



Marine Biodiscovery: Overview, hurdles and bottlenecks

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Why Use Marine Bioresources?

Offers advantage over comparable terrestrial resource:

Superior performance

Better economics

Unprecedented activity in particular application:

Enzymes: new reactivity/new biotransformation

Small molecules: new mechanism of action

Materials: new properties

Marine Natural Products on the Market



Vent Polymerase

Origin: Vent bacterium

Production: Recombinant



Priali for pain

Origin: Phillippino cone snail

Production: Recombinant



ω -3 polyunsaturated fatty acids
for heart disease Source: Fish
Production: Fish



Halaven for cancer

Origin: Japanese deep water sponge

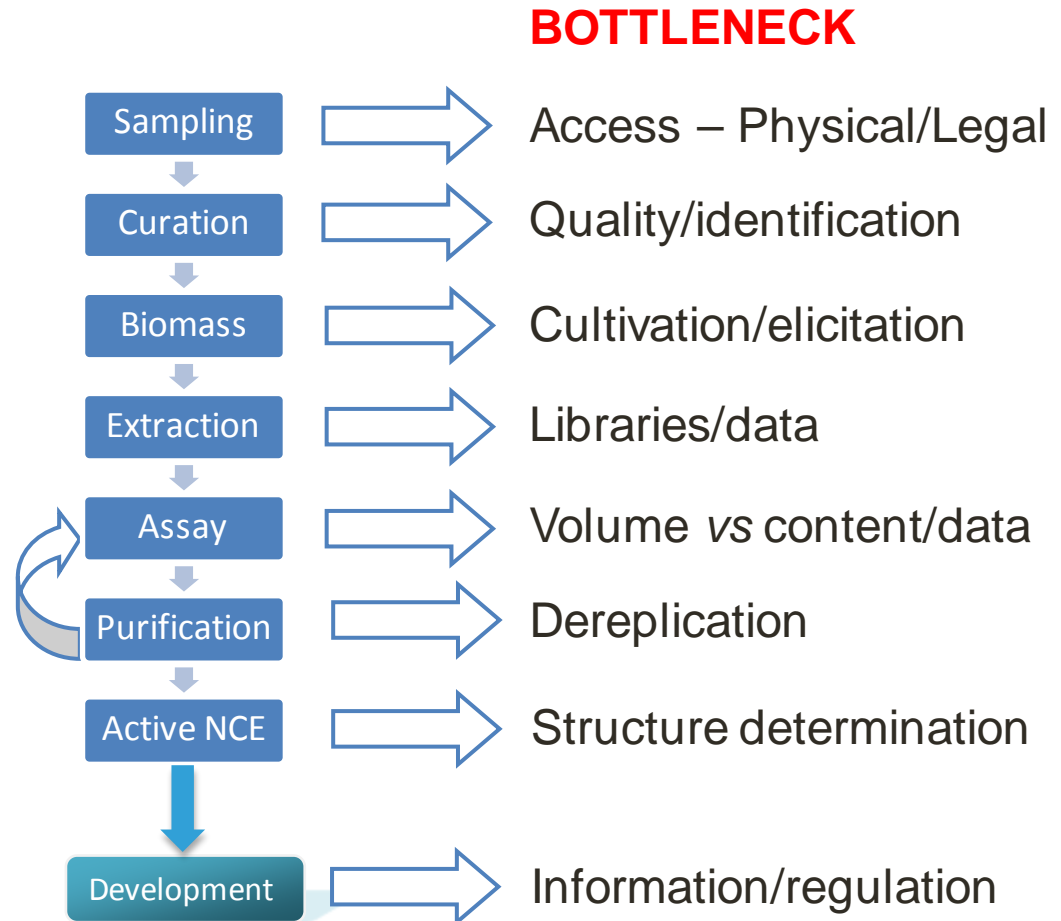
Production: Chemical synthesis

The Marine Biodiscovery Process

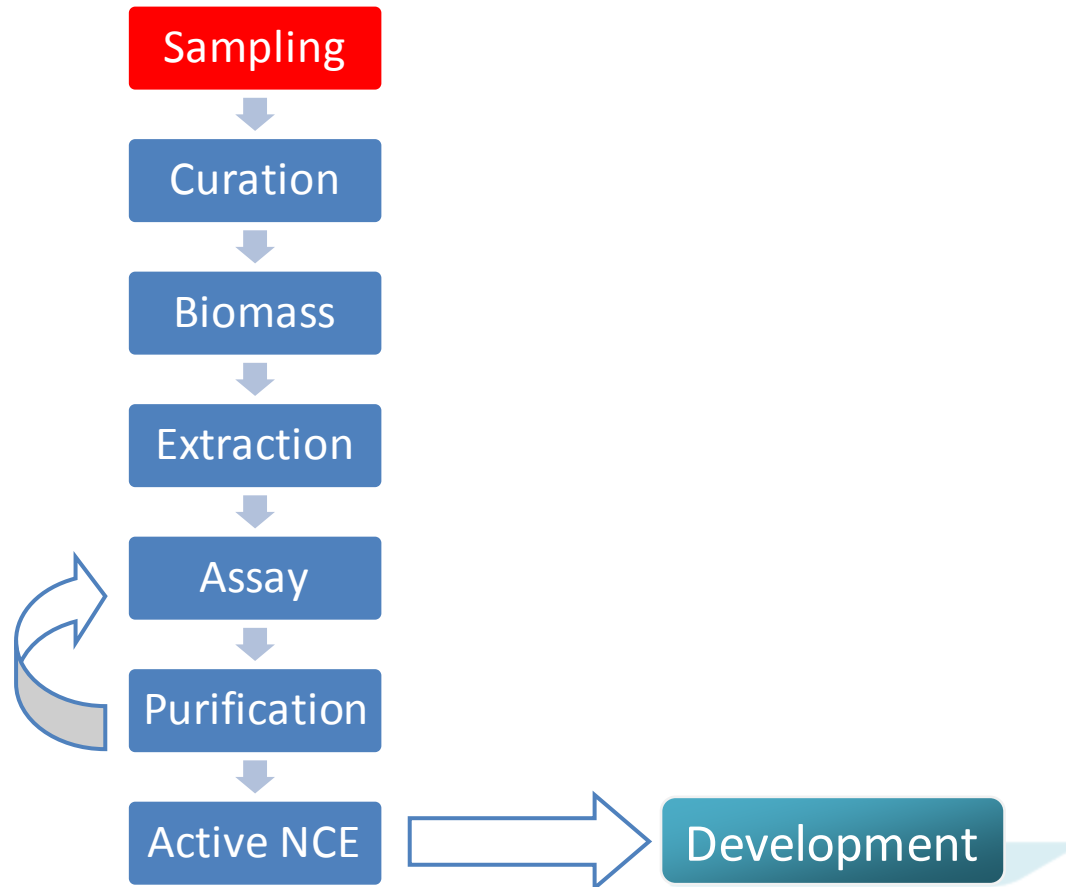
Biodiscovery is the discovery of compounds and associated ideas from natural sources to develop novel biomedicines.

