



The Marine Biodiscovery Pipeline

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- Member of the governing board of the Industrial Biotechnology Innovation Centre

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

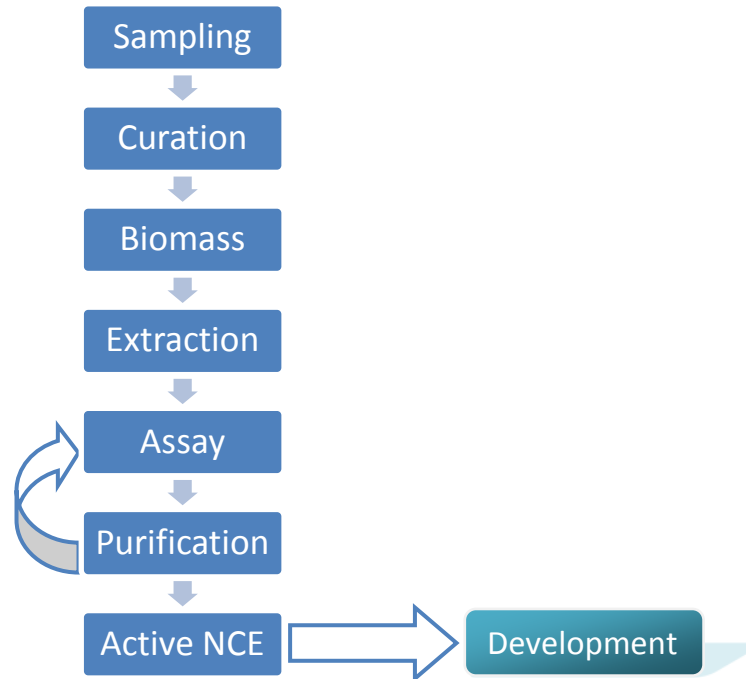
Materials: new properties

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.



PharmaSea: Increasing Value and Flow in the Marine Biodiscovery Pipeline

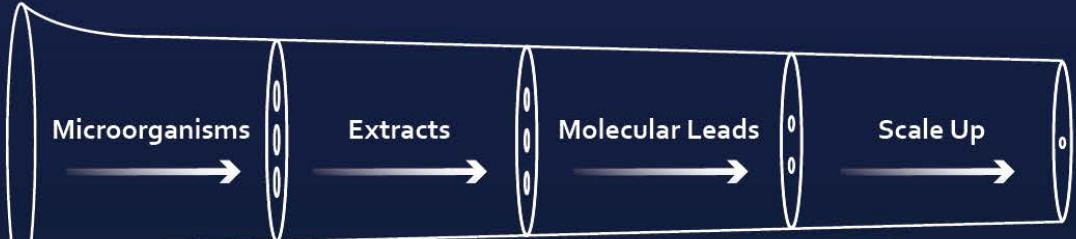


45%
From existing partner collections



55%
New samples from cold/hot/deep habitats

Up to -6,000 metres



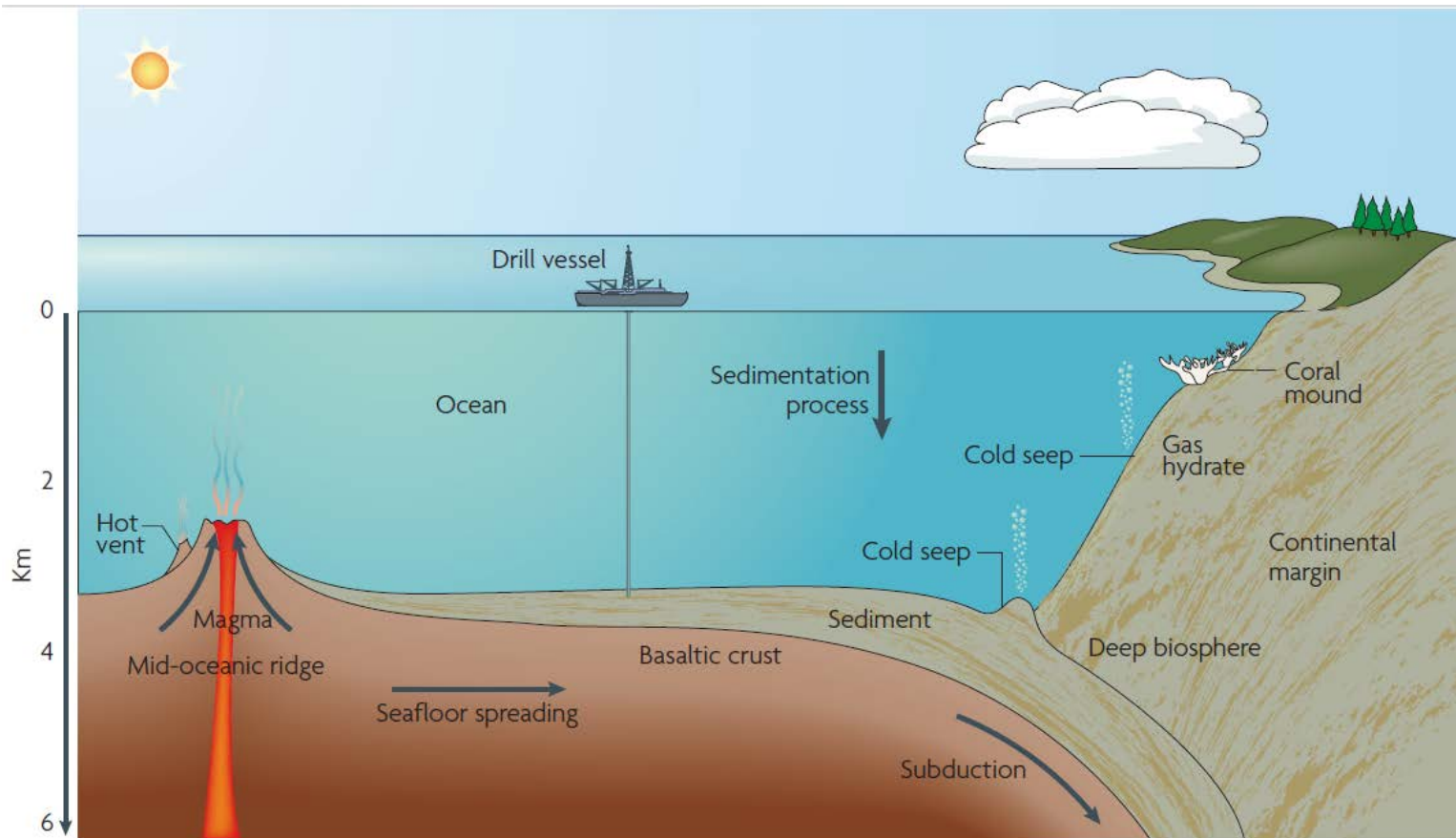
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Drug Leads

Screening	Screening	Screening
Microbial Library	Extract Library	Molecular Families
2,500	18,000	115
>1,200	>11,000	starting.....

Progress:

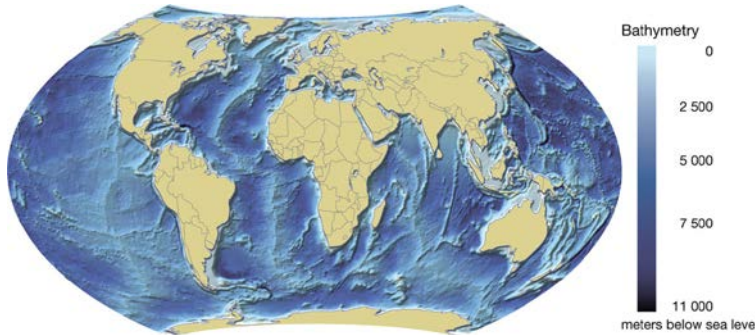
Why Marine?

