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Mare Geneticum

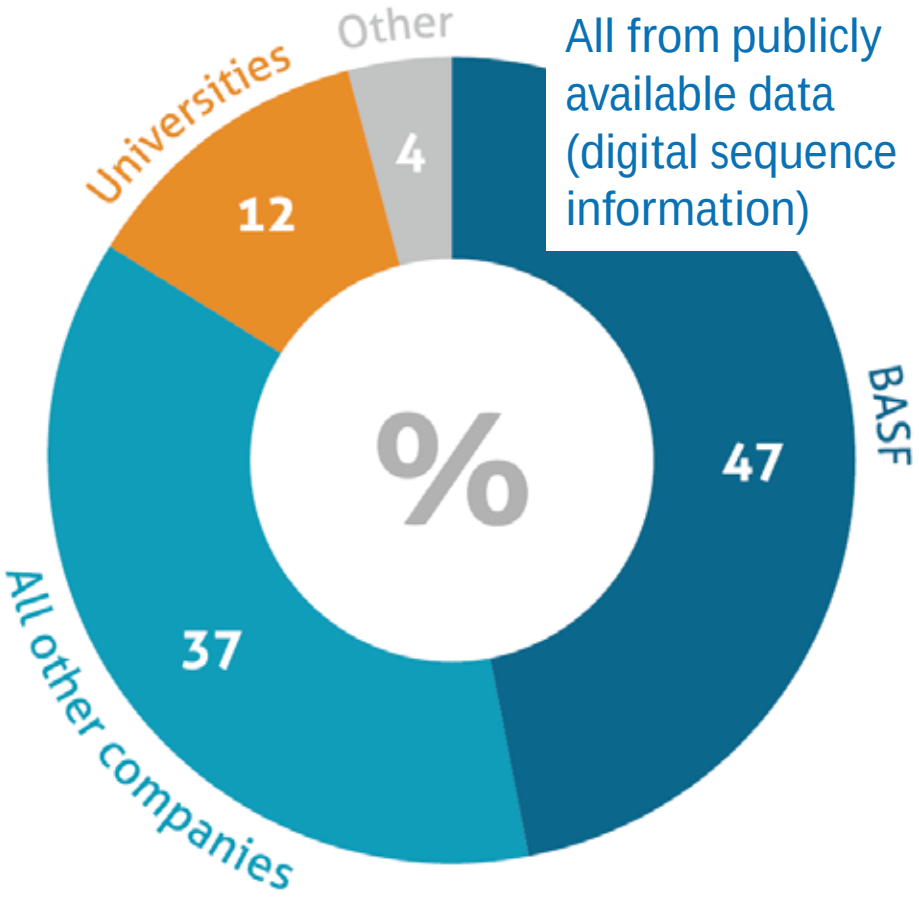
Arianna Broggiato, Thomas Vanagt, Laura Lallier, Marcel Jaspars, Geoff Burton, Dominic Muyldermans

Scientific and technical baseline

Are the expectations of large financial gains from the utilisation of MGR in ABNJ realistic?

There is currently little evidence of systematic commercial scale development of MGR from ABNJ (Leary and Juniper)

It is important not to conflate the potential of MGR in ABNJ with the more prolific commercialisation of marine biodiversity products from shallower waters (Oldham)



All from publicly available data (digital sequence information)

Fig. 2. Percentage of patents with international protection associated with MGRs that were registered over the period 1988–2017 by BASF, all other companies (n = 220), universities (n = 78), and other actors (n = 26; including governmental bodies, individuals, hospitals, and nonprofit research institutes).

[2] Blasiak, *Science Advances*, **2018**, *4*, eear5237

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Scientific and technical baseline

Where do the disparities between states lie?

The analysis should focus on the actual availability of MGR from ABNJ and the capacities needed to study and exploit them.

Uneven levels of access to MGR:

1. The cost of technology and its maintenance to sample in international waters and the deep sea.
2. The scientific skills to undertake research on marine biodiversity
3. The cost and scientific skills to undertake molecular screening and biodiversity assessment.
4. The scientific skills to analyse the data thereby produced.

The current uneven research capabilities across the globe are the primary source of inequity amongst states, more than disparities in accessing resources in situ (First Assessment of the Ocean, UN)

Premises for fair and equitable sharing of the benefits arising from utilisation of MGR in ABNJ

- Multilateral arrangement
- Support scientific research à Facilitated access
- Safeguard for private investments à Extended embargo
- Capacity building
- Inclusivity of developing states à Open access principle
- Involvement of the scientific community
  à Build on good practice
- Build on existing common pools: biorepositories and databases à Deposit samples and release raw data

Bridging the gap between those countries that hold knowledge, MGR and technologies, and those that do not

Mare Geneticum Provides Building Blocks Based on Scientific Good Practice

Access

Obligatory Prior Electronic Notification (OPEN)

