Animal Venoms in Medicine

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Introduction

Venomous animals occur in most animal phyla, including Cnidaria (sea anemones, jellyfishes, corals), Mollusca (marine snails, cephalopods), Annelida (leeches), Arthropoda (arachnids, insects, centipedes), Echinodermata (sea urchins, starfishes), and Chordata (fishes, reptiles, mammals). They are distributed throughout the Earth, inhabit a wide range of ecosystems, and have an evolutionary history dating back hundreds of millions of years. This broad evolutionary and environmental space has resulted in an extraordinarily diverse and powerful arsenal of molecules, yet all aiming toward one common goal: disablement of key physiological processes within seconds (Figure 1).

Venom Definition

'Venom' is defined as an animal secretion (by a specialized apparatus that is functionally and morphologically a separate unit within the body) used in feeding and/or defense, evolved to be delivered via physical trauma (by the parenteral route; e.g., by fang, harpoon, chelicerae) to an other animal causing a toxic (regardless of how weak or strong in magnitude but biologically beneficial for the producing organism) effect. (For simplicity, 'toxin' in this article refers to any venom component.)

Biology

Animal venoms evolved to harm, immobilize, or kill a wide spectrum of prey, predator, or adversary (e.g., intraspecific competition) species. In these target organisms, toxins aim at physiologically key and vulnerable body functions: neuromuscular signaling, vascular hemostasis, and the cardiovascular system, among others. Interfering with these functions allows for quick and powerful pharmacological intervention in a phylogenetically broad range of taxa.

Venom is a complex mixture of proteins, peptides, and low molecular weight organic and inorganic components, all acting synergistically. The peptidic components are enzymatic or nonenzymatic and are typically responsible for most, although not all, of the main pharmacological characteristics of crude venom. Venom from a single species is a mixture of about 50–200 different components (near extreme examples: 7–8 gene products in Tiger rattlesnake (*Crotalus tigris*), up to 600 peptide masses in Sydney funnel web spider (*Atrax robustus*)), and composition varies among and within species. Toxin molecules can be monomeric or homo/heteromultimeric

Figure 1 The manufacturer of a life-saving drug in the Arabian desert. The GPIIb/IIIa receptor antagonist toxin echistatin isolated from the Saw-scaled viper (*Echis carinatus*) venom served as a template for tirofiban (AGGRASTAT®) to treat unstable angina and non-Q-wave myocardial infarction (Photo: Dr Zoltan Takacs).

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complexes held together by covalent or noncovalent interactions.

History of Venoms in Medicine

Long before the current era of medicine, the life of Mithridates VI of Pontus (in 67 BC) is believed to be saved by Scythian sha mans in present day Turkey using viper (Viperidae) venom. The Ayurvedic texts of Susruta Samhita and Charaka Samhita (dates uncertain: first and second centuries AD) mention animal venoms in the context of medical use. Leech and bee venoms as therapeutic agents dates back thousands of years to a number of ancient cultures from the Far East to the Mediterranean region.

Modern experimental medicine credits two Italians as early pioneers of toxinology: Francesco Redi (1626 97) to show that it is not the snake's spirit that kills but its venom, and Felix Fontana (1730 1805) to show that viper venom affects blood. Around 1905, hirudin extract from the European medicinal leech (*Hirudo medicinalis*) was used as the first parenteral anti coagulant. Trials in 1934 with locally applied Russell's viper (*Daboia russelii*) venom diluted at 1:10 000 showed "success to stop haemorrhage following dental extraction." In 1938, Rus sell's viper venom was offered as a coagulant under the name Rusven. In 1936, "hämokoagulase" was purified from the Brazilian pit viper Jararaca (*Bothrops jararaca*), and this venom fraction is still in use today for hemorrhage.

In 1963, prolonged clotting defects were reported after Malayan pit viper (*Calloselasma rhodostoma*) bites, an observa tion that led to the isolation of a toxin called ancrod, and by 1968, turning it into a defibrinogenating therapeutic. Another milestone occurred in 1981 with the US Food and Drug Administration (FDA) approval of the antihypertensive agent captopril, derived from the Jararaca (*B. jararaca*) venom. This was the first example of reduction of a toxin to a small molecule mimic, and also the pharmaceutical company Squibb's first billion dollar drug. Venoms have also been instrumental for discoveries in many fields of basic science, for example, nucleic acid, ion channel, and nerve growth factor research, to name only a few.