Diversity of Habitat



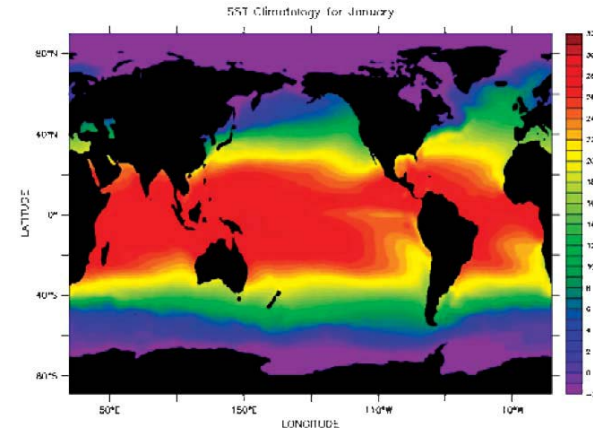
Jørgensen *Nat Rev Microbiology*, 2007, 5, 770

Extreme Marine Environments



Deep Oceans

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

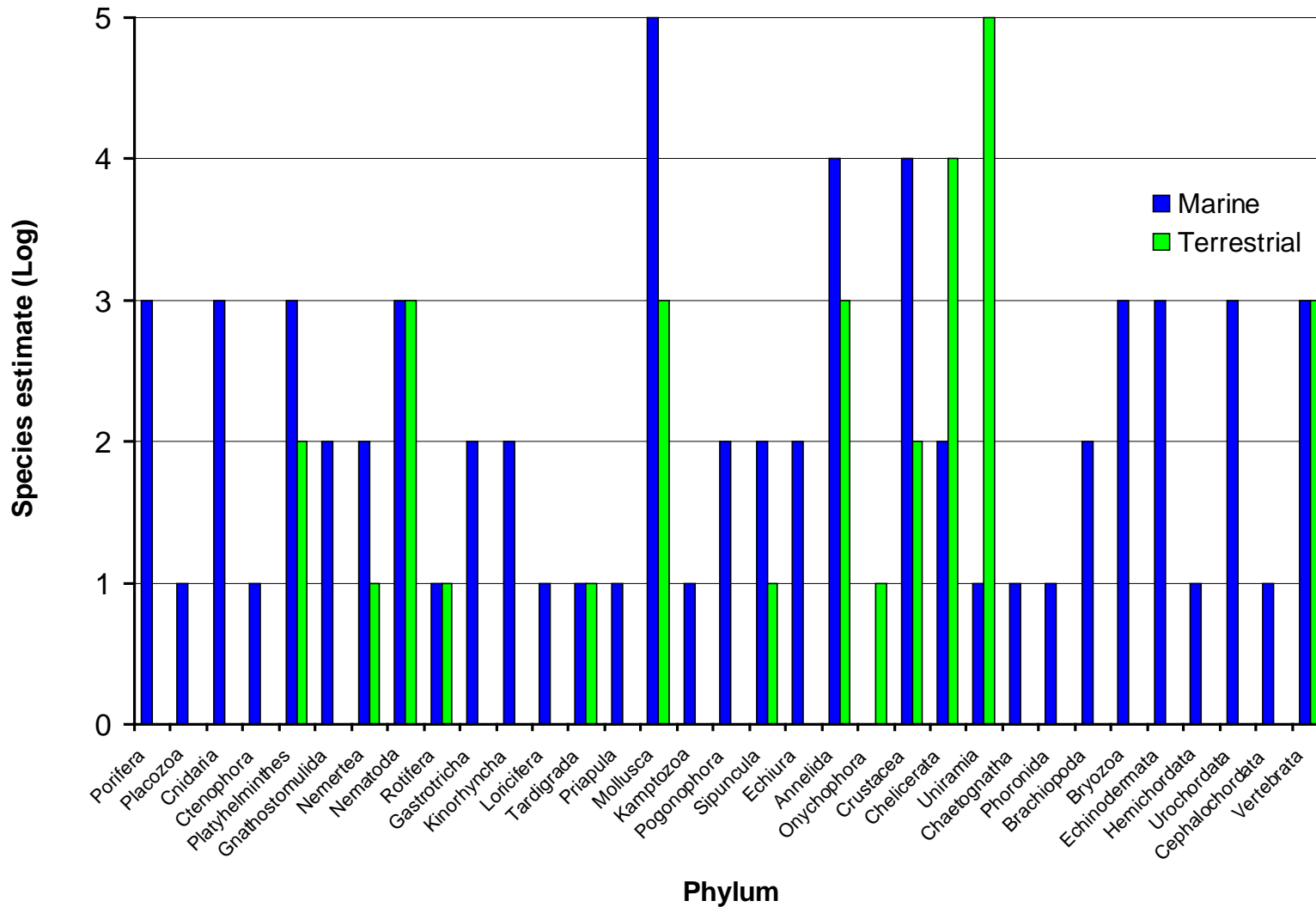


Cold Oceans

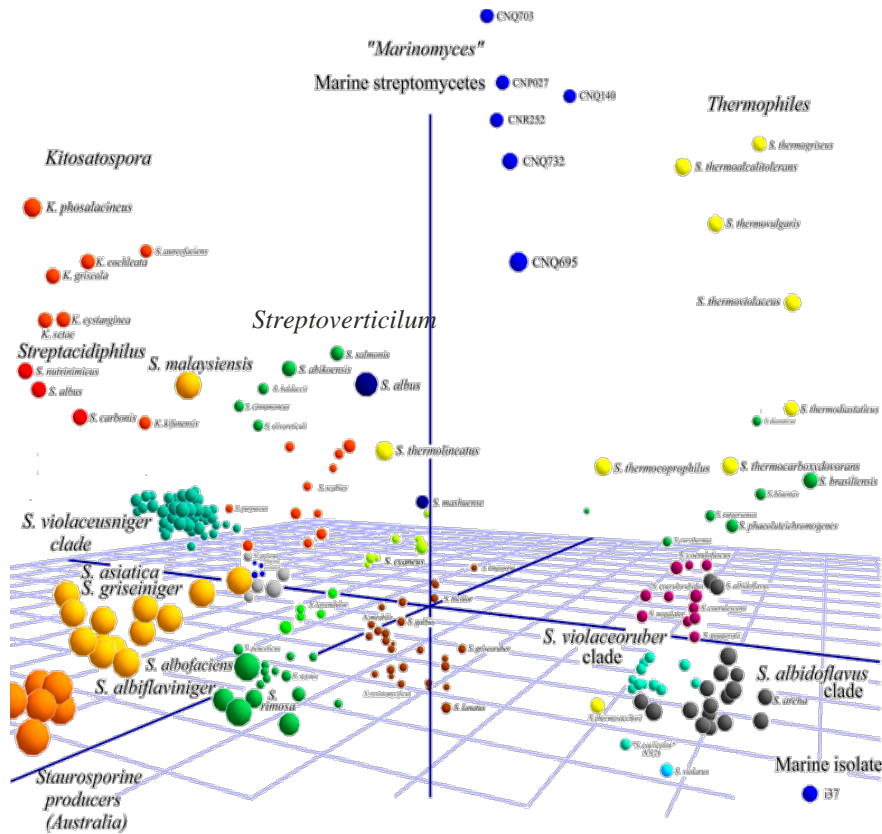
Thermal Vents



Marine Animal Biodiversity



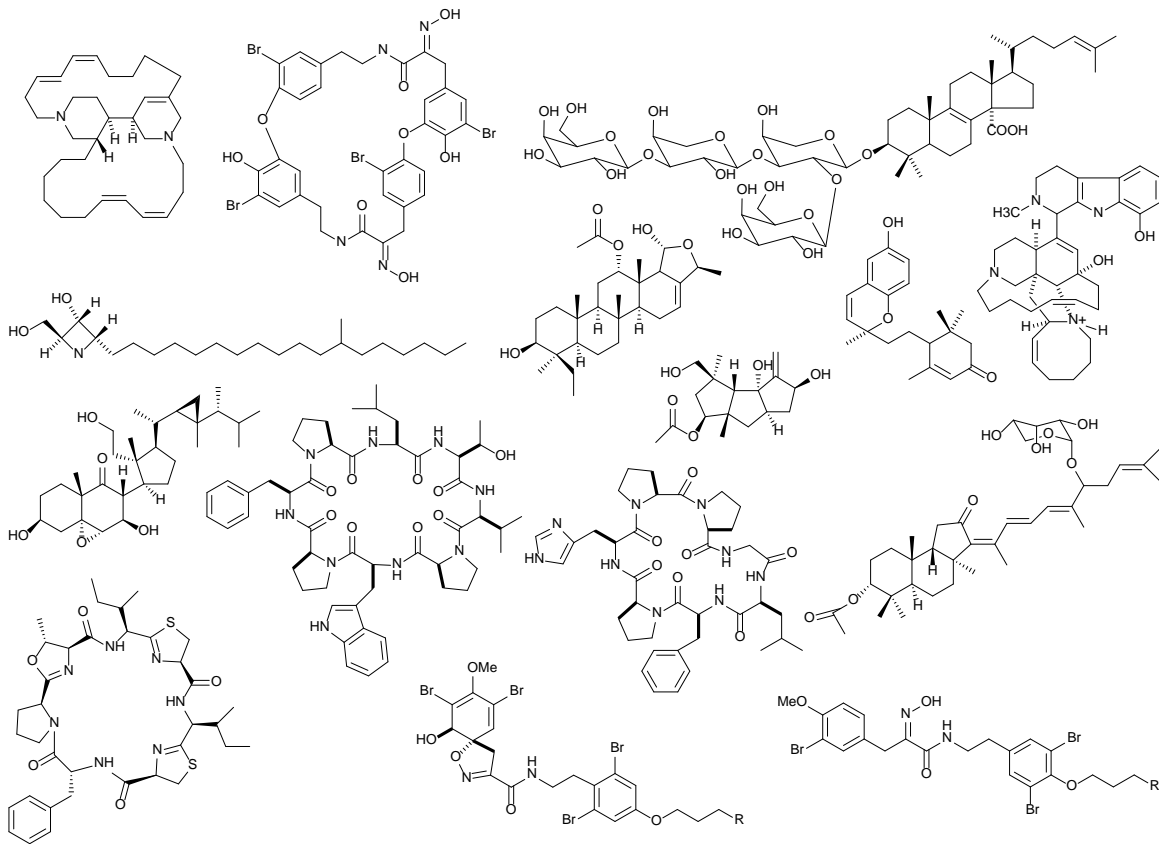
Marine Microbial Diversity



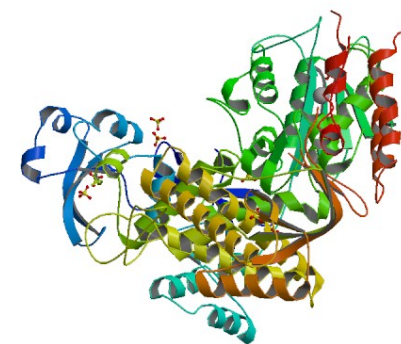
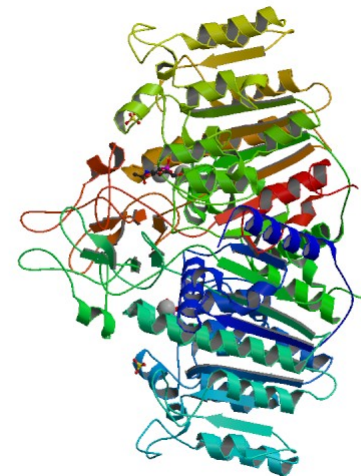
Taxonomic 'space'

Marine and terrestrial species clearly separated.