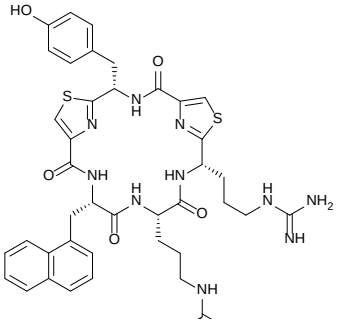
Update OPEN Exclusivity Period

Extend Exclusivity Period For a fee

Update OPEN

If IA requires monetary BS: royalties to be paid on commercialisation at % fixed by sector

Update OPEN



Benefit Sharing

Share Samples and Raw Data

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
13 September 2007 (13.09.2007)

(10) International Publication Number
WO 2007/103739 A2

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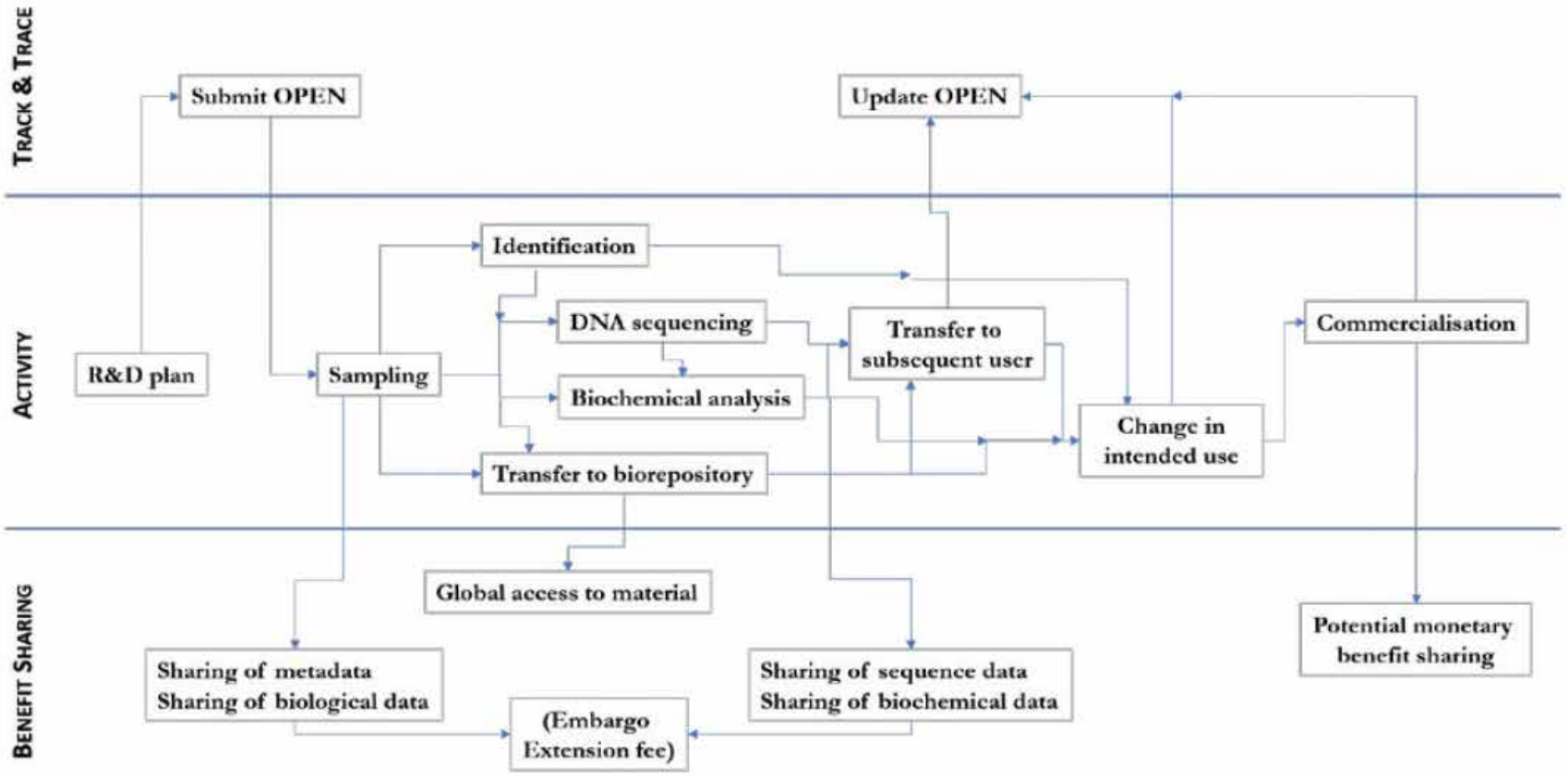
Mare Geneticum Flow Chart



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Photos: © E. Svendsen

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

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.

