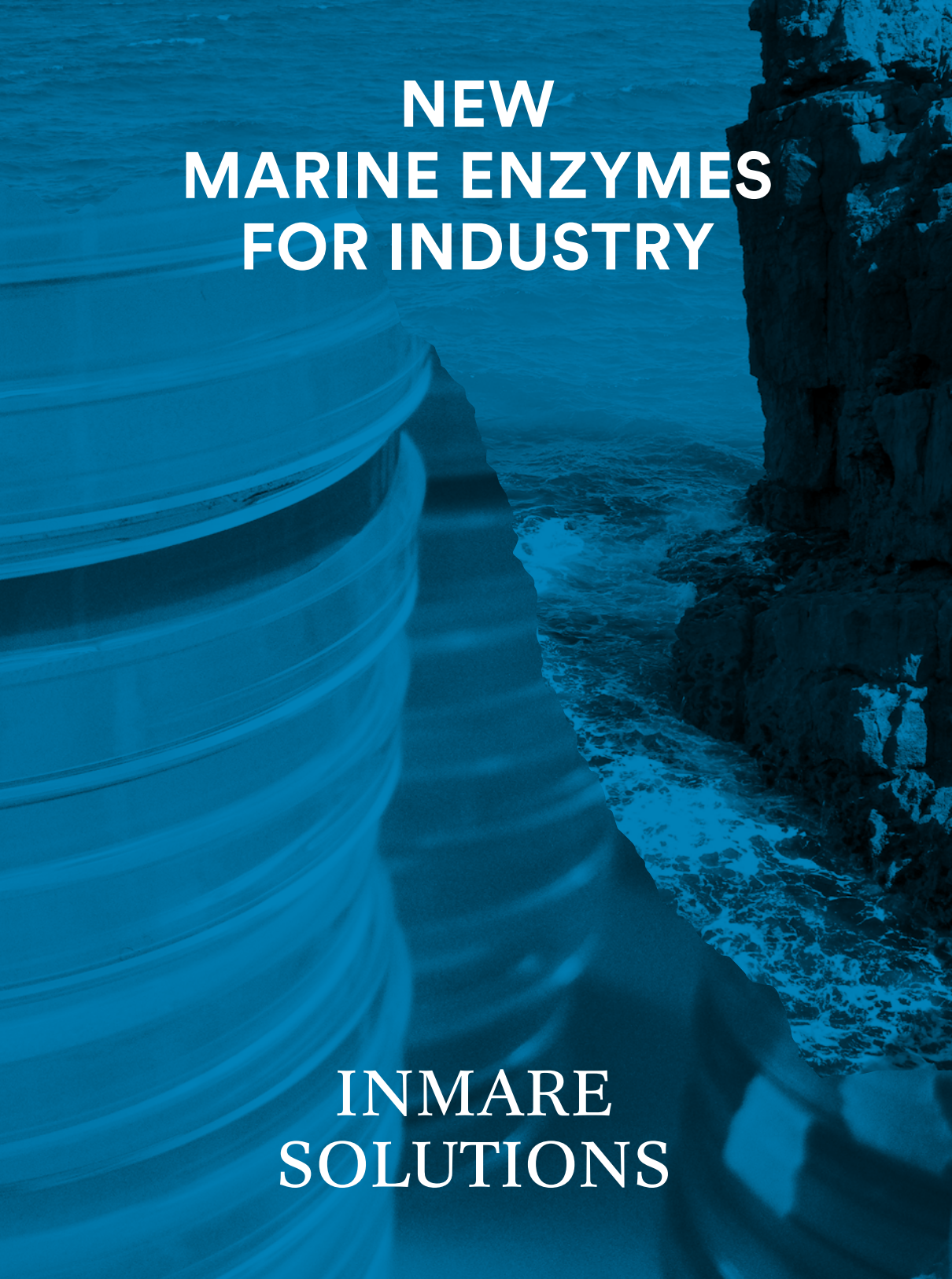

NEW MARINE ENZYMES FOR INDUSTRY

INMARE SOLUTIONS

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INMARE SOLUTIONS

ACKNOWLEDGEMENTS

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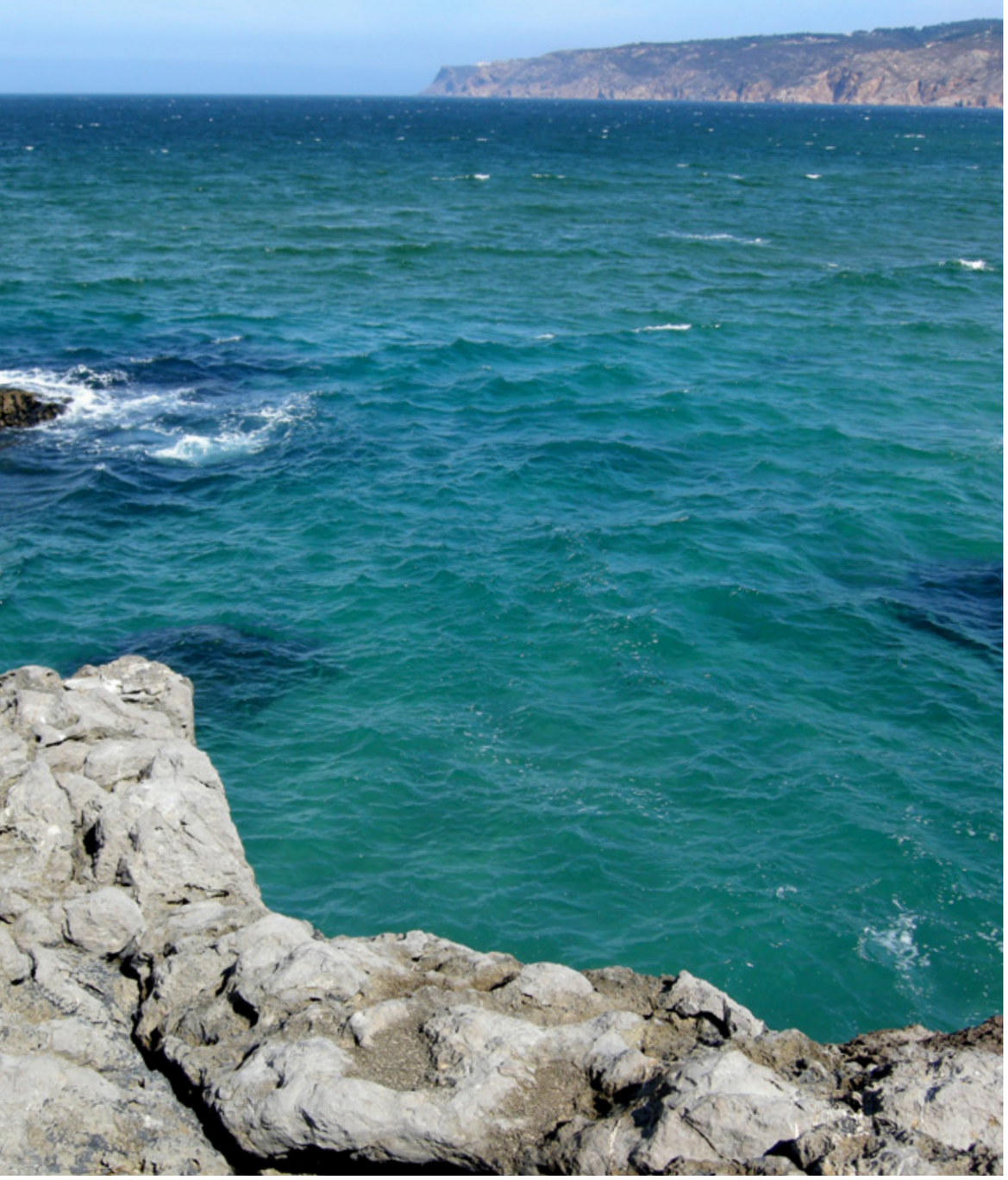
EXECUTIVE SUMMARY

Enzymes are nature's catalysts. Using enzymes in industrial processes makes them faster, cleaner and more energy and resource efficient. Traditionally enzymes have been used by many industrial sectors including the food, agricultural, cosmetic, and pharmaceutical industries, to name but a few. Global challenges such as limiting natural resources (food and energy) and pollution, have ignited the quest for more sustainable and cleaner industrial processes and bio-based products. This, in turn, is driving the demand for new industrially relevant enzymes, metabolites and small molecules.

INMARE (Industrial Applications of Marine Enzymes) a four-year research project, comprising a consortium of industrial and academic partners, set out to streamline the enzyme biodiscovery process. At the onset of INMARE, it took at least five to seven years to develop new bio-based chemicals using enzymes. INMARE aimed to reduce this timeline to less than three years, by tackling some of the main bottlenecks in the enzyme biodiscovery pipeline.

Recent technological advances in metagenomics and high-throughput sequencing, means that generating enzyme collections, from microbial sources, is relatively straightforward. The real challenge, however, is that only a very small percentage of the enzymes in a collection are



Guincho -
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useful in biocatalytic processes. INMARE focused its attention on this enzyme optimization phase, in order to improve the hit rate of positive clones and the overall value of these enzyme collections, by identifying so called enzyme 'all-rounders' or 'frequent hitters', enzymes, capable of accepting many substrates and therefore usable in more than one industrial setting. Increasing the hit rate of these collections would significantly reduce the time and costs expended to identify relevant enzymes.

INMARE implemented a series of actions to achieve their vision. They targeted samples of microbes from marine biodiversity hotspots, thus leveraging the unique bioactive potential of these microbes (adapted to living in extreme conditions) for industrial processes. They established innovative screening platforms, sequencing analysis pipelines and in vitro expression systems to allow early identification, production and testing of promising enzyme candidates. Finally, by identifying markers of enzyme promiscuity, INMARE was able to fast-track the identification of enzyme all-rounders.

Through developing one of the world's largest collections of enzyme all-rounders, some of which are already performing better than current commercial products, INMARE's ambitions to reduce the industrial enzyme biodiscovery pipeline from seven years to under three years, have been more than achieved. In some cases, the timeline has actually been reduced to a matter of months, (notwithstanding the time taken to implement subsequent commercial steps, where other factors must also be considered).

