (Boca-de-Sapo); Bothrops moojeni (Brazilian lancehead); Bothrops pauloensis (Boca-de-Sapo); Bothrops pirajai (Piraja's Lancehead); Bothrops urutu (Urutu)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Cytotoxic (tissue damage)

Camelid nanobodies (VHH) (against Cobra toxin) (Project)

Alternative name(s): Recombinant single-domain antigen-binding fragments from camelid heavy chain-only antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1474

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Cobra toxins

Route of administration: Not yet determined

Ig format: VHH

Ig final product type/preparation:

Thermostability: Thermostable properties, temperature unknown

Mechanism of action: Antibodies or antibody fragments (including VHHs) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

VHH antibodies (or nanobodies) are the antigen binding fragments of heavy chain only antibodies. Camelids naturally produce antibodies composed only of heavy chains in which the target recognition module is composed of a single variable domain (VHH or Nb). Advantageous features of nanobodies include their small size, high solubility, high stability, and excellent tissue penetration in vivo (https://pubmed.ncbi.nlm.nih.gov/29213270/). Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Camelid nanobodies (VHH) against cobra toxins are being developed by the Institut Pasteur de Tunis, Tunisia as part of a research programme funded by the Wellcome Trust. The COBRA-NGaV project brings together research teams with extensive experience in venomics and antivenomics. It will provide the proof-of-concept for cobra toxin-specific Nb (VHH) candidates as a novel generation of antivenoms, and address the dual obstacle to neutralise cobra toxins: weak immunogenicity and fast diffusion. Preliminary results obtained so far: Strong and specific responses were elicited in dromedaries immunised against the toxic fractions of N. legionis, N. haje and N. oxiana; Phage display screenings were adopted to rescue strong Nb binders specific towards relevant N. l., N. h. and N. o. toxins; Several clusters of Nb sequences specifically binding cobra toxins have been identified. As a result, Nb selections and combinations for optimal synergic effects and best cross-species performances are being generated. Best-in-class candidates will be tested in a pre-clinical study in mice and sheep according to good manufacturing practice rules. (https://wellcome.org/grant-funding/people-and-projects/grants-awarded/developing-next-generation-anti-venoms-improve

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: Institut Pasteur de Tunis

Key funders: Wellcome

Preclinical sources: https://wellcome.org/grant-funding/people-and-projects/grants-awarded/developing-next-generation-anti-venoms-improve

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Naja legionis (Egyptian cobra); Naja haje (Egyptian cobra); Naja oxiana (Central Asian cobra)
Snake family	Elapidae
Risk category	Both Category 1 & 2
Countries	Tunisia
Regions	North Africa

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja legionis (Egyptian cobra); Naja haje (Egyptian cobra); Naja oxiana (Central Asian cobra)	Naja legionis (Egyptian cobra); Naja haje (Egyptian cobra); Naja oxiana (Central Asian cobra)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: 3FTxs

Syndromic profiles: Neurotoxic (paralysis)

Camelid nanobodies (VHH) (against Daboia russelii)

Alternative name(s): Recombinant single-domain antigen-binding fragments from camelid heavy chain-only antibodies; anti-sPLA2, gp12B sdAb

Chemical name: N/A

CAS number: N/A

PCR ID: 1797

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Secretory phospholipase A2 gp 12B: Daboia russelii venom

Route of administration: Not yet determined

Ig format: VHH

Ig final product type/preparation:

Thermostability: Tm value 62.9 deg celcius; retention of secondary structures by the sdAbs at 4 deg C and 37 deg C for up to a month

Mechanism of action: Antibodies or antibody fragments (including VHHs) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

VHH antibodies (or nanobodies) are the antigen binding fragments of heavy chain only antibodies. Camelids naturally produce antibodies composed only of heavy chains in which the target recognition module is composed of a single variable domain (VHH or Nb). Advantageous features of nanobodies include their small size, high solubility, high stability, and excellent tissue penetration in vivo (https://pubmed.ncbi.nlm.nih.gov/29213270/). Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Camelid nanobodies (VHH) candidate against secretory phospholipase A2 of Daboia russelii (Russel's Viper RVV) venom were developed as follows: to select RVV specific single domain antibody fragments, a single round of biopanning was performed against plate bound complete RVV from the constructed phage display library of VHHs. Five clones with shared nucleotide sequences were selected. One was subcloned and expressed (named as clone MKSS1) in E. coli. The neutralizing potential of the VHH clone selected was demonstrated against secretory phospholipase A2, gp 12B, one of the components of RVV, not only using acellular and cellular assays but also in zebrafish as a vertebrate model organism. ((https://pubmed.ncbi.nlm.nih.gov/31689425/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Indian Institute of Science Education And Research Mohali (ISSER Mohali)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/31689425/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Daboia russelii (Russell's viper)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	India
Regions	South Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russelii (Russell's viper)	Daboia russelii (Russell's viper) Results suggested no cross reactivity of the sPLA2, gp12B specific sdAb (VHH) against Cobra venom components
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Not specified

Camelid nanobodies (VHH) (against necrosis-inducing venom toxins (NITs)) (Project)

Alternative name(s): Recombinant single-domain antigen-binding fragments from camelid heavy chain-only antibodies; pathology-specific antibodies for snake venom-induced necrosis

Chemical name: N/A

CAS number: N/A

PCR ID: 1476

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Necrosis-inducing venom toxins (NITs)

Route of administration: Not yet determined

Ig format: VHH

Ig final product type/preparation:

Thermostability: Thermostable properties, temperature unknown

Mechanism of action: Antibodies or antibody fragments (including VHHs) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

VHH antibodies (or nanobodies) are the antigen binding fragments of heavy chain only antibodies. Camelids naturally produce antibodies composed only of heavy chains in which the target recognition module is composed of a single variable domain (VHH or Nb). Advantageous features of nanobodies include their small size, high solubility, high stability, and excellent tissue penetration in vivo (https://pubmed.ncbi.nlm.nih.gov/29213270/). Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Camelid VHH against against necrosis-inducing venom toxins (NITs) is a pathology-specific candidate intended to treat snake venom-induced necrosis in India and sub-Saharan Africa. It is being developed as part of a research programme under the Liverpool School of Tropical Medicine funded by the Wellcome Trust, underpinned by the hypothesis is that rationally-selected recombinant, humanised camelid VHH targeting NITs will possess the efficacy, rapid in-tissue distribution, safety, thermostability, affordability and large scale production characteristics appropriate for future development of a community-dispensed therapy. The programme includes the following: To achieve this for Africa and India, project partners bring new approaches, platforms and required resources to select candidate recombinant NIT-specific monoclonal VHH from (i) B cells of NITimmunised camels and (ii) a synthetic VHH library. Deploying sequential in vitro, ex vivo human skin and mouse in vivo assays of venom-induced necrosis enables down-selection of the most efficacious, thermostable recombinant VHH. ‘Humanising’ the thermostable recombinant VHH gives the key safety criterion. E.coli expression enables inexpensive and large-scale production of humanised VHH.

(https://wellcome.org/grant-funding/people-and-projects/grants-awarded/novel-platforms-develop-polyspecifically-effective)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: Liverpool School of Tropical Medicine (LSTM)

Key funders: Wellcome

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Unknown
Snake family	
Risk category	Unknown
Countries	
Regions	

Immunizing venom protocol/strategy:

Production technique and/or immunization strategy: Recombinant antibody production

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Unknown	Unknown
Snake family		
Risk category		Unknown

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Cytotoxic (tissue damage)

Chicken scFv (egg yolk derived) (against Bungarus multicinctus)

Alternative name(s): Recombinant chicken single chain variable fragment antibodies; BMS1, BMS3, BMS6, BMS9, BML1, and BML10

Chemical name: N/A

CAS number: N/A

PCR ID: 1714

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Bungarus multicinctus (Many-banded krait) venom proteins

Route of administration: Not yet determined

Ig format: Single-chain variable fragments (scFv)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments (including scFV) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Single chain variable antibody fragments (scFvs) are fusion proteins of the variable regions of the heavy and light chains of an antibody (VH and VL) connected with a short linker peptide of 10–25 amino acids. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Chicken scFv (egg yolk derived) candidate against Bungarus multicinctus was developed as follows: Chickens were immunized with B. multicinctus proteins, and polyclonal immunoglobulin Y (IgY) antibodies were purified from eggs. IgY showed a binding activity to B. multicinctus proteins that was similar to horse antivenin, and its titer in chickens lasted for at least 6 months (see candidate 'Chicken IgY (egg yolk derived) (against Bungarus multicinctus)'). We constructed two antibody libraries by phage display antibody technology, which contain 1.0 × 107 and 2.9 × 108 transformants, respectively. After biopanning, a phage-based enzyme-linked immunosorbent assay (ELISA) indicated that specific clones were enriched. Thirty randomly selected clones expressing monoclonal single-chain variable-fragment (scFv) antibodies were classified into four groups with a short linker and two with a long linker.

These selected scFv antibodies (BMS1, BMS3, BMS6, BMS9, BML1, and BML10) showed specific binding activities to B. multicinctus proteins but not to the venomous proteins of other snakes. Polyclonal IgY demonstrated a similar neutralization efficiency as did horse-derived antivenin in mice that were injected with a minimum lethal dosage (MLD) of venom proteins. A mixture of several monoclonal anti-B. multicinctus scFv antibodies was also able to partially inhibit the lethal effect on mice. (https://pubmed.ncbi.nlm.nih.gov/27663029/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Taipei Medical University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/27663029/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Bungarus multicinctus (Many-banded krait)
Snake family	Elapidae
Risk category	Category 1 (Highest Medical Importance)
Countries	Taiwan
Regions	East Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bungarus multicinctus (Many-banded krait); Deinagkistrodon acutus (Chinese copperhead, Hundred-pace snake, Sharp-nosed pitviper); Trimeresurus stejnegeri (Chinese green tree pitviper, Stejneger's bamboo pitviper); Trimeresurus mucrosquamatus (Brown-spotted pit viper); Naja naja (Indian cobra, Spectacled cobra); Daboia russellii formosensis (Russell's viper)	Bungarus multicinctus (Many-banded krait)
Snake family		Elapidae
Risk category		Category 1 (Highest Medical Importance)

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Chicken scFv (egg yolk derived) (against D. acutus, Taiwan)

Alternative name(s): Recombinant chicken single chain variable fragment antibodies; DAS1, DAS5, DAS14, and DAL1

Chemical name: N/A

CAS number: N/A

PCR ID: 1881

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Deinagkistrodon acutus (DA) venom proteins, deduced as snake venom metalloproteinase proteins

Route of administration: Not yet determined

Ig format: Single-chain variable fragments (scFv)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments (including scFV) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Single chain variable antibody fragments (scFvs) are fusion proteins of the variable regions of the heavy and light chains of an antibody (VH and VL) connected with a short linker peptide of 10–25 amino acids. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Chicken svFv (egg yolk derived) candidate against D. acutus was developed as follows: yolk immunoglobulin (IgY) was purified from eggs, and DA protein was recognized using Western blotting and an enzyme-linked immunosorbent assay (ELISA), similar to therapeutic horse antivenin (see candidate 'Chicken IgY (egg yolk derived) (against D. acutus)'). To generate monoclonal single-chain variable fragment (scFv) antibodies, we used phage display technology to construct two libraries with short or long linkers, containing 6.24 × 10(8) and 5.28 × 10(8) transformants, respectively. After four rounds of biopanning, the eluted phage titer increased, and the phage-based ELISA indicated that the specific clones were enriched. Nucleotide sequences of 30 individual clones expressing scFv were analyzed and classified into four groups that all specifically recognized the DA venom protein. Four scFvs, DAS1, DAS5, DAS14, and DAL1, were successfully purified with binding affinity to DA protein. Furthermore, based on mass spectrometry, the scFv-bound protein was deduced to be snake venom metalloproteinase proteins. Both IgY and mixed scFv inhibited the lethal effect in mice injected with the minimum lethal dosage of the DA protein. (https://pubmed.ncbi.nlm.nih.gov/26475102/)

The four scFvs, DAS1, DAS5, DAS14, and DAL1 recognized the DA venom protein but not other venom proteins from Bungarus multicinctus [BM], Trimeresurus stejnegeri [TS], Trimersurus mucrosquamatus [TM], Naja naja atra [NNA], and Daboia russellii formosensis [DRF].

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Taipei Medical University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/26475102/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Deinagkistrodon acutus (Chinese copperhead)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Taiwan
Regions	East Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Deinagkistrodon acutus (Chinese copperhead); Bungarus multicinctus (Many-banded krait); Trimeresurus stejnegeri (Chinese green tree viper); Trimersurus mucrosquamatus (Brown-spotted pit viper); Naja naja atra (Chinese cobra); Daboia russellii formosensis (Russell's viper)	Deinagkistrodon acutus (Chinese copperhead)
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Not specified

Chicken scFv (egg yolk derived) (against Daboia russelii formosensis)

Alternative name(s): Recombinant chicken single chain variable fragment antibodies; DRFS3, DRFS6, DRFS9, DRFS13 and DRFL1

Chemical name: N/A

CAS number: N/A

PCR ID: 1788

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Daboia russelii formosensis (DRF) venom proteins

Route of administration: Not yet determined

Ig format: Single-chain variable fragments (scFv)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments (including scFV) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Single chain variable antibody fragments (scFvs) are fusion proteins of the variable regions of the heavy and light chains of an antibody (VH and VL) connected with a short linker peptide of 10–25 amino acids. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Chicken scFv (egg yolk derived) candidate against Daboia russelii formosensis was developed as follows: Glutaraldehyde-attenuated Daboia russelii formosensis (DRF) venom proteins were used to immunize chickens. Polyclonal yolk-immunoglobulin (IgY) antibodies were generated and showed a specific binding affinity (see candidate 'Chicken IgY (egg yolk derived) (against Daboia russelii formosensis)'). Phage display technology was used to generate two antibody libraries of single-chain variable fragments (scFvs) containing 3.4×10^7 and 5.5×10^7 transformants, respectively). Phage-based ELISA indicated that specific clones were enriched after bio-panning. The nucleotide sequences of scFv-expressing clones were analyzed and classified into six groups in the short linker and four groups in the long linker. These scFv antibodies specifically bound to DRF proteins, but not other venom proteins. Mass spectrometric data suggested that these scFv antibodies may recognize phospholipase A2 RV-4 or RV-7 (antibodies DRFS3, DRFS6, DRFS9, DRFS13 and DRFL1). In vivo studies showed that anti-DRF IgY exhibited complete protective effects and mixed scFv antibodies increased the survival rate and time of mice challenged with a lethal dose of DRF proteins.(https://pubmed.ncbi.nlm.nih.gov/29076991/

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Taipei Medical University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/29076991/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Daboia russelii formosensis (Russel's viper)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Taiwan
Regions	East Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russelii formosensis (Russel's viper)	Daboia russelii formosensis (Russel's viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Not specified

Chicken scFv (egg yolk derived) (against Naja naja atra)

Alternative name(s): Recombinant chicken single chain variable fragment antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1706

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Naja atra atra (aka NNA) (Chinese cobra) venom proteins

Route of administration: Not yet determined

Ig format: Single-chain variable fragments (scFv)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments (including scFV) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Single chain variable antibody fragments (scFvs) are fusion proteins of the variable regions of the heavy and light chains of an antibody (VH and VL) connected with a short linker peptide of 10–25 amino acids. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Chicken scFv (egg yolk derived) candidate/s against Naja naja atra were developed as follows: Hens were immunized with inactivated NNA venom proteins from the cobra Naja naja atra (NNA). Purified yolk IgY antibodies showed specific anti-NNA binding activity comparable to that of the equine-derived antivenin (see candidate 'Chicken IgY (egg yolk derived) (against Naja naja atra)'). Phage display technology was used to generate two antibody libraries containing 9.0×10^8 and 8.4×10^8 clones with a short or long linker, respectively. The phage ELISA indicated that anti-NNA clones displaying single-chain variable fragments (scFv) were significantly enriched after biopanning.

The nucleotide sequences of the light and heavy chain genes of 30 monoclonal scFv antibodies were determined and classified into six groups with the short linker and nine groups with the long linker. 15 scFv were purified: NNAS1, NNAS2, NNAS3, NNAS4, NNAS6, NNAS14, NNAL1, NNAL3, NNAL5, NNAL8, NNAL10 and NNAL13 and NNAL2, NNAL4 and NNAL11. The majority of these scFv clones specifically bound to NNA proteins but not to venom proteins from other snakes. Their binding affinities were further determined by competitive ELISA. Animal model studies showed that anti-NNA IgY antibodies exhibited complete protective effects, while a combination of scFv antibodies raised the survival rates and times of mice challenged with lethal doses of NNA venom proteins.(https://pubmed.ncbi.nlm.nih.gov/30248928/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Taipei Medical University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/30248928/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Naja naja atra (Chinese cobra)
Snake family	Elapidae
Risk category	Category 1 (Highest Medical Importance)
Countries	Taiwan
Regions	East Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja naja atra (Chinese cobra); Bungarus multicinctus (BM, Many-banded krait); Deinagkistrodon acutus (DA, Chinese copperhead, Hundred-pace snake, Sharp-nosed pitviper); Trimeresurus stejnegeri (TS, Chinese green tree pitviper, Stejneger's bamboo pitviper); Trimeresurus mucrosquamatus (Brown-spotted pitviper); Daboia russelii formosensis (DRF, Indian Russell's viper, Russell's viper, South Asian Russell's viper)	Naja naja atra (Chinese cobra); Partial cross-reactivity Deinagkistrodon acutus (Chinese copperhead); Trimeresurus mucrosquamatus (Brown-spotted pitviper)
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Chicken scFv (egg yolk derived) (against Trimeresurus mucrosquamatus)

Alternative name(s): Recombinant chicken single chain variable fragment antibodies; 3S10, 4S1, 4S9, 4S15

Chemical name: N/A

CAS number: N/A

PCR ID: 2014

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Snake venom serine protease: Trimeresurus mucrosquamatus (brown-spotted pit viper, Taiwanese habu and pointed-scaled pit viper)

Route of administration: Not yet determined

Ig format: Single-chain variable fragments (scFv)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments (including scFV) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Single chain variable antibody fragments (scFvs) are fusion proteins of the variable regions of the heavy and light chains of an antibody (VH and VL) connected with a short linker peptide of 10–25 amino acids. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Chicken scFv (egg yolk derived) candidate against Trimeresurus mucrosquamatus (TM) was developed as follows: chickens were used as an alternative animal model for immunization with TM venom. Using phage display technology to process four rounds of panning, selected single chain variable fragments (scFv) could specifically recognize TM venom proteins, which were later identified as a group of homogeneous venom serine protease. The specific scFv antibodies 3S10, 4S1, 4S9, 4S15 showed various inhibitory effects on sheep RBC lysis induced by TM venom using an indirect haemolytic assay in vitro. In addition, the survival times of mice were extended to certain degrees when treated with these scFv antibodies individually or in a combination with IgY whole antibodies (see candidate 'Chicken IgY (egg yolk derived) (against Trimeresurus mucrosquamatus)'). To elucidate the inhibitory mechanism, we used molecular modelling to build up the serine protease structure to simulate the possible interactions with scFv antibodies. The results suggested that the CDR-loop of the scFv antibodies (3S10 or 4S1) might bind at the 99-loop of venom serine protease so as to affect substrate access due to the partial collapse of the subsite S2 and the partial movement of the subsite S4. ScFv antibodies were assessed for their crossreactivity with crude venoms of Deinagkistrodon acutus, Bungarus multicinctus, Trimeresurus stejnegeri, T. mucrosquamatus, Naja

naja atra and Daboia siamensis by ELISA. Given the complexity and similarity of venom components in the same genus, the results showed that all 4 scFv antibodies tested had significant binding specificity only to TM snake venom (https://pubmed.ncbi.nlm.nih.gov/25769957/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Taipei Medical University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/25769957/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Trimeresurus mucrosquamatus (brown-spotted pit viper, Taiwanese habu and pointed-scaled pit viper)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Taiwan
Regions	East Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Trimeresurus mucrosquamatus (brown-spotted pit viper, Taiwanese habu and pointed-scaled pit viper); Deinagkistrodon acutus (Chinese copperhead, Hundred-pace snake, Sharp-nosed pitviper); Bungarus multicinctus (Many-banded krait); Trimeresurus stejnegeri (Chinese green tree pitviper, Stejneger's bamboo pitviper); Naja naja atra (Indian cobra, Spectacled cobra); Daboia siamensis (Indochinese Russell's viper, Siamese Russell's viper)	Trimeresurus mucrosquamatus (brown-spotted pit viper, Taiwanese habu and pointed-scaled pit viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVSPs

Syndromic profiles: Haemorrhagic (bleeding)

Chicken scFv (egg yolk derived) (against Trimeresurus stejnegeri)

Alternative name(s): Recombinant chicken single chain variable fragment antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1894

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: T. stejnegeri venom proteins

Route of administration: Not yet determined

Ig format: Single-chain variable fragments (scFv)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments (including scFV) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Single chain variable antibody fragments (scFvs) are fusion proteins of the variable regions of the heavy and light chains of an antibody (VH and VL) connected with a short linker peptide of 10–25 amino acids. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Chicken scFv (egg yolk derived) candidate against Trimeresurus stejnegeri was developed as follows: T. stejnegeri venom proteins were inactivated by glutaraldehyde in order to immunize hens for polyclonal immunoglobulin (IgY) antibodies production. After IgY binding assays, two antibody libraries were constructed expressing single-chain variable fragment (scFv) antibodies joined by the short or long linker for use in phage display antibody technology. Four rounds of biopanning were carried out. The selected scFv antibodies were then further tested for their binding activities and neutralization assays to TS proteins. In in vivo studies, the data demonstrated that anti-TS IgY provided 100% protective effects (see candidate 'Chicken IgY (egg yolk derived) (against Trimeresurus stejnegeri)'), while combined scFvs augmented partial survival time of mice injected with a lethal amount of TS proteins. (https://pubmed.ncbi.nlm.nih.gov/33281887/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Taipei Medical University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33281887/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Trimeresurus stejnegeri (Bamboo viper)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Taiwan
Regions	East Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Trimeresurus stejnegeri (Bamboo viper); Trimeresurus mucrosquamatus (Taiwanese habu)	Trimeresurus stejnegeri (Bamboo viper); Trimeresurus mucrosquamatus (Taiwanese habu)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Combined humanised IgG and camelid VHHs antivenom for Sub-Saharan Africa (Project)

Alternative name(s): Combined humanised broadly-neutralizing antibodies and camelid nanobodies (VHHs) for Sub-Saharan Africa; broad-spectrum (polyvalent) recombinant antivenom for SSA

Chemical name: N/A

CAS number: N/A

PCR ID: 1478

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Medically relevant, systemically-acting and deep tissue penetrating toxins found in the 24 medically most-relevant snake species from Sub-Saharan Africa

Route of administration: Not yet determined

Ig format: Other IgG plus VHH (combined)

Ig final product type/preparation:

Thermostability: Thermostable properties (VHH), temperature unknown

Mechanism of action: Antibodies or antibody fragments (including whole IgGs or fragment VHHs) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Fully human broadly neutralizing antibodies as whole immunoglobulins (IgGs) have very low immunogenicity and are easy to engineer recombinantly, so can be highly specific. VHH antibodies (or nanobodies) are the antigen binding fragments of heavy chain only antibodies. Camelids naturally produce antibodies composed only of heavy chains in which the target recognition module is composed of a single variable domain (VHH or Nb). Advantageous features of nanobodies include their small size, high solubility, high stability, and excellent tissue penetration in vivo (https://pubmed.ncbi.nlm.nih.gov/29213270/). Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Combined humanised IgG and camelid VHHs for Sub-Saharan Africa is a candidate recombinant antivenom intended to treat all 24 medically important snakes in Sub-Saharan Africa. It is part of a research programme through the University of Technical University of Denmark, funded by the Wellcome Trust. The programme is driven by a research trend emerging towards the use of human antibody formats as well as camelid heavy-domain antibody fragments due to their compatibility with the human immune system, beneficial therapeutic properties, and the ability to manufacture these molecules cost-effectively. The programme includes: the application of carefully designed mixtures of fully human monoclonal immunoglobulin G (IgG) antibodies for systemic acting toxins and nanobodies for locally acting toxins, provides a therapeutically promising and scientifically feasible solution. This takes advantage of well-established discovery pipelines and expertise in working with oligoclonal and broadly neutralising antibodies against toxins, to develop a broad-spectrum (polyvalent) recombinant antivenom for SSA. The project will focus on the following technical goals: Identification and isolation

of all medically relevant snake venom toxins that need to be neutralised by a recombinant antivenom for SSA; Discovery of a well-characterised panel of broadly neutralising IgGs and nanobodies that can neutralise all medically relevant, systemically-acting and deep tissue penetrating toxins found in the 24 medically most-relevant snake species from this region. (https://wellcome.org/grant-funding/people-and-projects/grants-awarded/recombinant-snakebite-antivenom-sub-saharan-africa)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: Technical University of Denmark

Key funders: Wellcome

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	24 medically important snakes of Sub-Saharan Africa
Snake family	
Risk category	Category 1 (Highest Medical Importance)
Countries	
Regions	Central Africa; East Africa; West Africa; Southern Africa

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production, details unclear

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	24 medically important snakes of Sub-Saharan Africa	24 medically important snakes of Sub-Saharan Africa
Snake family		
Risk category		Category 1 (Highest Medical Importance)

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Human anti-kaouthiagin scFv (15, 20, and 61) (against Naja kaouthia)

Alternative name(s): Recombinant human single chain variable fragment antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1765

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Kaouthiagin (SVMP) from Naja kaouthia (Thai cobra)

Route of administration: Not yet determined

Ig format: Single-chain variable fragments (scFv)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments (including scFvs) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibody fragments; immunological factors; antivenin; antidotes

Key features and challenges:

Single chain variable antibody fragments (scFvs) are fusion proteins of the variable regions of the heavy and light chains of an antibody (VH and VL) connected with a short linker peptide of 10–25 amino acids. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)
Human anti-kaouthiagin scFv candidate/s (15, 20, and 61) against Naja kaouthia (Thai cobra) was developed as follows: Kaouthiagin is a unique SVMP that binds and cleaves von Willebrand factor (vWF) at a specific peptide bond leading to inhibition of platelet aggregation, which enhances the hemorrhage. Kaouthiagin is a low abundant venom component of Thai cobra (Naja kaouthia); thus, most horse-derived antivenins used for cobra bite treatment do not contain adequate anti-kaouthiagin. Human single-chain antibody variable fragments that bind to and interfere with kaouthiagin activity were identified as follows: Kaouthiagin was purified from N. kaouthia-holovenom by a single-step gel-filtration chromatography. The purified venom component was used in phage-biopanning to select the kaouthiagin-bound scFv-displayed-phage clones from a human scFv-phage display library. Soluble HuscFvs expressed by three phage-transformed-E. coli clones (15, 20 and 61) interfered with cobra kaouthiagin binding to human vWF. Computerized simulation indicated that scFv of two phage-transformed E. coli clones formed contact interface with kaouthiagin residues at or near catalytic site and effectively inhibited fibrinogenolytic activity of the kaouthiagin.
(https://pubmed.ncbi.nlm.nih.gov/30513883/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Mahidol University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/30513883/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Naja kaouthia (Monocellate cobra, Thai cobra)
Snake family	Elapidae
Risk category	Both Category 1 & 2
Countries	Thailand
Regions	South East Asia

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja kaouthia (Monocellate cobra, Thai cobra)	Naja kaouthia (Monocellate cobra, Thai cobra)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding)

Human monoclonal antibodies (IgG) (broad spectrum anti-snake venom) (Project)

Alternative name(s): Broadly neutralizing fully human antivenom antibodies; fully human broad spectrum anti-snake venom; Snake antivenom program - Centivax; Research programme: snake venom poisoning therapeutics - Centivax

Chemical name: N/A

CAS number: N/A

PCR ID: 955

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Unspecified snake venom / toxins

Route of administration: Not yet determined

Ig format: Ig

Ig final product type/preparation: Unknown

Thermostability: Thermostabilized properties (unknown temperatures)

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Fully human broadly neutralizing antibodies as whole immunoglobulins (IgGs) have very low immunogenicity and are easy to engineer recombinantly, so can be highly specific. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Human monoclonal antibodies (IgG) are a candidate/s intended for use as the world's first fully human broad spectrum anti-snake venom. Monoclonal fully human-derived IgG are being developed by Centivax (a spin-off of Distributed Bio), for the treatment of snakebite envenoming under their Broad-Spectrum Anti-Venom portfolio (https://www.centivax.com/portfolio), funded by the US NIH. The candidates were originally developed by Distributed Bio. The project will identify and characterize a pool of cross-reactive, high affinity antibody candidates and characterize whole venom pool epitopes. The antibodies will be thermostabilized to enable lenient storage requirements and longer-shelf life. Preclinical development is underway in the US as of May 2021). The efficacy of the antivenom antibodies will be studied in mice by performing in vivo challenge studies. (https://grantome.com/grant/NIH/R43-AI147898-01). Centivax plans a clinical trial for the candidates for snakebite envenoming in 2023. (https://adisinsight.springer.com/drugs/800063580)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Centivax

Key funders: US National Institutes of Health (NIH)

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Unknown
Snake family	
Risk category	Unknown
Countries	
Regions	

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production, details unclear

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Unknown	Unknown
Snake family		
Risk category		Unknown

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Human oligoclonal recombinant IgG antibodies (against Dendroaspis polylepis)

Alternative name(s): Fully human recombinant IgG

Chemical name: N/A

CAS number: N/A

PCR ID: 1676

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Dendrotoxin: Dendroaspis polylepis (Black mamba)

Route of administration: Not yet determined

Ig format: Ig

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Fully human broadly neutralizing antibodies as whole immunoglobulins (IgGs) have very low immunogenicity and are easy to engineer recombinantly, so can be highly specific. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Human oligoclonal recombinant IgG antibody candidates against dendrotoxin-mediated neurotoxicity of D. polylepis (black mamba) was developed as follows: D. polylepis venom was fractionated to isolate key dendrotoxins. Following three rounds of panning, polyclonal ELISAs revealed that antibody binders had been enriched. A panel of unique scFv-formatted antibodies that yielded the highest binding signals in the ENC assay were selected for conversion to IgG format. In total, 24 out of 25 recombinant human IgGs targeting black mamba neurotoxins were tested in vivo. All IgGs were evaluated for neutralization of lethality by the intracerebroventricular (i.c.v.) route, where nine showed full (100%) protection against the venom fraction they were raised against. Antibody cocktails were designed to test whether dendrotoxin-mediated neurotoxicity of the whole venom could be completely abrogated using the discovered human IgGs. Both cocktails successfully provided full protection against whole venom when injected via the i.c.v. route at a challenge dose of 1.5 µg of whole venom pre-incubated with the IgG cocktails at IgG:toxin molar ratios of 4:1 and 3. (https://pubmed.ncbi.nlm.nih.gov/30279409/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Technical University of Denmark; IONTAS Limited

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/30279409/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Dendroaspis polylepis (Black Mamba)
Snake family	Elapidae
Risk category	Both Category 1 & 2
Countries	Kenya
Regions	East Africa

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Experimental recombinant antivenom developed via combined toxicovenomics and phage display , based on a cocktail of fully human immunoglobulin G (IgG) monoclonal antibodies

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Dendroaspis polylepis (Black Mamba)	Dendroaspis polylepis (Black Mamba)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: Dendrotoxins

Syndromic profiles: Neurotoxic (paralysis)

Human polyclonal scFv (against multiple Iranian snakes)

Alternative name(s): Recombinant human single chain variable fragment antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1919

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: combination of venom from six medically important snakes in Iran

Route of administration: Not yet determined

Ig format: Single-chain variable fragments (scFv)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments (including scFvs) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibody fragments; immunological factors; antivenin; antidotes

Key features and challenges:

Single chain variable antibody fragments (scFvs) are fusion proteins of the variable regions of the heavy and light chains of an antibody (VH and VL) connected with a short linker peptide of 10–25 amino acids. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Polyclonal human scFv candidate against multiple Iranian snakes was developed as follows: scFv antibodies were selected against the venom of the most venomous snakes in Iran using phage display technology: Naja naja oxiana, Cerastes cerastes gasperettii, Echis carinatus sochureki, Vipera lebetina obtusa; Agkistrodon intermedius caucasicus; Vipera xanthina venom. Phage particles harbouring anti-venom specific scFv were separated and scFv antibodies were produced in bacteria. In-vitro assay showed that polyclonal scFvs specifically bind to the venom. Furthermore, in-vivo experiment in mice BALB/c indicated effective toxin neutralization using 20 µg of polyclonal scFv. (https://pubmed.ncbi.nlm.nih.gov/33680030/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Shahid Beheshti University of Medical Sciences, Tehran

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33680030/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Naja naja oxiana (Central Asian/Iranian cobra); Cerastes cerastes gasperettii (Arabian horned viper); Echis carinatus sochureki (Eastern saw-scaled viper); Vipera lebetina obtusa (Levant viper); Agkistrodon intermedius caucasicus (central Asian pitviper); Vipera xanthina (Ottoman viper)
Snake family	Viperidae,Elapidae
Risk category	Both Category 1 & 2
Countries	Iran
Regions	Middle East

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja naja oxiana (Central Asian/Iranian cobra); Cerastes cerastes gasperettii (Arabian horned viper); Echis carinatus sochureki (Eastern saw-scaled viper); Vipera lebetina obtusa (Levant viper); Agkistrodon intermedius caucasicus (central Asian pitviper); Vipera xanthina (Ottoman viper)	Naja naja oxiana (Central Asian/Iranian cobra); Cerastes cerastes gasperettii (Arabian horned viper); Echis carinatus sochureki (Eastern saw-scaled viper); Vipera lebetina obtusa (Levant viper); Agkistrodon intermedius caucasicus (central Asian pitviper); Vipera xanthina (Ottoman viper)
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Human recombinant IgG antibodies (against Naja kaouthia/α-cobratoxin)

Alternative name(s): Fully human recombinant IgG

Chemical name: N/A

CAS number: N/A

PCR ID: 1799

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: α-cobratoxin: Naja kaouthia venom

Route of administration: Not yet determined

Ig format: Ig

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Fully human broadly neutralizing antibodies as whole immunoglobulins (IgGs) have very low immunogenicity and are easy to engineer recombinantly, so can be highly specific. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Human recombinant IgG antibodies candidate against Naja kaouthia/α-cobratoxin was developed as follows: six synthetic antibodies built on a human IgG framework were developed using phage-displayed synthetic antibody libraries against α-cobratoxin - the most abundant long-chain α-neurotoxin from Naja kaouthia venom. The synthetic antibodies exhibited sub-nanomolar affinities to α-cobratoxin and neutralized the curare-mimetic effect of the toxin in vitro. These results demonstrate that phage display technology based on synthetic repertoires can be used to rapidly develop human antibodies with drug-grade potencies as inhibitors of venom toxins. (https://pubmed.ncbi.nlm.nih.gov/35481650/). This work was funded through the European Union (grant agreement no. 850974, MABSTER https://cordis.europa.eu/project/id/850974)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: University of Toronto; Technical University of Denmark

Key funders: European Commission (EC)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/35481650/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Naja kaouthia (Thai cobra)
Snake family	Elapidae
Risk category	Both Category 1 & 2
Countries	
Regions	

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja kaouthia (Thai cobra)	Naja kaouthia (Thai cobra)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: 3FTxs

Syndromic profiles: Neurotoxic (paralysis)

Human recombinant polyclonal F(ab) (against Echis carinatus)

Alternative name(s): Fully human recombinant antibody fragments

Chemical name: N/A

CAS number: N/A

PCR ID: 1864

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Unspecified snake venom / toxins: Echis carinatus venom

Route of administration: Not yet determined

Ig format: Fab

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments (including Fab) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

F(ab) antibody fragments are derived from the region on an antibody that is antigen-binding, and is composed of one constant and one variable domain of each of the heavy and light chain. Fab fragments can be engineered by cleaving the entire Fc domain of whole IgG antibodies, leaving two single monovalent F(ab) fragments. Fully human antibodies or antibody fragments (including F(ab) fragments) have very low immunogenicity and are easy to engineer recombinantly, so can be highly specific. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Human recombinant Polyclonal F(ab) candidate against Echis carinatus was developed as follows: human recombinant F(ab) fragment antivenom was produced in Rosetta-g bacterium using a gene library constructed in a previous study. The prepared Fab was purified in several steps, desalted, and lipopolysaccharide-depleted using ammonium sulfate solution and dialysis against phosphate buffer and Triton X-114 solution, respectively. Subsequently, the product was initially confirmed by the sodium dodecyl sulfate polyacrylamide gel electrophoresis and enzyme-linked immunosorbent assay (ELISA), respectively. Finally, the neutralization potency of the product was investigated in laboratory Syrian Mice. The obtained results showed corresponding reduced bands to Fab fragment with the molecular weight of about 28 kDa at a concentration of 3.1 mg/ml. There was a significant difference between the groups in terms of ELISA test (<p>0.05). The neutralization potency of the product against the venom of Echis carinatus (E. carinatus) was about 7 LD50/ml (54.6 ug/mL) when tested on mice. Based on the results, the Fab fragment antivenom had the ability to neutralize the in vivo biological activity of the venom of Iranian E. carinatus. (https://pubmed.ncbi.nlm.nih.gov/31077118/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Razi Vaccine and Serum Research Institute, Agricultural Research, Education and Extension Organization (AREEO)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/31077118/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Echis carinatus (Saw-scaled viper)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Iran
Regions	Middle East

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Fab fragments produced in Rosetta-g bacterium using a priori-developed gene library

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Echis carinatus (Saw-scaled viper)	Echis carinatus (Saw-scaled viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Human scFv (against Macrovipera lebetina)

Alternative name(s): Recombinant human single chain variable fragment antibodies; scFv C37 and C69

Chemical name: N/A

CAS number: N/A

PCR ID: 2023

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Macrovipera lebetina (Kufi, Levant viper, Levantine viper)

Route of administration: Not yet determined

Ig format: Single-chain variable fragments (scFv)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments (including scFV) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Single chain variable antibody fragments (scFvs) are fusion proteins of the variable regions of the heavy and light chains of an antibody (VH and VL) connected with a short linker peptide of 10–25 amino acids. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

HUman scFv candidate against Macrovipera lebetina was developed as follows: scFvs against M. lebetina venom were isolated by phage display technique. Using three rounds of biopanning, two specific scFvs (C37 and C69) with the highest affinity were selected. The selected scFvs purified by nickel affinity chromatography. The specific binding of purified antibodies were confirmed by enzyme-linked immunosorbent assay. The LD50 as well as HD50 concentration of the crude venom were obtained to be 45 µg and 120 µg/ml, respectively. C69 neutralized 48% of the hemolysis activity of M. lebetina venom and C37 survived 66% of mice after 115 min of envenoming. Taken together, the results indicate the potential of human non-immune libraries for selection of functional antibodies against M. lebetina venom. (ttps://pubmed.ncbi.nlm.nih.gov/33905804/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Institut Pasteur in Iran

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33905804/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Macrovipera lebetina (Kufi, Levant viper, Levantine viper)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Iran
Regions	Middle East

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Macrovipera lebetina (Kufi, Levant viper, Levantine viper)	Macrovipera lebetina (Kufi, Levant viper, Levantine viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Haemorrhagic (bleeding)

Human scFv (B7, C11, and E9) (against Bothrops jararacussu and Crotalus durissus terrificus)

Alternative name(s): Recombinant human single chain variable fragment antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1745

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Bothrops jararacussu (Jararacussu); Crotalus durissus terrificus (South American rattlesnake)

Route of administration: Not yet determined

Ig format: Single-chain variable fragments (scFv)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments (including scFvs) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibody fragments; immunological factors; antivenin; antidotes

Key features and challenges:

Single chain variable antibody fragments (scFvs) are fusion proteins of the variable regions of the heavy and light chains of an antibody (VH and VL) connected with a short linker peptide of 10–25 amino acids. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Human scFv candidate/s (B7, C11 and E9) - 'Cro-Borthrumabs' - against B. jararacussu and C. d. terrificus were developed as follows: Human scFv that recognize both bothropic and crotalic crude venoms were identified via phage display. Promising purified scFvs (B7, C11 and E9), named ‘Cro-Bothrumabs', were tested for neutralizing capacity in vitro and in vivo. Cross-reactivity of Cro-Bothrumabs were demonstrated by ELISA and in vitro and in vivo experiments that showed that a combination of scFvs neutralizes in vitro toxic activities (e.g. indirect hemolysis and plasma-clotting) of crotalic and bothropic venoms as well as prolonged survival time of envenomed animals. (https://pubmed.ncbi.nlm.nih.gov/28887121/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: University of Sao Paulo (USP) (including FUSP and HCFMUSP)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/28887121/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Bothrops jararacussu (Jararacussu); Crotalus durissus terrificus (South American rattlesnake)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Brazil
Regions	South America

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops jararacussu (Jararacussu); Crotalus durissus terrificus (South American rattlesnake)	Bothrops jararacussu (Jararacussu); Crotalus durissus terrificus (South American rattlesnake)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Haemorrhagic (bleeding),Procoagulant (blood clotting)

Human scFv (C13, C24, C39, C43, and C45) (against Naja oxiana)

Alternative name(s): Recombinant human single chain variable fragment antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1839

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Naja oxiana

Route of administration: Not yet determined

Ig format: Single-chain variable fragments (scFv)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments (including scFvs) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibody fragments; immunological factors; antivenin; antidotes

Key features and challenges:

Single chain variable antibody fragments (scFvs) are fusion proteins of the variable regions of the heavy and light chains of an antibody (VH and VL) connected with a short linker peptide of 10–25 amino acids. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Human scFv candidate/s (C13, C24, C39, C43, and C45) against Naja oxiana was developed as follows: A human antibody library (non-immunized library) was used to isolate specific antibodies against N. oxiana venom components. Four rounds of biopanning were performed to enrich scFv-displaying phages against the venom of N. oxiana. Enrichment of scFv-displaying phages against N. oxiana venom was analysed by polyclonal Enzyme-Linked Immunosorbent Assay (ELISA). Specific antibody fragments against N. oxiana venom were selected through monoclonal ELISA, and were expressed in E. coli bacterial cells. Purification of the selected clones was performed by using nickel affinity chromatography. Neutralization and protective capacity of specific antibody fragments were analysed in C57BL/6 mice (i.v. injection). Results of biopanning and polyclonal ELISA demonstrate a successful enrichment process. Five specific antibody fragments with the highest signal in monoclonal ELISA were selected, expressed, and purified (C13, C24, C39, C43, and C45). The purity of expressed antibody fragments was monitored by SDS-PAGE and Western blot. The selected antibody fragments were able to neutralize two LD50 of N. oxiana venom and protected all mice when injected 15 min post-envenomation. (https://pubmed.ncbi.nlm.nih.gov/31622638/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Institut Pasteur in Iran

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/31622638/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Naja oxiana (Iranian cobra)
Snake family	Elapidae
Risk category	Both Category 1 & 2
Countries	Iran
Regions	Middle East

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja oxiana (Iranian cobra); Macrovipera lebetinus (Levantine Viper); Echis carinatus (Saw-scaled viper); Pseudocerastes persicus (Persian horned viper)	Naja oxiana (Iranian cobra)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Human scFv (G12F3) (against Naja oxiana)

Alternative name(s): Recombinant human single chain variable fragment antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1704

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: two (f3 and F4) toxic fractions of Iranian cobra (Naja oxiana) snake venom containing phospholipase A2 (PLA2)

Route of administration: Not yet determined

Ig format: Single-chain variable fragments (scFv)

Ig final product type/preparation: Unknown

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments (including scFvs) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibody fragments; immunological factors; antivenin; antidotes

Key features and challenges:

Single chain variable antibody fragments (scFvs) are fusion proteins of the variable regions of the heavy and light chains of an antibody (VH and VL) connected with a short linker peptide of 10–25 amino acids. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Human scFv candidate (G12F3) against Naja oxiana was developed as follows: Toxic fractions from cobra venom were prepared by chromatography and used as targets in phage display to isolate recombinant antibodies from a human scFv library. Candidate antibodies were expressed in E. coli HB2151 and purified by IMAC chromatography. The selected clones were analyzed in vivo and in vitro experiments. Venom toxicity was contained in two fractions. Around a hundred phage clones were isolated against each fraction, those showing the best promise were G12F3 and G1F4. While all chosen clones showed low but detectable neutralizing effect against Naja oxiana venom, clone G12F3 could inhibit PLA2 activity. (https://pubmed.ncbi.nlm.nih.gov/32695146/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Razi Vaccine and Serum Research Institute, Agricultural Research, Education and Extension Organization (AREEO)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/32695146/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Naja oxiana (Central Asian cobra, Transcaspian cobra)
Snake family	Elapidae
Risk category	Both Category 1 & 2
Countries	Iran
Regions	Middle East

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja oxiana (Central Asian/Iranian cobra)	Naja oxiana (Central Asian/Iranian cobra)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Not specified

Humanised murine mAbs (against venom-induced consumption coagulopathy) (Project)

Alternative name(s): mAbs; universal antivenom to treat snake venom-induced consumption coagulopathy

Chemical name: N/A

CAS number: N/A

PCR ID: 1482

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Venom-induced consumption coagulopathy (VICC)-induding toxins

Route of administration: Not yet determined

Ig format: Ig

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/).