Biodiscovery generates chemical diversity that is used to find initial biological activity in disease focused screens

Biodiscovery also includes the development of biomedical research tools, antifoulants, catalysts, nutraceuticals and cosmeceuticals.



The Marine Biodiscovery Process



Access - Legal

Create Science/Policy Interface

MGR Practitioners Research / Industry



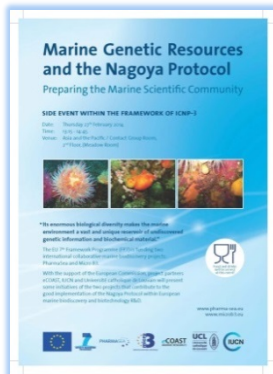
Legal Experts & Policy Makers

EC (DG MARE & DG ENV), UNDOALOS, CBD Secretariat, CIESM, ISA, CMS Secretariat

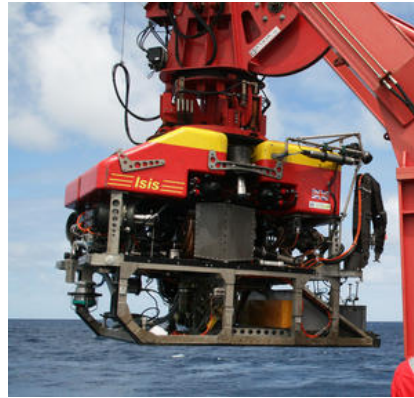
Inform Policy

Awareness Raising

Share best practice



Access - Physical



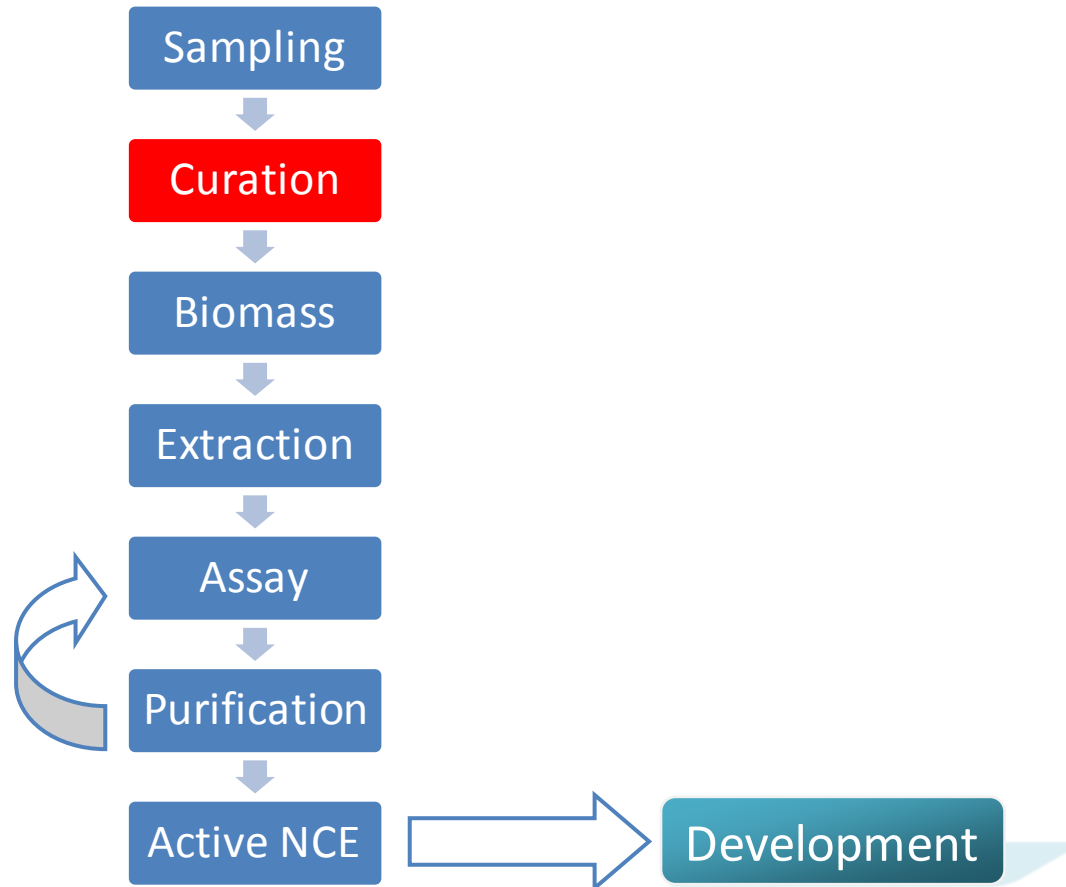
Bottlenecks

- High daily rate
- Limited number of vessels globally
- Access competitive
- Long time between bid for time and actual cruise
- Many different types of science accommodated may lead to compromises
- Data capture & storage