The success of INMARE, a four-year research project, is unprecedented. INMARE has demonstrated what can be achieved with the right combination of partners, working in collaboration towards a shared vision. INMARE leaves a rich legacy in terms of biological resources (microbial samples, genomic and metagenomics libraries and enzyme collections), state-of-the-art tools and technologies, as well as over 60 peer reviewed papers and book chapters which capture INMARE's scientific advances and knowledge. INMARE's contributions will contribute to establishing Europe as a global leadership in the area of biobased products and processes. INMARE has shown what is feasible as well as what remains to be done.

INMARE is an exemplar of how European collaborations can accelerate innovations in industrially relevant research and development. It demonstrates the crucial role of the European Union's Horizon Research and Innovation Programmes in driving innovation.

ENZYME BIODISCOVERY AND THE INMARE CHALLENGE

The market for industrial enzymes for non-therapeutic uses (foods, detergents, textiles, pulp and paper) has doubled in the last 15 years and has been recently estimated to be in the region of USD $4 billion per annum. Enzymes provide clean and energy efficient natural catalysts for chemical reactions in a variety of industries. With a growing global population, limiting natural resources and an urgent need to provide environmentally sensitive and sustainable alternatives to toxic industrial processes, demand for industrial enzymes will continue to grow. Europe is a market leader in this field, with 64% of the world's leading enzyme companies located in Europe. Thus the industrial enzyme sector represents significant potential for Europe in terms of escalating global leadership in the area of biobased products and processes.

Recognising the opportunity for Europe, the European Union's Horizon 2020 Research and Innovation Programme[1] awarded a grant of €6 million to fund 'INMARE', short for 'Industrial Applications of Marine Enzymes'.

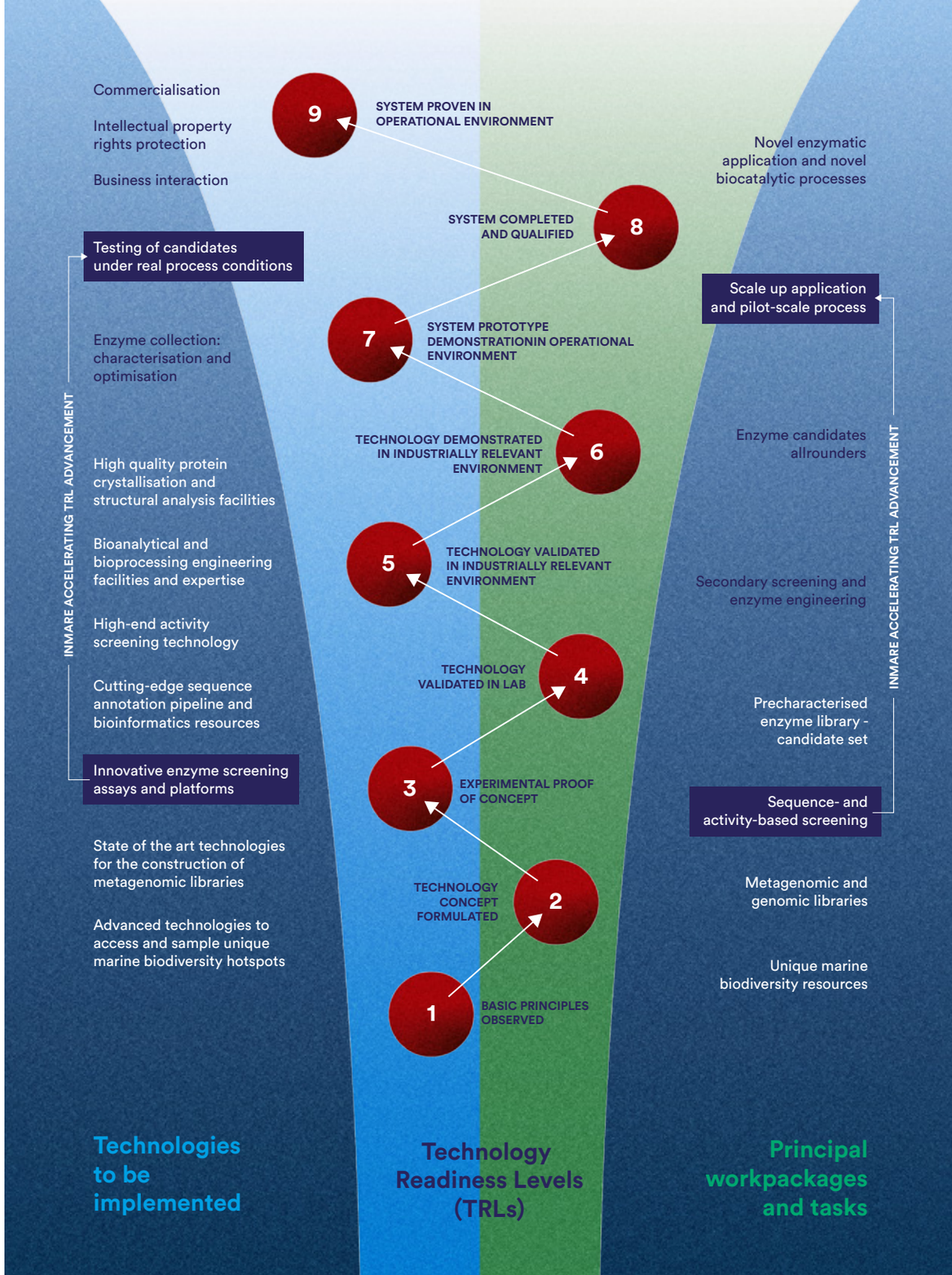
INMARE set out to explore marine biodiversity in diverse environments, with the aim to find novel enzymes to meet the needs of the growing industrial enzyme market. In doing so, INMARE sought to overcome known technological bottlenecks in marine enzyme biodiscovery, resulting in a greater efficiency in the discovery pipeline and in the enzyme identification-to-market success rate.