Toxins as Drug Templates

Evolutionary Aspect

Despite the vast number of toxins in nature's venoms, peptidic toxins fall into a handful of protein scaffolds encoded by gene superfamilies. The length of the peptide, the number and relative position of disulfide bonds, the signal peptide, and other sequence determinants are highly conserved and signa tory for a scaffold. Consequently, within a scaffold, the primary, secondary, and tertiary structures are extensively conserved, yet discrete amino acid substitutions along the peptide backbone are present and confer novel biological function.

Toxin genes typically evolve from genes of other body proteins with nontoxic physiological functions expressed in tissues other than the venom gland. For example, three finger toxin scaffold widespread in elapid snakes (Elapidae: cobras, mambas, sea snakes, etc.) is homologous to the Ly 6 superfamily of proteins, present from Cnidaria to Chordata. Lynx1 peptide, a member of the Ly 6 superfamily, is an endogenous physiological neuromodulator in the mammalian central nervous system, with no toxic function. Subtle amino acid changes on this scaffold theme, however, generated an amazingly different and wide range of molecules (now called toxins) with unique biological activities targeting the muscle type or neuronal nicotinic acetylcholine receptors (nAChRs), muscarinic acetylcholine (ACh) receptors, voltage gated Ca^{2+} (Ca_v) 1 channels, acid sensing ion channel, acetylcholines terase, platelet integrin GPIIb/IIIa, coagulation factor VIIa, and others.

The actual process of toxin evolution occurs by gene duplication, gene conversion, alternative splicing, and various forms of gene domain multiplication, or loss. The new gene is typically subject to rapid diversification by accelerated evolu tion and positive selection. Amino acid substitution rate correlates with surface accessibility of residue that is a driver for novel specificity, and toxin genes rank among the most rapidly evolving protein coding genes in Metazoa. The process is mostly attributed to the predator prey arms race, and the same protein scaffolds are often convergently recruited into the venom arsenal by different animal taxa. There is also evidence that toxin genes could potentially revert back to nontoxic physiological function.

The end result is an astonishing array of unique toxins each with a distinct, however subtle or pronounced, pharma cological property based on a handful of evolution tested, robust molecular scaffolds.

Chemistry

In medical applications, peptidic toxins could be used either in their native (natural or synthetic) form or as a modified molecule (peptidomimetic a molecule that mimics the desired action of the native peptide). In the native form, they bear high potency, and the conformationally restrained struc ture may minimize binding to nontargets, resulting in high selectivity. As venoms are meant to be injected into foreign tissues, intrinsic sequence properties and posttranslational modifications (disulfide bonds, inhibitory cysteine knot, *C* terminal amidation, etc.) often confer an inherent stability to toxins against degradation by proteases. Toxins are also soluble, a benefit in peptide therapeutics. Low accumulation in tissues and low toxicity are further advantages of peptidic drugs.

Undesirable aspects of using peptidic drugs are the need for parenteral administration (low oral bioavailability), suscepti bility to proteolysis, short half life, immunogenicity including triggering allergic reactions, and synthetic production issues (e.g., quantity, posttranslational modification). Toxin size and charge may also be limiting factors. At present, protein thera peutics are typically restricted to cell surface and extracellular targets. Furthermore, employing toxins directly purified from crude venom poses a challenge for quality control. To some degree, venom composition, including toxin sequence, varies (e.g., due to geographical origin of the specimen), and venom extraction, toxin purification/purity are also variables that must be controlled.

Reducing native toxins to peptide or nonpeptide (small molecule) peptidomimetic could offer more desirable pharmacokinetic properties such as increased bioavailability, enable membrane transport, and counter enzymatic degradation. However, designing peptidomimetics has many challenges. In successful therapeutic examples when toxins have been reduced to peptidomimetics, the structural elements responsible for activity (pharmacophore) were located in a continuous segment along the peptide backbone. Yet, in other toxins, the pharmacophore domain is contiguous in space rather than along the peptide backbone thus making it more problematic to develop mimics. The approach to develop captopril from the native toxin was one of the early examples of successfully reducing peptides to small molecules based on structure activity relationship. Biomedical utilization of the nonpeptidic components of animal venoms remains less explored.