Murine monoclonal antibodies (against venom-induced consumption coagulopathy) is a pathology-specific candidate intended to treat snake venom-induced consumption coagulopathy (VICC). It is being developed as part of a research programme under the Liverpool School of Tropical Medicine funded by the Wellcome Trust. The programme includes the following: The aim is to develop a single, pathology-specific, antivenom to be used throughout the world for treating venom-induced consumption coagulopathy caused by snakebite. The specific goals are: To identify the venom constituents that cause procoagulant bioactivities induced by different snake venoms; To determine whether a panel of murine monoclonal antibodies can neutralise procoagulation irrespective of snake species; To demonstrate proof of concept for humanising murine monoclonal antibodies specific to venom toxins. The team will characterise the specific venom toxins found in different snake species that cause VICC using small-scale proteomics and biochemical assays, and then design epitope-string immunogens to stimulate the production of antibodies specific to those toxins. Next, a monoclonal antibody approach will be employed to generate a first of its kind, pathology specific, antivenom that will be validated pre-clinically for future worldwide use for treating VICC. (https://wellcome.org/grant-funding/people-and-projects/grants-awarded/developing-universal-antivenom-treat-snake)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: Liverpool School of Tropical Medicine (LSTM)

Key funders: Wellcome

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Unknown
Snake family	
Risk category	Unknown
Countries	
Regions	

Immunizing venom protocol/strategy:

Production technique and/or immunization strategy: Peptide/toxin epitope string murine immunization for antibody production, followed by recombinant antibody development for humanised murine mAbs

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Unknown	Unknown
Snake family		
Risk category		Unknown

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Procoagulant (blood clotting)

PEO-1 plantivenom (camelid VHH, plant expressed) (against Bothrops asper)

Alternative name(s): Plant-made recombinant polyclonal antibodies; PEO_1; pluribodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1693

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Bothrops asper

Route of administration: Not yet determined

Ig format: VHH

Ig final product type/preparation:

Thermostability: Thermostable properties, temperature unknown

Mechanism of action: Antibodies or antibody fragments (including VHHs, and plant expressed 'pluribodies') bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes; Plantibodies

Key features and challenges:

VHH antibodies (or nanobodies) are the antigen binding fragments of heavy chain only antibodies. Camelids naturally produce antibodies composed only of heavy chains in which the target recognition module is composed of a single variable domain (VHH or Nb). Advantageous features of nanobodies include their small size, high solubility, high stability, and excellent tissue penetration in vivo (https://pubmed.ncbi.nlm.nih.gov/29213270/). Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/). To scale this production efficiently and cost-effectively, an approach is to employ plant-made recombinant polyclonal antibodies (termed pluribodies). The strategy takes advantage of virus superinfection exclusion to induce the formation of somatic expression mosaics in agroinfiltrated plants, which enables the expression of complex antibody repertoires (including camelid VHH) in a highly reproducible manner, to produce 'plantivenom'. (https://pubmed.ncbi.nlm.nih.gov/28850773/)

PEO-1 plantivenom (plant expressed camelid VHH) candidate against Bothrops asper was developed as follows: Pluribodies were developed using toxin-binding genetic information captured from peripheral blood lymphocytes of hyperimmunized camels to Bothrops asper venom, which recapitulated the overall binding activity of the immune response. Furthermore, an improved plant-made antivenom (plantivenom) was formulated using an in vitro selected pluribody against Bothrops asper snake venom toxins and was shown to neutralize a wide range of toxin activities and provide protection against lethal venom doses in mice. (https://pubmed.ncbi.nlm.nih.gov/28850773/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Valencia Polytechnic University (Universidad Politécnica de Valencia (UPV)); University of Costa Rica (including the Clodomiro Picado Institute)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/28850773/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Bothrops asper (Fer-de-lance); Crotalus scutulatus (Mohave rattlesnake); Crotalus simus (Central American rattlesnake)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Costa Rica
Regions	Central America

Immunizing venom protocol/strategy: Polyspecific (broad spectrum, multi-snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display, and plant expressed

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops asper (Fer-de-lance)	Bothrops asper (Fer-de-lance)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding)

scFvBaP1 (plant expressed) (against Bothrops asper)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1867

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: BAP1 Bothrops asper metalloproteinase 1

Route of administration: Not yet determined

Ig format: Single-chain variable fragments (scFv)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments (including scFV) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Single chain variable antibody fragments (scFvs) are fusion proteins of the variable regions of the heavy and light chains of an antibody (VH and VL) connected with a short linker peptide of 10–25 amino acids. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

scFvBaP1 (plant expressed) candidate (against Bothrops asper) was developed as follows: First, a recombinant scFv against BaP1 (scFvBaP1) from the venom of the pit viper B. asper was generated. BaP1 is an abundant P-I snake venom 6 metalloproteinase (SVMP) in the venom of B. asper. This toxin plays a relevant role in the associated local tissue damage. The scFvBaP1 was produced from the mRNA isolated from the BaP1-8 monoclonal antibody producing cells (MABaP1-8), expressed in Escherichia coli cytoplasm, and possesses neutralizing activities similar to those of the original monoclonal antibody. In this respect, the fragment was able to recognize the Bap1 toxin present in the venom of B. asper and neutralize its haemorrhagic, fibrinolytic, myotoxic and displayed pro12 inflammatory properties (https://pubmed.ncbi.nlm.nih.gov/30802471/). However, the main disadvantage of that scFvBaP1 was its low yield, which made its large-scale pharmaceutical production unfeasible. In a follow up experiment, the team developed high production levels of a recombinant single chain antibody fragment (scFv) deduced and modified from scFvBaP1, expressed transiently and stably in transgenic plants and in vitro cultures (callus and suspension cells). The antibodies produced by N. benthamiana cells possess neutralizing activities similar to those of the original scFvBaP1 antibody. The ability of the scFvBaP1 fragment to recognize the venom toxins was demonstrated by the ELISA assay. The fragment was capable of recognizing the homologous BaP1 toxin, present in the total venom of B. asper, as well as the isolated BnP1 and Atroxlysin Ia toxins, two related P-I-class SVMPs isolated from venoms of other species of Bothrops snakes: B. neuwiedi and B. atrox, respectively. (https://pubmed.ncbi.nlm.nih.gov/24887282/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Universidade Federal de Juiz de Fora

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/24887282/ https://pubmed.ncbi.nlm.nih.gov/30882471/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Bothrops asper (Barba amarilla, Cascabelle, Fer-de-lance)
Snake family	Viperidae
Risk category	Both Category 1 & 2
Countries	Brazil
Regions	South America

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production, then expressed in plants

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops asper (Barba amarilla, Cascabelle, Fer-de-lance); Bothrops neuwiedi (Cabeça-de-capanga, Jaraquinha); Bothrops atrox (Caiçaca, Common lancehead)	Bothrops asper (Barba amarilla, Cascabelle, Fer-de-lance); Bothrops neuwiedi (Cabeça-de-capanga, Jaraquinha); Bothrops atrox (Caiçaca, Common lancehead)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding)

scFv-Svmp (chicken derived, plant expressed) (against Bothrops pauloensis)

Alternative name(s): Recombinant chicken single chain variable fragment antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1838

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Bothrops pauloensis and neuwiedase metalloproteinase

Route of administration: Not yet determined

Ig format: Single-chain variable fragments (scFv)

Ig final product type/preparation:

Thermostability: Unknown

Mechanism of action: Antibodies or antibody fragments (including scFV) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

Single chain variable antibody fragments (scFvs) are fusion proteins of the variable regions of the heavy and light chains of an antibody (VH and VL) connected with a short linker peptide of 10–25 amino acids. Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

svFv-Svmp (chicken derived, plant expressed) candidate against Bothrops pauloensis was developed as follows: Chickens were immunized with B. pauloensis crude venom to select antibodies capable of neutralizing toxin activity. After expressing the scFv library in phage particles, selection of specific antibodies was carried out by panning against B. pauloensis crude venom. Four clones with greater signal intensity were selected for further analysis. The specificity of these selected clones (C5, F1, F5 and F8) to B. pauloensis crude venom and metalloproteinase purified neuwiedase was determined by ELISA. clone C5, called scFv-Svmp, for further testing. The transgenic N. tabacum plants were obtained from stable transformation with scFv -Svmp sequence expression. The ability of single-chain variable fragment (scFv) molecules to inhibit fibrinogenolytic, azocaseinolytic, coagulant and haemorrhagic actions of snake venom metalloproteinases (SVMPs) contained in B. pauloensis venom was verified through proteolytic assays. The antibody neutralized the toxic effects of envenomation, particularly those related to systemic processes, by interacting with one of the predominant classes of metalloproteinases. (https://pubmed.ncbi.nlm.nih.gov/32035152/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Federal University of Uberlandia

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/32035152/

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Bothrops pauloensis (São Paulo Lancehead)
Snake family	Viperidae
Risk category	Category 2 (Secondary Medical Importance)
Countries	Brazil
Regions	South America

Immunizing venom protocol/strategy: Monospecific (single snake venom specificity)

Production technique and/or immunization strategy: Recombinant antibody production via phage display, then expressed in tobacco plants

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	B. pauloensis (São Paulo Lancehead), B. moojeni (Brazilian lancehead), B. leucurus (Bahia lancehead), B. jararaca (Caiçaca), B. jararacussu (Jararacussu); Crotalus durissus collilineatus (Central American Rattlesnake)	B. pauloensis (São Paulo Lancehead), B. moojeni (Brazilian lancehead), B. leucurus (Bahia lancehead), B. jararaca (Caiçaca), B. jararacussu (Jararacussu); Crotalus durissus collilineatus (Central American Rattlesnake)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding),Procoagulant (blood clotting)

Vipax (synthetically evolved camelid nanobody-based antivenom)

Alternative name(s): Synthetically evolved nanobodies (SENs); VHHs; single-domain antibodies

Chemical name: N/A

CAS number: N/A

PCR ID: 1461

Technical profile

Biologics > Immunoglobulin products - recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Multiple snake species toxin: Unspecified medically important snakes across Asia, Africa, South America, and the U.S)

Route of administration: Not yet determined

Ig format: VHH

Ig final product type/preparation:

Thermostability: Thermostable properties, temperature unknown

Mechanism of action: Antibodies or antibody fragments (including VHHs) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant antibodies; immunological factors; antivenin; antidotes

Key features and challenges:

VHH antibodies (or nanobodies) are the antigen binding fragments of heavy chain only antibodies. Camelids naturally produce antibodies composed only of heavy chains in which the target recognition module is composed of a single variable domain (VHH or Nb). Advantageous features of nanobodies include their small size, high solubility, high stability, and excellent tissue penetration in vivo (https://pubmed.ncbi.nlm.nih.gov/29213270/). Recombinant antibodies and antibody fragments offer a potentially more efficient, antitoxin specific, and less immunogenic alternative to traditional plasma-derived antivenoms for snakebite envenoming. Antibody or antibody fragments to particular toxins can be identified and selected via hybridoma cell lines or biopanning of phage display libraries (whether human, murine, llama, chicken etc). (https://pubmed.ncbi.nlm.nih.gov/29534892/)

Venomyx Therapeutics, Inc. is funded by US NIH in collaboration with the Chang lab at UCSD to exploit a powerful platform to discover Synthetically Evolved Nbs (SENs) for high affinity and efficacy against venom targets of interest. The collaboration intends to generate low-cost, thermostable, broadly-effective Nbs against snake venom toxin (https://reporter.nih.gov/project-details/10255596). Venomyx' lead product - called Vipax (http://www.venomyx.com/our-research) - has shown promising results in preclinical studies against Naja kouthia venom, C. adamanteus venom, and other toxins from medically important snakes across Asia, Africa, South America and the US. (https://www.sec.gov/Archives/edgar/data/1755717/000167025418000499/document_8.pdf)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Venomyx Therapeutics; University of California, San Diego (UCSD)

Preclinical sources:
https://www.sec.gov/Archives/edgar/data/1755717/000167025418000499/document_8.pdf

Evidence of clinical trials? No

Production/source

	Derived from
Snake species	Unknown
Snake family	
Risk category	Unknown
Countries	
Regions	

Immunizing venom protocol/strategy:

Production technique and/or immunization strategy: Recombinant antibody production, details unclear

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja kouthia (Monocled cobra); Crotalus adamanteus (Eastern diamondback rattlesnake); others unspecified	Naja kouthia (Monocled cobra); Crotalus adamanteus (Eastern diamondback rattlesnake); others unspecified
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Non-immunoglobulin products – animal/naturally derived/recombinant

BJ46a (endogenous SVMPI) (against Bothrops jararaca)

Alternative name(s): Endogenous snake venom metalloendopeptidase inhibitor

Chemical name: N/A

CAS number: N/A

PCR ID: 1859

Include in data set: Yes

Technical profile

Biologics > Non-immunoglobulin products - animal/naturally derived; recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: SVMP jararhagin: Bothrops jararaca venom

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Peptides and proteins (synthetic or naturally derived) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Proteins

Key features and challenges:

Therapeutic proteins (synthetic or naturally derived) can bind specific components/toxins (antigens) within snake venom to neutralize its effects. Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other approaches are being investigated for novel therapeutics (natural or synthetic) that have have higher specificity and lower immunogenicity. Many venomous and nonvenomous snake species are naturally resistant to the deleterious actions of snake venom components. In many cases, this is due to the presence of specific antitoxins circulating in their blood. These alexeteric factors are proteins generated in the snake's liver, with native molecular masses ranging from 75 to 180 kDa, and include PLA2 inhibitors and SVMP inhibitors.

The natural resistance of the South American pit viper Bothrops jararaca to its venom is partly attributed to BJ46a, a natural snake venom metalloendopeptidase inhibitor (SVMPI). Upon complex formation, BJ46a binds non-covalently to the metalloendopeptidase, rendering it unable to exert its proteolytic activity. However, the structural features that govern this interaction are largely unknown. Upstream discovery work has applied structural mass spectrometry techniques (cross-linking-MS and hydrogen-deuterium exchange MS) and in silico analyses (molecular modeling, docking, and dynamics simulations) to understand the interaction between BJ46a and jararhagin, a metalloendopeptidase from B. jararaca venom. Commerical application of endogenous proteins is limited, however the structural understanding of snake venom metalloendopeptidases inhibition by BJ46a through this work supports the rational design of drugs to improve anti-snake venom therapeutics. (https://pubmed.ncbi.nlm.nih.gov/32247172/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: Oswaldo Cruz Foundation (FIOCRUZ), Fundação Oswaldo Cruz

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/32247172/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops jararaca (Jararaca)	Bothrops jararaca (Jararaca)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Not specified

Naked DNA (Calf thymus)

Alternative name(s): Calf thymus DNA; CT DNA

Chemical name: N/A

CAS number: 91080-16-9

PCR ID: 1686

Include in data set: Yes

Technical profile

Biologics > Non-immunoglobulin products - animal/naturally derived; recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Hyaluronidase; SVMPs; PLA2

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Unknown

MeSH headings / pharmacological class: DNA

Key features and challenges:

Calf Thymus DNA Solution was originally developed for use in hybridization protocols as a blocking agent to reduce the non-specific binding of a hybridization probe to the surface of the filter. It is not designed to serve as a DNA standard or reference solution, but is used and available commercially. Calf Thymus DNA Solution is prepared from highly pure, phenol-chloroform extracted DNA, and DNase-free, RNase-free (DEPC-treated), distilled, deionized water. Once dissolved, the DNA solution is sheared to an average size of ≤ 2000 bp. (https://assets.fishersci.com/TFS-Assets/LSG/manuals/15633019_Calf_Thymus_DNA_solution_man.pdf)

Leveraging a previous study that demonstrated a strong interaction between DNA and E. carinatus venom, investigators have directly tested the effect of DNA on E. carinatus venom. Calf thymus DNA interacted strongly with E. carinatus venom and inhibits its enzymatic and pharmacological activities such as proteolytic, haemolytic, hyaluronidase, L-amino acid oxidase, NETosis, haemorrhage, pro-coagulant, and lethality. Further, using immunoblots and immunofluorescence, the study demonstrates the inhibition of proteolytic cleavage of several surface receptors on PMNs, PBMCs, and platelets by the DNA. This study demonstrates the possible therapeutic application of it during snakebite management. (https://pubmed.ncbi.nlm.nih.gov/29425807/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: University of Mysore

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/29425807/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Echis carinatus (Saw-scaled viper)	Echis carinatus (Saw-scaled viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs,PLA2s,Hyaluronidase

Syndromic profiles: Haemorrhagic (bleeding),Procoagulant (blood clotting)

rAnti-3FTX nAChR-binding proteins (Ls-AChBP and humanized α7-AChBP)

Alternative name(s): nAChBPs; Nicotinic acetylcholine binding proteins; Recombinant AChBP from Lymnaea stagnalis and a humanized neuronal α7 version (α7-AChBP); nAChR receptor mimics; nAChR decoy receptors; Decoy nAChRs receptor mimics/inhibitor drug

Chemical name: N/A

CAS number: N/A

PCR ID: 1840

Include in data set: Yes

Technical profile

Biologics > Non-immunoglobulin products - animal/naturally derived; recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: 3FTXs: Elapid spp venom

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Peptides and proteins (synthetic, recombinant or naturally derived) bind specific components/toxins (antigens) within snake venom to neutralize its effects.

MeSH headings / pharmacological class: Proteins; decoy receptor mimics

Key features and challenges:

Therapeutic proteins (synthetic, recombinant or naturally derived) can bind specific components/toxins (antigens) within snake venom to neutralize its effects. Neurotoxic snake venoms contain small neurotoxins, including three-finger toxins (3FTxs), which can cause rapid paralysis in snakebite victims by blocking postsynaptic transmission via nicotinic acetylcholine receptors (nAChRs). These toxins are typically weakly immunogenic and thus are often not effectively targeted by current polyclonal antivenom therapies. nAChR mimics, also known as acetylcholine binding proteins (AChBPs), could potentially effectively capture 3FTxs and therefore be developed as a novel class of snake-generic therapeutics for combatting neurotoxic envenoming. (https://pubmed.ncbi.nlm.nih.gov/31417406/)

Recombinant anti-3FTX nAChR-binding proteins - one from Lymnaea stagnalis (Ls-AChBP) and another humanized α7-AChBP - were developed and tested in a decoy receptor approach as follows: First, the binding specificities of 3FTx from various medically important elapid snake venoms to nAChR were identified using two recombinant nAChR mimics: the AChBP from Lymnaea stagnalis and a humanized neuronal α7 version (α7-AChBP). Next these AChBP-bound and unbound fractions were characterised using SDS-PAGE and mass spectrometry. Interestingly, both mimics effectively captured long-chain 3FTxs from multiple snake species but largely failed to capture the highly related short-chain 3FTxs, suggesting a high level of binding specificity. Next nAChR mimics were investigated as to whether they could be used as snakebite therapeutics. It showed that while α7-AChBP alone did not protect against Naja haje (Egyptian cobra) venom lethality in vivo, it significantly prolonged survival times when co-administered with a nonprotective dose of antivenom. Thus, nAChR mimics are capable of neutralizing specific venom toxins and may be useful adjunct therapeutics for improving the safety and affordability of existing snakebite treatments by reducing therapeutic doses. (https://pubmed.ncbi.nlm.nih.gov/31417406/)

Wellcome is funding KU Leuven for a project entitled 'Decoy nAChRs receptor mimics/inhibitor drug (KU Leuven, Belgium).

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Catholic University of Leuven, (KU Leuven) (including the Rega Institute for Medical Research); VU University Amsterdam (Vrije Universiteit) (including Athena Institute and Medical Center); Liverpool School of Tropical Medicine (LSTM)

Key funders: Wellcome

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/31417406/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	N. haje; N. naja; N. kaouthia; D. viridis; B. caeruleus; M. fulvius; O. s. scutellatus	N. haje (delayed survival)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: 3FTxs

Syndromic profiles: Not specified

rBaltMIP (alpha snake blood PLA2 inhibitor) (from Bothrops alternatus)

Alternative name(s): Recombinant sbPLIs; αsbPLIs

Chemical name: N/A

CAS number: N/A

PCR ID: 2174

Include in data set: Yes

Technical profile

Biologics > Non-immunoglobulin products - animal/naturally derived; recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Peptides and proteins (synthetic, recombinant or naturally derived) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Recombinant proteins

Key features and challenges:

Therapeutic proteins (synthetic or naturally derived) can bind specific components/toxins (antigens) within snake venom to neutralize its effects. Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other approaches are being investigated for novel therapeutics (natural or synthetic) that have have higher specificity and lower immunogenicity. Many venomous and nonvenomous snake species are naturally resistant to the deleterious actions of snake venom components. In many cases, this is due to the presence of specific antitoxins circulating in their blood. These alexeteric factors are proteins generated in the snake's liver, with native molecular masses ranging from 75 to 180 kDa. These non-immunoglobulin antitoxins are PLA2 inhibitors (i.e., snake blood phospholipase A2 inhibitors, sbPLIs) and are used to protect the snake from the internal or external envenomation. These sbPLIs can be classified into three groups based on the homology of their amino acid sequence: α, β and γ. Since their discovery, there have been at least 15 kinds of αsbPLIs have been discovered in the different venomous snake families, four kinds of βsbPLIs have been found in three snake species, and twenty-three types of γsbPLIs in venomous and nonvenomous species. (https://pubmed.ncbi.nlm.nih.gov/29318152/)

Recombinant BaltMIP - an alpha snake blood PLA2 inhibitor originally derived from Bothrops alternatus - was developed and tested as as a potential candidate to complement the antivenom therapy as follows: Biochemical experiments showed that rBaltMIP presented pI 5.8 and molecular masses of ~21 kDa by SDS-PAGE and 19.57 kDa by MALDI/TOF MS. After tryptic peptides sequencing, the results were compared with other PLIs available in databases, showing 100% identity between rBaltMIP and its native inhibitor BaltMIP and from 92% to 96% identity with other inhibitors. Myotoxic activities of BthTX-I and BthTX-II toxins were measured via plasma CK levels, showing myotoxic effective concentrations (EC50) of 0.1256 µg/µL and 0.6183 µg/µL, respectively. rBaltMIP neutralized the myotoxicity caused by these two toxins up to 65%, without promoting primary antibody response against itself. Nevertheless, this recombinant PLI was immunogenic when standard immunization protocol with Freud's adjuvant was used. In paw edema assays, EC50 of 0.02581 µg/µL and 0.02810 µg/µL, respectively, were observed with edema reductions of up to 40% by rBaltMIP, suggesting its use as an additional antivenom. In addition, myotoxicity neutralization experiments with

the myotoxin BthTX-I showed that rBaltMIP was more effective in inhibiting muscle damage than the conventional antivenom. Thus, considering the severity of envenomations due to Bothrops alternatus (Rhinocerophis alternatus) and the low neutralization of their local effects (such as myotoxicity) by the current antivenoms, rBaltMIP is a promising molecule for the development of novel therapeutic strategies for clinical applications. (https://pubmed.ncbi.nlm.nih.gov/28327300/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Brazilian State University Paulista, Universidade Estadual Paulista (Unesp)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/28327300/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Borthops jararacussu (Jararacussu) (BthTX-I and BthTX-II toxins)	Borthops jararacussu (Jararacussu) (BthTX-I and BthTX-II toxins)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Not specified

rDM64 / DM64 protein (from opossum protein DM64)

Alternative name(s): Recombinant DM64 acidic glycoprotein isolated from serum of the opossum; Acidic glycoprotein isolated from serum of the opossum Didelphis aurita

Chemical name: N/A

CAS number: N/A

PCR ID: 1694

Include in data set: Yes

Technical profile

Biologics > Non-immunoglobulin products - animal/naturally derived; recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Myotoxin II (PLA2): Bothrops asper venom

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Peptides and proteins (synthetic or naturally derived) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Proteins

Key features and challenges:

Therapeutic proteins (synthetic or naturally derived) can bind specific components/toxins (antigens) within snake venom to neutralize its effects. Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other approaches are being investigated for novel therapeutics (natural or synthetic)that are cheaper, capable of rapid production, and have have higher specificity and lower immunogenicity. The South American Opossum (Didelphis aurita) is able to survive the bite of the Bothrops species. Several laboratories have purified proteins from the serum of opossum species and showed these proteins could neutralize various toxic components of cytotoxic snake venoms. Two virtually identical antihemorrhagic proteins isolated from either the North American opossum (D. virginiana) or the South American big-eared opossum (D. aurita), termed oprin or DM43 respectively, inhibit specific snake venom metalloproteinases (SVMPs) (https://pubmed.ncbi.nlm.nih.gov/33581173/), while DM64 from D. aurita can completely prevent myofiber breakdown caused by myotoxins I (Asp49) and II (Lys49) (PLA2) of B. asper venom. (https://pubmed.ncbi.nlm.nih.gov/27216643/)

Recombinant DM64 protein is from opossum protein oprin/DM64 recombinantly expressed in Pichia pastoris yeast, and was developed as follows: DM64 is an acidic glycoprotein isolated from Didelphis aurita (opossum) serum that has been characterized as an inhibitor of the myotoxicity induced by bothropic toxins bearing phospholipase A2 (PLA2) structures. (https://pubmed.ncbi.nlm.nih.gov/27216643/). This antitoxic protein can serve as an excellent starting template for the design of novel therapeutics against snakebite envenomation, particularly venom-induced local tissue damage. Therefore, the aim of this work was to produce a recombinant DM64 (rDM64) in the methylotrophic yeast Pichia pastoris and to compare its biological properties with those of native DM64. Yeast fermentation in the presence of Pefabloc, a serine protease inhibitor, stimulated cell growth (~1.5-fold), increased the rDM64 production yield approximately 10-fold and significantly reduced the susceptibility of rDM64 to proteolytic degradation. P. pastoris fermentation products were identified by mass spectrometry and Western blotting. The heterologous protein was efficiently purified from the culture medium by affinity chromatography (with immobilized PLA2

myotoxin) and/or an ion exchange column. Although both native and recombinant DM64 exhibit different glycosylation patterns, they show very similar electrophoretic mobilities after PNGase F treatment. rDM64 formed a noncovalent complex with myotoxin II (Lys49-PLA2) from Bothrops asper and displayed biological activity that was similar to that of native DM64, inhibiting the cytotoxicity of myotoxin II by 92% at a 1:1 molar ratio. (https://pubmed.ncbi.nlm.nih.gov/28759578/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Oswaldo Cruz Foundation (FIOCRUZ), Fundação Oswaldo Cruz

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/28759578/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops asper (Fer-de-lance)	Bothrops asper (Fer-de-lance)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Cytotoxic (tissue damage)

Recombinant endogenous snake toxin inhibitors (Project)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1480

Include in data set: Yes

Technical profile

Biologics > Non-immunoglobulin products - animal/naturally derived; recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Unspecified snake venom toxins

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Peptides and proteins (synthetic, recombinant or naturally derived) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Peptides; proteins

Key features and challenges:

Therapeutic proteins or peptides (short chains of amino acids linked by peptide bonds) bind specific components/toxins (antigens) within snake venom to neutralize its effects. In order to protect against auto-digestion by SVMPs, snake venom of several species are found to contain natural, endogenous protease inhibitors: citrate and small peptides. The latter bind selectively to SVMPs in the venom glands to protect glandular tissues and venom factors from self-digestion by SVMPs. As such, endogenous toxin inhibitors from snakes are of interest in studies of new treatment modalities for neutralization of the effect of toxins.

Recombinant endogenous snake toxin inhibitors from a variety of snakes are being investigated as potential therapeutics under a project by the University of Oxford funded by Wellcome. The project - called 'Utilising snake endogenous toxin inhibitors for the development of improved antivenom treatments' aims to: explore the use of snake inhibitors as antivenom components and to make steps towards developing a new method of production. This will involve identifying the toxins expressed in venom and the inhibitors expressed in body tissues. Once identified, candidate inhibitor proteins will be produced using human cell lines, requiring no live animals and possibly reducing the risk of immune reactions in patients. Experiments will then be carried out to test the effectiveness of these proteins in neutralising key effects of venoms which cause death. (https://wellcome.org/grant-funding/people-and-projects/grants-awarded/utilising-snake-endogenous-toxin-inhibitors). No other information is available.

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: University of Oxford

Key funders: Wellcome

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Unknown	Unknown
Snake family		
Risk category		N/A

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

rLTNF-11 peptide (from opossum protein oprin)

Alternative name(s): Lethal Toxin Neutralizing Factor (LTNF) 11-mer peptide; LTNF-11; LTNF11-CS; Didelphis virginiana

Chemical name: N/A

CAS number: N/A

PCR ID: 2026

Include in data set: Yes

Technical profile

Biologics > Non-immunoglobulin products - animal/naturally derived; recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Crotalus atrox / haemotoxic snake venom; SVMPs

Route of administration: Not yet determined

Thermostability: Formulations sought that have long term stability at room temperature and could be appropriate for delivery as a dry powder inhalable formulation or solubilized for alternative

Mechanism of action: Peptides and proteins (synthetic or naturally derived) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Peptides

Key features and challenges:

Therapeutic peptides are short chains of amino acids linked by peptide bonds. Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other approaches are being investigated for novel therapeutics (natural or synthetic)that are cheaper, capable of rapid production, and have have higher specificity and lower immunogenicity - such as peptides. The North American Opossum (Didelphis virginiana) is able to survive the bite of the C. atrox (CA) snake. Several laboratories have purified proteins from the serum of opossum species and showed these proteins could neutralize various toxic components of cytotoxic snake venoms (oprin, DM43, DM64). The N-terminus of several of these proteins was shown to be highly conserved. Work was published by B. Lipps demonstrating the ability of a short peptide composed of first 10–15 amino acids of one of these proteins (named Lethal Toxin Neutralizing Factor, LTNF) from the opossum serum to maintain the activity of the complete protein. (https://pubmed.ncbi.nlm.nih.gov/27718338/)

rLTNF-11 peptide is the first 11 amino acids of the Lethal Toxin Neutralizing Factor from opossum protein recombinantly expressed in E. coli. It was developed as follows: the 11-mer (LTNF-11) was expressed as a concatenated chain of eight peptides with a C-terminal 6xHIS tag to facilitate downstream purification of the peptide chain. The 11-mer was chosen because the eleventh amino acid is a unique tryptophan on the peptide and serves as a protease cleavage site to sever apart the peptides. On-column cleavage of the peptides was carried out and the final product was tested in mice and shown to have some neutralizing capacity against Crotalus atrox venom. LC/MS analysis of the product showed partial purification of the peptide. a Chemically synthesised version (LTNF11- CS) was also able to neutralize CA venom in mice when a lethal dose of the venom was pre-incubated with the peptide followed by intravenous injection. (https://pubmed.ncbi.nlm.nih.gov/27718338/). Further work is being undertaken with support from the US NIH, including research into formulations of the peptide that have long term stability at room temperature and could be appropriate for delivery as a dry powder inhalable formulation or solubilized for alternative delivery method.

(https://reporter.nih.gov/project-details/9560757). A process for producing highly purified rLTNF from E. coli has been developed. (https://pubmed.ncbi.nlm.nih.gov/30034071/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: San Jose State University (SJSU); Texas A&M University; Indian Institute of Technology Delhi (IIT Delhi)

Key funders: US National Institutes of Health (NIH)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/27718338/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotualus atrox (Western Diamondback rattlesnake)	Crotualus atrox (Western Diamondback rattlesnake)
Snake family		Viperidae
Risk category		Category 1 (Highest Medical Importance)

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

rOprin-like (DM43-like) protein (from opossum protein oprin/DM43)

Alternative name(s): Heterologous recombinant snake venom metalloproteinase inhibitor (based on opossum proteins oprin and DM43); Didelphis virginiana

Chemical name: N/A

CAS number: N/A

PCR ID: 1703

Include in data set: Yes

Technical profile

Biologics > Non-immunoglobulin products - animal/naturally derived; recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Crotalus atrox; SVMPs

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Peptides and proteins (synthetic or naturally derived) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Proteins

Key features and challenges:

Therapeutic proteins (synthetic or naturally derived) can bind specific components/toxins (antigens) within snake venom to neutralize its effects. Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other approaches are being investigated for novel therapeutics (natural or synthetic)that are cheaper, capable of rapid production, and have have higher specificity and lower immunogenicity. The North American Opossum (Didelphis virginiana) is able to survive the bite of the C. atrox (CA) snake. Several laboratories have purified proteins from the serum of opossum species and showed these proteins could neutralize various toxic components of cytotoxic snake venoms. Two virtually identical antihemorrhagic proteins isolated from either the North American opossum (D. virginiana) or the South American big-eared opossum (D. aurita), termed oprin or DM43 respectively, inhibit specific snake venom metalloproteinases (SVMPs). (https://pubmed.ncbi.nlm.nih.gov/33581173/)

Recombinant oprin-like (DM43-like) protein is from oprin/DM43, opossum protein, recombinantly expressed in E/ coli, and was developed as follows: The aim was to produce a recombinant snake venom metalloproteinase inhibitor (SVMPI) similar to the oprin and DM43 opossum proteins in Escherichia coli and determine if this bacterially produced protein inhibits the proteolytic properties of Western Diamondback rattlesnake (C. atrox) venom. The resulting heterologous SVMPI was produced with either a 6-Histidine or maltose binding protein (MBP) affinity tag on either the C-terminus or N-terminus of the protein, respectively. The presence of the solubility enhancing MBP affinity tag resulted in significantly more soluble protein expression. The inhibitory activity was measured using two complementary assays and the MBP labeled SVMPI showed 7-fold less activity as compared to the 6-Histidine labeled SVMPI. Thus, the bacterially derived SVMPI with an unlabeled N-terminus showed high inhibitory activity (IC50 = 4.5 μM). The use of a solubility enhancing MBP fusion protein construct appears to be a productive way to express sufficient quantities of this mammalian protein in E. coli for further study. (https://pubmed.ncbi.nlm.nih.gov/33581173/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Grand Valley State University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33581173/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotualus atrox (Western Diamondback rattlesnake)	Crotualus atrox (Western Diamondback rattlesnake)
Snake family		Viperidae
Risk category		Category 1 (Highest Medical Importance)

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

rTryptase β / Tryptase β (human mast cell tryptase)

Alternative name(s): Recombinant tryptase beta (human mast cell derived); Purified human mast cell tryptase

Chemical name: N/A

CAS number: N/A

PCR ID: 1835

Include in data set: Yes

Technical profile

Biologics > Non-immunoglobulin products - animal/naturally derived; recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom toxins (multiple): Agkistrodon contortrix contortrix; Crotalus atrox: Echis carinatus; Bothrops atrox; Daboia russelii; Naja pallida

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Peptides, enzymes and proteins (synthetic, recombinant or naturally derived) bind specific components/toxins (antigens) within snake venom to degrade, detoxify and neutralize its effects

MeSH headings / pharmacological class: N/A

Key features and challenges:

Therapeutic enzymes, proteins or peptides (short chains of amino acids linked by peptide bonds) bind specific components/toxins (antigens) within snake venom to detoxify, degrade and neutralize its effects. Mast cells constitute an innate immune mechanism to counteract the toxicity of venoms produced by various animals, including snakes. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8309910/) Mast cell proteinases, especially tryptase, have been shown to selectively cleaves venom toxins. (https://pubmed.ncbi.nlm.nih.gov/30038613/) Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other approaches - such as recombinant enzymes and proteins - are being investigated for novel therapeutics (natural or synthetic) that have higher specificity and lower immunogenicity.

