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## Increasing Value and Flow in the Marine Biodiscovery Pipeline

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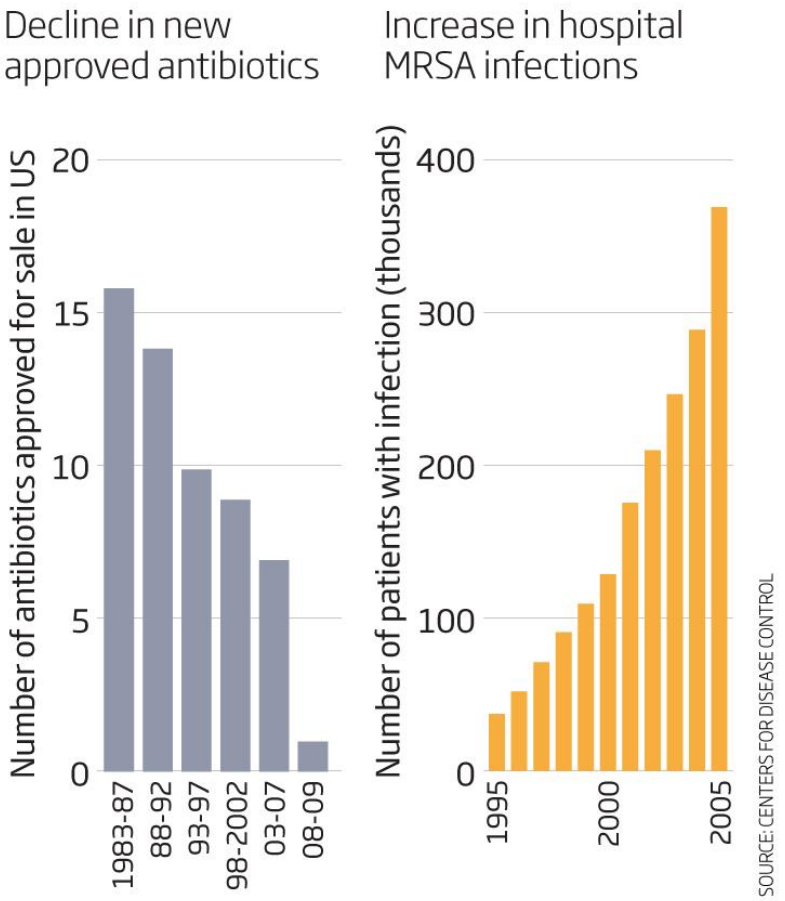
Presentation by
Alan Dobson

# Why PharmaSea?




- New therapeutics for microbial infections and CNS diseases
- Widen bottlenecks in marine biodiscovery pipeline
- Develop mechanisms to transfer marine biotechnology to end users
- Make marine bioproducts more attractive to develop for industry

Source: New Scientist



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# PharmaSea

- **Increasing Value and Flow in the Marine Biodiscovery Pipeline**
- EU Framework Programme 7 Consortium funded at EUR 9.5 million
- 24 Partners
- Norway, Denmark, UK, Belgium, Germany, Spain, Italy, Republic of Ireland, Chile, South Africa, China, New Zealand, Costa Rica
- *To improve the quality, volume and value of active agents discovered in the marine environment and increase the speed at which they can be delivered to the marketplace, by addressing bottlenecks and restrictions and adding technical booster-pumps*
- Start date 01/10/2012; Duration 48 months (& 6 extension)
- Project Coordinator Camila Esguerra/Peter de Witte, KU Leuven, Belgium



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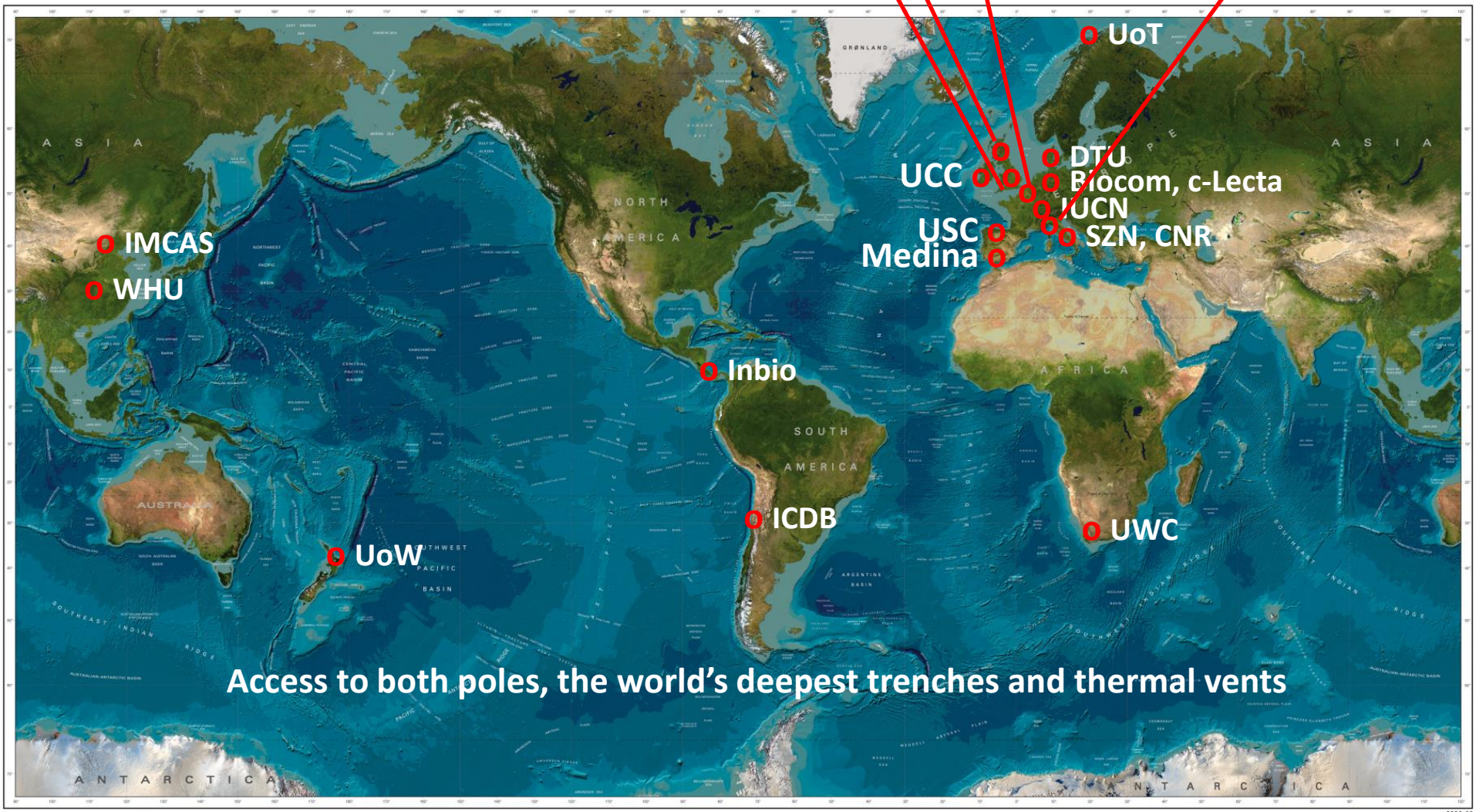
UniAbdn, DeepTek

