VENOMS FOR HEALTH

SEVENTH FRAMEWORK PROGRAMME

Venomics

Venomics

Venoms

173,000 Venomous animals | **40,000,000** Venom proteins

WHY VENOMICS?
FROM VENOMS TO DRUGS

Many therapeutic conditions are inadequately addressed by the current drug arsenal and represent significant unmet needs for large populations of patients. The range of drugs available to address many prevalent diseases such as pain, cancer, diabetes or cardiovascular diseases remains inadequate in many clinical situations where patient care requires novel therapeutic solutions and drugs with novel modes of action.

Natural products have been a major source of therapeutic innovation in the past and animal venoms represent an enormous untapped potential. Animal venoms are composed mostly of small proteins (peptides), encompassing a large variety of structures and modes of action. Due to their extreme pharmacological diversity, these miniproteins represent a novel and mostly unexplored resource for the discovery and development of innovative drugs. They often have a high target selectivity, an advantage over classical, small-molecule drugs.

The core objective of the VENOMICS project is the high-throughput investigation of venom diversity for the discovery of novel drug leads. Altogether venoms may contain more than 40,000,000 bioactive molecules with desirable pharmacological properties. The exploration of such diversity requires the implementation of a large-scale effort, using cutting-edge technologies for in-depth exploration of this biological resource.

Exploitation of the VENOMICS peptide library will offer economic perspectives. Novel drug leads generated by screening the VENOMICS peptide library will be of interest to large pharmaceutical companies, looking for innovative drug candidates to fill their development pipelines.

VENOM PEPTIDES
DISULFIDE LINKAGE

Peptides constitute the major component of venoms. They are miniproteins composed of 10-100 amino acids. Structures and properties differ for each zoological group, and even between species. Snake venoms will contain larger peptides and many proteins, while cone snail venoms will comprise mostly small peptides, characterized by numerous post-translational modifications.

Venom peptides are characterized by disulfide bridges. Disulfide bridges are formed between two cysteine residues and serve to stabilize the peptide in a specific three-dimensional structure. The position and number of disulfide bridges is variable, and characterize the structure of the peptide toxin, while serving as a structural platform for diversification of pharmacological properties and thus possible applications

Goals

50,000 Sequences | **10,000** Peptides bank

THE VENOMICS STRATEGY
AN INNOVATIVE WORKFLOW

The VENOMICS workflow goes from venoms to drug candidates. The VENOMICS strategy involves multiple, result-driven steps that lead to the selection of drug leads from venoms considered as natural compound libraries:

- Constitution of a venom and tissue biobank
- Proteomics investigation of venoms
- Transcriptomics analysis of venom gland tissues
- Creation of a large sequence database
- High-throughput *in vitro* peptide production
- Target selection
- Pharmacological screening and lead generation

A unique biobank will be assembled. The VENOMICS consortium will source more than 500 species of venomous animals, assembling the largest and most diverse venom-centered biological collection to date.

A combination of cutting-edge technological approaches will uncover venom diversity. The combined used of proteomic and transcriptomic technologies will permit in-depth exploration of venoms, in a semi-automated, high-throughput approach.

A new paradigm for venom-based drug discovery will emerge. The combination of a large sequence database with high-throughput, robotized protein production will replace the current slow bioassay-guided process, in effect re-creating venom molecular diversity *in vitro*.

A unique peptide collection will serve as a drug discovery platform. The pharmacological screening of a 10,000 venom-derived peptide bank will serve as a basis for the discovery of novel drugs leads. The peptide bank will be an attractive alternative to classical small-molecules collections for the development of innovative therapies.

PEPTIDE SEQUENCING
PROTEOMICS AND TRANSCRIPTOMICS

The initial venom exploration challenge lies in the sequencing of most venom peptides, starting from small amounts of material. The proteomics approach uses mass spectrometry to fragment peptides and derive sequences in a *de novo* sequencing process.
Transcriptomics, through the isolation of venom gland RNA followed by next-generation DNA sequencing, can yield hundreds of peptide sequences from a single venom gland.
In a complementary approach, the combination of techniques permits easier sequence construction and validation, and the identification of peptide modifications.

CUTTING-EDGE TECHNOLOGIES
TOWARDS NANOVENOMICS

Technological refinements will permit unmatched sensitivity. Animals of small size represent the majority of venomous species. The investigation of their venoms will be made possible by the use of the newest generation of mass spectrometry and sequencing instruments. Pilot studies have demonstrated that venom gland extracts from spiders of less than 5 mm can be successfully investigated, allowing the detection of more than 300 components.

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Partners

8 Partners | 5 Countries

HIGH-THROUGHPUT PEPTIDE PRODUCTION

The *in vitro* production of thousands of novel peptides is the ultimate challenge of the VENOMICS project. It will allow the reproduction of venom diversity in a format allowing exploitation of the full complement of venom peptides for drug discovery, bypassing the problems of animal supply and sample amounts.
High-throughput peptide production can be achieved using recombinant production in the bacteria *Escherichia coli*, in a robotized protein production platform, and by parallel peptide synthesis instruments. Both methods, mastered by VENOMICS consortium partners, will permit the generation of a 10,000 peptide library.

The peptide refolding and disulfide bridge assembly issue will be handled in a similar high-throughput manner by a proprietary peptide refolding platform, ensuring production of bioactive compounds for pharmacological screening.

A BALANCED CONSORTIUM
SCIENTIFIC EXCELLENCE AND INDUSTRIAL PERSPECTIVE

The VENOMICS consortium is well balanced. Eight partners from the academic and industrial worlds, representing five countries (France, Belgium, Spain, Portugal, and Denmark) compose a mix of academic laboratories and Small and Medium Enterprises. One partner is a leading mid-size pharmaceutical company.
The consortium is led by VenomeTech, a French startup specializing in venom-based drug development.

The construction of the consortium has followed a rational approach for success. The VENOMICS partners bring together sophisticated skills, cutting-edge technologies and equipment in a complementary manner. Each of the partners has been selected so as to provide high-end expertise, experience and skills to ensure the successful completion of all the major project tasks.

VENOMICS will lead to European leadership in the exploration and exploitation of venoms. The VENOMICS consortium partners will have the necessary critical mass and resources to reach a worldwide leadership position in this field, due to the unmatched size of their discovery efforts and technological resources.

The eight project partners are:
- VenomeTech (FR) – Promoter and scientific coordinator of the project
- CEA Saclay (FR) – Project coordinator, leader in peptide synthesis
- Université de la Méditerranée (FR) – Leader in HT protein production
- Université de Liège (BE) – Leader in proteomics analysis
- Sistemas Genomicos (SP) – Leader in transcriptomics analysis
- NZYTech (PT) – Leader in molecular biology
- Zealand Pharma (DK) – Leader in drug development
- Vitamib (FR) – Project management

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Partners:

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VENOMICS, A European project supported through the Seventh Framework Program (FP7 HEALTH), 2011-2015

October 2011 - Photos: Venomics, iStock/Gerenme, M. Kostich, C. Opstal, Fot/U. Bakunovich
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