To achieve their objectives, INMARE brought together some of the leading researchers in marine enzyme biodiscovery in Europe, from 24 multi-disciplinary academic and industrial entities across 12 countries. This partnership encompassed the necessary expertise, infrastructure, technology and industry networks to streamline the pathway from discovery of new marine enzymes and bioactive compounds to industrial application in specific areas. The four-year INMARE project adopted a multifaceted approach to its work. This is summarised in Figure 1.

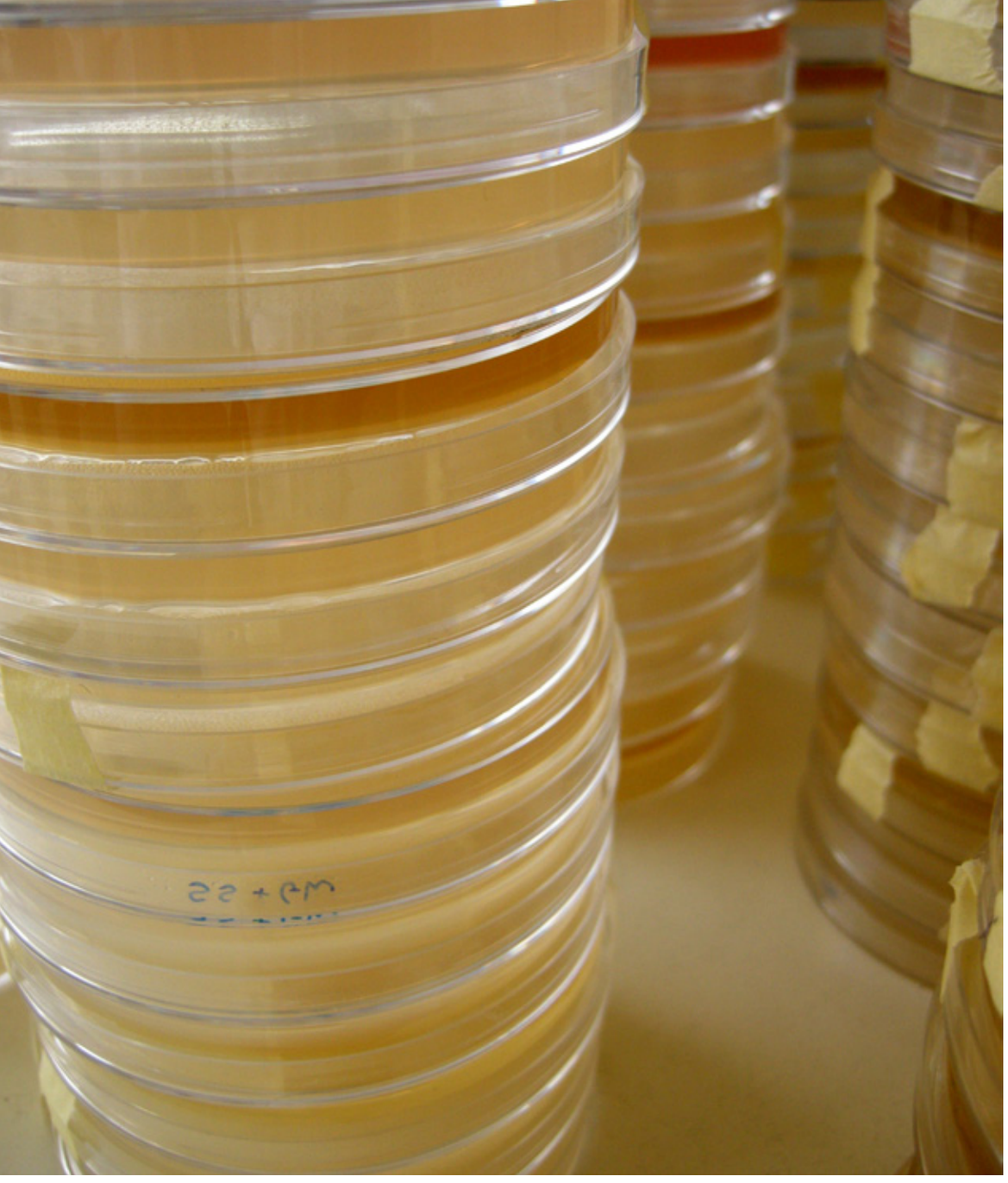
> "With a growing global population, limiting natural resources and an urgent need to provide environmentally sensitive and sustainable alternatives to toxic industrial processes, demand for industrial enzymes will continue to grow."