Pharmacology

The major advantage of toxins is that evolution perfected them to act on many of the same target molecules whose control is needed for therapeutic medical intervention. Often different scaffolds, from different taxa, are aimed at the same target molecule but with somewhat different binding sites. Toxin sequence diversity enables subtle distinction among target subtypes or the interaction with entirely different classes of targets, and thus induces an extremely wide variety of biological activities.

Enzymes, cell surface receptors of various types, including ion channels, control a wide range of key physiological processes and thus are among the major target classes for drugs. Hydrolases, G protein coupled receptors (GPCRs), and Ca^{2+} channels, are examples of the most prominent drug targets. For the very same reason controlling key physiological processes the enzymes/enzymatic pathways and cell surface receptors are also the principal target for animal toxins. Toxin targets with medical relevance include, but are not limited to, ligand gated nAChRs, *N* methyl D aspartate receptors, 5 hydroxytryptamine$_3$ receptors, and Ca_V, voltage gated Na^+ (Na_V), and voltage gated K^+ (K_V) channels, an array of GPCRs (e.g., α adrenergic, muscarinic ACh, neurotensin, endothelin, and vasopressin receptors), and the norepinephrine transporter. A myriad of other regulator molecules of blood coagulation, platelet aggregation, and cardiovascular system are also major toxin targets, such as prothrombin, fibrinogen, integrin, angiotensin converting enzyme (ACE), complement component C3, to name but a few. Nucleotides and lipids are also targeted by toxins.

Typically, a particular toxin scaffold interacts with a restricted number of target types and/or subtypes, such as a subset of K_V channels. This target biased nature of toxin scaffolds makes them an ideal starting pool to select drug leads, templates on which further optimization can be performed. The structure of toxin targets is also evolutionarily conserved across species. This means toxins that work in a nonhuman species will likely, but not always, have a similar effect on molecules in humans.

Toxins often tend to have pharmacological properties that are required or beneficial for a lead compound: high affinity, potency, specificity (distinction among receptor types) and selectivity (distinction among receptor subtypes), therapeutic efficacy, and suitable mechanism of action. Other times, one or more of these factors are clearly not met, and further screening or optimization is needed. Safety, pharmacokinetics, and delivery also have to be addressed.

Current Medical Application of Animal Venom Toxins

Diagnostics

Toxins are used in approximately 15 diagnostic assays in clinical hemostasis laboratories and as a test for myasthenia gravis. All toxins are originated from snake venoms (Table 1).

The vertebrate hemostatic system, a delicate interaction among thrombocytes (known also as platelets in mammalian vertebrates), endothelial cells, subendothelial structures, and plasma proteins is easily vulnerable to disruptive biochemical or biophysical factors. This very system is a major and multipoint target for toxins that can lead to lethal thromboembolic events or hemorrhage (Figure 2). The mechanism of action of toxins is often extremely similar to the corresponding physiological clotting factor, and they can activate or inactivate numerous phases of blood coagulation. Importantly, however, because of acting independently from cofactors, or by being resistant to inhibitors, or to proteolytic degradation, the target organism's own control mechanisms are ineffective against the action of toxins. As a result, toxins with defined mechanisms of action, restricted substrate specificity, and unaffected by the inhibitory pathways are valuable sources of diagnostic tools.

Current diagnostics are mostly enzymatic toxins; nonenzymatic examples are BOTROCETIN® or α bungarotoxin. They are typically purified directly from the crude venom, thus subject to taxonomic, geographic variability, and possibly misidentification. For example, geographical variability in Russell's viper venom (*D. russelii*) has been attributed to variability in the test results. Additionally, presence of toxin isoforms in a single venom could complicate test reproducibility.

