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Immune drug discovery from venoms

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Abstract

This review catalogues recent advances in knowledge on venoms as standalone therapeutic agents or as blueprints for drug design, with an emphasis on venom-derived compounds that affect the immune system. We discuss venoms and venom-derived compounds that affect total immune cell numbers, immune cell proliferation, immune cell migration, immune cell phenotype and cytokine secretion. Identifying novel compounds that ‘tune’ the system, up-regulating the immune response during infectious disease and cancer and down-regulating the immune response during autoimmunity, will greatly expand the tool kit of human immunotherapeutics. Targeting these pathways may also open therapeutic options that alleviate symptoms of envenomation. Finally, combining recent advances in venomomics with progress in low cost, high-throughput screening platforms will no doubt yield hundreds of prototype immune modulating compounds in the coming years

Introduction

There are approximately 8.7 million different species on Earth ^(Mora et al., 2011), many of which produce venoms that have been refined over 600 million years of evolution for optimal potency and selectivity ^(Mauri et al., 2017). Animal venoms have been used to treat various diseases by many cultures for millennia. In mithridatism practice, individuals regularly exposed themselves to small amounts of venom until immunity developed ^(Valle et al., 2012). In Chinese traditional medicine, venom from the glands of *Bufo bufo gargarizans* was used for treating infection and inflammation ^(Meng et al., 2009, Qi et al., 2014)

Venom is a complex mixture of peptides, proteins, enzymes, salts, and non-protein constituents. In terms of numbers of species, there are currently 600 leech species ^(Sket and Trontelj, 2008), 800 tick species ^(Cabezas-Cruz and Valdes, 2014), 3000 snake species ^(Wagstaff et al., 2006), 700 cone snail species ^(Puillandre et al., 2014), 1100 bat species ^(Jan et al., 2012), 2000 scorpion species ^(Cao et al., 2014), 10,000 cnidarians species ^(Cegolon et al., 2013) and 46,000 spider species ^(World Spider Catalog, 2017), although not all these species are venomous or dangerous to humans. Other venomous animals include centipedes, scorpions, octopus, sea anemones and fish ^(Fry et al., 2009). Advances in proteomic, genomic and transcriptomic platforms are rapidly defining animal venom complexity (termed venomomics) and are helping facilitate the translation of venom-derived compounds to novel therapeutics ^(Haney et al., 2014, Safavi-Hemami et al., 2014, Undheim et al., 2013). To date, six venom-derived drugs have been approved by FDA (**Table 1**) and many others are in preclinical development or clinical trials ^(King, 2011). The majority of venoms investigated thus far have been derived from snakes, due to the large amounts of venom these species produce for research ^(King, 2011). However, it should be noted that the venom yield is higher in captive snakes compared to the wild snakes and the amount of venom can be different depending on the type of bite, specifically a hunting or defensive bite ^(Mirtschin et al., 2006). Venoms and venom-derived compounds are known to activate or inhibit the immune response and synthetic venom-derived peptides are capable of modulating the human immune system. For example, the ShK peptide from the venom of sea anemone inhibits the Kv1.3 ion channel in T effector memory (T_{EM}) cells,

producing decreased cell proliferation and suppression of IL-2 production (Beeton et al., 2005). Furthermore, a derivative of ShK (dalazatide) recently completed a successful Phase I clinical trial in psoriasis patients (Tarcha et al., 2017)

