DE LA RECHERCHE À L'INDUSTRIE

cea

Institut des sciences du vivant Frédéric Joliot

Les défis de la Chimie

Fondation de la Maison de la Chimie

Les Substances Naturelles : *La Panacée ?*

Mercredi 27 Novembre 2019

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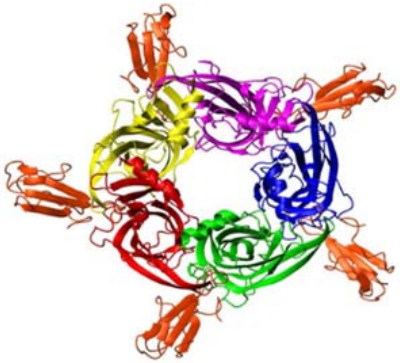
Menaces ou opportunités thérapeutiques des toxines animales

D. SERVENT. DMTS/SIMOPRO

SOMMAIRE

- Espèces venimeuses, envenimation, sérothérapie antivenimeuse

- Toxines: outils d'études de récepteurs et canaux ioniques cibles



- Toxines et applications thérapeutiques

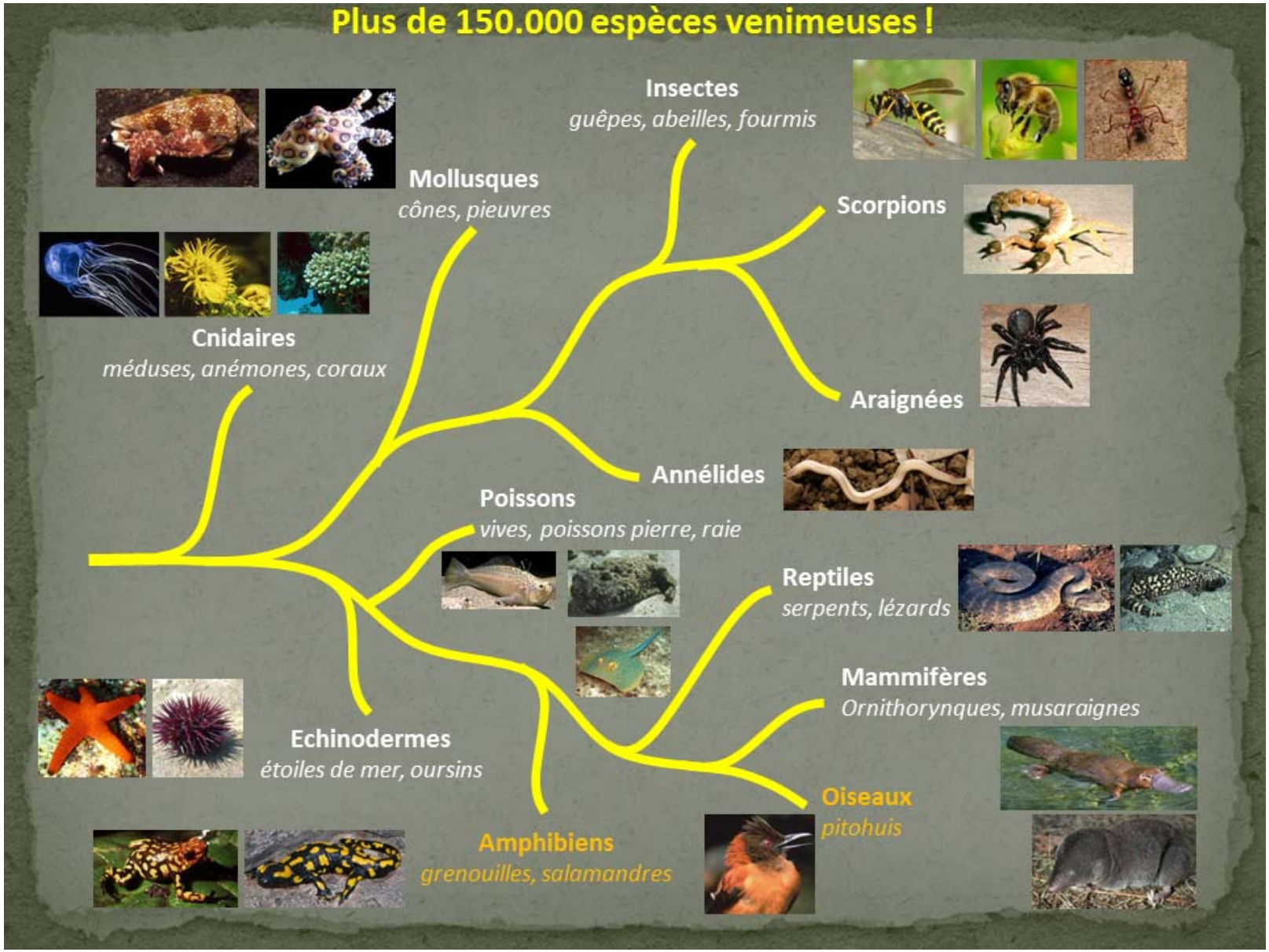
Définitions/Vocabulaire

- **Animal Venimeux**: Animal producteur d'un venin qui est élaboré au niveau d'une glande venimeuse et qui possède un appareil inoculateur permettant d'injecter le venin (crochet, aiguillon, dard, harpon, épines).
  Le venin est un mélange complexe, majoritairement composé d'enzymes et de toxines (peptides), permettant à l'animal venimeux de capturer une proie, éventuellement de la pré-digérer, ou de se défendre contre un prédateur.

- **Animaux ou organismes vénéneux**:

Produisent des composés toxiques ou hébergent des poisons venant de l'environnement (plantes, micro-organismes, animaux..).
Ils font un usage passif de ces composés qui sont principalement des métabolites (alcaloïdes).