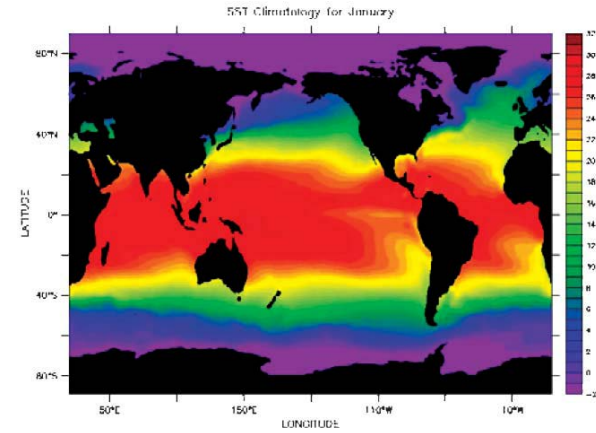
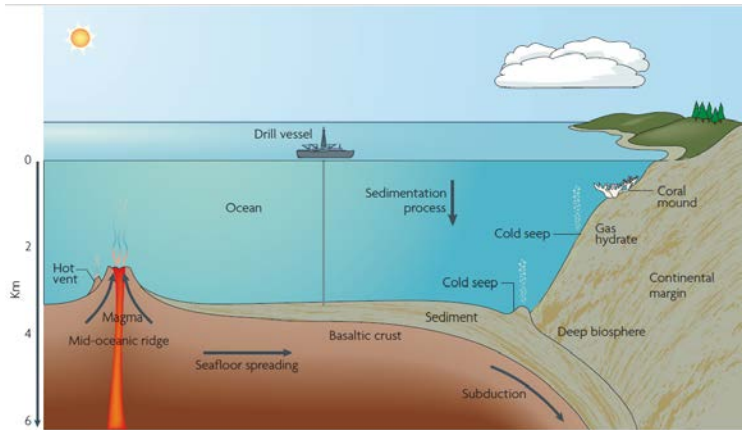
Possible Solutions

- Shared resources and bartering systems
- Sharing of samples
- Biobanks
- Cheaper sampling technology
- Systems to encourage data deposition

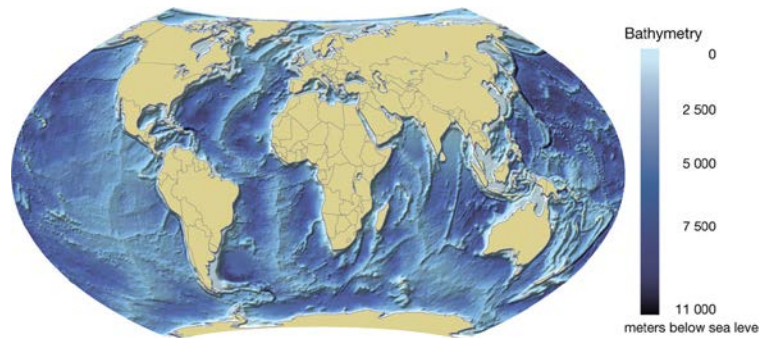
The Marine Biodiscovery Process



Quality of Marine Bioresources – Habitat Selection



Cold Oceans



Deep Oceans



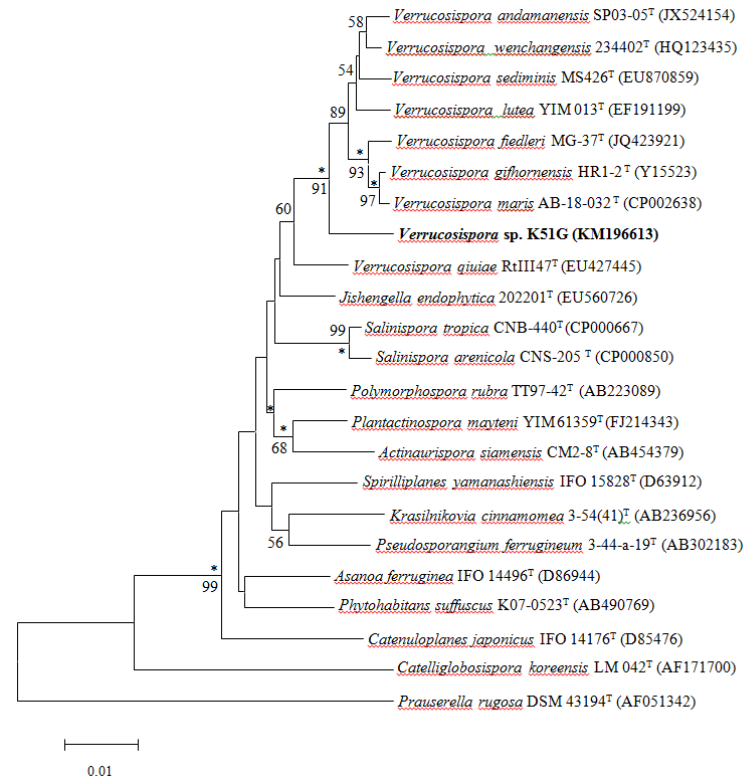
Thermal Vents

Quality of Marine Bioresources – Strain Isolation & ID



Selective Isolation Methods

Target particular taxa



Taxonomic Identification

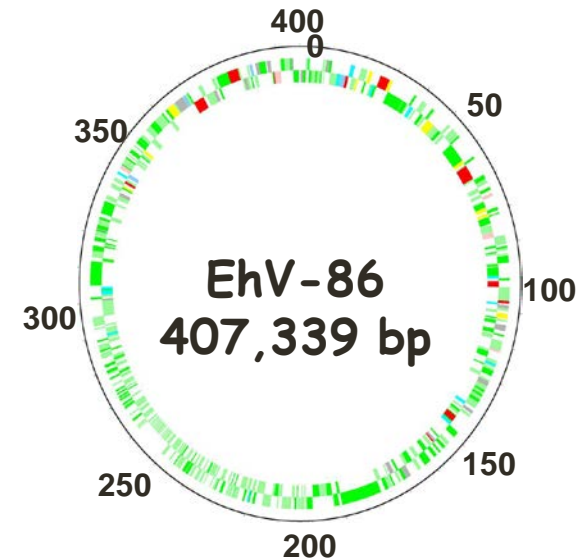
Polyphasic taxonomy:

