



The Opportunities and Challenges of Marine Genetic Resources in ABNJ

Professor Marcel Jaspars, FRSE

Director, Marine Biodiscovery Centre; Leader PharmaSea Consortium

University of Aberdeen

Scotland, UK

m.jaspars@abdn.ac.uk

Why use Marine Genetic Resources?

Offers advantage over comparable terrestrial resource:

- Superior performance

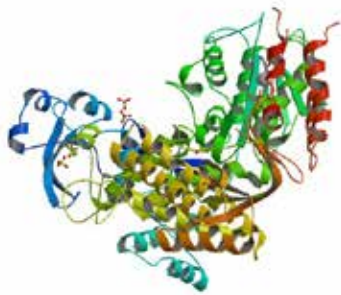
- Better economics

Unprecedented activity in particular application:

- Enzymes: new reactivity/new biotransformation

- Small molecules: novel chemical structures & new mechanism of action

- Materials: new properties



Vent Polymerase
for DNA amplification
Origin: Vent bacterium



Halaven for cancer
Origin:
Japanese sponge

MGR Derived Pharmaceutical Products on the Market



Soft tissue carcinoma



Ecteinascidia turbinata



Chronic pain (analgesic)



Conus magus



Breast cancer



Halichondria okadai



Ara-C
(cytarabine)
treatment of leukemia



Ara-A (vidarabine)
antiviral



Tethya crypta



Hodgkin's Lymphoma



Dolabella auricularia



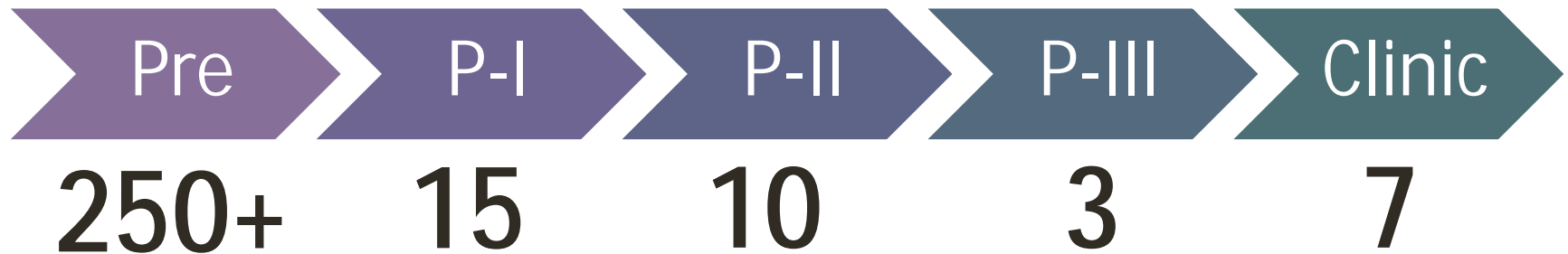
lowering very high
triglyceride levels



Purified
fish oil

All from EEZ apart from 1 (high seas) – All prior to CBD coming into force
None rely on harvesting natural source except fish oils

Pharmaceutical Pipeline



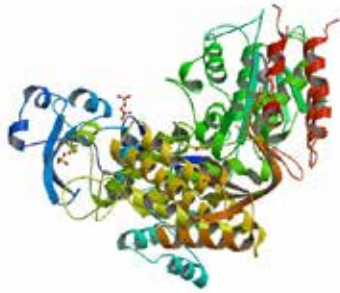
None from ABNJ – mainly reef derived

Mainly anti-cancer with a few analgesics and antivirals

Mainly start-ups at early stage with large pharma at late stage

<http://marinepharmacology.midwestern.edu/>

Non-Pharma MGR Derived Products on the Market



Vent Polymerase – for DNA amplification
Origin: Vent bacterium (Naples, Italy)

Production: Recombinant

Owner: New England Biolabs



Cosmetic screening infra-red rays

Origin: Vent bacterium (location unknown)

Production: Bacterial culture

Owner: Sederma (Croda)



THE NEXT-GENERATION, HIGH-PERFORMANCE
ALPHA-AMYLASE FOR MASH LIQUEFACTION

Fuelzyme – Enzyme used in biodiesel production

Origin: Deep sea bacterium (location unknown)

Production: Recombinant

Owner: Verenium (BASF)