Biological Diversity = Chemical Diversity



Small Molecules



Biomolecules

Marine and Terrestrial Chemical Diversity are Different

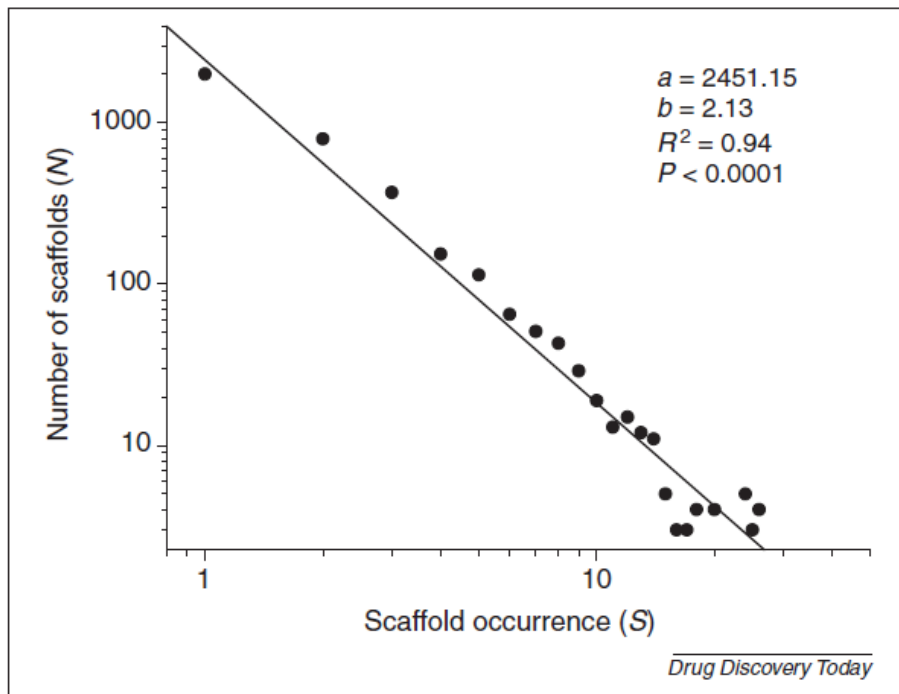


FIGURE 1

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

Origin: Vent bacterium

Production: Recombinant



Priali for pain

Origin: Phillippino cone snail

Production: Recombinant



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

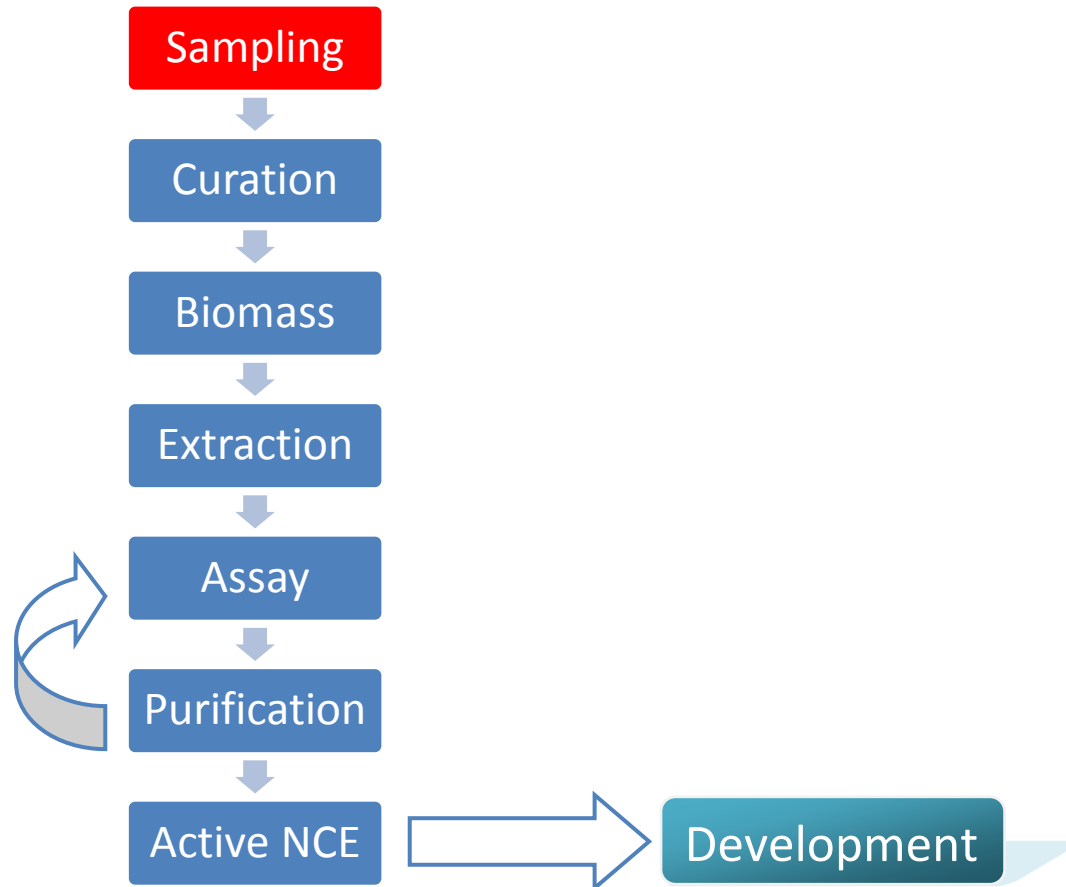


Halaven for cancer

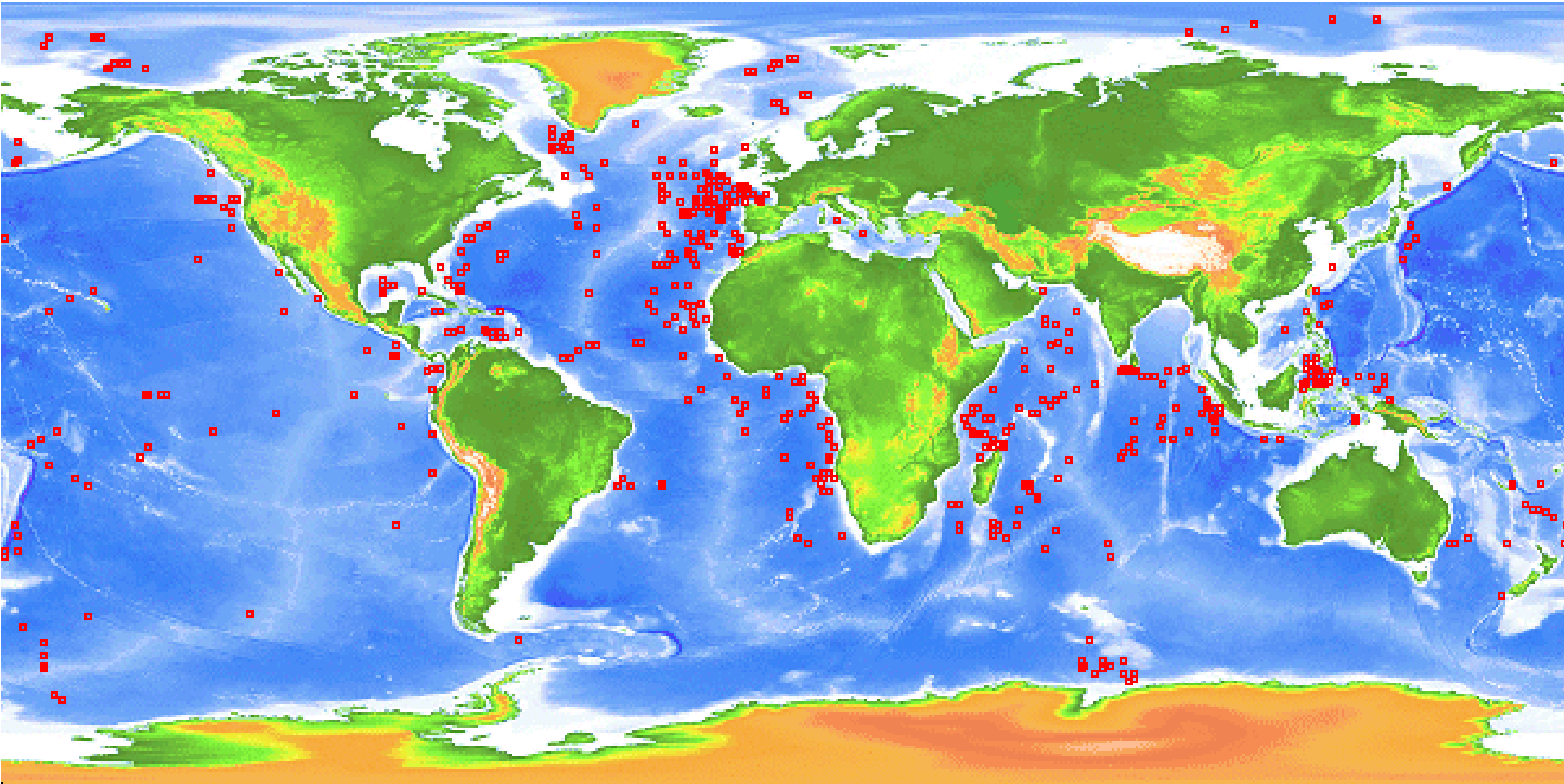
Origin: Japanese deep water sponge

Production: Chemical synthesis

The Marine Biodiscovery Process



Little Sampling Done Beyond 3000 m



Current Cruise Protocols Very Heterogeneous

Application

- Cruise path/stations/equipment.

Award

- Clarification for feasibility/equipment availability.
- Check MPAs not entered.

After Cruise

- Data is logged with central agency – cruise report
- Sample list/locations collected/location stored
- Environmental data/images and video

**No requirement for post cruise data (eg genetic data) to be deposited
Species may not be identified until later, if at all**

Cruise Application

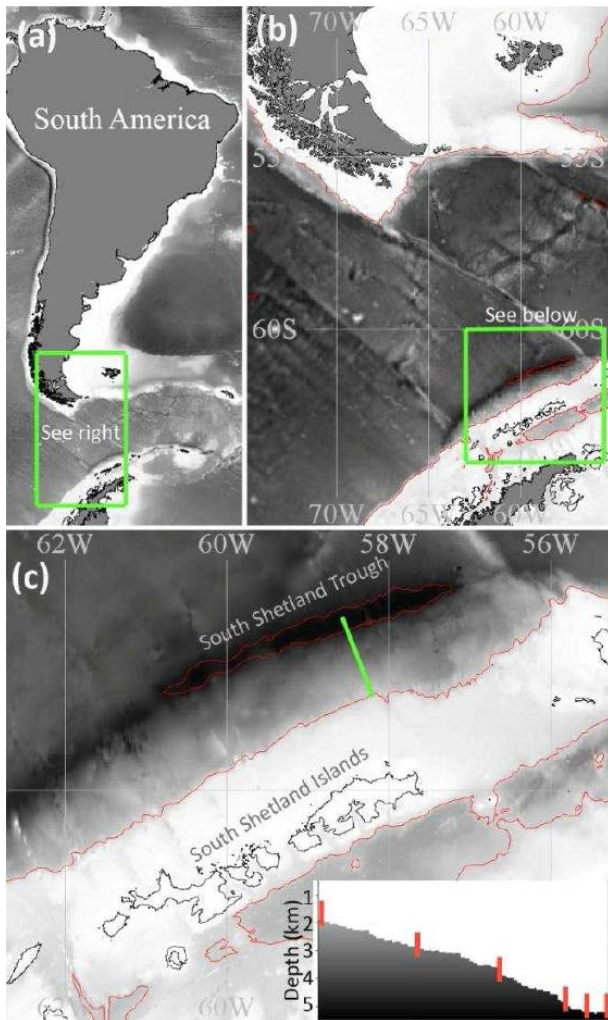


Table 1. Proposed sampling coordinates at each site (by nominal depth)