Morphology

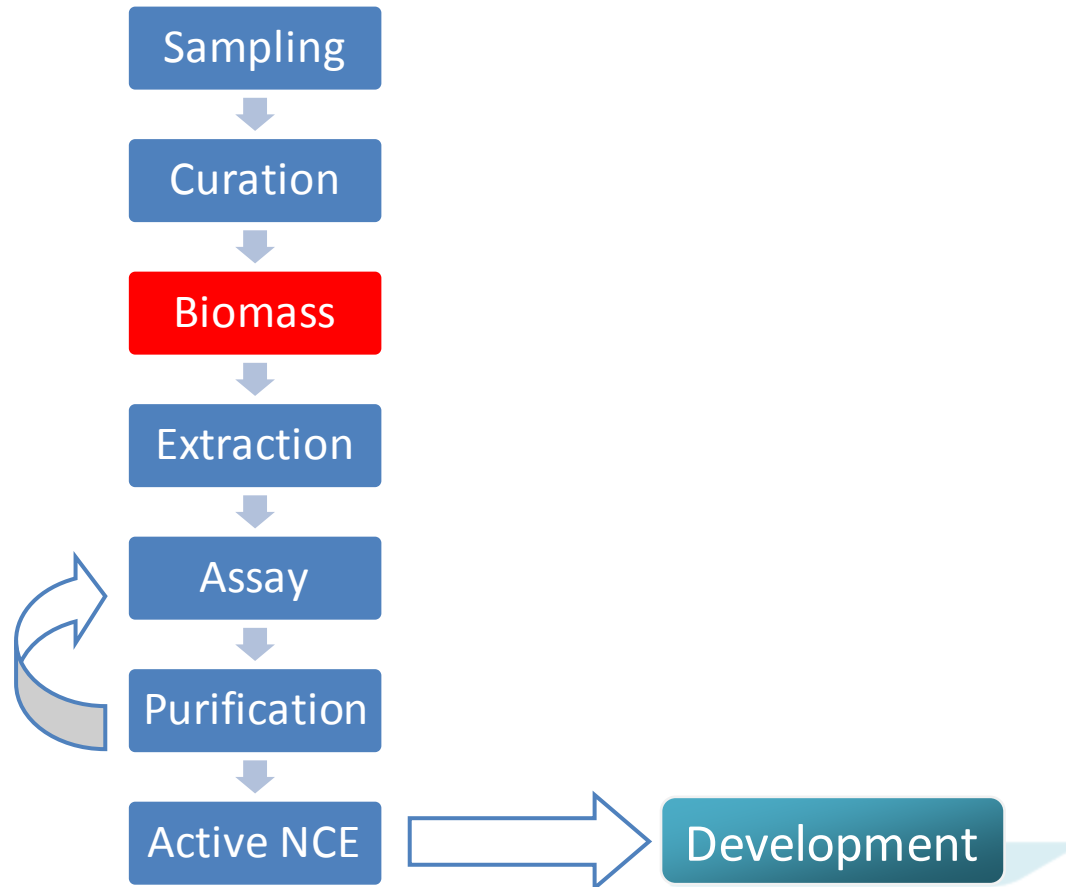
DNA-based

Chemotaxonomy

- Is genome and metagenome information sufficient?
 - Many genes found in marine species are not in the current bioinformatic databases
 - The function of many of these genes cannot be determined without laboratory work
- Impact of CBD/Nagoya
 - Who acquired/deposited the data and with what authority?
 - Who has access to the data?



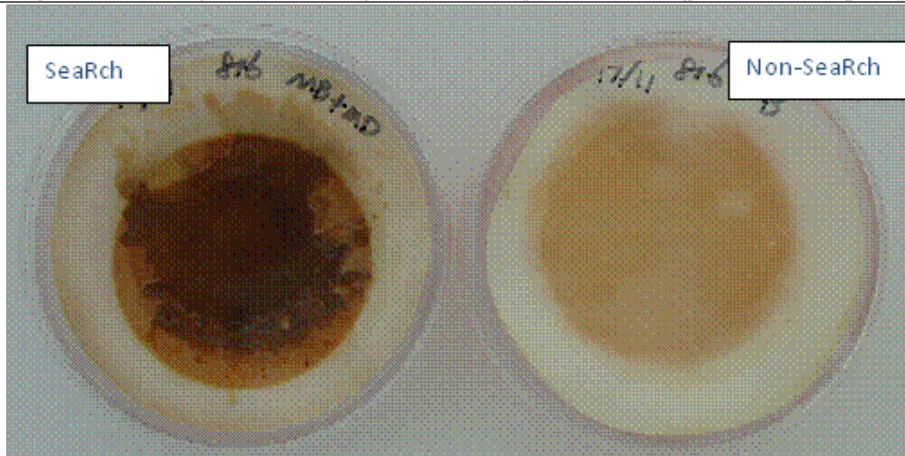
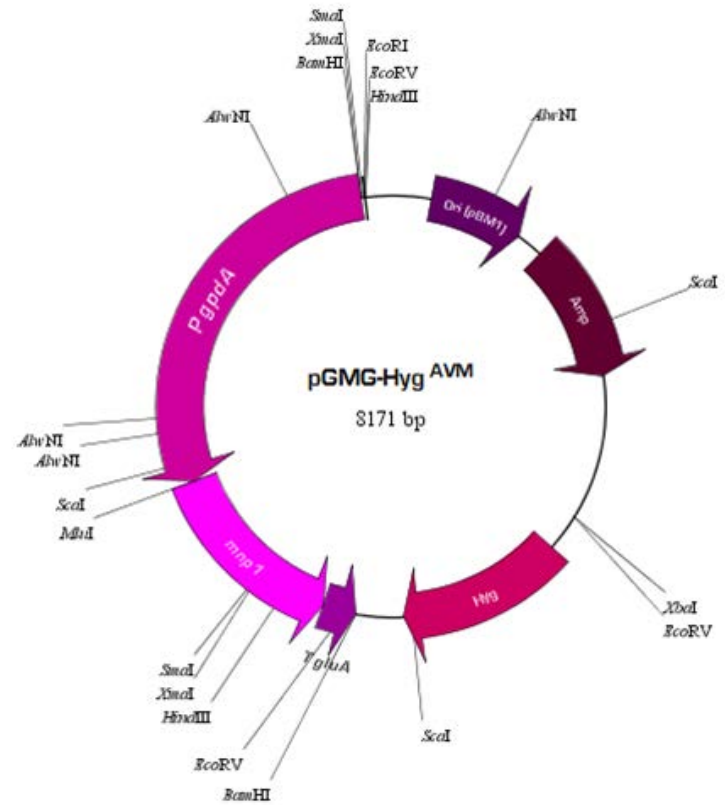
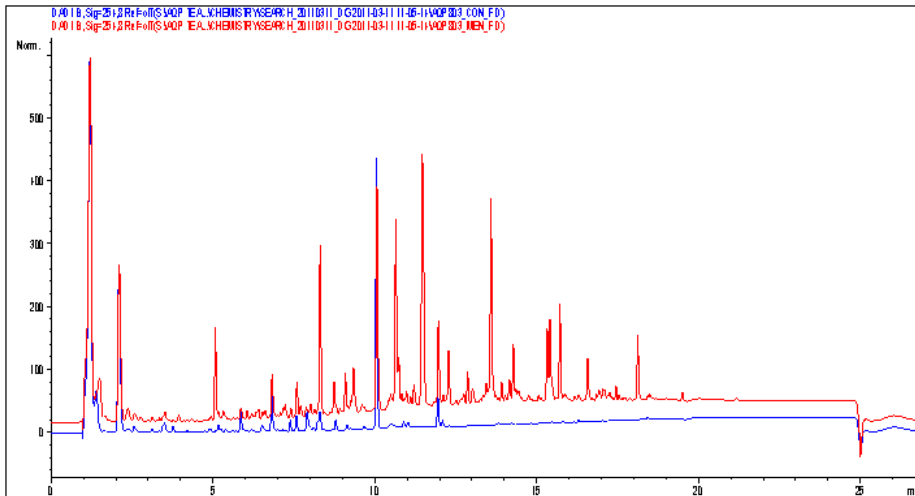
The Marine Biodiscovery Process