Anti biofilm agents

Origin: Red seaweed

Production: Chemical Synthesis

Owner: XXXXX

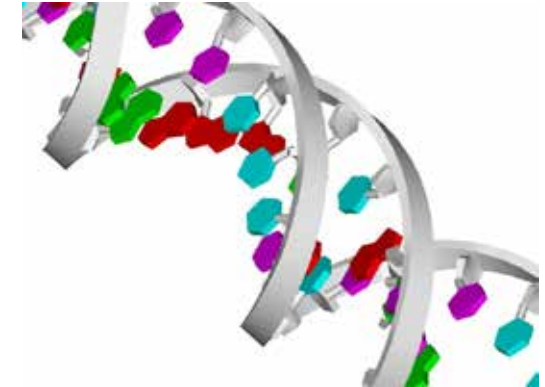
Fish as Commodity vs Fish Valued for its Genetic Properties



Food



Cod



Cod DNA



Fish Oils

Quantity	Size & Conc.	Article No.	Notes	Price
<input type="checkbox"/>	Pack size: 100 U Conc: 100 U/ml	#70003-001	i	\$300
<input type="checkbox"/>	Pack size: 1000 U Conc: 100 U/ml	#70003-002	i	\$1,200
<input type="checkbox"/>	Pack size: 2500 U Conc: 100 U/ml	#70003-003	i	\$3,000

Estimated Cost = US\$ 1 Bn/gramme
Sold in 'units' – market very small

A Definition of Marine Genetic Resources?

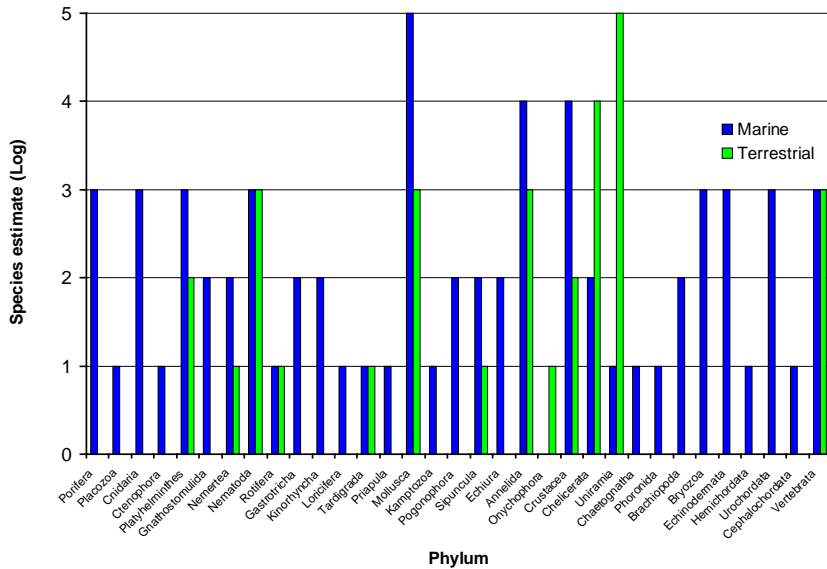
Marine Genetic Resources: Term has no meaning to biologists and is not defined in UNCLOS but is taken to mean the Nagoya Equivalent:

“Marine genetic material” means any material of plant, animal, microbial or other origin, **found in the marine environment**, containing functional units of heredity;

“Marine genetic resources” means **marine** genetic material of actual or potential value”

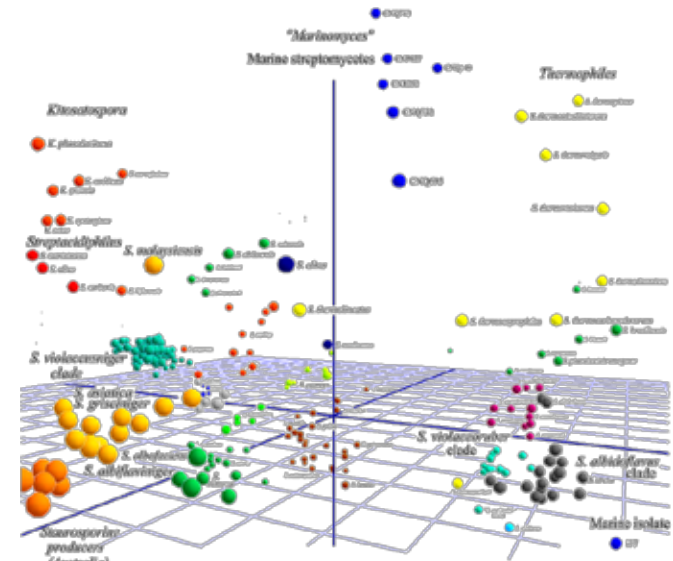
Marine Genetic Resource Diversity

Animal Diversity



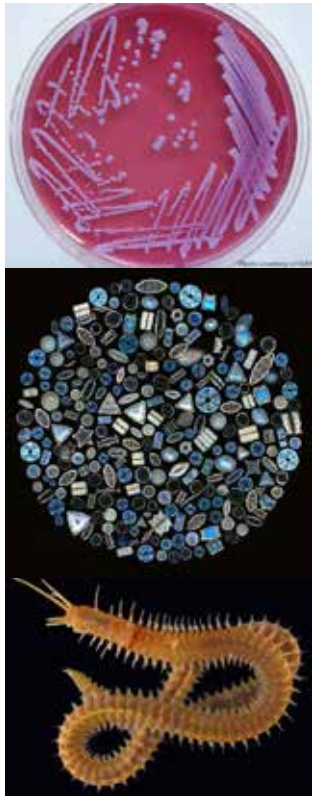
Of the major divisions of animal life ~20 have no representatives on land