Espèces « venimeuses » dans le règne animal



Le venin

Objectifs : Se défendre contre un prédateur
Immobiliser/tuer la proie et préparer sa digestion.

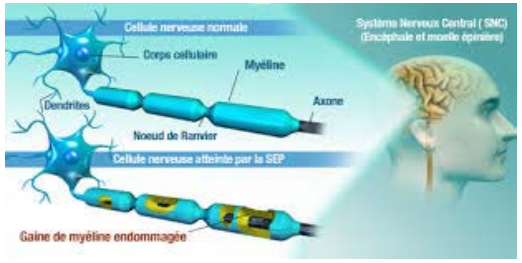
Le venin est une combinaison complexe de toxines, d'enzymes et autres protéines, représentant 90 % de son poids sec.
Sa composition varie au sein d'une même espèce selon la provenance géographique, le poids, la taille, l'âge de l'animal.

Un venin provoque majoritairement 3 types d'effet:

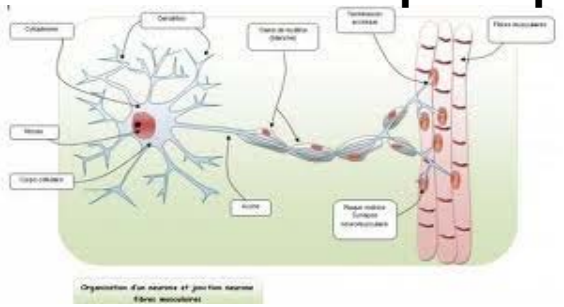
- hémotoxique (qui altère l'hémostase),
- cardiotoxique/cytotoxique/nécrotique (qui altère les cellules et les tissus cardiaques)
- neurotoxique (qui attaque le système nerveux)

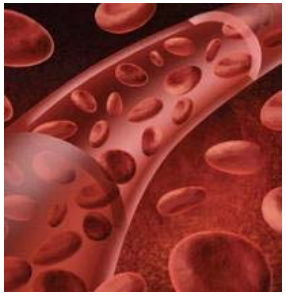
Systèmes Physiologiques ciblés par les venins