Nominal Depth (m)	Latitude	Longitude	Distance to next station (nm)
5200	61° 0304S	58° 6927W	3.5
5100	61° 0640S	58° 6481W	2.0
5000	61° 0806S	58° 6246W	2.1
4000	61° 1393S	58° 5316W	7.8
3000	61° 2420S	58° 3869W	6.2
2000	61° 3482S	58° 2949W	36*

Note: * = distance to King George Island

Table 2. Work Programme showing details of 24 stations spanning 6 sampling depths

Station #	Nominal Depth (m)	Gear	Time ¹ (h) [+turnaround time ²]	Total time per event (h)	Total time per depth (h)
Arrive ³	-	-	-	4	
1	5200	Multi-core	3.5 [+1]	4.5	
2	5200	Multi-core	3.5 [+2]	5.5	
3	5200	Box core	3.5	3.5	
5	5200	Piston core	3.5 [+2]	5.5	
5	5200	Piston core	3.5 [+2]	5.5	28.5

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

Alternatives for Collection in ABNJ

Charter Vessels

- Rapid access
- Lower cost
- Dedicated to one task
- No requirement to deposit data

Foundation Vessels

- Different requirements, eg image copyright, open access data etc

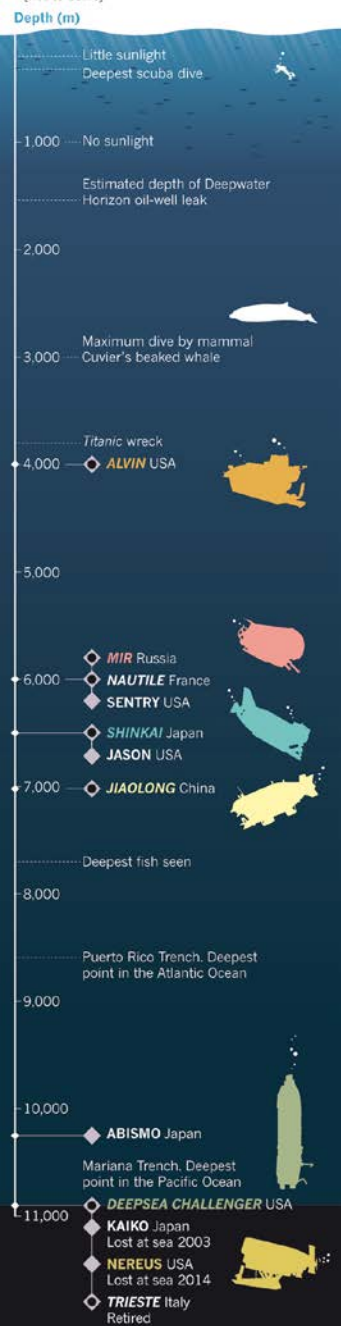
Survey Vessels

- Baseline surveys for companies often carried out by 'neutral' academic institutions
- Data can be used for publication with agreement
- No requirement to deposit data
- Cruise path may be commercially sensitive

INTO THE ABYSS

The world's fleet of deep-sea submersibles has dwindled further with the loss of Nereus.