The systematic study of the venom components and their interaction with the immune system may reveal novel therapeutics for a plethora of human diseases and therapeutics against envenomation symptoms. Venoms are engaged by the immune system and a response is generated to counterbalance their effects. This recognition is chiefly mediated by inflammation combined with the release of anti-inflammatory mediators in order to maintain homeostasis (Farsky et al., 2005, Leon et al., 2011, Petricevich, 2010). Crude venom and venom-derived compounds from spider, snake, scorpion and bee venom trigger inflammation (de Lima and Brochetto-Braga, 2003, Farsky et al., 2005, Petricevich, 2010, Rahmani et al., 2014). Inflammation refers to the complex reaction to harmful or noxious stimuli, including vascular changes, cell recruitment and cytokine release. The clinical signs of inflammation include redness, pain, heat, swelling and loss of function. It is also one of the steps in healing (Voronov et al., 1999). The immune system has evolved for approximately 1000 million years as a defensive system to protect the host (Buchmann, 2014). Initially, innate or natural immunity protects the body with a non-specific and fast response regulated through two lines of defense. The first line is comprised of physical and chemical barriers including skin, mucosa, cilia, tears, sweat, urine and bacterial flora. When the first defense line falls the second line is activated that includes the inflammatory response. Here diverse cell types are recruited (i.e. mast cells, neutrophils and eosinophils) and other chemical barriers such as the complement cascade are activated. The adaptive response can also be activated to generate immunological memory. Adaptive immunity is chiefly composed of T cells and B cells. T cells require antigen presentation by antigen presenting cells (APCs) via the Major Histocompatibility Complex (MHC). When APCs present antigen to T cells they become activated and secrete cytokines. B cells produce antibodies and plasma cells, the mature form of B cells, belong to the humoral immunity arm (Cota and Midwinter, Warrington et al., 2011). This review catalogues the potential of venom and their components as drugs or drug scaffolds, focusing on their potential as novel modulators of these immune cells (**Figure 1**).

The immune response to venom

Snake venom and immune modulation

Snake venom is synthesized by glands under the eye and they comprise a cluster of proteins that are determined by diet, geography (Daltry et al., 1996), age and gender (Woltering, 2012). Snake venom proteins are mixed with other components such as enzymes, amino acids, carbohydrates, lipids, amines and metal components (i.e. Zn^+ , Mg^+ , K^+ , Ca^+ and Na^+). Snake envenomation is a significant public health burden in tropics with over five million bites annually according to the World Health Organization (WHO) (Ahmed et al., 2008, Chippaux, 1998)

Post envenomation, venom components generate an immune response (Leon et al., 2011). Both the innate and adaptive immune arms then attempt to neutralize the venom components. The innate immune response commences first and triggers a non-specific inflammatory cascade mediated by neutrophils, eosinophils, basophils and macrophages that phagocytose antigen and release cytokines (Nicholson, 2016). Mast cells release histamine to expand the blood vessels enhancing cell recruitment and migration. Leukocytes and mast cells produce prostaglandin D₂ (PGD₂) that vasodilates and permeabilizes vessels. Prostaglandins also stimulate nerve endings causing pain (Ricciotti and FitzGerald, 2011, Urb and Sheppard, 2012). Bradykinins are released that modify cell junctions allowing neutrophils to migrate to the site of injury (Golias et al., 2007, Sukriti et al., 2014). Nitric oxide (NO) is a gas produced by endothelial cells that functions as a signaling molecule. NO is involved in the relaxation of blood vessels and can perform mediator activities in immune cells such as macrophages, neutrophils, APCs and T cells (Coleman, 2001). Snake venom is known to induce these mediators after envenomation. For example, the venom of *Bothrops erythromelas* induces NO production in

murine splenocytes (Luna et al., 2011) and the venom from *Bothrops jararacussu* enhances neutrophil chemotaxis (Wanderley et al., 2014). Snake envenomation can cause an increase of neutrophils and lymphocyte counts and one study found that an elevated neutrophil/lymphocyte ratio correlated with longer periods of hospitalization (Elbey et al., 2017), with selective proliferation likely due snake-derived L-amino acid oxidases (Pontes et al., 2016, Wei et al., 2009). Snake venom can induce systemic and local inflammation and it is well documented that the genus *Bothrops* can induce severe inflammation. In a murine model, the snake venom from *Bothrops asper* enhanced the production of IL-6, TNF α and eicosanoids (Zamuner et al., 2005) and venom-derived phospholipase A₂s (PLA₂s) improved phagocytic activity of macrophages *in vitro* (Rueda et al., 2013).