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)

fuelzyme™-LF
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

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MGR Derived Pharmaceuticals

Yondelis for cancer
Origin: Caribbean seasquirt
Production: Semi-synthesis

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

Prialt for pain
Origin: Phillippino cone snail
Production: Recombinant

Halaven for cancer
Origin: Japanese deep water sponge
Production: Chemical synthesis

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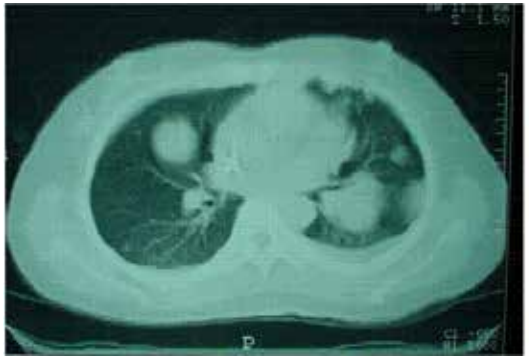
Discovery Timeline

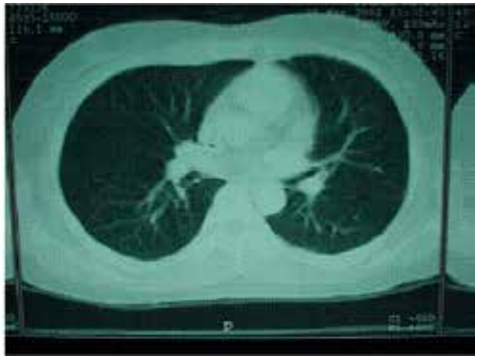
Yondelis™

- **1990** • Discovery
- **1996** • Total synthesis
- **2003** • Industry synthesis
- **2007** • EMA
- **2015** • FDA

Ecteinascidia turbinata.



Baseline



>18 Cycles

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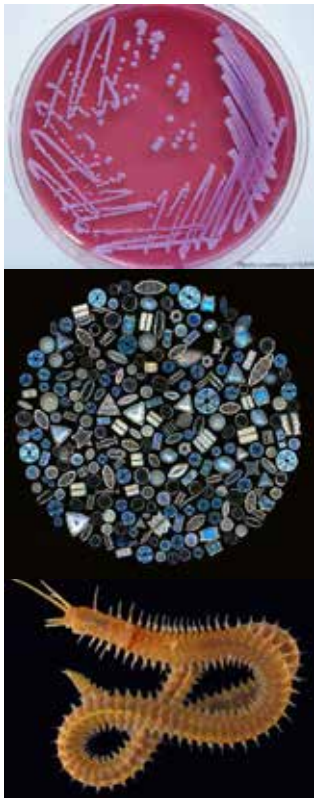
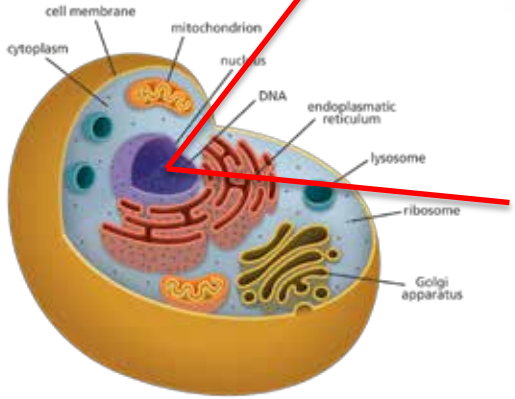
Biological Resources



Marine biological resource



Cells (one or more)

DNA (GR/Functional Units of Heredity)

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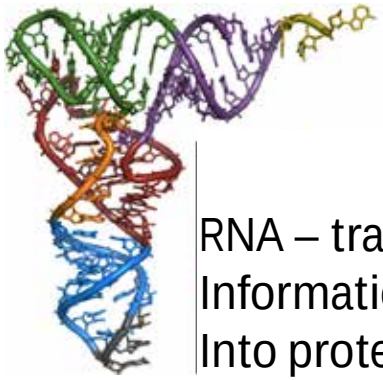
The Central Dogma of Molecular Biology

DNA (GR/Functional Units of Heredity)