● Crewed submersible (not to scale) ◆ Uncrewed



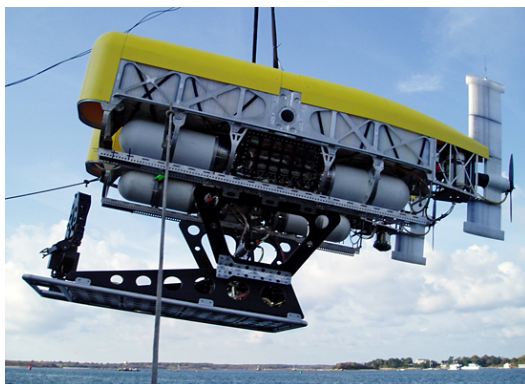
Submersibles



ROV Isis (UK)
(6500 m)



Shinkai (Japan)
(6500 m)



ROV Nereus (US)
(11000 m)



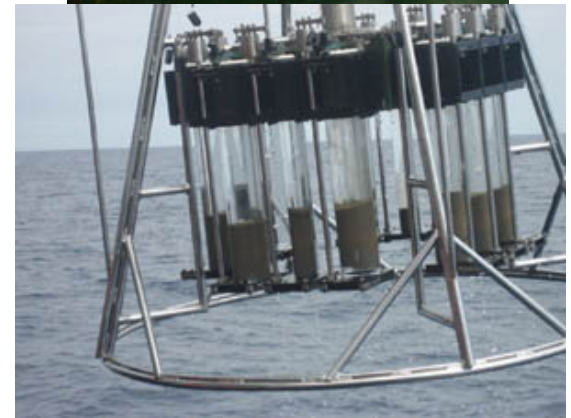
Deepsea challenger (US)
(11000 m)

Data Logging for Research Cruises

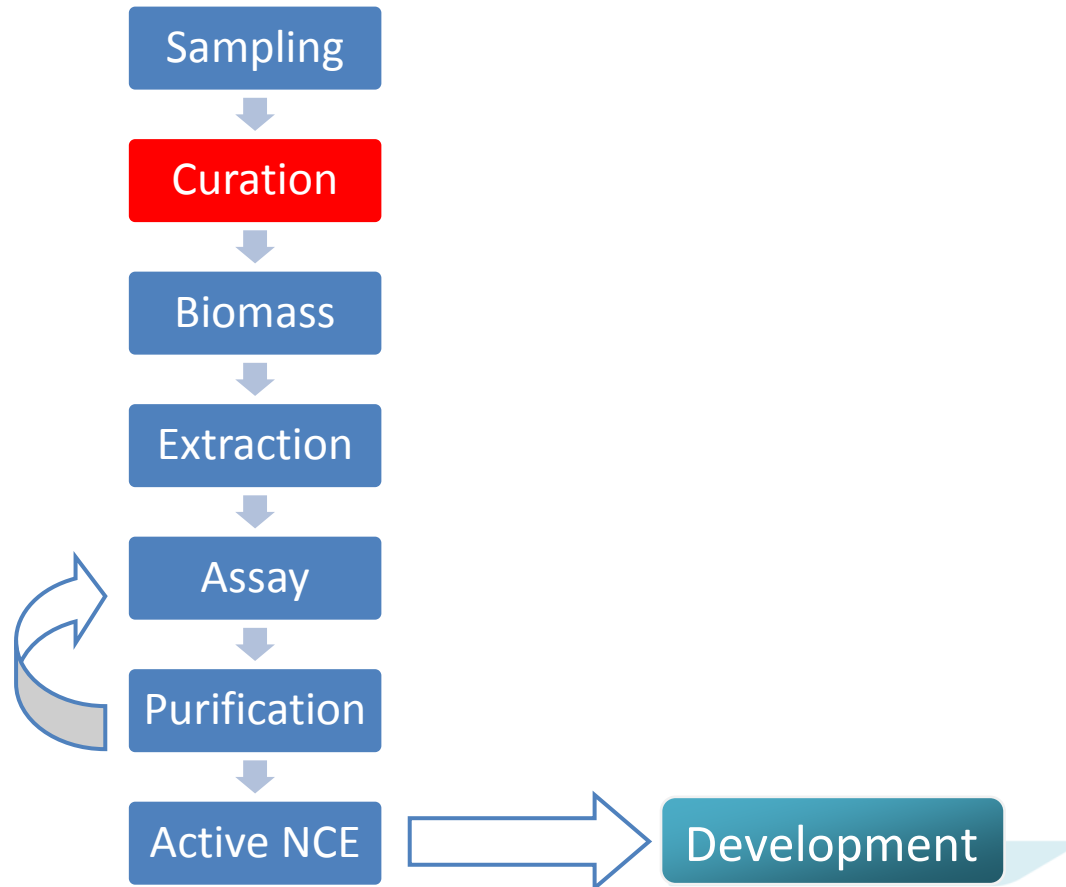
The screenshot displays the JAMSTEC Data Search Portal interface. The main map shows a dense network of yellow and orange lines representing research cruise tracks over a blue ocean background. A small inset map in the top left shows the location of the study area in the Pacific Ocean. The left sidebar contains map tools (Zoom In, Zoom Out, Pan, Global View, Previous View, Initialize) and search tools (Quick Search, Advanced Search, Clear Selection). The bottom left shows map information including coordinates (40.276, 137.26, -165.2, 6.6423) and a latitude field (30.023). The right sidebar is titled 'Data Selection' and features buttons for 'All', 'Clear', and 'Refresh'. Below these buttons is a list of data categories, each with a checked checkbox:

- 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:

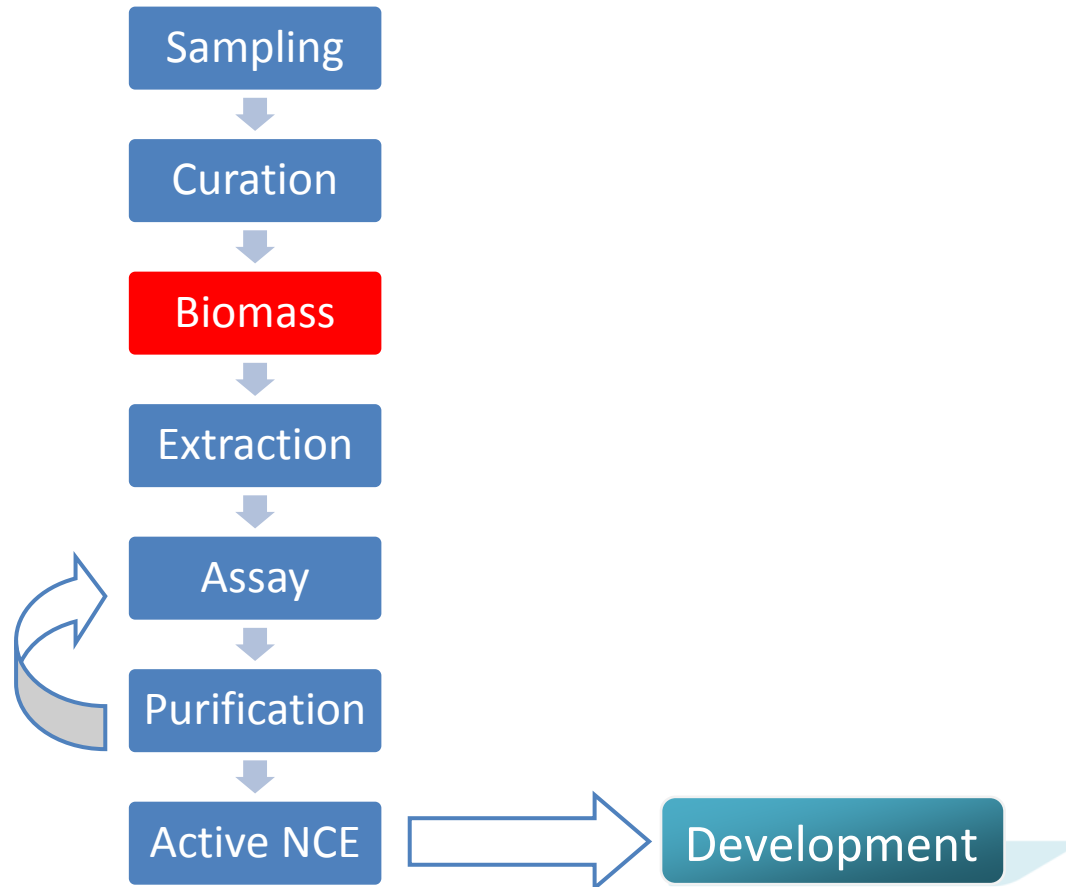
- Origin may be difficult to ascertain (eg location, depth, collector, date, ownership etc). A minimal data set is imperative.
- IP status not clear
- May not have been collected in a way consistent with proposed use
- May not have been stored correctly to ensure sufficient quality for proposed use.
- 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.

