



The Marine Biodiscovery Pipeline

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Professor Marcel Jaspars

- BA Hons (Cantab) in Natural Sciences (Chemistry)
- PhD in Synthetic Organic Chemistry
- Post-doc with Prof Phil Crews, University of California, Santa Cruz on Marine Natural Products
- Professor of Organic Chemistry & Director of Marine Biodiscovery Centre, University of Aberdeen
- Project Leader, PharmaSea Consortium
- Co-Author of ESF Marine Board Position Paper “Marine Biotechnology – A New Vision and Strategy for Europe”
- Visiting Professor (20%) at University of Tromsø
- Scientific advisor to MabCent, Tromsø
- Member of the Industrial Biotechnology Sector Group of the Biosciences Knowledge Transfer Network
- Unpaid advisor to Aquapharm Biodiscovery Ltd and Glycomar Ltd, UK.

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

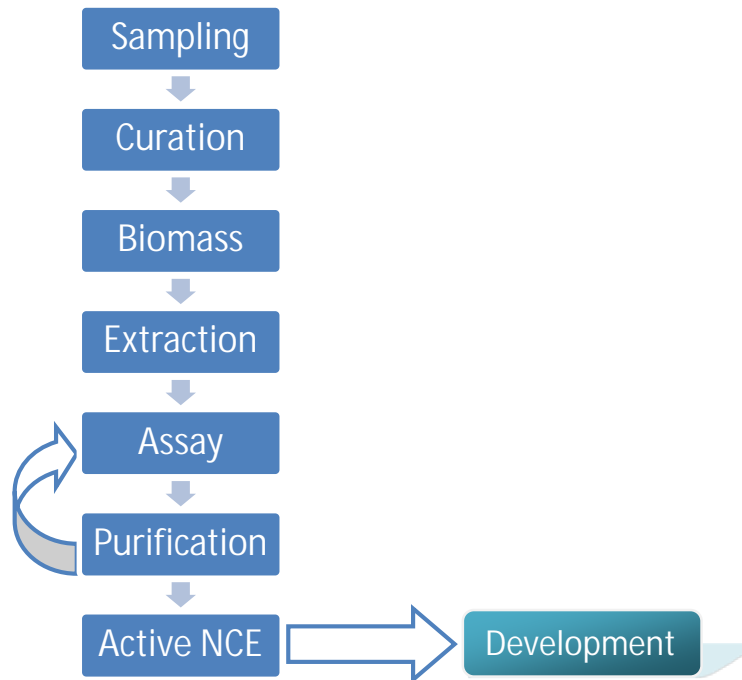
- Materials: new properties

The Marine Biodiscovery Process

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

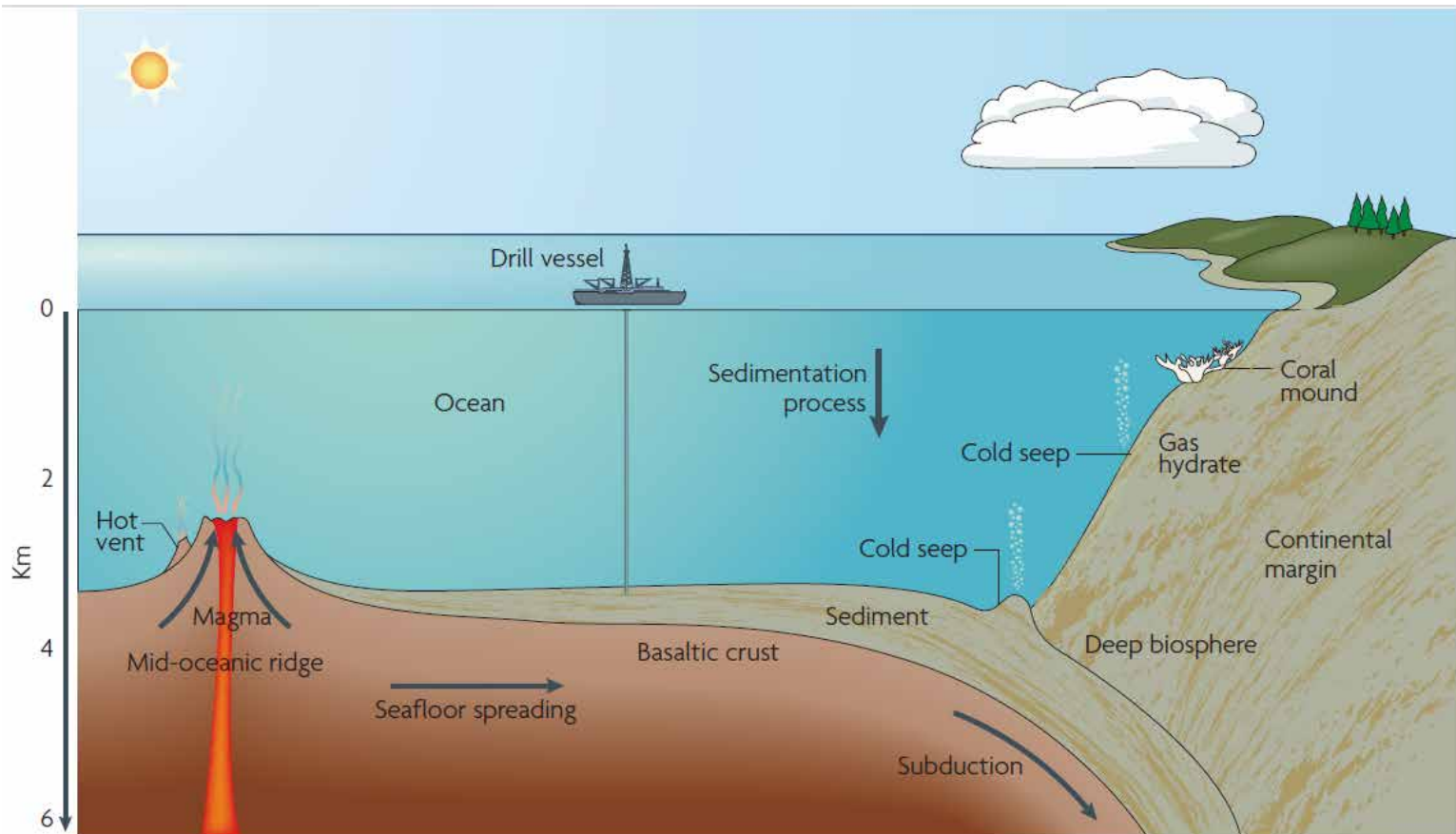
Biodiscovery generates chemical diversity that is used to find initial biological activity in disease focused screens

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



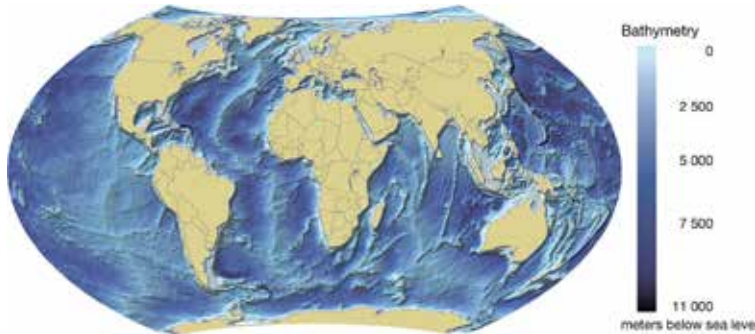
Why Marine?