Microbial Diversity

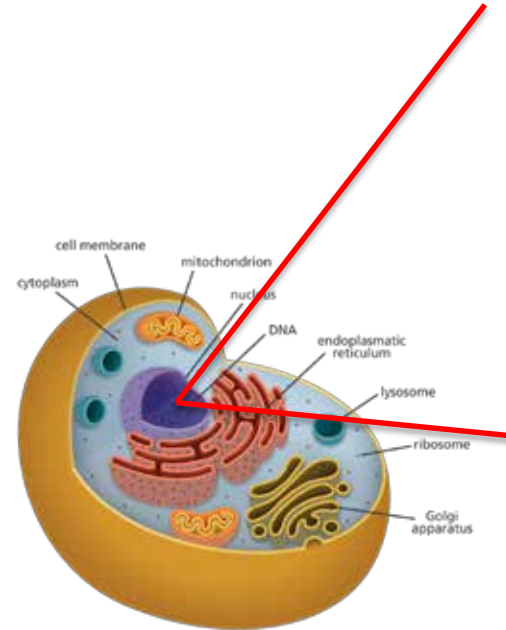


There is no clear estimate of marine microbial diversity or its economic value

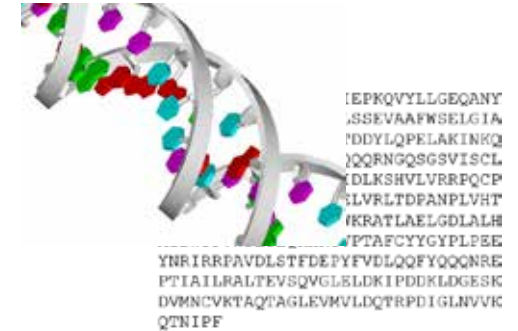
Biological Resources



Marine biological resource

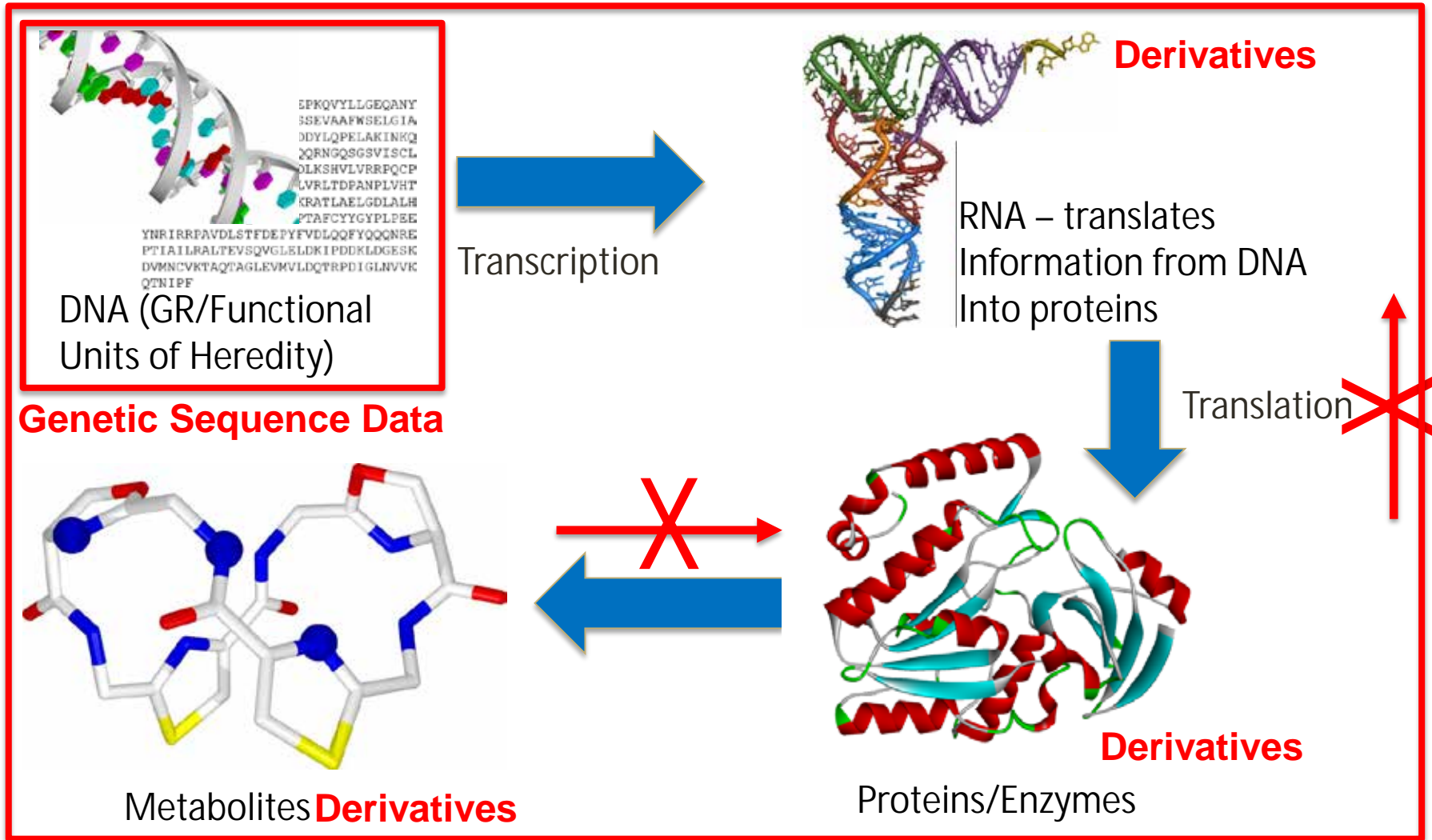


Cells (one or more)



DNA (GR/Functional Units of Heredity)

The Central Dogma of Molecular Biology



Bioprospecting vs Biodiscovery

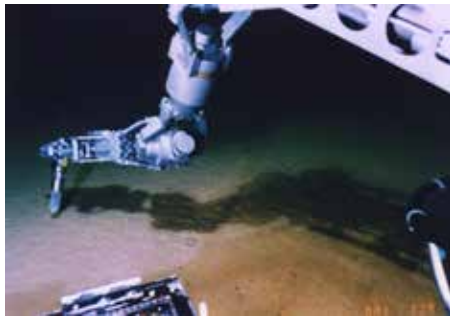
Bioprospecting (Oxford English Dictionary): “the search for plant and animal species from which medicinal drugs and other commercially valuable compounds can be obtained.”

Unlike seabed mining, marine genetic resources are not mined.

The MGR are used as **inspiration** to generate a product which is made by other means.

For this reason the words “**marine biodiscovery**” are used which suggest that it is the inspiration that is important and that the resource is not mined.

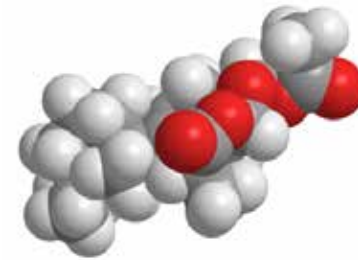
Marine Scientific Research/Bioprospecting



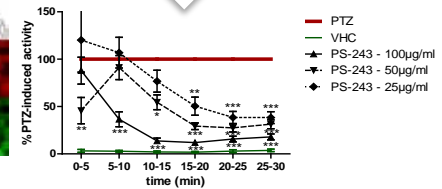
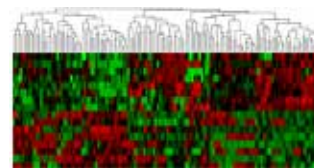
Sampling in ABNJ
Research