Recombinant tryptase beta from human mast cells as developed and investigated for neutralizing ability as follows: Human skin mast cells (hsMCs) were isolated and purified. After stimulation with venoms, human mast cells were separated by centrifugation into isolated Tryptase β'. Recombinant human tryptase β was expressed in Pichia pastoris and isolated. The ability of human mast cell proteases to detoxify six venoms from a spectrum of phylogenetically distinct snakes. To this end, a zebrafish model was developed to assess effects on the toxicity of the venoms and characterized the degradation of venom proteins by mass spectrometry. All snake venoms tested were detoxified by degradation of various venom proteins by the mast cell protease tryptase β, and not by other proteases. Data showed that recombinant human tryptase β degrades and detoxifies a phylogenetically wide range of venoms, indicating that recombinant human tryptase could possibly be developed as a universal antidote to venomous snakebites. (https://pubmed.ncbi.nlm.nih.gov/30038613/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Charite - University Medicine Berlin, Charité – Universitätsmedizin Berlin

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/30038613/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Agkistrodon contortrix contortrix (Southern copperhead); Crotalus atrox (Western diamondback rattlesnake); Echis carinatus (Saw-scaled viper); Bothrops atrox (Common lancehead; Daboia russelii (Russell's viper); Naja pallida (Red spitting cobra)	Agkistrodon contortrix contortrix (Southern copperhead); Crotalus atrox (Western diamondback rattlesnake); Echis carinatus (Saw-scaled viper); Bothrops atrox (Common lancehead; Daboia russelii (Russell's viper); Naja pallida (Red spitting cobra)
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

saPLIγ (gamma snake blood PLA2 inhibitor) (from Sinonatrix annularis)

Alternative name(s): sbPLIγ from Sinonatrix annularis

Chemical name: N/A

CAS number: N/A

PCR ID: 1699

Include in data set: Yes

Technical profile

Biologics > Non-immunoglobulin products - animal/naturally derived; recombinant > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Peptides and proteins (synthetic or naturally derived) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Proteins

Key features and challenges:

Therapeutic proteins (synthetic or naturally derived) can bind specific components/toxins (antigens) within snake venom to neutralize its effects. Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other approaches are being investigated for novel therapeutics (natural or synthetic) that have have higher specificity and lower immunogenicity. Many venomous and nonvenomous snake species are naturally resistant to the deleterious actions of snake venom components. In many cases, this is due to the presence of specific antitoxins circulating in their blood. These alexeteric factors are proteins generated in the snake's liver, with native molecular masses ranging from 75 to 180 kDa. These nonimmunoglobulin antitoxins are PLA2 inhibitors (i.e., snake blood phospholipase A2 inhibitors, sbPLIs) and are used to protect the snake from the internal or external envenomation. These sbPLIs can be classified into three groups based on the homology of their amino acid sequence: α, β and γ. Since their discovery, there have been at least 15 kinds of αsbPLIs have been discovered in the different venomous snake families, four kinds of βsbPLIs have been found in three snake species, and twenty-three types of γsbPLIs in venomous and nonvenomous species (https://pubmed.ncbi.nlm.nih.gov/29318152/)

Snake venom PLA2s have been explored extensively to elucidate the potential for a novel, wide spectrum antivenom drug targeting svPLA2s (https://pubmed.ncbi.nlm.nih.gov/29318152/). SaPLIγ is a novel gamma phospholipase A2 inhibitor (PLI) recently isolated from Sinonatrix annularis, a Chinese endemic non-venomous snake (https://pubmed.ncbi.nlm.nih.gov/26546697/).To explore the neutralization effects of saPLIγ in snakebite envenomation, a dose equivalent to LD50 of Deinagkistrodon acutus, Agkistrodon halys and Naja atra venom with/without saPLIγ was inoculated into the gastrocnemius muscle of female Kunming mice. The ability of saPLIγ to inhibit myonecrosis and systemic toxicity were evaluated through investigations of muscle histopathology, and determination of the serum levels of creatine kinase (CK), lactate dehydrogenase isoenzyme1 (LDH1) and aspartate transferase (AST). Edema of the gastrocnemius muscle was evaluated by calculating the width difference between the inoculated limb and the contralateral leg. Desmin loss in the gastrocnemius muscle was determined by Western blot analysis. Co-immunoprecipitation and shotgun LC-MS/MS analyses were performed to identify venom proteins that interact with saPLIγ. All

the envenomed mice had significantly elevated serum CK, LDH1 and AST levels, whereas the levels were decreased significantly in the presence of saPLIγ. Histopathological evaluation of gastrocnemius muscle sections showed severe snake venom-induced damage, characterized by leukocyte infiltration and erythrocyte leakage, leading to local edema. Myonecrosis, hemorrhage and desmin loss were significantly attenuated by saPLIγ. SaPLIγ interacted with a wide range of venom proteins, including PLA2s, metalloproteinases and C type lectins, which may contribute to broad anti-venom effects. (https://pubmed.ncbi.nlm.nih.gov/28746861/)

Other indications investigated: Inflammation

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: Nanchang University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/28746861/ https://pubmed.ncbi.nlm.nih.gov/26546697/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Deinagkistrodon acutus (Chinese copperhead); Agkistrodon halys (Halys pitviper); Naja atra (Chinese cobra)	Deinagkistrodon acutus (Chinese copperhead); Agkistrodon halys (Halys pitviper); Naja atra (Chinese cobra)
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

Drugs

Therapeutic – synthetic

1-(2-methyl-8-naphthalen-1-yl-imidazo-[1,2-α]pyridin-3-yl)ethanone

Alternative name(s): Novel imidazopyridine derivative; 3f

Chemical name: 1-(2-methyl-8-naphthalen-1-yl-imidazo-[1,2-α]pyridin-3-yl)ethanone

CAS number: N/A

PCR ID: 1928

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: PLA2s

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; binds the active site of PLA2s

MeSH headings / pharmacological class: N/A

Key features and challenges:

Imidazole derivatives are the distinct class of heterocyclic compounds which exhibit remarkable pharmacological activities across a wide range of therapeutic targets.

A discovery/preclinical study has reported a high-yield one pot synthesis of 1-(2-methyl-8-aryl-substitued-imidazo[1,2-α]pyridin-3-yl)ethan-1-one. Subsequently, in silico mode-of-action analysis was performed, and predicted that the synthesized imidazopyridines targets Phospholipase A2 (PLA2). In vitro analysis confirmed the predicted target PLA2 for the novel imidazopyridine derivative1-(2-Methyl-8-naphthalen-1-yl-imidazo [1,2-α]pyridine-3-yl)-ethanone (compound 3f) showing significant inhibitory activity towards snake venom PLA2 with an IC50 value of 14.3 μM. The molecular docking analysis suggested that imidazopyridine compound was able to bind to the active site of the PLA2 with strong affinity, whose affinity values are comparable to nimesulide. Furthermore, the potential for oral bioavailability by Lipinski's Rule of Five was estimated. Hence, it is concluded that the compound 3f could be a lead molecule against snake venom PLA2. (https://pubmed.ncbi.nlm.nih.gov/26196520/; https://pubmed.ncbi.nlm.nih.gov/34565143/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: Bangalore University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/26196520/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russelii (Russel's viper)	Daboia russelii (Russel's viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Not specified

4-(2-aminoethyl) benzenesulfonyl fluoride hydrochloride (AEBSF)

Alternative name(s): N/A

Chemical name: 4-(2-aminoethyl)benzenesulfonyl fluoride;hydrochloride

CAS number: 30827-99-7

PCR ID: 1796

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: Serine proteinase (SVSP)

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; inhibits thrombin-like serine proteinase

MeSH headings / pharmacological class: Serine Proteinase Inhibitors

Key features and challenges:

AEBSF or 4-(2-aminoethyl)benzenesulfonyl fluoride hydrochloride is a water-soluble, irreversible serine protease inhibitor, which inhibits proteases like chymotrypsin, kallikrein, plasmin, thrombin, and trypsin (https://pubchem.ncbi.nlm.nih.gov/compound/186136). Due to its serine proteinase inhibiting properties, it is of interest in snakebite therapeutic research.

AEBSF is often used in snakebite studies to identify toxins (https://pubmed.ncbi.nlm.nih.gov/31509773/; https://pubmed.ncbi.nlm.nih.gov/34044056/). However in one preclinical study, AEBSF was used to assess the effect of inhibitors on the lethal activity and associated alterations induced by B. asper venom in mice. It was shown to significantly prolong the clotting time of a fibrinogen solution to which venom was added, evidencing the inhibition of a thrombin-like serine proteinase present in this venom. Likewise, after three hours of incubation, pBPB reduced by 80% the PLA2 activity of the venom, in agreement with inhibition of a myotoxic PLA2 isolated from B. asper venom. However it did not protect mice from lethality, and the times of death did not differ significantly from mice receiving venom alone. Further studies are required to determine the use of AEBSF for treatment of snakebite envenoming. (https://pubmed.ncbi.nlm.nih.gov/25447772/)

Other indications investigated: Inflammation; nerve degeneration

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: University of Costa Rica (including the Clodomiro Picado Institute)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/25447772/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops asper (Fer-de-lance)	Bothrops asper (Fer-de-lance)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVSPs

Syndromic profiles: Procoagulant (blood clotting)

4-benzoyl-3-hydroxyphenyl benzoate (BHB)

Alternative name(s): Benzoyl phenyl benzoate group

Chemical name: (4-benzoyl-3-hydroxyphenyl) benzoate

CAS number: 18803-25-3

PCR ID: 1888

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: N/A

Key features and challenges:

4-benzoyl-3-hydroxyphenyl benzoate (BHB) is a chemical compound analog of the scaffold class benzoyl phenyl benzoates. It has been reported as PLA2 inhibitor. Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other approaches are being investigated for novel therapeutics (natural or synthetic) that are cheaper, capable of rapid production, and have have higher specificity and lower immunogenicity - such a small toxin-binding synthetic molecules. BHB was identified in a 2016 integrated study involving homology modeling, molecular dynamics and molecular docking studies on VRV-PL-V (Vipera russellii venom phospholipase A2 fraction-V) belonging to Group II-B secretory PLA2 from Daboia russelli pulchella, in order to study the structure-based inhibitor design. The accuracy of the model was validated using multiple computational approaches. The molecular docking study of this protein was undertaken using different classes of experimentally proven, structurally diverse synthetic inhibitors of secretory PLA2 whose selection is based on IC50 value that ranges from 25 μM to 100 μM. Estimation of protein-ligand contacts by docking analysis sheds light on the importance of His 47 and Asp 48 within the VRV-PL-V binding pocket as key residue for hydrogen bond interaction with ligands. The virtual analysis revealed that compounds with different scaffold binds to the same active site region. ADME analysis was also further performed to filter and identify the best potential specific inhibitor against VRV-PL-V. Additionally, the e-pharmacophore was generated for the best potential specific inhibitor against VRV-PL-V and reported here. Based on virtual homology modeling, molecular dynamics, molecular docking and ADME approaches of representative synthetic analogs with diverse scaffolds from above mentioned groups, the authors reported BHB belonging to the benzoyl phenyl benzoate group as the best potential lead inhibitor against VRV-PL-V. BHB is believed to result in prevention of synthesis of all downstream pro-inflammatory mediators signifying prevention of local effects. It is further proposed that BHB backbone structural scaffold as obtained by the e-pharmacophore approach could serve as fragment building block in screening/molecular recognition of further new snake venom sPLA2 specific inhibitors that can potentially dually bind to both the pro-inflammatory response eliciting region and anti-coagulant eliciting region thereby effectively causing inhibition of sPLA2 and abrogating all the local effects due to Vipera Russelli snake venom lethality (https://pubmed.ncbi.nlm.nih.gov/26218369/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: Shanmugha Arts, Science, Technology & Research Academy (SASTRA University)

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	N/A	N/A
Snake family		
Risk category		N/A

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Not specified

Abiotic hydrogel nanoparticle (against Elapids)

Alternative name(s): Abiotic synthetic polymer nanoparticle; NP: PLA2 neutralizing synthetic polymer nanoparticle formulation; bioinspired synthetic nanoparticles as broad-spectrum antidotes with antibody-like affinity and improved toxin-neutralizing capacity

Chemical name: N/A

CAS number: N/A

PCR ID: 1473

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: PLA2; 3FTx: Elapids

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Nanoparticles bind toxins to prevent their spread throughout the body: binds and inhibits the catalytic activity of PLA2 and 3FTx

MeSH headings / pharmacological class: Nanoparticles

Key features and challenges:

Nanoparticles offer a potential inexpensive alternative to current antivenoms via sequestrants capable of broad-spectrum neutralization across various protein isoforms. The synthesis of abiotic protein/peptide affinity reagents have been developed as a novel approach.

This abiotic hydrogel nanoparticle has been engineered to bind to and modulate the activity of a diverse array of PLA2 and 3FTX isoforms found in Elapidae snake venoms. Preclinical studies have established that this abiotic synthetic polymer NP dose-dependently inhibits the dermo-necrotic activity of N. nigricollis venom, the most important clinical manifestation of envenoming by African spitting cobras (https://pubmed.ncbi.nlm.nih.gov/30286075/). This NP development is the follow on from earlier work from University of California Irvine and ICP in Costa Rica (https://pubmed.ncbi.nlm.nih.gov/27960254/) and also leverages work through a grant supported by the US Department of Defense to Luna Innovations to develop bioinspired synthetic nanoparticles as broad-spectrum antidotes with antibody-like affinity and improved toxin-neutralizing capacity (https://www.sbir.gov/node/983545).

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: University of California, Irvine; University of Costa Rica (including the Clodomiro Picado Institute); Luna Labs USA

Key funders: US Department of Defense (DOD)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/27960254/ https://pubmed.ncbi.nlm.nih.gov/30286075/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja mossambica (Mozambique spitting cobra); Naja nigricollis (Black-necked spitting cobra); Bungarus caeruleus (Indian krait); Dendroaspis polylepsis (Black mamba)	Naja mossambica (Mozambique spitting cobra); Naja nigricollis (Black-necked spitting cobra); Bungarus caeruleus (Indian krait); Dendroaspis polylepsis (Black mamba)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s,3FTxs,Dendrotoxins

Syndromic profiles: Neurotoxic (paralysis),Cytotoxic (tissue damage)

Abiotic synthetic nanoparticle TIMP-mimicking polymers (against SVMPs)

Alternative name(s): Abiotic Mimic of Endogenous Tissue Inhibitors of Metalloproteinases (TIMP); NP

Chemical name: N/A

CAS number: N/A

PCR ID: 2544

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: SVMPs

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Nanoparticles bind toxins to prevent their spread throughout the body: binds and inhibits the catalytic activity of SVMPs by mimicking endogenous tissue inhibitors of metalloproteinases

MeSH headings / pharmacological class: Nanoparticles

Key features and challenges:

Nanoparticles offer a potential inexpensive alternative to current antivenoms via sequestrants capable of broad-spectrum neutralization across various protein isoforms. The synthesis of abiotic protein/peptide affinity reagents have been developed as a novel approach.

A synthetic polymer nanoparticle (NP) that functions as an effective, broad-spectrum metalloproteinase inhibitor was developed as follows: Inhibition is achieved by incorporating three functional elements in the NP: a group that interacts with the catalytic zinc ion, functionality that enhances affinity to the substrate-binding pocket, and fine-tuning of the chemical composition of the polymer to strengthen NP affinity for the enzyme surface. The approach is validated by synthesis of a NP that sequesters and inhibits the proteolytic activity of snake venom metalloproteinases from five clinically relevant species of snakes. The mechanism of action of the NP mimics that of endogenous tissue inhibitors of metalloproteinases. (https://pubmed.ncbi.nlm.nih.gov/31918547/).

A follow on study engineered abiomimetic of endogenous tissue inhibitors of metalloproteinases (TIMPs) by introducing three binding elements to a synthetic tetrapolymer. The contribution of composition, size, and shape of the TIMP-mimicking polymers to the inhibition of BaP1, a P-I class snake venom metalloproteinase (SVMP), was evaluated. Inhibition was achieved when the size of the linear polymer (LP) was comparable to or greater than that of the enzyme, indicating the efficacy requires binding to a significant portion of the enzyme surface in the vicinity of the active site. The efficacy of a low cross-linked polymer hydrogel nanoparticle (NP) of substantially greater molecular weight was comparable to that of the LPs despite differences in size and shape, an important finding forin vivoapplications. The abiotic TIMP was effective against two classes of SVMPs in whole snake venom. The results can serve as a design principle for biomimetic polymer inhibitors of enzymes. (https://pubmed.ncbi.nlm.nih.gov/34181420/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: University of California, Irvine; University of Costa Rica (including the Clodomiro Picado Institute)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/31918547/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bitis arietans (Puff adder); Bitis gabonica (East African Gaboon viper); Echis ocellatus (Ocellated carpet viper); Echis carinatus (Saw-scaled viper); Crotalus atrox (Western diamondback rattlesnake)	Bitis arietans (Puff adder); Bitis gabonica (East African Gaboon viper); Echis ocellatus (Ocellated carpet viper); Echis carinatus (Saw-scaled viper); Crotalus atrox (Western diamondback rattlesnake)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Not specified

Acetylsalicylic acid (ASA)

Alternative name(s): Aspirin

Chemical name: 2-acetyloxybenzoic acid

CAS number: 50-78-2

PCR ID: 2208

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: PLA2: MjTX-I (Bothrops spp)

Route of administration: Not yet determined

Thermostability: Thermostable properties

Mechanism of action: Small molecules bind specific components/toxins (antigens) within snake venom to neutralize its effects: inhibition of PLA2

MeSH headings / pharmacological class: Anti-Inflammatory Agents, Non-Steroidal; Fibrinolytic Agents; Platelet Aggregation Inhibitors; Cyclooxygenase Inhibitors; Antipyretics

Key features and challenges:

Acetylsalicylic acid, also known as aspirin, is a widely available orally administered non-steroidal anti-inflammatory agent. Acetylsalicylic acid binds to and acetylates serine residues in cyclooxygenases, resulting in decreased synthesis of prostaglandin, platelet aggregation, and inflammation. This agent exhibits analgesic, antipyretic, and anticoagulant properties (https://pubchem.ncbi.nlm.nih.gov/compound/2244). ASA has been shown to inhibit the catalytic activity of pancreatic PLA2, offering some interest for snakebite therapeutics.

Acetylsalicylic acid (ASA) and a plant compound with antiophidian properties (rosmarinic acid, RA) were investigated using myographic, crystallographic and bioinformatics experiments with a phospholipase A2-like toxin, MjTX-II. MjTX-II/RA and MjTX-II/ASA crystal structures were solved at high resolution and revealed the presence of ligands bound to different regions of the toxin. However, in vitro myographic assays showed that only RA is able to prevent the myotoxic effects of MjTX-II. In agreement with functional results, molecular dynamics simulations showed that the RA molecule remains tightly bound to the toxin throughout the calculations, whereas ASA molecules tend to dissociate. This approach aids the design of effective inhibitors of PLA2-like toxins and, eventually, may complement serum therapy. (https://pubmed.ncbi.nlm.nih.gov/30679550/)

Other indications investigated: Pain; fever; inflammation; preeclampsia; preterm labour; other

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Marketed (Pain; fever; inflammation)

Development status: Active

Developers/investigators: Brazilian State University Paulista, Universidade Estadual Paulista (Unesp)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/30679550/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Unknown	Unknown
Snake family		
Risk category		Unknown

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Not specified

ADDovenom: ADDomer and ADDobody protein-based NP neutralizing superbinders (Project)

Alternative name(s): Protein-based nanoparticles; Megadalton sized, thermostable synthetic virus-like particle

Chemical name: N/A

CAS number: N/A

PCR ID: 1463

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Snake venom toxin repertoire of eight medically important snakes in Sun-Saharan Africa

Route of administration: Not yet determined

Thermostability: Room temperature storage

Mechanism of action: A disruptive protein-based nanoscaffold called ADDomer – a megadalton-sized, thermostable synthetic virus-like particle with 60 high-affinity binding sites to neutralise and eliminate venom toxins from the bloodstream

MeSH headings / pharmacological class: N/A

Key features and challenges:

Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, entirely novel approaches are being explored to overcome challenges with snake venom production, namely limited quantity, high cost, and challenges with animal captivity, as well as in the search for pan-specific or broad spectrum antivenoms, which would be more convenient and cost effective than current mono- or poly-specific antivenoms.

ADDovenom exploits a disruptive new, protein-based nanoscaffold – the ADDomer – a megadalton sized, thermostable synthetic virus-like particle that offers 60 high-affinity binding sites to rapidly eliminate venom toxins from the blood stream. The project will deploy ADDobody, a small, stable protein motif with randomized flexible loops that will be utilized as a naïve library to select and evolve high-affinity binders in vitro by Ribosome Display.

The ADDovenom project brings to bear cutting-edge proteomics, transcriptomics and bioinformatics to inventorise the toxin repertoire of eight snakes that inflict the most clinically-challenging envenoming syndromes in sub-Saharan Africa: haemorrhage, coagulopathy, paralysis and tissue necrosis. Consortium partners (University of Bristol, LSTM, University of Liège, CNRS-University of Aix Marseille, Instituto de Biologia Experimental e Tecnologica (iBET, Portugal)) - funded by the European Union will implement rational design and high-throughput expression to produce antigens for project selections, based on the major toxin groups targeted. Consensus-toxins and epitope strings will be designed combining conserved sequences, to achieve maximal intergeneric efficacy of the ADDobody binders, boosting neutralizing efficacy for entire toxin families simultaneously. State-of-the-art bioprocessing will be developed to manufacture ADDomer-based antivenoms at pharma scale, preparing for future clinical trials. Based on non-conventional techniques and designs, new protein-based nanoparticles – ADDobodies and ADDomers – will be implemented with cost-effective technologies and compatible with industrial processes and quality control. (https://addovenom.com/research/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: Liverpool School of Tropical Medicine (LSTM); University of Bristol; University of Liege, Université de Liège (ULiège); Aix-Marseille University (AMU) (including IHU); Instituto de Biologia Experimental e Tecnológica (iBET)

Key funders: European Commission (EC)

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Unknown	Unknown
Snake family		
Risk category		Unknown

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Neurotoxic (paralysis),Haemorrhagic (bleeding),Cytotoxic (tissue damage),Procoagulant (blood clotting)

Anti-batroxobin (SVSPIs) peptides (pepC and pepB) (against Bothrops jararaca)

Alternative name(s): Serine protease inhibitors; synthetic 6-mer peptides against Bothrops jararaca/Bothrops spp; snake venom serine protease inhibitors

Chemical name: N/A

CAS number: N/A

PCR ID: 1917

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: SVSP (batroxobin): Bothrops jararaca

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Peptides and proteins (synthetic or naturally derived) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Peptides

Key features and challenges:

Therapeutic peptides are short chains of amino acids linked by peptide bonds. Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other approaches are being investigated for novel therapeutics (natural or synthetic)that are cheaper, capable of rapid production, and have have higher specificity and lower immunogenicity - such as peptides.

Anti-batroxobin (SPKI) peptides (pepB and pepC) against Bothrops species were developed as follows: 6-mer peptides were designed based on a specific substrate for Bothrops jararaca venom serine proteases, and then synthesized, with the intention to selectively inhibit these enzymes. Using batroxobin as a snake venom serine protease model, two structurally similar inhibitor peptides were identified (pepB and pepC). When tested on B. jararaca venom, one of the new inhibitors displayed a good potential to inhibit the activity of the venom serine proteases (pepC). These inhibitors do not affect human serine proteases as human factor Xa and thrombin, due to their selectivity. (https://pubmed.ncbi.nlm.nih.gov/33488681/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Butantan Institute, Fundacao Butantan

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33488681/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops jararaca (Jararaca)	Bothrops jararaca (Jararaca)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVSPs

Syndromic profiles: Not specified

Anti-dendrotoxin peptides (via phage display) (against Dendroaspis polylepis)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1791

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Dendrotoxin: Dendroaspis polylepis (Black mamba) venom

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Peptides and proteins (synthetic or naturally derived) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Peptides

Key features and challenges:

Therapeutic peptides are short chains of amino acids linked by peptide bonds. Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other approaches are being investigated for novel therapeutics (natural or synthetic)that are cheaper, capable of rapid production, and have have higher specificity and lower immunogenicity - such as peptides. Phage display techniques offer a powerful tool for the selection of phage-expressed peptides, which can bind with high specificity and affinity towards venom components.(https://pubmed.ncbi.nlm.nih.gov/29285351/)

Anti-dendrotoxin peptides against Dendroaspis polylepis were developed via phage display as follows: Smaller peptides of varying lengths were first discovered using synthetic peptide phage display libraries, after which they were synthetized and tested for binding ability to their target toxin and related homologs. Peptide binders were discovered for a dendrotoxin from Dendroaspis polylepis, as well as myotoxin II from B. asper (see candidate 'Anti-myotoxin peptides (via phage display) (against B. asper)'), and α-cobratoxin from Naja kaouthia (see candidate 'Anti-α-cobratoxin peptides (via phage display) (against Naja kaouthia)'). For peptide 33535, a Kd was determined to 20 μM and truncated versions of this peptide (peptide 7 and peptide 8) were synthesised, was capable of abrogating α-cobratoxin induced inhibition (at a concentration of 40μM peptide and 100 μM α-cobratoxin) of the nicotinic acetylcholine receptor, responsible for neuromuscular transmission. (https://pubmed.ncbi.nlm.nih.gov/30274438/; https://orbit.dtu.dk/en/publications/recombinant-antivenoms)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Technical University of Denmark

Preclinical sources: https://orbit.dtu.dk/en/publications/recombinant-antivenoms

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Dendroaspis polylepis (Black mamba)	Dendroaspis polylepis (Black mamba)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: Dendrotoxins

Syndromic profiles: Not specified

Anti-myotoxin II peptides (via phage display) (against Bothrops asper)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1792

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Myotoxin II (PLA2): Bothrops asper venom

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Peptides and proteins (synthetic or naturally derived) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Peptides

Key features and challenges:

Therapeutic peptides are short chains of amino acids linked by peptide bonds. Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other approaches are being investigated for novel therapeutics (natural or synthetic)that are cheaper, capable of rapid production, and have have higher specificity and lower immunogenicity - such as peptides. Phage display techniques offer a powerful tool for the selection of phage-expressed peptides, which can bind with high specificity and affinity towards venom components.(https://pubmed.ncbi.nlm.nih.gov/29285351/)

Anti-myotoxin II peptides against Bothrops asper were developed via phage display as follows: Smaller peptides of varying lengths were first discovered using synthetic peptide phage display libraries, after which they were synthetized and tested for binding ability to their target toxin and related homologs. Peptide binders were discovered for a dendrotoxin from Dendroaspis polylepis (see candidate 'Anti-dendrotoxin peptides (via phage display) (against D. polylepis)') as well as myotoxin II from B. asper, and α-cobratoxin from Naja kaouthia (see candidate 'Anti-α-cobratoxin peptides (via phage display) (against Naja kaouthia)'). For peptide 33535, a Kd was determined to 20 μM and truncated versions of this peptide (peptide 7 and peptide 8) were synthesised, was capable of abrogating α-cobratoxin induced inhibition (at a concentration of 40μM peptide and 100 μM α-cobratoxin) of the nicotinic acetylcholine receptor, responsible for neuromuscular transmission. (https://pubmed.ncbi.nlm.nih.gov/30274438/; https://orbit.dtu.dk/en/publications/recombinant-antivenoms).

In a follow up study, anti-myotoxin II peptide JB006 was tested in vivo, and shown capable of binding to and neutralizing the toxic effects of myotoxin II in vitro and in vivo. (https://pubmed.ncbi.nlm.nih.gov/35571794/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Technical University of Denmark

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/35571794/
https://orbit.dtu.dk/en/publications/recombinant-antivenoms

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops asper (Fer-de-lance)	Bothrops asper (Fer-de-lance)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Not specified

Anti-necrotic enzyme inhibitors (against necrosis-inducing venom toxins) (Project)

Alternative name(s): Anti-necrosis enzyme inhibitors; Anti-necrotic snake venom enzyme inhibitors; Neutralizing enzyme inhibitors for snake venom induced necrosis

Chemical name: N/A

CAS number: N/A

PCR ID: 1479

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: PLA2; SVMPs

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Enzymes bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Enzymes

Key features and challenges:

Therapeutic enzymes (synthetic or naturally derived) can bind specific components/toxins (antigens) within snake venom to neutralize its effects. Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other approaches are being investigated for novel therapeutics (natural or synthetic) that are cheaper, easier to produce, and have higher specificity and lower immunogenicity.

Anti-necrotic enzyme inhibitors against necrosis-inducing venom toxins (NITs)) are being developed by LSTM through a project funded by Wellcome. Through the project, the validity of neutralising necrotic snake venoms will be tested with an alternative approach - enzyme inhibitors, which will target the toxin families (snake venom metalloproteinases and phospholipases A2) known to cause local tissue destruction. A range of repurposed small molecules that have been licensed as human medicines or demonstrated to be safe in clinical trials will be screened to facilitate rapid translation. In-house, small-scale, biochemical assays will be used to characterise the metalloproteinase and phospholipase activity of ten known necrotic venoms, before assessing the neutralising capability of the inhibitors in the same assays. Matrigel will be used as a substrate representing the basement membrane extracellular matrix for degradation based assessments. The results of these assays will identify the optimal combination of anti-necrosis enzyme inhibitors that can be taken forward into preclinical assessments of in vivo venom neutralisation in the future. (Wellcome 211450/Z/18/Z)

Other indications investigated: Unspecified

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Marketed (Other, unspecified)

Development status: Active

Developers/investigators: Liverpool School of Tropical Medicine (LSTM)

Key funders: Wellcome

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Unknown	Unknown
Snake family		
Risk category		Unknown

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs,PLA2s

Syndromic profiles: Cytotoxic (tissue damage)

Anti-PLA2 peptides (via phase display/on M13 phages) (against Western cottonmouth)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1689

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Phospholipase 2 (PLA2): Western cottonmouth venom

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Peptides and proteins (synthetic or naturally derived) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Peptides

Key features and challenges:

Therapeutic peptides are short chains of amino acids linked by peptide bonds. Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other approaches are being investigated for novel therapeutics (natural or synthetic)that are cheaper, capable of rapid production, and have higher specificity and lower immunogenicity - such as peptides. Phage display techniques offer a powerful tool for the selection of phage-expressed peptides, which can bind with high specificity and affinity towards venom components.(https://pubmed.ncbi.nlm.nih.gov/29285351/)

Anti-Phospholipase 2 (anti-PLA2) peptides candidate against against Western cottonmouth were developed via phase display/on M13 phages as follows: the amino acid sequences of Phospholipase A2 (PLA2) from multiple cottonmouth species were analysed, and a consensus peptide synthesized. Three phage display libraries were panned against this consensus peptide, crosslinked to capillary tubes, followed by a modified surface panning procedure. This high throughput selection method identified four phage clones with anti-PLA2 activity against Western cottonmouth venom, and the amino acid sequences of the displayed peptides were identified.Cross-species anti-PLA2 activity was tested against five major snake venoms in North America (Western cottonmouth, Eastern diamondback rattlesnake, Western diamondback rattlesnake, Mojave rattlesnake, and broad-banded copperhead) using one of selected anti-PLA2 clones. Results showed approximately 40% inhibition in Western cottonmouth venom and 30% inhibition in the other crotalid venoms This is the first report identifying short peptide sequences capable of inhibiting PLA2 activity of Western cottonmouth venom in vitro, using a phage display technique. Additionally, this report utilizes synthetic panning targets, designed using venom proteomic data, to mimic epitope regions. M13 phages displaying circular 7-mer or linear 12-mer peptides with antivenom activity may offer a novel alternative to traditional antibody-based therapy. (https://pubmed.ncbi.nlm.nih.gov/29285351/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Naval Medical Research Unit San Antonio

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/29285351/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Agkistrodon piscivorus leucostoma (Western cottonmouth); Crotalus atrox (Western diamondback rattlesnake); Crotalus adamanteus (Eastern diamondback rattlesnake); Crotalus scutulatus (Mojave rattlesnake); Agkistrodon contortrix laticinctu (Broad-banded copperhead)	Agkistrodon piscivorus leucostoma (Western cottonmouth); Crotalus atrox (Western diamondback rattlesnake); Crotalus adamanteus (Eastern diamondback rattlesnake); Crotalus scutulatus (Mojave rattlesnake); Agkistrodon contortrix laticinctu (Broad-banded copperhead)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Not specified

Anti-α-cobratoxin peptides (via phage display) (against Naja kaouthia)

Alternative name(s): Anti-α-cobratoxin peptides inhibitors of the nicotinic acetylcholine receptor interaction; nAChR

Chemical name: N/A

CAS number: N/A

PCR ID: 1793

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: α-cobratoxin: Naja kaouthia (Thai cobra) venom

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Peptides and proteins (synthetic or naturally derived) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Peptides

Key features and challenges:

Therapeutic peptides are short chains of amino acids linked by peptide bonds. Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other approaches are being investigated for novel therapeutics (natural or synthetic)that are cheaper, capable of rapid production, and have have higher specificity and lower immunogenicity - such as peptides. Phage display techniques offer a powerful tool for the selection of phage-expressed peptides, which can bind with high specificity and affinity towards venom components.(https://pubmed.ncbi.nlm.nih.gov/29285351/)

Anti-α-cobratoxin peptides against Naja kaouthia were developed via phage display as follows: Smaller peptides of varying lengths were first discovered using synthetic peptide phage display libraries, after which they were synthetized and tested for binding ability to their target toxin and related homologs. Peptide binders were discovered for a dendrotoxin from Dendroaspis polylepis (see candidate 'Anti-dendrotoxin peptides (via phage display) (against Dendroaspis polylepis))'), as well as myotoxin II from B. asper (see candidate 'Anti-myotoxin peptides (via phage display) (against B. asper)'), and α-cobratoxin from Naja kaouthia. For peptide 33535, a Kd was determined to 20 μM and truncated versions of this peptide (peptide 7 and peptide 8) were synthesised, was capable of abrogating α-cobratoxin induced inhibition (at a concentration of 40μM peptide and 100 μM α-cobratoxin) of the nicotinic acetylcholine receptor, responsible for neuromuscular transmission. (https://pubmed.ncbi.nlm.nih.gov/30274438/; https://orbit.dtu.dk/en/publications/recombinant-antivenoms).

Follow on studies combining high-throughput discovery and subsequent structure-function characterization, have identified simple peptides that bind α-cobratoxin (α-Cbtx) and prevent its inhibition of nicotinic acetylcholine receptors (nAChRs) as a lead for the development of alternative antivenoms. Candidate peptides were identified by phage display and deep sequencing, and hits were characterized by electrophysiological recordings, leading to an 8-mer peptide that prevented α-Cbtx inhibition of nAChRs. (https://pubmed.ncbi.nlm.nih.gov/33143415/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Technical University of Denmark

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33143415/ https://orbit.dtu.dk/en/publications/recombinant-antivenoms

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja kaouthia (Thai cobra)	Naja kaouthia (Thai cobra)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: 3FTxs

Syndromic profiles: Not specified

Batimastat

Alternative name(s): BB-94

Chemical name: N/A

CAS number: 130370-60-4

PCR ID: 1633

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: SVMP (snake venom metalloproteinases)

Route of administration: Intravenous

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; batimastat inhibits SVMPs by chelating Zn2+ ions and thereby inhibit metalloprotease activity

MeSH headings / pharmacological class: Metalloproteases antagonists/inhibitors; Antineoplastics; Small molecules

Key features and challenges:

Batimastat [BB 94, collagenase inhibitors-1] is a synthetic low molecular weight (474 Da) broad-spectrum collagenase and matrix metalloprotease inhibitor (MMPI) originally synthesized by British Biotech. Batimastat is the lead compound of this class which also includes another hydroxamate MMPI, BB 2516 (see candidate 'Marimastat'). (https://adisinsight.springer.com/drugs/800002787)

Batimastat was undergoing phase II clinical trials in the UK for the treatment of pleural effusions, but development was stopped because of lack of efficacy and associated severe peritonitis leading to distress and even death. Pivotal phase III clinical trials of batimastat in the treatment of malignant ascites were suspended by British Biotech following unexpected adverse effects (inflammation and pain in the abdomen) among patients. However, although UK approval was granted for clinical trials to recommence with a dose-ranging study, British Biotech has since discontinued clinical development of batimastat for the treatment of malignant ascites. (https://adisinsight.springer.com/drugs/800002787)

Because of its ability as a MMPI, its role in snakebite is of interest. In preclinical studies, Batimastat abrogated haemorrhage, lethality and defibrinogenation when injected after the venom. When Batimastat was administered immediately after venom, a complete abrogation of haemorrhagic activity was observed. Inhibition was less efficient as the time interval between venom and Batimastat increased. Batimastat, alongside Marimastat was effective in the abrogation of the main toxic effects induced by E. ocellatus venom in a mouse experimental model and by assessing in vitro coagulant and proteinase activities. (https://pubmed.ncbi.nlm.nih.gov/28400263/; https://pubmed.ncbi.nlm.nih.gov/34209691/)

Other indications investigated: Cancer; Malignant ascites; Pleural effusion

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Phase III (Malignant ascites; Pleural effusion)

Development status: Active

Developers/investigators: University of Costa Rica (including the Clodomiro Picado Institute)

Preclinical sources: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8309910/
https://www.sciencedirect.com/science/article/pii/S1871678417301966?via%3Dihub
https://pubmed.ncbi.nlm.nih.gov/28400263/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Echis ocellatus (Ocellated carpet viper)	Echis ocellatus (Ocellated carpet viper)
Snake family		Viperidae
Risk category		Category 1 (Highest Medical Importance)

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding)

C60 fullerene nanoparticle

Alternative name(s): Buckminsterfullerene; Fullerene C60; Fullerene

Chemical name: (C60-Ih)[5,6]fullerene

CAS number: 99685-96-8

PCR ID: 1778

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: Crude snake venom

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Nanoparticles bind toxins to prevent their spread throughout the body

MeSH headings / pharmacological class: Nanoparticles

Key features and challenges:

C60 fullerene, or Carbon 60, or Buckminsterfullerene is a molecule made up of 60 carbon atoms. The layout of the atoms forms a molecule shaped like a soccer ball - hence its name 'Buckyball'. Carbon 60 was first used in nanotechnology and electronics. Recently there is interest in using carbon 60 in medicine and health, particularly due to its antioxidant properties. It is marketed and widely available commercially as a dietary supplement. Nanoparticles offer a potential inexpensive alternative to current antivenoms via sequestrants capable of broad-spectrum neutralization across various protein isoforms.

A proof-of-concept study to test the ability of C60 fullerene to neutralize rattlesnake venom in a cricket model was conducted. Crickets injected with C60-fullerene has higher rates of survival than those that weren't. C60 fullerene conferred significant protection against rattlesnake envenomation in a cricket model. Accordingly, C60 fullerene merits further consideration as a simple, low-cost treatment for snakebite and potentially many other forms of poisoning and envenomation. (https://www.ingentaconnect.com/contentone/asp/jnn/2016/00000016/00000007/art00164_

Other indications investigated: Dietary supplement; COVID-19; cancer; other

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Dietary supplement)

Development status: Active

Developers/investigators: Loma Linda University

Preclinical sources:
https://www.ingentaconnect.com/contentone/asp/jnn/2016/00000016/00000007/art00164

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotalus oreganus helleri (Southern Pacific rattlesnake)	Crotalus oreganus helleri (Southern Pacific rattlesnake)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Carbodithioates (benzyl 4-nitrobenzenecarbodithioate)

Alternative name(s): N/A

Chemical name: benzyl 4-nitrobenzenecarbodithioate

CAS number: 154424-50-7

PCR ID: 1803

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; inhibition of PLA2 may be due to interactions of the studied compounds with amino acids in the catalytic site and the cofactor Ca2

MeSH headings / pharmacological class: N/A

Key features and challenges:

Carbodithioates R-C(S)-S-R', a family closely related to thioesters R-C(O)-S-R'. Because administration of animal-derived antivenoms has limited efficacy against the venom-induced local tissue damage, which often leads to permanent disability, there is a need to find inhibitors against toxins responsible for local damage.

Benzyl 4-nitrobenzenecarbodithioate was used in a study assessing sulphur compounds as inhibitors of enzymatic activity of a snake venom phospholipase A2. This study demonstrated that the analogous compounds, benzyl 4-nitrobenzenecarbodithioate (I) and 4-nitrothiobenzoic acid S-benzyl ester (II) (see candidate 'Thioesters (2-Sulfenyl Ethylacetate derived)'), exhibit similar inhibitory capacity on myotoxic Asp49-PLA2 isolated from C. durissus cumanensis venom. The catalytic activity was reduced by about 50% using a concentration near to 50 µM for both compounds. (https://pubmed.ncbi.nlm.nih.gov/32197309/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: Universidad de Antioquia, Colombia

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/32197309/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotalus durissus cumanensis (Cascabel Rattlesnake)	Crotalus durissus cumanensis (Cascabel Rattlesnake)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Cytotoxic (tissue damage)

Dexketoprofen

Alternative name(s): N/A

Chemical name: (2S)-2-[3-(benzoyl)phenyl]propanoic acid

CAS number: 22161-81-5

PCR ID: 2536

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: L-amino acid oxidase (LAAO)

Route of administration: Not yet determined

Thermostability: Room temperature stable

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom toxins to neutralize its effects; Dexketoprofen is a non-steroidal anti-inflammatory drug (NSAID) that reduces prostaglandin synthesis via inhibition of cyclooxygenase pathway (both COX-1 and COX-2) activity, but might also inhibit snake venom LAAO.