When the inflammatory response is generated by external dangers the complement system activates a sequence of proteins that induces cell lysis and antigen presentation to the adaptive immune system. The activation of complement is part of the innate immune response and includes more than 30 proteins (Sarma and Ward, 2011). There are three biochemical pathways; the classic pathway, the alternative pathway and lectin pathway (Sarma and Ward, 2011). The main role of the complement system is to amplify the immune response through the stimulation of phagocytosis and cell killing (Sarma and Ward, 2011). Venom from *Bothrops jararacussu* and *Bothrops pirajai* can activate the classic and lectin pathways (Ayres et al., 2015). Venom from the *Elapidae* family *Micrurus* genus can also activate a specific complement cascade that induces B cell and T cell function (Tanaka et al., 2012). A P-I metalloproteinase derived from the venom of *Bothrops pirajai* can activate complement proteins that induce mast cells to produce histamine, enhancing phagocytosis and enhancing immune cell migration (Pidde-Queiroz et al., 2013). Similarly, venom from *Daboia Russelii* can activate complement proteins and induce IL-6 and IL-10 (Stone et al., 2013). Conversely, a P-III metalloproteinase from *Naja naja atra* venom is considered an anticomplement molecule (Sun and Bao, 2010). Another study found that *Naja naja atra* venom enhanced innate and humoral immune responses while inhibiting CD4⁺ and CD8⁺ T cell proliferation in response to mitogen (Kou et al., 2014). *Naja naja atra* venom also induced production of IFN γ and IL-4 and inhibited IL-17 production. Mice injected with *Crotalus durissus terrificus* venom showed increased plasma levels of IL-4, IL-5, IL-6, TNF α , IL-10 and NO (Hernandez Cruz et al., 2008) and decreased phagocytosis by neutrophils (Lima et al., 2012). A L-amino acid oxidase from *Agkistrodon blomhoffii ussurensis* venom induced IL-2, IL-6 and IL-12 from primary human monocytes and T cells (Wei et al., 2007) and a PLA₂ from *Bothrops leucurus* venom induced IL-1 β , IL-6, IL-12p40 and TNF α from primary human mononuclear cells (Nunes et al., 2011). Snake venom can also suppress the immune system with *Naja kaouthia* venom able to protect against induced arthritis in rats (Gomes et al., 2010).

Scorpion venom and immune modulation

Scorpions are arthropods that have evolved for >400 million years (Ma et al., 2012) and *Buthidae* is the family with medical significance (Smith et al., 2011). Scorpion venom is comprised of proteins, enzymes, peptides, amino acids, carbohydrates, inorganic salts, lipids and amines (Quintero-Hernández et al., 2013) and shares similarities with tick and spider venom (Cordeiro et al., 2015). Scorpion venom is also rich in neurotoxins that can cause alterations in the central nervous system (Watt and Simard, 1984). Scorpion envenomation is a significant public health burden in several tropical and subtropical countries such as Brazil (Furtado Sda et al., 2016), Mexico (Isbister and Bawaskar, 2014), and Iran (Jalali and Rahim, 2014). In addition, over one million cases are reported globally every year (Isbister and Bawaskar, 2014). Clinical symptoms in envenomed patients include sweating, hypertension, nausea, extreme pain, vomiting, tachycardia and convulsions (Isbister and Bawaskar, 2014) and envenomation can induce a systemic inflammatory response syndrome, a result of abnormal cytokine production (Voronov et al., 1999). Scorpion venom is known to interact with Na⁺, K⁺, Ca⁺ and Cl⁻ ion channels (Quintero-Hernández et al., 2013).

Previous studies have shown that the main cytokines released in response to scorpion envenomation are IL-1, IL-6 and TNF α (Fukuhara et al., 2003, Jalali et al., 2011). One study showed that systemic IL-6 plays an important role in scorpion envenomation (Sofer et al., 1996). In another scorpion envenomation study, there was

an increase of systemic IL-6, soluble IL-6 receptor, TNF α , and RANTES, with high levels correlating with fatal outcomes (Abdel-Haleem et al., 2006). Venom from *Androctonus australis hector*, *Centruroides noxius* and *Tityus serrulatus* can initiate systemic IL-1 release in humans, triggering a complex cascade of other inflammatory/regulatory cytokines including IL-6, IL-10 and TNF α (Petricevich, 2010). Another study showed that *Tityus serrulatus* envenomation initiated systemic release of IL-1, IL-6, IL-8, TNF α and IL-10 (Fukuhara et al., 2003)