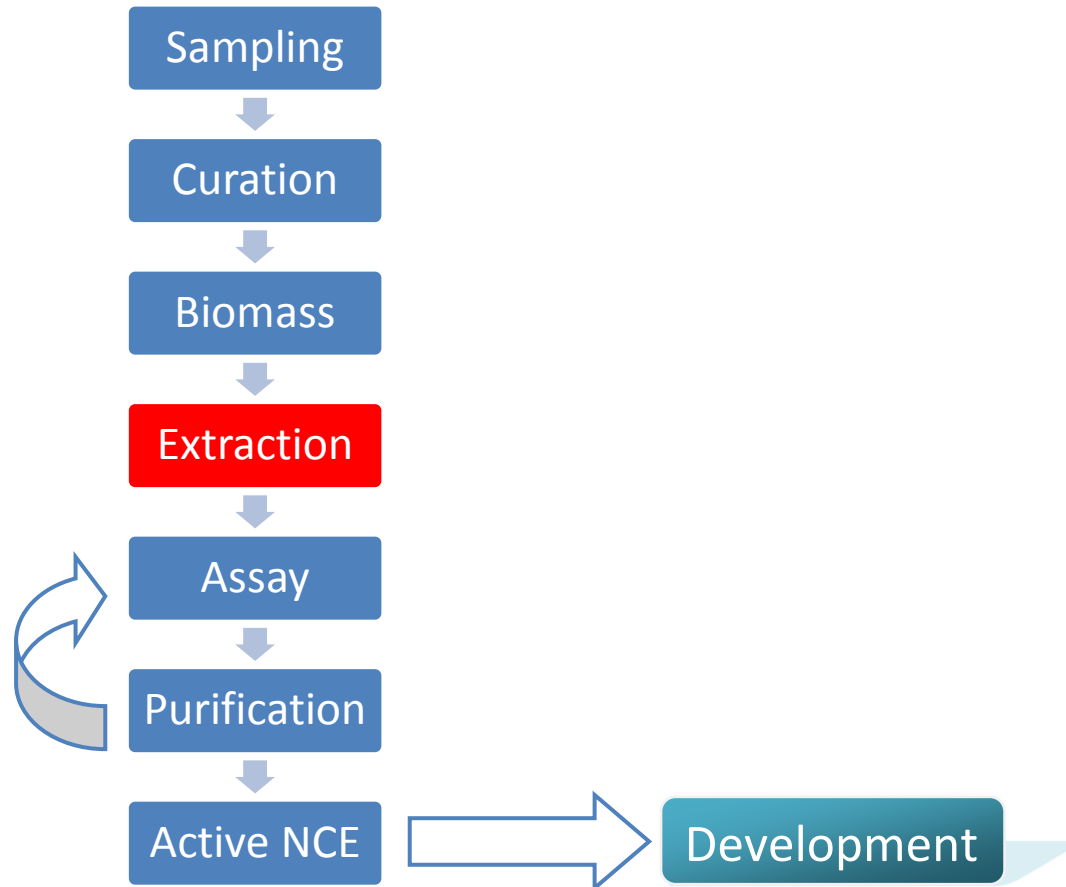
The Marine Biodiscovery Process



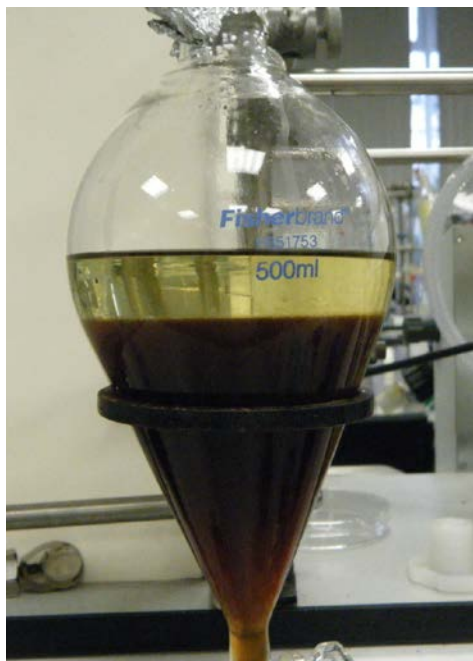
Biomass



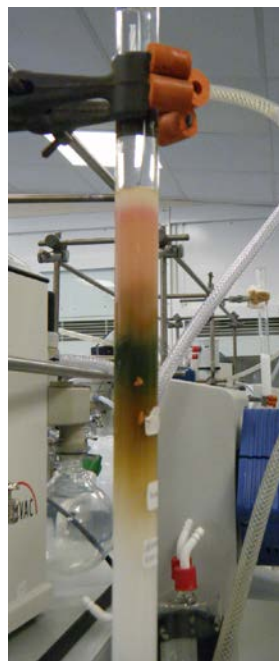
The Marine Biodiscovery Process



Extraction and Purification



Solvent-solvent
partition

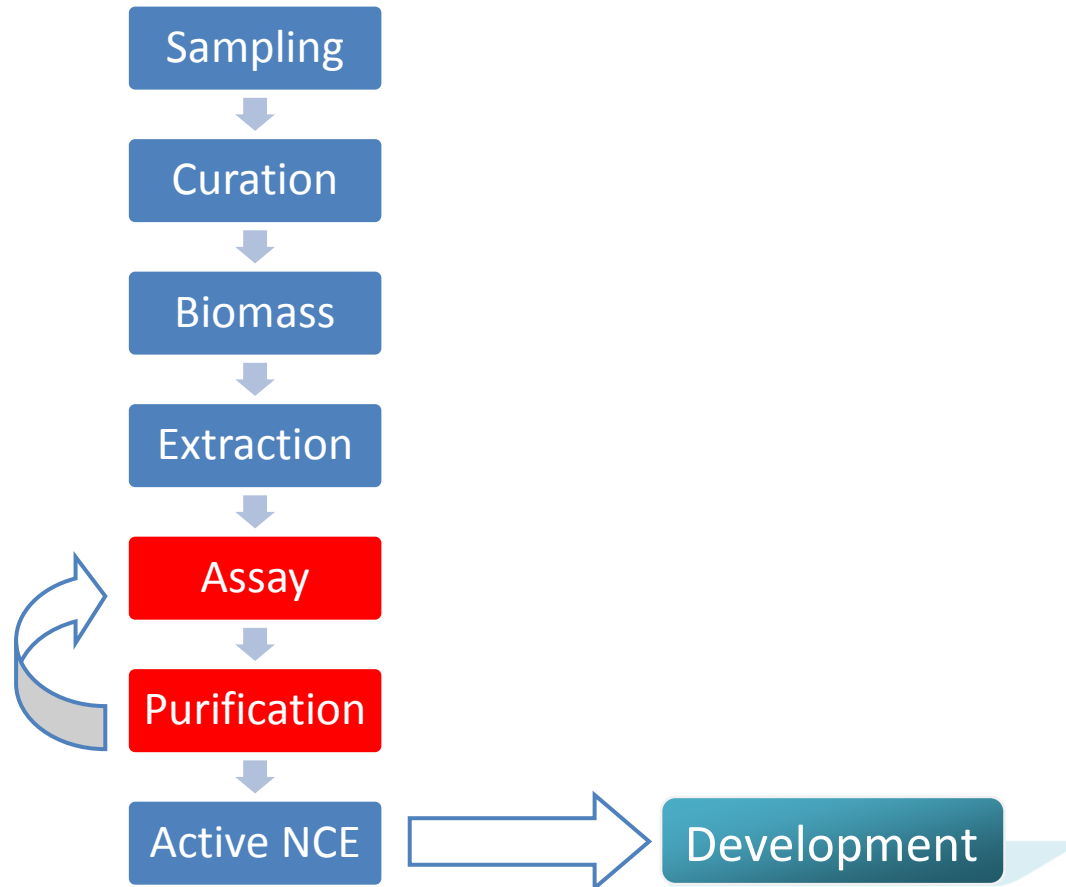


Size-exclusion
chromatography