Genetic Sequence Data

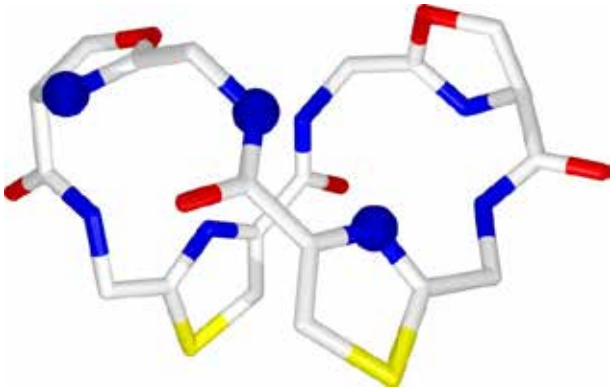
Transcription



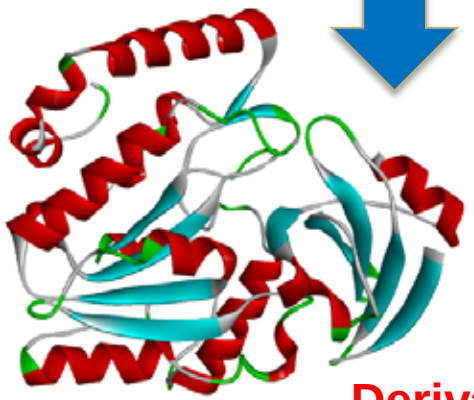
Derivatives

RNA – translates Information from DNA Into proteins

Translation



Metabolites **Derivatives**



Proteins/Enzymes **Derivatives**

***In Silico* Data**

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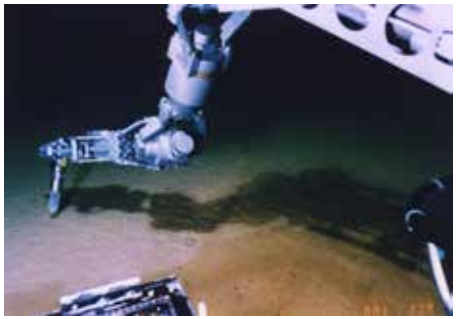
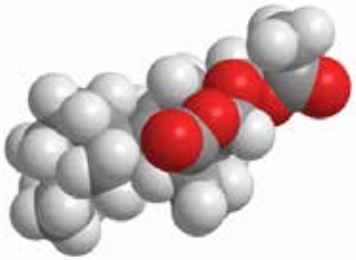
Marine Scientific Research/Bioprospecting



Sampling in ABNJ
Research

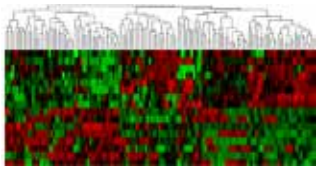
MGR
Research

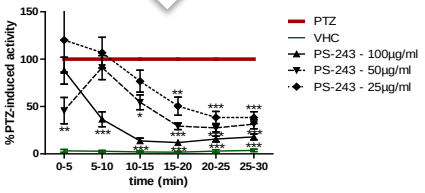


Chemistry
Research

Product

Commercialisation





Bioassay
Research

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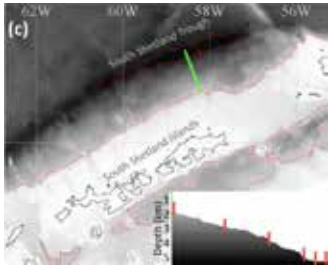
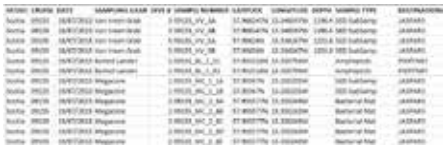
MSR vs Bioprospecting

Application
- Cruise plan



Award
- Feasibility
- Checks

After Cruise
- Cruise report



MSR
- Most cruises are for basic research
- Freedom of MSR
- File cruise report to funder

How Might Bioprospecting be Accommodated?
- Require updates on cruise report to alert to change of use
- Notify when commercialisation occurs

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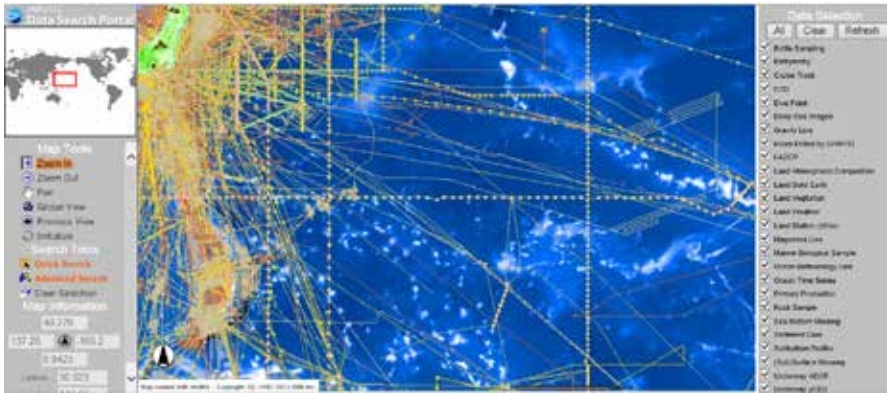
Good Practice for Cruise Data and Samples

Metadata may include

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



Sample storage

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

Needs standardisation

Mare Geneticum Provides Building Blocks Based on Scientific Good Practice

Access

Obligatory Prior Electronic Notification (OPEN)

Update OPEN

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Mare Geneticum Obligatory Prior Electronic Notification

Data on OPEN could include:

- Information on collector and contact point
- Geographical area of sampling
- Period of sampling
- Research project description (cruise plan)
- Expected nature of what will be collected (grab, core, sediment, invertebrate, plankton etc)
- Description of targeted MGR when possible
- Commitment to release samples and data in open access biorepository (but conditional on intended use)
- Commitment to update OPEN at certain milestones.