Système Nerveux Central



Système Nerveux Périphérique



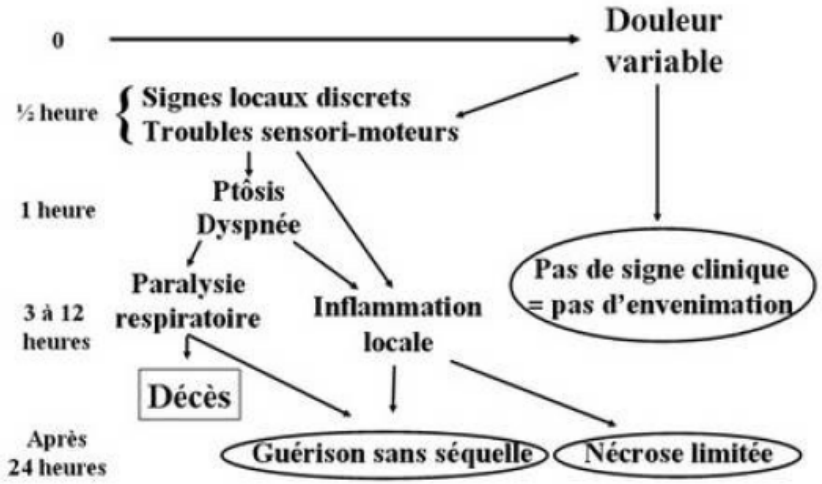


Système de l’Hémostase

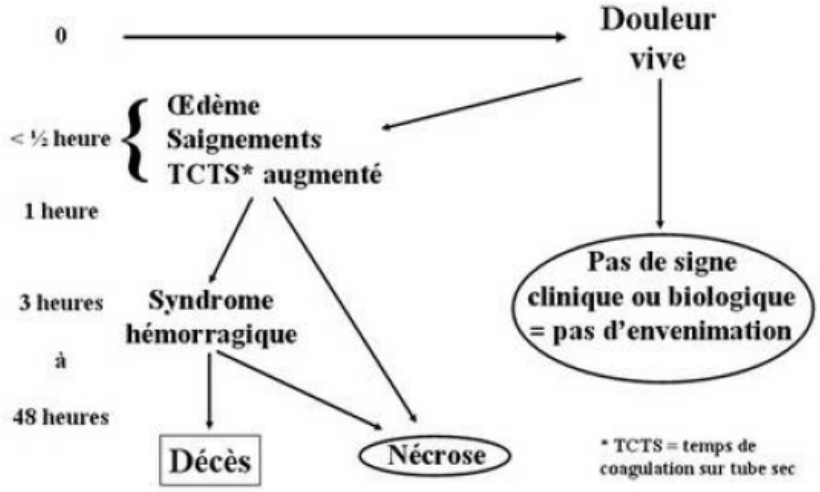
Système Cardio-Vasculaire

Symptômes après morsures de serpents

Elapidae: Taipan, Cobras, Mambas…

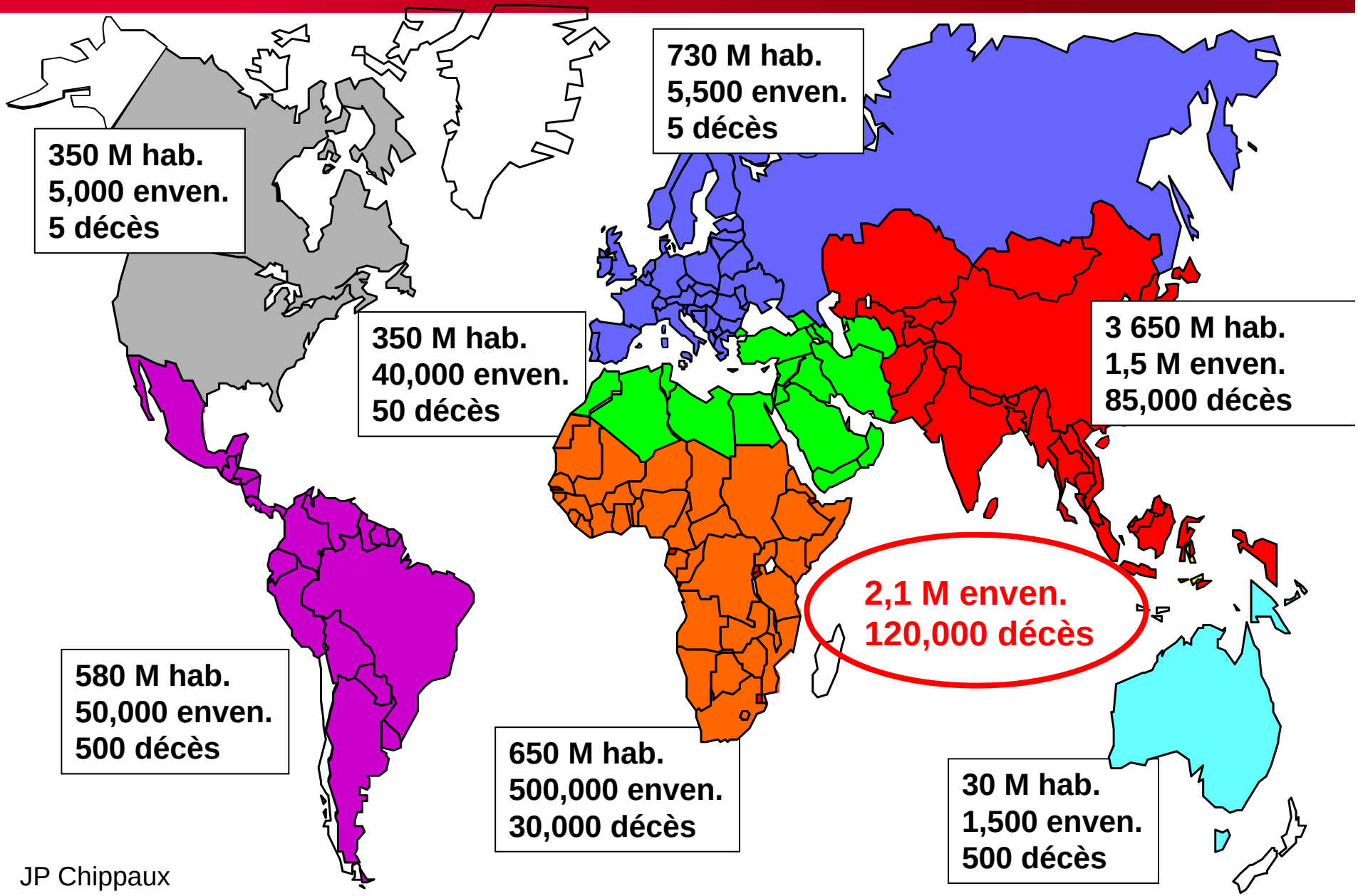


Viperidae: Crotales, Vipères…



Incidence et mortalité par morsures de serpents

3500 espèces, 700 venimeuses, 40 intérêt médical



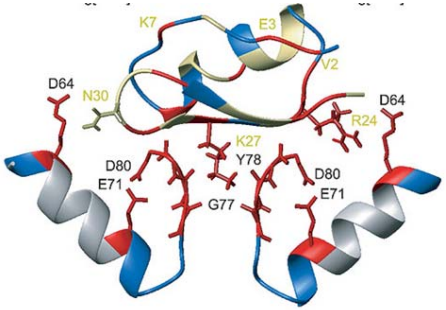
JP Chippaux

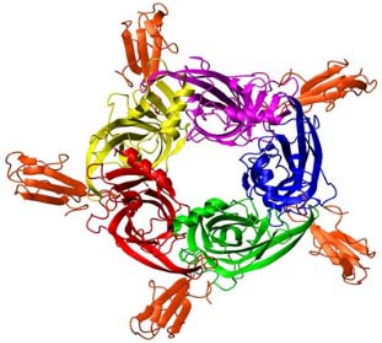
Seul traitement efficace: Sérothérapie antivenimeuse

1894 : Découverte de la sérothérapie antivenimeuse

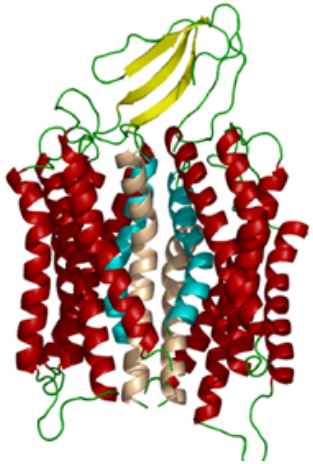
- **C.Phisalix et G.Bertrand** (*Vipera aspis*)
- **A.Calmette** (*Naja kaouthia*)
- **Vital Brazil** (Bothrops, Crotalus)