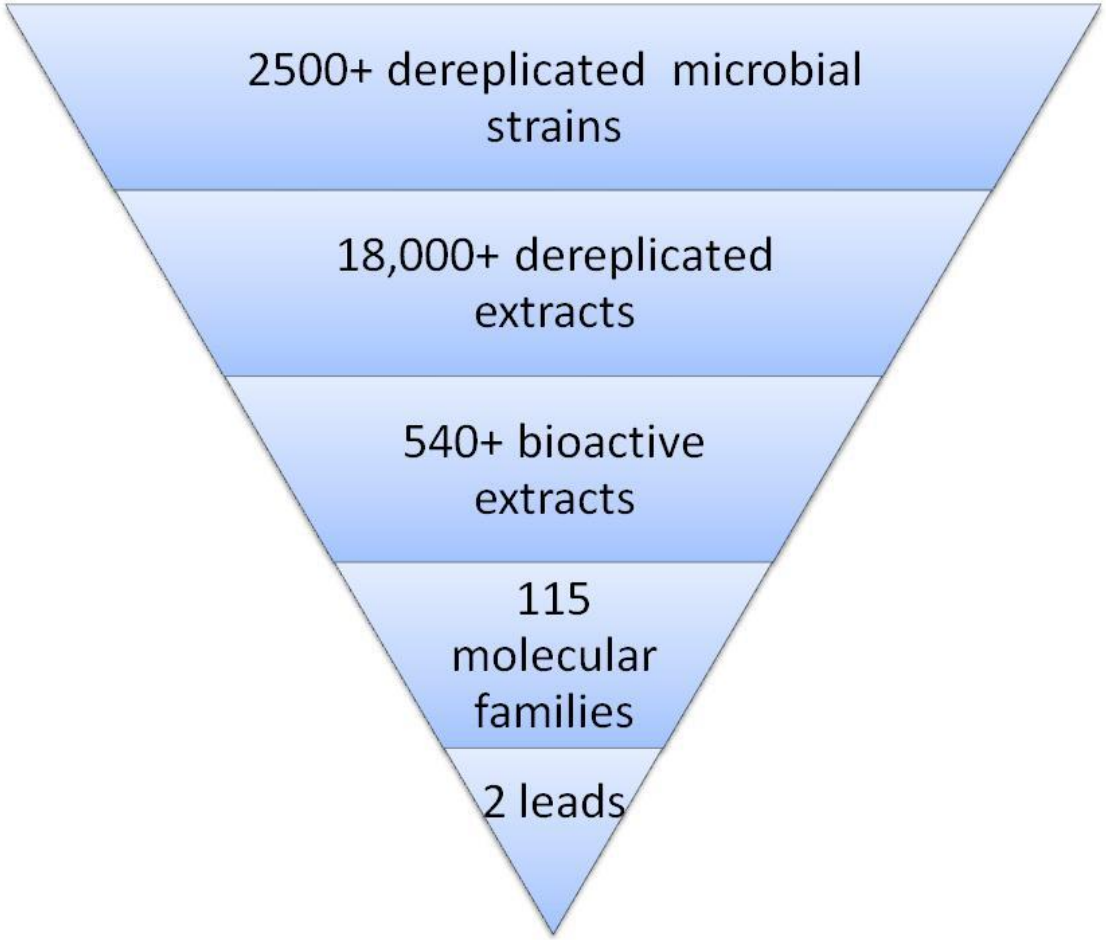
ACDLabs, RSC, BioBridge

KULeuven, eCoast

SeaLife Pharma



# Discovery Funnel



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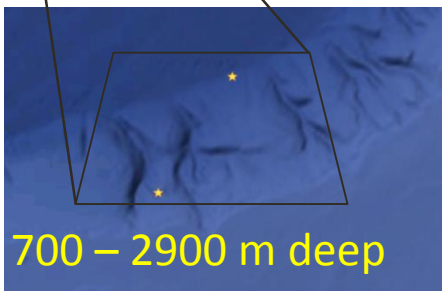
# WP1 Strain Collections (n = 13,689)

**Legacy Collections:** Arctic, Antarctic, Ireland, South Africa and Argentina

**New Collections:** Antarctic, South Africa

**Scheduled Collections:** South Shetland Trench (-5200 m)

# WP1 Deep Sea Sampling



*RV* Celtic Explorer

ROV Holland I

Live HD Video of sampling

*Inflatella pellicula*

750/2900 m

*Lissodendoryx diversichela*

1,350 m

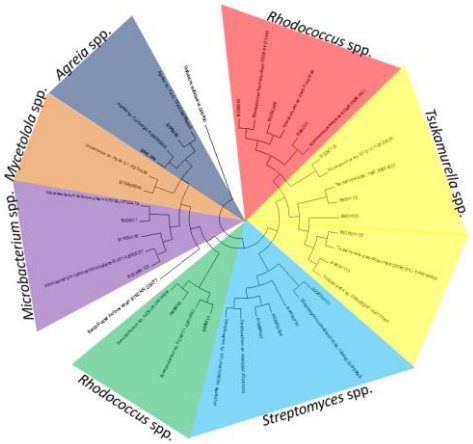
*Stelletta normani*

1,350 m

*Poecillastra compressa*

2,100 m

Sediments
750 m – 2,900 m



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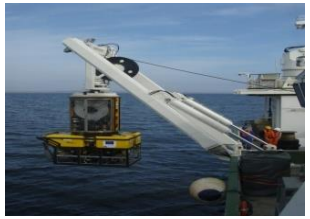
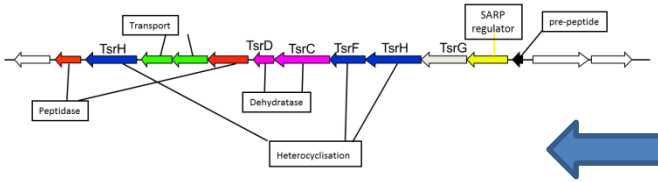
# WP1-4 Assembling the Marine Biodiscovery Pipeline



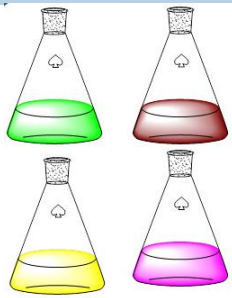
*Stelletta normani* (1,300m)

*Lissodendoryx diversichela* (1,300m)

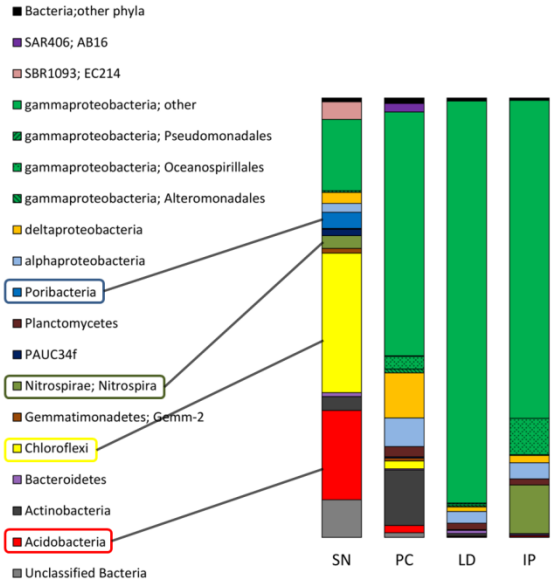
*Inflatella pellicula* (2,900m)