MeSH headings / pharmacological class: Anti-Inflammatory Agents, Non-Steroidal

Key features and challenges:

Dexketoprofenis an NSAID that is the R(-)-enantiomer of racemic ketoprofen with analgesic and anti-inflammatory properties used for the treatment of mild to moderate pain. Itreduces prostaglandin synthesis via inhibition of cyclooxygenase pathway (both COX-1 and COX-2) activity.It is available in various countries in Europe, Asia and Latin America. It has analgesic, antipyretic and anti-inflammatory properties.(https://go.drugbank.com/drugs/DB09214)

A discovery stage, drug repurposing study concluded that dexketoprofen could be a promising inhibitor ofsnake venom l-amino acid oxidase (LAAO). The study was as follows:SinceCrotalus adamanteusLAAO has no crystal structure in the protein data bank, first, its 3D structure was constructed by homology modeling using 1REO as the template and then modeled structure was evaluated by several algorithms. Then, the authors screened the FDA-approved drugs by structure-based virtual screening, molecular dynamics (MD) simulation, and Molecular Mechanics Poisson Boltzmann Surface Area (MM/PBSA) to identify new inhibitors for the snake venom LAAO. Interestingly, docking results revealed that half of the hits belong to the propionic acid derivatives drugs. In addition, MD simulation was performed to assess the interaction profile of the docked protein-hits complexes. Meanwhile, Arg88, Gln112, Lys345, Trp356 form consistent hydrogen bond interactions with Dexketoprofen, Flurbiprofen, Ketoprofen, Morphine, and Citric acid during simulation. According to the results, each of the four compounds can be an appropriate inhibitor of LAAO and since our study was based on drug repurposing could be evaluated in phase II clinical trials. (https://pubmed.ncbi.nlm.nih.gov/31668098/)

Other indications investigated: Pain; inflammation

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Marketed (Pain; inflammation)

Development status: Active

Developers/investigators: Golestan University

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotalus adamanteus (Eastern diamondback rattlesnake)	N/A
Snake family		
Risk category		N/A

Direct action on toxins? Yes

Target toxin class: Low toxicity toxins

Specific target toxin class: LAAO

Syndromic profiles: Not specified

Diethylene triamine pentaacetic acid (DTPA)

Alternative name(s): Pentetic acid

Chemical name: 2-[bis[2-[bis(carboxymethyl)amino]ethyl]amino]acetic acid

CAS number: 67-43-6

PCR ID: 1903

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: SVMPs

Route of administration: Not yet determined

Thermostability: Melting point 219-220 ºC

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; chelates and removes Zn2+ from the active site of Zn2+-dependent SVMPs

MeSH headings / pharmacological class: Chelating agents; metal chelators

Key features and challenges:

Pentetic acid, also known as diethylenetriaminepentaacetic acid (DTPA), is a synthetic polyamino carboxylic acid with eight coordinate bond forming sites that can sequester metal ions and form highly stable DTPA-metal ion complexes. DTPA, along with its calcium and zinc trisodium salts, are the only FDA approved agents for the treatment of internal contamination by transuranics (i.e. radionuclides such as plutonium, americium or curium). It is currently considered, in all the dosage forms, as a member of the list of approved inactive ingredients for drug products by the FDA. DPTA was developed by the pharmaceutical company CIS US and FDA approved on April 14, 2004. (https://go.drugbank.com/drugs/DB14007). It is an edetate and a chelating agent used in preparing radiopharmaceuticals, and has a strong affinity for iron, and r other heavy metals, and is thereby is used in the treatment of iron-storage disease and poisoning from heavy and radioactive metals (https://pubchem.ncbi.nlm.nih.gov/compound/3053). Due to its metal chelating properties, it is of interest in snakebite therapeutic research.

In a preclinical study assessing inhibitory potential of DTPA against the proteolytic, haemorrhagic, and myotoxic activities of Echis carinatus venom DTPA completely blocked the haemorrhagic and myotoxic activities of ECV in a dose dependent manner. Evaluation of inhibitory potentials of DTPA towards Zn2+ dependent ECVMPs revealed the protective effect of Zn2+ specific chelating agents against ECV induced local tissue damages and haemostatic alterations with minimal adverse effects. (https://pubmed.ncbi.nlm.nih.gov/25447774/)

Other indications investigated: Radionuclide contamination; medical imaging

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Radionuclide contamination; medical imaging)

Development status: Active

Developers/investigators: University of Mysore

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/25447774/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Echis carinatus (Saw-scaled viper)	Echis carinatus (Saw-scaled viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

Dimercaprol

Alternative name(s): British anti-Lewisite (BAL); 2,3-Dimercapto-1-propanol

Chemical name: 2,3-bis(sulfanyl)propan-1-ol

CAS number: 59-52-9

PCR ID: 1628

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: SVMPs (snake venom metalloproteinases)

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; dimercaprol most probably acts by chelating and removing Zn2+ from the active site of Zn2+-dependent SVMPs

MeSH headings / pharmacological class: Metal chelators

Key features and challenges:

Dimercaprol is a traditional chelating agent developed by British biochemists at Oxford University during World War II. It was developed as an experimental antidote against the arsenic-based poison gas Lewisite. It has been used clinically since 1949 in arsenic, cadmium and mercury poisoning. In addition, it has in the past been used for the treatment of Wilson's disease, a genetic disorder in which the body tends to retain copper. Dimercaprol has toxic potential, and its use may be followed by a variety of adverse effects. (https://go.drugbank.com/drugs/DB06782). However, the advantages of repurposing licensed medicines such as dimercaprol are that these molecules have demonstrated safety profiles and thus drug development times could be significantly shortened as these agents have extensive pharmacokinetic, bioavailability and tolerance data already associated with them. Because of its metal (zinc) chelating properties, it is of interest in snakebite envenoming in species' venom where SVMPs are in high quantity.

It was recently shown that both dimercaprol and DMPS (see candidate 'DMPS (Unithiol)') displayed potential for repurposing as small molecule chelators to treat snake envenoming, most probably by chelating and removing Zn2+ from the active site of Zn2+-dependent SVMPs, and proved to be at least partially effective at neutralising Viperinae snake venoms (https://pubmed.ncbi.nlm.nih.gov/32825484/). However, in another preclinical study dimercaprol failed to confer any protection to Dispholidus typus (boomslang) venom at the doses tested. (https://pubmed.ncbi.nlm.nih.gov/35321116/)

Other indications investigated: Treatment of acute heavy metal poisoning (arsenic, gold and mercury, lead)

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Heavy metal poisoning)

Development status: Active

Developers/investigators: Vrije Universiteit Amsterdam; Liverpool School of Tropical Medicine (LSTM)

Preclinical sources: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8935517/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7555180/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Dispholidus typus (Boomslang); Echis ocellatus (Ocellated carpet viper); Echis carinatus (Saw-scaled viper); Daboia russelii (Russel's viper); Bitis arietans (Puff adder)	Partial neutralisation: Echis ocellatus (Ocellated carpet viper); Echis carinatus (Saw-scaled viper); Daboia russelii (Russel's viper); Bitis arietans (Puff adder)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding)

Disulfiram

Alternative name(s): Antabuse; TTD

Chemical name: diethylcarbamothioylsulfanyl N,N-diethylcarbamodithioate

CAS number: 97-77-8

PCR ID: 1800

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: SVMPs

Route of administration: Not yet determined

Thermostability: Melting point 71.5 °C

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; chelates and removes Zn2+ from the active site of Zn2+-dependent SVMPs

MeSH headings / pharmacological class: Metal chelators; Metalloproteases antagonists

Key features and challenges:

Disulfiram, also called Tetraethyl thiuram disulfide (TTD) is an oral drug used to support the treatment of alcohol use disorder by producing an acute sensitivity to ethanol (drinking alcohol). Disulfiram works by inhibiting the enzyme acetaldehyde dehydrogenase, and is a zinc metal chelator. It has been investigated for numerous other conditions, but is also of interest in snakebite due to its metal chelating properties.

TTD has been shown to inhibit MMP-2 and MMP-9 activity by directly interacting with them via a Zn++ chelating mechanism, and hence have been investigated as a potential treatment for SBE. In preclinical studies, TTD inhibited Echis carinatus SVMPs-induced skin haemorrhage and footpad tissue necrosis by reduced expression of citrullinated H3 and myeloperoxidase in mice footpad tissue. TTD also neutralized Echis carinatus venom-induced systemic haemorrhage and conferred protection against lethality in mice. This shows promising protective efficacy of TTD which can be extrapolated to treat severe tissue necrosis complementing anti-snake venom (ASV). (https://pubmed.ncbi.nlm.nih.gov/33529194/; https://pubmed.ncbi.nlm.nih.gov/25447774/)

Other indications investigated: Alcohol use disorder; age-related macular degeneration; non-small cell lung cancer;

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Alcohol use disorder)

Development status: Active

Developers/investigators: University of Mysore

Preclinical sources: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8309910/
https://pubmed.ncbi.nlm.nih.gov/25447774/
https://pubmed.ncbi.nlm.nih.gov/33529194/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Echis carinatus (Saw-scaled viper)	Echis carinatus (Saw-scaled viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

DMPS (Unithiol)

Alternative name(s): Dimaval; Unithiol; Sodium 2,3-dimercapto-1-propanesulfonate; Sodium 2,3-dimercaptopropane-1-sulfonate

Chemical name: sodium;2,3-bis(sulfanyl)propane-1-sulfonate

CAS number: 74-61-3

PCR ID: 1459

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: SVMPs (snake venom metalloproteinases)

Route of administration: Oral; Intravenous

Thermostability: Thermostable properties

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; chelates and removes Zn2+ from the active site of Zn2+-dependent SVMPs

MeSH headings / pharmacological class: Metal chelators

Key features and challenges:

Dimercaptopropane sulfonate (2,3-dimercapto-1-propane-sulfonate) - DMPS or 'unithiol' - is a water-soluble and possibly less toxic derivative of dimercaprol, used in poisoning with arsenic, bismuth, mercury, and other heavy metals. DMPS is a chelating agent which has been used clinically for the treatment of heavy metal intoxication, including mercury, arsenic, and lead. (https://www.sciencedirect.com/topics/medicine-and-dentistry/unithiol)

In preclinical studies, DMPS has partially neutralized venom of Echis carinatus, Echis ocellatus, Daboia russelii and Bitis arietans (https://pubmed.ncbi.nlm.nih.gov/32825484/). However DMPS has also exhibited impressive in vivo neutralization of the local and systemic effects of SVMP-rich venom from the saw-scaled viper Echis ocellatus, including outperforming marimastat in a pre-incubation model of envenoming, and providing protection against lethality when delivered post-venom delivery, including when dosed orally. It has also performed well in neutralisation of Dispholidus typus (https://pubmed.ncbi.nlm.nih.gov/35321116/). These findings, coupled with DMPS already being a licensed medicine and exhibiting good oral bioavailability, make it a strong candidate for transition into clinical trials for the treatment of snakebite. (https://pubmed.ncbi.nlm.nih.gov/32376771/)

DMPS (unithiol) is currently undergoing a Phase I trial called the TRUE-1: Trial of Repurposed Unithiol for snakebite Envenoming phase 1', to test the safety, tolerability, pharmacokinetics and pharmacodynamics in healthy Kenyan adults. (https://pubmed.ncbi.nlm.nih.gov/35372700/; https://wellcomeopenresearch.org/articles/7-90/v1)

Other indications investigated: Treatment of heavy metal poisoning

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Phase I

Highest R&D stage (any condition): Marketed (Heavy metal poisoning)

Development status: Active

Developers/investigators: Liverpool School of Tropical Medicine (LSTM); Vrije Universiteit Amsterdam

Key funders: Wellcome

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/34209691/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7555180/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8935517/

Evidence of clinical trials? Yes

Phase I(Status: , March 2021-): *Unithiol Phase I* (CT number: PACTR202103718625048, CT source: https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=15722)

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Dispholidus typus (Boomslang); Echis ocellatus (Ocellated carpet viper); Echis carinatus (Saw-scaled viper); Daboia russelii (Russel's viper); Bitis arietans (Puff adder)	Dispholidus typus (Boomslang); Echis carinatus (Saw-scaled viper); Partial neutralisation Echis ocellatus (Ocellated carpet viper); Daboia russelii (Russel's viper); Bitis arietans (Puff adder)
Snake family		Viperidae,Colubridae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage),Procoagulant (blood clotting)

DNA aptamers (against Bungarus multicinctus/α-bungarotoxin)

Alternative name(s): bgt1; bgt2; bgt3; bgt4; α-Bgt

Chemical name: N/A

CAS number: N/A

PCR ID: 1862

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: α-bungarotoxin: Bungarus multicinctus venom, and cardiotoxin 3 (CTX3): N. atra

Route of administration: Not yet determined

Thermostability: Thermostable properties, temperature unspecified

Mechanism of action: DNA aptamers bind with high specificity to snake toxins to neutralize their effects

MeSH headings / pharmacological class: Aptamers; nucleotides

Key features and challenges:

DNA aptamers are short synthetic oligonucleotides (20–100 nucleotides) that can bind to a molecular target by their unique three-dimensional structure with high affinity and specificity, and as such, have clinical potential as macromolecular drugs. Aptamers are usually created by selecting from a large random sequence pool, but natural aptamers also exist in riboswitches. The use of aptamers for snakebite shows promise, having been shown to inhibit toxins from cone snails. Research is also being carried out on a large range of alternative binding scaffolds (AbScaffs) which due to low cost of production, high stability and engineerability could play a key role in future therapeutics for SBE (https://pubmed.ncbi.nlm.nih.gov/31226842/). DNA aptamer based antivenoms could be mass produced at lower cost than traditional antisera with longer shelf-lives at ambient temperatures.

DNA aptamers (against Bungarus multicinctus α-bungarotoxin (α-Bgt) have been developed previously. In a recent study, their cross-reactivity to Taiwan Cobra Cardiotoxins was tested as follows: Bungarus multicinctus α-bungarotoxin (α-Bgt) and Naja atra cardiotoxins (CTXs) share a common structural scaffold, and their tertiary structures adopt three-fingered loop motifs. Four DNA aptamers against α-Bgt have been reported previously. Given that the binding of aptamers with targeted proteins depends on structural complementarity, in this study, it was investigated whether DNA aptamers against α-Bgt could also recognize CTXs. It was found that N. atra cardiotoxin 3 (CTX3) reduced the electrophoretic mobility of aptamers against α-Bgt. Analysis of the changes in the fluorescence intensity of carboxyfluorescein-labeled aptamers upon binding toxin molecules revealed that CTX3 and α-Bgt could bind the tested aptamers. Moreover, the aptamers inhibited the membrane-damaging activity and cytotoxicity of CTX3. In addition to CTX3, other N. atra CTX isotoxins also bound to the aptamer against α-Bgt. Taken together, our data indicate that aptamers against α-Bgt show cross-reactivity with CTXs. The findings that aptamers against α-Bgt also suppress the biological activities of CTX3 highlight the potential utility of aptamers in regard to the broad inhibition of snake venom three-fingered proteins. (https://pubmed.ncbi.nlm.nih.gov/26959062/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: National Sun Yat-Sen University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/26959062/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bungarus multicinctus (Many banded krait); Naja atra (Chinese cobra)	Bungarus multicinctus (Many banded krait); Naja atra (Chinese cobra)
Snake family		Elapidae
Risk category		Category 1 (Highest Medical Importance)

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: 3FTxs

Syndromic profiles: Neurotoxic (paralysis),Cytotoxic (tissue damage)

DNA aptamers (against Daboxin P/Daboia russelii)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1821

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Daboxin P (PLA2): Daboia russelii venom

Route of administration: Not yet determined

Thermostability: Thermostable properties, temperature unspecified

Mechanism of action: DNA aptamers bind with high specificity to snake toxins to neutralize their effects

MeSH headings / pharmacological class: Aptamers; nucleotides

Key features and challenges:

DNA aptamers are short synthetic oligonucleotides (20–100 nucleotides) that can bind to a molecular target by their unique three-dimensional structure with high affinity and specificity, and as such, have clinical potential as macromolecular drugs. Aptamers are usually created by selecting from a large random sequence pool, but natural aptamers also exist in riboswitches. The use of aptamers for snakebite shows promise, having been shown to inhibit toxins from cone snails. Research is also being carried out on a large range of alternative binding scaffolds (AbScaffs) which due to low cost of production, high stability and engineerability could play a key role in future therapeutics for SBE (https://pubmed.ncbi.nlm.nih.gov/31226842/). DNA aptamer based antivenoms could be mass produced at lower cost than traditional antisera with longer shelf-lives at ambient temperatures.

DNA aptamers against Daboxin P, a major PLA2 enzyme of Daboia russelii venom, were developed as follows: The aptamers were designed by adding nucleic acid chain on the surface of Daboxin P, a major PLA2 enzyme of Indian Daboia russelii venom. Binding characteristics of the aptamers were confirmed by docking to Daboxin P as well as acidic and basic PLA2s from different snake species using in silico docking. The aptamers folded into different tertiary structures and bound to the active and Ca2+ binding site of PLA2 enzymes. Molecular dynamics simulation analysis of Daboxin P-aptamer complexes showed that the complexes were stable in an aqueous environment. The electrophoretic mobility shift assay further confirmed the binding of the synthetic aptamers to Daboxin P and other snake venom PLA2 enzymes. The aptamers inhibited the sPLA2 activity with an IC50 value ranging between 0.52 μM and 0.77 μM as well as the anticoagulant activity of Daboxin P. The aptamers could also inhibit the PLA2 activity of Echis carinatus crude venom and anti-coagulant activity of Bungarus caeruleus crude venom, members of big four snakes. However, the aptamers didn't inhibit fibrinogenolytic or proteolytic activity of big four venom as well as the coagulation and haemolytic activities. Thus, aptamers can be rationally designed to inhibit the biochemical and biological activities of snake venom proteins. (https://pubmed.ncbi.nlm.nih.gov/34619285/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Tezpur University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/34619285/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russelii (Russel's viper); Echis carinatus (Saw-scaled viper); Bungarus caeruleus (Indian krait)	Daboia russelii (Russel's viper); Echis carinatus (Saw-scaled viper); Bungarus caeruleus (Indian krait)
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Haemorrhagic (bleeding)

DNA aptamers (against Naja melanoleuca)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1779

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Naja melanoleuca

Route of administration: Not yet determined

Thermostability: Thermostable properties, temperature unspecified

Mechanism of action: DNA aptamers bind with high specificity to snake toxins to neutralize their effects

MeSH headings / pharmacological class: Aptamers; nucleotides

Key features and challenges:

DNA aptamers are short synthetic oligonucleotides (20–100 nucleotides) that can bind to a molecular target by their unique three-dimensional structure with high affinity and specificity, and as such, have clinical potential as macromolecular drugs. Aptamers are usually created by selecting from a large random sequence pool, but natural aptamers also exist in riboswitches. The use of aptamers for snakebite shows promise, having been shown to inhibit toxins from cone snails. Research is also being carried out on a large range of alternative binding scaffolds (AbScaffs) which due to low cost of production, high stability and engineerability could play a key role in future therapeutics for SBE (https://pubmed.ncbi.nlm.nih.gov/31226842/). DNA aptamer based antivenoms could be mass produced at lower cost than traditional antisera with longer shelf-lives at ambient temperatures.

DNA aptamers against Naja melanoleuca (and purified honey bee phospholipase A2 (PLA2) were developed as follows: Two hundred base long DNA aptamers were developed against crude black cobra (Naja melanoleuca) venom and purified honey bee phospholipase A2 (PLA2). These aptamers were screened for the ability to inhibit PLA2 via a colorimetric assay and for the ability to protect murine NIH 3T3 fibroblasts from cobra venom in culture as assessed by trypan blue dye exclusion. Several aptamers were identified which could inhibit cobra venom up to 44% and bee PLA2 over 56%, while an unrelated aptamer and randomly chosen oligonucleotide could not inhibit the enzymatic activity of bee PLA2. Some aptamers were also identified which protected 3T3 cells from cobra venom in vitro (i.e., enhanced viability from 68% to 86%–89% in the presence of cobra venom). Although, snake venoms are complex mixtures of various tissue degradative enzymes such as PLA2, neurotoxins and other toxins, the existence of these aptamers provides proof-of-principle that aptamer-based antidotes for snake, insect and other venomous bites are feasible. DNA aptamer based antivenoms could also be mass produced at lower cost than traditional antisera with longer shelf-lives at ambient temperatures to aid envenomated victims in underdeveloped countries. (https://www.ingentaconnect.com/content/asp/jobn/2015/00000009/00000004/art00003)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Nanohmics Inc

Preclinical sources:
https://www.ingentaconnect.com/content/asp/jobn/2015/00000009/00000004/art00003#expand/collapse

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja melanoleuca (Black and white cobra, Forest cobra)	Naja melanoleuca (Black and white cobra, Forest cobra)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Not specified

EDTA / CaNa2EDTA

Alternative name(s): Ethylenediaminetetraacetic acid; Edetic acid; Versene

Chemical name: Ethylenediaminetetraacetic acid

CAS number: 60-00-4

PCR ID: 1702

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: SVMPs (snake venom metalloproteinases)

Route of administration: Not yet determined

Thermostability: Thermostable properties

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; Chelates zinc ions to inhibit metalloproteinase activity

MeSH headings / pharmacological class: Metal chelators

Key features and challenges:

Ethylenediaminetetraacetic acid (EDTA) is an aminopolycarboxylic acid which is widely used to bind to zinc, iron and calcium ions. It binds these ions as a hexadentate chelating agent. It is used for the reduction of blood levels and depot stores of lead in lead poisoning (acute and chronic) and lead encephalopathy, in both pediatric populations and adults. (https://go.drugbank.com/drugs/DB00974), Because of its zinc chelating properties, it is of interest in snakebite envenoming in species with high quantities of SVMPs.

Preclinical studies have demonstrated that pre-incubation of venom with EDTA protected mice from lethality caused by one of the world's most medically important snake species, E. ocellatus, providing evidence of metal chelators preventing venom-induced murine lethality in vivo. In combination with prior reports of EDTA neutralising specific markers of haematopathology caused by snake venoms these results suggest that metal chelation could be an effective means to inhibit zinc-dependant SVMP toxins in vivo. (https://pubmed.ncbi.nlm.nih.gov/30271920/)

Another study found that incubation of B. asper venom with 300 mM the calcium sodium versenate version (CaNa2EDTA) abrogated hemorrhagic activity. Venom inhibited with CaNa2EDTA showed a drastic reduction in the extent of hemorrhage, as compared to mice injected with venom alone. Incubation of venom with the chelating agent CaNa2EDTA resulted in the survival of approximately 40% of mice injected, and in the prolongation of the time of death of mice that did not survive, thus underscoring the relevance of SVMPs in venom-induced lethality. (https://pubmed.ncbi.nlm.nih.gov/25447772/)

Other indications investigated: Heavy metal poisoning (mercury, lead, iron)

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Heavy metal poisoning)

Development status: Active

Developers/investigators: University of Costa Rica (including the Clodomiro Picado Institute); Liverpool School of Tropical Medicine (LSTM); Vrije Universiteit Amsterdam

Preclinical sources: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6123674/ https://pubmed.ncbi.nlm.nih.gov/25447772/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Echis ocellatus (Ocellated carpet viper); B. asper (Fer-de-lance)	Echis ocellatus (Ocellated carpet viper); B. asper (Fer-de-lance)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding),Procoagulant (blood clotting)

Flurbiprofen

Alternative name(s): Ansaid; Ocufen; Strepfen

Chemical name: (RS)-2-(2-fluorobiphenyl-4-yl)propanoic acid

CAS number: 5104-49-4

PCR ID: 2539

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: L-amino acid oxidase (LAAO)

Route of administration: Not yet determined

Thermostability: Room temperature stable

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom toxins to neutralize its effects; Flurbiprofen is a non-steroidal anti-inflammatory drug (NSAID) that reduces prostaglandin synthesis via inhibition of cyclooxygenase pathway (both COX-1 and COX-2) activity, but might also inhibit snake venom LAAO.

MeSH headings / pharmacological class: Analgesics; Anti-Inflammatory Agents; Non-Steroidal Cyclooxygenase Inhibitors

Key features and challenges:

Flurbiprofen, a propionic acid derivative, is a nonsteroidal anti-inflammatory agent (NSAIA) with antipyretic and analgesic activity. Oral formulations of flurbiprofen may be used for the symptomatic treatment of rheumatoid arthritis, osteoarthritis and anklylosing spondylitis. Flurbiprofen may also be used topically prior to ocular surgery to prevent or reduce intraoperative miosis. Flurbiprofen is structurally and pharmacologically related to fenoprofen, ibuprofen, and ketoprofen. (https://go.drugbank.com/drugs/DB00712)

A discovery stage, drug repurposing study concluded that flurbiprofen could be a promising inhibitor ofsnake venom l-amino acid oxidase (LAAO). The study was as follows:SinceCrotalus adamanteusLAAO has no crystal structure in the protein data bank, first, its 3D structure was constructed by homology modeling using 1REO as the template and then modeled structure was evaluated by several algorithms. Then, the authors screened the FDA-approved drugs by structure-based virtual screening, molecular dynamics (MD) simulation, and Molecular Mechanics Poisson Boltzmann Surface Area (MM/PBSA) to identify new inhibitors for the snake venom LAAO. Interestingly, docking results revealed that half of the hits belong to the propionic acid derivatives drugs. In addition, MD simulation was performed to assess the interaction profile of the docked protein-hits complexes. Meanwhile, Arg88, Gln112, Lys345, Trp356 form consistent hydrogen bond interactions with Dexketoprofen, Flurbiprofen, Ketoprofen, Morphine, and Citric acid during simulation. According to the results, each of the four compounds can be an appropriate inhibitor of LAAO and since our study was based on drug repurposing could be evaluated in phase II clinical trials. (https://pubmed.ncbi.nlm.nih.gov/31668098/)

Other indications investigated: Pain; inflammation (rheumatoid arthritis, osteoarthritis and anklylosing spondylitis)

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Marketed (Pain; inflammation)

Development status: Active

Developers/investigators: Golestan University

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotalus adamanteus (Eastern diamondback rattlesnake)	N/A
Snake family		
Risk category		

Direct action on toxins? Yes

Target toxin class: Low toxicity toxins

Specific target toxin class: LAAO

Syndromic profiles: Not specified

Gold nanoparticle conjugated andrographolide (GNC-andrographolide)

Alternative name(s): AuNPs; GNP; Conjugated gold nanoparticles (AuNPs); andrographolide-GNC

Chemical name: N/A

CAS number: N/A

PCR ID: 2206

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: D. russelli

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Nanoparticles bind toxins to prevent their spread throughout the body; or act as carriers for other small molecules

MeSH headings / pharmacological class: Conjugated metal nanoparticles

Key features and challenges:

In recent years, gold nanoparticles and their properties have led to new and exciting developments with enormous potential in biology and medicine. Antisnake venom serums (ASVS) - the only specific treatment against snake envenomation - have many limitations, not only low efficiency but also considerable side effects. Targeted drug therapy using nanoparticles, an emerging area of nanotechnology, is one potential alternative to ASVS, largely as a high-specificity carrier.

Gold nanoparticles can be conjugated to other compounds. Daboia russellii envenomation followed by treatment with andrographolide-AuNPs provided protection against venom induced edema, hemorrhage, defibrination, organ toxicity and inflammation in animal model. Gold nanoparticles can be conjugated to other compounds. Daboia russellii envenomation followed by treatment with andrographolide-AuNPs provided protection against venom induced edema, hemorrhage, defibrination, organ toxicity and inflammation in animal model. (https://pubmed.ncbi.nlm.nih.gov/31748033/)

Gold nanoparticles have been conjugated to other compounds and tried in snakebite therapeutics (https://pubmed.ncbi.nlm.nih.gov/33976002/; https://pubmed.ncbi.nlm.nih.gov/30183223/; https://pdfs.semanticscholar.org/c1be/1b168238ce8cd1969a4)6a4d25398819e7a84.pdf)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: University of Calcutta

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/31748033/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russelli (Russel's viper)	Daboia russelli (Russel's viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Haemorrhagic (bleeding)

Gold nanoparticle Vitex negundo conjugated (VN-GNP)

Alternative name(s): AuNPs; GNP; Conjugated gold nanoparticles (AuNPs)

Chemical name: N/A

CAS number: N/A

PCR ID: 2207

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Naja kaouthia

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Nanoparticles bind toxins to prevent their spread throughout the body; or act as carriers for other small molecules

MeSH headings / pharmacological class: Conjugated metal nanoparticles

Key features and challenges:

In recent years, gold nanoparticles and their properties have led to new and exciting developments with enormous potential in biology and medicine. Antisnake venom serums (ASVS) - the only specific treatment against snake envenomation - have many limitations, not only low efficiency but also considerable side effects. Targeted drug therapy using nanoparticles, an emerging area of nanotechnology, is one potential alternative to ASVS, largely as a high-specificity carrier.

Gold nanoparticles can be conjugated to other compounds. Preclinical studies have shown that Vitex negundo gold nanoparticle (VN-GNP) significantly antagonized toxicity, acute stress, proinflammatory cytokines response, increased anti-inflammatory cytokine response induced by Naja kaouthia venom in a mouse model.
(https://pdfs.semanticscholar.org/c1be/1b168238ce8cd1969a46a4d25398819e7a84.pdf)

Gold nanoparticles have been conjugated to other compounds and tried in snakebite therapeutics (https://pubmed.ncbi.nlm.nih.gov/31748033/;https://pubmed.ncbi.nlm.nih.gov/33976002/; https://pubmed.ncbi.nlm.nih.gov/30183223/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: University of Calcutta

Preclinical sources:
https://pdfs.semanticscholar.org/c1be/1b168238ce8cd1969a46a4d25398819e7a84.pdf

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja kaouthia (Thai cobra)	Naja kaouthia (Thai cobra)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Gold nanoparticle-conjugated 2-hydroxy-4-methoxybenzoic acid (GNP-HMBA)

Alternative name(s): AuNPs; GNP; Conjugated gold nanoparticles (AuNPs)

Chemical name: N/A

CAS number: N/A

PCR ID: 2038

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Nanoparticles bind toxins to prevent their spread throughout the body; or act as carriers for other small molecules

MeSH headings / pharmacological class: Conjugated metal nanoparticles

Key features and challenges:

In recent years, gold nanoparticles and their properties have led to new and exciting developments with enormous potential in biology and medicine. Antisnake venom serums (ASVS) - the only specific treatment against snake envenomation - have many limitations, not only low efficiency but also considerable side effects. Targeted drug therapy using nanoparticles, an emerging area of nanotechnology, is one potential alternative to ASVS, largely as a high-specificity carrier.

A gold nanoparticle conjugated with 2-hydroxy-4-methoxy benzoic acid (HMBA) has been shown to inhibit lethality, inflammation and oxidative stress from D.russelli and Naja kaouthia venom (https://pubmed.ncbi.nlm.nih.gov/33976002/; https://pubmed.ncbi.nlm.nih.gov/30183223/) (Also see candidate '2-hydroxy-4-methoxybenzoic acid').

Gold nanoparticles have been conjugated to other compounds and tried in snakebite therapeutics (https://pubmed.ncbi.nlm.nih.gov/31748033/; https://pdfs.semanticscholar.org/c1be/1b168238ce8cd1969a4)6a4d25398819e7a84.pdf)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: University of Calcutta

Preclinical sources: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8216123/
https://www.ingentaconnect.com/contentone/asp/jnn/2020/00000020/00000006/art00010?
https://pdfs.semanticscholar.org/c1be/1b168238ce8cd1969a46a4d25398819e7a84.pdf
https://pubmed.ncbi.nlm.nih.gov/33976002/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja kaouthia (Thai cobra); Daboia russelii (Russell's viper);	Naja kaouthia (Thai cobra); Daboia russelii (Russell's viper);
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Not specified

Heparin / LMWH

Alternative name(s): Low molecular weight heparins

Chemical name: N/A

CAS number: 9005-49-6

PCR ID: 1716

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: Crude snake venom; PLA2

Route of administration: Intravenous; Oral

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; heparins form a complex with all isoforms of basic venom myotoxins, held at least in part by electrostatic interactions

MeSH headings / pharmacological class: Anticoagulants; Fibrinolytic Agents

Key features and challenges:

Heparin is an anticoagulant indicated for thromboprophylaxis and to treat thrombosis associated with a variety of conditions such as pulmonary embolism and atrial fibrillation. (https://go.drugbank.com/drugs/DB01109). Heparin has been assessed - and is often used - as an adjunct therapy for snakebite envenomation (https://pubmed.ncbi.nlm.nih.gov/16749547/), however there it not any benefit in faster reversion of clotting defect as assessed by the recovery of prothrombin time, clotting time and bleeding time, showing that there may be no benefit in using heparin for haematological envenoming caused by viper bites in India. (https://pubmed.ncbi.nlm.nih.gov/32780827/). Other clinical studies show some positive results, but need larger studies. (https://pubmed.ncbi.nlm.nih.gov/17844693/). However, other preclinical studies have shown that mast cells constitute an innate immune mechanism to counteract the toxicity of venoms, and heparin, a mast cell-derived substance was shown to inhibit myotoxic and cytotoxic toxins in viperid venoms (https://pubmed.ncbi.nlm.nih.gov/34565143/; https://pubmed.ncbi.nlm.nih.gov/34209691/). This includes a 2015 study into the anticoagulant mechanism and platelet deaggregation property of a non-cytotoxic, acidic phospholipase A2 purified from Indian cobra (Naja naja) venom, and the inhibition of its anticoagulant activity by low molecular weight heparin (https://pubmed.ncbi.nlm.nih.gov/25576831/)

Other indications investigated: Disseminated intravascular coagulation; Peripheral arterial occlusive disorders; Pulmonary embolism; Thromboembolism; Venous thrombosis

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Venous thrombosis; pulmonary embolism; other)

Development status: Active

Developers/investigators: University of New South Wales (UNSW); Tezpur University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/25576831/ https://pubmed.ncbi.nlm.nih.gov/8185661/

Evidence of clinical trials? Yes

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops asper (Fer-de-lance); Naja naja (Indian cobra); Naja sumatrana (Equitorial spitting cobra)	Bothrops asper (Fer-de-lance); Naja naja (Indian cobra); Naja sumatrana (Equitorial spitting cobra)
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

Ketoprofen

Alternative name(s): N/A

Chemical name: (RS)-2-(3-benzoylphenyl)propanoic acid

CAS number: 22071-15-4

PCR ID: 2541

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: L-amino acid oxidase (LAAO)

Route of administration: Not yet determined

Thermostability: Room temperature stable

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom toxins to neutralize its effects; Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) that reduces prostaglandin synthesis via inhibition of cyclooxygenase pathway (both COX-1 and COX-2) activity, but might also inhibit snake venom LAAO.

MeSH headings / pharmacological class: Anti-Inflammatory Agents; Non-Steroidal Cyclooxygenase Inhibitors

Key features and challenges:

Ketoprofenis an NSAID used to treat rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, dysmenorrhea, mild to moderate muscle pain, postoperative pain, and postpartum pain. (https://go.drugbank.com/drugs/DB01009)

A discovery stage, drug repurposing study concluded that ketoprofen could be a promising inhibitor ofsnake venom l-amino acid oxidase (LAAO). The study was as follows:SinceCrotalus adamanteusLAAO has no crystal structure in the protein data bank, first, its 3D structure was constructed by homology modeling using 1REO as the template and then modeled structure was evaluated by several algorithms. Then, the authors screened the FDA-approved drugs by structure-based virtual screening, molecular dynamics (MD) simulation, and Molecular Mechanics Poisson Boltzmann Surface Area (MM/PBSA) to identify new inhibitors for the snake venom LAAO. Interestingly, docking results revealed that half of the hits belong to the propionic acid derivatives drugs. In addition, MD simulation was performed to assess the interaction profile of the docked protein-hits complexes. Meanwhile, Arg88, Gln112, Lys345, Trp356 form consistent hydrogen bond interactions with Dexketoprofen, Flurbiprofen, Ketoprofen, Morphine, and Citric acid during simulation. According to the results, each of the four compounds can be an appropriate inhibitor of LAAO and since our study was based on drug repurposing could be evaluated in phase II clinical trials. (https://pubmed.ncbi.nlm.nih.gov/31668098/)

Other indications investigated: Pain; inflammation (rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, dysmenorrhea, mild to moderate muscle pain, postoperative pain, and postpartum pain)

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Marketed (Pain; inflammation)

Development status: Active

Developers/investigators: Golestan University

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotalus adamanteus (Eastern diamondback rattlesnake)	N/A
Snake family		
Risk category		

Direct action on toxins? Yes

Target toxin class: Low toxicity toxins

Specific target toxin class: LAAO

Syndromic profiles: Not specified

Marimastat

Alternative name(s): BB-2516

Chemical name: (2R,3S)-N-[(2S)-3,3-dimethyl-1-(methylamino)-1-oxobutan-2-yl]-N',3-dihydroxy-2-(2-methylpropyl)butanediamide

CAS number: 154039-60-8

PCR ID: 1627

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: SVMPs (snake venom metalloproteinases)

Route of administration: Oral

Thermostability: Thermostable properties

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; marimastat works by binding to the active site of matrix metalloproteinases where it coordinates the metal ion in the binding pocket

MeSH headings / pharmacological class: Metalloproteases antagonists/inhibitors; Antineoplastics; Small molecules

Key features and challenges:

Marimastat is a second-generation anticancer drug originally developed with British Biotech in Europe and North America. It is an orally active metalloprotease inhibitor of the same class as batimastat, and is the first compound in this class to have completed a pivotal phase III clinical trial. Marimastat also has collagenase and angiogenesis inhibiting properties. Marimastat, as a broad-spectrum matrix metalloproteinase inhibitor, covalently binds to the zinc(II) ion in the active site of matrix metalloproteinases (MMPs), thereby inhibiting the action of MMPs, inducing extracellular matrix degradation, and inhibiting angiogenesis, tumour growth and invasion, and metastasis. (https://adisinsight.springer.com/drugs/800004324)

Marimastat is a promising drug candidate for treating snakebite due to its inhibitory capabilities against SVMP toxins, and has been trialled in numerous preclinical studies. Marimastat was found to effectively inhibit the haemorrhagic, coagulant and defibrinogenating effects and proteinase activities induced by Echis ocellatus venom, and in another study, to provide a significant degree of preclinical protection against the lethal effects of D. typus venom. (https://pubmed.ncbi.nlm.nih.gov/28400263/; https://pubmed.ncbi.nlm.nih.gov/32825484/; https://pubmed.ncbi.nlm.nih.gov/35321116/; https://pubmed.ncbi.nlm.nih.gov/35268832/)

Evidence supports that marimastat should be further explored as a potentially valuable early intervention therapeutic to broadly treat snakebite envenoming, as well as in combination with other small molecules such as Varespladib. (https://pubmed.ncbi.nlm.nih.gov/33922825/)

Other indications investigated: Breast cancer; Gastric cancer; Glioma; Head and neck cancer; Lung cancer; Non-small cell lung cancer; Ovarian cancer; Pancreatic cancer; Prostate cancer; Small cell lung cancer

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Phase III (Pancreatic cancer; Ovarian cancer)

Development status: Active

Developers/investigators: Vrije Universiteit Amsterdam; Liverpool School of Tropical Medicine (LSTM); University of Costa Rica (including the Clodomiro Picado Institute); Ophirex Inc

Preclinical sources:
https://www.sciencedirect.com/science/article/pii/S0041010117301174?via%3Dihub
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8935517/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8911647/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8309910/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8145175/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7555180/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Echis ocellatus (Ocellated carpet viper); Daboia russelii (Russel's viper); Bitis arietans (Puff adder); Dispholidus typus (Boomslang)	Echis ocellatus (Ocellated carpet viper); Daboia russelii (Russel's viper); Bitis arietans (Puff adder); Dispholidus typus (Boomslang)
Snake family		Viperidae,Colubridae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding)

Marimastat Varespladib mixture

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1471

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: SVMPs and PLA2s

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Preventing venom induced coagulopathy

MeSH headings / pharmacological class: Snake Bites / drug therapy*

Key features and challenges:

Marimastat, a broad-spectrum matrix metalloproteinase inhibitor was developed as an anti-neoplastic drug, while Varespladib was primarily developed to treat inflammatory disturbances associated with high levels of serum phospholipase A2. These two drugs have been trialled together in a preclinical study looking at combinations of repurposed small molecule-based toxin inhibitors as broad-spectrum therapeutics for snakebite. This study found that the dual mixture of marimastat and varespladib (MV) protected mice from the lethal effects of the most medically-important vipers of Africa, South Asia and Central America for the duration of the experiment. The inhibitor combination of marimastat and varespladib provides broad preclinical efficacy against venom lethality in an in-vivo 'challenge then treat' model of envenoming. MV is capable of preventing coagulopathy, and in the case of B. asper, inhibiting toxins acting to disrupt certain components of the endothelium. (https://pubmed.ncbi.nlm.nih.gov/33432119/ originally from https://pubmed.ncbi.nlm.nih.gov/33323937/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Liverpool School of Tropical Medicine (LSTM)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33432119/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Echis ocellatus; Echis carinatus(Saw scaled viper); Bothrops asper (Barba amarilla, Cascabelle, Fer-de-lance); Bitis arietans (Puff adder); Daboia russelii (Russell's viper)	Echis ocellatus; Echis carinatus(Saw scaled viper); Bothrops asper (Barba amarilla, Cascabelle, Fer-de-lance); Bitis arietans (Puff adder); Daboia russelii (Russell's viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs,PLA2s

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage),Procoagulant (blood clotting)

Methyl-varespladib

Alternative name(s): LY333013; A-002

Chemical name: N/A

CAS number: 172733-08-3

PCR ID: 1630

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Oral

Thermostability: Thermostable properties

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; interactions of methyl-varespladib appear to be with two specific regions of PLA2 and PLA2-like toxins, suggesting inhibition occurs by physical blockage of its allosteric activation, preventing the alignment of its functional sites and, consequently, impairing its ability to disrupt membranes.