While some tests have limited use, venoms are used, for example, to identify factor V Leiden mutation, one of the most common hereditary procoagulant states. Dilute Russell's viper venom time is widely used to detect lupus anticoagulants, a major risk factor for arterial and venous thrombosis, accounting for ~15% of patients with thromboembolic events. The availability of direct diagnosis (e.g., by sequencing) is expected to overtake the utilization of some toxin based tests.

Therapeutics

Toxins are used in approximately 15 different medications (Table 2). Drugs from toxins include potentially life saving (e.g., eptifibatide, captopril, enalapril), first in class (e.g., ACE inhibitors, incretin peptide mimetics), and some of the top selling medications in the history of medicine (e.g., captopril/ACE inhibitors). Toxins as drugs are either used as a natural toxin purified directly from crude venom (e.g., batroxobin), synthetic version of the natural toxin (e.g., exenatide, ziconotide), or as a peptide (e.g., eptifibatide) or nonpeptide (e.g.,

Table 1 Clinical diagnostics derived from animal venom toxins

Test/Reagent name	*Species origin*	*Mechanism of action*	*Test for*
anti-Ca_v2 antibodies assay	Geography cone snail (*Conus geographus*) or Magician's cone snail (*Conus magus*)	radioiodinated (*Cg*) ω-conotoxin GVIA or (*Cm*) ω-conotoxin MVIIC binding to $Ca_v2.2$, 2.1 respectively	Lambert-Eaton myasthenic syndrome
Anti-nAChR antibodies assay	Many-banded krait (*Bungarus multicinctus*) or 'Cobras' (*Naja* spp.)	Radioiodinated (*Bm*) α-bungarotoxin or (*N*) cobratoxin binding to nAChR	Myasthenia gravis
Anti-nAChR antibodies assay	Monocellate cobra (*Naja kaouthia*)	Eu^{3+}-α-cobratoxin binding to nAChR	Myasthenia gravis
BOTROCETIN®	Neuwied's lancehead (*Bothrops neuwiedi*) or Jararaca (*Bothrops jararaca*)	Induces von Willebrand factor (vWF) dependent platelet aggregation	von Willebrand factor (vWF) level
Factor V activator (RVV-V)	Russell's viper (*Daboia russelii*)	Activates factor V	Factor V determination
PEFAKIT® PiCT®	Russell's viper (*Daboia russelii*)	Activates factor V	Anticoagulant activity based on factor Xa and/or factor IIa inhibition
PEFAKIT® APC-R Factor V Leiden	Russell's viper (*Daboia russelii*); and Tiger snake (*Notechis scutatus*)	(*Dr*) activates factor V; and (*Ns*) activates prothrombin	Factor V Leiden mutation (FV:Q506)
PROTAC®	Copperhead (*Agkistrodon contortrix*)	Activates protein C	Protein C and protein S levels
PROC® GLOBAL	Copperhead (*Agkistrodon contortrix*)	Activates protein C	Protein C and protein S pathway abnormalities
CRYOCHECK™ CLOT C™	Copperhead (*Agkistrodon contortrix*); and Russell's viper (*Daboia russelii*)	(*Ac*) activates protein C; and (*Dr*) activates factor X	Protein C activity
CRYOCHECK™ CLOT S™	Copperhead (*Agkistrodon contortrix*); and Russell's viper (*Daboia russelii*)	(*Ac*) activates protein C; and (*Dr*) activates factor X	Protein S activity
REPTILASE® Time	Common lancehead (*Bothrops atrox*) or Brazilian lancehead (*Bothrops moojeni*)	Cleaves Aα-chain of fibrinogen	Fibrinogen level and function; heparin contamination
Textarin time	Eastern brown snake (*Pseudonaja textilis*)	PL dependent prothrombin activator	Activated protein C resistance; lupus anticoagulants
Textarin/ecarin ratio	Eastern brown snake (*Pseudonaja textilis*); and Saw-scaled viper (*Echis carinatus*)	(*Pt*) PL dependent prothrombin activator; and (*Ec*) activates prothrombin to meizothrombin in the absence of PL	Confirmation of lupus anticoagulants
Ecarin clotting time	Saw-scaled viper (*Echis carinatus*)	Activates prothrombin to meizothrombin in the absence of PL	Direct thrombin inhibitors; prothrombin quantification; lupus anticoagulants
Factor X activator (RVV-X)	Russell's viper (*Daboia russelii*)	Activates factor X	Lupus anticoagulants; distinguishing between factor VII and factor X deficiency
SPECTROZYME® FXa	Russell's viper (*Daboia russelii*)	Activates factor X	Factor X activity
STACLOT® APC-R	Western rattlesnake (*Crotalus oreganus*)	Activates factor X	Activated protein C resistance
Stypven time (Russell's viper venom time)	Russell's viper (*Daboia russelii*)	Activates factor X	Factor VII or X deficiency
Dilute Russell's viper venom time (dRVVT)	Russell's viper (*Daboia russelii*)	Activates factor X	Lupus anticoagulants
Dilute Russell's viper venom confirm DVVCONFIRM®	Russell's viper (*Daboia russelii*)	Activates factor X; extra PL corrects dRVVT	Confirmation of lupus anticoagulants
Taipan snake venom time	Taipan (*Oxyuranus scutellatus*)	Prothrombin activator, stimulated by PL	Lupus anticoagulants