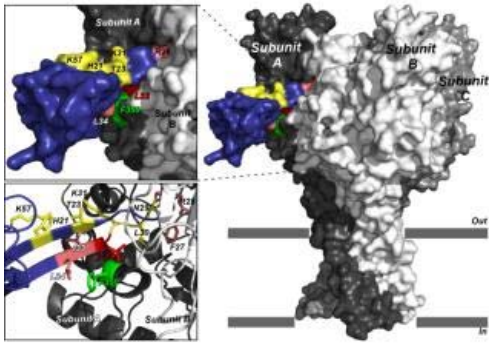
20 SAV utilisés dans le monde





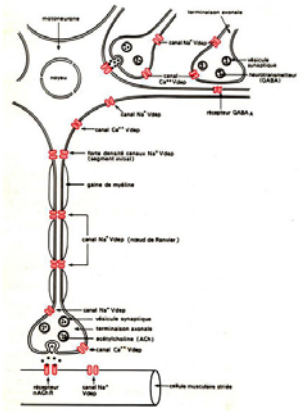
Les Toxines:
Outils d'études de récepteurs cibles

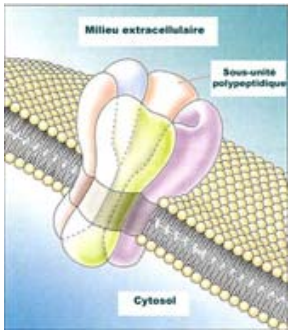




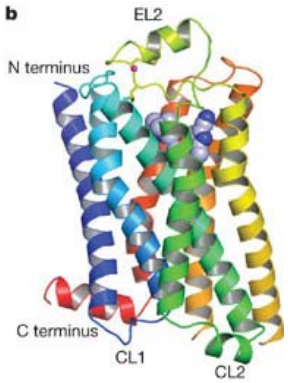
Systèmes Physiologiques et cibles moléculaires des toxines

Canaux Ioniques



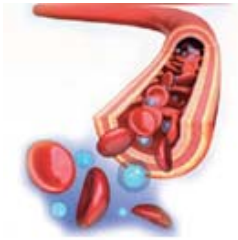


RCPG



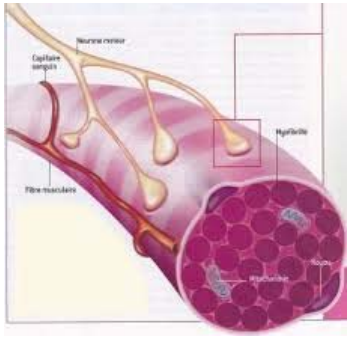
SNC; JNM

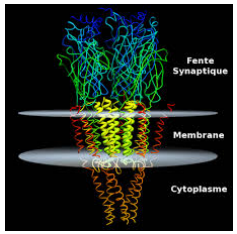
Système Cardio-vasculaire



Système de l'hémostase

nAChRs





Enzymes

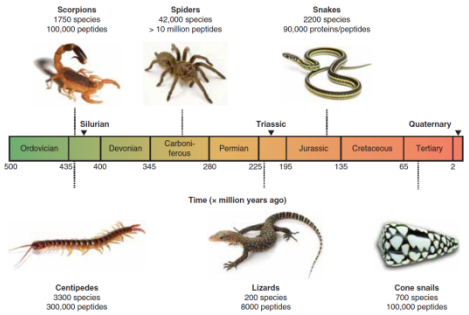
AChE

ACE

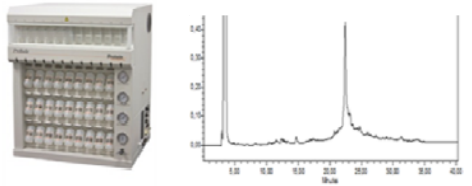
Facteurs de coagulation (Thrombine, Factors V, X, XIIIa…)

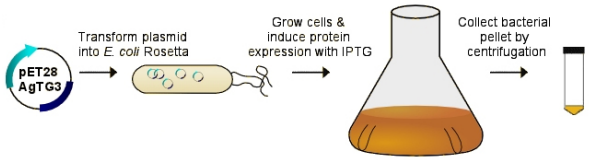
Les Toxines: des outils pharmacologiques hors normes