MeSH headings / pharmacological class: Phospholipase A2 Inhibitors / therapeutic use*

Key features and challenges:

Methyl-Varespladib is the orally bioavailable prodrug of Varespladib (see candidate 'Varespladib'), both of which are toxin targeting, phospholipase A2 (sPLA2) inhibitor, being developed by Ophirex. They were originally developed by Eli Lilly in collaboration with Shionogi, for the treatment of sepsis-induced systemic inflammatory response syndrome and acute organ failure; however, development for these indications was discontinued in 2003 following disappointing results. The drug was subsequently licensed to Anthera. Anthera was developing an intravenous (IV) formulation of Varespladib (A 001) for the prevention of acute chest syndrome in patients with sickle cell disease (acute lung injury in the phase table) and an oral formulation of Varespladib (A 002) - i.e. Methyl-Varespladib - for once-daily treatment of acute coronary syndromes. A 002 was in phase III development in North America, Europe, Australia, India, Lebanon and Russia, and in phase II development in the US; however, following the termination of a phase II trial of the oral formulation in the treatment of acute coronary syndromes and the termination of the VISTA-16 trial due to a lack of efficacy, all ongoing trials of the drug were terminated and development of both the formulations was discontinued. (https://adisinsight.springer.com/drugs/800009544)

More than thirty preclinical studies have shown both forms of Varespladib to be a potent inhibitor of snake venom PLA2 in >50 different snake venoms across six continents. Varespladib looks promising as a candidate broad-spectrum, single agent initial treatment for snakebite or in combination with, for example, metalloprotease inhibitors (see Marimastat-varespladib). Preclinical studies have shown that Varespladib and methyl-Varespladib are not only effective against the activity of anti-coagulant PLA2 toxins, but also shows some inhibitory activity against procoagulant venom toxins. Varespladib and methyl-Varespladib potently and completely inhibited the anticoagulant activities detected in all venoms, except for D. russelii, for which almost complete inhibition was observed. Furthermore, Varespladib and methyl-Varespladib showed some degree of inhibition against procoagulant venom activities across the various venoms, despite these activities not known to be mediated by PLA2 toxins. (https://pubmed.ncbi.nlm.nih.gov/27571102/; https://pubmed.ncbi.nlm.nih.gov/32093386/

A murine model of lethal envenoming by a Papuan taipan (Oxyuranus scutellatus) demonstrates that LY333013, even with delayed oral administration, improves the chances of survival. Furthermore, LY333013 improves the performance of antivenom even after it no longer reverses neurotoxic signs. (https://pubmed.ncbi.nlm.nih.gov/30241297/)

As both Varespladib and methyl-Varespladib have been extensively tested in Phase II and III clinical trials for unrelated indications, these compounds could be rapidly and economically evaluated as an initial treatment for snakebite. This could be done alone and in combination with other small molecule therapeutics, e.g. marimastat (https://pubmed.ncbi.nlm.nih.gov/33432119/; https://pubmed.ncbi.nlm.nih.gov/33323937/)

Methyl-Varespladib is currently in Phase II clinical trials for snakebite envenoming in the United States and India (https://clinicaltrials.gov/ct2/show/NCT04996264)

Other indications investigated: Inflammatory conditions (incl acute coronary syndrome)

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Phase II

Highest R&D stage (any condition): Phase III (Acute coronary syndrome)

Development status: Active

Developers/investigators: Ophirex Inc; University of Costa Rica (including the Clodomiro Picado Institute)

Preclinical sources: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8309910/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6215158/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5037474/
https://pubmed.ncbi.nlm.nih.gov/29318152/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5037474/

Evidence of clinical trials? Yes

Phase II(Status: , November 2021-): *A study of Broad-spectrum Rapid Antidote: Varespladib Oral for Snakebite (BRAVO).* (CT number: CTRI/2021/11/037901, CT source: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=57690)

Phase II(Status: , August 2021-October 2022): *Broad-spectrum Rapid Antidote: Varespladib Oral for Snakebite* (CT number: NCT04996264, CT source: https://clinicaltrials.gov/show/NCT04996264)

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Acanthophis antarcticus; Agkistrodon blomhoffii brevicaudus; Agkistrodon contortrix; Agkistrodon piscivorus; Bitis gabonica; Bothrops asper; Bothrops jararaca; Bungarus caeruleus; Bungarus fasciatus; Calloselasma rhodostoma; Crotalus adamanteus; Crotalus atrox; Crotalus durissus terrificus; Crotalus scutulatus scutulatus; Dendroaspis polylepis; Echis carinatus; Laticauda semifasciata; Micrurus fulvius; Naja naja atra; Naja naja kaouthia; Naja naja naja; Notechis scutatus scutatus; Ophiophagus hannah; Oxyuranus scutellatus; Pseudechis australis; Trimersurus elegans; Vipera berus; Vipera russelli	Acanthophis antarcticus; Agkistrodon blomhoffii brevicaudus; Agkistrodon contortrix; Agkistrodon piscivorus; Bitis gabonica; Bothrops asper; Bothrops jararaca; Bungarus caeruleus; Bungarus fasciatus; Calloselasma rhodostoma; Crotalus adamanteus; Crotalus atrox; Crotalus durissus terrificus; Crotalus scutulatus scutulatus; Dendroaspis polylepis; Echis carinatus; Laticauda semifasciata; Micrurus fulvius; Naja naja atra; Naja naja kaouthia; Naja naja naja; Notechis scutatus scutatus; Ophiophagus hannah; Oxyuranus scutellatus; Pseudechis australis; Trimersurus elegans; Vipera berus; Vipera russelli
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Neurotoxic (paralysis),Haemorrhagic (bleeding),Cytotoxic (tissue damage)

Morphine

Alternative name(s): N/A

Chemical name: (4R,4aR,7S,7aR,12bS)-3-Methyl-2,3,4,4a,7,7a-hexahydro-1H-4,12-methano[1]benzofuro[3,2-e]isoquinoline-7,9-diol

CAS number: 57-27-2

PCR ID: 2542

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: L-amino acid oxidase (LAAO)

Route of administration: Not yet determined

Thermostability: Thermostable properties

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom toxins to neutralize its effects; Morphine and its metabolites act as agonists of the mu and kappa opioid receptors, but might also inhibit snake venom LAAO.

MeSH headings / pharmacological class: Analgesics; Opioid; Narcotics

Key features and challenges:

Morphineis an opioid agonist used for the relief of moderate to severe acute and chronic pain. (https://go.drugbank.com/drugs/DB00295)

A discovery stage, drug repurposing study concluded that morphine could be a promising inhibitor ofsnake venom l-amino acid oxidase (LAAO). The study was as follows:SinceCrotalus adamanteusLAAO has no crystal structure in the protein data bank, first, its 3D structure was constructed by homology modeling using 1REO as the template and then modeled structure was evaluated by several algorithms. Then, the authors screened the FDA-approved drugs by structure-based virtual screening, molecular dynamics (MD) simulation, and Molecular Mechanics Poisson Boltzmann Surface Area (MM/PBSA) to identify new inhibitors for the snake venom LAAO. Interestingly, docking results revealed that half of the hits belong to the propionic acid derivatives drugs. In addition, MD simulation was performed to assess the interaction profile of the docked protein-hits complexes. Meanwhile, Arg88, Gln112, Lys345, Trp356 form consistent hydrogen bond interactions with Dexketoprofen, Flurbiprofen, Ketoprofen, Morphine, and Citric acid during simulation. According to the results, each of the four compounds can be an appropriate inhibitor of LAAO and since our study was based on drug repurposing could be evaluated in phase II clinical trials. (https://pubmed.ncbi.nlm.nih.gov/31668098/)

Other indications investigated: Pain

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Marketed (Pain)

Development status: Active

Developers/investigators: Golestan University

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotalus adamanteus (Eastern diamondback rattlesnake)	N/A
Snake family		
Risk category		

Direct action on toxins? Yes

Target toxin class: Low toxicity toxins

Specific target toxin class: LAAO

Syndromic profiles: Not specified

N,N,N',N'-tetrakis (2-pyridylmethyl) ethane-1,2-diamine (TPEN)

Alternative name(s): N,N,N',N'-Tetrakis(2-pyridylmethyl)ethylenediamine; TPEDA

Chemical name: N,N,N',N'-tetrakis(pyridin-2-ylmethyl)ethane-1,2-diamine

CAS number: 16858-02-9

PCR ID: 1904

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: SVMPs

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; chelates and removes Zn2+ from the active site of Zn2+-dependent SVMPs

MeSH headings / pharmacological class: Chelating agents; metal chelators

Key features and challenges:

N,N,N',N'-tetrakis (2-pyridylmethyl) ethane-1,2-diamine, or TPEN, is a membrane-permeable zinc chelator, which has been involved in research around apoptosis and cancer (https://pubchem.ncbi.nlm.nih.gov/compound/5519). Because of its metal chelating abilities, it is of interest in snakebite therapeutic research.

TPEN has high affinity for Zn2+ and revealed potent inhibition of Echis carinatus venom (ECV) metalloproteases (ECVMPs) in vitro. Further, TPEN completely blocked the hemorrhagic and myotoxic activities of ECV in a dose dependent manner upon co-injection, and successfully neutralized hemorrhage and myotoxicity following independent injection. Histological examinations revealed that TPEN effectively prevents degradation of dermis and basement membrane surrounding the blood vessels in mouse skin sections. TPEN also prevents muscle necrosis and accumulation of inflammatory cells at the site of ECV injections. (https://pubmed.ncbi.nlm.nih.gov/25447774/; https://pubmed.ncbi.nlm.nih.gov/26274501/)

Other indications investigated: Cancer; Jembrana disease virus (JDV)

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: University of Mysore

Preclinical sources: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4537139/ https://www.sciencedirect.com/science/article/pii/S0041010114005856?via%3Dihub

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Echis carinatus (Saw-scaled viper)	Echis carinatus (Saw-scaled viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

Nafamostat

Alternative name(s): Nafamostat mesylate

Chemical name: (6-carbamimidoylnaphthalen-2-yl) 4-(diaminomethylideneamino)benzoate

CAS number: 81525-10-2

PCR ID: 1830

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: SVSPs

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; inhibits serine proteases (SVSPs)

MeSH headings / pharmacological class: Benzene and substituted derivatives

Key features and challenges:

Nafamostat mesylate, or nafamostat, is a synthetic serine protease inhibitor that is commonly formulated with hydrochloric acid due to its basic properties. It has been used in trials studying the prevention of Liver Transplantation and Postreperfusion Syndrome. The use of nafamostat in Asian countries (including Japan) is approved as an anticoagulant therapy for patients undergoing continuous renal replacement therapy due to acute kidney injury. (https://go.drugbank.com/drugs/DB12598) As a synthetic serine protease inhibitor, it is a short-acting anticoagulant, and is also used for the treatment of pancreatitis. It also has some potential antiviral and anti-cancer properties.

Nafamostat inhibits the in vitro serine protease activities of several geographically distinct viper venoms. In preclinical studies, the SVSP activities were broadly neutralized in a dose-dependent manner by nafamostat, with the highest doses (150 and 15 μM) completely inhibiting SVSP activity, irrespective of venom. However, nafamostat has potential detrimental off-target effects for use in snake envenoming via interaction with cognate coagulation cascade serine proteases, has a short half-life (~8 min), and requires intravenous administration, thereby limiting its utility and applicability as a potential prehospital snakebite therapeutic. https://pubmed.ncbi.nlm.nih.gov/33323937/)

Other indications investigated: Blood coagulation disorders; Disseminated intravascular coagulation; Pancreatitis; Atherosclerosis; Autoimmune disorders; Cancer; Reperfusion injury; Xenotransplant rejection

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Blood coagulation disorders; Disseminated intravascular coagulation; Pancreatitis)

Development status: Active

Developers/investigators: Liverpool School of Tropical Medicine (LSTM); Vrije Universiteit Amsterdam

Preclinical sources: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8374517/ https://pubmed.ncbi.nlm.nih.gov/33323937/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Echis ocellatus (Oscillated carpet viper); Echis carinatus (Saw-scaled viper); Bothrops asper (Fer-de-lance); Bitis arietans (Puff adder); Daboia russelii (Russell's viper)	Echis ocellatus (Oscillated carpet viper); Echis carinatus (Saw-scaled viper); Bothrops asper (Fer-de-lance); Bitis arietans (Puff adder)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVSPs

Syndromic profiles: Procoagulant (blood clotting)

Oral broad small molecule toxin inhibitors (Project)

Alternative name(s): Small molecule toxin inhibitors for use as broadly effective, inexpensive, oral, prehospital snakebite treatments

Chemical name: N/A

CAS number: N/A

PCR ID: 2188

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: Snake venom toxins (unspecifed)

Route of administration: Oral

Thermostability: Thermostable properties (unspecfied)

Mechanism of action: Small molecules bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: N/A

Key features and challenges:

Therapeutic synthetic small molecules can bind specific components/toxins (antigens) within snake venom with high specificity to neutralize its effects. Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other approaches are being investigated for novel therapeutics (natural or synthetic) that are cheaper, easier to produce, and have higher specificity and lower immunogenicity. Small molecule toxin inhibitors offer great potential to rapidly deliver inexpensive, safe and efficacious oral interventions in the community soon after a snakebite, prior to subsequent admission to a healthcare facility. Despite such promise, only a handful of toxin inhibitors have been robustly explored to date. (https://wellcome.org/grant-funding/people-and-projects/grants-awarded/discovery-and-early-translation-small-molecule)

Broadly effective, inexpensive, oral, prehospital small molecules toxin inhibitors for snakebite treatment are being explored and developed by the LSTM through a project funded by Wellcome. Through this project, LSTM will expand the chemical space available for snakebite treatments by employing a comprehensive drug discovery approach. Using toxin-specific assays, diverse compound libraries (> 50,000 molecules) will be screened, including using the Human Pharmacopoeia and Phase-1 approved molecules in a repurposing approach, for hits that demonstrate broad toxin family neutralisation. Thereafter, the project will rationally identify lead series by defining the toxin-specificity, kinetics, phenotypic potency and medicinal chemistry characteristics of hits, before performing murine preclinical efficacy and pharmacokinetic experiments to rationally define oral dosage regimens of lead candidates capable of achieving systemic inhibitory concentrations throughout a snakebite treatment period. Finally, therapeutic combinations of lead candidates will be evaluated by performing dose optimisation via PK/PD modelling, and preclinical efficacy and drug-drug interactions studies. This comprehensive drug discovery pipeline will deliver a portfolio of lead candidates (and numerous backups) ready for translation into clinical studies to assess their tolerability and efficacy as next-generation snakebite therapeutics. (https://wellcome.org/grant-funding/people-and-projects/grants-awarded/discovery-and-early-translation-small-molecule)

Other indications investigated: Unspecified

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Phase I (Other, unspecified)

Development status: Active

Developers/investigators: Liverpool School of Tropical Medicine (LSTM)

Key funders: Wellcome

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Unknown	Unknown
Snake family		
Risk category		Unknown

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

p-bromophenacyl bromide (pBPB)

Alternative name(s): 2,4'-Dibromoacetophenone; 4-Bromophenacyl bromide

Chemical name: 2-bromo-1-(4-bromophenyl)ethanone

CAS number: 99-73-0

PCR ID: 1795

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Not yet determined

Thermostability: Melting point 111.0 °C

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; inhibits snake venom PLA2s

MeSH headings / pharmacological class: Phospholipidase A(2) inhibitor

Key features and challenges:

p-bromophenacyl bromide is used to enhance ultraviolet detection of water-soluble organic acid. It is used to identify carboxylic acids, and is a known potent phospholipidase A(2) inhibitor. Because its anti-PLA2 activity, it is of interest as potential snakebite therapeutic. (https://pubchem.ncbi.nlm.nih.gov/compound/7454)

A study in the late 1990s examined the ability of para-bromophenacyl bromide (as well as wedelolactone and heparin) to antagonize the myotoxic activity in mice of venoms from Crotalus viridis viridis and Agkistrodon contortrix laticinctus and two phospholipase A2 myotoxins, CVV myotoxin and ACL myotoxin, isolated from them. para-bromophenacyl bromide (pBPB) reduced the myotoxic effect of both myotoxins (more than either wedelolactone or heparin). (https://pubmed.ncbi.nlm.nih.gov/9920492/)

Since then it has been used in other studies to assess the effect of inhibitors on the lethal activity and associated alterations induced by B. asper venom in mice, where pBPB reduced by 80% the PLA2 activity of the venom, in agreement with inhibition of a myotoxic PLA2 isolated from B. asper venom. (https://pubmed.ncbi.nlm.nih.gov/25447772/)

Other indications investigated: Blood platelet disorders; Edema

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: University of Costa Rica (including the Clodomiro Picado Institute); Brazilian Federal University of Rio de Janeiro (UFRJ)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/9920492/ https://pubmed.ncbi.nlm.nih.gov/25447772/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops asper (Fer-de-lance); Crotalus viridis viridis (Prairie rattlesnake); Agkistrodon contortrix laticinctus (Broad-banded copperhead)	Bothrops asper (Fer-de-lance); Crotalus viridis viridis (Prairie rattlesnake); Agkistrodon contortrix laticinctus (Broad-banded copperhead)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Cytotoxic (tissue damage)

Prinomastat

Alternative name(s): AG 3340

Chemical name: (S)-2,2-dimethyl-4-[[p-(4-pyridyloxy)phenyl]sulfonyl]-3-thiomorpholinecarbohydroxamic acid

CAS number: 192329-42-3

PCR ID: 1782

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: SVMPs (snake venom metalloproteinases)

Route of administration: Oral

Thermostability: Thermostable properties

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; Inhibition of SVMP activity

MeSH headings / pharmacological class: Metalloproteases antagonists/inhibitors; Antineoplastics; Small molecules

Key features and challenges:

Prinomastat is a synthetic hydroxamic acid derivative with potential antineoplastic activity. It is a matrix metalloproteinases inhibitor, thereby inducing extracellular matrix degradation, and inhibiting angiogenesis, tumor growth and invasion, and metastasis. As a lipophilic agent, prinomastat crosses the blood-brain barrier. Prinomastat was the orally available lead compound of a series of highly selective, non-peptidic, matrix metalloproteinase inhibitors developed by Pfizer. It has also been shown to inhibit angiogenesis in animal studies. Prinomastat was in phase III trials for non-small cell lung cancer in Australia, Europe and North America, a phase II trial in the US for glioblastoma multiforme and a phase II trial in the US for age-related macular degeneration. However, the development of prinomastat has been discontinued for these indications. (https://adisinsight.springer.com/drugs/800006391)

Because of its matrix metalloproteinases inhibitor, it is of interest for snakebite therapeutics. Prinomastat has shown promising results in numerous preclinical trials across a range of different snake venoms. Prinomastat showed inhibitory activity against the haemorrhagic effects of both purified SVMPs and the crude venom of E. ocellatus, and potently neutralised the procoagulant effects of D. typus venom (https://pubmed.ncbi.nlm.nih.gov/35321116/). Other studies have demonstrated the strong inhibitory effects of prinomastat against the anticoagulant activity of spitting cobra venoms. Prinomastat highly neutralized not only Vipera representatives also Daboia and Macrovipera (major metalloprotease dependent venoms) representatives at 0.2 mM concentration. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8911647/; https://pubmed.ncbi.nlm.nih.gov/34177943/)

Other indications investigated: Cancer; Age-related macular degeneration

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Phase III (Lung cancer)

Development status: Active

Developers/investigators: Liverpool School of Tropical Medicine (LSTM); Ophirex Inc; The University of Queensland

Preclinical sources: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8911647/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8222980/ https://pubmed.ncbi.nlm.nih.gov/35321116/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Dispholidus typus (Boomslang) E. ocellatus (Oscillated carpet viper); Naja species (cobras) including Naja ashei, N. katiensis, N. mossambica, N. nigricincta, N. nigricollis, N. nubiae, and N. pallida; Crotalus culminatus, C. mictlantecuhtli, C. molossus, and C. tzabcan	Dispholidus typus (Boomslang) E. ocellatus (Oscillated carpet viper); Naja species (cobras)
Snake family		Viperidae,Elapidae,Colubridae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding),Procoagulant (blood clotting)

Silver nanoparticles (AgNPs)

Alternative name(s): AgNPs

Chemical name: N/A

CAS number: N/A

PCR ID: 1468

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Philodryas olfersii; Bothrops jararacussu; Daboia russelli

Route of administration: Not yet determined

Thermostability: Thermostable properties, unknown temperature

Mechanism of action: Nanoparticles bind toxins to prevent their spread throughout the body

MeSH headings / pharmacological class: Metal nanoparticles

Key features and challenges:

Silver nanoparticles (AgNPs) are one of several metallic nanoparticles that are involved in biomedical applications. AgNPs play an important role in nanoscience and nanotechnology, particularly in nanomedicine. Therapeutically, AgNPs have been focused on potential applications in cancer diagnosis and therapy. (https://pubmed.ncbi.nlm.nih.gov/27649147/) Since these materials are thought to prevent the spread of venom through the body by binding toxins, silver nanoparticles hold promise in snakebite envenoming therapeutics.

AgNPs have been shown to promote protection against the neuromuscular blockade induced by Bothrops jararacussu venom (https://pubmed.ncbi.nlm.nih.gov/29961355/) and the proteolytic effects of Daboia russelli venom (https://pubmed.ncbi.nlm.nih.gov/30450270/) and against Philodryas olfersii venom (https://pubmed.ncbi.nlm.nih.gov/34079248/).

Other indications investigated: Cancer

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; cancer)

Development status: Active

Developers/investigators: University of Sorocaba, Universidade de Sorocaba (UNISO); University of Mumbai

Key funders: Brazilian Support Foundation for Research and Innovation in the State of Espirito Santo (FAPES)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/29961355/ https://pubmed.ncbi.nlm.nih.gov/30450270/

https://pubmed.ncbi.nlm.nih.gov/34079248/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Philodryas olfersii (South American green racer); Bothrops jararacussu (Jararacussu); Daboia russelii (Russell's viper)	Philodryas olfersii (South American green racer); Bothrops jararacussu (Jararacussu); Daboia russelii (Russell's viper)
Snake family		Viperidae,Colubridae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Neurotoxic (paralysis),Haemorrhagic (bleeding)

Sodium silicate complex (SSC)

Alternative name(s): Sodium silicate pentahydrate

Chemical name: sodium;silicate;pentahydrate

CAS number: N/A

PCR ID: 1916

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: Crude snake venom (potentially SVMPs); hyaluronidases

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; suspected role in inhibition of SVMPs

MeSH headings / pharmacological class: N/A

Key features and challenges:

Sodium silicate is a generic name for a group of chemical compounds, which are generally colourless transparent solids or white powders, and soluble in water in various amounts. Sodium silicates are used primarily in detergents, paper, water treatment, and construction materials. It has been investigated as a potential therapeutic agent in cancer and anti-viral studies. (https://pubmed.ncbi.nlm.nih.gov/33466634/)

Previous in vitro and in vivo studies showed that a silica-derived reagent, sodium silicate complex (SSC), was able to neutralize hemorrhagic and proteolytic activities induced by pit viper venoms, including Crotalus atrox, Agkistrodon contortrix contortrix and Agkistrodon piscivorus leucostoma. A more recent study validated that SSC could neutralize enzymatic and toxic effects caused by the venom of P. mucrosquamatus. It found that SSC inhibited the hemolytic and proteolytic activities induced by P. mucrosquamatus venom in vitro, and could block intradermal hemorrhage caused by P. mucrosquamatus venom in a mouse model. Finally, SSC could neutralize lethal effects of P. mucrosquamatus venom in the mice. Therefore, SSC is a candidate for further development as a potential onsite first-aid treatment for P. mucrosquamatus envenoming. (https://pubmed.ncbi.nlm.nih.gov/33466634/)

Other indications investigated: Cancer; anti-viral

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: Taipei Veterans General Hospital

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33466634/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotalus atrox (Western diamondback rattlesnake), Agkistrodon contortrix contortrix (Copperhead); Agkistrodon piscivorus leucostoma (Western cottonmouth); Protobothrops mucrosquamatus (Brown-spotted pitviper)	Crotalus atrox (Western diamondback rattlesnake), Agkistrodon contortrix contortrix (Copperhead); Agkistrodon piscivorus leucostoma (Western cottonmouth); Protobothrops mucrosquamatus (Brown-spotted pitviper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: SVMPs,Hyaluronidase

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

Suramin

Alternative name(s): Naganol; Suramine; Fourneau; Germanin

Chemical name: 8-[[4-methyl-3-[[3-[[3-[[2-methyl-5-[(4,6,8-trisulfonaphthalen-1-yl)carbamoyl]phenyl]carbamoyl]phenyl]carbamoylamino]benzoyl]amino]benzoyl]amino]naphthalene-1,3,5-trisulfonic acid

CAS number: 145-63-1

PCR ID: 1832

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: PLA2s MjTX-I, MjTX-II, myotoxin-II and BthTx (Bothrops spp)

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; inhibition of PLA2-like toxins

MeSH headings / pharmacological class: Antinematodal Agents; Antineoplastic Agents Trypanocidal Agents

Key features and challenges:

Suramin is polyanionic compound and 100-year-old drug developed to treat African trypanosomiasis, and is used clinically with diethylcarbamazine to kill the adult Onchocerca. It has also been shown to have potent antineoplastic properties. Suramin is manufactured by Bayer in Germany as Germanin. Though it has been investigated for other diseases, including cancer, it is not approved for any therapeutic use in the United States. (https://pubmed.ncbi.nlm.nih.gov/31844000/)

Suramin has also been shown to inhibit the myotoxic and cytotoxic activities of Lys49 PLA2 homologues. Suramin has been tested as an inhibitory molecule for different PLA2-like toxins, including BthTX-I from B. jararacussu, myotoxin-II from B. asper, MjTX-II from B. moojeni and MjTX-I. Preclinical studies have demonstrated that suramin neutralizes the myotoxic effect of MjTX-I (https://pubmed.ncbi.nlm.nih.gov/26457430/; https://pubmed.ncbi.nlm.nih.gov/29985425/).

Other indications investigated: African sleeping sickness; river blindness; cancer

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (African sleeping sickness)

Development status: Active

Developers/investigators: University of Costa Rica (including the Clodomiro Picado Institute)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/29985425/
https://pubmed.ncbi.nlm.nih.gov/26457430/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops moojeni (Brazilian lancehead); Bothropas jararacussu (Jararacussu); Bothrops asper (Fer-de-lance)	Bothrops moojeni (Brazilian lancehead); Bothropas jararacussu (Jararacussu); Bothrops asper (Fer-de-lance)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Cytotoxic (tissue damage)

Synthetic peptides from atPLIγ (gamma snake blood PLA2 inhibitor) (from Bothrops atrox)

Alternative name(s): sbPLIγ from Bothrops atrox

Chemical name: N/A

CAS number: N/A

PCR ID: 1932

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Peptides and proteins (synthetic or naturally derived) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Peptides

Key features and challenges:

Therapeutic proteins (synthetic or naturally derived) can bind specific components/toxins (antigens) within snake venom to neutralize its effects. Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other approaches are being investigated for novel therapeutics (natural or synthetic) that have have higher specificity and lower immunogenicity. Many venomous and nonvenomous snake species are naturally resistant to the deleterious actions of snake venom components. In many cases, this is due to the presence of specific antitoxins circulating in their blood. These alexeteric factors are proteins generated in the snake's liver, with native molecular masses ranging from 75 to 180 kDa. These nonimmunoglobulin antitoxins are PLA2 inhibitors (i.e., snake blood phospholipase A2 inhibitors, sbPLIs) and are used to protect the snake from the internal or external envenomation. These sbPLIs can be classified into three groups based on the homology of their amino acid sequence: α, β and γ. Since their discovery, there have been at least 15 kinds of αsbPLIs have been discovered in the different venomous snake families, four kinds of βsbPLIs have been found in three snake species, and twenty-three types of γsbPLIs in venomous and nonvenomous species (https://pubmed.ncbi.nlm.nih.gov/29318152/)

Synthetic peptides derived from atPLIγ - a gamma snake blood PLA2 inhibitor from Bothrops atrox were evaluated for their ability to reduce phospholipase and myotoxic activities as follows: Peptides were subjected to molecular docking with a homologous Lys49 PLA2 from B. atrox venom modeled by homology. Phospholipase activity neutralization assay was performed with BthTX-II and different ratios of the peptides. A catalytically active and an inactive PLA2 were purified from the B. atrox venom and used together in the in vitro myotoxic activity neutralization experiments with the peptides. The peptides interacted with amino acids near the PLA2 hydrophobic channel and the loop that would be bound to calcium in Asp49 PLA2. They were able to reduce phospholipase activity and peptides DFCHNV and ATHEE reached the highest reduction levels, being these two peptides the best that also interacted in the in silico experiments. The peptides reduced the myotubes cell damage with a highlight for the DFCHNV peptide, which reduced by about 65%. It has been suggested that myotoxic activity reduction is related to the sites occupied in the PLA2 structure, which could corroborate the

results observed in molecular docking. (https://pubmed.ncbi.nlm.nih.gov/31345152/) (https://pubmed.ncbi.nlm.nih.gov/34565143/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Oswaldo Cruz Foundation (FIOCRUZ), Fundação Oswaldo Cruz

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/31345152/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops atrox (Fer-de-lance)	Bothrops atrox (Fer-de-lance)
Snake family		Viperidae
Risk category		Category 1 (Highest Medical Importance)

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Not specified

Synthetic SVMPI peptides: pERW and pEKW (against Daboia russelii siamensis)

Alternative name(s): synthetic peptide SVMPIs; synthetic Snake Venom Metalloproteinase Inhibitors

Chemical name: N/A

CAS number: N/A

PCR ID: 1933

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: SVMP: Daboia russelii siamensis venom

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Peptides and proteins (synthetic or naturally derived) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Peptides

Key features and challenges:

Therapeutic peptides are short chains of amino acids linked by peptide bonds. In order to protect against auto-digestion by SVMPs, snake venom of several species are found to contain natural, endogenous protease inhibitors: citrate and small peptides. The latter bind selectively to SVMPs in the venom glands to protect glandular tissues and venom factors from self-digestion by SVMPs. As such, endogenous inhibitors - including SVMP inhibitors (SVMPIs) - from snakes are of interest in studies of new treatment modalities for neutralization of the effect of toxins. (https://pubmed.ncbi.nlm.nih.gov/28042812/)

Synthetic SVMPI peptides pERW and pEKW were developed to mirror two endogenous SVMPIs in Daboia russelii siamensis venom as follows: Two major snake venom metalloproteinases (SVMPs): RVV-X and Daborhagin were purified from Myanmar Russell's viper venom using a new purification strategy. Using the Next Generation Sequencing (NGS) approach to explore the Myanmar RV venom gland transcriptome, mRNAs of novel tripeptide SVMP inhibitors (SVMPIs) were discovered. Two novel endogenous tripeptides, pERW and pEKW were identified and isolated from the crude venom. Both purified SVMPs showed caseinolytic activity. Additionally, RVV-X displayed specific proteolytic activity towards gelatin and Daborhagin showed potent fibrinogenolytic activity. These activities were inhibited by metal chelators. Notably, the synthetic peptide inhibitors, pERW and pEKW, completely inhibit the gelatinolytic and fibrinogenolytic activities of respective SVMPs at 5 mM concentration. These complete inhibitory effects suggest that these tripeptides deserve further study for development of a therapeutic candidate for Russell's viper envenomation. (https://pubmed.ncbi.nlm.nih.gov/28042812/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Chulalongkorn University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/28042812/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russelii siamensis (Myanmar Russell's viper)	Daboia russelii siamensis (Myanmar Russell's viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding)

Synthetic variant peptide BLG-col (from β-Lactoglobulin, Buffalo Colostrum)

Alternative name(s): β-Lactoglobulin Peptide from Buffalo (Bubalus bubalis) Colostrum

Chemical name: N/A

CAS number: N/A

PCR ID: 1710

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: SVMPs: Echis carinatus

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Peptides and proteins (synthetic or naturally derived) bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: Peptides

Key features and challenges:

Therapeutic peptides are short chains of amino acids linked by peptide bonds. Because traditional plasma derived antivenoms from horses is expensive, labour intensive, and highly immunogenic, often causing severe side effects such as serum sickness or anaphylactic shock, other approaches are being investigated for novel therapeutics (natural or synthetic)that are cheaper, capable of rapid production, and have have higher specificity and lower immunogenicity - such as peptides.(https://pubmed.ncbi.nlm.nih.gov/29285351/).

Synthetic variant peptide BLG-col, originally derived from β-Lactoglobulin in Buffalo Colostrum was developed and tested for its anti-SVMP ability as follows: Colostrum is a rich natural source of bioactive peptides with many properties elucidated such as anti-thrombotic, anti-hypertensive, opioid, immunomodulatory, etc. In this study, a variant peptide derived from β-lactoglobulin from buffalo colostrum was evaluated for the anti-ophidian property by targeting snake venom metalloproteinases. These are responsible for rapid local tissue damages that develop after snakebite such as edema, hemorrhage, myonecrosis, and extracellular matrix degradation. The synthesised peptide identified by LC-MS/MS effectively neutralized hemorrhagic activity of the Echis carinatus venom in a dose-dependent manner. Histological examinations revealed that the peptide mitigated basement membrane degradation and accumulation of inflammatory leucocytes at the venom-injected site. Inhibition of proteolytic activity was evidenced in both casein and gelatin zymograms. Also, inhibition of fibrinolytic and fibrinogenolytic activities was seen. The UV-visible spectral study implicated Zn2+ chelation, which was further confirmed by molecular docking and dynamic studies by assessing molecular interactions, thus implicating the probable mechanism for inhibition of venom-induced proteolytic and hemorrhagic activities. The present investigation establishes newer vista for the BLG-col peptide with anti-ophidian efficacy as a promising candidate for therapeutic interventions. (https://pubmed.ncbi.nlm.nih.gov/28155167/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: University of Mysore; Karolinska Institute, Karolinska Institutet

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/28155167/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Echis carinatus (Saw-scaled viper)	Echis carinatus (Saw-scaled viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding)

Thioesters (2-Sulfenyl Ethylacetate derived)

Alternative name(s): Ethyl 2-((4-chlorobenzoyl)thio)acetate, Ethyl 2-((3-nitrobenzoyl)thio)acetate and Ethyl 2-((4-nitrobenzoyl)thio)acetate

Chemical name: Ethyl 2-((4-chlorobenzoyl)thio)acetate; Ethyl 2-((3-nitrobenzoyl)thio)acetate; Ethyl 2-((4-nitrobenzoyl)thio)acetate

CAS number: N/A

PCR ID: 1802

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: PLA2 (C. d. cumanensis); SVMP (Batx-I/B. atrox)

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; inhibition of PLA2 may be due to interactions of the studied compounds with amino acids in the catalytic site and the cofactor Ca2

MeSH headings / pharmacological class: N/A

Key features and challenges:

Thioesters are compounds with the functional group R–S–CO–R'. They are analogous to carboxylate esters with the sulphur in the thioester playing the role of the linking oxygen in the carboxylate ester. They are the product of esterification between a carboxylic acid and a thiol. Because administration of animal-derived antivenoms has limited efficacy against the venom-induced local tissue damage, which often leads to permanent disability, there is a need to find inhibitors against toxins responsible for local damage.

Thioesters derived from 2-sulfenyl ethylacetate were evaluated in preclinical studies for inhibitory effects on two snake venom toxins. Ethyl 2-((4-chlorobenzoyl)thio)acetate (I), Ethyl 2-((3-nitrobenzoyl)thio)acetate (II) and Ethyl 2-((4-nitrobenzoyl)thio)acetate (III) were synthesized. The inhibitory capacity of compounds (I–III) was evaluated on a phospholipase A2 isolated from the venom of Crotalus durissus cumanensis and the P-I type metalloproteinase Batx-I isolated from Bothrops atrox. Thioesters derived from 2-sulfenyl ethylacetate inhibited, in a specific way, PLA2 activity in micromolar concentrations. Results also suggest that compound III (ethyl 2-((4-nitrobenzoyl)thio)acetate) may be subject to further studies to develop inhibitors of snake venom PLA2 (https://pubmed.ncbi.nlm.nih.gov/31126073/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Universidad de Antioquia, Colombia

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/31126073/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotalus durissus cumanensis (Cascabel Rattlesnake); Bothrops atrox (Fer-de-lance)	Crotalus durissus cumanensis (Cascabel Rattlesnake); Bothrops atrox (Fer-de-lance)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs,PLA2s

Syndromic profiles: Cytotoxic (tissue damage)

Thiosemicarbazones (5A and 5B)

Alternative name(s): N/A

Chemical name: N-[4-[(carbamothioylhydrazinylidene)methyl]phenyl]acetamide

CAS number: 104-06-3

PCR ID: 1789

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: SVMP (BpMP-I): Bothrops pauloensis

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Thiosemicarbazone bind zinc, abrogating the function of SVMPs which rely on zinc for their catalytic mechanism.

MeSH headings / pharmacological class: Thiosemicarbazones; antituberc agents

Key features and challenges:

Thiosemicarbazones are the analogs of the semicarbazides with a sulphur atom in place of the oxygen atom. They are readily prepared by the condensation reaction between a ketone (or aldehyde) and a thiosemicarbazide. These compounds are versatile chelators toward a range of metal ions, such as divalent metal ions (Cu2+, Zn2+) and trivalent metal ions (Co3+, Fe3+, Re3+, Ga3+, In3+), with sulphur and azomethine nitrogen atoms. Biologically, these compounds have a broad spectrum of therapeutic properties with antibacterial, antimalarial, antiviral, and antitumor activities, through potentially binding to cellular copper, iron, or zinc ions. Numerous forms have been synthesized for examination of anticancer properties. (https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/thiosemicarbazone-derivative). Because of their zinc chelating properties, they are of interest for snakebite therapeutics, given zinc ions are needed for the catalytic mechanism of metalloproteinases.

Thiosemicarbazone candidates have been investigated and synthesised in a recent study, with two - 5a and 5b - showing promise. In this work, a structure-based molecular modelling strategy was used for the rational design, by means of a homology 3D model of an SVMP isolated from Bothrops pauloensis (Sao Paulo Lancehead) venom (BpMP-I), followed by synthesis and in vitro evaluation of new thiosemicarbazones as the first inhibitors of the B. pauloensis SVMP. Besides being effective for the SVMP inhibition, two molecules were shown to be effective also in vivo, inhibiting hemorrhage caused by the B. pauloensis whole venom. Docking studies on metalloproteinases from other snake species suggest that the thiosemicarbazones activity is not confined to BpMP-I, but seems to be a common feature of metzincins. (https://pubmed.ncbi.nlm.nih.gov/29152044/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: Rural Federal University of Rio de Janeiro, Universidade Federal Rural do Rio de Janeiro (UFRRJ)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/29152044/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops asper (Barba amarilla, Cascabelle, Fer-de-lance); Bothrops moojeni (Brazilian lancehead); Crotalus atrox (The western diamondback rattlesnake, Texas diamond-back); Crotalus adamanteus (Eastern diamondback rattlesnake); Agkistrodon acutus (Sharp nosed viper); Protobothrops mucrosquamatus (Brown-spotted pit viper, Taiwanese habu) (docking studies)	Bothrops asper (Barba amarilla, Cascabelle, Fer-de-lance); Bothrops moojeni (Brazilian lancehead); Crotalus atrox (The western diamondback rattlesnake, Texas diamond-back); Crotalus adamanteus (Eastern diamondback rattlesnake); Agkistrodon acutus (Sharp nosed viper); Protobothrops mucrosquamatus (Brown-spotted pit viper, Taiwanese habu) (docking studies)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding)

Titanium dioxide nanoparticles (TiO2-NPs)

Alternative name(s): Ultrafine titanium dioxide; nanocrystalline titanium dioxide

Chemical name: dioxotitanium

CAS number: 13463-67-7

PCR ID: 1860

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: Crude snake venom/PLA2: Daboia russelii, Naja kaouthia.

Route of administration: Not yet determined

Thermostability: Melting point 1855 °C

Mechanism of action: Nanoparticles bind toxins to prevent their spread throughout the body; thought to inhibit PLA2 activity

MeSH headings / pharmacological class: Nanoparticles

Key features and challenges:

Titanium dioxide nanoparticles (TiO2-NPs) are particles of titanium dioxide (TiO2) with diameters less than 100nm. TiO2-NPs are used in sunscreens due to its ability to block ultraviolet radiation while remaining transparent on the skin.

A preclinical study found that TiO2-NPs successfully neutralized the Daboia russelii venom (DRV) and Naja kaouthia venom (NKV)-induced lethal activity. Viper venom induced haemorrhagic, coagulant and anticoagulant activities were effectively neutralized both in in-vitro and in-vivo studies. The cobra and viper venoms-induced sterile inflammatory molecules (IL-6, HMGB1, HSP70, HSP90, S100B and vWF) were effectively neutralised by the TiO2-NPs in experimental animals. The TiO2-NPs were also found to be more effective in viper venom induced pathophysiological changes than the cobra venom. The exact mechanism of action is still unclear. (https://pubmed.ncbi.nlm.nih.gov/31371738/)

Other indications investigated: Dermal protection from UV (sunscreen); solar urticaria

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Sunscreen)

Development status: Active

Developers/investigators: NIT Goa

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/31371738/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russelii (Russell's viper); Naja kaouthia (Thai cobra)	Daboia russelii (Russell's viper); Naja kaouthia (Thai cobra)
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

Varespladib

Alternative name(s): LY-315920

Chemical name: 2-[3-(2-Amino-2-oxoacetyl)-1-benzyl-2-ethyl-1H-indol-4-yloxy]acetic acid

CAS number: 172732-68-2

PCR ID: 954

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Intravenous

Thermostability: Thermostable properties

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; crystallographic and bioinformatics analyses revealed interactions of Varespladib with two specific regions of the PLA2 toxin, suggesting inhibition occurs by physical blockage of its allosteric activation preventing the alignment of its functional sites and, consequently, impairing its ability to disrupt membranes

MeSH headings / pharmacological class: Phospholipase A2 Inhibitors

Key features and challenges:

Varespladib is a toxin targeting, phospholipase A2 (sPLA2) inhibitor, being developed by Ophirex, under a license from Eli lilly and Shinogi for the treatment of snakebite. The company is developing oral formulation for use in field, while the intravenous formulation is being developed for use in hospital settings to prevent the victim's reaction to venom and improve the efficacy of antivenoms which are not perfectly matched to the snake's venom. Clinical trials are underway in the US.

