AXE 4 : *Evaluation toxicologique et toxicité potentielle à l'échelle individuelle et populationnelle*

Phycotox
Groupement de Recherche

1) Evaluation toxicologique

- Toxines émergentes (palytoxine et congénères) : études de toxicité par voie orale et par inhalation
- Caractérisation du mécanisme d'action par méthodes non-ciblées
- Investigation des TEFs
- Imines cycliques : affinité pour récepteurs nicotiniques; implication dans maladies neurodégénératives; recherche de nouvelles substances d'intérêt
- Effets toxiques des toxines lipophiles à l'aide de tests in vitro multi-paramétriques
- Etude de la métabolisation des toxines
- Effets combinés des toxines

AXE 4 : *Evaluation toxicologique et toxicité potentielle à l'échelle individuelle et populationnelle*

Phycotox
Groupement de Recherche

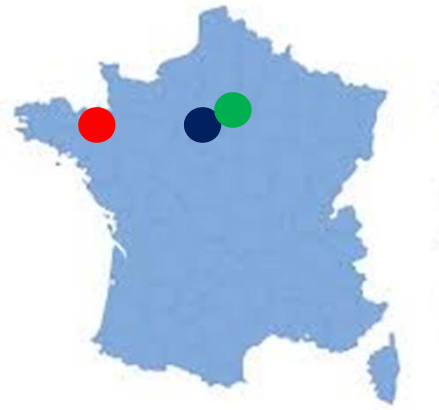
2) Modélisation mathématique du risque potentiel pour la population humaine dans certaines situations théoriques

- Tester l'impact de différentes situations de contamination ou de différentes mesures de gestion

- Tester les chaines de causalité en fonction de la contamination (dose, exposition à court ou long terme,…)

AXE 4 : *Evaluation toxicologique et toxicité potentielle à l'échelle individuelle et populationnelle*

Phycotox
Groupement de Recherche



Anses laboratoire de Fougères, unité Toxicologie des contaminants
Anses, Direction de l'évaluation des risques de Maisons-Alfort
CNRS, Gif/Yvette

Toxicologie des contaminants

- Acute toxicology with lipophilic toxins
- Intestinal absorption kinetics
- Mechanism of action
- Mixtures
- Development of new tools for toxicity prediction or detection of compounds

Research activity per scientist

Valérie Fessard: Toxicology

Ludovic Le Hégarat: Genotoxicity, development of cell models

Kevin Hogeveen : In vitro High Content Screening

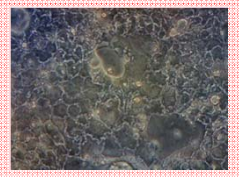
Antoine Huguet: Intestinal absorption kinetics, mechanism of action

Pierre-Jean Ferron: In vitro High Content Screening, mixtures

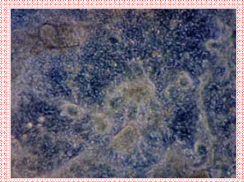
Models

Human intestinal cells

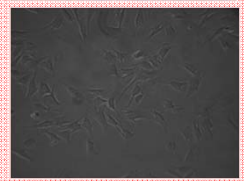
Caco2



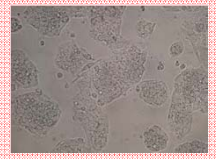
HT29-MTX



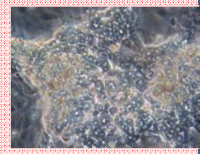
HIEC



Human liver cells



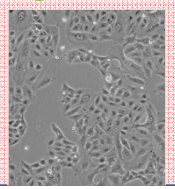
HepG2



HepaRG

Human lung cells

A549



Toxicologie des contaminants

En cours

Thèse CLIMPHYC : Nouvelles approches in vitro pour l'étude des effets toxiques des phycotoxines lipophiles, seules ou combinées, susceptibles d'émerger suite à un dérèglement climatique
Collaboration avec INRA (R. Rahmani), université Sherbrooke (Canada, JF Beaulieu)