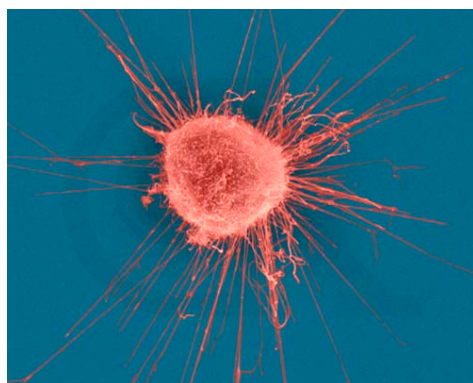
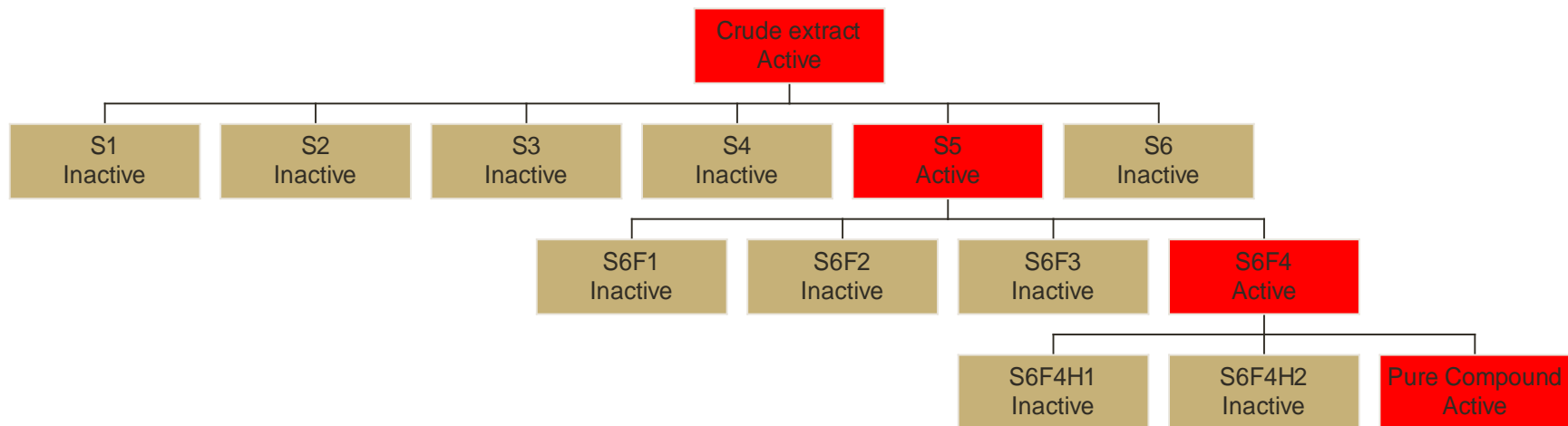


High performance
Liquid chromatography

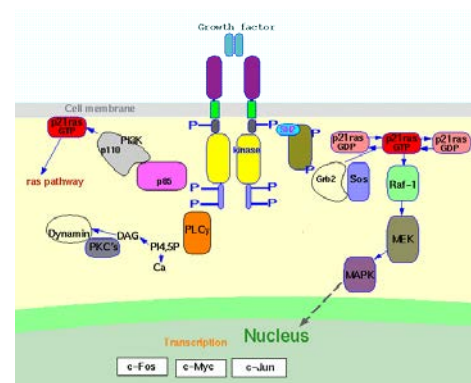
The Marine Biodiscovery Process



Assay

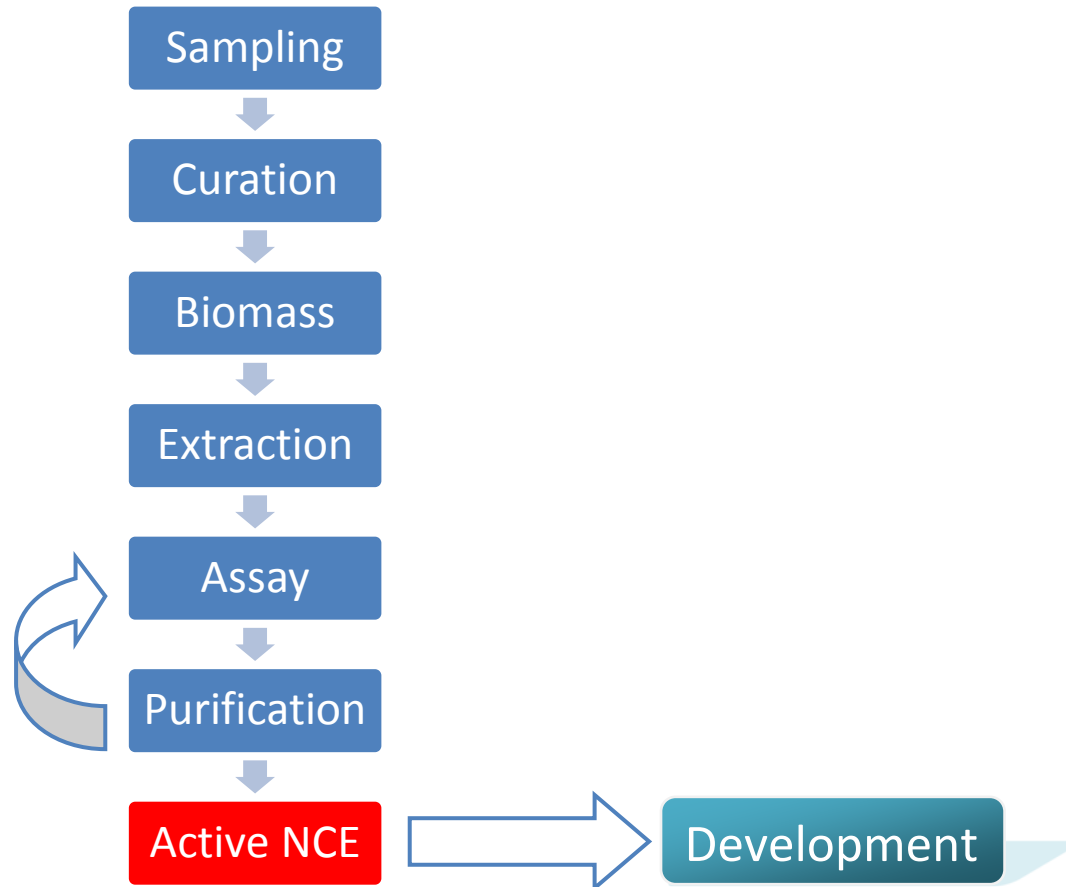


Cell based



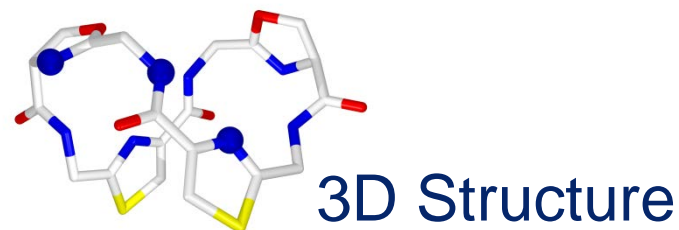
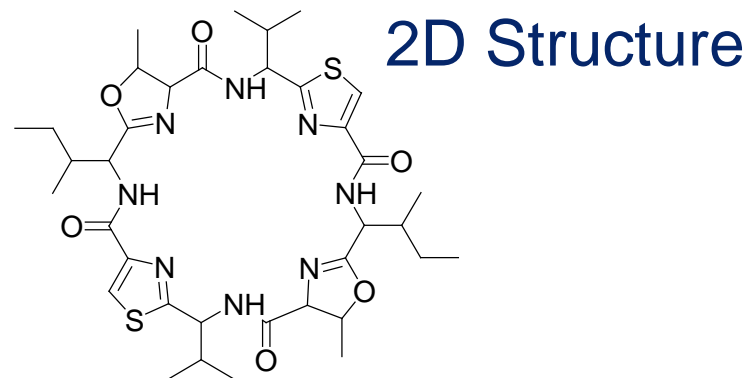
Enzyme based