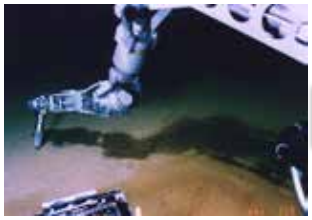
Benefits to Scientists of the OPEN System

Global data sharing platform and clearing house mechanism for marine biodiversity data in all ocean basins including ABNJ

A mechanism for international cooperation in MSR, coordination in global ocean observation and development of standards, manual and guidelines and codes of conduct in MSR and data sharing protocols

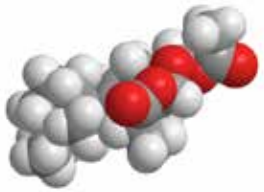
A global network of regional centres to enhance capacity, by training the next generation of scientists and area managers in applying international standards and best practices

Monitoring Sample and Data Flows

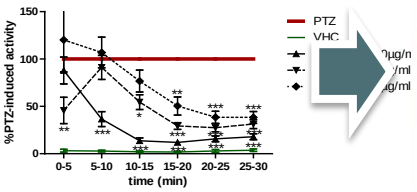


Sampling in ABNJ

MGR

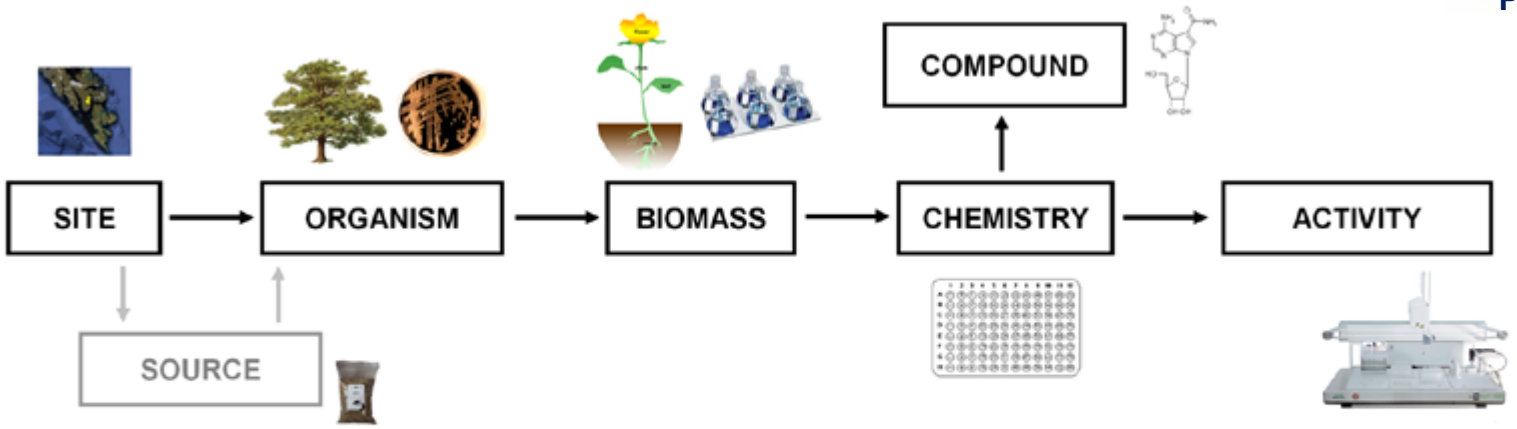


Chemistry



Bioassay

Product



OpenNAPIS™

Functional Design

White Point Systems, Inc.
20100626

Possible to track sample from origin to exploitation

Needs improved data infrastructure

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Tracking Samples can be Tricky

Vent Polymerase
For DNA amplification

NCBI Resources How To

Genome

Genome | Thermococcus litoralis[orgn] | 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:

Organism Overview ID: 12449

Thermococcus litoralis

Thermococcus litoralis overview

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

England Biolabs, Inc.
nplete Genome
pe:Cocci
mumTemperature:85C, TemperatureRange:Hyperthermophilic
icRelationship:FreeLiving, TrophicLevel:Heterotroph
_000246985.3 ASM24698v3 **scaffolds:** 1 **contigs:** 1 **N50:** 2,215,172 **L50:** 1
NA81925
l length (Mb): 2.21517
tein count: 2292
%: 43.1

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

Journal of Bacteriology
JB Article | Journal Info. | Authors | Reviewers | Permissions | Journals.ASM.org

J Bacteriol. 2012 May; 194(9): 2375–2376. PMCID: PMC3347054
doi: 10.1128/JB.00123-12

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

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

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ABSTRACT Go to:

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:

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).

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Benefit Sharing

- Must be multilateral compared to bilateral for Nagoya Protocol
- 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)
  - Upfront/milestone payments & royalties

Is an Open Access Approach Possible?