Note: Order is based on the molecular weight of the principal (or first) toxin molecule responsible for activity. The extent of utilization, test name, and classification varies. Per classification, some tests may overlap. Test variations exist (e.g., Taipan snake venom time/ecarin time). Only one brand name (in parentheses) is provided as an example. PL, phospholipid.

tirofiban, captopril) peptidomimetic of the natural toxin. In 'hemocoagulases,' a crude venom fraction containing two natural toxins is utilized.

Currently drugs are derived from the venoms of various species of vipers (Viperidae), the European medicinal leech (*H. medicinalis*), Gila monster (*Heloderma suspectum*), and the marine snail Magician's cone (*Conus magus*). Representative indications include unstable angina, type 2 diabetes mellitus, hypertension, congestive cardiac failure, prevention of hemorrhage during surgery, and chronic pain. As an example of the impact venom based agents have had on medicine, two out of the three available agents in the platelet glycoprotein

Figure 2 Viper venom targets blood coagulation. 20 min whole blood clotting test. Left: Healthy control. Right: Adult patient in Nepal, bitten by a suspected Mountain pit viper (*Ovophis monticola*) and displays signs of consumption coagulopathy (Photo: Dr Zoltan Takacs).

inhibitor class of drugs are snake venom derived (Figure 3). These agents constitute cornerstone therapy for the most lethal types of heart attacks (e.g., ST segment elevation). Only captopril and other ACE inhibitors are taken orally, the rest have to be administered parenterally, and/or, in limited cases, topically. BYDUREON® is formulated in biodegradable polymeric microspheres that encapsulate exenatide and provide extended release.

Globally, tens of millions of patients are treated with drugs derived from toxins, with many lives saved. The annual global sales figures (in 2013) range between US$ ~ 27 million for PRIALT® and US$ ~ 698 million for BYETTA®/BYDUREON®, while ACE inhibitors as a class was the fourth most widely prescribed medicine in the United States (2009).

Other Biomedical Applications

Animal venoms have a number of other biomedical applications outside the scope of this text. There is one cosmetic derived from a neurotoxin of the Wagler's pit viper (*Tropidolaemus wagleri*) acting on the nAChR. It is marketed to smoothen wrinkle lines when rubbed on the facial skin. Venoms are also the starting materials to manufacture antivenom for the clinical management of animal venom poisoning, responsible for ~20 000 100 000 fatalities a year, globally. Toxins are also used for preparative applications, for example, to produce defibrinogenated plasma or meizothrombin, and for attempts to develop pesticides. In various basic science disciplines, toxins are essential research tools, which, in turn, also fuels the development of toxin derived medications.