The compound was originally developed by Eli Lilly in collaboration with Shionogi, for the treatment of sepsis-induced systemic inflammatory response syndrome and acute organ failure; however, development for these indications was discontinued in 2003 following disappointing results. The drug was subsequently licensed to Anthera. Anthera was developing an intravenous (IV) formulation of Varespladib (A 001) for the prevention of acute chest syndrome in patients with sickle cell disease (acute lung injury in the phase table) and an oral formulation of Varespladib (A 002) for once-daily treatment of acute coronary syndromes (see candidate 'Methyl-Varespladib'). A 002 was in phase III development in North America, Europe, Australia, India, Lebanon and Russia, and in phase II development in the US; however, following the termination of a phase II trial of the oral formulation in the treatment of acute coronary syndromes and the termination of the VISTA-16 trial due to a lack of efficacy, all ongoing trials of the drug were terminated and development of both the formulations was discontinued. The US FDA granted Varespladib orphan drug status for the prevention of acute chest syndrome in patients with sickle cell disease in December 2007. Anthera has also received fast track status from the US FDA for IV Varespladib for acute chest syndrome.

In August 2017, Ophirex entered into a license agreement for data related to sPLA2 inhibitors from Eli Lilly and Company and Shionogi for Ophirex's development programme for the field treatment of envenomation, especially by snakes. It's inhibitory action against PLA2 has made it a promising candidate for treatment of snakebite envenoming. (https://adisinsight.springer.com/drugs/800009544)

Many preclinical studies have shown Varespladib to be a potent inhibitor of snake venom PLA2 in 28

different snake species across six continents, and looks promising as a candidate broad-spectrum, single agent initial treatment for snakebite. Preclinical studies have shown that Varespladib is not only effective against the activity of anti-coagulant PLA2 toxins, but also shows some inhibitory activity against procoagulant venom toxins. Varespladib potently and completely inhibited the anticoagulant activities detected in all venoms, except for D. russelii, for which almost complete inhibition was observed. Furthermore, Varespladib showed some degree of inhibition against procoagulant venom activities across the various venoms, despite these activities not known to be mediated by PLA2 toxins. (https://pubmed.ncbi.nlm.nih.gov/27571102/; https://pubmed.ncbi.nlm.nih.gov/29439513/; https://pubmed.ncbi.nlm.nih.gov/31748642/; https://pubmed.ncbi.nlm.nih.gov/32825484/;https://pubmed.ncbi.nlm.nih.gov/32093386/; https://pubmed.ncbi.nlm.nih.gov/32512199/; https://pubmed.ncbi.nlm.nih.gov/32485836/; https://pubmed.ncbi.nlm.nih.gov/33197555/; https://pubmed.ncbi.nlm.nih.gov/33922825/)

As both Varespladib and methyl-Varespladib have been extensively tested in Phase II clinical trials for unrelated indications, these compounds could be rapidly and economically evaluated as an initial treatment for snakebite. This could be done alone and in combination with other small molecule therapeutics, e.g. marimastat (https://pubmed.ncbi.nlm.nih.gov/33432119/; https://pubmed.ncbi.nlm.nih.gov/33323937/)

Other indications investigated: Acute coronary syndromes; Acute lung injury; Coronary artery disease; Multiple organ failure; Systemic inflammatory response syndrome

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Phase II (Acute chest syndrome; Sepsis-induced systemic inflammatory response syndrome)

Development status: Active

Developers/investigators: Ophirex Inc

Preclinical sources: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7555180/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6017252/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5727668/
https://pubmed.ncbi.nlm.nih.gov/28552814/
https://pubmed.ncbi.nlm.nih.gov/31748642/
https://pubmed.ncbi.nlm.nih.gov/32093386/
https://pubmed.ncbi.nlm.nih.gov/32512199/
https://pubmed.ncbi.nlm.nih.gov/32485836/
https://pubmed.ncbi.nlm.nih.gov/33197555/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8145175/
https://pubmed.ncbi.nlm.nih.gov/27571102/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Acanthophis antarcticus; Agkistrodon blomhoffii brevicaudus; Agkistrodon contortrix; Agkistrodon piscivorus; Bitis gabonica; Bothrops asper; Bothrops jararaca; Bungarus caeruleus; Bungarus fasciatus; Calloselasma rhodostoma; Crotalus adamanteus; Crotalus atrox; Crotalus durissus terrificus; Crotalus scutulatus scutulatus; Dendroaspis polylepis; Echis carinatus; Laticauda semifasciata; Micrurus fulvius; Naja naja atra; Naja naja kaouthia; Naja naja naja; Notechis scutatus scutatus; Ophiophagus hannah; Oxyuranus scutellatus; Pseudechis australis; Trimersurus elegans; Vipera berus; Vipera russelli	Acanthophis antarcticus; Agkistrodon blomhoffii brevicaudus; Agkistrodon contortrix; Agkistrodon piscivorus; Bitis gabonica; Bothrops asper; Bothrops jararaca; Bungarus caeruleus; Bungarus fasciatus; Calloselasma rhodostoma; Crotalus adamanteus; Crotalus atrox; Crotalus durissus terrificus; Crotalus scutulatus scutulatus; Dendroaspis polylepis; Echis carinatus; Laticauda semifasciata; Micrurus fulvius; Naja naja atra; Naja naja kaouthia; Naja naja naja; Notechis scutatus scutatus; Ophiophagus hannah; Oxyuranus scutellatus; Pseudechis australis; Trimersurus elegans; Vipera berus; Vipera russelli
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

X-Aptamers (against North American snakes) (Project)

Alternative name(s): Raptamers; Raptamer cocktail

Chemical name: N/A

CAS number: N/A

PCR ID: 2025

Include in data set: Yes

Technical profile

Drugs > Therapeutic - synthetic > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crotamine: C. o. helleri, plus other major toxin classes: N. American venomous snake venom

Route of administration: Not yet determined

Thermostability: Thermostable properties, temperature unspecified

Mechanism of action: DNA aptamers bind with high specificity to snake toxins to neutralize their effects

MeSH headings / pharmacological class: Aptamers; nucleotides

Key features and challenges:

DNA aptamers are short synthetic oligonucleotides (20–100 nucleotides) that can bind to a molecular target by their unique three-dimensional structure with high affinity and specificity, and as such, have clinical potential as macromolecular drugs. Aptamers are usually created by selecting from a large random sequence pool, but natural aptamers also exist in riboswitches. The use of aptamers for snakebite shows promise, having been shown to inhibit toxins from cone snails. Research is also being carried out on a large range of alternative binding scaffolds (AbScaffs) which due to low cost of production, high stability and engineerability could play a key role in future therapeutics for SBE (https://pubmed.ncbi.nlm.nih.gov/31226842/). DNA aptamer based antivenoms could be mass produced at lower cost than traditional antisera with longer shelf-lives at ambient temperatures.

X-Aptamers are developed via X-Aptamer selection technology, a proprietary system from Fannin Partners LLC that utilizes bead-based oligo DNA combinatorial libraries in which certain bases contain protein-like side modifications to enhance binding affinity. Under a project funded by the US NIH, X-Aptamers are being generated against a set of major toxin classes found in N. American venomous snakes, to develop novel antivenom formulation with a better safety profile than current antibody-based antivenoms. Preliminary studies have demonstrated selection of aptamers capable of neutralizing myotoxin (crotamine) from Southern Pacific rattlesnakes (C. o. helleri) in a hind limb paralysis model in mice. The project aims are: 1) Generate high-affinity oligonucleotide X-Aptamers against the five major classes of N. American snake venom toxins and measure the dissociation constant for each X-Aptamer and its target toxin; 2) Demonstrate in vivo efficacy of X-Aptamers against snake venom toxins and crude venom, using mouse models of haemorrhagic activity, creatine kinase activity, hind-limb paralysis, and lethality, to determine the effective dose for each aptamer; 3) Perform dose-ranging and toxicology studies in rats with the blended aptamer antivenom formulation. The completion of these studies will demonstrate safety and efficacy of a novel aptamer-based formulation which will have a strong impact and market potential in the emergency treatment of snake bite envenomation. (https://reporter.nih.gov/project-details/10157731)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: Fannin

Key funders: US National Institutes of Health (NIH)

Preclinical sources: https://fannininnovation.com/wp-content/uploads/2021/08/FanninRaptamerAntivenomAward_press-release-2021_08_04f.pdf

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotalus oreganus helleri (Southern Pacific rattlesnake)	Crotalus oreganus helleri (Southern Pacific rattlesnake)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Not specified

Therapeutic – natural/botanical

14-acetylandrographolide (Andrographis paniculata extract isolate)

Alternative name(s): N/A

Chemical name: [(3S,4E)-4-[2-[(1R,4aS,5R,6R,8aS)-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2-methylidene-3,4,4a,6,7,8-hexahydro-1H-naphthalen-1-yl]ethylidene]-5-oxooxolan-3-yl] acetate

CAS number: N/A

PCR ID: 2550

Include in data set: Yes

Technical profile

Drugs > Therapeutic -fds natural/botanical > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: SVMPs

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibits SVMPs

MeSH headings / pharmacological class: N/A

Key features and challenges:

14-acetylandrographolide is a phytochemical extract isolate from Andrographis paniculata.

A computational analysis examined the inhibition of metalloproteinase by phytochemicals present in Andrographis paniculata. Molecular docking studies revealed interaction of A. paniculata phytochemicals with the catalytic M domain's active site amino acid residues, namely ASN203, ARG293, PHE203, LEU206, LYS199, and ALA122, similar to that of the reference compound Batimastat. 14-acetylandrographolide, 14-deoxy-11,12 didehydroandrographolide, Andrograpanin, Isoandrographolide, and 14-deoxy-11-oxoandrographolide displayed high binding energy and inhibition against the metalloproteinase. Molecular dynamic simulation analysis revealed less root mean square fluctuation of amino acid residues of metalloproteinase-14-acetylandrographolide complex than metalloproteinase-Batimastat complex indicating the high stability for metalloproteinase with the phytochemical. In silico analysis of parameters like ADME properties and drug-likeness of the phytochemicals exhibited good pharmacokinetic properties. Ligand-based virtual screening of phytochemicals to identify similarity to FDA-approved drugs and identification of their possible targets were also performed. The outcome of the current study strengthens the significance of these phytochemicals as promising lead candidates for the treatment of snakebite envenomation. Moreover, the study also encourages the in vivo and in vitro evaluation of the phytochemicals to validate the computational findings. (https://pubmed.ncbi.nlm.nih.gov/34997448/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: B.S.Abdur Rahman Crescent Institute of Science and Technology

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russeli (Russel's viper)	N/A
Snake family		
Risk category		

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Not specified

14-deoxy-11,12 didehydroandrographolide (Andrographis paniculata extract isolate)

Alternative name(s): N/A

Chemical name: 14-deoxy-11,12 didehydroandrographolide

CAS number: N/A

PCR ID: 2551

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: SVMPs

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibits SVMPs

MeSH headings / pharmacological class: N/A

Key features and challenges:

14-deoxy-11,12 didehydroandrographolide is a phytochemical extract isolate from Andrographis paniculata.

A computational analysis examined the inhibition of metalloproteinase by phytochemicals present in Andrographis paniculata. Molecular docking studies revealed interaction of A. paniculata phytochemicals with the catalytic M domain's active site amino acid residues, namely ASN203, ARG293, PHE203, LEU206, LYS199, and ALA122, similar to that of the reference compound Batimastat. 14-acetylandrographolide, 14-deoxy-11,12 didehydroandrographolide, Andrograpanin, Isoandrographolide, and 14-deoxy-11-oxoandrographolide displayed high binding energy and inhibition against the metalloproteinase. Molecular dynamic simulation analysis revealed less root mean square fluctuation of amino acid residues of metalloproteinase-14-acetylandrographolide complex than metalloproteinase-Batimastat complex indicating the high stability for metalloproteinase with the phytochemical. In silico analysis of parameters like ADME properties and drug-likeness of the phytochemicals exhibited good pharmacokinetic properties. Ligand-based virtual screening of phytochemicals to identify similarity to FDA-approved drugs and identification of their possible targets were also performed. The outcome of the current study strengthens the significance of these phytochemicals as promising lead candidates for the treatment of snakebite envenomation. Moreover, the study also encourages the in vivo and in vitro evaluation of the phytochemicals to validate the computational findings. (https://pubmed.ncbi.nlm.nih.gov/34997448/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: B.S.Abdur Rahman Crescent Institute of Science and Technology

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russeli (Russel's viper)	N/A
Snake family		
Risk category		

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Not specified

14-deoxy-11-oxoandrographolide (Andrographis paniculata extract isolate)

Alternative name(s): N/A

Chemical name: 4-[2-[(1R,4aS,5R,6R,8aR)-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2-methylidene-3,4,4a,6,7,8-hexahydro-1H-naphthalen-1-yl]-2-oxoethyl]-2H-furan-5-one

CAS number: N/A

PCR ID: 2555

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: SVMPs

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibits SVMPs

MeSH headings / pharmacological class: N/A

Key features and challenges:

14-deoxy-11-oxoandrographolide is a phytochemical extract isolate from Andrographis paniculata.

A computational analysis examined the inhibition of metalloproteinase by phytochemicals present in Andrographis paniculata. Molecular docking studies revealed interaction of A. paniculata phytochemicals with the catalytic M domain's active site amino acid residues, namely ASN203, ARG293, PHE203, LEU206, LYS199, and ALA122, similar to that of the reference compound Batimastat. 14-acetylandrographolide, 14-deoxy-11,12 didehydroandrographolide, Andrograpanin, Isoandrographolide, and 14-deoxy-11-oxoandrographolide displayed high binding energy and inhibition against the metalloproteinase. Molecular dynamic simulation analysis revealed less root mean square fluctuation of amino acid residues of metalloproteinase-14-acetylandrographolide complex than metalloproteinase-Batimastat complex indicating the high stability for metalloproteinase with the phytochemical. In silico analysis of parameters like ADME properties and drug-likeness of the phytochemicals exhibited good pharmacokinetic properties. Ligand-based virtual screening of phytochemicals to identify similarity to FDA-approved drugs and identification of their possible targets were also performed. The outcome of the current study strengthens the significance of these phytochemicals as promising lead candidates for the treatment of snakebite envenomation. Moreover, the study also encourages the in vivo and in vitro evaluation of the phytochemicals to validate the computational findings. (https://pubmed.ncbi.nlm.nih.gov/34997448/)

Other indications investigated: Leishmaniasis

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Preclinical (Leishmaniasis)

Development status: Active

Developers/investigators: B.S.Abdur Rahman Crescent Institute of Science and Technology

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russeli (Russel's viper)	N/A
Snake family		
Risk category		

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Not specified

2-hydroxy-4-methoxybenzaldehyde (polyphenol plant extract isolates)

Alternative name(s): Janakia arayalpatra root extract isolates; synthetic HMBA analogues

Chemical name: 2-hydroxy-4-methoxybenzaldehyde

CAS number: 673-22-3

PCR ID: 1930

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: PLA2s

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; binds two amino acids, Asp49 and Gly30, located in the binding pocket of the PLA2 enzyme

MeSH headings / pharmacological class: N/A

Key features and challenges:

2-Hydroxy-4-methoxybenzaldehyde (HMBA) is a vanillin tasting compound found in black walnut, which makes 2-hydroxy-4-methoxybenzaldehyde a potential biomarker for the consumption of this food product, and is extracted from Janakia arayalpatra root extract. It is approved for use as a food additive.

The immunoadjuvant potential of this compound was assessed in previous preclinical experiments through hyperimmunization of rabbits with the Daboia rusellii venom (0.7 mg/kg) associated with the HMBA (200 mg/kg) by subcutaneous (s.c.) route in the late 1990s (https://pubmed.ncbi.nlm.nih.gov/9723840/). Since then, a follow on study has reviewed the inhibitory activity of synthetic analogues of the phenolic compound 2-hydroxy-4-methoxybenzaldehyde using in vitro, in vivo and in silico approaches against the lethality, hemorrhagic, coagulant, anti-coagulant, and PLA2 activities of D. russelii and lethal activity of N. kaouthia venoms. The degree of protection against the viper venom of D. russelii (11-fold) was found to be higher than that of the N. kaouthia cobra venom, effectively antagonized the defibrinogenating activity induced by D. russelii venom. effectively neutralized the crude D. russelii venom-induced pro-coagulant and PLA2 activity in vitro. However, further studies are warranted to establish the mechanism of action(s) of this phenolic compound against venom-induced pathophysiological changes, toxicity, and pre-clinical safety before they can be developed as anti-snake venom lead molecules. (https://pubmed.ncbi.nlm.nih.gov/26986086/)

In addition, a gold nanoparticle conjugated HMBA has been shown to inhibit lethality, inflammation and oxidative stress from D.russelli and Naja kaouthia venom (https://pubmed.ncbi.nlm.nih.gov/33976002/; https://pubmed.ncbi.nlm.nih.gov/30183223/) (See candidate 'Gold nanoparticle-conjugated 2-hydroxy-4-methoxybenzoic acid (GNP-HMBA)').

Other indications investigated: Food additive

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Food additive)

Development status: Active

Developers/investigators: Tezpur University; Hamdard Institute of Medical Sciences & Research; University of Calcutta

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/26986086/ https://pubmed.ncbi.nlm.nih.gov/9723840/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja kaouthia (Thai cobra); Daboia russelii (Russell's viper); Echis carinatus (Saw-scaled viper); Ophiophagus hannah (King cobra)	Naja kaouthia (Thai cobra); Daboia russelii (Russell's viper); Echis carinatus (Saw-scaled viper); Ophiophagus hannah (King cobra)
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Haemorrhagic (bleeding),Procoagulant (blood clotting)

4',7-dihydroxy-5-methoxyflavone-8-C-β-D-glucopyranoside (Oxalis corniculata extract isolate)

Alternative name(s): Oxalidaceae

Chemical name: N/A

CAS number: N/A

PCR ID: 1887

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Unclear

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibits hyaluronidase

MeSH headings / pharmacological class: Hyaluronoglucosaminidase antagonists & inhibitors; Wood Sorrel; Oxalidaceae; Oxalidales

Key features and challenges:

4′,7-dihydroxy-5-methoxyflavone-8-C-β-d-glucopyranoside from Oxalis corniculata was identified as a non-tannin hyaluronidase inhibitor, and was tested in a study looking at the use of the high-resolution hyaluronidase inhibition platform, which shows promise for advancing future snake bite necrosis inhibitor discovery from plant extracts (https://pubmed.ncbi.nlm.nih.gov/26386983/).

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: University of Copenhagen, Kobenhavens Universitet

Preclinical sources:
https://www.sciencedirect.com/science/article/pii/S0031942215300844?via%3Dihub

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Deinagkistrodon acutus (Chinese copperhead)	N/A
Snake family		
Risk category		N/A

Direct action on toxins? Yes

Target toxin class: Low toxicity toxins

Specific target toxin class: Hyaluronidase

Syndromic profiles: Not specified

Andrograpanin (Andrographis paniculata extract isolate)

Alternative name(s): N/A

Chemical name: 4-[2-[(1R,4aS,5R,8aS)-5-(hydroxymethyl)-5,8a-dimethyl-2-methylidene-3,4,4a,6,7,8-hexahydro-1H-naphthalen-1-yl]ethyl]-2H-furan-5-one

CAS number: 82209-74-3

PCR ID: 2552

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: SVMPs

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibits SVMPs

MeSH headings / pharmacological class: N/A

Key features and challenges:

Andrograpanin is a phytochemical extract isolate from Andrographis paniculata.

A computational analysis examined the inhibition of metalloproteinase by phytochemicals present in Andrographis paniculata. Molecular docking studies revealed interaction of A. paniculata phytochemicals with the catalytic M domain's active site amino acid residues, namely ASN203, ARG293, PHE203, LEU206, LYS199, and ALA122, similar to that of the reference compound Batimastat. 14-acetylandrographolide, 14-deoxy-11,12 didehydroandrographolide, Andrograpanin, Isoandrographolide, and 14-deoxy-11-oxoandrographolide displayed high binding energy and inhibition against the metalloproteinase. Molecular dynamic simulation analysis revealed less root mean square fluctuation of amino acid residues of metalloproteinase-14-acetylandrographolide complex than metalloproteinase-Batimastat complex indicating the high stability for metalloproteinase with the phytochemical. In silico analysis of parameters like ADME properties and drug-likeness of the phytochemicals exhibited good pharmacokinetic properties. Ligand-based virtual screening of phytochemicals to identify similarity to FDA-approved drugs and identification of their possible targets were also performed. The outcome of the current study strengthens the significance of these phytochemicals as promising lead candidates for the treatment of snakebite envenomation. Moreover, the study also encourages the in vivo and in vitro evaluation of the phytochemicals to validate the computational findings. (https://pubmed.ncbi.nlm.nih.gov/34997448/)

Other indications investigated: Inflammation; infection

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE, other)

Development status: Active

Developers/investigators: B.S.Abdur Rahman Crescent Institute of Science and Technology

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russeli (Russel's viper)	N/A
Snake family		
Risk category		

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Not specified

Aristolochic acid (Artistolochia sp. extract isolate)

Alternative name(s): N/A

Chemical name: N/A

CAS number: 313-67-7

PCR ID: 1637

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: PLA2s (phospholipase A2s); LAAOs (L-amino acid oxidases)

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: N/A

Key features and challenges:

Aristolochic acids are a family of carcinogenic, mutagenic, and nephrotoxic phytochemicals commonly found in the flowering plant family Aristolochiaceae. It is the most abundant of the aristolochic acids and is found in almost all Aristolochia (birthworts or pipevines) species. It has been tried in a number of treatments for inflammatory disorders, mainly in Chinese and folk medicine. However, there is concern over their use as aristolochic acid is both carcinogenic and nephrotoxic. It has a role as a nephrotoxin, a carcinogenic agent, a mutagen, a toxin and a metabolite. It is a monocarboxylic acid, a C-nitro compound, a cyclic acetal, an organic heterotetracyclic compound and an aromatic ether. (https://pubchem.ncbi.nlm.nih.gov/compound/2236)

Studies have revealed that aristolochic acid interacts with phospholipase A2 (PLA2) from Trimeresurus flavoviridis and Vipera russellii venoms and competitively inhibits the action of three different PLA2 enzymes from T. jlavoviridis, showing the most potent effect against the most toxic basic enzyme TFV L-PX. Aristolochic acid may also reduce inflammation via inhibition of nuclear factor (NF)-κB. Venom PLA2s and PLA2-like proteins also contribute to skeletal muscle necrosis - the ability of aristolochic acid to neutralise the myotoxic activity of piratoxin-I, a Lys49-PLA2 from Bothrops pirajai venom, via binding at two independent sites of interaction between Lys49-PLA2 and muscle membrane, indicated its potential usefulness to prevent the permanent injuries caused by these proteins in snakebite victims.(https://pubmed.ncbi.nlm.nih.gov/26192963/; https://pubmed.ncbi.nlm.nih.gov/28179114/; https://pubmed.ncbi.nlm.nih.gov/32980485/)

In another study, aristolochic acid showed an inhibitory effect over the myotoxic activity of Bothrops jararacussu and Bothrops asper venoms, being also effective against the indirect hemolytic activity of B. asper venom. Aristolochic acid also inhibited the myotoxic activity of BthTX-I and MTX-II with an efficiency greater than 60% against both myotoxins. (https://pubmed.ncbi.nlm.nih.gov/32613196). Aristolochic acid also inhibits activity of snake venom L amino acid oxidase (https://pubmed.ncbi.nlm.nih.gov/28803055/)

Other indications investigated: Inflammatory disorders (Chinese medicine)

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: Presidency University; Federal University of Sao Paulo, Universidade Federal de Sao Paulo (UNIFESP); Brazilian State University Paulista, Universidade Estadual Paulista (Unesp)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/28179114
https://pubmed.ncbi.nlm.nih.gov/28803055/
https://pubmed.ncbi.nlm.nih.gov/32980485/
https://www.sciencedirect.com/science/article/pii/S0041010117302398?via%3Dihub
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7322210/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8309910/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4508052/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russelii (Russell's viper); Bothrops pirajai (Pirajai); Trimeresurus flavoviridis (Habu); Bothrops jararacussu (Jararcussu); Bothrops asper (Fer-de-lance)	Daboia russelii (Russell's viper); Bothrops pirajai (Pirajai); Trimeresurus flavoviridis (Habu); Bothrops jararacussu (Jararcussu); Bothrops asper (Fer-de-lance)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: PLA2s,LAAO,Hyaluronidase

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

Bakuchiol (plant extract isolate)

Alternative name(s): N/A

Chemical name: 4-[(1E,3S)-3-ethenyl-3,7-dimethylocta-1,6-dienyl]phenol

CAS number: 10309-37-2

PCR ID: 1913

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: PLA2s

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; interacts with the calcium binding residues of Ca2+ dependent PLA2s which disturbs the binding of Ca2+ to the PLA2s

MeSH headings / pharmacological class: Phospholipase A2 Inhibitors

Key features and challenges:

Bakuchiol is a meroterpene phenol abundant in and mainly obtained from the seeds of the Psoralea corylifolia plant, which is widely used in Indian as well as in Traditional Chinese medicine to treat a variety of diseases. Bakuchiol is under investigation in clinical trial NCT03112863 (Comparison of the Cosmetic Effects of Bakuchiol and Retinol), and has been investigated for various other conditions, such as acne and cancers. (https://pubchem.ncbi.nlm.nih.gov/compound/5468522)

In preclinical investigation for snakebite envenoming, bakuchiol was found to be interact with Daboxin P - a PLA2 from Indian Daboia russelii - with high affinity in silico. Bakuchiol interacted with the Ca2+ binding residues of Daboxin P. Bakuchiol could also neutralize the anti-coagulatory activity of Daboxin P as well as of the big four crude venom. Further studies are needed to assess the effectiveness of this candidate as a treatment for SBE. (https://pubmed.ncbi.nlm.nih.gov/33035526/)

Other indications investigated: Prostate cancer; acne

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Phase I (Acne; Cosmetic)

Development status: Active

Developers/investigators: Tezpur University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33035526/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russelii (Russell's viper)	Daboia russelii (Russell's viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Procoagulant (blood clotting)

Betulinic acid

Alternative name(s): Mairin; Betulic acid; Lupatic Acid

Chemical name: (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-prop-1-en-2-yl-1,2,3,4,5,6,7,7a,9,10,11,11b,12,13,13a,13b-hexadecahydrocyclopenta[a]chrysene-3a-carboxylic acid

CAS number: 472-15-1

PCR ID: 1805

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: SVMP (incl. Batx-I (Bothrops atrox)

Route of administration: Not yet determined

Thermostability: Melting point 316-318°C

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibits SVMP

MeSH headings / pharmacological class: N/A

Key features and challenges:

Betulinic acid is a naturally occurring pentacyclic triterpenoid which has antiretroviral, antimalarial, and anti-inflammatory properties, as well as a more recently discovered potential as an anticancer agent, by inhibition of topoisomerase. (https://pubchem.ncbi.nlm.nih.gov/compound/64971). It is marketed and available as a dietary supplement.

Preclinical studies have demonstrated that Betulinic acid partly inhibits the proteolytic, phospholipase A2 and hyaluronidase activities of B. atrox venom (https://pubmed.ncbi.nlm.nih.gov/33984369/), as well inhibiting proteolytic, haemorrhagic, myotoxic and edema-forming activities of the metalloproteinase Batx-I isolated from B. atrox venom (https://pubmed.ncbi.nlm.nih.gov/29203373/)). Consequently, triterpenic acids could mitigate venom-induced local tissue damage not only by directly inhibiting venom metalloproteinases, but also, by their widely reported anti-inflammatory activity and their reported ability to inhibit other venom toxins implied in this effect such as myotoxic PLA2. Molecular docking studies suggest that triterpenic acids may block substrate binding cleft, affecting the proteolytic activity of the enzyme. (https://pubmed.ncbi.nlm.nih.gov/29203373/)

Another study showed that betulin has a similar efficacy as commercial antivenoms in attenuating the neuromuscular effects of B. jararacussu venom in vivo and could be a useful complementary measure to antivenom therapy for treating snakebite (https://pubmed.ncbi.nlm.nih.gov/26633987/).

Other indications investigated: Dietary supplement; cancer; HIV; malaria; dysplastic nevus syndrome; wound healing

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Dietary supplement; Topical wound heaing)

Development status: Active

Developers/investigators: Universidad de Antioquia, Colombia; Military Institute of Engineering, Rio de Janeiro

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/26633987/
https://pubmed.ncbi.nlm.nih.gov/33984369/
https://pubmed.ncbi.nlm.nih.gov/29203373/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops atrox (Fer-de-lance); Bothrops jararacussu (Jararacussu)	Bothrops atrox (Fer-de-lance); Bothrops jararacussu (Jararacussu)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Neurotoxic (paralysis),Haemorrhagic (bleeding),Cytotoxic (tissue damage)

BRS-P19 (Bauhinia rufescens seed extract isolate)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1809

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: PLA2s

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Inhibition of VPLA2s and antioxidant activity

MeSH headings / pharmacological class: Bauhinia

Key features and challenges:

BRS-P19 is a potential anti snake venom peptide isolated from Bauhinia rufescens seed (Kharoub Tree). It has been investigated as a potential alternative to serum-based antivenoms. It was tested using venom-PLA2s isolated from Naja nigricollis venom.

Findings from this study established that BRS-P19 has anti-snake venom effect through inhibition of PLA2 and antioxidant activity as the possible mechanisms of action, and showed that BRS-P19 is a potent inhibitor of PLA2 as compared to the standard antivenin (https://pubmed.ncbi.nlm.nih.gov/35314419/;

https://ideas.repec.org/a/arp/rjbarp/2020p18-26.html)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Kebbi State University of Science and Technology

Preclinical sources:
https://www.sciencedirect.com/science/article/pii/S0378874122002471?via%3Dihub
https://ideas.repec.org/a/arp/rjbarp/2020p18-26.html

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja nigricollis (Black-necked spitting cobra)	Naja nigricollis (Black-necked spitting cobra)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Cytotoxic (tissue damage)

Butein (plant extract isolate)

Alternative name(s): 2',3,4,4'-Tetrahydroxychalcone; 2',4',3,4-Tetrahydroxychalcone; 3,4,2',4'-Tetrahydroxychalcone

Chemical name: (E)-1-(2,4-dihydroxyphenyl)-3-(3,4-dihydroxyphenyl)prop-2-en-1-one

CAS number: 487-52-5

PCR ID: 1914

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: PLA2s

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibition of PLA2s

MeSH headings / pharmacological class: Phospholipase A2 Inhibitors

Key features and challenges:

Butein (20, 40, 3, 4-tetrahydroxychalcone), is a chalcone that has exhibited a wide range of pharmacological effects such as anti-inflammatory, anticancer, antioxidant, and antiangiogenic in diverse disease models. (https://pubchem.ncbi.nlm.nih.gov/compound/5281222)

Preclinical studies showed that butein could neutralize the PLA2 activity and anti-coagulatory property Daboxin P in vitro. It was shown that butein binds to Daboxin P with high affinity and interacted with the catalytic triad but mimosine and bakuchiol interacted with the Ca2+ binding residues of Daboxin P. In vitro validation showed that butein inhibited the sPLA2 activity of Daboxin P. Butein could also neutralize the PLA2 activity of Indian big four venoms dose dependently. However, butein couldn't neutralize the anti/pro-coagulatory property of crude venom of big four. This may be due to interaction of butein at the active site of PLA2s, but further studies are needed to confirm the effectiveness as snakebite treatment. (https://pubmed.ncbi.nlm.nih.gov/33035526/)

Other indications investigated: Breast cancer

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: Tezpur University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33035526/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russelii russelii (Russell's viper)	Daboia russelii russelii (Russell's viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Haemorrhagic (bleeding)

Caffeic acid (polyphenol plant extract isolate)

Alternative name(s): N/A

Chemical name: 3,4-Dihydroxycinnamic acid

CAS number: 331-39-5

PCR ID: 1775

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Not yet determined

Thermostability: Melting points 225 °C

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; binds to protein sites responsible for enzymatic and myotoxic activities of PLA2

MeSH headings / pharmacological class: Antioxidants

Key features and challenges:

Caffeic acid (CA) is a phenolic compound synthesized by all plant species and is present in foods such as coffee, wine, tea, and popular medicines such as propolis. It is an orally bioavailable, hydroxycinnamic acid derivative and polyphenol, with potential anti-oxidant, anti-inflammatory, and antineoplastic activities. Caffeic acid acts as an antioxidant and prevents oxidative stress, thereby preventing DNA damage induced by free radicals. It has been investigated for treatment of cancer, immune thrombocytopenia, and is active ingredient in at least six drugs (https://pubchem.ncbi.nlm.nih.gov/compound/).

Preincubation of venom with caffeic acid partially neutralized the muscle damage promoted by PrTX-I from Bothropspirajai venom. As CA is a Rosmarinic acid precursor, it was expected that its inhibitory activities against PrTX-I effects would be similar in the phrenic-diaphragm preparation. On the other hand, light microscopy analysis of muscle preparations submitted to myographic experiments showed that CA protected against the myotoxic effect induced by PrTX-I by 40% and 65% (PrTX-I/CA at ratios of 1:1 and 1:5, respectively). The lack of effect on neuromuscular blockade by caffeic acid contrasts with that of rosmarinic acid, a derivative of caffeic acid, that markedly attenuates the neuromuscular blockade by PrTX-I. (https://pubmed.ncbi.nlm.nih.gov/26192963; https://pubmed.ncbi.nlm.nih.gov/34979199/). However, separate studies showed that CA can be a potent inhibitor of acidic and basic PLA2s due to binding to protein sites responsible for its enzymatic and myotoxic activities. (https://pubmed.ncbi.nlm.nih.gov/34822584/)

Other indications investigated: Immune thrombocytopenia; cancer

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Phase III (Immune thrombocytopenia)

Development status: Active

Developers/investigators: University of Sorocaba (UNISO), Brazil; Brazilian State University Paulista, Universidade Estadual Paulista (Unesp)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/34822584/ https://pubmed.ncbi.nlm.nih.gov/26192963/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops pirajai (Pirijai); Crotalus durissus terrificus (South American rattlesnake); Crotalus durissus cumanensis (Venezuelan rattlesnake)	Bothrops pirajai (Pirijai); Crotalus durissus terrificus (South American rattlesnake); Crotalus durissus cumanensis (Venezuelan rattlesnake)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Cytotoxic (tissue damage)

Caftaric acid (polyphenol plant extract isolate)

Alternative name(s): N/A

Chemical name: (2R,3R)-2-[(E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy-3-hydroxybutanedioic acid

CAS number: 67879-58-7

PCR ID: 1817

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: PLA2: BthTX-I/Bothropstoxin-I (B. jararcussu)

Route of administration: Not yet determined

Thermostability: Melting point 125°C

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibits BthTX-I

MeSH headings / pharmacological class: N/A

Key features and challenges:

Caftaric acid is a phenolic acid derived from caffeic and tartaric acid, abundant in several varieties of grapes and wines.

Preclinical studies have investigated the interaction between Bothropstoxin-I (BthTX-I, the main PLA2-like protein isolated from Bothrops jararacussu snake venom) and caftaric acid (CFT), and found that caftaric acid neutralizes the myotoxic effects promoted by a PLA2-like protein. This acid inhibited 91% of the neuromuscular blocking and 95% of the myotoxic action caused by BthTX-I. (https://pubmed.ncbi.nlm.nih.gov/31978419/; https://pubmed.ncbi.nlm.nih.gov/34979199/)

Other indications investigated: COVID-19; antioxidant; anti-inflammatory; antimutagenic; anticarcinogenic; hepatoprotective

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: Brazilian State University Paulista, Universidade Estadual Paulista (Unesp)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/31978419/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops jararacussu (Jararacussu)	Bothrops jararacussu (Jararacussu)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Neurotoxic (paralysis),Cytotoxic (tissue damage)

Casuarictin (Laguncularia racemosa extract isolate)

Alternative name(s): Sanguiin H 11

Chemical name: [(1R,2S,19R,20S,22R)-7,8,9,12,13,14,28,29,30,33,34,35-dodecahydroxy-4,17,25,38-tetraoxo-3,18,21,24,39-pentaoxaheptacyclo[20.17.0.02,19.05,10.011,16.026,31.032,37]nonatriaconta-5,7,9,11,13,15,26,28,30,32,34,36-dodecaen-20-yl] 3,4,5-trihydroxybenzoate

CAS number: 79786-00-8

PCR ID: 1774

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; forms a complex with PLA2

MeSH headings / pharmacological class: N/A

Key features and challenges:

Casuarictin is an ellagitannin, a type of hydrolysable tannin, and is a natural product found in many types of plants. It has been investigated for its anti-cancer, anti-inflammation and anti-viral properties (https://pubchem.ncbi.nlm.nih.gov/).

In preclinical studies, the pharmacological and biological effects of Casuarictin were evaluated on isolated sPLA2 from the rattlesnake (Crotalus durissus terrificus) and using a plant bacterial strain. The compound was able to form a protein complex consisting of a stable sPLA2 + Casuarictin complex. Molecular interactions of Casuarictin with sPLA2 were able to virtually abolish the native edematogenic effect as well as myonecrosis induced by the protein when injected 10 min after sPLA2. Therefore, Casuarictin may be considered a potential anti-inflammatory that can be used to treat edema and myonecrosis induced by serine-secreting phospholipase A2. (https://pubmed.ncbi.nlm.nih.gov/31288445/)

Other indications investigated: Cancer; antiviral

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: Instituto de Biociências, UNESP, Brazil

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/31288445/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotalus durissus terrificus (South American rattlesnake)	Crotalus durissus terrificus (South American rattlesnake)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Cytotoxic (tissue damage)

Chicoric acid (polyphenol plant extract isolate)

Alternative name(s): N/A

Chemical name: (2R,3R)-2,3-bis[[(E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy]butanedioic acid

CAS number: 70831-56-0

PCR ID: 1818

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: PLA2 (BthTX-I)

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; binds BthTX-I to adopt different oligomeric conformations

MeSH headings / pharmacological class: N/A

Key features and challenges:

Chicoric acid is a hydroxycinnamic acid, extracted from chicory and the purple coneflower plant. Chicoric acid has been shown to stimulate phagocytosis in both in vitro and in vivo studies, to inhibit the function of hyaluronidase, to protect collagen from damage and to inhibit the function of HIV-1 integrase.

Preclinical studies have demonstrated that chicoric acid (CA) is an efficient inhibitor of the PLA2-like myotoxin, BthTX-I from Bothrops jararacussu, and does this through inducing BthTX-I to adopt different oligomeric conformations. (https://pubmed.ncbi.nlm.nih.gov/30251662/; https://pubmed.ncbi.nlm.nih.gov/33333169/; https://pubmed.ncbi.nlm.nih.gov/34979199/)

Other indications investigated: COVID-19; inflammation

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: Universidade Estadual Paulista (UNESP)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33333169/ https://pubmed.ncbi.nlm.nih.gov/30251662/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops jararacussu (Jararacussu)	Bothrops jararacussu (Jararacussu)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Neurotoxic (paralysis),Cytotoxic (tissue damage)

Chlorogenic acid (polyphenol plant extract isolate)

Alternative name(s): Chlorogenate

Chemical name: (1S,3R,4R,5R)-3-[(E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy-1,4,5-trihydroxycyclohexane-1-carboxylic acid

CAS number: 202650-88-2

PCR ID: 1772

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Not yet determined

Thermostability: Melting point 205-209°C

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects

MeSH headings / pharmacological class: N/A

Key features and challenges:

Chlorogenic acid (CA), belongs to the hydroxycinnamic acid family, and is formed by caffeic acid and quinic acid. CA is produced in plants in the shikimic acid pathway during aerobic respiration. This compound is an active ingredient in foods, traditional Chinese medicine preparations and at least three other drug products, although it is not in itself indicated or available as a drug or supplement. Clinical trials are underway to test the safety and efficacy of CA for a number of indications including lung and other advanced cancers. (https://pubchem.ncbi.nlm.nih.gov/compound/1794427)

Chlorogenic acid was found to mitigate the effects of B. leucurus venom in a preclinical study, as well as modulating the inflammatory activity of PLA2 in C. d. terrificus venom. Chlorogenic acid however was found to not protect against C. d. terrificus induced neuromuscular blockade in-vitro. (https://pubmed.ncbi.nlm.nih.gov/35247716/; https://pubmed.ncbi.nlm.nih.gov/34822584/; https://pubmed.ncbi.nlm.nih.gov/34979199/)

Other indications investigated: Diabetes; COVID-19; cancer

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Phase II (Diabetes; Lung cancer)

Development status: Active

Developers/investigators: Federal University of Rio Grande do Norte; University of Sorocaba (UNISO), Brazil

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/35247716/ https://pubmed.ncbi.nlm.nih.gov/34822584/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	C. d. terrificus (South American Rattlesnake); Bothrops leucurus (Bahia lancehead); Daboia russellii (Russell's viper); Protobothrops flavoviridis (Habu)	C. d. terrificus (South American Rattlesnake); Bothrops leucurus (Bahia lancehead); Daboia russellii (Russell's viper); Protobothrops flavoviridis (Habu)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Cytotoxic (tissue damage)

Crepiside E beta glucopyranoside (Elephantopus scaber extract isolate)

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1892

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: PLA2s

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Inhibition via the active site of PLA2s

MeSH headings / pharmacological class: N/A

Key features and challenges:

Crepiside E beta glucopyranoside is an extract isolated from Elephantopus scaber, a tropical plant species which has been recognized for its various pharmacological activities, and especially anti-snake venom property.