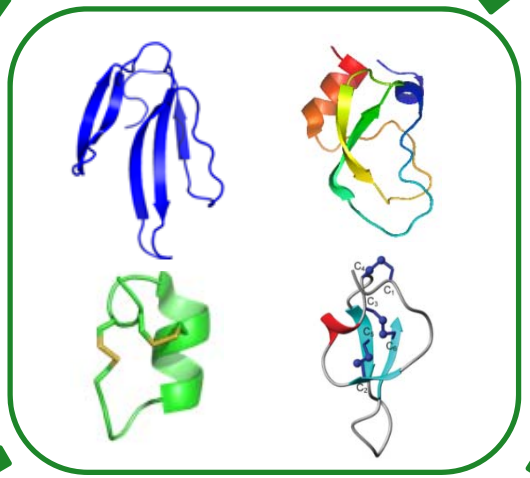
Affinité et **Sélectivité**



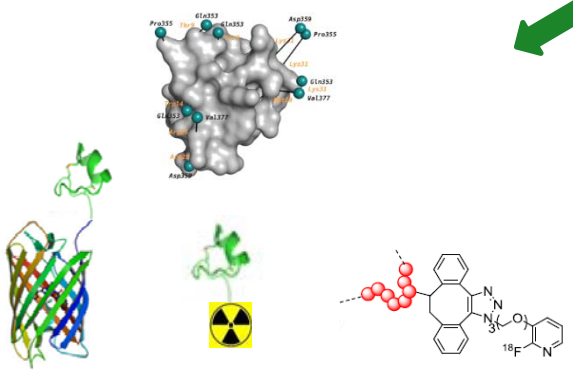
Stabilité, Accessibilité



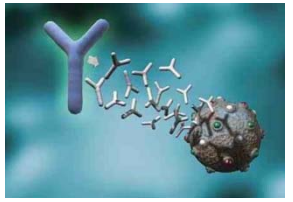


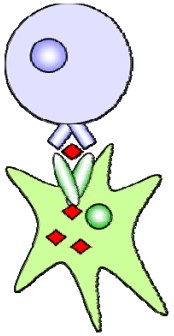


Modifiables, Traçables



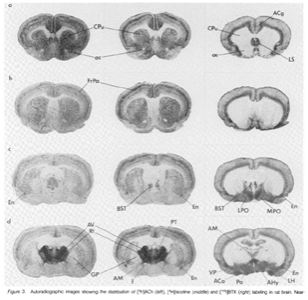
Peu Immunogène

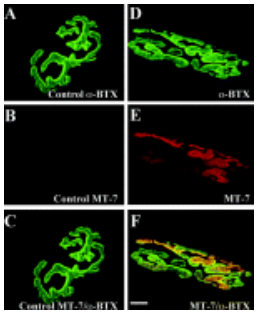




Les Toxines: des outils pharmacologiques hors normes

Identifier, Localiser la cible



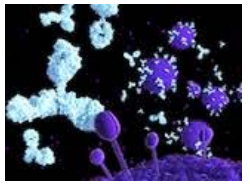


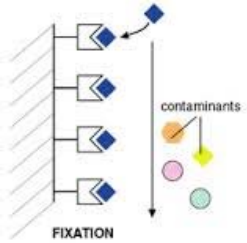
Purifier la cible

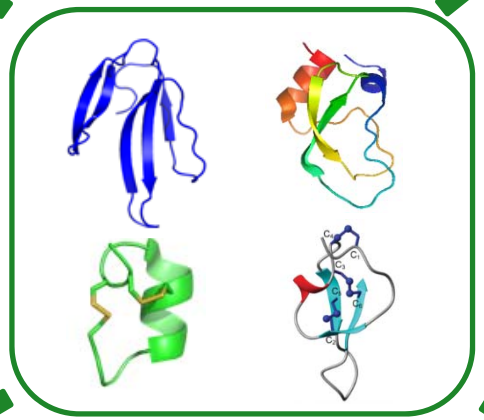
Biochim Biophys Acta. 1997 Feb 21;1324(1):37-46.

Purification of the nicotinic acetylcholine receptor protein by affinity chromatography using a regioselectively modified and reversibly immobilized alpha-toxin from Naja nigricollis.

Ringler P[1], Kessler P, Ménez A, Brisson A.





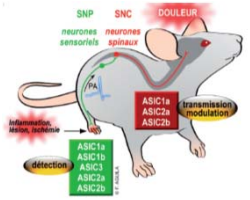


Classifier

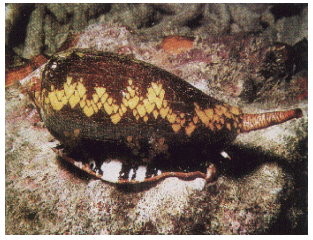
- NaV TTX_R ou TTX_S
- CaV sensibles ou pas aux ω-conotoxines, ω-agatoxines
- nAChRs sensibles ou pas à l'α-Bgtx

Comprendre

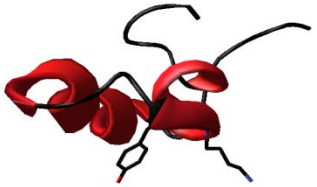
Mode de fonctionnement de la cible et son rôle physiologique



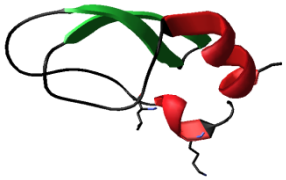
Evolution convergente de motifs fonctionnels de toxines potassiques