Diversity of Habitat



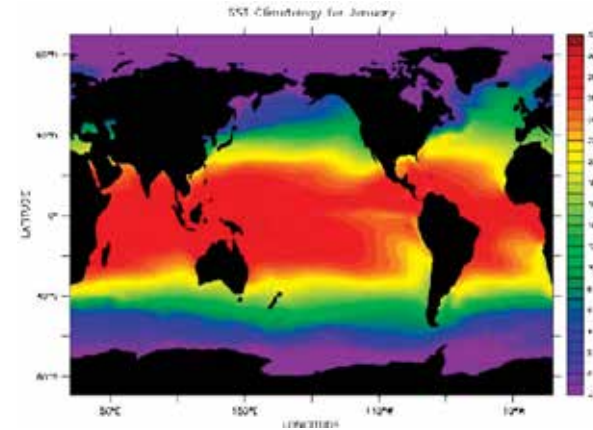
Jørgensen *Nat Rev Microbiology*, 2007, 5, 770

Extreme Marine Environments



Deep Oceans

95 % > 1000 m deep
50 % > 3000 m deep
Average depth = 3790 m
1-3% trench ecosystems

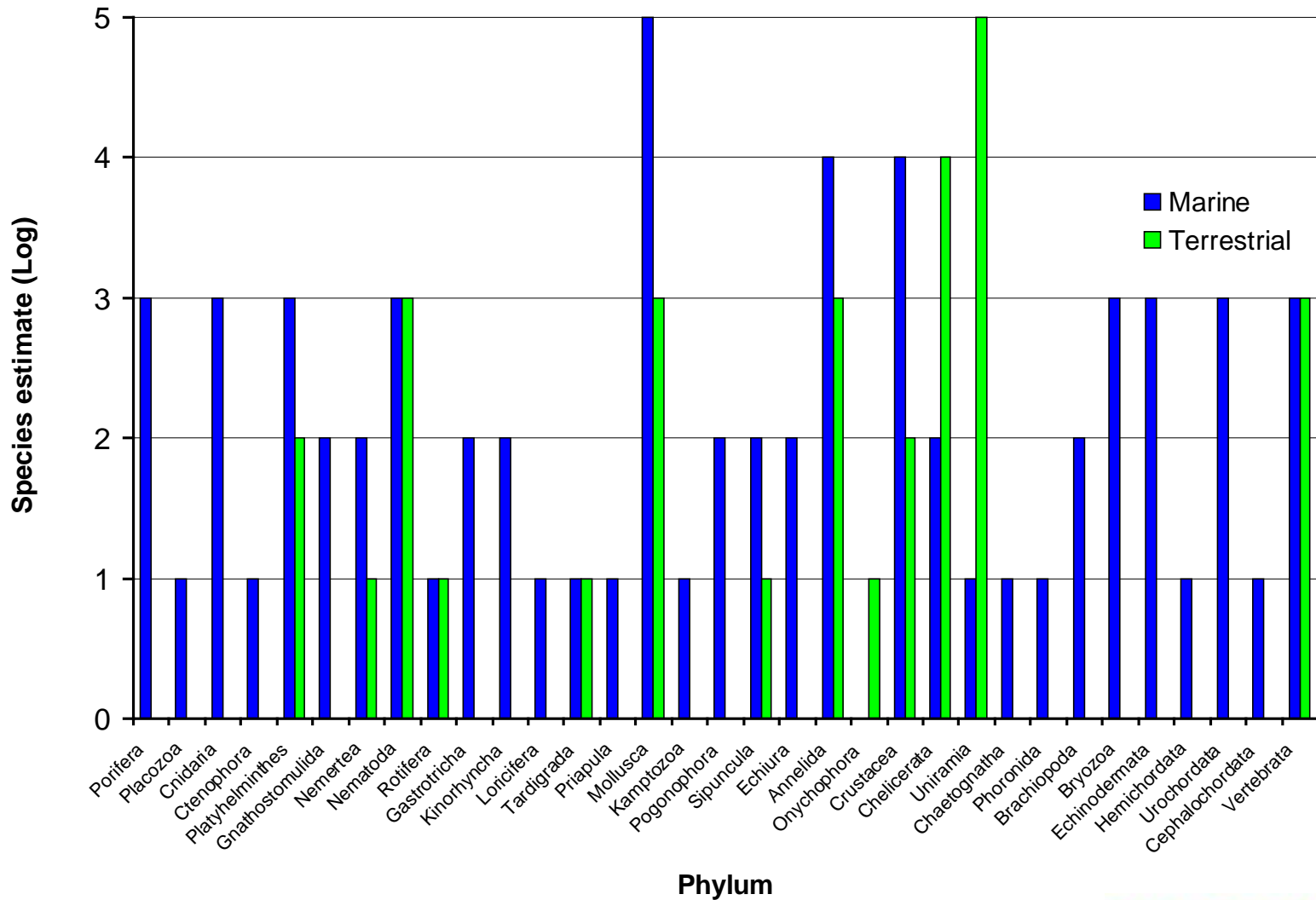


Cold Oceans

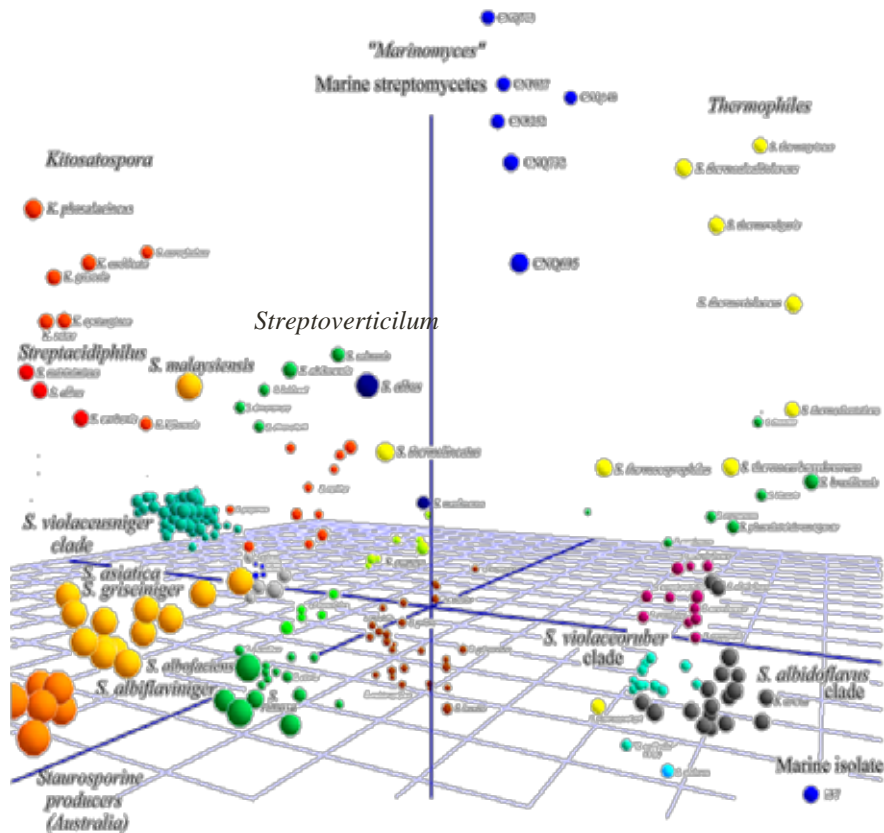
Thermal Vents



Marine Animal Biodiversity



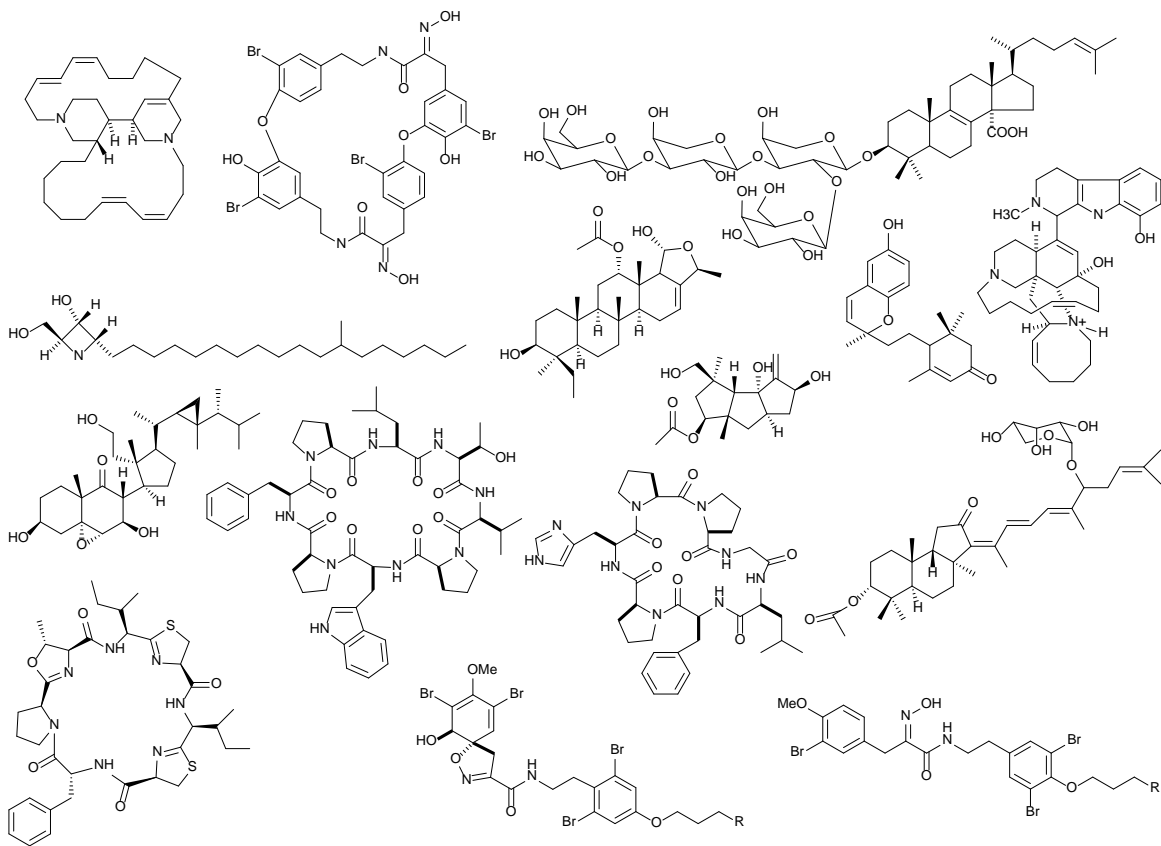
Marine Microbial Diversity



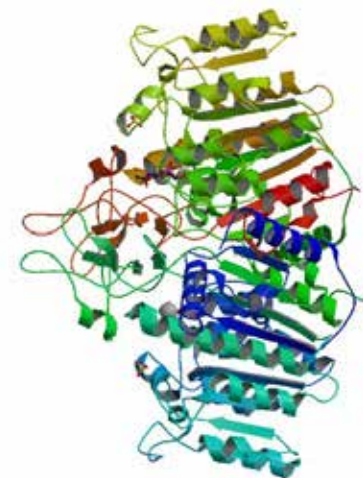
Taxonomic 'space'

Marine and terrestrial species clearly separated.

Biological Diversity = Chemical Diversity