Projet DGAl/DGS PINNA : Etude de pinnatoxines en lien avec l'espèce *Vulcanodinium rugosum*
Intestinal barrier kinetics and effects on intestinal cell lines of pinnatoxin G and A and mussel extracts;
Collaboration avec CNRS Gif/Yvette (R. Araoz)

Thèse Palytoxine/ovatoxines:
Various effects on human intestinal, liver and pulmonary cell lines;
Collaboration avec IRTA Tarragone (L. Solino, J. Diogène)

Etude brévétoxines:
Intestinal absorption kinetics of brevetoxins and metabolites
Collaboration avec NOAA (J. Ramsdell)

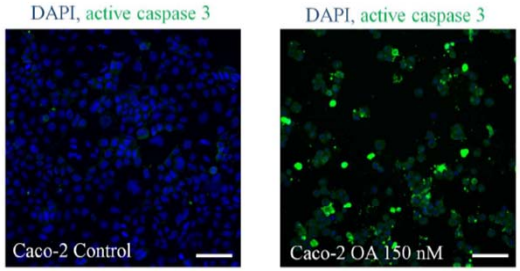
En attente de réponse

Thèse COMEBACk : Effect of CO-exposure to MarinE lipophilic Biotoxins on the intestinal barrier, bioActivation and identification of molecular modes of aCtions
Intestinal barrier and metabolism of lipophilic phycotoxins alone and in mixtures
Co financement Anses/BfR, collaboration avec équipe A. Lampen (Department of Food Safety, Federal Institute for Risk Assessment)

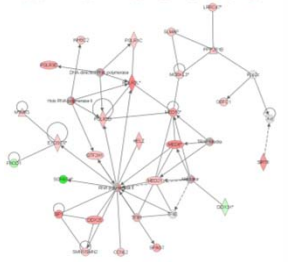
Thèse sur projet ANR CARISMATIG : Réactivité chimique et détection des ciguatoxines et maitotoxines dans des cultures de microalgues et dans des poissons
Collaboration avec l'Ifremer Nantes; Mise en place du test Neuro2A pour la détection des ciguatoxines

Toxicologie des contaminants

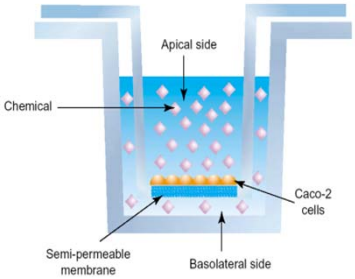
Effet toxiques sur modèles cellulaires humains intestinaux

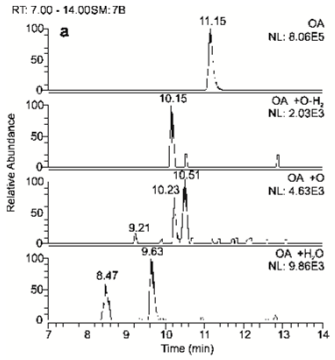


Mécanisme d'action?



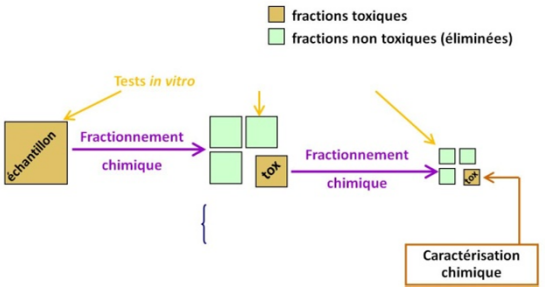
Passage de la barrière intestinale à l'aide d'un modèle *in vitro*





Effet toxiques sur modèles cellulaires humains hépatiques Métabolisation

Approche intégrée bio-analytique (EDA)



CNRS-Gif / Equipe MOLGO: Une approche multi-échelle pour déterminer le mécanisme d'action de phycotoxines neurotoxiques