Toxin-Derived Drugs in Advanced Stages of Development

A number of toxins and toxin derived compounds are in various stages of development ranging from the experimental phase to clinical trials. Examples in clinical trials in 2014 include Eastern green mamba (*Dendroaspis angusticeps*) cenderitide (CD NP) for congestive cardiac failure, Sun anemone (*Stichodactyla helianthus*) ShK 186 for various autoimmune diseases, and Common vampire bat (*Desmodus rotundus*) desmoteplase to treat acute ischemic stroke. CD NP elegantly builds on the evolutionary relationship of nontoxin and toxin body proteins. It is a chimeric human mamba peptide that exhibits more desirable pharmacology than either of the templates, the human C type natriuretic peptide or *Dendroaspis* natriuretic peptide. ShK 186 is a result of a decade long work that generated hundreds of analogs of the K^+ channel blocking toxin ShK to improve target selectivity and stability. Desmoteplase is a recombinant form of *Desmodus* salivary plasminogen activator α1 with high fibrin specificity isolated from the bat saliva.

Efforts in the clinical phase are also under way in China to develop alternatives to the natural toxin ingredients of batroxobin and hemocoagulase, currently purified from snakes living in South America. Strategies include recombinant toxin production and competing products that are based on toxins isolated from the venom of the Chinese moccasin (*Deinagkistrodon acutus*) and other species native to the Far East.

Medical Potential of Animal Venoms

A combination of key parameters make animal toxins an unparalleled arsenal for biomedical applications: immense diversity, inherent biological properties, advances in technology to isolate, screen, engineer, and formulate/deliver peptides and derived peptidomimetic compounds.

The global diversity of venomous animals ranges about 100 000 170 000 species. Collectively, it is estimated that there are more than 20 million unique animal toxins existing in nature. Approximately, the number of crude venoms screened for various biological activities is in the many hundreds, toxins known to science is in the scale of 10 000, while it is likely no more than 1000 toxins have been studied in detail. This effort resulted in about 15 medications. The sheer magnitude of these

Table 2 Drugs derived from animal venom toxins

Drug name	*Species origin*	*Mechanism of action*	*Indication*
Captopril (CAPOTEN®)	Jararaca (*Bothrops jararaca*)	Angiotensin-converting enzyme inhibitor	Hypertension, cardiac failure
Enalapril[a] (VASOTEC®)	Jararaca (*Bothrops jararaca*)	Angiotensin-converting enzyme inhibitor	Hypertension, cardiac failure
Exenatide (BYETTA®)	Gila monster (*Heloderma suspectum*)	Glucagon-like peptide-1 receptor agonist	Type 2 diabetes mellitus
Exenatide (BYDUREON®)	Gila monster (*Heloderma suspectum*)	Glucagon-like peptide-1 receptor agonist (extended release)	Type 2 diabetes mellitus
Ziconotide (PRIALT®)	Magician's cone snail (*Conus magus*)	$Ca_V2.2$ channel antagonist	Management of severe chronic pain
Bivalirudin (ANGIOMAX®)	European medicinal leech (*Hirudo medicinalis*)	Reversible direct thrombin inhibitor	Anticoagulant in percutaneous coronary intervention
Lepirudin (REFLUDAN®)	European medicinal leech (*Hirudo medicinalis*)	Binds irreversibly to thrombin	Anticoagulation in heparin-associated thrombocytopenia; related thromboembolic disease
Desirudin (IPRIVASK®)	European medicinal leech (*Hirudo medicinalis*)	Selective and near-irreversible inhibitor of thrombin	Prevention of venous thrombotic events
Tirofiban (AGGRASTAT®)	Saw-scaled viper (*Echis carinatus*)	Antagonist of fibrinogen binding to GPIIb/IIIa receptor	Acute coronary syndrome
Eptifibatide (INTEGRILIN®)	Pigmy rattlesnake (*Sistrurus miliarius*)	Prevents binding of fibrinogen, von Willebrand factor, and other adhesive ligands to GPIIb/IIIa receptor	Acute coronary syndrome; percutaneous coronary intervention
Batroxobin (DEFIBRASE®)	Common lancehead (*Bothrops atrox*) or Brazilian lancehead (*Bothrops moojeni*)	Cleaves Aα-chain of fibrinogen	Acute cerebral infarction; unspecific angina pectoris; sudden deafness
Platelet gel (PLATELTEX-ACT®)	Common lancehead (*Bothrops atrox*)	Cleaves Aα-chain of fibrinogen	Gelification of blood for topical applications in surgery
Fibrin sealant (VIVOSTAT®)	Brazilian lancehead (*Bothrops moojeni*)	Cleaves Aα-chain of fibrinogen	Autologous fibrin sealant in surgery
Thrombin-like enzyme	Chinese moccasin (*Deinagkistrodon acutus*) or Siberian pit viper (*Gloydius halys*) or Ussuri mamushi (*Gloydius ussuriensis*)	Fibrinogenase	'Antithrombotics'; 'defibrinating agent for the treatment and prevention of thromboembolic diseases'
Hemocoagulase (REPTILASE®)	Common lancehead (*Bothrops atrox*) or Jararaca (*Bothrops jararaca*) or Brazilian lancehead (*Bothrops moojeni*)	Cleaves Aα-chain of fibrinogen; factor X and/or prothrombin activation	Prophylaxis and treatment of hemorrhage in surgery
Medicinal leech therapy	Medicinal leech (*Hirudo verbana*) or other Hirudinida species	Inhibit platelet aggregation and the coagulation cascade	Skin grafts and reattachment surgery