- 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

Mare Geneticum Provides Building Blocks Based on Scientific Good Practice

Access

Obligatory Prior Electronic Notification (OPEN)

Benefit Sharing

Update OPEN Exclusivity Period

Share Samples and Raw Data

Many Precedents in Science ‘Open Innovation’

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Open Access Publication/Data

Open Access in Horizon 2020

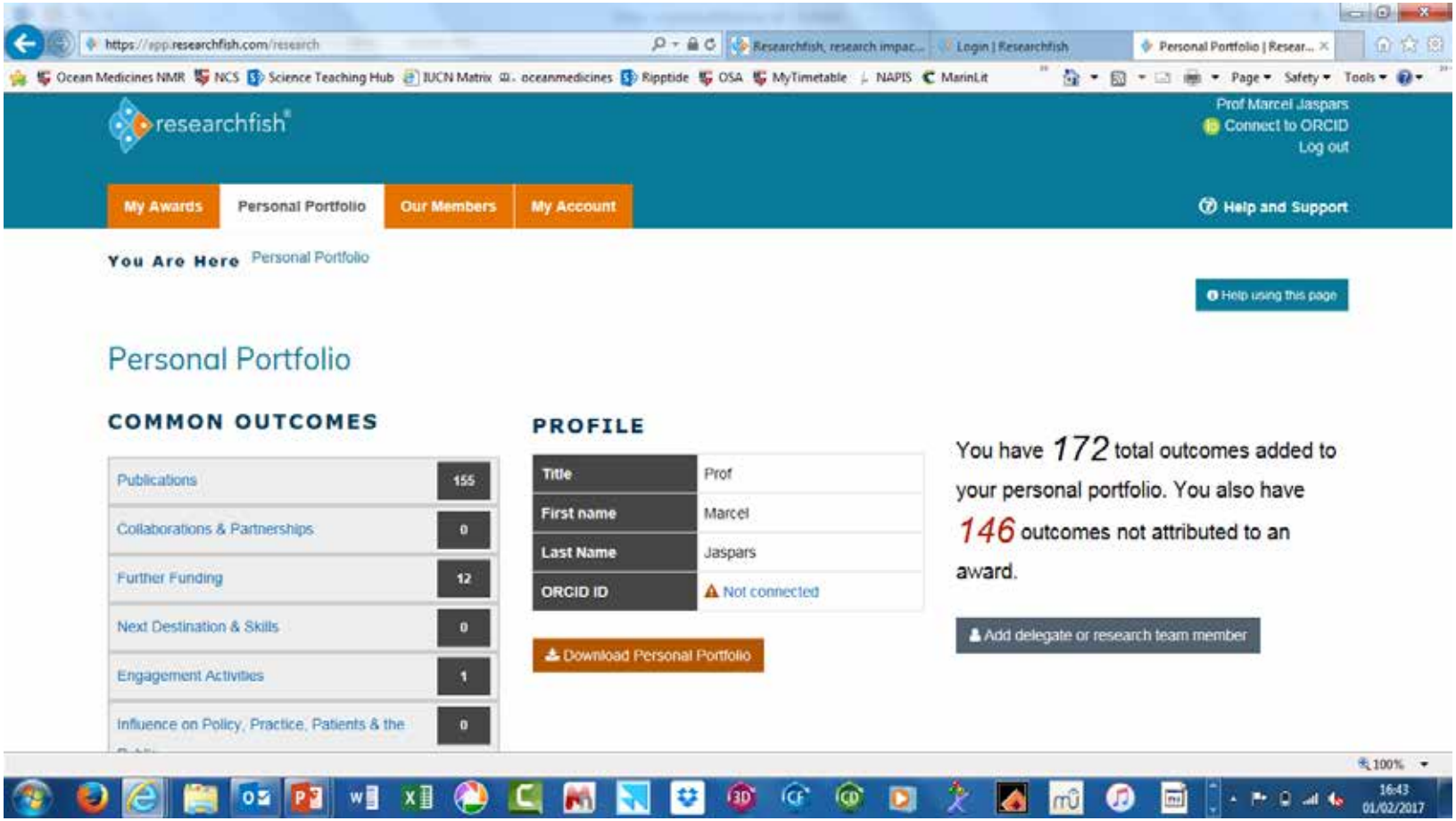
Peer-reviewed scientific publications

All projects receiving Horizon 2020 funding are **required** to make sure that any peer-reviewed journal article they publish is openly accessible, free of charge (article 29.2. Model Grant Agreement).

Research data

The Commission is running a **pilot on open access** to research data in Horizon 2020: the Open Research Data (ORD) pilot. This pilot takes into account the need to balance openness with the protection of scientific information, commercialisation and Intellectual Property Rights (IPR), privacy concerns, and security, as well as questions of data management and preservation.

Reporting Research Outcomes



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Open Access to Research Materials Aids Open Innovation

nature

Availability of data, material and methods

An inherent principle of publication is that others should be able to replicate and build upon the authors' published claims. A condition of publication in a Nature journal is that **authors are required to make materials, data, code, and associated protocols promptly available to readers without undue qualifications**. Any restrictions on the availability of materials or information must be disclosed to the editors at the time of submission. Any restrictions must **also** be disclosed in the submitted manuscript.

After publication, readers who encounter refusal by the authors to comply with these policies should contact the chief editor of the journal. In cases where editors are unable to resolve a complaint, the journal may refer the matter to the authors' funding institution and/or publish a formal statement of correction, attached online to the publication, stating that readers have been unable to obtain necessary materials to replicate the findings.