Biomass



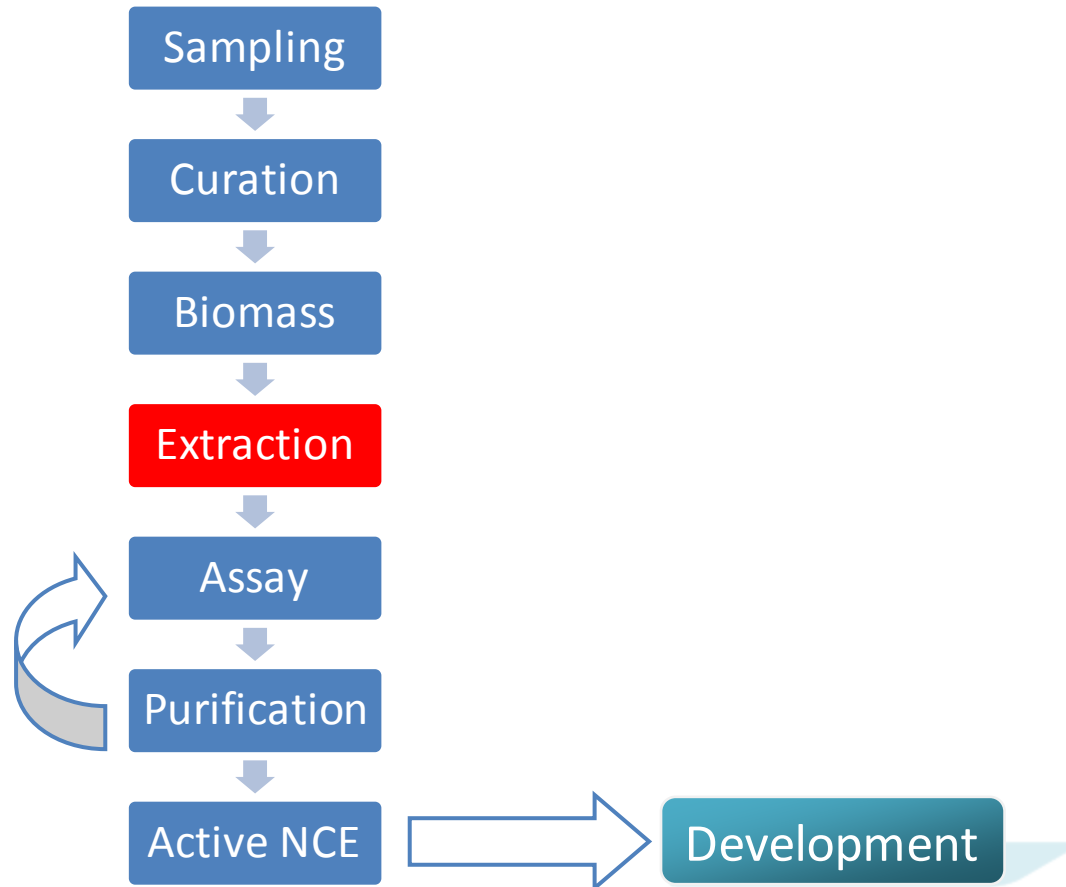
Elicitation/Stress and Molecular Tools



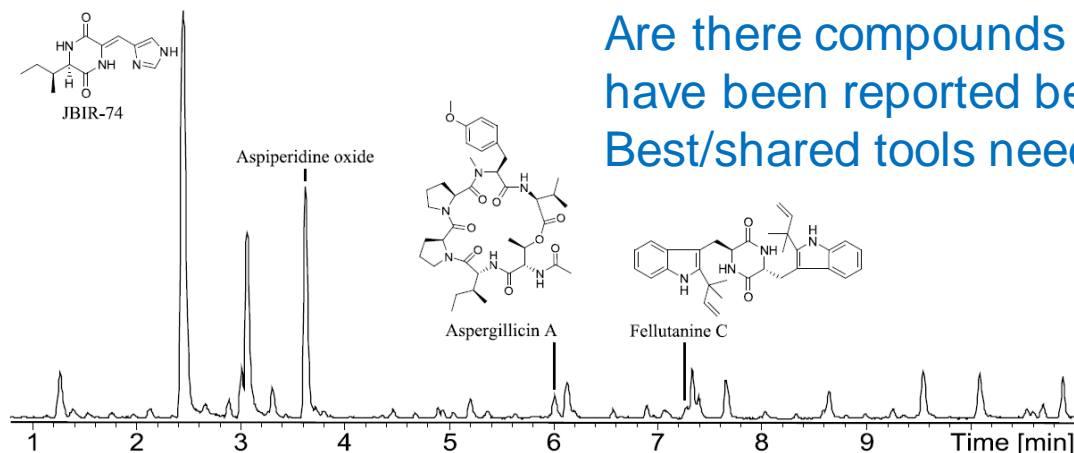
What stresses/media to use?