Cytokines can be released at different time points depending on the cytokine and the stimulus (Sullivan et al., 2000). Experiments performed on rats have shown that the plasma cytokines IL-1, IL-6 and TNF α peak three hours post injection of *Mesobuthus eupeus* venom and that antivenom can dampen the inflammatory response (Razi Jalali et al., 2015). The scorpion venom of *Tityus serrulatus* and its fractions were tested in a murine macrophage cell line pretreated with the mitogen lipopolysaccharide (LPS). Crude venom and two fractions augmented TNF α , IL-6 and NO release. In contrast, a separate fraction inhibited the release of TNF α and IL-6 and induced IL-10 suggesting anti-inflammatory activity (Zoccal et al., 2011). The venom of *Androctonus crassicauda* is known to enhance IL-12 production in human monocytes (Saadi et al., 2015). IL-12 is a pleiotropic cytokine driving T helper 1 (Th1) differentiation, IFN γ production, and T cell proliferation (Miles et al., 2015, Saadi et al., 2015). T cells are central for anti-pathogen and anti-cancer immunity and their dysfunction underlies autoimmunity (Miles et al., 2011). Additionally, the venom of the *Hemiscorpius lepturus* induces IL-12 release from human monocytes *in vitro* (Hadaddezfali et al., 2015) and a fraction from *Tityus serrulatus* venom induced IL-1, IL-6, TNF α and IL-10 from murine monocytes *in vitro* (Petricevich et al., 2007). Venoms can also interfere with immune cell proliferation. The venom of *Tityus serrulatus* increases IL-6 secretion in PBMC and inhibits proliferation in T cells activated by mitogen (Casella-Martins et al., 2015)

The recognition of external threat is performed by Toll-like receptors (TLRs) which are membrane-spanning proteins in the innate immune system, mainly expressed in macrophages and dendritic cells (DCs) (Kawai and Akira, 2010). TLRs are able to recognize ligands from microbes (bacteria, viruses and fungi) and then activate immune responses (Kawai and Akira, 2010). Ten TLRs have been identified in humans and TLR agonists induce activation and maturation of the immune system (Kawai and Akira, 2010). Venoms are known to engage the innate immune system including TLRs. For example, crude *Tityus serrulatus* venom and a venom fraction are sensed by murine TLR2 and TLR4 and induce the NF- κ B and MAPK signaling pathways in macrophages resulting in release of IL-6, TNF α , PGE₂ and LTB₄ (Zoccal et al., 2014). *Tityus serrulatus* venom fractions have also been observed to modulate APC phenotype and function (Petricevich et al., 2008)

The interaction between venom-derived compounds and ion channels and has been well studied (King, 2011). Venom-derived peptides are highly selective for these targets, and they have been described as promising candidates for new therapeutic approaches and drug development (Bagal et al., 2013). Ion channels, specifically K⁺ channels, are involved in T cell activation and are a chief target for immunomodulation. Other lineages also express K⁺ channels (DCs, monocytes, and macrophages) (Zhao et al., 2015). Scorpion venom and its components can manipulate K⁺ channels for immune modulation (Hmed et al., 2013, Petricevich et al., 2007). For example, several scorpion peptides are known to inhibit K⁺ ion channels (Dutertre and Lewis, 2010, Swartz, 2013) including Margatoxin (MgTX) peptide from the venom of *Centruroides margaritatus*. MgTX can inhibit Kv 1.3 channels expressed by T cells and B cells (Bartok et al., 2014, Garcia-Calvo et al., 1993). A second example is Kaliotoxin (KTx) peptide from the venom of *Androctonus mauretanicus mauretanicus* which can inhibit both Ca⁺ and K⁺ channels (Crest et al., 1992)

Bee venom and immune modulation

The venom of *Apis mellifera* also has applications for immune modulation. 50–60% of the dry venom comprises a single melittin peptide (Raghuraman and Chattopadhyay, 2007) and 2–3% of the dry venom comprises

the apamin peptide (Gmachl and Kreil, 1995). Bee venom also contains enzymes such as hyaluronidase, PLA₂ and histamine (Hwang et al., 2015)