Small Molecules



Biomolecules

Marine and Terrestrial Chemical Diversity are Different

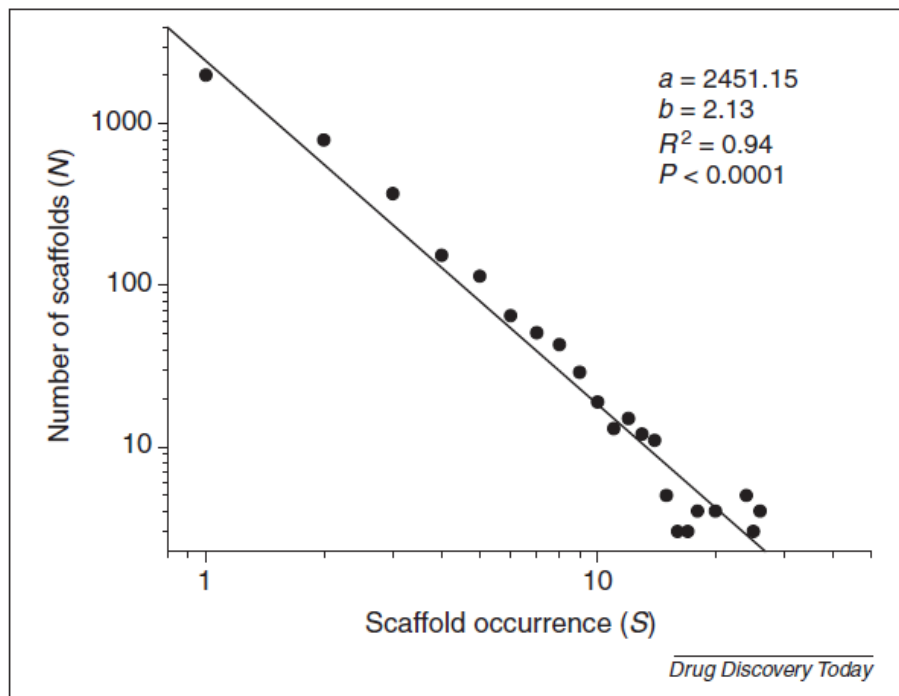


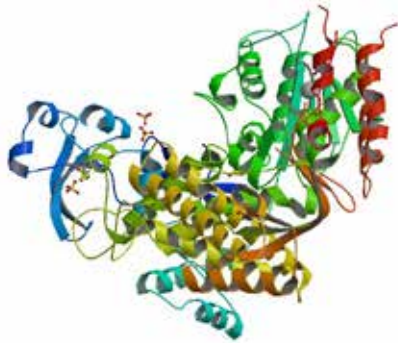
FIGURE 1

Power-law behavior of novel scaffolds in marine agent space. The number of scaffolds (N) decays with the increase of their occurrence in agent space (S) and follows the equation $N = aS^{-b}$.

Kong, *Drug Discovery Today*, 2010, 15, 884

- 71% of scaffolds are exclusively marine
- These cover only 30% of marine natural products
- Many marine natural products scaffolds appear only once