Difficulty in cloning genes of marine origin due to lack of suitable tools (vectors/hosts)

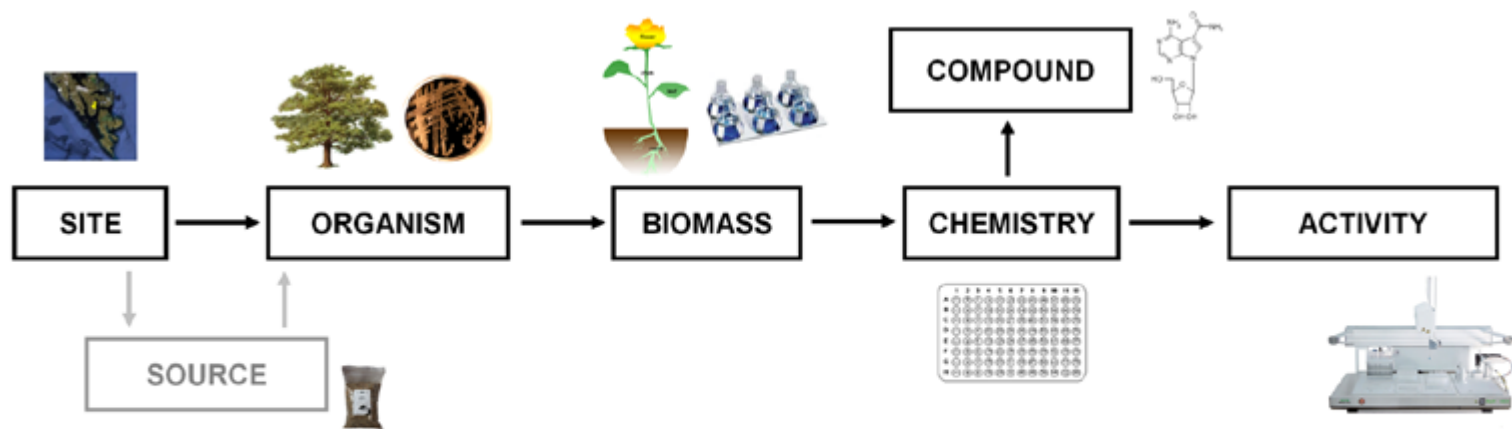
The Marine Biodiscovery Process



Dereplication and Data Management



Are there compounds in your mixture that have been reported before?
Best/shared tools needed