DCs are the chief lineage for antigen presentation and they initiate both naïve and memory T cell responses (Randolph et al., 2005). Immature DCs are able to digest antigens by endocytosis, micropinocytosis and phagocytosis and, once they uptake antigen, DC migrate to lymph nodes where they mature and encounter T cells (Randolph et al., 2005). DCs express well known surface markers and costimulatory molecules that increase in expression during maturation (CD40, CD80, CD83 and CD86) and a mature DC phenotype correlates directly with potent T cell responses (Hubo et al., 2013). PLA₂ from bee venom can enhance the maturation of DC and PLA₂, in combination with TNF α and IL-1 β , can induce the upregulation of costimulatory molecules CD83, CD86, both important for T cell stimulation (Aerts-Toegaert et al., 2007, Jeannin et al., 2000, Van Kaer, 2015). Immune cells express classic antigen presenting molecules MHC class I and class II but can also express non-classical molecules including CD1 (Rossjohn et al., 2015). Bee venom PLA₂ can activate human T cells via CD1 molecules (Bourgeois et al., 2015) and can also induce a Th2 response via the release of IL-33 (Palm et al., 2013), a cytokine common in the skin and intestine (Miller, 2011). Thus, bee venom is a potent immune modulator and it has been used for over a hundred years in autoimmune diseases such as rheumatoid arthritis and allergic disorders like asthma (Pak, 2016). Bee venom is known to induce T regulatory (Treg) cells (Park et al., 2015), an important regulatory lineage that corrects erroneous activities of other T cell subsets. Treg cells produce TGF β and IL-10 that suppress the immune system and therefore reduce autoimmunity, inflammation and allergy (Wan and Flavell, 2007). Bee venom is known to induce Treg populations effectively and therapeutic application decreases inflammation of the bronchi in a murine asthma model (Choi et al., 2013)

Sea anemone toxin and immune modulation

A toxin rather than a venom, the ShK peptide derived from the *Stoichactis helianthus* anemone (Pennington et al., 2012) shows promise as a selective immune suppressor (Norton et al., 2004). Analogs of the toxin have shown similar activities and modes of action (Lanigan et al., 2001). The anemone produces the toxin for protection against predators. Autoimmunity is the failure of the immune system to differentiate external threats from healthy operations resulting in unintended tissue damage. Most autoimmune diseases have no cures and researchers are actively exploring natural sources for novel therapeutics (Smallwood et al., 2017). The ShK peptide is known to block Kv1.3 channel found on the surface of T_{EM} cells, which are central to the damage cascade in autoimmunity (Beeton et al., 2005). The Dalazatide peptide recently underwent clinical trials in psoriasis and the patients showed an improvement of this condition. The clinical trial data has now been published (Tarcha et al., 2017)

Conclusions

Recent advances in omics technologies paired with advances in synthetic peptide production and rapid recombinant expression (cell-free systems) is leading to an explosion in basic and applied venomics. Indeed, an estimated 20 million venom-derived compounds are thought to remain unexplored in nature (Escoubas and King, 2009). Combining advances in venomics with progress in low cost, high-throughput screening platforms will no doubt yield hundreds of prototype compounds applicable to the ~10,000 diseases known to medicine (WHO). At present, six venom-derived drugs have been FDA approved with many more in preclinical development and in clinical trials. Current research shows that venom has the capacity to induce potent effects on the immune response. These include customizer compounds that tune immune cell numbers, phenotype and function. For instance, snake and bee venom compounds that regulate immune cell subsets numbers and cell trafficking would be useful across autoimmunity, infectious disease and cancer. Snake venom compounds that induce IL-2 and IFN γ would be useful in the emerging field of cancer immunotherapy and snake venom compounds that augment humoral immunity might be useful as adjuvants for antibody-based vaccines. Scorpion venom compounds that induce IL-12 would be useful for DC-based vaccines and snake and scorpion venom compounds that induce IL-10

might be useful in autoimmune disorders. Snake and scorpion venom compounds that selectively shut off T cell and B cell function would also be useful in autoimmune disorders and transplant medicine. Additionally, targeting these immune pathways may also open new therapeutic options that help alleviate envenomation symptoms associated with immune dysfunction. With these examples in mind, it is likely that venom-derived immune drug development is still in its infancy and these data emphasize the importance of preserving biodiversity to sustain future discoveries.