The Marine Biodiscovery Process

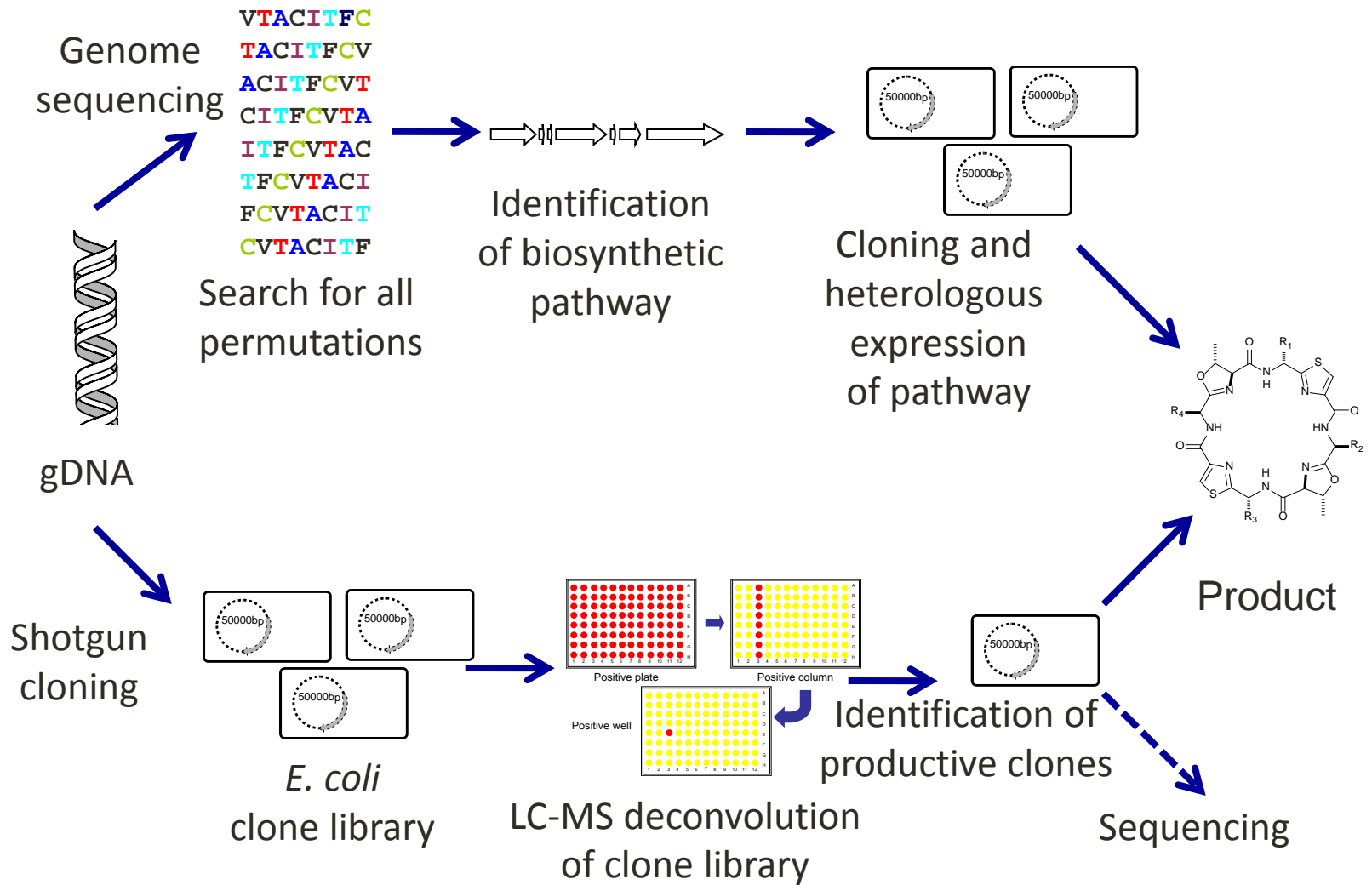


Structure Determination

Spectroscopic data

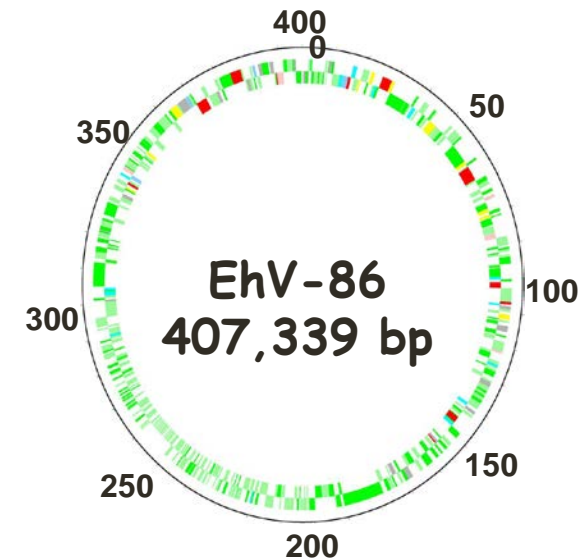


Metagenomic Approach



Bioinformatic Databases and the Metagenomic Approach

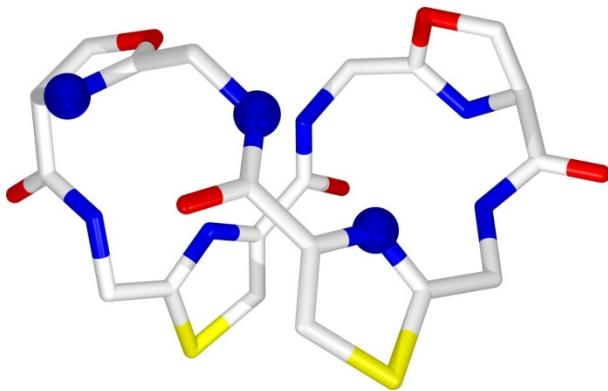
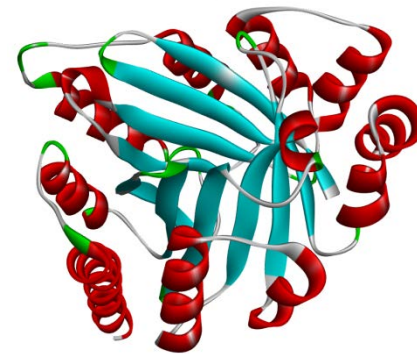
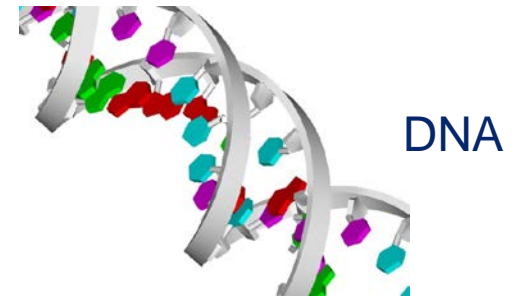
- Who acquired/deposited the data and with what authority?
- Who has access to the data?
- Is genome and metagenome information sufficient?
- Many genes found in marine species are not in the current bioinformatic databases
- The function of many of these genes cannot be determined without laboratory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



Gene Synthesis

GATTACAGGACGCTT
ATTTTTCGACGATGC
TTGGGGAAATGCAAA
GATTCAGCTAAAGTC

Gene sequence



Conclusions

- The marine environment clearly provides an exciting source of new bioactive compounds
- The marine environment and its biodiversity is largely unexplored compared to the terrestrial environment and so cruises and sampling will continue and are necessary for both basic and applied research purposes
- A greater degree of coordination of relevant activities within the scientific community is necessary at a global level
- Capacity building is required to support these efforts

PHARMASEA



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