Ktx



BgK

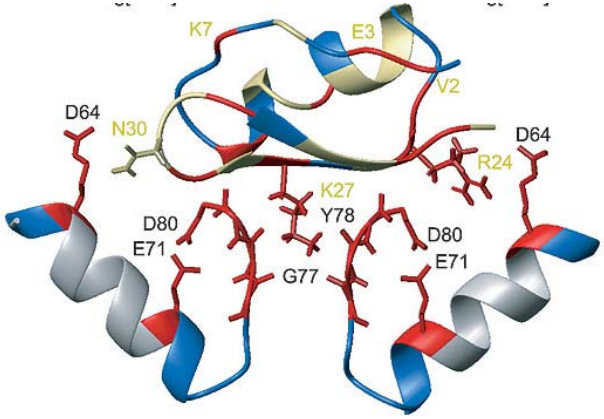


Dtx-I

Conotoxine PVIIa

2 résidus Majeurs

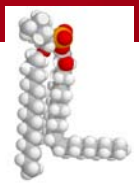
Canal KcsA



Lange et al. Nature 2006

Exploitation d'une plateforme structurale multi-fonctionnelle

PLA2

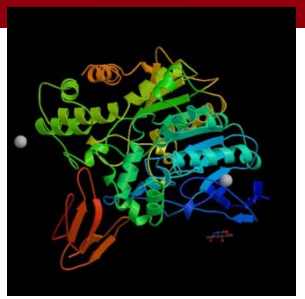


Phospholipides

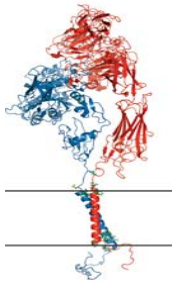
PLA2 Inhibitor

Cytotoxins

Fasciculins



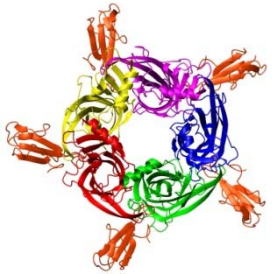
Acetylcholinesterase



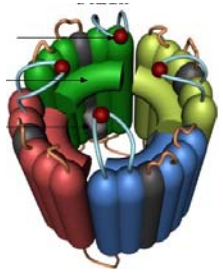
Integrins Receptors

Desintegrins

Nicotinic Toxins
Gabaergic Toxins



nAChRs,
$GABA_A$



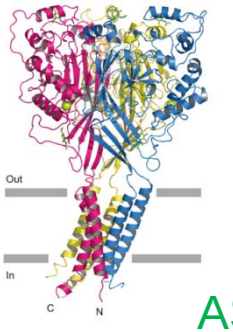
Calcium Channel

Calciseptins

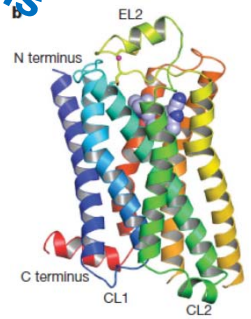
Hemextins

Muscarinic Toxins
Adrenergic Toxins
Dopaminergic Toxins

Mambalgin



ASIC



GPCRs

Factor VIIa

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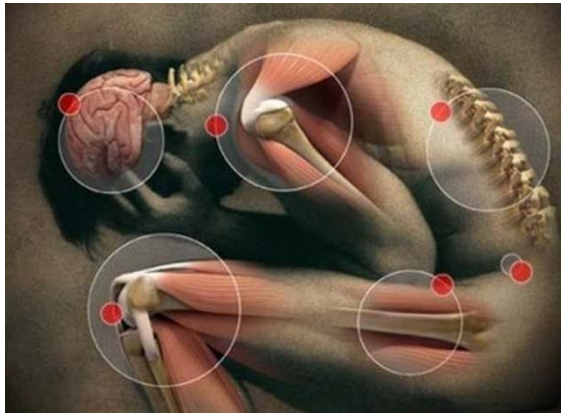
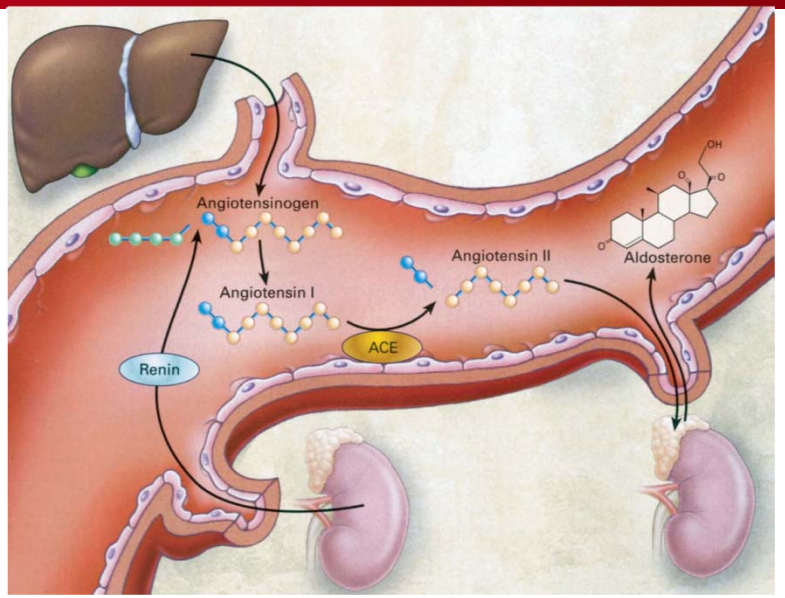