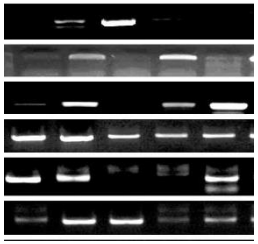



Discovery of new genes giving new products

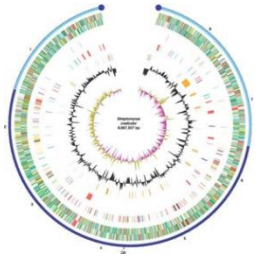


Fermentation under different conditions

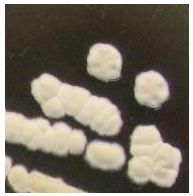


Gene expression analysis



Genome sequencing



Isolation of bacteria

Bacterial diversity in sponges



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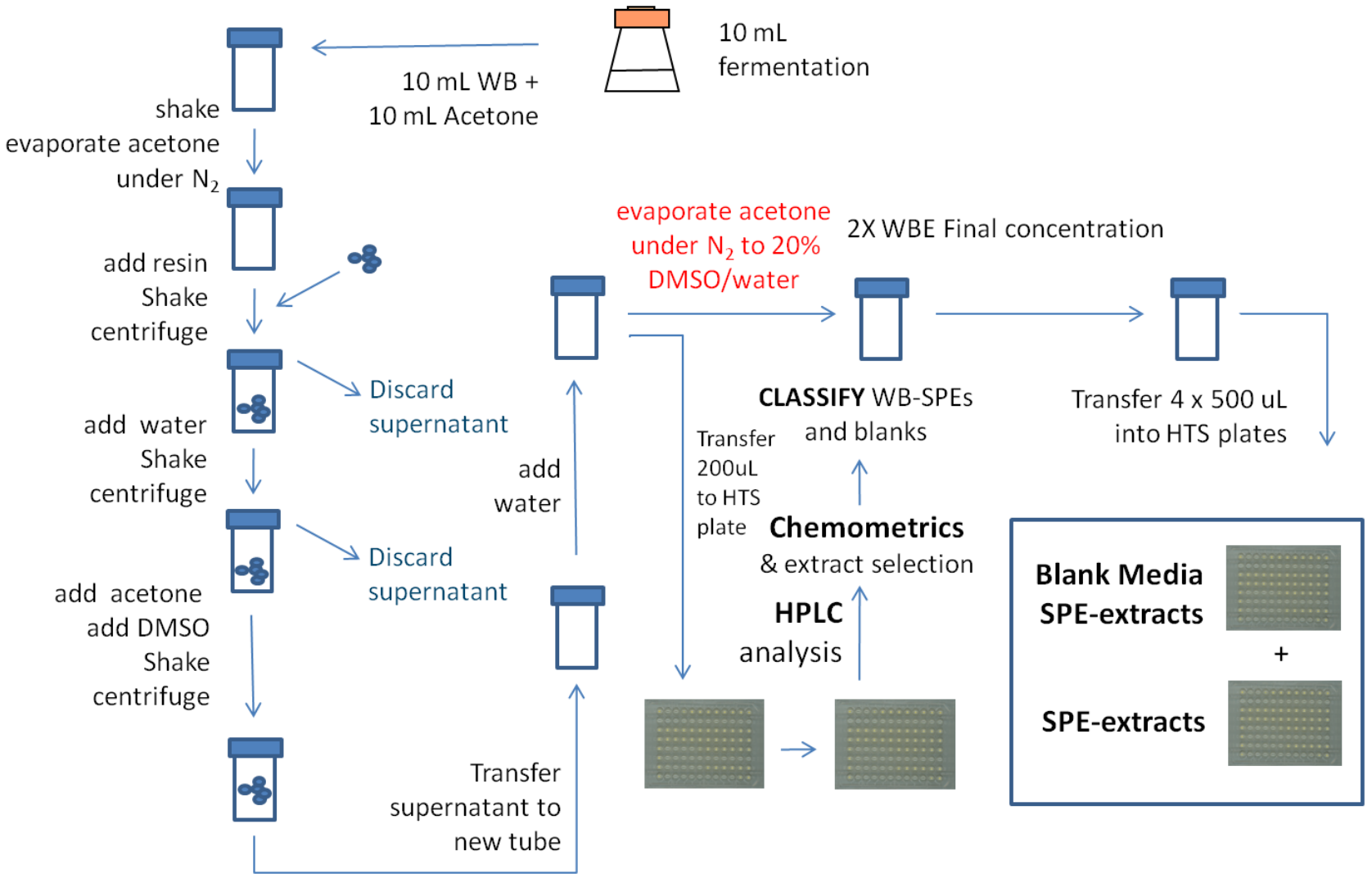
# WP2 Standardised Fermentation and Extraction Protocols



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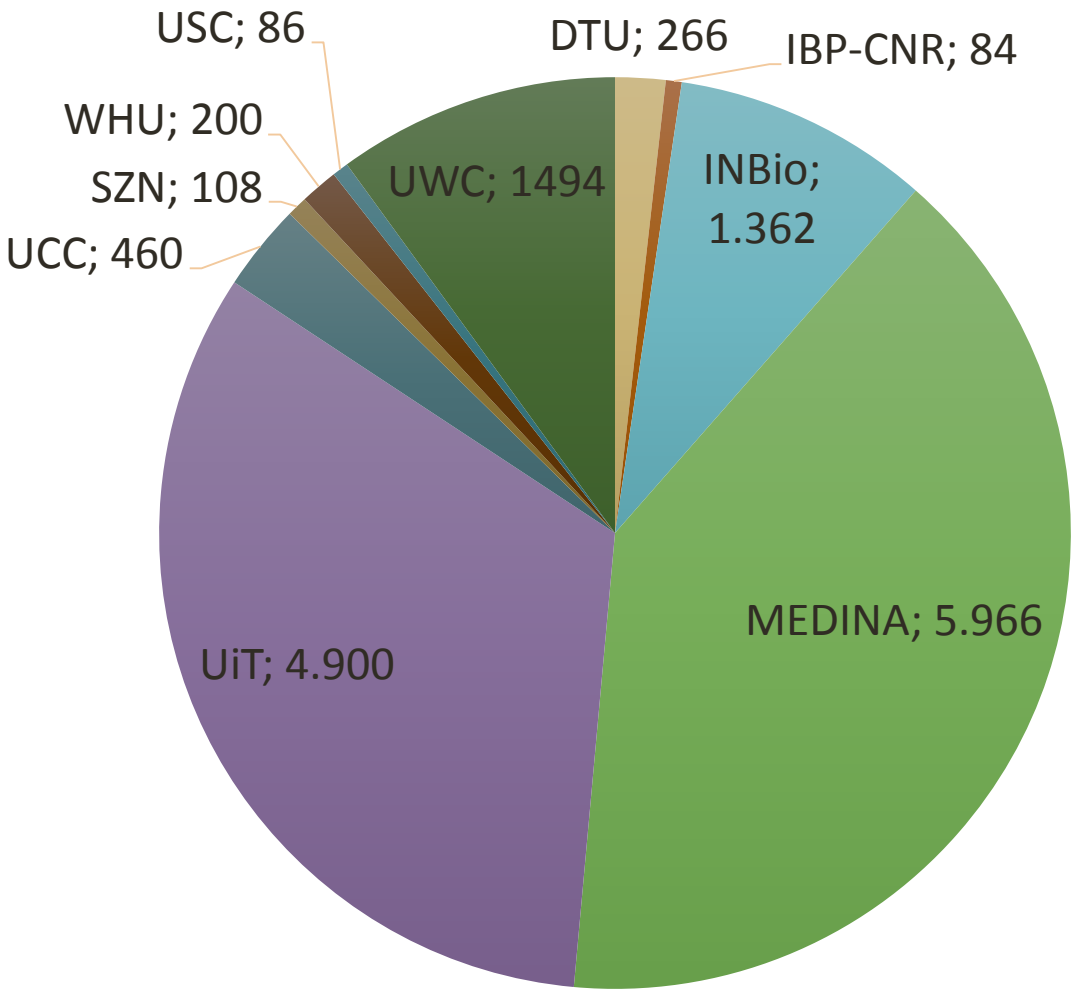
# WP2 – Extracts and Fractions (n=14,962; 83% of total)