INMARE builds on the huge progress that has already been made through previous European Framework Programme funded research initiatives to explore the genomic and biochemical potential of marine bio-resources, INMARE has drawn from these previous efforts in terms of expertise, resources and technologies.

1. https://ec.europa.eu/programmes/horizon2020/



Right: Figure 1. Pipeline representing the technical solutions provided by INMARE to significantly shorten the time needed from discovery to application in different technological levels. The innovative screening methodologies developed by INMARE reduce the time taken to achieve higher Technology Readiness Levels (TRL) and move from screening to testing and scale-up, as indicated by the white brackets.



Bacterial screening plates -
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ENZYMES FOR INDUSTRIAL APPLICATIONS: THE POTENTIAL OF MARINE MICROBES

Increasingly, attention is shifting towards the Ocean as a sustainable source of materials, food and energy, as well as resources with potential for the development of new drugs and biotechnological applications. Because enzymes offer a greener, safer and cheaper alternative to chemical (production) processes, marine microbial resources hold promise for innovation in industrial biotechnology.

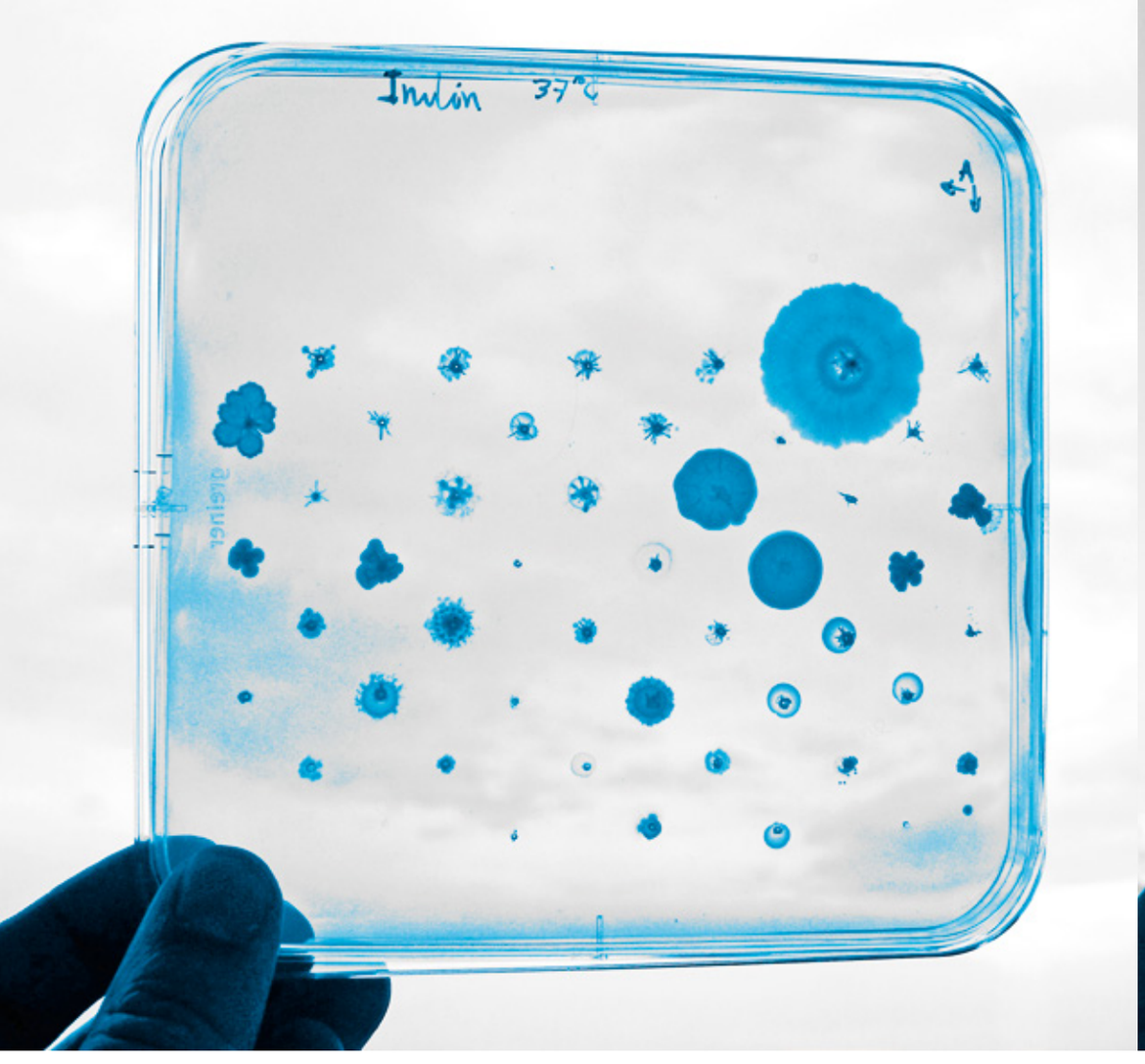
Most industrial biotechnology processes are microbial-based, and it is anticipated that new biotech processes and applications will emerge from the yet unknown microbial biodiversity or so-called “microbial dark matter”. The marine environment hosts some of the most challenging conditions on Earth, from high pressures in the deepest parts of the ocean, to temperatures of more than 300°C at hydrothermal vents, and extreme chemical conditions in hypersaline brine pools and at cold seeps. The metabolic diversity of microorganisms adapted to survive in these conditions suggests that they may harbour enzymes uniquely able to perform in industrial settings characterised by harsh physical and chemical conditions.