Phycotox
Groupement de Recherche

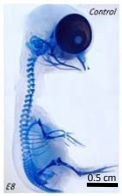
Septembre 2014

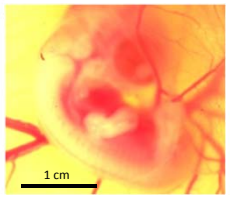
Organisme

Cell/Tissue

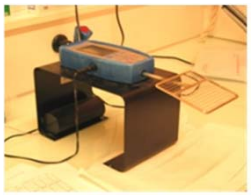
Molecule

In-vivo

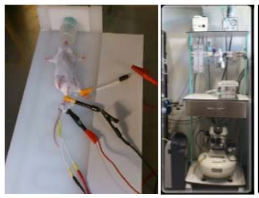





Développement de l'embryon de poulet
(A. COUESNON)

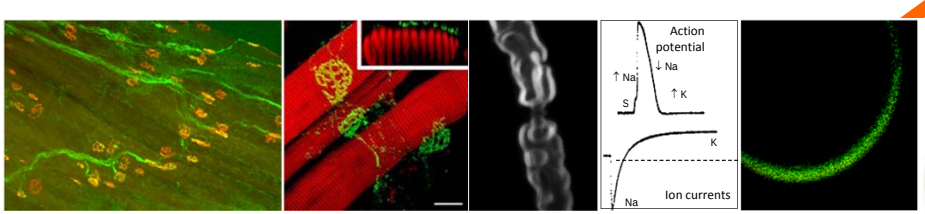


Force de préhension
E. BENOIT

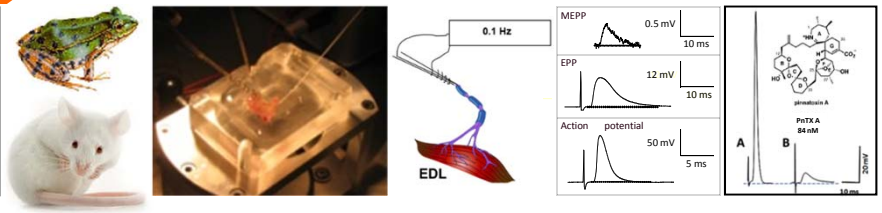


Excitabilité neuromusculaire *in-vivo*
(E. BENOIT)

Ex-vivo

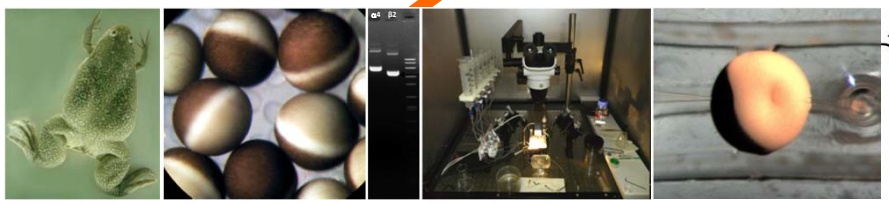


Imagerie : jonction neuromusculaire/ électrophysiologie : fibre nerveuse
[A. COUESNON (m. confocale) E. BENOIT (électrophysiologie)

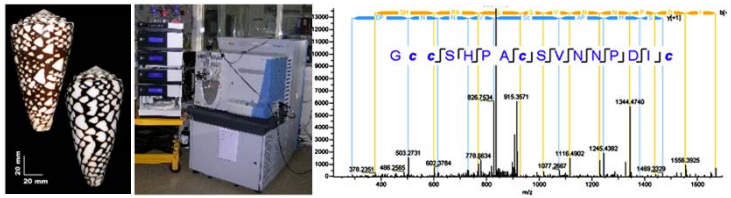


Electrophysiologie de la jonction neuromusculaire
(J. MOLGO, A. COUESNON)

In-vitro



Pharmacologie des récepteurs nicotiniques de l'acétylcholine. Potentiel impose à double microélectrodes (R. ARAOZ)