MGR
Research



Chemistry
Research



Bioassay
Research



Commercialisation

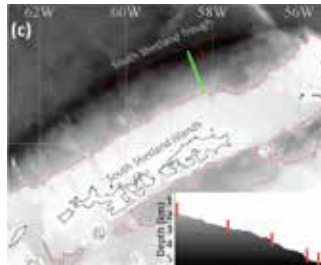


Product

MSR vs Bioprospecting

Application

- Cruise plan



Award

- Feasibility
- Checks



After Cruise

- Cruise report

MSR ID	CRUISE DATE	CRUISE NAME	CRUISE ID	CRUISE TYPE	CRUISE STATUS	CRUISE DURATION	CRUISE LOCATION	CRUISE CONTACT	CRUISE DESCRIPTION
MSR001	2010/01/15	North Atlantic	NA_001	Research	Completed	10 days	45N-15W	Dr. Smith	Basic research
MSR002	2010/02/20	North Atlantic	NA_002	Research	In Progress	15 days	48N-20W	Dr. Jones	Bioprospecting
MSR003	2010/03/10	North Atlantic	NA_003	Research	Completed	12 days	50N-25W	Dr. Brown	Basic research
MSR004	2010/04/05	North Atlantic	NA_004	Research	Completed	8 days	52N-30W	Dr. White	Bioprospecting
MSR005	2010/05/20	North Atlantic	NA_005	Research	Completed	10 days	55N-35W	Dr. Black	Basic research
MSR006	2010/06/15	North Atlantic	NA_006	Research	Completed	12 days	58N-40W	Dr. Green	Bioprospecting
MSR007	2010/07/10	North Atlantic	NA_007	Research	Completed	10 days	60N-45W	Dr. Grey	Basic research
MSR008	2010/08/05	North Atlantic	NA_008	Research	Completed	12 days	62N-50W	Dr. Yellow	Bioprospecting
MSR009	2010/09/20	North Atlantic	NA_009	Research	Completed	10 days	65N-55W	Dr. Purple	Basic research
MSR010	2010/10/15	North Atlantic	NA_010	Research	Completed	12 days	68N-60W	Dr. Blue	Bioprospecting

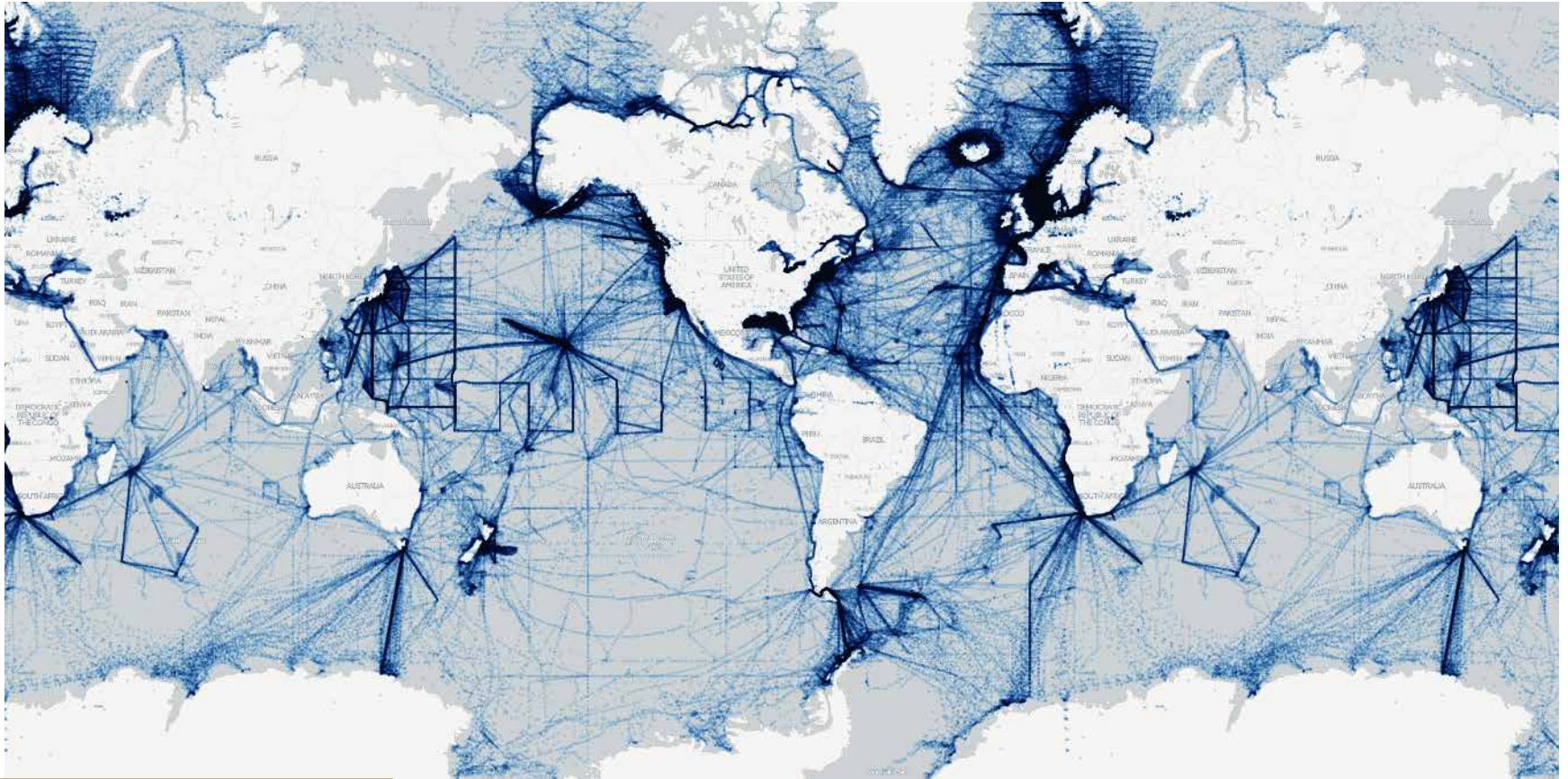
MSR

- Most cruises are for basic research
- Freedom of MSR, but notify central organisation
- File cruise report (where?)