Marine Natural Products on the Market



Vent Polymerase



w-3 polyunsaturated fatty acids
for heart disease

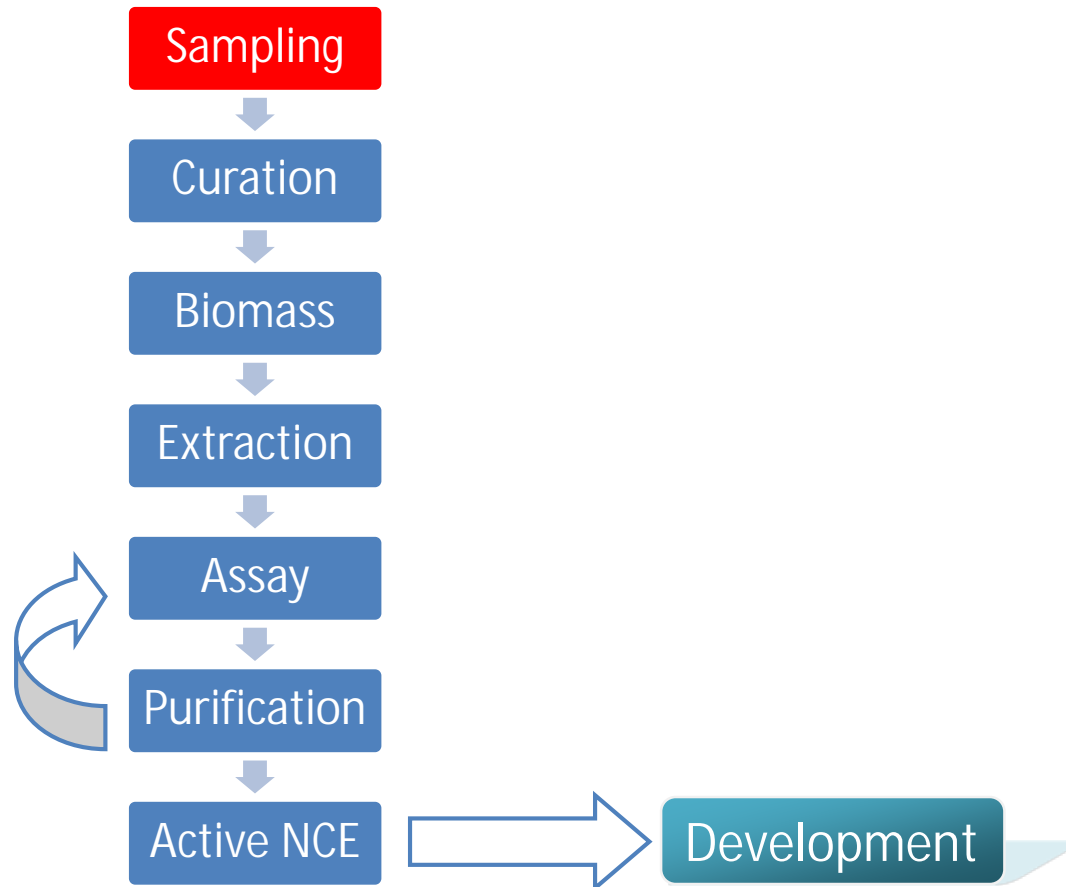


Prialt for pain

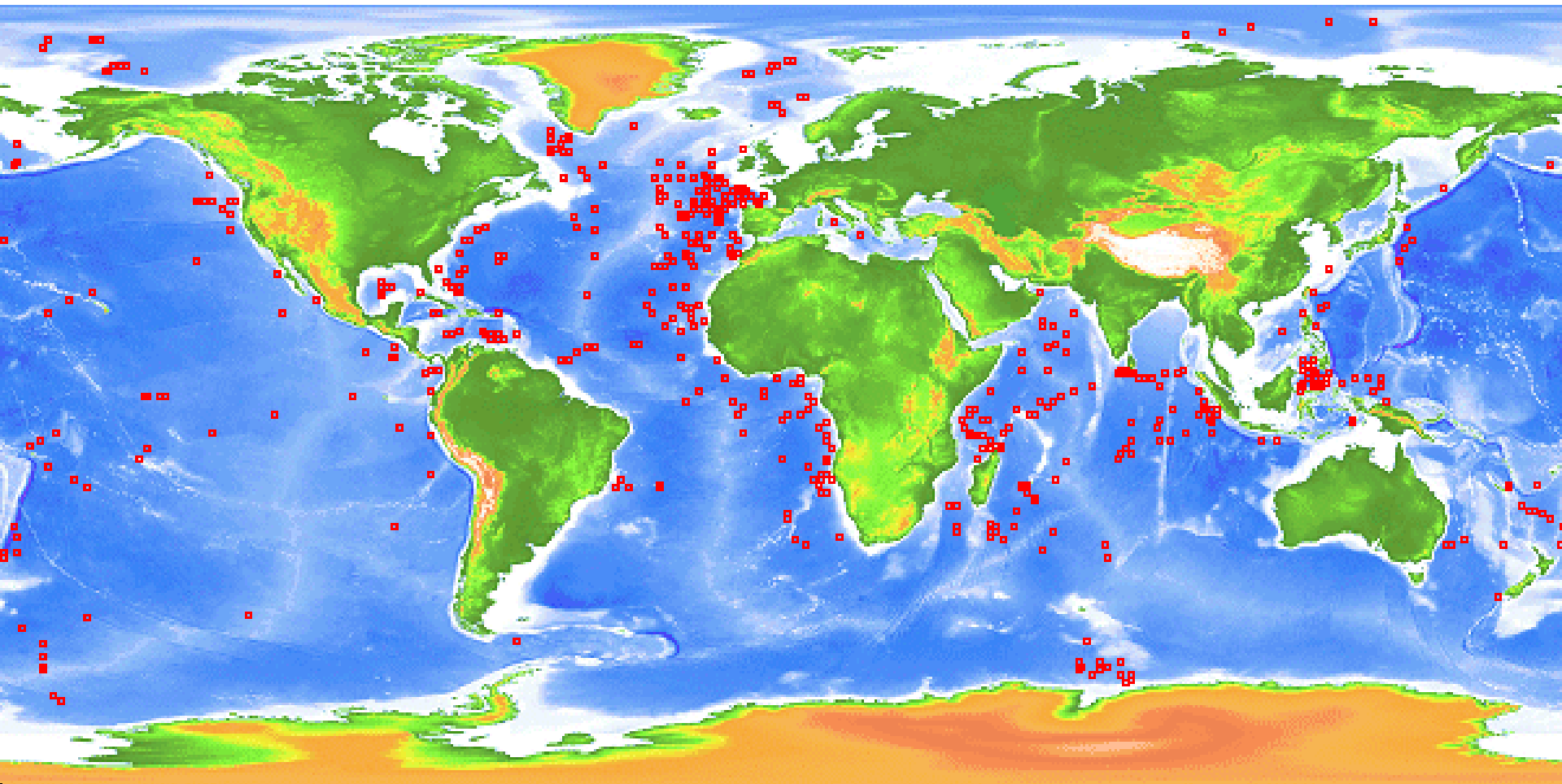


Halaven for cancer

The Marine Biodiscovery Process



Little Sampling Done Beyond 3000 m



Research Vessels



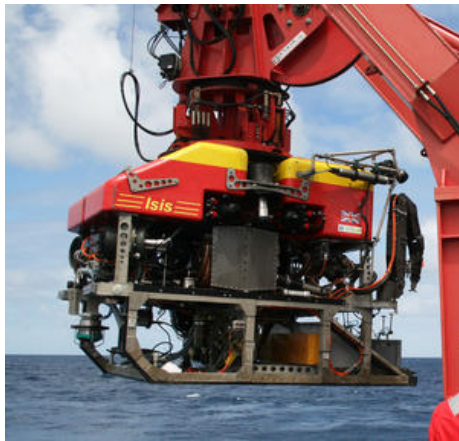
RRS Discovery (UK)



Chikyu (Japan)

- 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
- Shared resources and bartering systems operate to optimise usage

Submersibles



ROV Isis (UK)
(6500 m)



Shinkai (Japan)
(6500 m)



ROV Nereus (US)
(11000 m)



Deepsea challenger (US)
(11000 m)

Data Logging for Research Cruises

JAMSTEC Data Search Portal

Map Tools

- Zoom In
- Zoom Out
- Pan
- Global View
- Previous View
- Initialize

Search Tools

- Quick Search
- Advanced Search
- Clear Selection

Map Information

40.276

137.26 -165.2

6.6423

Latitude: 30.023

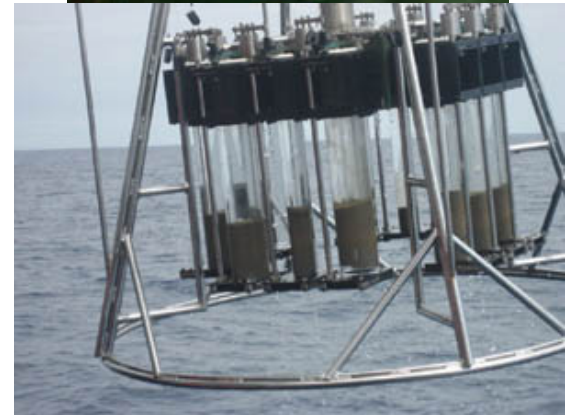
Map created with ArcIMS - Copyright (C) 1992-2013 ESRI Inc.