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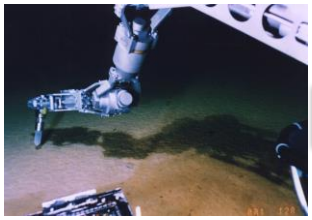
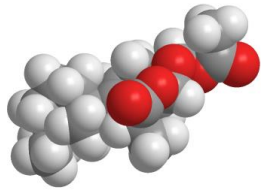
# WP2/3 Data Management

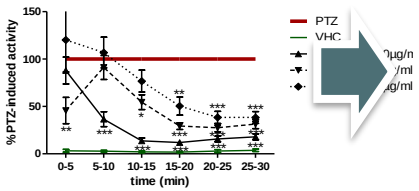


Sampling in ABNJ

MGR

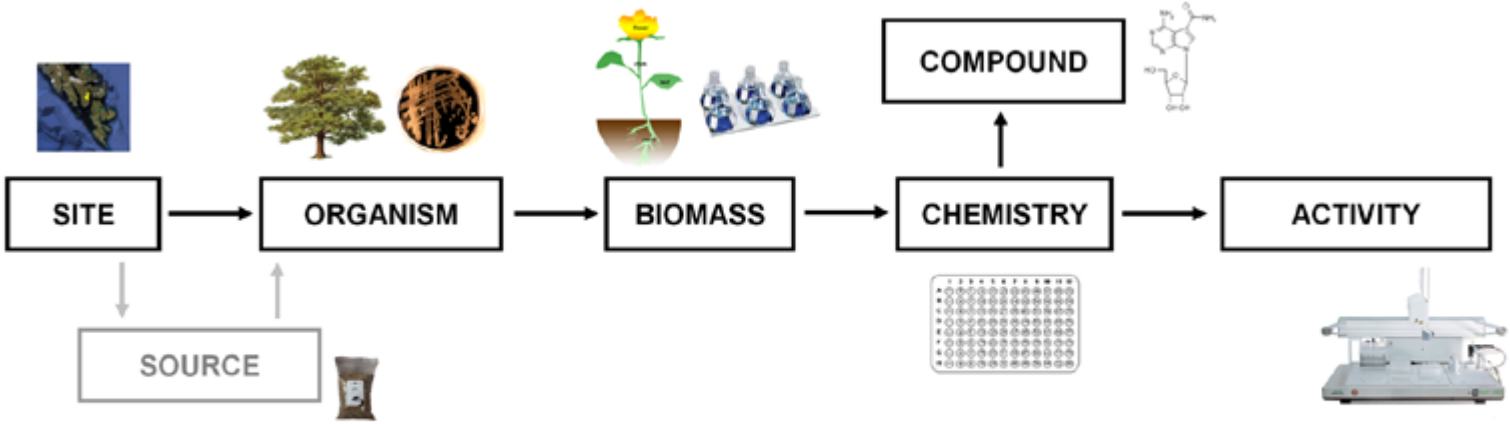


Chemistry




Bioassay

Product




**OpenNAPIS**tm

**Functional Design**

White Point Systems, Inc.
20100626



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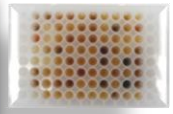
# WP3 PharmaSea Anti-infective assays

Crude extracts or fractions


Inoculum assay


**T0** absorbance

612 nm

Incubation
18-20 h 37ºC
(7-14 days
Anti-TB)