Note: Order is based on the complexity (disulfide bonds, sequence length) of the lead toxin molecule or venom fraction, less complex first. The extent of utilization, drug name, and drug classification varies. Per classification, drugs may overlap. In some cases, species origin is uncertain, and available references are limited. Drug misnaming is known to occur in the industry. Only one brand name (in parentheses) is provided as an example. List does not include terminated and/or data deficient agents, such as ancrod (ARVIN®), ximelagatran (EXANTA®), and 'hemocoagulase' *Daboia russelii* and *Gloydius ussuriensis*.

[a]Enalapril and other ACE inhibitors are regarded as later generation derivatives of captopril.

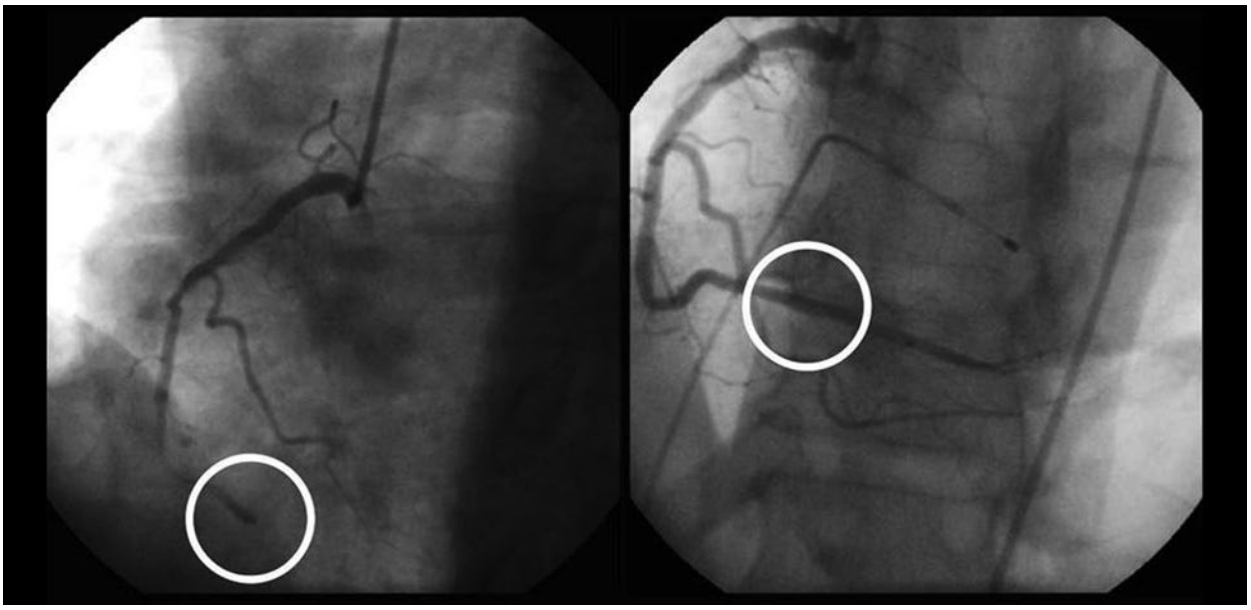

Figure 3 Viper venom–based eptifibatide in a heart attack patient. Left: The presence of occlusive thrombus (blood clot, circled) within a coronary artery and resulting diminishment or cessation of blood flow, is the hallmark finding on angiography in patients afflicted with a heart attack. After direct (intracoronary) and systemic (intravenous) administration of eptifibatide to promote disaggregation of accumulated blood platelets, the occluded segment of clot is first mechanically disrupted using a balloon catheter and then, definitively addressed via placement of a coronary stent (miniature metal scaffold). Right: The final result (previously occluded segment circled) reveals patency of the right coronary artery with restoration of flow into the branch vessels, facilitated by eptifibatide (Angiogram: Dr Sandeep Nathan).

numbers reflects the untapped potential in nature's venoms for medicine.

Pharmaceutical target identification and validation, and establishing novel and robust chemical starting points are among the biggest challenges in drug discovery. Given their evolutionary origin/diversity and pharmacology, animal toxins possess vast potential to address these and related challenges. As examples of potential impact, five of the seven pharmacological sites on the Na_V channels are defined by animal toxins, and 10% of the first 30 toxins isolated from marine snail venoms have reached at least phase I clinical trials.

With advances in genomics, proteomics, and bio informatics, along with the diverse array of high throughput screening methods, we are reaching the stage where the large scale screening of toxins is a reality and the limiting factor is less of a technological challenge but more of actually accessing samples from nature. A major facilitating factor is the requirement for less venom/tissue samples for proteomic and genomic characterization.