Bioprospecting

- Require yearly update on cruise report to alert to change of use
- Only needed on commercialisation (not just IP filing, but actual use)

Where Do Research Vessels Go?



Impact of Sampling

Trawling impact ranges from 0.005 to 0.009 km²

Gravity coring leaves a 10cm diameter hole that close within 1 h.

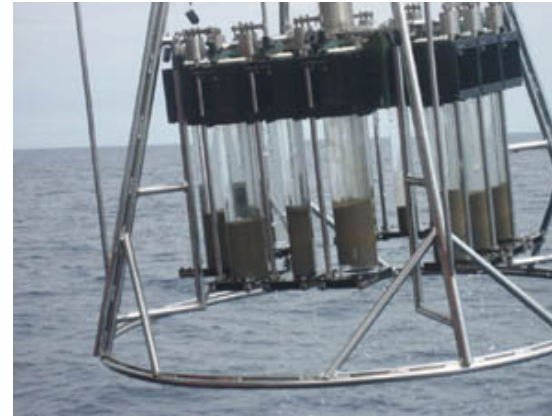
Mega coring in a typical cruise will impact ~0.5m² of seafloor

Removing 0.5m² of seafloor in ABNJ = 0.19cm² of Yellowstone national park



Impact of Sediment Sampling (Estimate)

- Volume of a 1 m long core 15 cm Ø = 20 liters
- Estimate 5 cores sampled at same time = 100 liters
- Total sampling points recorded = 100,000*
- Total volume = 10,000,000 liters = 10,000 m³
- Equivalent to 150 x 40 foot shipping containers (66 m³ each)
- Equivalent to a layer 32 picometers (32 x 10⁻¹² m) thick covering ABNJ
- 32 picometers is equivalent to radius of Helium atom



Good Practice for Cruise Data and Samples

Metadata may include

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

Sample storage

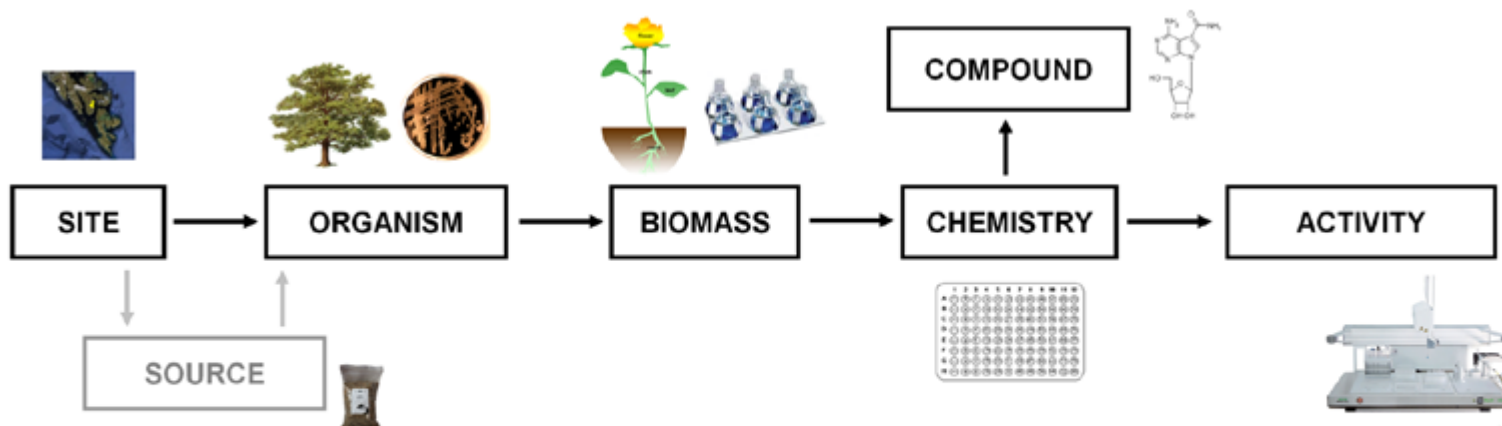
- | Ambient temperature
- | Cooler (4°C)
- | Freezer (-20°C)
- | -80°C Freezer
- | Liquid nitrogen (-196°C)
- | Formaldehyde
- | Ethanol
- | DNA/RNA preservation liquids