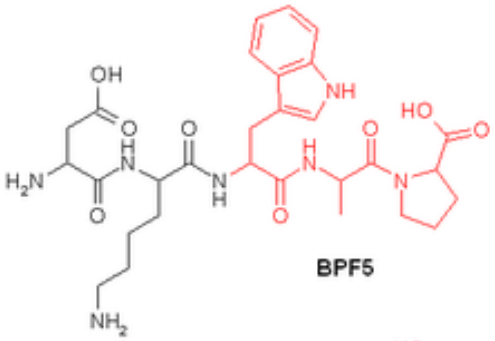
Toxines et opportunités thérapeutiques

Le Captopril : Premier médicament conçu à partir d'une toxine animale

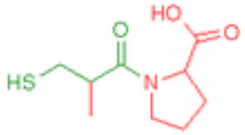
BPP de *Bothrops jararaca*

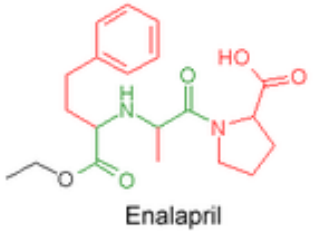
Mauricio Rocha e Silva



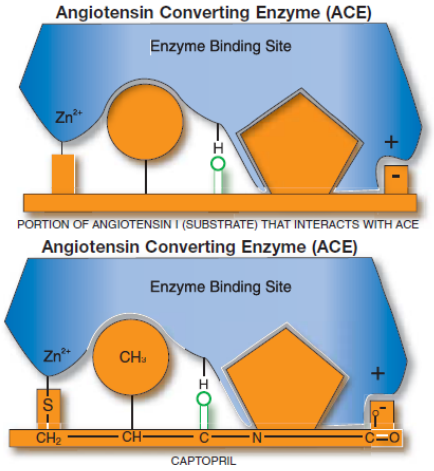


Sir John Vane





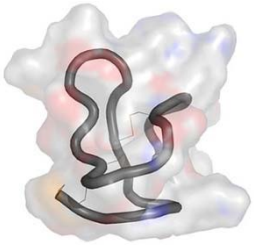
Captopril: Antihypertenseur IEC

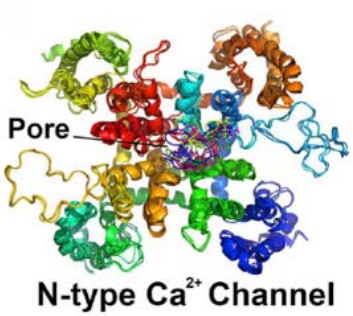


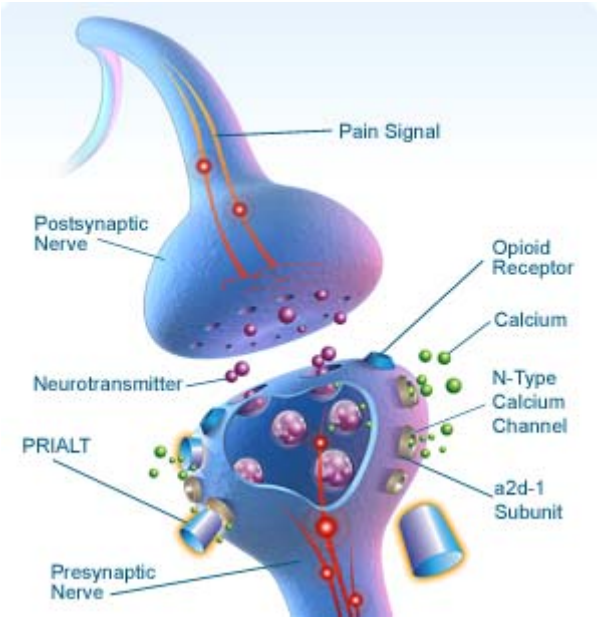
5 b $/an

Le Ziconotide - Prialt

Ziconotide/Prialt : Nouvel analgésique développé pour le traitement des douleurs sévères réfractaires aux morphiniques. Forme synthétique de l'ω-conotoxine MVII-A, bloqueur spécifique des canaux calciques de type N.



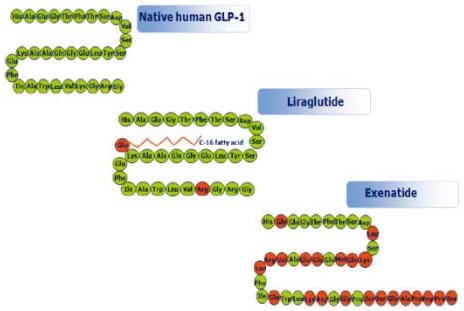




Intrathecal formulation

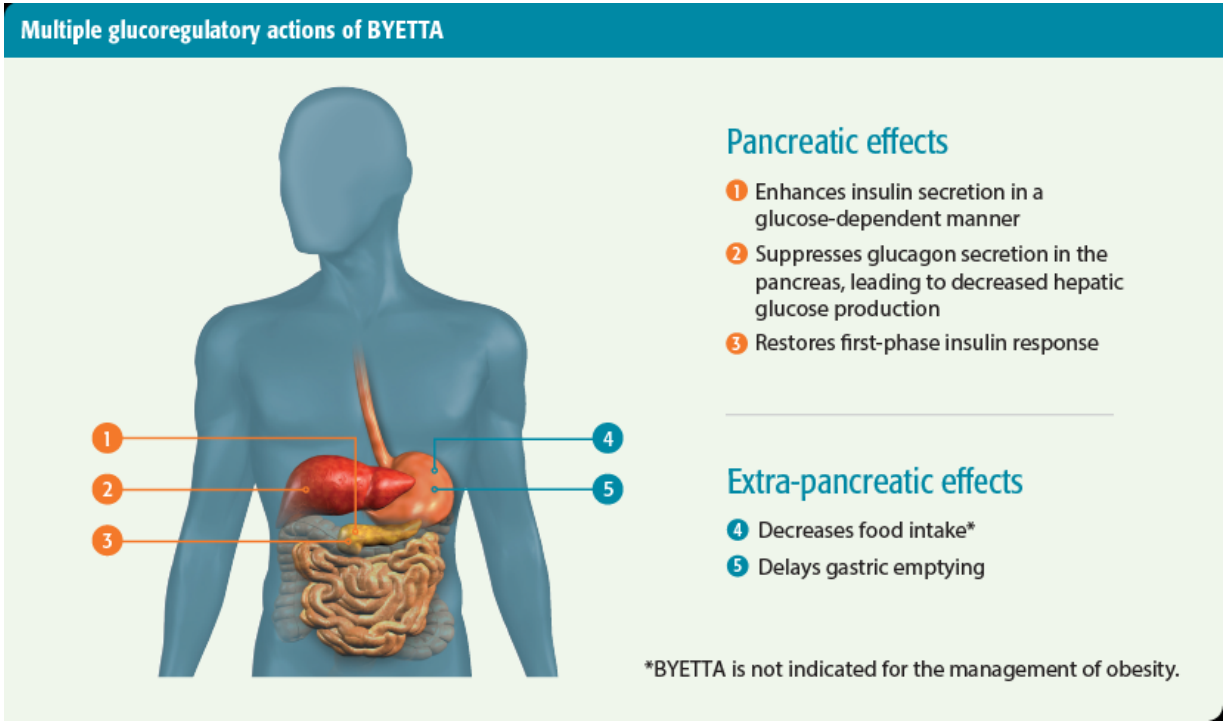
Byetta : traitement du diabète de type 2