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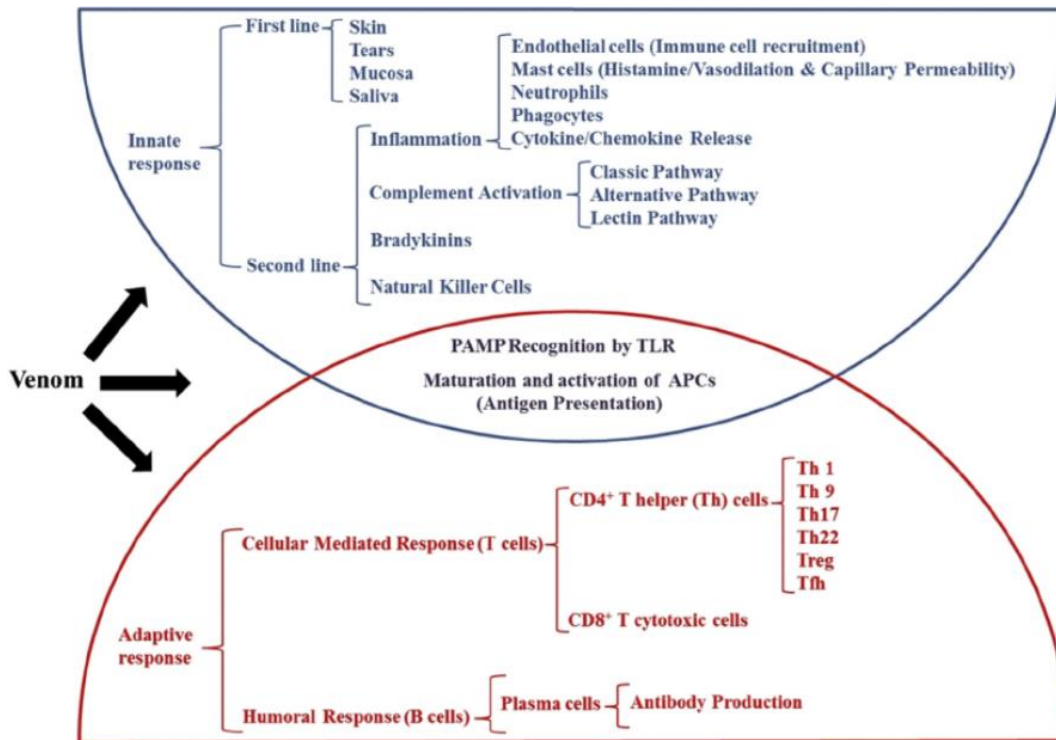
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Fig 1



Immune pathways modulated by venom. The innate (blue) and adaptive (red) immune arms can be modulated by crude venom and venom components. Cells at the junction of the innate and adaptive immune arms, including DCs and APCs (black), can also be modulated by venom and venom components. The ability to selectively target each of these subsystems using synthetically-derived venom components will open novel immunotherapies across infectious disease, cancer and autoimmunity.

Table 1
FDA approved therapeutics from venom-derived proteins.

Name	Active Ingredients	Indication and Mechanism of Action	Route	Year	Derived from
Prialt®	Ziconotide SNX-111 Non-opioid and analgesic medication	Severe and Chronic Pain with Neuropathic Origin The obstruction of the ion channel by the chemical composition of the drug impedes the secretion of neurotransmitters, blocking the signal of pain to the brain.	Intrathecal administration	2004	Cone snail <i>Conus magus</i>
Byetta®	Exenatide Synthetic	Diabetes Type 2 Increases the release of glucose-dependent insulin by the stimulation of pancreatic beta-cells. Delays gastric emptying.	Subcutaneous administration	2005	Gila Monster <i>Heloderma suspectum</i>
^a Bydureon®	Exenatide Synthetic		Subcutaneous administration	2012	Gila Monster <i>Heloderma suspectum</i>
Angiomax®	Bivalirudin	Anticoagulant Inhibits clot formation, interacts with thrombin in cascade coagulation.	Intravenous administration	2000	Medicinal Leech <i>Hirudo medicinalis</i>
Capoten®	Captopril	Hypertension Interfering in the transformation between angiotensin I and Angiotensin II by the inhibition of angiotensin converting enzyme (ACE).	Oral, tablet	1981	Viper Snake <i>Bothrops jararaca</i>
Aggrastat®	Tirofiban Hydrochloride	Inhibitor of Platelet Aggregation This drug binds to the main platelet surface receptor (GP IIb/IIIa).	Intravenous administration	1999	Viper Snake <i>African saw-scaled</i>
Integrilin®	Eptifibatide	Antiplatelet Drug Reduces the binding of fibrinogen von Willebrand factor and ligands to GP IIb/IIIa.	Intravenous administration	1998	Viper Snake <i>Sistrurus miliarius barbouri</i>

Bydureon is a long acting derivative of Byetta®. The administration of these drugs is in combination with other Diabetes Type 2 medications