“Venomics” or: The Venomous Systems Genome Project

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Introduction

Venomous animals possess potent factories, the venom glands, which produce a diversity of compounds tailored to act efficiently on key physiological systems of vertebrates and/or invertebrates that have already led to the successful development of novel drugs. The latest FDA approved example is Prialt, a peptide originating from the venom of a cone snail (*Conus magus*). The Venomics project consists in studying the genetics, transcriptomics and proteomics of this evolutionary tripartite combination: animal, venomous system and toxins. Based on deep investigations on a few selected model animals, the project is anticipated to clarify various essential biological aspects of this harmonious triad, and especially their associated evolutionary processes. It is also expected to have important practical consequences, including the discovery of new drugs and the development of novel protective strategies against envenomation. Our main goal is to elucidate the genome of at least four venomous animals, together with their transcriptome and proteome, to better understand the **“Venomous System”** .

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Reference: Ménez A, Stöcklin R and Mebs D, 2006. ‘Venomics’ or: The venomous systems genome project. *Toxicon*, p. 255–259.

See http://www.toxinomics.org and http://www.conco.eu.

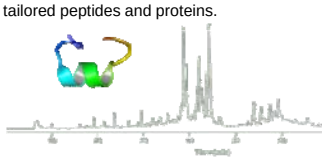
The Venomics Project & Primary Objectives

“From the genomic up to potential therapeutic properties of all the putative bioactive compounds that can be synthesised by venomous organisms”

We present the first innovative post-genomic project dedicated to the discovery and development of novel biopharmaceuticals generated by the broad marine biodiversity of cone snails. The project aims at characterizing from the genomic up to potential therapeutic properties all the putative bioactive compounds that can be synthesised by one selected cone snail species, namely *Conus consors*. The genome and transcriptome of this cone snail will be exhaustively studied. Currently, large amounts of venom are fractionated and submitted to proteomic studies to generate a biochemically characterized “natural library” of compounds. Large scale synthesis of each identified candidate are in process to achieve a “synthetic library” of compounds. The biological activity of these two libraries are also investigated on a panel of physiological targets that are recognized of therapeutic value. Selected hits will be optimised and validated *in vivo*. Transcriptomic and proteomic investigations will also be conducted on a broader range of cone snail specimen to conduct biodiversity, ecological and molecular evolution studies. A publicly accessible web-based database will be developed and annotated to integrate and share all the knowledge generated by the project. Our primary objectives are:

- To understand the “Venomous System” and its remarkable capacity to produce a diversity of tailored peptides and proteins.
- To discover new peptides and proteins with therapeutic potential.
- To understand the Genetics of Venomous animals.
- To bring new concepts in treatments of envenomation.

“20 expert laboratories”



This first Venomics project presently involves 18 expert European laboratories, the prestigious Craig Venter Institute (USA) has agreed to join forces for high throughput genome sequencing, and the non-for-profit Toxinomics Foundation was recently created to synchronise the efforts on a worldwide basis. We believe that the Venomics project will pave the way to a new generation of bioactive ingredients of primary biomedical relevance.

CONCO:
The first step of the Venomics project

- Initiation of the full genome sequencing of one cone snail species
- EST libraries of its venom gland (transcriptomics)
- Proteomics of its venom
- Identification, characterization and synthesis of novel bioactive compounds
- High throughput bioactivity screening
- Discover new medically relevant peptides
- Initiate clinical trials
- Generation of an annotated database

The Toxinomics Foundation

The Toxinomics Foundation is a legal, neutral and non-profit entity that represents the IST (International Society of Toxinology) and will participate in the different Venomics projects.The purpose of the Foundation is to promote the knowledge on animals, plants and micro-organisms producing toxins and related substances, for the benefits of mankind and nature.

Specific objectives:
Fund-raising to support scientific research, medical development, education, and communication.

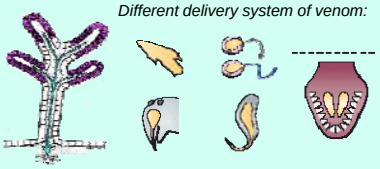
1. To out-license and develop any possible drug candidates and cosmetics out of toxins; to stimulate creation of start-up companies to create jobs.
2. To coordinate preclinical and clinical studies, to act as an incubator for promoting new discoveries and to seek additional resources for related Venomics project.
3. To promote the protection of toxin-making organisms and their environment to conserve this living bio-source of yet-to-be discovered bioactive compounds.
4. To develop communication, training and teaching activities in the above domains.

The « Venomous Function » is:

- A complex physiological system which usually includes an exocrine gland, with a lumen and a duct that is connected to a delivery system: harpoons, nematocysts, fangs, skin exudation, *etc.*

- A system that produces a diversity of hundreds of compounds acting exogenously and tailored to subdue prey and/or for defense purposes, efficiently.

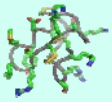
Different delivery system of venom:



The « Venomous system » produces a huge diversity of peptides and proteins. The venom of one single animal will typically be made of 100-1000 compounds acting on dozens of physiological targets.

Examples of toxin drugs:

- **Captopril**
Bradykinin-potentiating peptides from *Bothrops jararaca*.
Decrease hypertension. Drug approved in 1982.
Ferreira S, 1965, *J. Pharm.* 24, 163 ; Cushman et al., 1977, *Biochemistry*, 16, 5484



- **Prialt**
ω-conotoxin MVIIA from *Conus magus*
Block N-type Ca2+ channels : Cancer pain.
Drug (2004 USA, 2005 EU)
Malmberg et al., 1995, *Pain,* 83

- **Aggrastat** (tirofiban)
African saw-scaled viper : *Echis carinatus*.
Inhibits platelet aggregation : prevents clots from growing. Drug approved in 1998.
Hartman et al., 1992, *J. Med. Chem*, 36, 4640