Crepiside E (deacylcynaropicrin-3' beta-glucopyranoside) has shown interactions with the conserved catalytic active site residues, His 48 and Asp 49, in both the PLA2s. Further, molecular dynamic simulations for 60 ns confirmed the stability of crepiside E in the active site of PLA2s and were found to be stable throughout the simulation. The results from molecular docking and dynamic studies suggest that crepiside E could serve as a potent inhibitor against group I and II PLA2 by hindering the interactions of active-site catalytic residues (https://pubmed.ncbi.nlm.nih.gov/30847632/).

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: University of Kerala

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/30847632/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	N/A	N/A
Snake family		
Risk category		N/A

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Not specified

Fucoidan (Brown seaweed extract isolate)

Alternative name(s): Polysaccharide

Chemical name: [(2S,3S,4S,5S,6R)-4-hydroxy-5-methoxy-2,6-dimethyloxan-3-yl] hydrogen sulfate

CAS number: N/A

PCR ID: 1728

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Not yet determined

Thermostability: High

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; neutralize the cytolytic and myotoxic effects of a number of group II PLA2s and PLA2 homologs (Lys49 PLA2s).

MeSH headings / pharmacological class: N/A

Key features and challenges:

Fucoidan is a natural polysaccharide extracted from Ecklonia cava, Sargassum vachellianum and other brown seaweeds. (https://pubchem.ncbi.nlm.nih.gov/compound/129532628). It is available over the counter as a dietary supplement. Fucoidan inhibits myotoxic phospholipases A(2), and is therefore of interest in snakebite therapeutics. It specifically neutralize the cytolytic and myotoxic effects of a number of group II PLA2s and PLA2 homologs (Lys49 PLA2s) present in the venoms of crotalid snakes. The mechanism underlying this inhibition was shown to involve the direct interaction of the polyanionic fucoidan chains with the cationic C-terminal region 115–129 of the myotoxins, forming complexes.

A study in 2008 evaluated the influence of molecular weight on the ability of fucoidan to prevent muscle necrosis when rapidly administered after injection of a purified myotoxin or crude venom of Bothrops asper, in a mouse model, with promising results (https://pubmed.ncbi.nlm.nih.gov/18061642/). Since then it has been used in other studies to assess the effect of inhibitors on the lethal activity and associated alterations induced by B. asper venom in mice (https://pubmed.ncbi.nlm.nih.gov/25447772/).

Other indications investigated: Dietary supplement

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Dietary supplement)

Development status: Active

Developers/investigators: University of Costa Rica (including the Clodomiro Picado Institute)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/25447772/ https://pubmed.ncbi.nlm.nih.gov/18061642/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops asper (Fer-de-lance)	Bothrops asper (Fer-de-lance)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Cytotoxic (tissue damage)

Gallic acid (polyphenol plant extract isolate)

Alternative name(s): N/A

Chemical name: 3,4,5-trihydroxybenzoic acid

CAS number: 149-91-7

PCR ID: 1814

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: PLA2: BthTX-I and BthTX-II

Route of administration: Not yet determined

Thermostability: Melting point 258-265°C

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; forms a complex with the two main myotoxins of the Bothrops venom, thus inhibiting it's myotoxic effects

MeSH headings / pharmacological class: N/A

Key features and challenges:

Gallic acid (GA) is a hydroxybenzoic acid, and myotixin inhibitor obtained from Anacardium humile. Gallic acid is a trihydroxybenzoic acid. It has a role as an astringent, a cyclooxygenase 2 inhibitor, a plant metabolite, an antioxidant, an antineoplastic agent, a human xenobiotic metabolite, an apoptosis inducer and a geroprotector. It is also a food additive. Gallic acid is the active ingredient in at least five approved drugs, including for asthma. (https://pubchem.ncbi.nlm.nih.gov/compound/370).

A number of studies have investigated tannins as snakebite therapeutics, including gallic acid. More recent preclinical studies have shown that GA alone was able to inhibit the myotoxic activity induced by the crude venom of Bothrops jararacussu and its two main myotoxins, BthTX-I and BthTX-II. It suggested that GA does this by forming a complex with BthTX-I and II. This study demonstrated GA's ability to bind to and inhibit a snake venom PLA2, thus proposing a new mechanism of PLA2, inhibition, and presenting more evidence of GA's potential as an antivenom compound. (https://pubmed.ncbi.nlm.nih.gov/34197854/; https://pubmed.ncbi.nlm.nih.gov/34979199/)

Other indications investigated: Food additive; COVID-19

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Food additive)

Development status: Active

Developers/investigators: Universidade Federal de Uberlândia

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/34197854/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops jararacussu (Jararcussu); Crotalus durissus cumanensis (Venezuelan rattlesnake); Daboia russellii (Russell's viper)	Bothrops jararacussu (Jararcussu); Crotalus durissus cumanensis (Venezuelan rattlesnake); Daboia russellii (Russell's viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

Go3 (Green seaweed extract isolate)

Alternative name(s): Polysaccharide; green marine algae Gayralia oxysperma

Chemical name: N/A

CAS number: N/A

PCR ID: 2205

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Bothrops jararaca; Lachesis muta

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects

MeSH headings / pharmacological class: N/A

Key features and challenges:

Go3 is a polysaccharide extracted from the green marine alga Gayralia oxysperma. Other marine algae extracts have demonstrated PLA2 inhibiting abilities.

Preclinical studies have analyzed the ability of a polysaccharide from the green marine alga Gayralia oxysperma (Go3) to inhibit the effects of venom from Bothrops jararaca and Lachesis muta. B. jararaca or L. muta venoms were incubated together with sulfated heterorhamnans from Go3, and the in vitro (coagulation, proteolytic, and hemolytic) and in vivo (hemorrhagic, myotoxic, edematogenic, and lethal) activities of venoms were assessed. Additionally, Go3 was injected before and after the injection of venoms, and the toxic activities were further tested. When incubated with the venoms, Go3 inhibited all activities, though results varied with different potencies. Moreover, Go3 neutralized hemorrhagic, myotoxic, and edematogenic activities when injected before or after injection with B. jararaca and L. muta venom. Go3 also blocked the coagulation of plasma in mice caused by the venoms in an ex vivo test. Therefore, Go3 has the potential to be used as antivenom for B. jararaca and L. muta bites, notably exhibiting higher efficacy on L. muta venom. (https://pubmed.ncbi.nlm.nih.gov/30373238/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Federal Fluminense University, Brazil

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/30373238/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops jararaca (Jararaca); Lachesis muta (Amazonian bushmaster)	Bothrops jararaca (Jararaca); Lachesis muta (Amazonian bushmaster)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: N/A

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage),Procoagulant (blood clotting)

Hesperetin (citrus extract isolate)

Alternative name(s): Hst; Orange bagasse flavone; citrus bioflavanoid; hesperadin (Hdt)

Chemical name:
(2S)-5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-3,4-dihydro-2H-1-benzopyran-4-one

CAS number: 520-33-2

PCR ID: 2085

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: SVSPS

Route of administration: Not yet determined

Thermostability: Melting point 227.5 °C

Mechanism of action: Hesperetin reduces or inhibits the activity of acyl-coenzyme A:cholesterol acyltransferase genes (ACAT1 and ACAT2) and it reduces microsomal triglyceride transfer protein (MTP) activity. Hesperetin also seems to upregulate the LDL receptor. This leads to the reduced assembly and secretion of apoB-containing lipoproteins and enhanced reuptake of those lipoproteins, thereby lowering cholesterol levels.

MeSH headings / pharmacological class: N/A

Key features and challenges:

Hesperetin belongs to the flavanone class of flavonoids. Hesperetin, in the form of its glycoside hesperidin, is the predominant flavonoid in lemons and oranges. It is a cholesterol lowering flavonoid found in a number of citrus juices. It appears to reduce cholesteryl ester mass and inhibit apoB secretion by up to 80%. Hesperetin may have antioxidant, anti-inflammatory, anti-allergic, hypolipidemic, vasoprotective and anticarcinogenic actions. (https://pubchem.ncbi.nlm.nih.gov/compound/Hesperetin) (https://go.drugbank.com/drugs/DB01094) It is approved as a food additive and dietary supplement.

Snake venom serine proteases provoke blood coagulation in snakebite victims because of their fibrinolytic activity. In one study, a protease from Bothrops jararaca (B. jararaca) was isolated and characterized, as well as the orange bagasse flavone (hesperetin, Hst), with interactions between the targets, enzyme, and hesperetin investigated. The purified serine protease was named BjSP24 because of its molecular mass and proteolytic activity. Hesperetin acted as a mixed inhibitor for the serine protease (SVSP) from Bothrops jararaca snake venom observed in three different in vitro experiments, fluorescence, kinetics, and SSTD-NMR. It is still to determine if hesperetin might aid-in reverting the on site blood clotting problems just after snakebite accidents. (https://pubmed.ncbi.nlm.nih.gov/33940046/). In another study, two thrombin-like serine proteases from the Crotalus simus snake venom - SVSP1 and SVSP2 - were isolated, and tested with hesperetin, and showed that is its excellent inhibitor. (https://pubmed.ncbi.nlm.nih.gov/29337219/)

Other indications investigated: Cancer; inflammation; high-cholesterol; haemorrhoids; varicose veins; thrombosis

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Dietary supplement)

Development status: Active

Developers/investigators: Brazilian State University of Campinas, Universidade Estadual de Campinas (Unicamp)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/29337219/ https://pubmed.ncbi.nlm.nih.gov/33940046/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops jararaca (Jararaca); Crotalus simus (Central American rattlesnake)	Bothrops jararaca (Jararaca); Crotalus simus (Central American rattlesnake)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVSPs

Syndromic profiles: Not specified

Hispidulin (Moquiniastrum floribundum/Aegiphila integrifolia extract isolate)

Alternative name(s): N/A

Chemical name: N/A

CAS number: 1447-88-7

PCR ID: 1777

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: sPLA2s

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Inhibition of pro-inflammatory activity of sPLA2

MeSH headings / pharmacological class: Phospholipases A2; secretory antagonists and inhibitors; flavanoids

Key features and challenges:

Hispidulin is a naturally occurring flavone with potential antiepileptic activity in rats, and is extracted from plants such as Moquiniastrum floribundum.

In preclinical studies, hispidulin was identified as one of the components present in the Moquiniastrum floribundum leaf and the ability of this isolated compound to neutralize the inflammatory activity of sPLA2 from Crotalus durissus terrificus was evaluated. Hispidulin showed promising activity against acute inflammation induced by sPLA2 and its identification was possible using a new method bioguided by molecular and functional bioaffinity against sPLA2 from Crotalus durissus terrificus to identify some potential secondary plant metabolites in various extracts. Hispidulin was crucial for decreasing edema and myonecrosis (https://pubmed.ncbi.nlm.nih.gov/31936688/). It has also been isolated fromAegiphila integrifolia and shown topartially inhibit the proteolytic, phospholipase A2 and hyaluronidase activities of B. atrox venom, and the skin hemorrhage induced by this venom in mice. (https://pubmed.ncbi.nlm.nih.gov/33984369/)

Other indications investigated: Epilepsy; cancer

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; epilepsy)

Development status: Active

Developers/investigators: Instituto de Biociências, UNESP, Brazil

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/31936688/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotalus durissus terrificus (South American rattlesnake)	Crotalus durissus terrificus (South American rattlesnake)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

Ikshusterol3-O-glucoside (Clematis gouriana extract isolate)

Alternative name(s): Ikshusterol3-O-glucoside isolated from Clematis gouriana Roxb. ex DC. root

Chemical name: 2-[[17-(5-ethyl-6-methylheptan-2-yl)-7-hydroxy-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl]oxy]-6-(hydroxymethyl)oxane-3,4,5-triol

CAS number: N/A

PCR ID: 1808

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: PLA2: Naja naja venom

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; interacts with amino acids at the active site of PLA2

MeSH headings / pharmacological class: N/A

Key features and challenges:

Ikshusterol3-O-glucoside is a bioactive compound which was isolated from Clematis gouriana Roxb. ex DC. The Clematis gouriana Roxb. ex DC. has been traditionally used by the tribal populations of Western Ghats of India to treat snakebites.

Through in silico approaches, it has been observed that the compound interacts with four amino acids (GLY31, ASP48, GLU55 and TYR63) in the active site of N. naja venom PLA2, and these findings were validated through in vitro assessment. This study concluded that while Ikshusterol3-O-glucoside could be developed to a potent inhibitor against N. naja PLA2 enzyme, it would be more beneficial if further studies are conducted to determine its inhibitory activity towards venoms of other snake species. (https://pubmed.ncbi.nlm.nih.gov/29171346/; https://pubmed.ncbi.nlm.nih.gov/35314419/)

This followed PLA2 and plant extract isolate matching computational and in vitro insight studies which identified Ikshusterol3-O-glucoside as a lead compound for elapid/Naja spp envenomation therapeutics.(https://pubmed.ncbi.nlm.nih.gov/26422703/; https://pubmed.ncbi.nlm.nih.gov/27355444/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Alagappa University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/27355444/
https://pubmed.ncbi.nlm.nih.gov/26422703/
https://pubmed.ncbi.nlm.nih.gov/29171346/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja naja (Indian cobra)	Naja naja (Indian cobra)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Haemorrhagic (bleeding)

Isoandrographolide (Andrographis paniculata extract isolate)

Alternative name(s): N/A

Chemical name: 4-[(3aR,5aS,6R,7R,9aR,9bS)-7-hydroxy-6-(hydroxymethyl)-3a,6,9a-trimethyl-2,4,5,5a,7,8,9,9b-octahydro-1H-benzo[e][1]benzofuran-2-yl]-2H-furan-5-one

CAS number: N/A

PCR ID: 2553

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: SVMPs

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibits SVMPs

MeSH headings / pharmacological class: N/A

Key features and challenges:

Isoandrographolide is a phytochemical extract isolate from Andrographis paniculata.

A computational analysis examined the inhibition of metalloproteinase by phytochemicals present in Andrographis paniculata. Molecular docking studies revealed interaction of A. paniculata phytochemicals with the catalytic M domain's active site amino acid residues, namely ASN203, ARG293, PHE203, LEU206, LYS199, and ALA122, similar to that of the reference compound Batimastat. 14-acetylandrographolide, 14-deoxy-11,12 didehydroandrographolide, Andrograpanin, Isoandrographolide, and 14-deoxy-11-oxoandrographolide displayed high binding energy and inhibition against the metalloproteinase. Molecular dynamic simulation analysis revealed less root mean square fluctuation of amino acid residues of metalloproteinase-14-acetylandrographolide complex than metalloproteinase-Batimastat complex indicating the high stability for metalloproteinase with the phytochemical. In silico analysis of parameters like ADME properties and drug-likeness of the phytochemicals exhibited good pharmacokinetic properties. Ligand-based virtual screening of phytochemicals to identify similarity to FDA-approved drugs and identification of their possible targets were also performed. The outcome of the current study strengthens the significance of these phytochemicals as promising lead candidates for the treatment of snakebite envenomation. Moreover, the study also encourages the in vivo and in vitro evaluation of the phytochemicals to validate the computational findings. (https://pubmed.ncbi.nlm.nih.gov/34997448/)

Other indications investigated: Inflammation; Non-fatty acid liver disease

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Preclinical (Inflammation)

Development status: Active

Developers/investigators: B.S.Abdur Rahman Crescent Institute of Science and Technology

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Daboia russeli (Russel's viper)	N/A
Snake family		
Risk category		

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Not specified

Jatromollistatin (Jatropha mollissima extract isolate)

Alternative name(s): Jatrophidin; Pohlianin A

Chemical name: 2-[(6S,9S,12S,15S,18S,24S)-6-(1H-indol-3-ylmethyl)-9,15,18-tris(2-methylpropyl)-2,5,8,11,14,17,20,23-octaoxo-1,4,7,10,13,16,19,22-octazabicyclo[22.3.0]heptacosan-12-yl]acetamide

CAS number: N/A

PCR ID: 1811

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: SVMPs

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; interaction of the peptide with the catalytic site of the metalloendopeptidase

MeSH headings / pharmacological class: N/A

Key features and challenges:

Jatropha mollissima is a medicinal plant endemic to Brazil and is used for traditional medicinal purposes, including the treatment of snakebite. Jatromollistatin is a cyclic heptapeptide, which has been isolated from the latex of Jatropha molissima. It was previously described as jatrophidin and pohlianin A (https://pubmed.ncbi.nlm.nih.gov/35218251/; https://pubchem.ncbi.nlm.nih.gov/compound/101873937).

Jatromollistatin has been evaluated, by molecular docking, as a possible inhibitor of adamalysin, a well-known metalloendopeptidase toxin from the Crotalus adamanteus. SVMPs triggers proteolytic events that culminate in tissue damage (hemorrhage, necrosis, and edema) after rattlesnake envenomation. Further studies need to be conducted to determine the inhibitory effects of this compound against snake venom components. (https://pubmed.ncbi.nlm.nih.gov/35218251/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: University of Fortaleza, Universidade de Fortaleza (UNIFOR)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/35218251/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotalus adamanteus (Eastern diamondback rattlesnake)	Crotalus adamanteus (Eastern diamondback rattlesnake)
Snake family		Viperidae
Risk category		Category 1 (Highest Medical Importance)

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Not specified

Kolaviron (flavanoid plant extract isolate)

Alternative name(s): Kolaflavanone

Chemical name: (2R,3R)-8-[(2S,3R)-5,7-dihydroxy-2-(4-hydroxyphenyl)-4-oxo-2,3-dihydrochromen-3-yl]-3,5,7-trihydroxy-2-(3-hydroxy-4-methoxyphenyl)-2,3-dihydrochromen-4-one

CAS number: 68705-66-8

PCR ID: 1820

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: PLA2, LAAO, SVSP

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; inhibits PLA2, SVSP, LAAO venom hydrolytic enzymes

MeSH headings / pharmacological class: N/A

Key features and challenges:

Kolaviron, or kolaflavanone, is a biflavonoid isolated from the seeds of Garcinia kola that has been shown to exhibit hepatoprotective activity. It has a role as a hepatoprotective agent and a plant metabolite. It is a biflavonoid, a ring assembly, a member of dihydroflavonols, a secondary alpha-hydroxy ketone and a member of 4'-methoxyflavanones. It has been investigated as it therapeutic role in diabetes and inflammation. (https://pubchem.ncbi.nlm.nih.gov/compound/155169)

Kolaviron has been investigated for its inhibitory effect against Naja n. nigricollis (NNN) snake venom hydrolytic enzymes involved in local tissue damage. Kolaviron was evaluated for its ability to inhibit the hydrolytic enzyme activities of NNN venom phospholipase A2 (PLA2), protease, hyaluronidase and l-amino acid oxidase (LAAO). Kolaviron inhibited the PLA2, protease, hyaluronidase and LAAO enzyme activities of NNN venom in a dose-dependent manner. Furthermore, myotoxic, edemic, hemolytic and procoagulant effects induced by NNN venom enzyme were neutralized significantly. (https://pubmed.ncbi.nlm.nih.gov/34898137/)

Other indications investigated: Ulcerative colitis; diabetes; inflammation; malaria

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: Cross River University of Technology, Nigeria

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/34898137/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja n. nigricollis (Black-necked spitting cobra)	Naja n. nigricollis (Black-necked spitting cobra)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s,SVSPs,LAAO

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage),Procoagulant (blood clotting)

Lansiumamide B (Clausena excavata extract isolate)

Alternative name(s): N/A

Chemical name: N/A

CAS number: 121817-37-6

PCR ID: 1884

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: Hyaluronidase

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibits hyaluronidase

MeSH headings / pharmacological class: Hyaluronoglucosaminidase antagonists & inhibitors; Cinnamates; Styrenes

Key features and challenges:

Lansiumamide B belongs to the class of organic compounds known as cinnamic acids, and is extracted from Clausena excavata. Lansiumamide B is proven to be a promising lead compound for the development of novel antifungal agents.

Discovery research support the selective identification of hyaluronidase inhibitors seen in the high-resolution hyaluronidase inhibition profiles; and especially lansiumamide B from C. excavata might be a promising inhibitor against snakebite of D. acutus (https://pubmed.ncbi.nlm.nih.gov/26386983/).

Other indications investigated: Antifungal; leukaemia

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Preclinical (Leukaemia; other)

Development status: Active

Developers/investigators: University of Copenhagen, Kobenhavens Universitet

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/26386983/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Deinagkistrodon acutus (Chinese copperhead)	N/A
Snake family		
Risk category		N/A

Direct action on toxins? Yes

Target toxin class: Low toxicity toxins

Specific target toxin class: Hyaluronidase

Syndromic profiles: Not specified

Lupeol (Aegiphila integrifolia extract isolate)

Alternative name(s): N/A

Chemical name: (1R,3aR,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a,5a,5b,8,8,11a-hexamethyl-1-prop-1-en-2-yl-1,2,3,4,5,6,7,7a,9,10,11,11b,12,13,13a,13b-hexadecahydrocyclopenta[a]chrysen-9-ol

CAS number: 545-47-1

PCR ID: 2057

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: Hyaluronidases

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibits hyaluronidase

MeSH headings / pharmacological class: Anti-inflammatory agents

Key features and challenges:

Aegiphila species are common plants from the Brazilian Amazon and are used to treat snakebites. Lupeol in in clinical development for acne and other conditions. (https://pubchem.ncbi.nlm.nih.gov/compound/259846) An ethanolic extract from the species was evaluated through in vitro and in vivo experiments to verify their antiophidic activity against Bothrops atrox crude venom.

Aegiphila integrifolia extract isolates (e.g. lupeol, pectolinarigenin and hispidulin) showed remarkable inhibition of venom hyaluronidase activity, while the proteolytic and phospholipase activities were partially inhibited. Phospholipase and proteolytic enzymes are related to myotoxic and haemorrhagic activities, respectively. Hyaluronidase is an important enzyme for the spread of venom toxins in tissues after a snakebite, enhancing the local effects of the venom. Data from this study show that Aegiphila integrifolia had promising inhibitory effects against the B. atrox venom, due to enzymatic inhibition and antagonizing the skin haemorrhage (https://pubmed.ncbi.nlm.nih.gov/33984369/).

Other indications investigated: Cancer; acne

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Phase I/II (Acne vulgaris)

Development status: Active

Developers/investigators: Military Institute of Engineering, Rio de Janeiro

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33984369/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops atrox (Fer-de-lance/Caiçaca)	Bothrops atrox (Fer-de-lance/Caiçaca)
Snake family		Viperidae
Risk category		Category 1 (Highest Medical Importance)

Direct action on toxins? Yes

Target toxin class: Low toxicity toxins

Specific target toxin class: Hyaluronidase

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

Mannitol (Aegiphila integrifolia extract isolate)

Alternative name(s): Osmitrol; D-mannitol

Chemical name: (2R,3R,4R,5R)-hexane-1,2,3,4,5,6-hexol

CAS number: 69-65-8

PCR ID: 2060

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: Hyaluronidases

Route of administration: Not yet determined

Thermostability: Melting point 168 °C

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibits hyaluronidase

MeSH headings / pharmacological class: N/A

Key features and challenges:

Mannitol is an osmotic diuretic that is metabolically inert in humans and occurs naturally, as a sugar or sugar alcohol, in fruits and vegetables. Mannitol elevates blood plasma osmolality, resulting in enhanced flow of water from tissues, including the brain and cerebrospinal fluid, into interstitial fluid and plasma. As a result, cerebral edema, elevated intracranial pressure, and cerebrospinal fluid volume and pressure may be reduced. Mannitol may also be used for the promotion of diuresis before irreversible renal failure becomes established; the promotion of urinary excretion of toxic substances; as an Antiglaucoma agent; and as a renal function diagnostic aid. On October 30, 2020, mannitol was approved by the FDA as add-on maintenance therapy for the control of pulmonary symptoms associated with cystic fibrosis in adult patients and is currently marketed for this indication under the name BRONCHITOL by Chiesi USA Inc. (https://go.drugbank.com/drugs/DB00742).

Aegiphila species (from which mannitol can be derived) are common plants from the Brazilian Amazon and are used to treat snakebites. Its ethanolic extract was evaluated through in vitro and in vivo experiments to verify their antiophidic activity against Bothrops atrox crude venom. A. integrifolia extracts, eg mannitol, pectolinarigenin and hispidulin showed remarkable inhibition of venom hyaluronidase activity, while the proteolytic and phospholipase activities were partially inhibited. Phospholipase and proteolytic enzymes are related to myotoxic and hemorrhagic activities, respectively. Hyaluronidase is an important enzyme for the spread of venom toxins in tissues after a snakebite, enhancing the local effects of the venom. Data from this study show that A. integrifolia extract isolates had promising inhibitory effects against the B. atrox venom, due to enzymatic inhibition and antagonizing the skin hemorrhage. (https://pubmed.ncbi.nlm.nih.gov/33984369/)

Other indications investigated: Pulmonary symptoms associated with cystic fibrosis; asthma; other

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Pulmonary symptoms associated with cystic fibrosis)

Development status: Active

Developers/investigators: Military Institute of Engineering, Rio de Janeiro

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33984369/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops atrox (Fer-de-lance)	Bothrops atrox (Fer-de-lance)
Snake family		Viperidae
Risk category		Category 1 (Highest Medical Importance)

Direct action on toxins? Yes

Target toxin class: Low toxicity toxins

Specific target toxin class: Hyaluronidase

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

Mimosine (Mimosa pudica extract isolate)

Alternative name(s): 2-amino-3-(3-hydroxy-4-oxopyridin-1(4H)-yl)propanoic acid; 2-amino-3-(3-hydroxy-4-oxopyridin-1-yl)propanoic acid

Chemical name: 2-amino-3-(3-hydroxy-4-oxopyridin-1-yl)propanoic acid

CAS number: 2116-55-4

PCR ID: 1854

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; neutralisation of PLA2s

MeSH headings / pharmacological class: N/A

Key features and challenges:

Mimosine is a non-protein amino acid that interferes with pyridoxine-dependent reactions, and which also chelates the essential metals iron, zinc, and copper. It is grown in tropical and subtropical climates and is isolated from Mimosa pudica.

Mimosine was found to interact with Daboxin P (a major PLA2 enzyme present in the venom of Indian Daboia russelli) with high affinity in silico and could neutralize the PLA2 activity and anti-coagulatory property of Daboxin P in vitro. It was also found that Mimosine could neutralize the PLA2 activity and anti/pro-coagulatory property of venom of the Indian big four snakes (Daboia russelii, Bungarus caeruleus, Naja naja, and Echis carinatus). (https://pubmed.ncbi.nlm.nih.gov/33035526/; https://pubmed.ncbi.nlm.nih.gov/31652115/; https://pubmed.ncbi.nlm.nih.gov/34274442/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE)

Development status: Active

Developers/investigators: Ahmadu Bello University, Nigeria

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33035526/ https://pubmed.ncbi.nlm.nih.gov/31652115/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja nigricollis (Black-necked spitting cobra); Bitis arietans (Puff adder); Daboia russelii (Indian Russell's viper); Bungarus caeruleus (Indian krait); Naja naja (Indian cobra); Echis carinatus (Saw-scaled viper)	Naja nigricollis (Black-necked spitting cobra); Bitis arietans (Puff adder); Daboia russelii (Indian Russell's viper); Bungarus caeruleus (Indian krait); Naja naja (Indian cobra); Echis carinatus (Saw-scaled viper)
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Haemorrhagic (bleeding),Procoagulant (blood clotting)

Myricetin (polyphenol plant extract isolate)

Alternative name(s): myricetin 3-O-b-D-glucopyranoside; flavanoid

Chemical name: 3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)chromen-4-one

CAS number: 529-44-2

PCR ID: 1771

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: SVMPs (Batx-I from Bothrops); Hyaluronidases

Route of administration: Not yet determined

Thermostability: Melting point 357 °C

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibition of SVMPs and hyaluronidases

MeSH headings / pharmacological class: Antioxidants; dietary supplements

Key features and challenges:

Myricetin is a member of the flavonoid class of polyphenolic compounds, with antioxidant properties. Common dietary sources include vegetables, fruits, nuts, berries, tea, and red wine. Myricetin is a hexahydroxyflavone that is flavone substituted by hydroxy groups at positions 3, 3', 4', 5, 5' and 7. It has been isolated from the leaves of Myrica rubra and other plants. It has a role as a cyclooxygenase 1 inhibitor, an antineoplastic agent, an antioxidant, a plant metabolite, a food component, a hypoglycemic agent and a geroprotector. It is a conjugate acid of a myricetin(1-). (https://pubchem.ncbi.nlm.nih.gov/compound/5281672)

Preclinical studies have determined the inhibitory ability of flavonoids on the in-vitro proteolytic activity of Bothrops atrox venom and on the haemorrhagic, edema-forming and myonecrotic activities of SVMP Batx-I, myricetin was the most active compound, exhibiting an IC 50 value of 150 μ M and 1021 μ M for the inhibition of proteolytic and haemorrhagic activity, respectively. Molecular dynamics simulations coupled with the adaptive biasing method suggest that myricetin can bind to the metalloproteinase active site via formation of hydrogen bonds between the hydroxyl groups 3', 4' and 5' of the benzyl moiety and amino acid Glu143 of the metalloproteinase. Based on this evidence, myricetin constitutes a candidate for the development of inhibitors to reduce local tissue damage in snakebite envenomation. (https://pubmed.ncbi.nlm.nih.gov/30332829/). In another, myricetin 3-O-β-D-glucopyranoside from Androsace umbellata was identified and isolated, with demonstrated high-resolution hyaluronidase inhibition profile against snake venom https://pubmed.ncbi.nlm.nih.gov/26386983/).

Other indications investigated: Dietary supplement

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Dietary supplement)

Development status: Active

Developers/investigators: Universidad de Antioquia, Colombia; University of Copenhagen, Kobenhavens Universitet

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/30332829/ https://pubmed.ncbi.nlm.nih.gov/26386983/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops atrox (Fer-de-lance); Gloydius blomhoff (Mamushi); Deinagkistrodon acutus (Chinese copperhead); Naja naja atra (Chinese cobra): Trimeresurus stejnegeri (Chinese green tree pitviper)	Bothrops atrox (Fer-de-lance)
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: SVMPs,Hyaluronidase

Syndromic profiles: Haemorrhagic (bleeding)

Oleanolic acid

Alternative name(s): Oleanic acid; Caryophyllin; Astrantiagenin C

Chemical name: (4aS,6aR,6aS,6bR,8aR,10S,12aR,14bS)-10-hydroxy-2,2,6a,6b,9,9,12a-heptamethyl-1,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydropicene-4a-carboxylic acid

CAS number: 508-02-1

PCR ID: 1806

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: SVMP: Batx-I (Bothrops atrox)

Route of administration: Not yet determined

Thermostability: Melting point 310°C

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibits SVMP

MeSH headings / pharmacological class: Oleanane Triterpenes

Key features and challenges:

Oleanolic acid is a pentacyclic triterpenoid with widespread occurrence throughout the plant kingdom. These compounds are widely recognized by their pharmacological and biological properties, such as anti-tumoral, anti-inflammatory, anti-microbial and hepatoprotective activity.

Oleanolic acid inhibits toxic activities of a snake venom metalloproteinase. Preclinical studies showed that oleanolic acid inhibited the proteolytic activity of Batx-I (from Bothrops atrox) on gelatin, as well as inhibition of the hemorrhagic activity and myotoxicity and edema-forming activity of Batx-I. Molecular docking studies suggested that these compounds could occupy part of the substrate binding cleft of the enzyme affecting its catalytic cycle. In this manner, triterpenic acids, such as oleanolic acid are candidates for the development of inhibitors for the prevention of local tissue damage in snakebite envenomation. (https://pubmed.ncbi.nlm.nih.gov/29203373/)

Other indications investigated: Cancer; HIV; HCV; inflammation

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: Universidad de Antioquia, Colombia

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/29203373/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops atrox (Fer-de-lance)	Bothrops atrox (Fer-de-lance)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

p-Coumaric acid (polyphenol plant extract isolate)

Alternative name(s): 4-Hydroxycinnamic acid

Chemical name: (E)-3-(4-hydroxyphenyl)prop-2-enoic acid

CAS number: 501-98-4

PCR ID: 1819

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: PLA2: SVMPs

Route of administration: Not yet determined

Thermostability: Melting point 211.5°C

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects' binds and inhibits PLA2

MeSH headings / pharmacological class: Antioxidants; anti-infectives

Key features and challenges:

p-Coumaric acid (4-hydroxycinnamic acid) is a phenolic acid found in many fruits and plants such as peanuts, tomatoes, carrots, basil, and garlic. It has antioxidant, anti-infective and free radical scavenging abilities, and has been investigated for cancer and hepatic injury amongst others. (https://pubchem.ncbi.nlm.nih.gov/compound/637542). It has also been tested against the effects of snake venoms PLA2s and SVMPs.

Preclinical studies have shown that p-Coumaric acid was able to inhibit the action of PLA2 and SVMPs present in snakes venoms of the genus Bothrops: Lys49-PLA2s (BnSp-6) from Bothrops pauloensis venom, SVMP (BleucMP) from Bothrops leucurus venom and SVMP (Jararhagin) from Bothrops jararaca venom (https://pubmed.ncbi.nlm.nih.gov/34979199/), as well as showing strong binding affinity to Asp49-PLA2s from Daboia russelli pulchella venom (https://pubmed.ncbi.nlm.nih.gov/25541253/). Others show p-Coumaric acid inhibited the phospholipase, hemolytic, thrombolytic, thrombotic, coagulant, proteolytic and fibrinogenolytic activities of Bothrops jararaca venom, Bothrops moojeni venom, Bothrops jararacussu venom, Bothrops atrox venom, Crotalus durissus terrificus venom and SVMP (bothropasin) from B. jararaca venom (https://pubmed.ncbi.nlm.nih.gov/31016790/).

Other indications investigated: Cancer; hepatic injury

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: Federal University of Rio Grande do Norte

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/25541253/ https://pubmed.ncbi.nlm.nih.gov/31016790/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops pauloensis (São Paulo Lancehead); Bothrops leucurus (Bahia lancehead); Bothrops jararaca (Jararaca); Bothrops moojeni (Brazilian lancehead); C. durissus terrificus (South American rattlesnake); Daboia russelli (Russell's viper); Bothrops atrox (Fer-de-lance)	Bothrops pauloensis (São Paulo Lancehead); Bothrops leucurus (Bahia lancehead); Bothrops jararaca (Jararaca); Bothrops moojeni (Brazilian lancehead); C. durissus terrificus (South American rattlesnake); Daboia russelli (Russell's viper); Bothrops atrox (Fer-de-lance)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs,PLA2s

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage),Procoagulant (blood clotting)

Pectolinarigenin (Aegiphila integrifolia extract isolate)

Alternative name(s): Pectolinaringenin; 5,7-Dihydroxy-4',6-dimethoxyflavone; 4'-Methylcapillarisin

Chemical name: 5,7-dihydroxy-6-methoxy-2-(4-methoxyphenyl)chromen-4-one

CAS number: 520-12-7

PCR ID: 2061

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: Hyaluronidases

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibits hyaluronidase

MeSH headings / pharmacological class: N/A

Key features and challenges:

Pectolinarigenin is a dimethoxyflavone that is the 6,4'-dimethyl ether derivative of scutellarein. It has a role as a plant metabolite. (https://pubchem.ncbi.nlm.nih.gov/compound/5320438). Aegiphila species (from which pectolinarigenin can be derived) are common plants from the Brazilian Amazon and are used to treat snakebites. its ethanolic extract was evaluated through in vitro and in vivo experiments to verify their antiophidic activity against Bothrops atrox crude venom.

A. integrifolia extracts, pectolinarigenin and hispidulin showed remarkable inhibition of venom hyaluronidase activity, while the proteolytic and phospholipase activities were partially inhibited. Phospholipase and proteolytic enzymes are related to myotoxic and hemorrhagic activities, respectively. Hyaluronidase is an important enzyme for the spread of venom toxins in tissues after a snakebite, enhancing the local effects of the venom. Data from this study show that A. integrifolia had promising inhibitory effects against the B. atrox venom, due to enzymatic inhibition and antagonizing the skin hemorrhage. (https://pubmed.ncbi.nlm.nih.gov/33984369/)

Other indications investigated: Cancer; inflammation

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: Military Institute of Engineering, Rio de Janeiro

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33984369/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops atrox (Fer-de-lance)	Bothrops atrox (Fer-de-lance)
Snake family		Viperidae
Risk category		Category 1 (Highest Medical Importance)

Direct action on toxins? Yes

Target toxin class: Low toxicity toxins

Specific target toxin class: Hyaluronidase

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

Pinostrobin (Renealmia alpinia extract isolate)

Alternative name(s): 5-Hydroxy-7-methoxy-2-phenylchroman-4-one

Chemical name: (S)-2,3-Dihydro-5-hydroxy-7-methoxy-2-phenyl-4-benzopyrone

CAS number: 480-37-5

PCR ID: 1804

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects: forms hydrogen bonds with residues His48 and Asp49 of PLA2

MeSH headings / pharmacological class: Phospholipase A2 Inhibitors

Key features and challenges:

Pinostrobin is a flavanone isolated from Renealmia alpinia, a plant used in folk medicine to treat snakebites.

Studies have demonstrated that pinostrobin inhibits the enzymatic activity of the snake venom PLA2 with IC50 values of 1.76 mM and 1.85 mM, when either aggregated or monodispersed substrates were used. In addition, the inhibition of pinostrobin was reversible as determined in dialysis study. It also inhibited edema-forming and anticoagulant activities of the PLA2 and inhibited paw-edema provoked by the venom PLA2 in preincubation assay. These results propose that pinostrobin is a candidate for the development of inhibitors to be used in snakebite envenomation and inflammatory pathologies. (https://pubmed.ncbi.nlm.nih.gov/27109758/; https://pubmed.ncbi.nlm.nih.gov/25941768/)

Other indications investigated: Cancer

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: Universidad de Antioquia, Colombia

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/25941768/ https://pubmed.ncbi.nlm.nih.gov/27109758/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotalus durissus cumanensis (Venezuelan rattlesnake); Bothrops asper (Fer-de-lance)	Crotalus durissus cumanensis (Venezuelan rattlesnake); Bothrops asper (Fer-de-lance)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

Piperine (Piper longum L extract isolate)

Alternative name(s): N/A

Chemical name: (2E,4E)-5-(2H-1,3-Benzodioxol-5-yl)-1-(piperidin-1-yl)penta-2,4-dien-1-one

CAS number: 94-62-2

PCR ID: 1748

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Not yet determined

Thermostability: Thermostable properties

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects

MeSH headings / pharmacological class: Antioxidants; dietary supplements

Key features and challenges:

Piperine is an alkaloid isolated from the plant Piper nigrum. It has a role as a NF-kappaB inhibitor, a plant metabolite, a food component and a human blood serum metabolite. It is a member of benzodioxoles, a N-acylpiperidine, a piperidine alkaloid and a tertiary carboxamide. Bioperine has been used in trials studying the treatment of Multiple Myeloma and Deglutition Disorders, among others. It is approved as a food additive. (https://pubchem.ncbi.nlm.nih.gov/compound/638024;https://go.drugbank.com/drugs/DB12582).