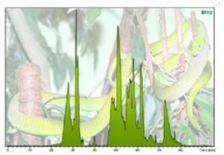


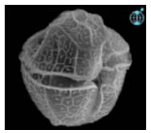
Purification et caractérisation physico-chimique de neurotoxines
[B. NGUYEN (conopeptides) R. ARAOZ (alkaoïdes)

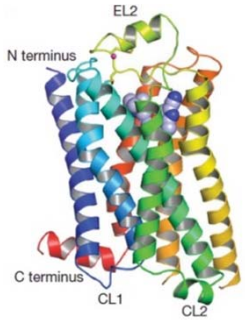
Toxines, Récepteurs et Canaux

CEA/ibiTecS/SIMOPRO – D. Servent

Natural toxins as tools to study receptors/channels function and source of imaging or therapeutic agents





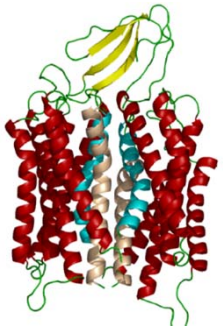


Identification of new toxins active on receptors and channels

• Screening of venoms and natural sources on receptors and channels

• Venoms and toxins purification

• High throughput solid phase peptide synthesis and refolding of reticulated peptides (10-70 aa)

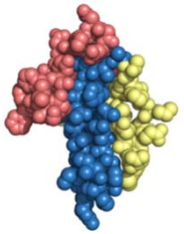


Structure/Function studies

• Pharmacological characterization of toxin-receptor interaction (radioactive binding assays , fluorescent/HTRF experiments)

• Mutational analysis

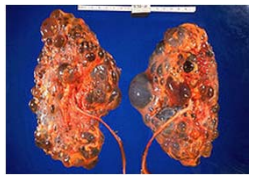
•Modeling of toxin/receptor complexes



Toxins Engineering

•Synthesis of non-natural, chimeric and labelled toxins (fluorescent, radioactive derivatives) with new functional properties

•Structure-based/phage display/phylogenetic engineering



Imaging, therapeutic applications

• Patents of toxins according to their pharmacological properties

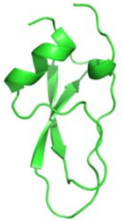
• Biodistribution of radioactive toxins

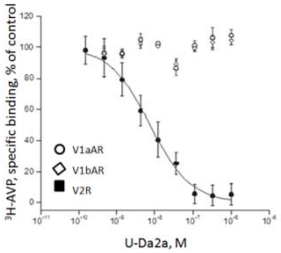
•Collaborations to explore ex-vivo and in-vivo the therapeutic potentials of toxins

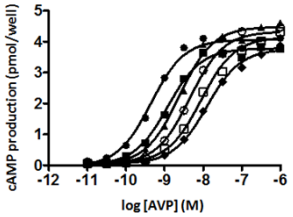
CNRS/TRIPSYN/NED - CEA/ibiTecS/SIMOPRO : HIGHLIGHTS

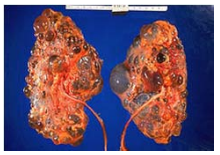
Phycotox
Groupement de Recherche

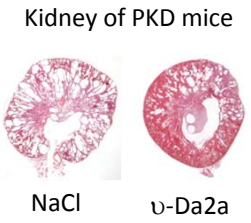
Identification of the first toxin active on the Vasopressin V2 receptor with potential effect on kidney disease (patented in 2012)











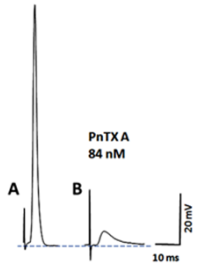
u-Da2a
First selective V2-R antagonist

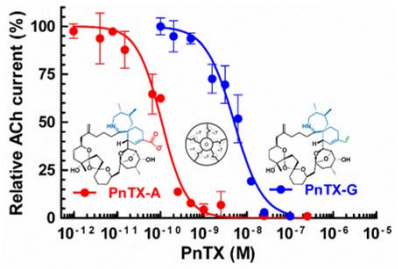
Full antagonist on the 3 signalling pathways