In spite of their potential for industrial applications, to date very few (marine) microbial enzymes have actually made it to the commercial market. This is partly because the enzyme optimisation process, which seeks to make enzymes more stable and perform better in the harsh environment of industrial processes, is laborious and costly, thereby forming an important bottleneck in industrial applications.

To tackle this problem, INMARE scientists focused on early stages of the biodiscovery pipeline towards finding better natural enzyme variants – so called ‘enzyme all-rounders’, *i.e.* enzymes with multiple activities and broad substrate spectra displaying stability in a wide range of physico-chemical conditions. These features allow such enzymes to perform a range of desirable functions under a set of realistic industrial conditions.

INMARE isolated samples from a wide range of marine environments, ranging from shallow coastal inlets to the deep sea, and from an array of organisms, such as macroalgae, sponges and marine invertebrates. INMARE scientists have successfully sampled and processed materials from unique microbial biodiversity hotspots.

> “The metabolic diversity of marine microorganisms adapted to survive in extreme environments suggests that they may harbour enzymes uniquely able to perform in harsh industrial settings.”



Biocatalyst screening
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Bacterial screening single plate
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5L fermenter
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ACCELERATING MARINE ENZYME BIODISCOVERY: INMARE SOLUTIONS

Troughout its four-year journey, INMARE amassed a wealth of curated resources, including samples, genomic and metagenomic libraries, enzyme collections as well as bio-informatics and bio-catalytic data. These resources, together with the technological innovations in screening, sequence analyses, expression and substrate profiling fast tracks the identification of the most promising enzyme candidates in an industrial process. These recourses also provide raw material and tools for current and future bioprospecting of new metabolites and enzymes with applications in biocatalysis, bioremediation and drug discovery. Proof of INMARE's success is evidenced by the fact that they have already delivered one of the most extensive, curated collection of enzymes worldwide, some of which are already performing better than current commercial products.

Some of the most relevant and important achievements are detailed below:

- Through a targeted sampling campaign, in both known and previously unexplored marine biodiversity hotspots, INMARE amassed a curated catalogue of samples, genomic and metagenomics libraries. This provided a vast resource for INMARE work, but also a collection that will be available for future biodiscovery.

- State-of-the-art in vitro and in vivo screening platforms were developed, allowing identification of relevant gene products much earlier in the biodiscovery pipeline.

- The construction of novel sequence analysis pipelines which target industrially relevant enzymes streamlined the identification of genes of interest from sequence data.

- The establishment of multiple and complementary in vitro expression platforms facilitated production of enzymes of interest.

- INMARE's biotechnological blueprinting of marine microbes has contributed to the creation of one of the world's largest collections of enzymes from genomic and metagenomics resources, totalling about a thousand, with a selective focus on those most requested by industry. Of these approximately 94% are available in ready to use expression systems and 32% have been characterised.

- Bioinformatics tools that can predict enzyme properties were developed by combining experimental, structural and 3D model data with computational analysis.

- The enzyme collection amassed by INMARE is diverse and non-redundant in terms of their amino-acid sequences, geographical distribution and taxonomic origin. They demonstrate sequence identity of as low as 5% compared to sequences in

> "Through developing one of the world's largest collections of enzyme all-rounders, some of which are already performing better than current commercial products, INMARE's ambitions to reduce the industrial enzyme biodiscovery pipeline from seven years to under three years, has been more than achieved."

> “By identifying markers of enzyme promiscuity, INMARE was able to fast-track the identification of so called enzyme ‘all-rounders’, i.e. enzymes that are capable of accepting many substrates and therefore applicable in more than one industrial setting.”

databases and comprise enzymes from at least 193 geographically distinct sites and from at least 283 known bacterial and archaeal genera, with approximately 607 with unclear taxonomic affiliations.

- The production of bio-catalytic data was a key priority for INMARE and facilitated the testing of enzyme candidates under application conditions at the very early discovery phase.
- By identifying markers of enzyme promiscuity, INMARE was able to fast-track the identification of these versatile enzymes
- Substrate profiling allowed assignment of functions to a number of previously unannotated enzymes, expanded our fundamental understanding of sequence space and substrate specificity profile relationships.
- Versatile biocatalysts were discovered whose in-depth analysis and potential application in biotransformation are currently being explored.
- The design and development of small-scale reactors meant that the biocatalytic performance of previously unannotated enzymes could be assessed.
- INMARE advanced discussions regarding access and utilisation of genetic resources in research & development resulting in a recommendation[2] as a first guide to developing principles of due diligence to support Access and Benefit-Sharing (ABS) compliance under EUR 511/2014[3]. This is one of the first interdisciplinary attempts internationally to give content to the meaning of due diligence in an ABS context.