A study investigated binding mechanism and kinetics of inhibition of Piperine (major constitute of Piper nigrum) with sPLA2using DFT, MD simulation, MM-PBSA, and SPR method. Frontier MO properties were suggested that it procured better chemical reactivity and druglikeness and binding mode of Piperine with EcPLA2defined that it occupied well in N-terminal hydrophobic cleft. The persistence of Piperine interactions with and without calcium ion was analyzed and confirmed by MD simulation analysis. The dPCA-based FEL shows the nature of apo- and Piperine-bound conformational behavior of EcPLA2including intermediate forms. Further, binding energy of Piperine was calculated by high-throughput MM-PBSA which states that calcium ion presence enhances the Piperine binding by additional electrostatic interactions. Finally, kinetics of inhibition between Piperine and EcPLA2implied that it secured better binding affinity (KD: as 1.708 pM) and the result gives clear evidence for the binding mechanism and binding energy calculated. In conclusion, Piperine was authenticated with better drug ability, entrenched binding interaction, and robust kinetics of inhibition with EcPLA2through which it can become an exceeding drug candidate for pharmacological as well as catalytic activity of sPLA2. (https://pubmed.ncbi.nlm.nih.gov/27960631/)

Other indications investigated: Multiple myeloma; deglutition disorders

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Marketed (Food additive)

Development status: Active

Developers/investigators: Pondicherry University

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Echis carinatus (Indian saw-scaled viper)	N/A
Snake family		
Risk category		

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Not specified

Quercetin (polyphenol plant extract isolate)

Alternative name(s): N/A

Chemical name: 3,3′,4′,5,7-Pentahydroxyflavone

CAS number: 117-39-5

PCR ID: 1729

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Not yet determined

Thermostability: Melting point 316.5 °C

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects

MeSH headings / pharmacological class: Antioxidants; dietary supplements

Key features and challenges:

Quercetin is a natural flavonoid found in foods and natural supplement products. Extracts of quercetin have been used to treat or prevent diverse conditions including cardiovascular disease, hypercholesterolemia, rheumatic diseases, infections and cancer but have not been shown to be effective in clinical trials for any medical condition. Quercetin as a nutritional supplement is well tolerated and has not been linked to serum enzyme elevations or to episodes of clinically apparent liver injury. Although the mechanism of action of action is not fully known, the following effects have been described with this agent in vitro: decreased expression of mutant p53 protein and p21-ras oncogene, induction of cell cycle arrest at the G1 phase and inhibition of heat shock protein synthesis. This compound also demonstrates synergy and reversal of the multidrug resistance phenotype, when combined with chemotherapeutic drugs, in vitro. Quercetin also produces anti-inflammatory and anti-allergy effects mediated through the inhibition of the lipoxygenase and cyclooxygenase pathways, thereby preventing the production of pro-inflammatory mediators (https://pubchem.ncbi.nlm.nih.gov/compound/5280343).

Quercetin has been evaluated for its anti-PLA2 abilities in regards to snakebite envenoming directly, and was shown an ability to inhibit the enzymatic activity and some pharmacological activities of sPLA2, including its antibacterial activity, its ability to induce platelet aggregation, and its myotoxicity by approximately 40%, but was not able to reduce the inflammatory and neurotoxic activities of sPLA2. (https://pubmed.ncbi.nlm.nih.gov/21056032/). More recently, quercetin was evaluated for its ability to protect against in vitro neurotoxicity and in vivo lethality of Crotalus durissus terrificus (South American Rattlesnake) venom, although no protective qualities were observed (https://pubmed.ncbi.nlm.nih.gov/34822584/).

Other indications investigated: Cardiovascular disease; hypercholesterolemia; rheumatic diseases; infections; cancer; COVID-19; dietary supplement

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Dietary supplement)

Development status: Active

Developers/investigators: University of Sorocaba, Universidade de Sorocaba (UNISO); Brazilian State University of Campinas, Universidade Estadual de Campinas (Unicamp)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/34822584/ https://pubmed.ncbi.nlm.nih.gov/21056032/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotalus durissus terrificus (South American Rattlesnake)	N/A
Snake family		
Risk category		

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Not specified

Quercitrin (Euphorbia hirta/polyphenol extract isolate)

Alternative name(s): Quercetin-3-O-rhamnoside

Chemical name: 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxychromen-4-one

CAS number: 522-12-3

PCR ID: 2113

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Not yet determined

Thermostability: Melting point 176-179 °C

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects

MeSH headings / pharmacological class: Antioxidants

Key features and challenges:

Quercetin-3-O-rhamnoside - also known as quercitrin - is a glycoside formed from the flavanoid quercetin and the deoxy sugar rhamnose. It has a role as an antioxidant, an antileishmanial agent, an EC 1.1.1.184 [carbonyl reductase (NADPH] inhibitor, an EC 1.1.1.21 (aldehyde reductase) inhibitor, an EC 1.14.18.1 (tyrosinase) inhibitor and a plant metabolite. (https://pubchem.ncbi.nlm.nih.gov/compound/5280459)

Quercetin-3-O-α-rhamnoside (QR) was identified as the bioactive fraction in a experiments subjecting Euphorbia hirta extract to bioactivity guided fractionation. The fractions that inhibited different enzyme activities of Naja naja venom in vitro was structurally characterized. In vitro experiments indicated that protease, phospholipase-A(2), hemolytic activity and hemorrhage inducing activity of the venom were inhibited completely at a ratio of 1:20 (venom: QR) w/w. At the same concentration, the edema ratio was drastically reduced from 187% to 107%. Significant inhibition (93%) of hyaluronidase activity was also observed at a slightly higher concentration of QR (1:50). Further, in in vivo analysis, QR significantly prolonged the survival time of mice injected with snake venom. (https://pubmed.ncbi.nlm.nih.gov/27033089/)

Other indications investigated: Cancer; COVID-19; pain; other

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: Vellore Institute of Technology (VIT University)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/27033089/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja naja (Indian cobra)	Naja naja (Indian cobra)
Snake family		Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s,SVSPs,Hyaluronidase

Syndromic profiles: Haemorrhagic (bleeding)

Rosmarinic acid (polyphenol plant extract isolate)

Alternative name(s): N/A

Chemical name: (2R)-3-(3,4-dihydroxyphenyl)-2-[(E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxypropanoic acid

CAS number: 20283-92-5

PCR ID: 1773

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: PLA2; PrTX-I, MjTX-II

Route of administration: Not yet determined

Thermostability: Melting point 171-175 °C

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; binds PLA2

MeSH headings / pharmacological class: Antioxidants; Anti-Inflammatory Agents, Non-Steroidal

Key features and challenges:

Rosmarinic acid (RA) is a hydroxylated compound frequently found in herbal plants and is mostly responsible for anti-inflammatory and antioxidative activity. When extracted from plant sources or synthesized in manufacturing, rosmarinic acid can be used in foods or beverages as a flavouring, in cosmetics or as a dietary supplement. It has also been investigated in Phase I, II and III trials for dementia and Alzheimer's disease. (https://pubchem.ncbi.nlm.nih.gov/compound/5281792)

Rosmarinic acid (RA) has been investigated in snakebite therapeutics in a number of studies. It has been shown to mitigate the effects of B. leucurus venom in preclinical studies, and was able to inhibit the haemorrhagic effect of the venoms of T. flavoviridis, C. atrox, G. blomhoffii, and B. arientans and others. Rosmarinic acid was also able to reduce neuromuscular blocking caused by PrTX-I when it was preincubated for 30 min with the toxin.(https://pubmed.ncbi.nlm.nih.gov/34979199/) Other studies have noted effects against Bothrops spp (https://pubmed.ncbi.nlm.nih.gov/30679550/)

Results of preclinical studies have evidenced the antiophidic potential of RA with data that support their capacity for enzymatic inhibition of toxins, as well as a high efficacy in vivo against local and systemic effects induced by B. leucurus venom. Thus, there is important evidence that this inhibitor is a promising candidates for future adjuvants to be used to complement currently available antivenom serotherapy. (https://pubmed.ncbi.nlm.nih.gov/35247716/)

Other indications investigated: Dietary supplement; Dementia; Alzheimer's disease

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Dietary supplement)

Development status: Active

Developers/investigators: Federal University of Rio Grande do Norte; Brazilian State University Paulista, Universidade Estadual Paulista (Unesp)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/35247716/ https://pubmed.ncbi.nlm.nih.gov/30679550/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops leucurus (Bahia lancehead); Protobothrops flavoviridis (Habu); Crotalus atrox (Western diamondback rattlesnake); Gloydius blomhoffii (Mamushi); Bitis arietans (Puff adder); Bothrops jararacussu (Jararacussu); Agkistrodon bilineatus (Cantil); Deinagkistrodon acutus (Chinese copperhead); Bothrops pirajai (Pirajai); Micrurus fulvius (Florida coral snake); Bothrops moojeni (Brazilian lancehead)	Bothrops leucurus (Bahia lancehead); Protobothrops flavoviridis (Habu); Crotalus atrox (Western diamondback rattlesnake); Gloydius blomhoffii (Mamushi); Bitis arietans (Puff adder); Bothrops jararacussu (Jararacussu); Agkistrodon bilineatus (Cantil); Deinagkistrodon acutus (Chinese copperhead); Bothrops pirajai (Pirajai); Micrurus fulvius (Florida coral snake); Bothrops moojeni (Brazilian lancehead)
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Neurotoxic (paralysis),Haemorrhagic (bleeding)

Rutin/Rutin succinate (polyphenol plant extract isolate)

Alternative name(s): Quercetin-3-O-rutinoside; sophorin; rutoside

Chemical name: 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxychromen-4-one

CAS number: 153-18-4

PCR ID: 1810

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: SVMP

Route of administration: Not yet determined

Thermostability: Melting point 125°C

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects

MeSH headings / pharmacological class: Antioxidants; dietary supplements

Key features and challenges:

Rutin is a rutinoside that is quercetin with the hydroxy group at position C-3 substituted with glucose and rhamnose sugar groups. It has a role as a metabolite and an antioxidant. It is a flavonoid found in over-the-counter vitamin supplements. (https://go.drugbank.com/drugs/DB01698). Rutin has been investigated for its potential biological effects in reducing post- thrombotic syndrome, venous insufficiency, endothelial dysfunction, COVID-19. (https://pubchem.ncbi.nlm.nih.gov/compound/5280805)

Rutin was evaluated both on the biological activities of crude Bothrops jararaca (BjV) venom in vitro, and in vivo by the ability of rutin (14.4 mg/kg b.w.) to modulate haematological, haemostatic and redox status markers altered by BjV injection (1.6 mg/kg b.w., s.c.) in mice. In vitro, rutin failed to inhibit BjV-induced platelet aggregation and biological activities of major BjV enzymes (metalloproteinases, phospholipases A2, serine proteases, and L-amino acid oxidases). However, rutin attenuated local haemorrhage, and the increase in reactive species, prevented the fall in RBC counts and fibrinogen levels, diminished tail bleeding and shortened prothrombin time (PT) evoked by envenomation. Furthermore, rutin reduced tissue factor (TF) activity and altered the protein expression of TF in liver, lungs, heart and skin. In conclusion, the disturbances in redox status and hemostatic system induced by B. jararaca envenomation were modulated by rutin, suggesting it has a great potential to be used as an ancillary therapeutic agent for snakebites. (https://pubmed.ncbi.nlm.nih.gov/30307940/)

In a follow on study, rutin and rutin succinate (RS) (its water-soluble form) was tested for effect on haemostatic parameters, and against toxic activities of crude BjV in vitro. RS showed the characteristic activities described for rutin – i.e., antioxidant and inhibitor of protein disulfide isomerase – but also prolonged the clotting time of fibrinogen and plasma in vitro. Differently from rutin, RS inhibited typical proteolytic activities of SVMP, as well as the coagulant activity of BjV. Importantly, both rutin and RS completely abrogated the lethal activity of BjV, in the same degree as o-phe. Rutin and RS also improved the recovery of platelet counts and fibrinogen levels, and the development of haemorrhages was totally blocked in mice injected with BjV incubated with RS. Only

RS inhibited directly BjV biological activities, even though both flavonoids neutralized B. jararaca toxicity in vivo. (https://pubmed.ncbi.nlm.nih.gov/35264963/)

Other indications investigated: Post-thrombotic syndrome; venous insufficiency; endothelial dysfunction; COVID-19

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Dietary supplement)

Development status: Active

Developers/investigators: Butantan Institute, Fundacao Butantan

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/35264963/ https://pubmed.ncbi.nlm.nih.gov/30307940/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops jararaca (Jararaca)	Bothrops jararaca (Jararaca)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding)

Scutellarin (flavanoid plant extract isolate)

Alternative name(s): TCM3290; Breviscapin

Chemical name: (2S,3S,4S,5R,6S)-6-[5,6-dihydroxy-2-(4-hydroxyphenyl)-4-oxochromen-7-yl]oxy-3,4,5-trihydroxyoxane-2-carboxylic acid

CAS number: 27740-01-8

PCR ID: 1837

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; binds to TYR63 and GLY31 key residues in the active region of the PLA2 protein, inhibiting PLA2 activity

MeSH headings / pharmacological class: N/A

Key features and challenges:

Scutellarin is an herbal flavonoid glucuronide with multiple pharmacological activities. It has a role as an antineoplastic agent and a proteasome inhibitor, and has been investigated for it's anti-oxidant, anti-inflammation, vascular relaxation, anti-platelet and anti-coagulation properties. (https://pubchem.ncbi.nlm.nih.gov/compound/185617)

A study used virtual screening and molecular docking studies to find a potent inhibitor against PLA2 using Traditional Chinese Medicine Database (TCM), and identified Scutellarin (TCM3290). In vitro analysis showed that TCM3290 significantly neutralised PLA2, confirming that Scutellarin has a potent snake venom neutralizing capacity and could hypothetically be used for therapeutic drives of snakebite envenomation. (https://pubmed.ncbi.nlm.nih.gov/31838071/). No specific snake species identified as effective against, only in-vitro analysis of inhibition of PLA2.

Other indications investigated: Stroke; myocardial infarction; diabetes complications; breast cancer

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; cancer)

Development status: Active

Developers/investigators: Shanghai Jiao Tong University

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/31838071/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	N/A	N/A
Snake family		
Risk category		N/A

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Not specified

Silymarin (milk thistle extract isolate)

Alternative name(s): Milk Thistle isolate

Chemical name: 3,5,7-trihydroxy-2-[3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]-2,3-dihydrochromen-4-one

CAS number: 65666-07-1

PCR ID: 1929

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: Crude snake venom/PLA2; hyaluronidases: Echis carinatus

Route of administration: Not yet determined

Thermostability: Melting point 167°C

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; likely inhibits PLA2 and hyaluronidase activity

MeSH headings / pharmacological class: Antioxidants; enzyme inhibitors

Key features and challenges:

Silymarin (SLN) is a mixture of flavonoids extracted from seeds of the milk thistle Silybum marianum. It consists primarily of silybin and its isomers, silicristin and silidianin. Silymarin displays antioxidant and membrane stabilizing activity. It protects various tissues and organs against chemical injury, and shows potential as an antihepatoxic agent, and is therefore and is used in the treatment of toxic liver damage and as adjunctive therapy in chronic hepatitis and cirrhosis. (https://pubchem.ncbi.nlm.nih.gov/compound/5213) Silibinin is the major active constituent of silymarin, Silibinin has also demonstrated in vitro anti-cancer effects against human prostate adenocarcinoma cells, estrogen-dependent and -independent human breast carcinoma cells, human ectocervical carcinoma cells, human colon cancer cells, and both small and nonsmall human lung carcinoma cells. (https://go.drugbank.com/drugs/DB09298)

Experimental results from preclinical studies have shown that SLN can be a part of first aid in the management of venomous snake bites, particularly viperid and crotalid bites alongside antivenom. A preclinical study demonstrated the protective efficacy of inhibitor cocktail containing equal ratios of N,N,N',N'-tetrakis (2-pyridylmethyl) ethane-1,2-diamine (TPEN) (see candidate 'TPEN') and silymarin against progressive local toxicity induced by Echis carinatus venom, with promising results. This included evaluation of in vitro inhibitory potentials of SLN towards PLA2s and hyaluronidases in ECV in addition to docking studies. (https://pubmed.ncbi.nlm.nih.gov/26274501/). Further studies are needed to confirm this potential.

Other indications investigated: Diabetes; indigestion; liver disease; dietary supplement

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Dietary supplement; liver disease)

Development status: Active

Developers/investigators: University of Mysore

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/26274501/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Echis carinatus (Saw-scaled viper)	Echis carinatus (Saw-scaled viper)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: Both high and low toxicity toxins

Specific target toxin class: PLA2s,Hyaluronidase

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

Spiro [androst-5-ene-17,1'-cyclobutan]-2'-one,3-hydroxy-(3β,17β)

Alternative name(s): Spiro derivatives (citrus extract isolate)

Chemical name: 3-hydroxy-10,13-dimethylspiro[1,2,3,4,7,8,9,11,12,14,15,16-dodecahydrocyclopenta[a]phenanthrene-17,2'-cyclobutane]-1'-one

CAS number: N/A

PCR ID: 2547

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > New chemical or biological entity

Indication: Treatment of snakebite envenoming

Target: PLA2 (phospholipase A2)

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects

MeSH headings / pharmacological class: N/A

Key features and challenges:

Spiro compoundsare compounds that have at least twomolecular rings with only one common atom. Spiro [androst-5-ene-17,1'-cyclobutan]-2'-one,3-hydroxy-(3β,17β) is a spiro derivative isolated from citrus peel extract.

Following citrus extract snake venom neutralisation experiments, molecular docking studies of citrus metabolites showed binding affinity ofSpiro [androst-5-ene-17,1'-cyclobutan]-2'-one,3-hydroxy-(3β,17β) to PLA2 in cobra venom. (https://pubmed.ncbi.nlm.nih.gov/31953201/)

Other indications investigated: N/A

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Discovery (SBE)

Development status: Active

Developers/investigators: Vellore Institute of Technology (VIT University)

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Naja naja (Indian cobra)	Naja naja (Indian cobra)
Snake family		
Risk category		

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Not specified

Stigmasterol (Aegiphila integrifolia extract isolate)

Alternative name(s): N/A

Chemical name: (3S,8S,9S,10R,13R,14S,17R)-17-[(E,2R,5S)-5-ethyl-6-methylhept-3-en-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol

CAS number: 83-48-7

PCR ID: 2059

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: Hyaluronidases

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibits hyaluronidase

MeSH headings / pharmacological class: N/A

Key features and challenges:

Stigmasterol is a steroid derivative characterized by the hydroxyl group in position C-3 of the steroid skeleton, and unsaturated bonds in position 5-6 of the B ring, and position 22-23 in the alkyl substituent. Stigmasterol is found in the fats and oils of soybean, calabar bean and rape seed, as well as several other vegetables, legumes, nuts, seeds, and unpasteurized milk. In the European Union, it is a food additive listed with E number 499, and may be used in food manufacturing to increase the phytosterol content, potentially lowering the levels of LDL cholesterol. (https://pubchem.ncbi.nlm.nih.gov/compound/5280794). Aegiphila species (from which stigmasterol can be derived) are common plants from the Brazilian Amazon and are used to treat snakebites. its ethanolic extract was evaluated through in vitro and in vivo experiments to verify their antiophidic activity against Bothrops atrox crude venom.

A. integrifolia extracts eg stigmasterol, pectolinarigenin and hispidulin showed remarkable inhibition of venom hyaluronidase activity, while the proteolytic and phospholipase activities were partially inhibited. Phospholipase and proteolytic enzymes are related to myotoxic and hemorrhagic activities, respectively. Hyaluronidase is an important enzyme for the spread of venom toxins in tissues after a snakebite, enhancing the local effects of the venom. Data from this study show that A. integrifolia had promising inhibitory effects against the B. atrox venom, due to enzymatic inhibition and antagonizing the skin hemorrhage. (https://pubmed.ncbi.nlm.nih.gov/33984369/)

Other indications investigated: Benign prostatic hyperplasia; blood cholesterol; food additive

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: Military Institute of Engineering, Rio de Janeiro

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33984369/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops atrox (Fer-de-lance)	Bothrops atrox (Fer-de-lance)
Snake family		Viperidae
Risk category		Category 1 (Highest Medical Importance)

Direct action on toxins? Yes

Target toxin class: Low toxicity toxins

Specific target toxin class: Hyaluronidase

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

Sulfated agaran (Red seaweed extract isolate)

Alternative name(s): Polysaccharide; Red seaweed isolate; Laurencia aldingensis, Laurencia dendroidea; Laurencia spp. extract isolate

Chemical name: N/A

CAS number: N/A

PCR ID: 1642

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: PLA2 (phospholipase A2)

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; inhibits PLA2s

MeSH headings / pharmacological class: N/A

Key features and challenges:

Sulfated agaran is a polysaccharide isolate of the red seaweed Laurencia aldingensis. It has been investigated for treatment of gastric mucosa injury and for its antiviral, anticoagulant, and antithrombotic activities. It has also been investigated as well as a potential treatment for snakebite envenoming.

A preclinical study characterised, for the first time, a sulfated polysaccharide from the red seaweed, Laurencia aldingensis, including its neutralizing effect on some toxic activities of Lacheis muta venom. In vitro and in vivo assays showed that this sulfated agaran inhibited hemolysis, coagulation, proteolysis, edema, and hemorrhage of L. muta venom. Neutralization of hemorrhagic activity was also observed when the agaran was administered by different routes and after or before the venom injection. Furthermore, the agaran blocked the edema caused by a phospholipase A2 isolated from the L. muta venom. Experimental evidence therefore indicates that the sulfated agaran of L. aldingensis has potential to aid antivenom therapy of accidents caused by L. muta venom and may help to develop more effective antivenom treatments of snake bites in general. (https://pubmed.ncbi.nlm.nih.gov/27888371/)

Another study showed sulfated agaran to inhibit proteolysis and hemolysis induced by Lachesis muta and Bothrops jararaca venoms, as well as Bothrops jararaca lethality in mice.(https://pubmed.ncbi.nlm.nih.gov/31221314/)

Other indications investigated: Gastric mucosa injury; antiviral; anticoagulant; antithrombotic

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: Federal Fluminense University, Brazil; Brazilian Federal University of Parana, Universidade Federal do Parana (UFPR)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/27888371/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Lachesis muta (Southern American bushmaster); Bothrops jararaca (Jararaca)	Lachesis muta (Southern American bushmaster); Bothrops jararaca (Jararaca)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage),Procoagulant (blood clotting)

Tannic acid (polyphenol plant extract isolate)

Alternative name(s): Glycerite; Gallotannin; Gallotannic acid

Chemical name: [2,3-dihydroxy-5-[[(2R,3R,4S,5R,6S)-3,4,5,6-tetrakis[[3,4-dihydroxy-5-(3,4,5-trihydroxybenzoyl)oxybenzoyl]oxy]oxan-2-yl]methoxycarbonyl]phenyl] 3,4,5-trihydroxybenzoate

CAS number: 1401-55-4

PCR ID: 1776

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: Crude snake venom: Crotalus spp

Route of administration: Not yet determined

Thermostability: Melting point 200 °C

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects

MeSH headings / pharmacological class: N/A

Key features and challenges:

Tannic acid is a naturally occurring plant polyphenol and can be found in practically all aerial plant tissues. Tannic acid was historically used for the treatment of diarrhoea, topically to dress skin burns and rectally for treatment of unspecified rectal disorders. It is indicated for cold sores, fever blisters, diaper rash, minor burn or sunburn and prickly heat. Vaginally, tannic acid is used as a douche for leukorrhea. It has been also indicated for sore throat, inflamed tonsils, spongy or receding gums, and acute dermatitis. (https://go.drugbank.com/drugs/DB09372)

Tannins are common in plant extracts investigated for anti-venom activity, and various studies have examined the effects of purified tannins on snake venoms and their toxins, especially PLA2. The protective effect of tannic acid injected subcutaneously on the lethality and other actions of Crotalus admanteus venom in mice has been investigated. Studies have found that tannic acid is effective in protecting against snake venom-induced neuromuscular blockade in vitro. When co-injected with five lethal doses of venom, tannic acid provided much greater protection against lethality than flavonoids. Findings from preclinical studies suggest that tannic acid could be a potentially useful ancillary treatment for envenomation by C. d. terrificus. (https://pubmed.ncbi.nlm.nih.gov/34822584/)

Other indications investigated: Diarrhoea; cold sores; diaper rash

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Cold sores; fever blister; other)

Development status: Active

Developers/investigators: University of Sorocaba (UNISO), Brazil

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/34822584/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Crotalus durissus terrificus (South American rattlesnake)	Crotalus durissus terrificus (South American rattlesnake)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Neurotoxic (paralysis)

Ursolic acid

Alternative name(s): Urson; prunol; malol

Chemical name: (1S,2R,4aS,6aR,6aS,6bR,8aR,10S,12aR,14bS)-10-hydroxy-1,2,6a,6b,9,9,12a-heptamethyl-2,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydro-1H-picene-4a-carboxylic acid

CAS number: 77-52-1

PCR ID: 1807

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: SVMPs: Batx-I, (Bothrops atrox)

Route of administration: Not yet determined

Thermostability: Melting point 284 °C

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; occupies part of the substrate binding cleft of the enzyme affecting its catalytic cycle

MeSH headings / pharmacological class: N/A

Key features and challenges:

Ursolic Acid is a pentacyclic triterpenoid found in various fruits, vegetables and medicinal herbs, with a variety of potential pharmacologic activities including anti-inflammatory, antioxidative, antiviral, serum lipid-lowering, and antineoplastic activities. Ursolic acid may promote apoptosis and inhibit cancer cell proliferation through multiple mechanisms. (https://pubchem.ncbi.nlm.nih.gov/compound/64945) It is widely marketed and available as a dietary supplement.

Ursolic acids inhibit toxic activities of a snake venom metalloproteinase. Preclinical studies showed that ursolic acid inhibited the proteolytic activity of Batx-I on gelatin, as well as inhibition of the hemorrhagic activity and myotoxicity and edema-forming activity of Batx-I. Molecular docking studies suggested that these compounds could occupy part of the substrate binding cleft of the enzyme affecting its catalytic cycle. In this manner, triterpenic acids are candidates for the development of inhibitors for the prevention of local tissue damage in snakebite envenomation. (https://pubmed.ncbi.nlm.nih.gov/29203373/)

Other indications investigated: Dietary supplement; cancer

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Dietary supplement)

Development status: Active

Developers/investigators: Universidad de Antioquia, Colombia

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/29203373/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops atrox (Fer-de-lance)	Bothrops atrox (Fer-de-lance)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)

Vanillic acid (polyphenol plant extract isolate)

Alternative name(s): N/A

Chemical name: 4-hydroxy-3-methoxybenzoic acid

CAS number: 121-34-6

PCR ID: 1815

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: PLA2s; SVSPs

Route of administration: Not yet determined

Thermostability: Melting point 211.5 °C

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibits PLA2 and SVSPs

MeSH headings / pharmacological class: N/A

Key features and challenges:

Vanillic acid is a benzoic acid, used as a flavouring agent. Vanillic acid (4-hydroxy-3-methoxybenzoic acid) (VA) is a phenolic compound found in greater amounts in plant roots of Angelica sinensis and is an intermediate in the production of vanillin from ferulic acid. Vanillic acid has its beneficial effects already demonstrated on inflammation and related diseases.

An in vitro study investigating the interactions between vanillic acid and the enzymes present in snake venoms Bothrops and Crotalus spp. showed that vanillic acid promotes a better inhibitory action over metalloproteinases, followed by median inhibition in serine protease, and a lesser inhibition in PLA2s. Vanillic acid inhibited the proteolytic action of venoms on casein, fibrinogen, and BAPNA substrates. (https://pubmed.ncbi.nlm.nih.gov/32420666/; https://pubmed.ncbi.nlm.nih.gov/34979199/)

Other indications investigated: Food additive; Cancer; Alzheimer's disease

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Food additive)

Development status: Active

Developers/investigators: Federal University of Lavras, Brazil

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/32420666/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops jararacussu (Jararacussu); Bothrops alternatus (Cruzeria); Crotalus durissus terrificus (South American rattlesnake); Bothrops moojeni (Brazilian lancehead); Bothrops atrox (Fer-de-lance)	Bothrops jararacussu (Jararacussu); Bothrops alternatus (Cruzeria); Crotalus durissus terrificus (South American rattlesnake); Bothrops moojeni (Brazilian lancehead); Bothrops atrox (Fer-de-lance)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: SVMPs,PLA2s,SVSPs

Syndromic profiles: Cytotoxic (tissue damage),Procoagulant (blood clotting)

Vitamin B complex

Alternative name(s): N/A

Chemical name: N/A

CAS number: N/A

PCR ID: 1655

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: PLA2 (phospholipase A2)

Route of administration: Not yet determined

Thermostability: Thermostable properties

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; potential inhibition of snake venom proteases and PLA2

MeSH headings / pharmacological class: Antioxidants

Key features and challenges:

B vitamins are a class of water-soluble vitamins that play important roles in cell metabolism and synthesis of red blood cells.

Vitamins of the B complex may contribute to repair mechanisms, acting on the damage caused to cellular membrane by free radicals generated by toxin activity. The B vitamin complex showed inhibitory potential on activities, mainly the ones induced by proteases and PLA2, the major classes of toxins present in the snake venoms from the Viperidae family. (https://pubmed.ncbi.nlm.nih.gov/27737338/)

Other indications investigated: Dietary supplement

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Dietary supplement)

Development status: Active

Developers/investigators: Universidade Federal de Lavras, Brazil

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/27737338/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops atrox (Fer-de-lance); Crotalus durissus (South American rattlesnake)	Bothrops atrox (Fer-de-lance); Crotalus durissus (South American rattlesnake)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Cytotoxic (tissue damage)

Vitamin C (Ascorbic acid)

Alternative name(s): Vitamin C; ascorbic acid

Chemical name: (2R)-2-[(1S)-1,2-dihydroxyethyl]-3,4-dihydroxy-2H-furan-5-one

CAS number: 50-81-7

PCR ID: 1645

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: PLA2 (phospholipase A2)

Route of administration: Not yet determined

Thermostability: Thermostable properties

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; inhibition of snake venom proteases and PLA2

MeSH headings / pharmacological class: Antioxidants

Key features and challenges:

Ascorbic acid is a natural water-soluble vitamin (Vitamin C). Ascorbic acid is a potent reducing and antioxidant agent that functions in fighting bacterial infections, in detoxifying reactions, and in the formation of collagen in fibrous tissue, teeth, bones, connective tissue, skin, and capillaries. (https://pubchem.ncbi.nlm.nih.gov/compound/54670067)

Ascorbic acid has shown inhibitory potential on activities involved in snakebite envenomation, mainly the ones induced by proteases and PLA2, the major classes of toxins present in the snake venoms from the Viperidae family. One study evaluated possible interactions between vitamins and enzymes that comprise Bothrops atrox and Crotalus durissus terrificus venoms, in vitro. Proteolysis inhibition assays (substrates: azocasein, collagen, gelatin and fibrinogen), hemolysis, coagulation, hemagglutination were carried out using different proportions of vitamins in face of to inhibit minimum effective dose of each venom. The vitamins (including C) were responsible for reducing 100% of breaking azocasein by C.d.t. venom, thrombolysis induced by B. atrox and fibrinogenolysis induced by both venoms. It is suggested the presence of interactions between vitamin and the active site of enzymes, for example the interactions between hydrophobic regions present in the enzymes and vitamin E, as well as the inhibitions exercised by antioxidant mechanism. (https://pubmed.ncbi.nlm.nih.gov/27737338/) Previous studies have also show snake venom PLA2 inhibiting capacity of ascorbic acid (https://pubmed.ncbi.nlm.nih.gov/21682683/)

Other indications investigated: Dietary supplement

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Dietary supplement)

Development status: Active

Developers/investigators: Universidade Federal de Lavras, Brazil

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/27737338/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops atrox (Fer-de-lance); Crotalus durissus (South American rattlesnake)	Bothrops atrox (Fer-de-lance); Crotalus durissus (South American rattlesnake)
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Cytotoxic (tissue damage)

Vitamin E

Alternative name(s): Tocopherol; α-tocopherol

Chemical name: (2R)-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-3,4-dihydrochromen-6-ol

CAS number: 59-02-9

PCR ID: 1654

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: PLA2 (phospholipase A2)

Route of administration: Not yet determined

Thermostability: Thermostable properties

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; Membrane stabilisation

MeSH headings / pharmacological class: Antioxidants

Key features and challenges:

Vitamin E is an important vitamin required for the proper function of many organs in the body. It is also an antioxidant and occurs naturally in foods. Vitamin E is a term used to describe 8 different fat soluble tocopherols and tocotrienols, alpha-tocopherol being the most biologically active. Vitamin E acts as an antioxidant, protecting cell membranes from oxidative damage. The antioxidant effects are currently being researched for use in the treatment of diseases causing bone loss, cardiovascular diseases, diabetes mellitus and associated comorbidities, eye diseases, inflammatory diseases (including skin conditions), lipid disorders, neurological diseases, and radiation damage. Though this research is so far inconclusive, vitamin E remains a popular supplement and is generally considered safe by the FDA. (https://go.drugbank.com/drugs/DB00163)

Preclinical studies have shown that vitamin E inhibited the lipid peroxidation of the cell membrane of human erythrocytes induced by the Vipera russeli venom - exhibiting the membrane stabilizing effect of vitamin E against the damaging action of viper venom phospholipase A2 (PLA2). (https://pubmed.ncbi.nlm.nih.gov/27737338/). Other molecular docking studies of citrus metabolites have shown binding affinity ofα-tocopherol (vitamin E) to PLA2 in cobra venom. (https://pubmed.ncbi.nlm.nih.gov/31953201/)

Other indications investigated: Dietary supplement; bone loss; cardiovascular diseases; diabetes mellitus and associated comorbidities; eye diseases; inflammatory diseases (including skin conditions); lipid disorders; neurological diseases; radiation damage

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Dietary supplement)

Development status: Active

Developers/investigators: Universidade Federal de Lavras, Brazil

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/27737338/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrops atrox; Crotalus durissus terrificus	Bothrops atrox; Crotalus durissus terrificus
Snake family		Viperidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Cytotoxic (tissue damage)

Vitexin (flavanoid plant extract isolate)

Alternative name(s): Vitex agnus-castus extract isolate; Apigenin 8-C-glucoside

Chemical name: apigenin-8-C-glucoside

CAS number: 3681-93-4

PCR ID: 1886

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: Hyaluronidase

Route of administration: Not yet determined

Thermostability: Melting point 203 to 204 °C

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibits hyaluronidase

MeSH headings / pharmacological class: Hyaluronoglucosaminidase antagonists/inhibitors

Key features and challenges:

Vitexin is an apigenic flavone glycoside, which is found in the passion flower, bamboo leaves and pearl millet. It is an active component of many traditional Chinese medicines, and is found in various medicinal plants. It has a role as a platelet aggregation inhibitor, an EC 3.2.1.20 (alpha-glucosidase) inhibitor, an antineoplastic agent and a plant metabolite. It is a conjugate acid of a vitexin-7-olate. Vitexin (apigenin-8-C-glucoside) has recently received increased attention due to its wide range of pharmacological effects, including but not limited to anti-oxidant, anti-cancer, anti-inflammatory, anti-hyperalgesic, and neuroprotective effects. It has been investigated for a number of conditions including cancer, inflammation, sexual dysfunction and infertility. (https://pubchem.ncbi.nlm.nih.gov/compound/5280441)

Vitexin was isolated and identified for its potential antivenom properties as follows: Inhibition of the necrotizing hyaluronidase, phospholipase A2 and protease enzymes in four snake venoms by crude water and ethanol extracts of 88 plant species used against snakebites in traditional Chinese medicine was measured. High-resolution hyaluronidase inhibition profiles were constructed for the 22 plants showing highest hyaluronidase inhibition, and the results were used to guide subsequent structural analysis towards specific hyaluronidase inhibitors. Structural analysis was performed by high-performance liquid chromatography, high-resolution mass spectrometry, solid-phase extraction and nuclear magnetic resonance spectroscopy, i.e., HPLC-HRMS-SPE-NMR. This allowed identification of four non-tannin inhibitors, i.e., lansiumamide B from Clausena excavata Burm.f., myricetin 3-O-β-D-glucopyranoside from Androsace umbellata, vitexin, and 4',7-dihydroxy-5-methoxyflavone-8-C-β-D-glucopyranoside from Oxalis corniculata L. (https://pubmed.ncbi.nlm.nih.gov/26386983/). Further studies are needed.

Other indications investigated: Cancer; diabetes; inflammation; sexual dysfunction; fertility impairment

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Discovery

Highest R&D stage (any condition): Preclinical (Cancer; other)

Development status: Active

Developers/investigators: University of Copenhagen, Kobenhavens Universitet

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/26386983/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Gloydius blomhoffi (Mamushi), Deinagkistrodon acutus (Chinese copperhead), Naja naja atra (Chinese cobra), and Trimeresurus stejnegeri (Chinese green tree pitviper)	N/A
Snake family		
Risk category		N/A

Direct action on toxins? Yes

Target toxin class: Low toxicity toxins

Specific target toxin class: Hyaluronidase

Syndromic profiles: Cytotoxic (tissue damage)

Zinc / zinc oxide (ZnO) complex (ZC)

Alternative name(s): N/A

Chemical name: Zn/ZnO

CAS number: 1314-13-2

PCR ID: 1766

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (approved)

Indication: Treatment of snakebite envenoming

Target: PLA2

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Small molecule inhibitors bind specific components/toxins (antigens) within snake venom to neutralize its effects; inhibits PLA2

MeSH headings / pharmacological class: Trace elements

Key features and challenges:

Zinc is an essential mineral that is naturally present in some foods, added to others, and available as a dietary supplement. It is used in many of the body's normal functions and systems, including the immune system, wound healing and blood clotting. Zinc and zinc oxide complexes have been investigated for potential use in treating snakebite envenoming.

In a preclinical study, it was concluded that zinc ions could be a new candidate to aid antivenom treatment against the myonecrotic effects induced by the most abundant toxin in some bothropic snake venoms, as a result of it's effective inhibition of BthTX-1. (https://pubmed.ncbi.nlm.nih.gov/27531710/). Zn ions simultaneously inhibited BthTX-I through two different mechanisms: i) preventing fatty acid binding to H48 and thus avoiding the state transition from the inactive to active state, and ii) by binding directly to the MDiS region, preventing the membrane disruption process. Another study, using a Zinc Oxide complex (ZC) showed that ZC could widely absorb snake venoms, reducing the concentration of toxic protein in the blood, as well as demonstrating antibacterial and wound healing properties, with opportunities for its role as a first-aid snakebite therapeutic. (https://pubmed.ncbi.nlm.nih.gov/33959736/)

Other indications investigated: Burns; cuts; rash; sunscreen; dietary supplement

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Marketed (Dietary supplement; other)

Development status: Active

Developers/investigators: Nanchang University; Brazilian State University Paulista, Universidade Estadual Paulista (Unesp)

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33959736/
https://pubmed.ncbi.nlm.nih.gov/27531710/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bungarus fasciatus (Banded krait); Bothrops jararacussu (Jararacussu)	Bungarus fasciatus (Banded krait); Bothrops jararacussu (Jararacussu)
Snake family		Viperidae,Elapidae
Risk category		Both Category 1 & 2

Direct action on toxins? Yes

Target toxin class: High toxicity toxins

Specific target toxin class: PLA2s

Syndromic profiles: Cytotoxic (tissue damage)

β-sitosterol (Aegiphila integrifolia/citrus extract isolate)

Alternative name(s): N/A

Chemical name: N/A

CAS number: 83-46-5

PCR ID: 2058

Include in data set: Yes

Technical profile

Drugs > Therapeutic - natural/botanical > Repurposed (investigational)

Indication: Treatment of snakebite envenoming

Target: Hyaluronidases

Route of administration: Not yet determined

Thermostability: Unknown

Mechanism of action: Plant derived isolated chemical compounds bind toxins to neutralize their effects; inhibits hyaluronidase

MeSH headings / pharmacological class: N/A

Key features and challenges:

β-sitosterol is one of several phytosterols with chemical structures similar to that of cholesterol. It is a white, waxy powder with a characteristic odor, and is one of the components of the food additive E499. Phytosterols are hydrophobic and soluble in alcohols. β-sitosterol has been investigated for benign prostatic hyperplasia; blood cholesterol. Aegiphila species (from which beta sitosterol can be derived) are common plants from the Brazilian Amazon and are used to treat snakebites. Its ethanolic extract was evaluated through in vitro and in vivo experiments to verify their antiophidic activity against Bothrops atrox crude venom.

A. integrifolia extracts eg B-sitosterol, pectolinarigenin and hispidulin showed remarkable inhibition of venom hyaluronidase activity, while the proteolytic and phospholipase activities were partially inhibited. Phospholipase and proteolytic enzymes are related to myotoxic and hemorrhagic activities, respectively. Hyaluronidase is an important enzyme for the spread of venom toxins in tissues after a snakebite, enhancing the local effects of the venom. Data from this study show that A. integrifolia had promising inhibitory effects against the B. atrox venom, due to enzymatic inhibition and antagonizing the skin hemorrhage. (https://pubmed.ncbi.nlm.nih.gov/33984369/).Other molecular docking studies of citrus metabolites have shown binding affinity of β-sitosterol to PLA2 in cobra venom. (https://pubmed.ncbi.nlm.nih.gov/31953201/)

Other indications investigated: Benign prostatic hyperplasia; blood cholesterol; food additive

Development lifecycle

Investigational snakebite candidate

Current R&D stage (SBE): Preclinical

Highest R&D stage (any condition): Preclinical (SBE; other)

Development status: Active

Developers/investigators: Military Institute of Engineering, Rio de Janeiro

Preclinical sources: https://pubmed.ncbi.nlm.nih.gov/33984369/

Evidence of clinical trials? No

Effectiveness

	Tested in	Effective against (any efficacy data)
Snake species	Bothrop atrox (Fer-de-lance)	Bothrop atrox (Fer-de-lance)
Snake family		Viperidae
Risk category		Category 1 (Highest Medical Importance)

Direct action on toxins? Yes

Target toxin class: Low toxicity toxins

Specific target toxin class: Hyaluronidase

Syndromic profiles: Haemorrhagic (bleeding),Cytotoxic (tissue damage)