Data Selection

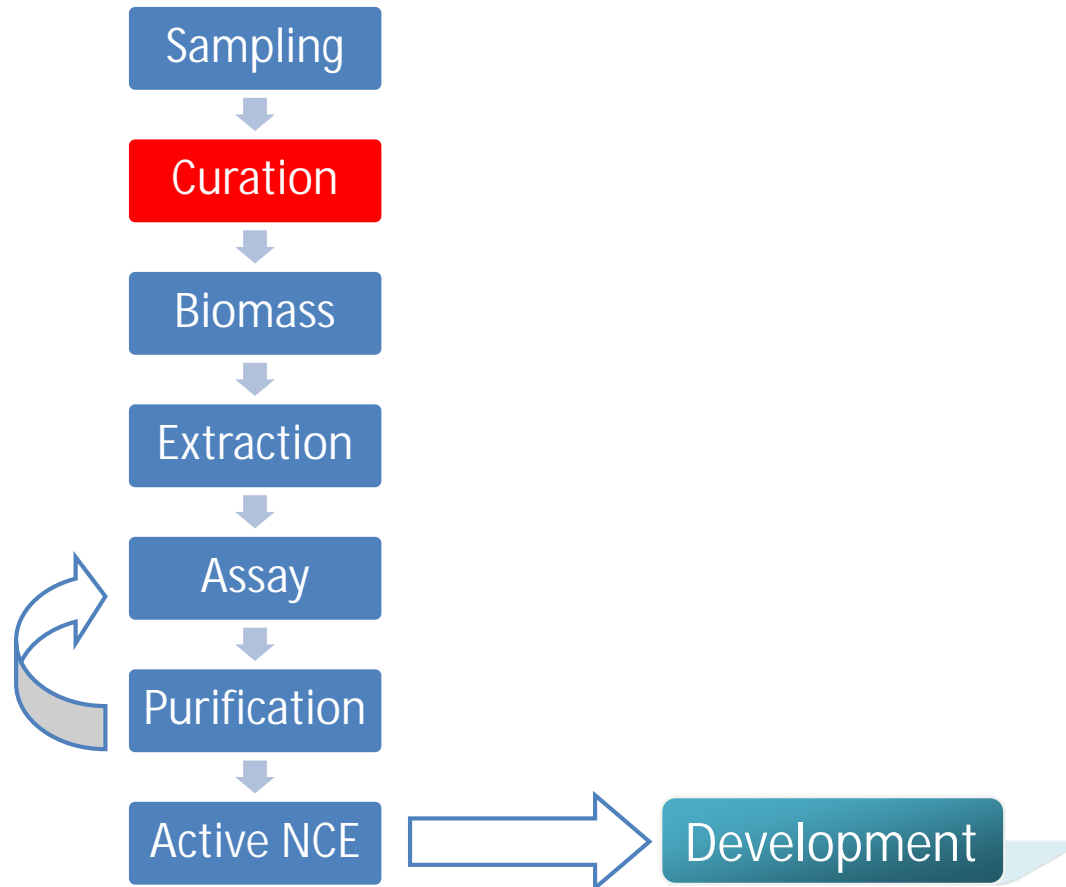
All Clear Refresh

- Bottle Sampling
- Bathymetry
- Cruise Track
- CTD
- Dive Point
- Deep-Sea Images
- Gravity Line
- Holes Drilled by CHIKYU
- LADCP
- Land Atmospheric Composition
- Land Solid Earth
- Land Vegetation
- Land Weather
- Land Station (other)
- Magnetics Line
- Marine Biological Sample
- Ocean Meteorology Line
- Ocean Time Series
- Primary Production
- Rock Sample
- Sea-Bottom Mooring
- Sediment Core
- Subbottom Profiler
- (Sub)Surface Mooring
- Underway ADCP
- Underway pCO2

Sampling Devices



The Marine Biodiscovery Process



Sample Data and Storage

Metadata may include

- I Location
- I Depth
- I Temperature
- I Salinity
- I pH
- I Oxygen content
- I Seafloor conditions

Sample storage

- I Ambient temperature
- I Cooler (4°C)
- I Freezer (-20°C)
- I -80°C Freezer
- I Liquid nitrogen (-196°C)
- I Formaldehyde
- I Ethanol
- I DNA/RNA preservation liquids

Are Current Repositories Sufficient?

Further sampling is essential for the following reasons:

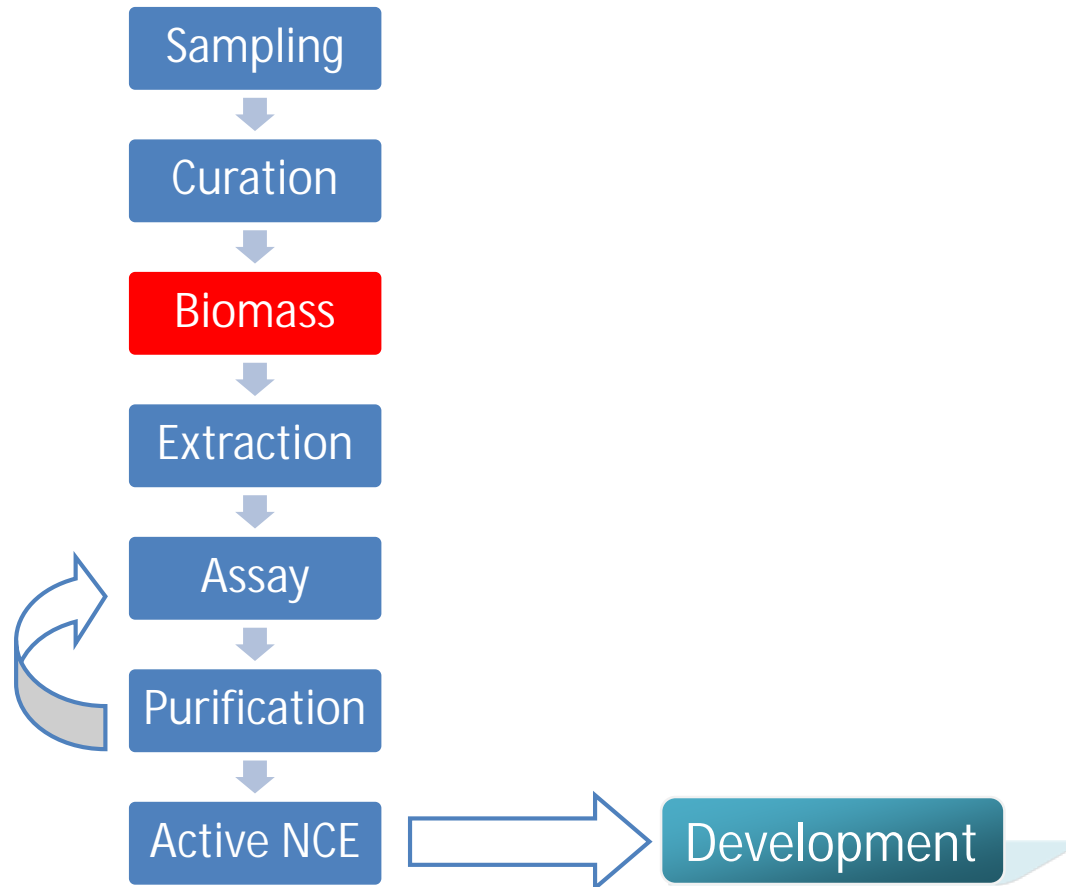
- Origin may be difficult to ascertain (eg location, depth, collector, date, ownership etc). A minimal data set is imperative.
- IP status not clear
- May not have been collected in a way consistent with proposed use
- May not have been stored correctly to ensure sufficient quality for proposed use.
- The amount of material may not be sufficient for proposed multiple uses.
- Very few locations have been sampled so repository may not be representative of ABNJs.