**TF** absorbance

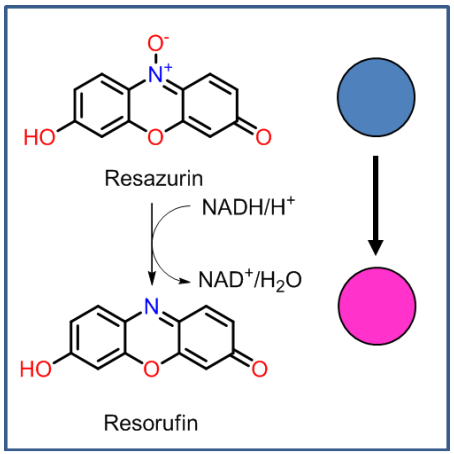
612 nm

**Absorbance / Resazurin dye** 0.002%

Incubation
2 h 37ºC


Fluorescence

570 nm excitation/600 nm emission




Data analysis
**Screener Program**

**HIT SELECTION**

Active extracts Non active extracts



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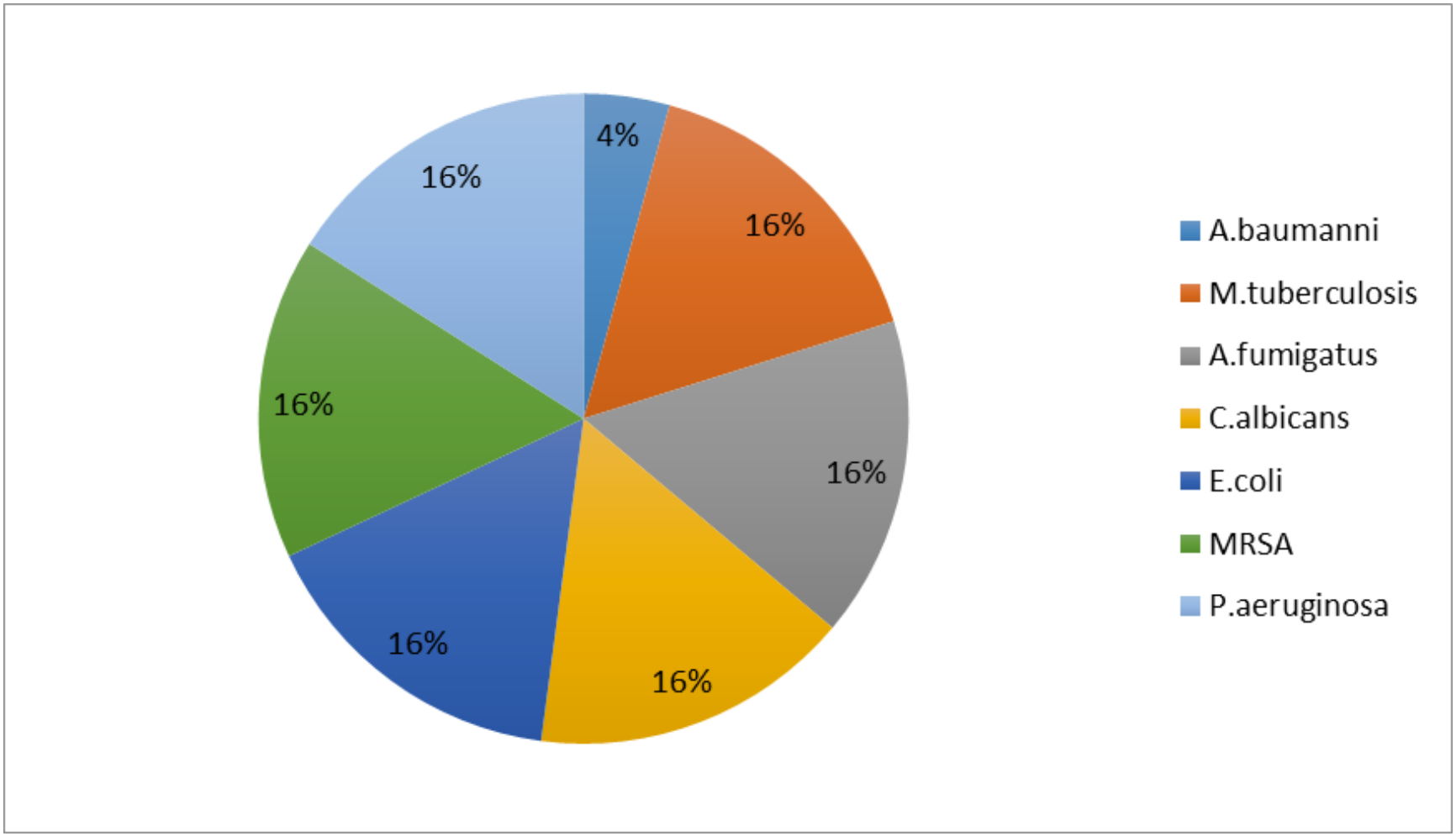
# WP3 – Anti-infective Screening Events (n = 87,356)



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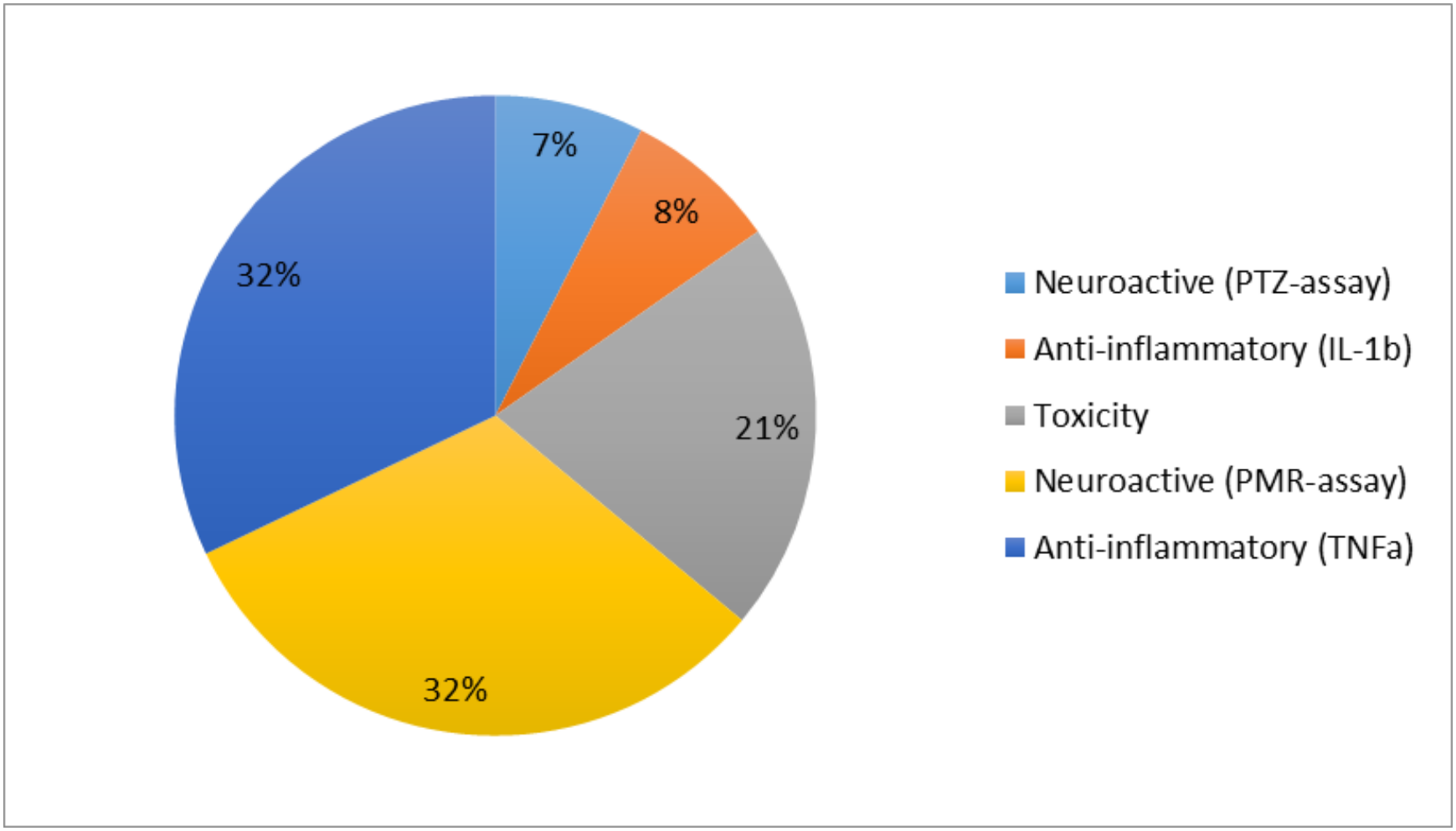
# WP 3 – Other Screening Events (n = 24,538)