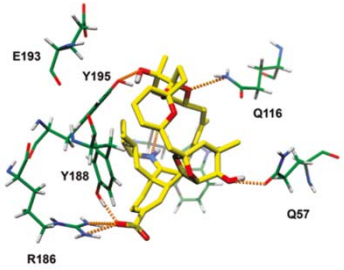
Diuretic effect of u-Da2a
Treatment of polycystic kidney diseases (PKD)

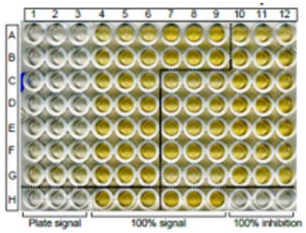
Pharmacological, structural characterization of toxins interacting with mAChRs and engineering to modify their functional property (Marquer et al. JBC. 2011; Fruchart et al. PlosOne, 2012)

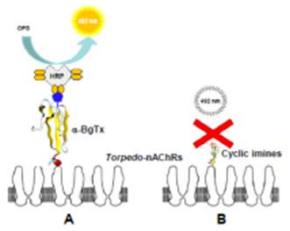
Elucidation of the mechanism of action of gymnodimine A, 13-desmethyl spirolide C and pinnatoxins A and G. Development of functional detection methods (patented in 2012).











Pinnatoxin A is a very potent antagonist of human neuronal α7 nicotinic acetylcholine receptors

Microplate-receptor binding assay for detection of cyclic imine toxins and cholinergic ligands (anatoxin-a)

CNRS/TRIPSYN/NED - CEA/ibiTecS/SIMOPRO: PROJETS (Past/ Present/ Futur)

Phycotox
Groupement de Recherche

European & International Grants

VENOMICS (FP7, 8 partners) (2012-2016): High-throughput peptidomics and transcriptomics of animal venoms for discovery of novel therapeutic peptides. *Coordinator of the project*

NIH Subaward grant KK1036 # 056280 (responsible: A. ZAKARIAN). Source: US National Institutes of Health (NIH) program # 3RO1 GM077379-02S1 (01/8/2009 - 31/05/2013).

PHARMATLANTIC : # 2009-1/117 (coordinator: L.M. BOTANA), Source: EU's Atlantic Area Programme (01/04/2010 - 01/12/2013) http:// www.pharmatlantic.org.

ATLANTOX : # STC-CP 2008-1-555612 (coordinator: L.M. BOTANA). Source: EU's Atlantic Area Programme (01/01/2009 - 31/12/2011; prolonged to 01/12/2013)

National Grants

AQUANEUROTOX : # ANR-12-ASTR-0037-01 (coordinator: J. MOLGÓ). Source: Agence Nationale de la Recherche (01/2/2013 - 31/1/2016).

ANR RPIB (2012-2015), VenomPicoScreen

ANR BiotechS (2010-2013), PeptoMed

ARISTOCYA : # 052805 (coordinator: D. LAURENT). Source: Agence Nationale de la Recherche. (01/12/2008 - 30/11/2012).

NEUROSPIROIMINE : # 07-PCVI-0008-01 (coordinator: J. MOLGÓ). Source: Agence Nationale de la Recherche (29/11/2007 - 28/11/2010).

Submitted Grants

Contrat ANSES: Appels à projets de recherche sur la santé environnement et la santé au travail. Coordinateur : E. BENOIT. Titre : NeuroTox - Etudes de neurotoxines marines émergentes présentant un risque potentiel pour la santé publique.

ANR: Appel à projets "Grands défis sociétaux: Santé et bien-être". Coordinateur: D. JOSEPH. Titre: Rational Design and Synthesis of Scaffolds targeting Nicotinic Receptors by Atomic Resolution.