Needs standardisation

Monitoring Sample and Data Flows

Possible to track sample from origin to exploitation
(but better databases are needed)

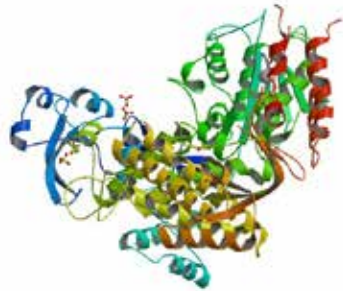


OpenNAPIS™
Functional Design

White Point Systems, Inc.
20100626

Modifications to DNA or compound may make it hard to trace MGR origin

Tracking Samples can be Tricky



Vent Polymerase For DNA amplification

NCBI Resources How To

Genome Search

Create alert Limits Advanced

Thermococcus litoralis
Representative genome: Thermococcus litoralis DSM 5473
Download sequences in FASTA format for **genome**, **protein**
Download genome annotation in GFF, **GenBank** or **tabular** format
BLAST against Thermococcus litoralis **genome**, **protein**

Display Settings: Overview

Send to: v

Organism Overview

ID: 12449

Thermococcus litoralis

Thermococcus litoralis overview

Lineage: Archaeal[545]; Euryarchaeota[344]; Thermococci[25]; Thermococcales[25]; Thermococcaceae[24]; Thermococcus[17]; Thermococcus litoralis[1]



J Bacteriol. 2012 May; 194(5): 2375-2376.
doi: 10.1128/JB.00123-12

PMCID: PMC3347054

Genome Sequence of the Model Hyperthermophilic Archaeon *Thermococcus litoralis* NS-C

Andrew F. Gardner¹, Sanjay Kumar, and Francine B. Perler

Author information | Article notes | Copyright and License information

This article has been cited by other articles in PMC.

ABSTRACT

Go to: v

The hyperthermophilic archaeon *Thermococcus litoralis* strain NS-C, first isolated in 1985, has been a foundational organism for archaeal research in biocatalysis, DNA replication, metabolism, and the discovery of inteins. Here, we present the genome sequence of *T. litoralis* with a focus on the replication machinery and inteins.

GENOME ANNOUNCEMENT

Go to: v

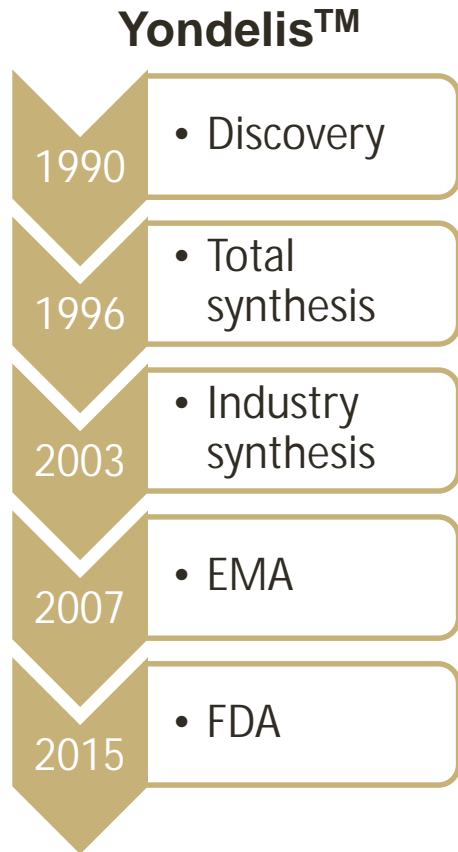
Thermococcus litoralis strain NS-C was isolated from a shallow submarine hot spring at Lucrino Beach near Naples, Italy (1), and successfully grown in culture (14). Since then, *T. litoralis* has been the focus of studies on biocatalysis (10), archaeal metabolism (2, 3, 6, 7, 9, 11, 13, 17, 21), DNA replication (4, 5, 8, 12, 20), and protein splicing (15).