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Case Study: MarBank as an MGR Repository

http://www.imr.no/marbank/en

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MarBank Objectives

MarBank offers *Ex situ* access to Marine Genetic Resources for research and exploitation purposes

Marine organisms are collected from their natural habitat and kept alive or processed and conserved in the biobank

Safe and easy access to quality assured marine samples

Opportunity for researchers that do not have the ability to collect MGRs *In situ*

The NCI Open Repository

Extracts from:
80,000 plants
20,000 marine organisms

Collected via contractors
'Letter of collection'
covers ABS issues

Extracts prepared using
standardised protocols

Samples made available
without cost to anyone
working on cancer
Requires signing MTA

Limited exclusivity

https://dtp.cancer.gov/organization/npb/introduction.htm

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Mare Geneticum Provides Building Blocks Based on Scientific Good Practice

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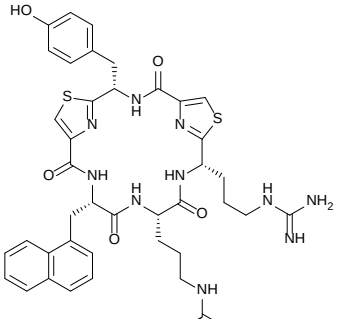

Update OPEN

Benefit Sharing

Share Samples and Raw Data

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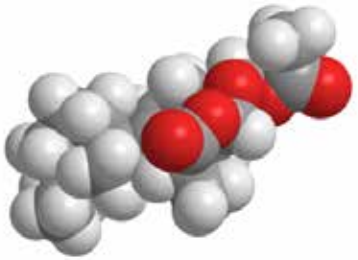
PharmaSea Case Study Using NCI Open Repository

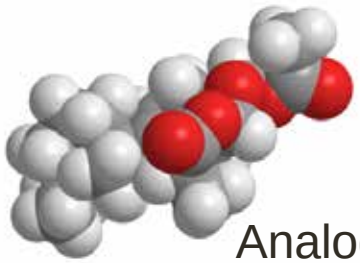
Spongionella sp
0CDN 8588-T
Collected by CRF

Benefit sharing obligation (from NCI 'Letter of Collection' & MTA) to be agreed with relevant Philippine authorities at point of commercialisation



Discovery of new Molecule with anti-Alzheimer properties

Effective in animal models



Analogues made and tested IP/Publication soon

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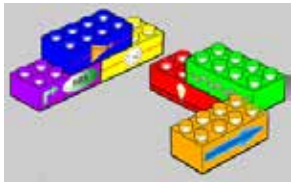
Open Access Approach

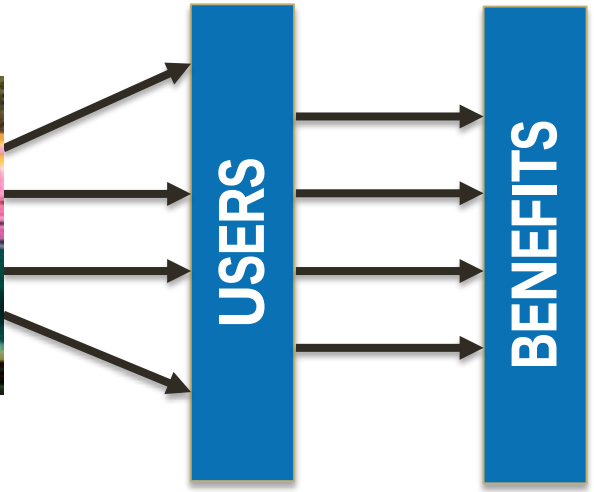


Biobricks

open source

OPEN SOURCE DRUG DISCOVERY

& Raw Data



- 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**

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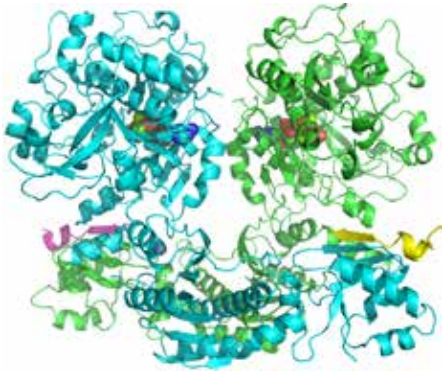
Exclusivity Periods in Scientific Practice

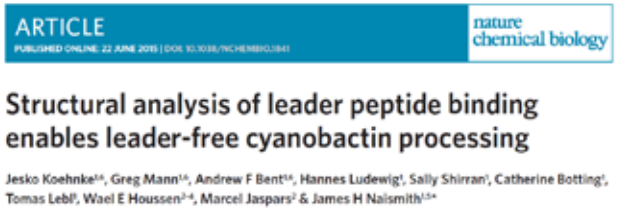
Protein Data Bank entries are placed on hold for one year from the date of deposition. They may be released earlier on a date specified by the Contact Author. When the corresponding electronic or paper publication occurs, the entry must be released if the journal policy requires release upon publication.