An ABNJ Sample Biorepository?

If previous points can be addressed then such a repository might be viable

- The rules for terrestrial biorepositories may not apply for their marine equivalent.
- Much information on biorepositories is based on situation with respect to plants where samples can be propagated.
- A deepsea core sample or a marine macroorganism collected on one sampling expedition is finite.
- Microbes can be cultured but again culturing a microbe from a hydrothermal vent is quite different from culturing a microbe from a terrestrial habitat.

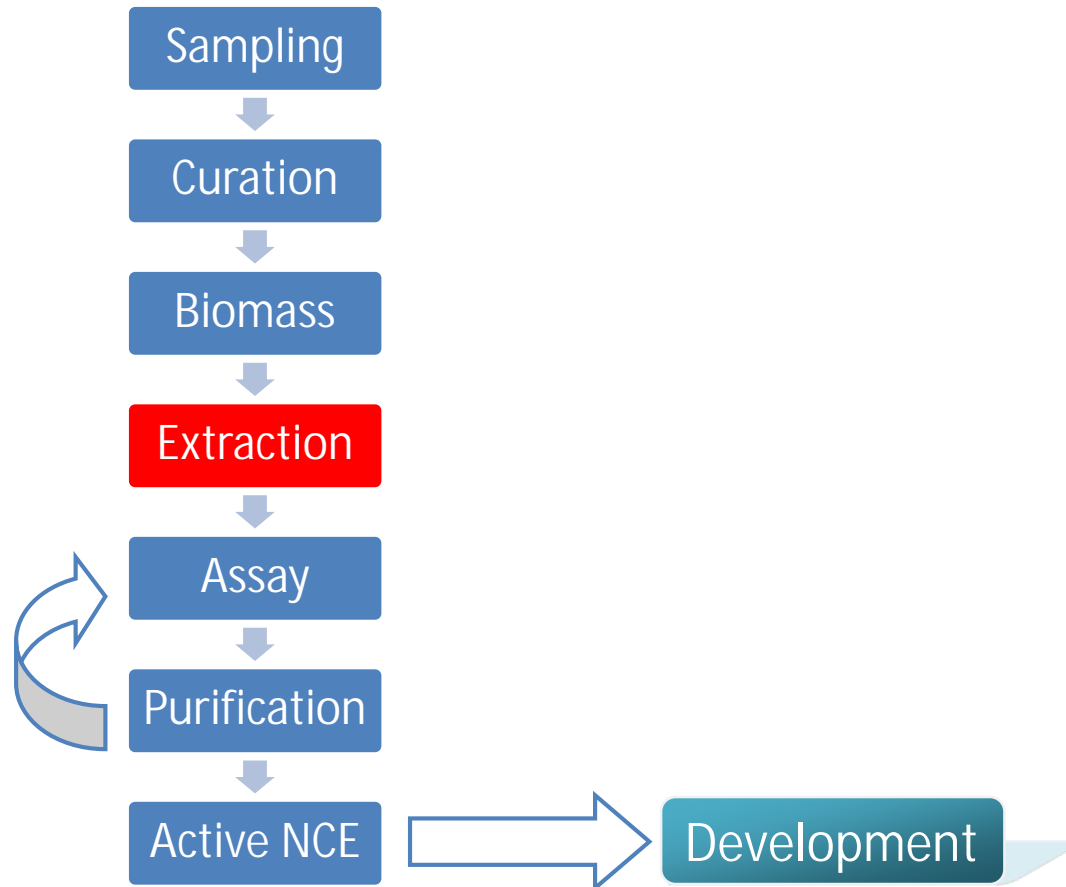
The Marine Biodiscovery Process



Biomass