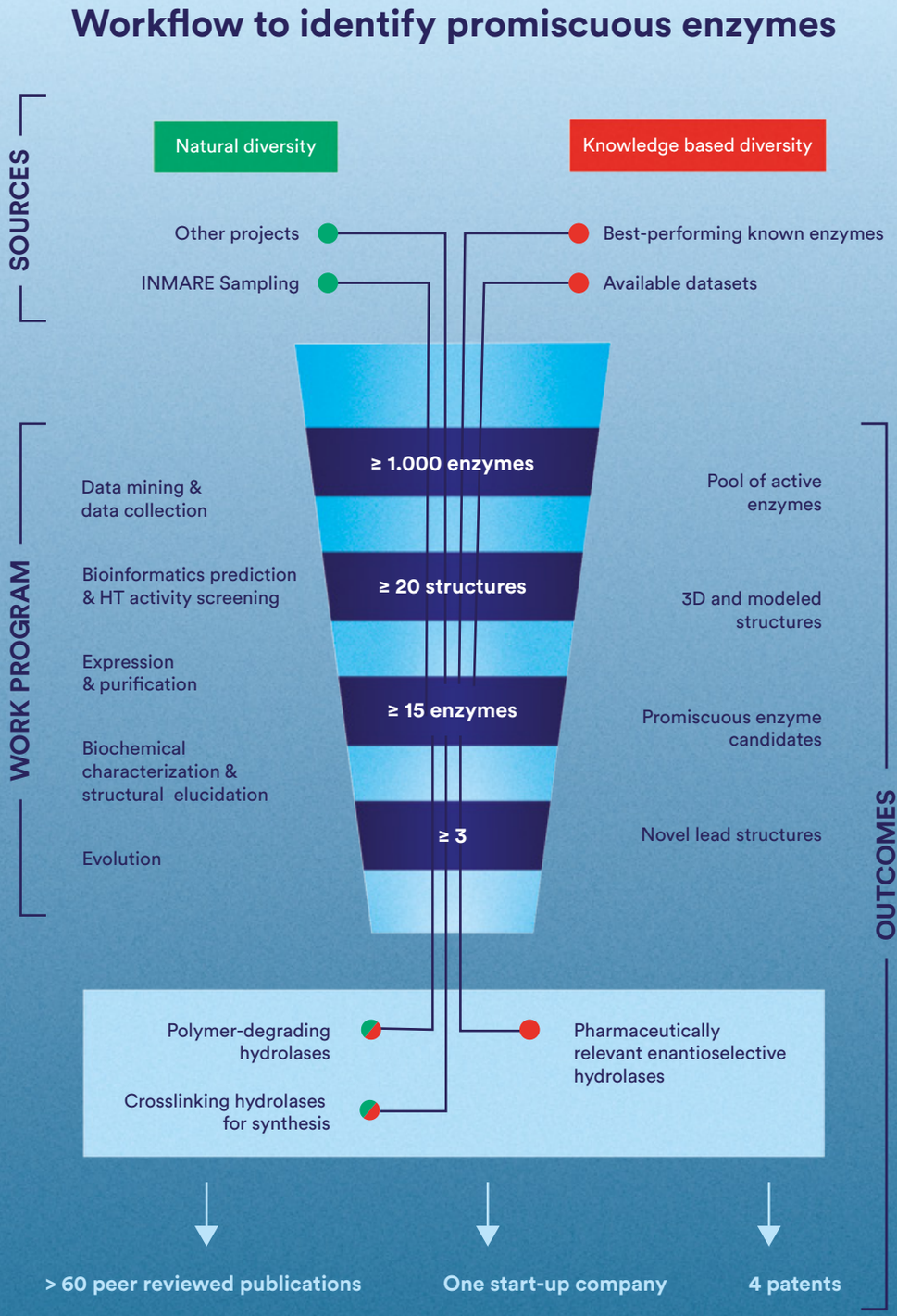
INMARE’s work, discoveries and advances have been captured in over 60 peer reviewed papers and 11 book chapters. These are all available from the INMARE website[4].

2. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3323389

3. Regulation (EU) No 511/2014 of the European Parliament and of the Council on compliance measures for users from the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization

4. http://www.inmare-h2020.eu/

Right: Figure 2. Graphical representation of the INMARE workflow and main outcomes. Adapted from Karl-Erich Jaeger and Manuel Ferrer.



Result of fermentation -
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Cascais -
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Azores - intertidal zone
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INDUSTRIAL MARINE ENZYME BIODISCOVERY: THE REMAINING CHALLENGES

INMARE succeeded in short-circuiting the arduous enzyme biodiscovery pipeline, but in doing so the INMARE team also identified a number of issues that remain to be tackled in future projects to fast-track innovation in marine biodiscovery research.

These encompass technological, research and development, legal, regulatory and communication challenges. These are detailed below:

> "INMARE succeeded in short-circuiting the arduous enzyme biodiscovery pipeline, but also identified a number of challenges that remain must be addressed to fast-track innovation in marine biodiscovery research."