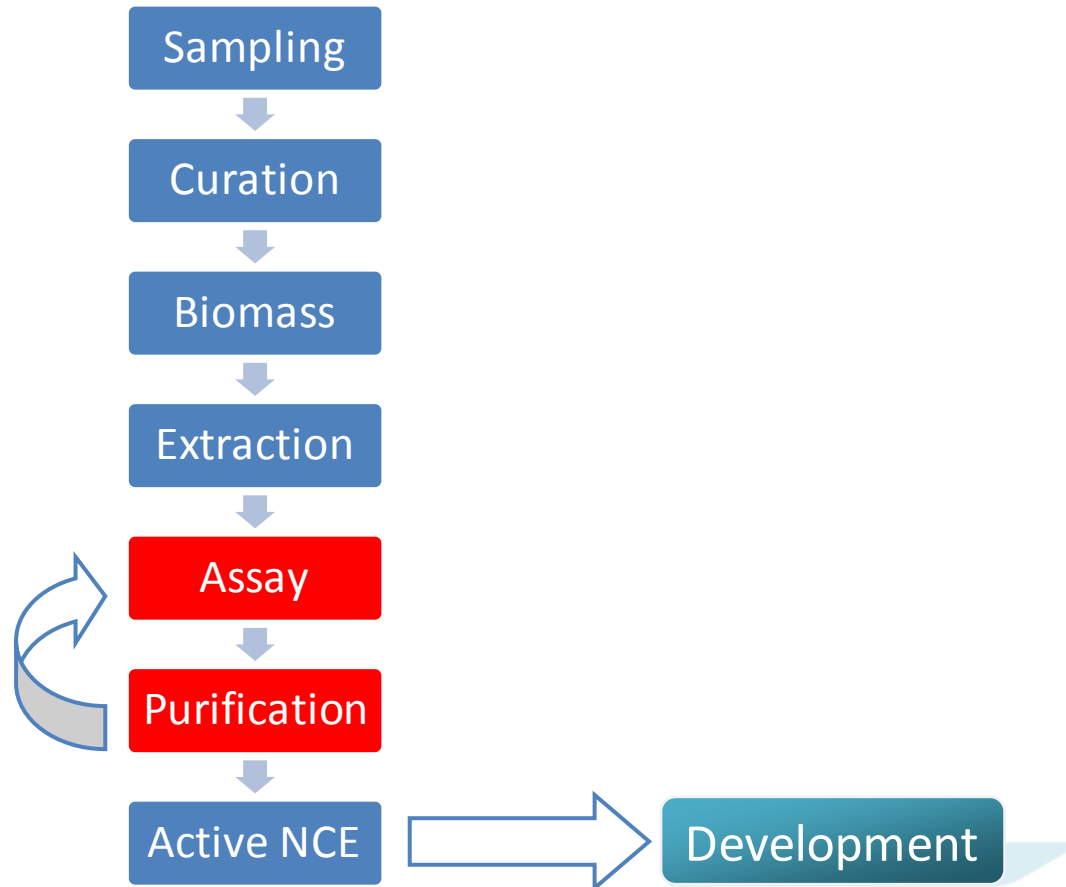


OpenNAPIS™
Functional Design

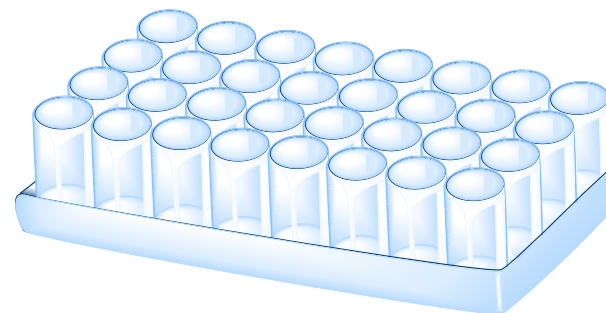
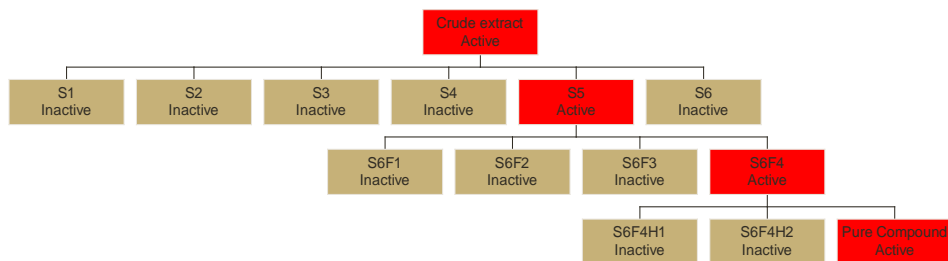
White Point Systems, Inc.
20100626



The Marine Biodiscovery Process



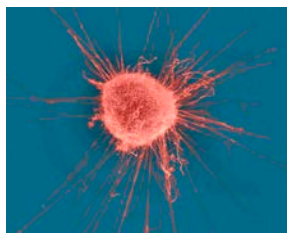
Purification & Assays



Bioassay guided isolation

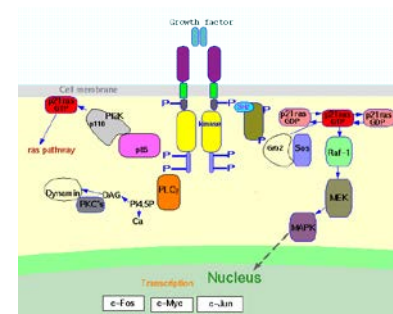


Whole animal



Cell based

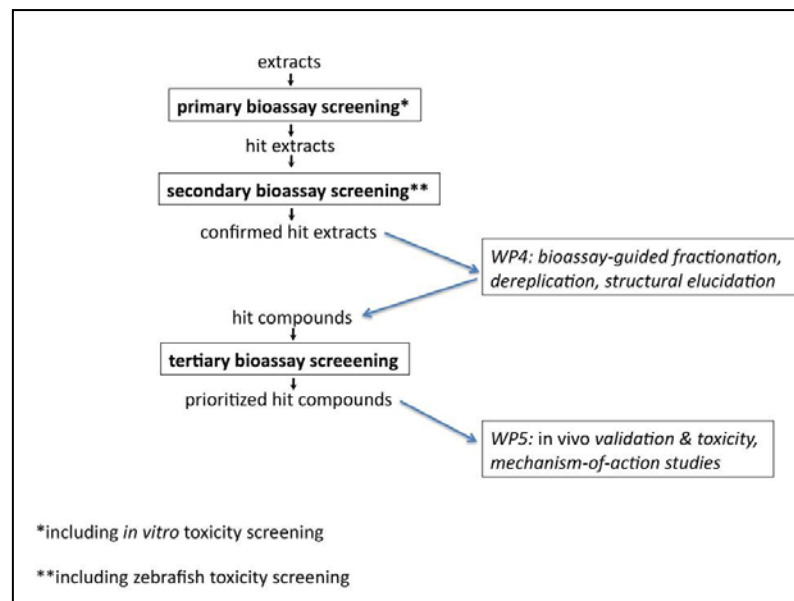
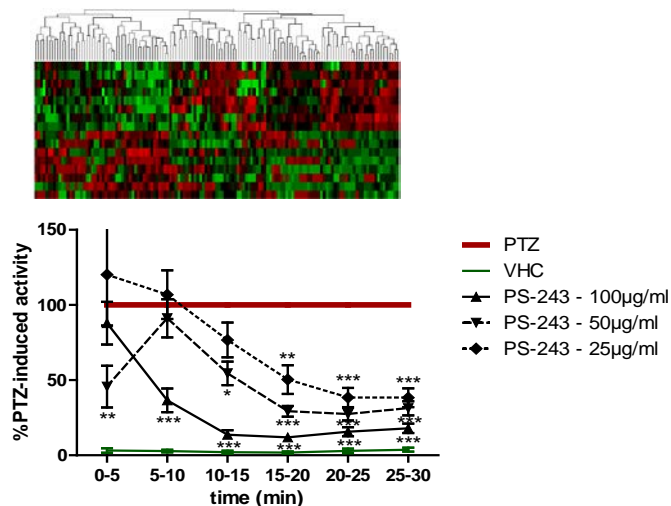
Extract library