England Biolabs, Inc.
Complete Genome
Genome Type: Cocci
Minimum Temperature: 85C, Temperature Range: Hyperthermophilic
Genomic Relationship: Free Living, Trophic Level: Heterotroph
Accession Number: GCF_000246985.3 ASM24698v3 scaffolds: 1 contigs: 1 N50: 2,215,172 L50: 1 NA81925
Genome Length (Mb): 2.21517
GC Content: 2292
GC Content (%): 43.1

of the model hyperthermophilic archaeon *Thermococcus litoralis* NS-C. Gardner AF, et al. J Bacteriol 2012 May



Real Benefit Scenario



- Typical industry royalties on natural products developed into drugs is 1-3%
- Halaven (Eisai), derived from a Japanese sponge makes US\$200 M per year – in principle yielding US\$ 2-6 M pa.
- Currently 7 approved marine drugs – total royalties would be US\$ 10-50 M.
- Blockbuster drug (> US\$ 1 Bn pa income) would yield US\$10-30 M pa
- Currently 7 approved marine drugs come from ~28,000 discovered marine compounds (1 in 4000 chance) – none are 'blockbusters'
- All examples were discovered pre-CBD – not clear if actual royalties are being paid
- Other markets – nutraceuticals/cosmeceuticals, lower risk, quicker to market, lower investment and lower returns.

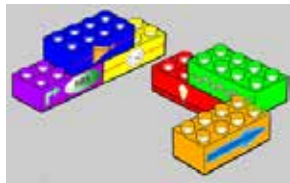
Benefit Sharing

- Must be multilateral compared to bilateral for Nagoya Protocol
- In most cases most important benefits from use of MGR are non-monetary.
- Non-monetary benefits may include:
 - Scientific exchanges/training
 - Technology transfer
 - Capacity building (infrastructure)
 - Enhanced reputation
 - Increased number/quality of scientific publications
 - Biodiversity conservation
 - Valuable regional resources developed (knowledge, samples, data)
- Non-monetary benefits still cost money – however they are upfront compared to royalties

Is a Public Domain/Open Access Approach Possible?

- Public domain/Open Access approach may be used when:
 - There is no desire/need to control access
 - There is more than enough of a resource for all to utilise
- Precedents in biology/software/semiconductors
- Low cost – commensurate with size of problem

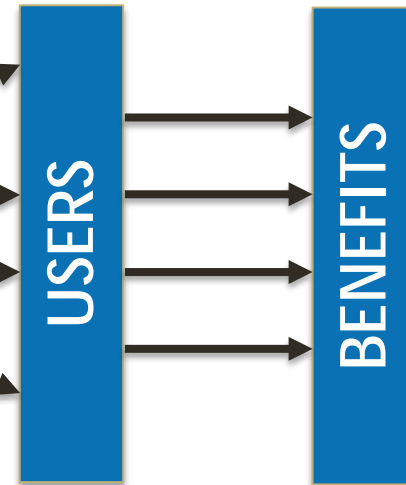
Public Domain Approach



Biobricks



open source™



- All should be able to benefit from discoveries
- This approach will lead to greater innovation, transparency and openness
- Access for landlocked & developing countries
- Make sure all can benefit and can exploit - requires capacity building to ensure fairness

How to Facilitate MSR Whilst Allowing Commercialisation



```

MQPTALQIKPHFHVVEIEPKQVYLLGEGQNHALTGQLY
LSRLVEKGYLTVAPELSLEVAWFSELGIAPSVVAEG
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HCLAQRRLRGNREVEASVLQKRALQERNQONKNGAVSC
NAIA
RATT
DSQS
PHRF
RDSV
IGFG
RWSJ
PLAE
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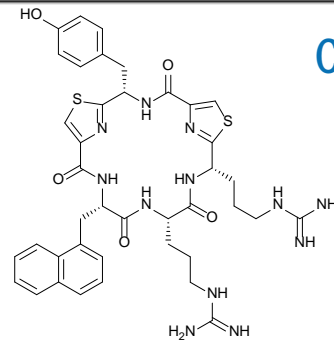
MGR samples
and raw data



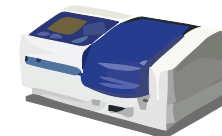
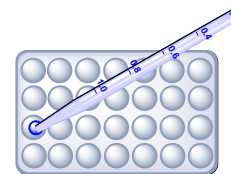
Share samples and data

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)
 (19) World Intellectual Property Organization
 International Bureau
 (43) International Publication Date
 13 September 2007 (13.09.2007)
 (10) International Publication Number
 WO 2007/103739 A2

Commercialisation
(not just IP filing
but use of IP)



Basic
research



Summary

Define extent of marine biodiversity relevant to bioprospecting

Need definition of MGR – get input from marine scientists

Need case studies of non-pharmaceutical products based on MGRs and their origins

Need to obtain realistic benefit scenarios

Propose light touch regime based on current good practice

Develop mechanisms to track developments based on MGRs

Propose common domain/open access model – needs capacity building/technology transfer to ensure fairness

Implementing agreement needs to be flexible to accommodate rapid progress in science

PHARMASEA



“The research leading to these results has received funding from the European Union's Seventh Framework Programme (FP7/2007-2013 under grant agreement n ° 312184)”