Advances in production of target focused toxin libraries, engineering protein scaffolds, reducing the native toxins to peptidomimetics, formulating/delivering peptidic toxins by nanotechnology or by other means are all opening up new avenues. For example, melittin, a toxin from the European honeybee (*Apis mellifera*), forms pores on lipid membranes, although somewhat indiscriminately. Nanoparticles carrying melittin and polyethylene glycol (PEG; as molecular spacers) on their surface attenuate HIV 1 infectivity. Cells, much bigger in size than HIV 1, are not affected, due to steric restriction to melittin by PEG.

Since toxins affect an extremely diverse set of targets and organs, their potential extend to many different types of conditions, for instance, cardiovascular diseases, cancer, diabetes, autoimmune and nervous system disorders. Rele vant global market forecasts, for example, for glucagon like peptide 1 agonists for diabetes is US$6 billion (by 2015) and for overall autoimmune disease therapeutics is $59 billion (by 2018). Time span between lead toxin identi fication and FDA approval varies between 7 years (eptifiba tide) and 25 years (ziconotide).

Lastly, extracting biological samples necessitate an ethical and legal responsibility. Proper scientific sampling of venoms should not have a detrimental effect on species and habitats. Yet, the results obtained from it should, ideally, be shared with communities, conservation efforts at the site of origin, and possibly beyond. A drug from venom could be seen as an ultimate gift by nature, and should be posi tioned, locally and globally, for efforts to conserve biolog ical diversity.

See also: Angiotensin Converting Enzyme (ACE) Inhibitors; Botulinum Toxin; Cardiovascular System; Centipedes; Ciguatoxin; Cosmetics and Personal Care Products; Dose–Response Relationship; Drug and Poison Information Centers; Marine Venoms and Toxins; Neurotoxicity; Saxitoxin; Scorpions; Shellfish Poisoning, Paralytic; Snakes; Spiders; Tetrodotoxin; 'Toxic' and 'Nontoxic': Confirming Critical Terminology Concepts and Context for Clear Communication; Toxicology.

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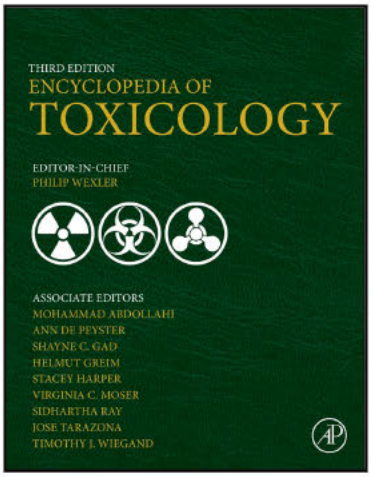

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