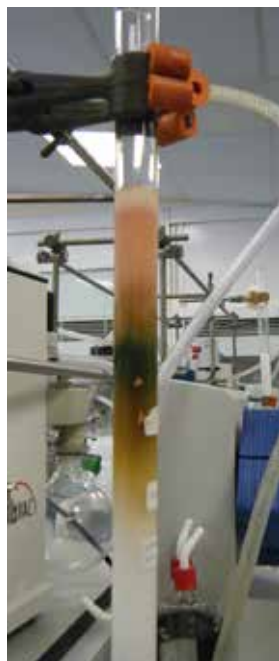
The Marine Biodiscovery Process



Extraction and Purification



Solvent-solvent
partition

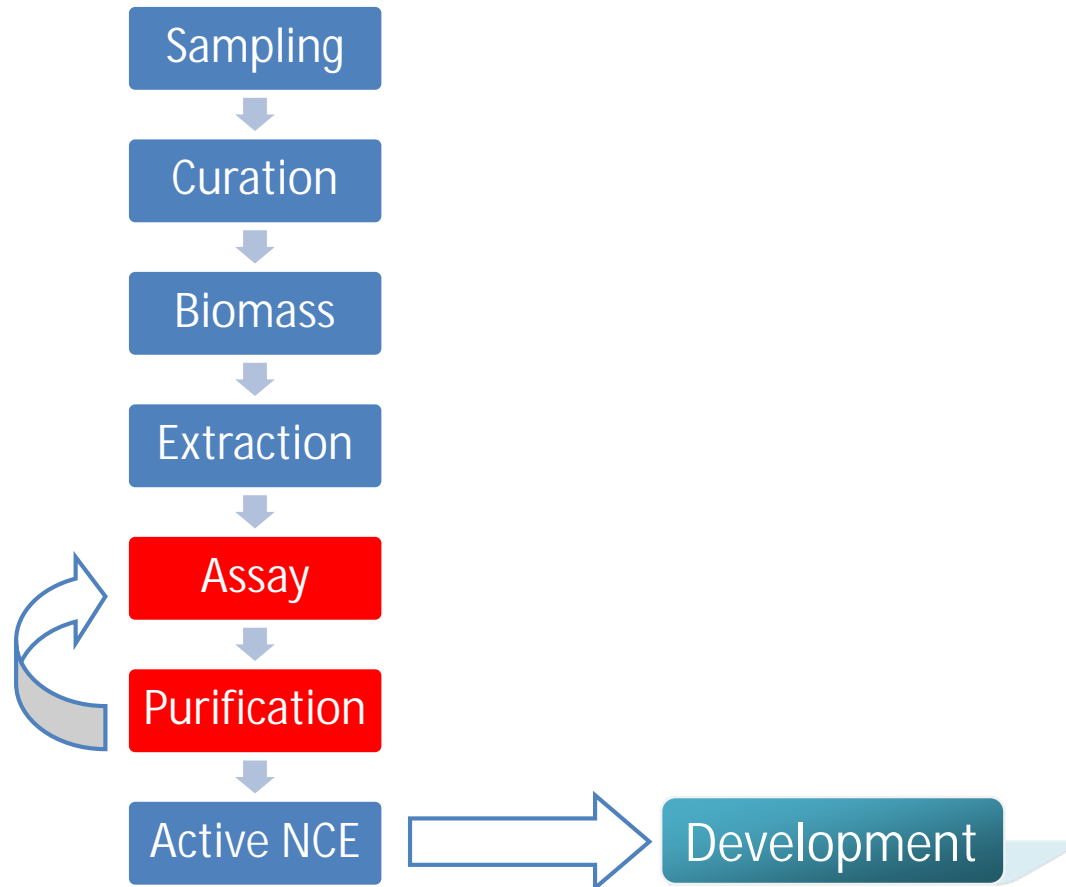


Size-exclusion
chromatography

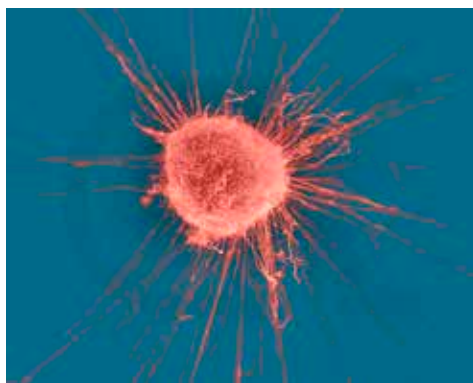
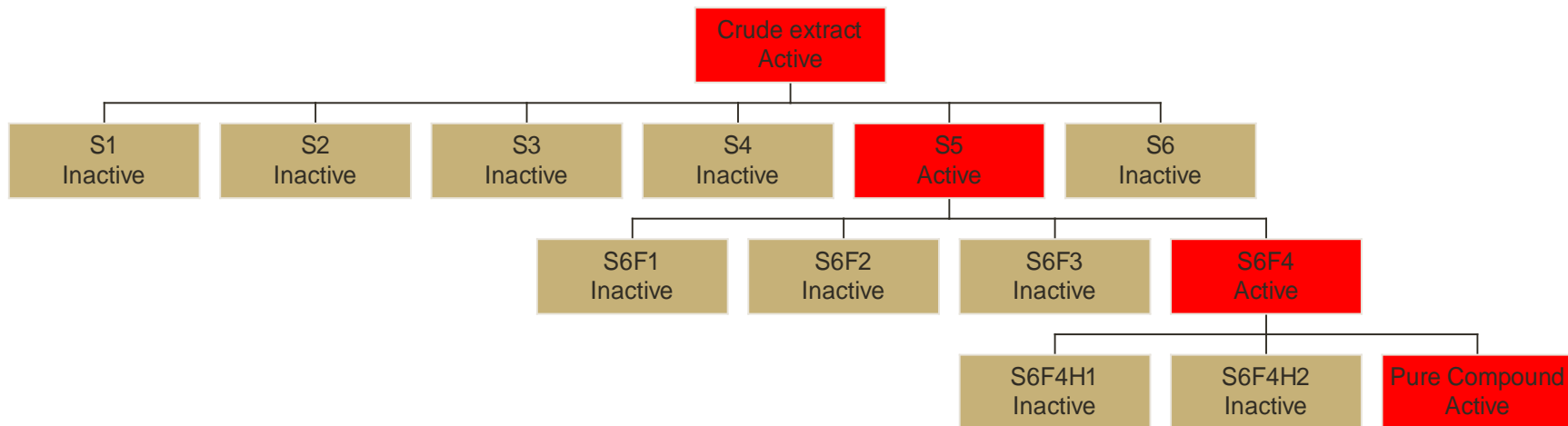


High performance
Liquid chromatography

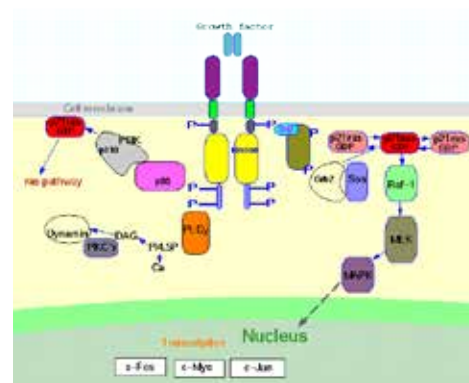
The Marine Biodiscovery Process



Assay

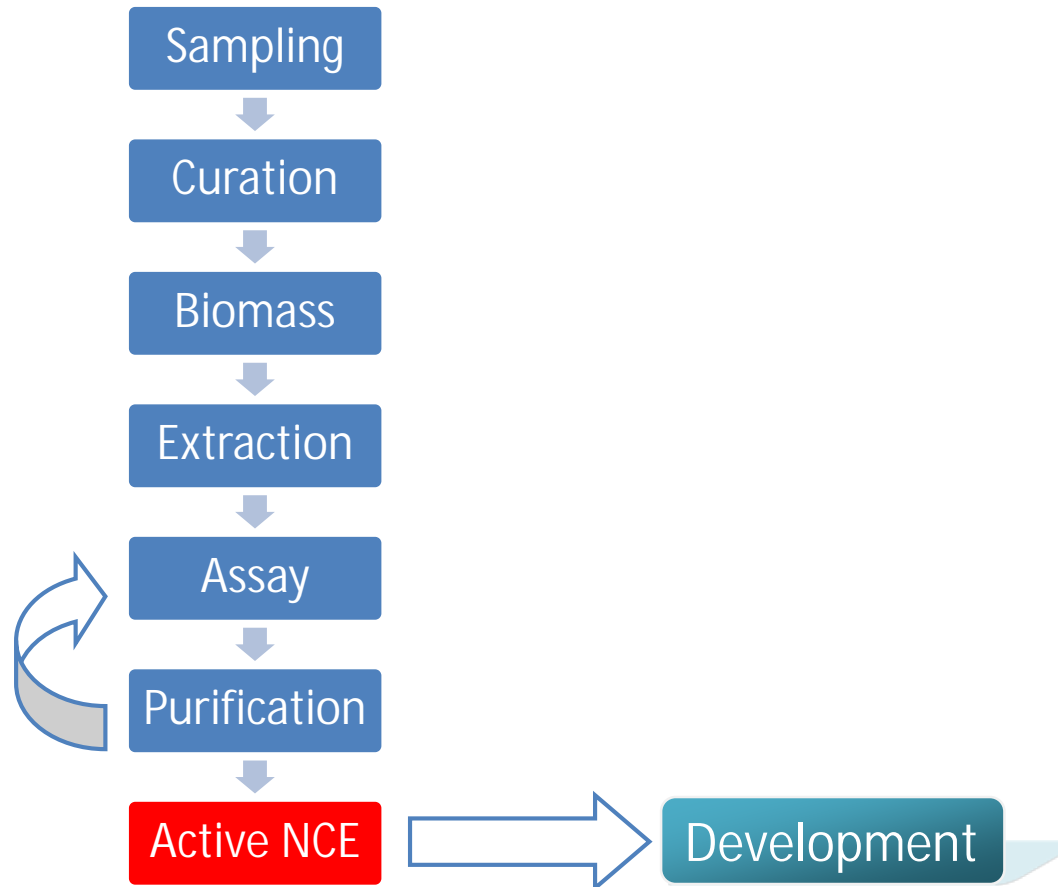


Cell based

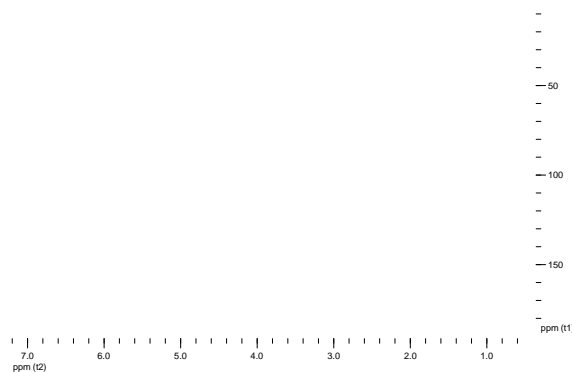


Enzyme based

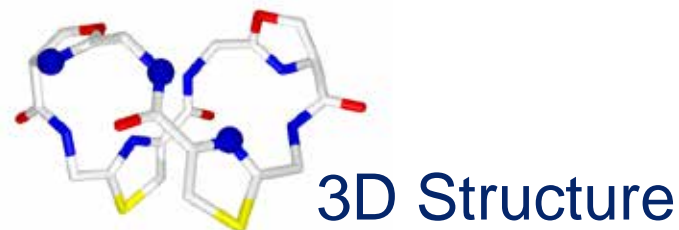
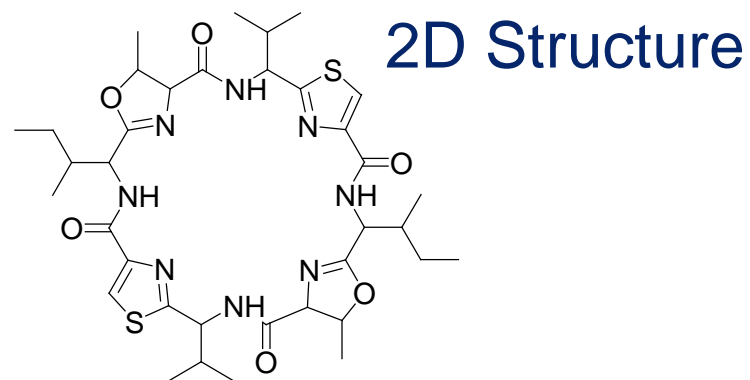
The Marine Biodiscovery Process