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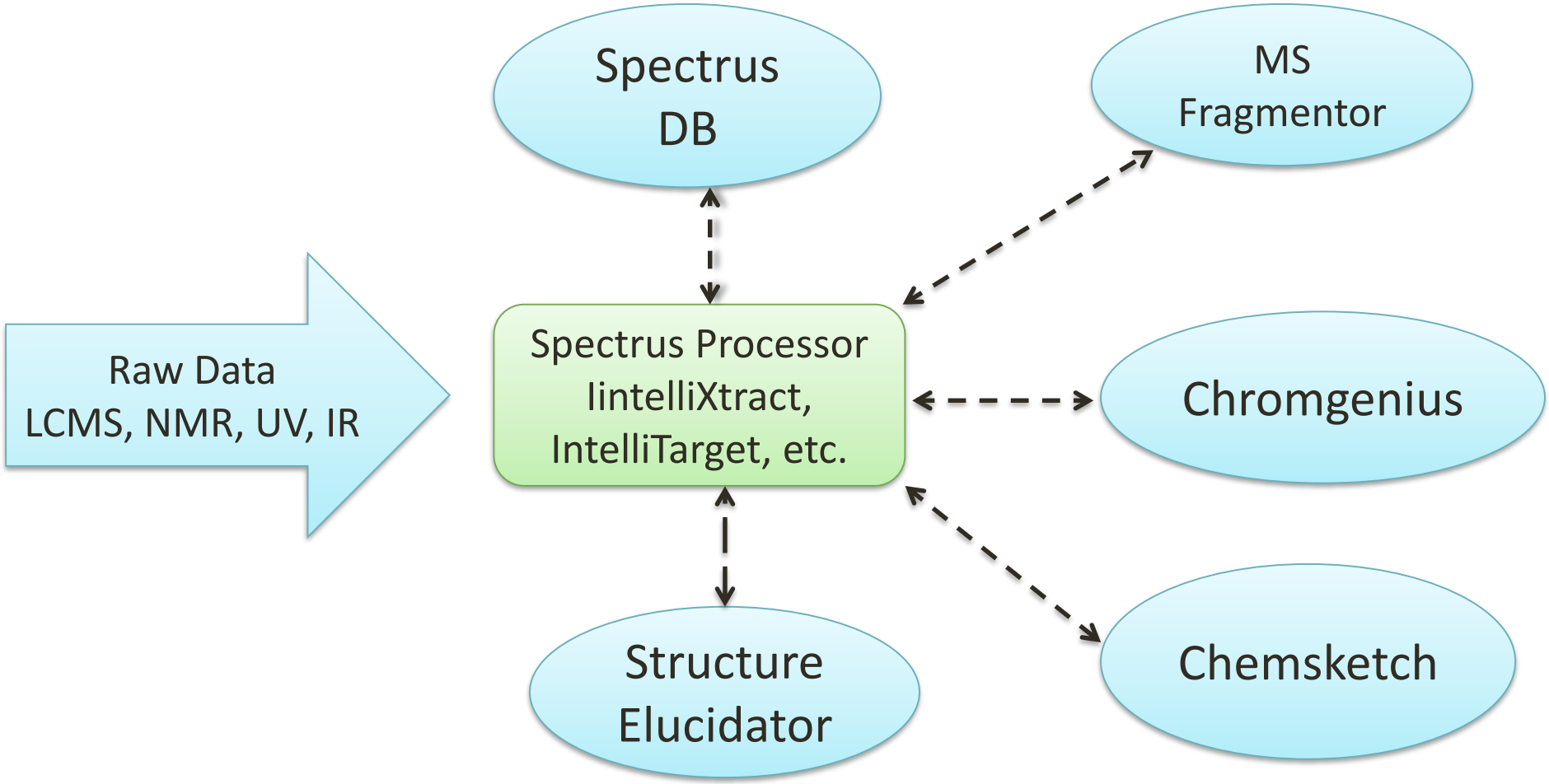
# WP4 New dereplication tools by developing ACD/Labs software tools



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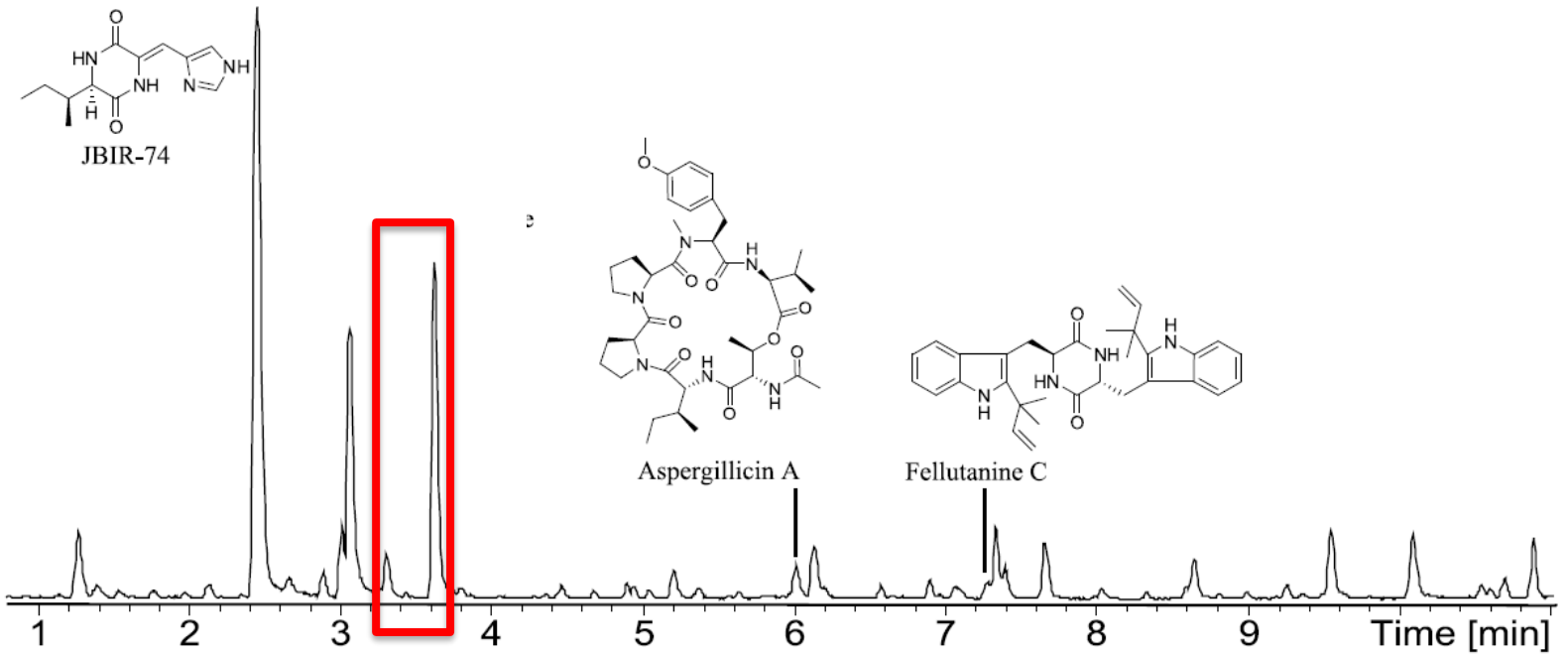
# Dereplication – Is your material known or new?

**Options:**

1.) Targeted dereplication – search all members of a database against your LC-MS data.