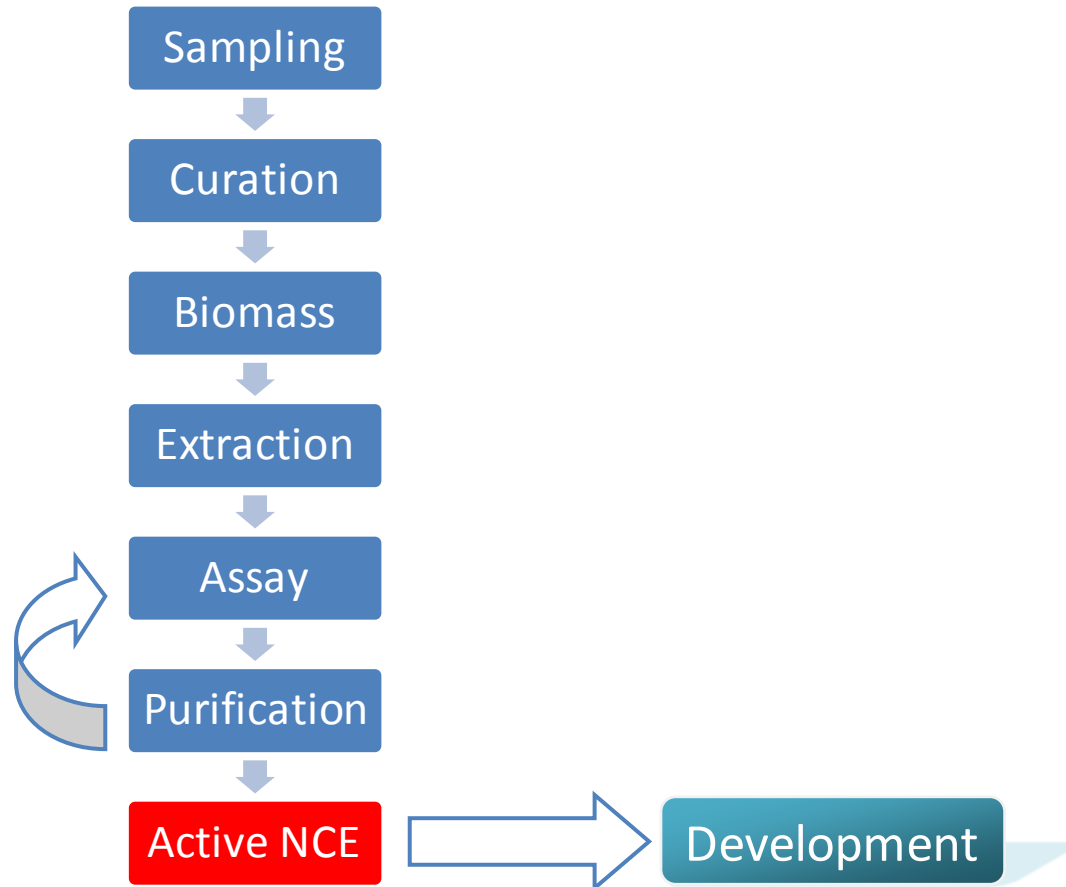
Enzyme based

Assay Considerations

- Assay validation
- Throughput vs information content
- Artefacts (false positives/negatives)
- Pan-interferences
- Counterscreens/secondary assays
- Data management
- Decision protocol for follow-up studies



The Marine Biodiscovery Process



Novelty/Structure Determination

Better chemical informatics

- Find known compounds & reduces wasted effort
- Discover known families
- Pinpoints new compounds
- Automated processing of large volume of data

Rapid Structure Elucidation

- State-of-the-art equipment
- Computer aided methods
- Data management

ChemSpider
Search and share chemistry

About | More Searches | Web APIs | Help

Search term: **halicyclamine a** (Found by approved synonym)

Halicyclamine A

ChemSpider ID: **8654897**
Molecular Formula: $C_{32}H_{50}N_2$
Average mass: 462.752808 Da
Monoisotopic mass: 462.3974 Da

▼ Systematic name
(4E,6Z,14S,19Z,21Z,29S,30R)-1,16-Diazatetracyclo[27.3.1.1^{12,16}.0^{14,30}]tetratriaconta-4,6,12,19,21-pentaene

► SMILES and InChIs
► Cite this record

2D 3D Save Zoom
- Double-bond stereo
- 3 of 3 defined stereocentres

Use of open source databases

The Best Structure

Generated Molecule
Current Structure

Properties

- $M_{calc}^{12}C_1$: 0.202 (v-12.00)
- $M_{calc}^{12}C_2$: 0.335
- $M_{calc}^{12}C_3$: 0.324 (v-12.01)
- $M_{calc}^{12}C_4$: 0.259
- $M_{calc}^{12}C_5$: 2.454
- $M_{calc}^{12}C_6$: 1.205
- $M_{calc}^{12}C_7$: 0.485
- $M_{calc}^{12}C_8$: 1.706
- $M_{calc}^{12}C_9$: 0.462
- $M_{calc}^{12}C_{10}$: 0.476
- Formula: $C_{32}H_{50}N_2$
- RI: 292.039
- M_{calc} : 392.3474
- $M_{calc}^{12}C_1$: 0.202 (v-12.00)
- $M_{calc}^{12}C_2$: 0.207

Automated structure determination workflow

Mechanisms to transfer marine biotechnology to end users whilst acknowledging:

- Current bottlenecks in marine biodiscovery pipeline

- Need for legal certainty over marine biodiversity collection (CBD/NP & UNCLOS).

- Regulatory stress on companies (EMEA/EFSA).

- Lack of risk taking by companies due to shareholder pressure.

Possible actions

- Address technical challenges in pipeline

- Provide information/organise meetings to raise awareness of opportunities

- Work with regulators and practitioners to develop appropriate framework

People, Facilities and Projects

Problem

- Lack of expertise in marine biotechnology (microbiology/genetics/chemistry/assays etc)
- Lack of interdisciplinary training capacity.
- Few integrated facilities covering the whole pipeline
- Decentralisation of current projects
More management
Slower sample transfer
Decision protocols slower

Possible Solution

- Build networks and consortia to introduce scientists from other disciplines
- Develop integrated MSc/PhD programmes (eg ITN)
- Build marine biotechnology centres
- Simplify management processes
- Allow more autonomy
- Better communication

Overarching Problems

Problem

- Large scale production of materials
- Long term maintenance of data
 - Genomic*
 - Assay*
 - Compound*
- Long term maintenance of material
 - Strains*
 - Extracts*
 - Compounds*

Possible Solution

Better cultivation facilities
Better molecular tools

Bioinformatic databases
Assay databases/LIMS/OPENSOURCE
Open source databases/ChemSpider

Biobanks
Central screening facility/OPENSOURCE
Central compound repository (*cf* Open Source Drug Discovery in India)

Project Lifetimes

- Limited lifetime projects come to a sudden end jeopardising
 - Continuity – promising compounds will not be pursued
 - Maintenance and use of data acquired
 - Maintenance and use of materials generated
 - Fragmentation of highly functioning teams
- Consider continuing support for successful projects (grant renewal)
 - Must be competitive and based on previous results and track record
 - Do this without disadvantaging new projects (eg by including new partners in renewals)
 - Ensure maintenance of data and materials

PHARMASEA



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