Exenatide extrait de la salive du monstre de Gila

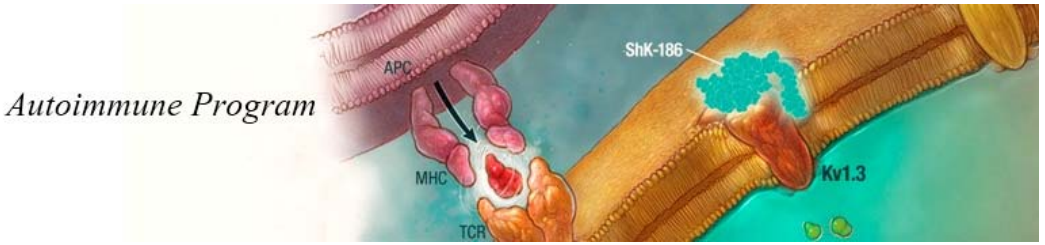


Plus résistant au clivage par la DPP-4

1.2b $/an



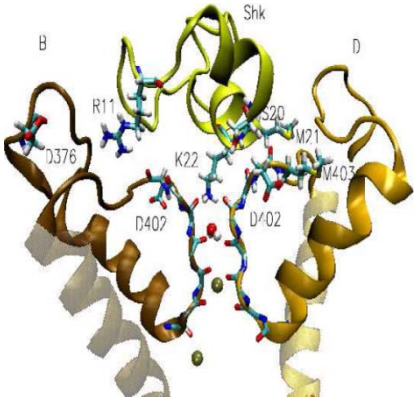
Shk toxine et maladies auto-immunes:
Sclérose en plaques, psoriasis, lupus



Current Medicinal Chemistry, 2004, *11*, 3141-3152 3141

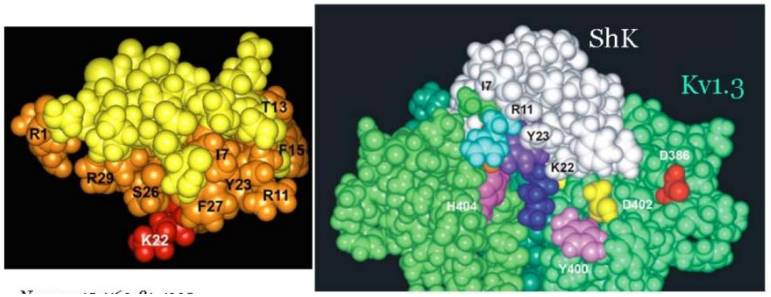
Potassium Channel Blockade by the Sea Anemone Toxin ShK for the Treatment of Multiple Sclerosis and Other Autoimmune Diseases

Raymond S. Norton*, [1], Michael W. Pennington[2] and Heike Wulf



KINETA®

ShK docked in Kv1.3
"cork in a wine bottle"

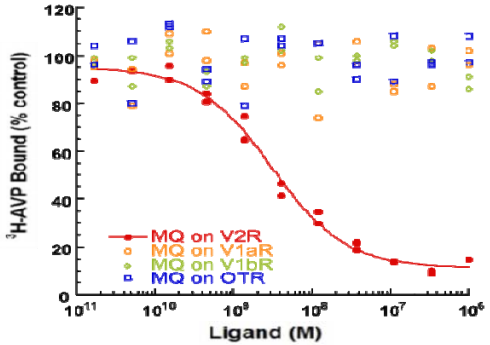


PRESS RELEASE

Kineta Announces the Opening of the First Psoriasis Clinical Trial Using Novel ShK-186

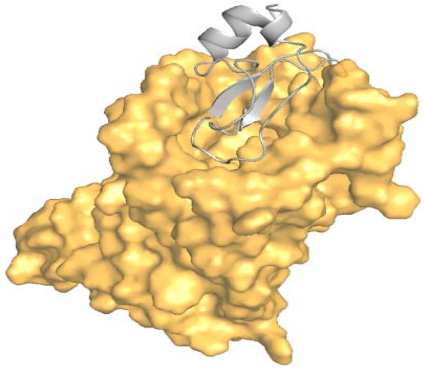
SEATTLE, WA, October 14, 2014 – Kineta, Inc., a biotechnology company focused on the development of immune modulating drugs for critical diseases, announced today that the company has opened a Phase 1B proof-of-concept clinical trial for psoriasis using its drug candidate, ShK-186. ShK-186 is a novel, immune-sparing therapeutic in development for a variety of autoimmune diseases. Kineta is planning on initiating an additional clinical trial in patients with psoriatic arthritis in the coming months.

Mambaquaretin, a highly selective V2R antagonist for kidney diseases treatment



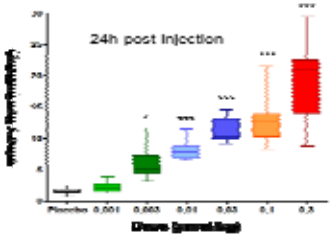
MQ: Ki=1,17±0,2 nM
No activity on 130 other targets

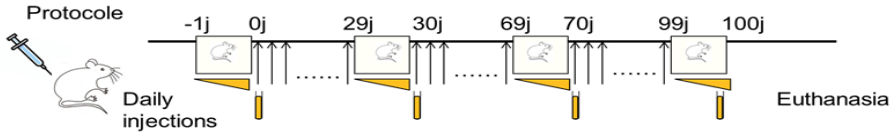
MQ Structure



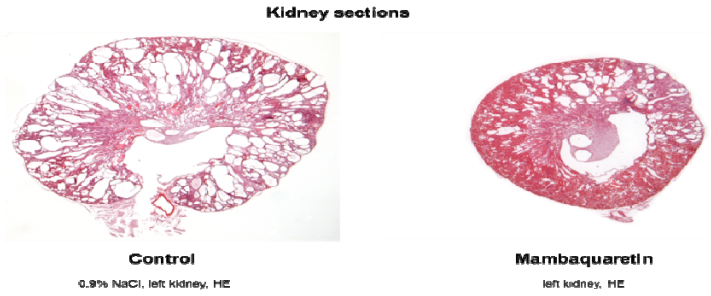
MQ-V2R Model

Diuretic effect of MQ





0,1µmol/kg/day



Inhibition of the cysts development by MQ

Gilles et al. Patent. 2013
Ciolek et al. PNAS. 2017

DE LA RECHERCHE À L'INDUSTRIE

cea