2.) Untargeted dereplication – search all peaks in your LC-MS in a comprehensive database



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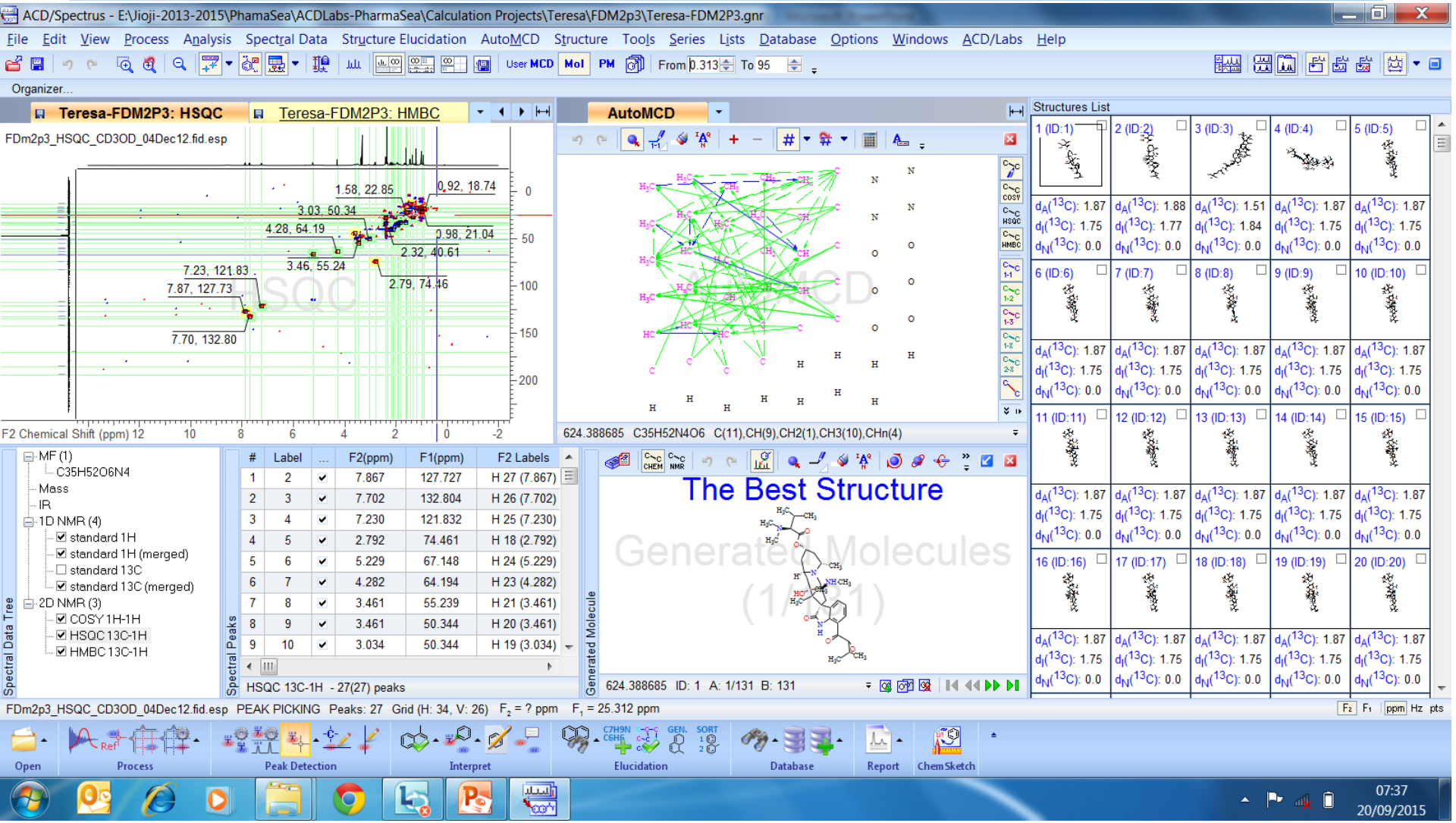
# Dereplication by NMR






Citrinadin A from a marine-derived fungal extract

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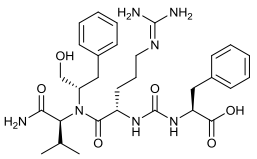
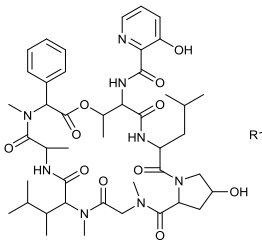
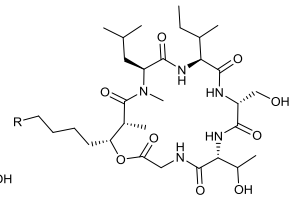
# WP4 Some of the Chemical Diversity Isolated to Date
# Several selected for scale up and further work



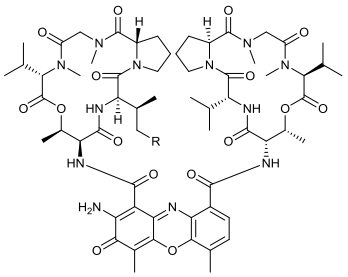
**Mer-N 5075A**
Family 1



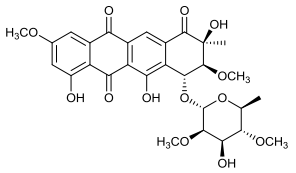
**viridogrisein**
Family 3



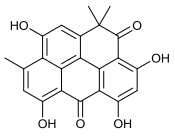
**antibiotic SF 1902A1** (R = $C_2H_5$)
**antibiotic SF 1902A2** (R = H)
Family 4



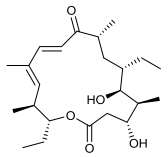
**actinomycin D** (R = H)
**actinomycin C2** (R = $CH_3$)
Family 5



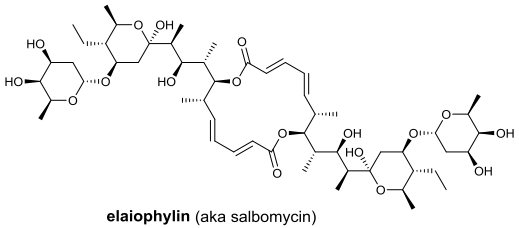
**steffimycin B**
Family 11



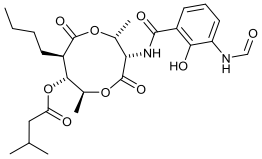
**resistomycin**
Family 12



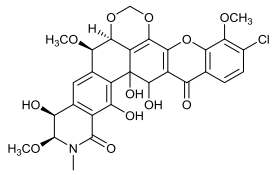
**protylonolide**
Family 6



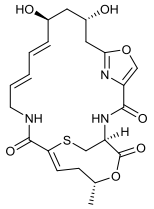
**elaiophylin** (aka salbomycin)
Family 7



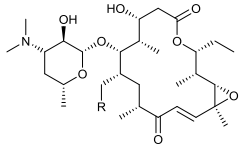
**blastmycin**
Family 21



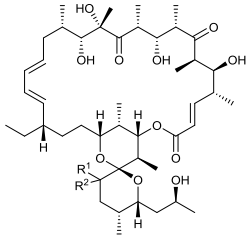
**lysolipin X**
Family 22



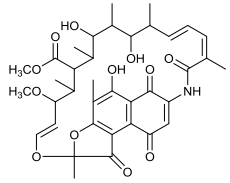
**griseoviridin**
Family 23



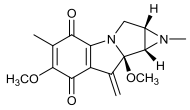
**rosamicin** (R = CHO)
**juvenimicin** (R = H, stereoisomer)
Family 8



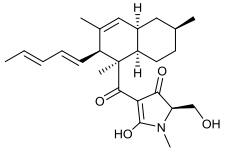
**oligomycin A** ($R^1$= H, $R^2$ = H)
**oligomycin B** ($R^1$, $R^2$ = =O)
Family 9