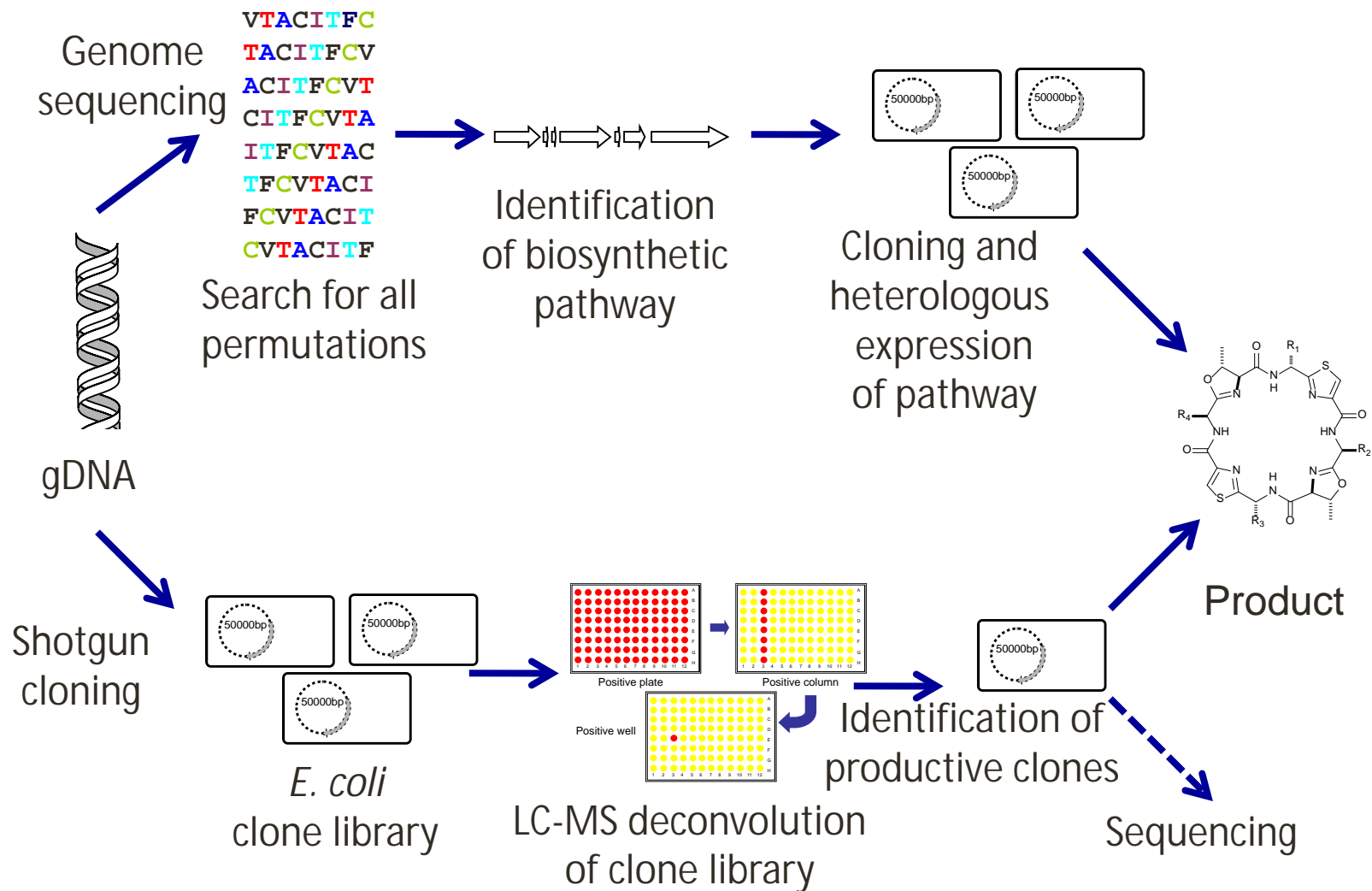
Structure Determination



Spectroscopic data

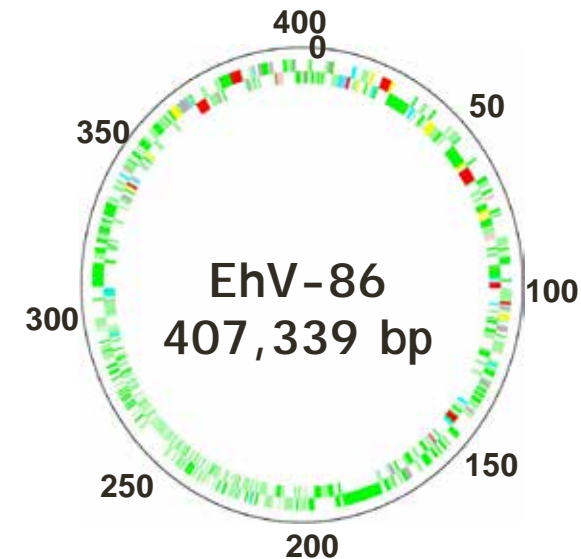


Metagenomic Approach



Bioinformatic Databases and the Metagenomic Approach

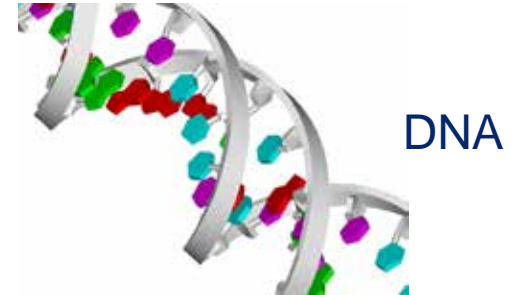
- Who acquired/deposited the data and with what authority?
- Who has access to the data?
- Is genome and metagenome information sufficient?
- Many genes found in marine species are not in the current bioinformatic databases
- The function of many of these genes cannot be determined without laboratory work
- Difficulty in cloning genes of marine origin
- Lack of suitable tools (vectors/hosts)



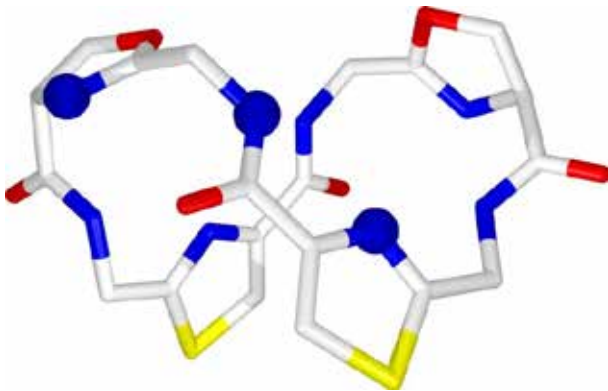
Gene Synthesis

GATTACAGGACGCTT
ATTTTTCGACGATGC
TTGGGGAAATGCAAA
GATTCAGCTAAAGTC

Gene sequence



Protein



Molecule

PHARMASEA