Solve protein crystal structure

RCSB PDB PROTEIN DATA BANK

Deposit data
Get PDB ID



1 Year

Data Released

http://www.rcsb.org/pdb/home/home.do

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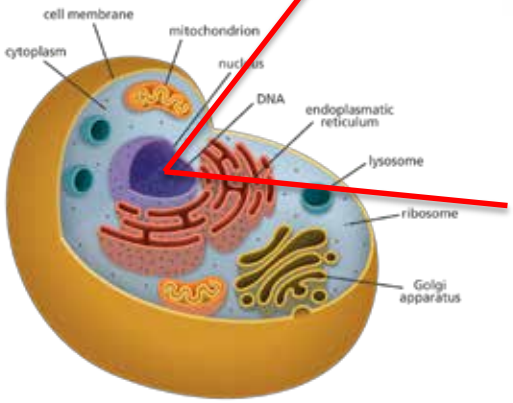
Types of Data the *Mare Geneticum* Proposal Could Cover:

Categories of information	Explanation	Types of data
Data only	**Raw data (e.g. genetic sequence data)**	· **Metadata associated with the samples** · Initial taxonomic analysis of the samples · **Genetic sequence data (DNA)** · Transcriptome data (RNA of the genes that are functional at that time) · Automatic gene/transcriptome function annotations · Protein sequence data (DNA/RNA data automatically translated to give amino acid sequence)
Data and analysis	Genetic sequence data which has been annotated with putative gene functions using an algorithm	· Initial taxonomic analysis of the samples (DNA methods?) · Automatic gene/transcriptome automatic function annotations · Protein sequence data (DNA/RNA data automatically translated to give amino acid sequence) · *Protein structure data (Embargo)* · *Metabolite data (mainly commercial databases)*
Data, analysis and interpretation	Critical evaluation of the data and its analysis conducted by an expert	· Full taxonomic analysis of the samples · Manual gene/transcriptome function annotations · *Protein structure data (Embargo)* · *Metabolite data (mainly commercial databases)*

Mare Geneticum proposes open access to samples and raw data with exclusivity period

Possibility to extend exclusivity period for a fee.



DNA (GR/Functional Units of Heredity)

Raw Genetic Sequence Data

Samples and Associated metadata

VESSEL	CRUISE	DATE	SAMPLING GEAR	DIVE #	SAMPLE NUMBER	LATITUDE	LONGITUDE	DEPTH	SAMPLE TYPE	DESTINATION
Scotia	09155	18/07/2015	Van Veen Grab	3	09155_VV_3A	57.968247N	15.548597W	1196.4	SED SubSamp	JASPARS
Scotia	09155	18/07/2015	Van Veen Grab	3	09155_VV_3B	57.968247N	15.548597W	1196.4	SED SubSamp	JASPARS
Scotia	09155	18/07/2015	Van Veen Grab	5	09155_VV_5A	57.95626N	15.536247W	1203.8	SED SubSamp	JASPARS
Scotia	09155	18/07/2015	Van Veen Grab	5	09155_VV_5B	57.95626N	15.536247W	1203.8	SED SubSamp	JASPARS
Scotia	09155	19/07/2015	Baited Lander	1	09155_BL_1_E1	57.953318N	15.550793W		Amphipods	PIERTNEY
Scotia	09155	19/07/2015	Baited Lander	1	09155_BL_1_R1	57.953318N	15.550793W		Amphipods	PIERTNEY
Scotia	09155	19/07/2015	Megacore	1	09155_MC_1_1A	57.95567N	15.550255W		SED SubSamp	JASPARS
Scotia	09155	19/07/2015	Megacore	1	09155_MC_1_1B	57.95567N	15.550255W		SED SubSamp	JASPARS
Scotia	09155	19/07/2015	Megacore	2	09155_MC_2_6A	57.955577N	15.550243W		Bacterial Mat	JASPARS
Scotia	09155	19/07/2015	Megacore	2	09155_MC_2_6B	57.955577N	15.550243W		Bacterial Mat	JASPARS
Scotia	09155	19/07/2015	Megacore	2	09155_MC_2_6C	57.955577N	15.550243W		Bacterial Mat	JASPARS
Scotia	09155	19/07/2015	Megacore	2	09155_MC_2_6D	57.955577N	15.550243W		Bacterial Mat	JASPARS
Scotia	09155	19/07/2015	Megacore	2	09155_MC_2_6E	57.955577N	15.550243W		Bacterial Mat	JASPARS

PHARMASEA

Summary

- Open access to raw data and samples
- Benefits to scientists by standardising data and providing central resource (OPEN)
  - OPEN standardises data management, taxonomy and species identification
  - OPEN enhances international research coordination and cooperation
- Requires capacity building/technology transfer to ensure fairness
  - Targeted training and sharing of expertise, methodology, guidelines and best practices

PHARMASEA

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