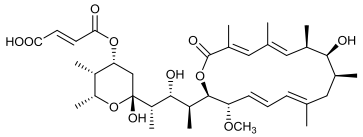
**rifamycin S**
Family 24



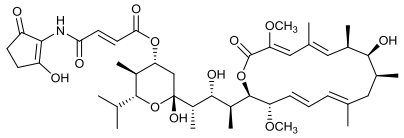
**mitomycin K**
Family 25



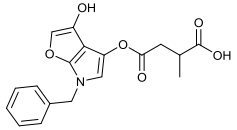
**phomasetin**
Family 26



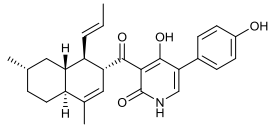
**hygrolidin**



**bafilomycin $B_1$**
Family 10



**tensidol B**
Family 27



**ilicicolin H**
Family 28



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# WP6 Access - Legal

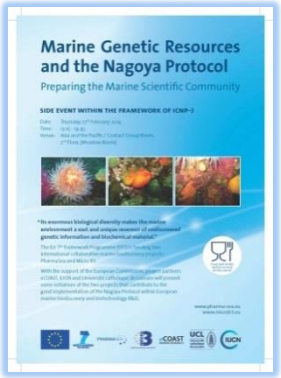
## Create Science/Policy Interface

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

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# WP7 Communication and dissemination: Radio and news articles


**BBC: Drugs in dirt – Scientists appeal for help**

US scientists are asking the public to join them in their quest to mine the Earth's soil for compounds that could be turned into vital new drugs... **» (read)**

Copyright: http://www.bbc.com
20.01.2015


**New Scientist: "Antibiotic abyss – the extreme quest for new medicines"**

As antibiotic resistance increases, audacious expeditions are taking the quest to the ocean depths, and not a moment too soon... **» (read)**

Copyright: www.newscientist.com


**CNN: Arctic waters could hold secret to creating life-saving drugs**

It is early afternoon on board the "Helmer Hanssen," and the Arctic sun is already starting to set. Near the back of the ship, two people dressed in orange rain slickers are anxiously waiting... **» (watch)**

Copyright: http://edition.cnn.com


**BBC Radio 4 Shared Planet: Medicinal Planet**

**Radio interview** with PharmaSea's Project Leader Marcel Jaspars (Duration: 28 minutes)

In recent years some conventional medicines such as antibiotics have become less effective in treating diseases and infections. With an increasing human population worldwide, the need to discover new medicines for the benefit of human health will... **listen**.


**Reuters: Extreme medicine – The search for new antibiotics**

Marcel Jaspars, a professor of organic chemistry at Britain's University of Aberdeen, is leading a dive deep into the unknown to search for bacteria that have, quite literally, never before seen the light of day.... **» (read)**

Copyright: www.reuters.com
17.08.2014


**Welt Online: Neue Antibiotika schlummern in der Tiefsee**

Antibiotika-Resistenzen breiten sich zunehmend aus. Um neue Wirkstoffe gegen die Superbakterien zu finden, starten Wissenschaftler jetzt eine Expedition zu den tiefsten Stellen der Tiefsee. ...» **read**

Copyright: Welt Online



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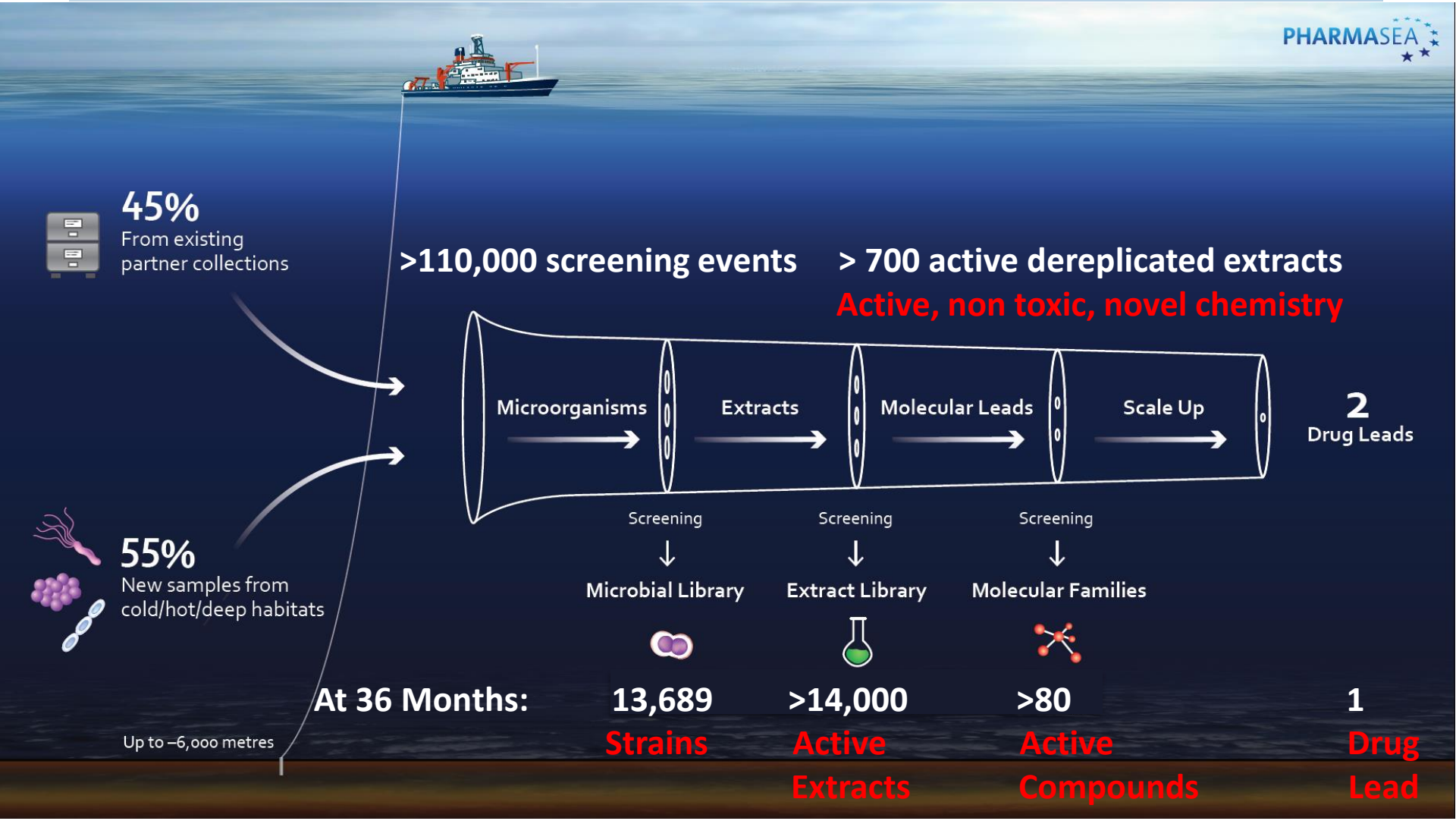
# PharmaSea Progress to Date



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# Conclusions

- PharmaSea will make marine biodiscovery more attractive for industry to adopt.
- PharmaSea is widening the bottlenecks
  - High quality biodiversity
  - Streamlined biodiscovery pipeline
  - New chemistry with new activity
- PharmaSea will provide mechanisms to transfer findings to end users whilst acknowledging:
  - Need for legal certainty over marine biodiversity collection.
  - Regulatory stress on companies.
  - Lack of risk taking by companies due to shareholder pressure.

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http://pharma-sea.eu/


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