ANSES – DER
(direction de l'évaluation des risques)

-Main Activity: health risk assessment
(for human consumers)

-Research activity (linked to GdR) :

- review of toxicity data (*in vitro, in vivo,* humans)
- analysis of occurrence data
- dietary exposure analysis
- quantitative risk assessment/management (modeling)
- scientific support to risk manager and regulation (FR, EU, *Codex*)

Educational background & Research activity per scientist

Anne Thébault: PhD in epidemiology & biomathematics, doctor in veterinary medecine ; marine biology, biostatistics, math. modeling

Nathalie Arnich: PhD in toxicology, educ. in biology & marine biology ; risk assessment associated with contaminants in food, toxicity of biotoxins

ANSES – DER
(direction de l'évaluation des risques)

Projects in progress

- ANR « ACCUTOX »: Physiological and genetic determinism, risk assessment and social issues of paralytic toxins (PST) accumulation by oyster *Crassostrea gigas* (2013-2017)
- ANR « FISH-PARASITES »: parasites in fish - hazard identification, impact, and researches to define an efficient strategy of prevention (2010-2014)

Requests from French Ministries (linked to GdR) in progress

- update the strategy for setting « at-risk » periods for lipophilic phycotoxins
- review the « vigilance » system for lipophilic phycotoxins in place in France since 2010
- ciguatoxins/sharks/Réunion island
- efficiency of seawater treatments for on-land shellfish ponds

Past & Present research projects

- 4 ANR; 3 linked to marine biology : FISH-PARASITES, COQENPATH, ACCUTOX
- 5 European projects; 2 linked to marine biology

International peer-reviewed publications: 19 (Anne) + 12 (Nathalie)

International conferences: oral/poster at ICMSS (all since 2004), HAB 2010
scientific & edition committee of ICMSS-2009 in France

Figure représentative de l'équipe

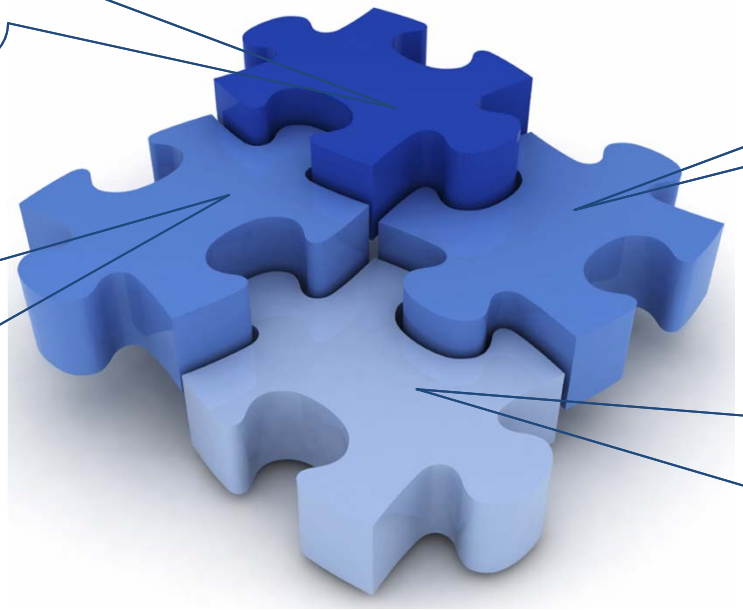
Phycotox
Groupement de Recherche

1. Hazard identification

What are the potential adverse health effects? One or several compounds?

2. Hazard characterization

What are the nature and the severity of the health effects at different exposure levels (dose-response)?



3. Exposure assessment

What is the amount of the contaminant to which people were exposed or could be exposed?

4. Risk characterization

What is the health risk caused by the contaminant in the exposed population (likelihood and severity of an adverse effect)?

anses
French agency for food, environmental and occupational health & safety

Health risk assessment process