Quest Drugs From The Ocean

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What is a Natural Product?

Natural Product = a chemical compound produced by a living organisms often having biological/pharmacological properties used as LEAD for the development of new drugs
In early ’80s
Marine Natural Products: the ERA of Blue Chemistry begins!
Approved marine-derived drugs

- Cytosar-U®: Pain
- Prialt®: Ziconotide, µ-conotoxin MVIIA
- Conus sp.: Pain
- Tethya sp.: APPROVED
- Ecteinascidia turbinata: Trabectedin, ET-743
- Vira-A®: Cancer, EU registered
- Vidarabine, Ara-A: Antiviral, ophthalmic, Not in US
- Yondelis®: Cancer, EU registered

TRENDS in Pharmacological Sciences
2008-2014 Main Research Projects

**NatPharma**
Reinforcement of research potential for the realization of a complete drug development scheme from natural compounds
REGPOT-2008-11
Coordinator: Prof. Ernesto Fattorusso
Università di Napoli Federico II
Work Package 5 leader: V. Costantino

**Bluegenics**
From gene to bioactive products
KBBE 2012-2016
Coordinator: Prof. W. Mueller, University of Mainz
Work Package 3 leader: University of Naples

**Studies on glycolipid profile of marine fungi**
Italian-Israel Cooperation
(Italian Foreign Office-January 2012-January 2014)
PI: Prof. V. Costantino

**Antitumor-Antibiotics from Arabian Marine Sponges**
Funded by Qatar National Foundation, NPRP 6-006-3-002
Co-PI: Prof. V. Costantino
Expertises:

isolation and stereostructural determination of new molecules using (much!) less than 1 mg of pure compounds

quali/quantitative analysis of extracts
Marine sponges are sessile animals that contain highly diverse and dense microbial communities. More than 10 bacterial phyle (including Proteobacteria, Actinobacteria, Nitrospira, Chloroflexi, Planctomycetes, Cyanobacteria, Acidobacteria) have been found in sponges. Microorganisms can be up to 40% of the volume of the sponge.
Structural elucidation on 7 ug of pure compounds
Extracted ion chromatograms for chlorinated compounds from a crude extract of *Smenospongia aurea* (experiment performed on a Thermo LTQ Orbitrap XL high-resolution LC-ESI-MS instrument).
Smenamides from *Smenospongia aurea*

Smenamides share structural features with Dolastatin-15, one of the marine natural products that has advanced to clinics.

Evaluation by MTT assay of Calu-1 cell viability after 72 h of treatment with (A) compound 1 and (B) compound 2. ** $P < 0.0005$. 
Evaluation of pro-apoptotic activity of smenamides using the Annexin-V FITC/PI assay. (A) The percentage of apoptosis for cells treated for 72 h with compound 1 at 1, 10, 50, and 100 nM was, respectively, 4%, 4%, 40%, and 80%; the remaining cells remained viable. (B) The percentage of apoptosis for cells treated for 72 h with compound 2 at 1, 10, 50, and 100 nM was, respectively, 6%, 6%, 23%, 40%; the remaining cells remained viable except at concentration of 100 nM, where 47% of cells were necrotic. ** $P < 0.0005$, * $P < 0.001$. 
Are Cyanobacteria the producers of Smenamides?

Smenamides share structural features with some known cyanobacterial metabolites.

The presence of a pendent vinyl chloride in the middle of the polyketide chain is a motif shared with jamaicamides from the cyanobacterium *Lyngbia majuscula*.

The dolapyrrolidinone terminus is the same as in dolastatin-15, a depsipeptide isolated from the sea hare *Dolabella auricolaria* believed to be of likely cyanobacterial origin.
16S rRNA Metagenomic Analysis

Metagenomic DNA extraction from the Caribbean sponge Smenospongia aurea

PCR screening of metagenomic DNA with cyanobacterial-specific 16S rRNA primers CYA106F and CYA781R(a) or CYA781R(b) produced clear bands at the expected length of about 670 bp.

A 16S rRNA gene library was then constructed from the amplicons and 24 clones were sequenced. Except for three sequences not related to cyanobacteria, all the cyanobacterial sequences were identical at a 99% sequence identity threshold, and assigned to Candidatus Synechococcus spongiarum.

Are Cyanobacteria the producers of Smenamides?
Cyanobacteria metabolites can be analysed from a different point of view...
Cyanobacteria in Drug Discovery: Mycrocystin as antitumor agent

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0091476
Cyanobacteria proposal in H2020

Studying Cyanobacteria from different points of view

Cyanobacteria

Microcystins, Nodularins, but also many other metabolites...
Cyanobacteria proposal in H2020

Studying Cyanobacteria from different points of view

CyanoToxins

Novel bioactive metabolites

Cyanobacteria
Cyanobacteria

Toxins

• Health policies for beaches and recreational areas
• Managing drink water
• Info for public

Novel bioactive metabolites

New Drugs

Cyanobacteria
Cyanobacteria proposal in H2020

Some ideas

• Studying Cyanobacteria from different points of view
• studies on ocean waters samples and fresh waters samples

IMPACT on

• Environment
• Public health
• Definition of best practices and policies
• Innovation and Drug Research (new pharmacologically active molecules for drugs)
Cyanobacteria proposal in H2020

EU Consortium of Universities, Research Labs, Companies, Others

CyanoResearch

CyanoEducation
Quest Drugs From The Ocean

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