TECHNOLOGICAL

- Producing enzymes from some marine bacteria at high yields remains a bottleneck. The production of enzymes by wild marine strains or hosts usually results in low production yields. This limits the next step of bioprocess development because the number of possible reactions is restricted by the amount of enzyme available.
- Faster and more reliable screening processes and biocatalytic models for marine bacteria are required. Without a proper development pipeline, operating conditions, reactor configuration and process parameters have to be evaluated for each biocatalyst and reaction tested.
- High throughput analytical methods are not available for some of the most interesting substrates. In particular, analysis of chiral substrates and/or products requires expensive, technical and time-consuming equipment.
- Expression and screening of large numbers of potential enzymes in parallel is still a challenge. Enzymes of various classes have very different properties and require individual solutions for expression and screening.
- The scale up of bioprocesses is difficult. No unifying engineering tool is currently available allowing a reliable scale up of the various steps of a bioprocess. The step related to bacterial growth is particularly critical and biomass and production yields are not usually maintained across scales, requiring adjustment of conditions and bioreactor design.
- Implementation of a biocatalytic process requires scale-up and process development with robust enzymes withstanding high temperatures and, in particular, high concentrations of organic solvents.
- Handling and sharing vast amounts of complex data within and among partners in a large consortium presents challenges.

LEGAL / GOVERNANCE

- The scientific community recognises the need to comply with the EU regulation[3] No 511/2014 to implement the Nagoya Protocol, but are much less clear on what this means in practice. Researchers who utilise genetic resources in their R&D must comply with, as well as seek, keep and transfer to other users any Access and Benefit-Sharing (ABS) obligations associated to the genetic resource (sample/derivative). If they lack the required information about a sample, then they must cease further work on that sample/derivative. General good scientific practice necessitates good record keeping regarding sample origin and associated information. The difficulty arises, however, when trying to establish whether or not there are ABS obligations associated to a sample. Scientists often ask, 'can we use this sample for X/Y/Z purpose'. The answer, however, is often quite complex. It will depend on whether the country of origin of the sample was controlling access to its genetic resources at the time of access, or has since put in place retroactive ABS legislation. It will also depend on the planned use of the sample/ derivative. Finding the relevant ABS information can be difficult, particularly from other jurisdictions, often because national governments have not fully elaborated their ABS laws, or the information is not easily accessible from the access and benefit-sharing clearing house[5] or from the relevant national focal points. In the absence of clarity, samples cannot be used and this represents a significant waste of resources.

> "The scientific community recognises the need to comply with the EU regulation to implement the Nagoya Protocol, but are much less clear on what this means in practice."

- Synthetic biology presents a considerable challenge in the context of the Nagoya Protocol. A final compound of interest to a commercial entity may contain none of the original biological material from a sample, but may incorporate synthetic genes developed based on sequence data derived from one or more samples (possibly from different origins). If this final compound has also been the result of R&D by multiple partners, a very confusing situation emerges when trying to establish and comply with applicable access and benefit-sharing obligations.

- If a commercial enterprise is interested in an enzyme they will first try to establish who owns the intellectual property (IP). It is often the case, particularly in a collaborative research project, that multiple partners from different countries are involved in the R&D pipeline and contributed to the development of a synthetic gene product. The commercial entity has to establish first the origin of any sample used in the R&D, and whether benefit-sharing applies under the Nagoya Protocol, as well who owns the IP. A complex situation such as is described above is very off putting for a commercial entity that requires legal clarity and that prefers to deal with a single entity in terms of 'payment'.

- The expectation from major project funding organisations to create large, representative consortia, including leading researchers, institutes and businesses can create difficulties in managing and protecting intellectual property. For example, information regarding process conditions, promising substrates, reaction media composition, are valuable for both academic and industrial partners and are not easily shared.

- Science and technology moves faster than the law and this will have impact for any current conversations on the inclusion of Digital Sequence Information (DSI) within the scope of the Nagoya Protocol, as well as current discussions at the UN General Assembly about a legally binding instrument under UNCLOS on the conservation and sustainable use of marine biological diversity areas beyond national jurisdiction.

COMMUNICATION AND KNOWLEDGE TRANSFER

- Although Europe is moving towards open innovation, there remains a culture of secrecy around some innovations, even within a collaborative project. This can cause conflicts for the project given the funding body's requirement for active outreach and dissemination of research outputs.

- The commercial value of a newly discovered enzyme is often overestimated by start-up companies and academia. Industry and academia should be more realistic and transparent in their expectations and in any external communication about economic potential. This requires industry and academia to jointly work on a better understanding and exchange of their expectations.

- The time taken to develop a commercial product, considering the R&D, demonstration and business phases often extends beyond the typical three to four year time scales of research and innovation projects. Expections both within and beyond the project need to be managed through more effective communication.

- Bringing a new enzyme to market can encompass various scenarios. Companies can offer to pay for testing of an enzyme, or pay for a small amount of the enzyme to test themselves. More complex issues arise following 'proof of concept' when a commercial enterprise is interested in commercializing or using the enzyme. Some companies wish to pay only a few thousand euro for non-exclusive use, indicating that the academic institution can licence the enzyme to other companies for

> "The time taken to develop a commercial product, considering the research, development, demonstration and business phases often extends beyond the typical three-four year time scales of research and innovation projects."

5. https://absch.cbd.int/

any use other than that for which they have paid. The company places more value on the process, than on the enzyme. It is difficult for any academic entity to sign such an agreement as they would not benefit from royalties. This represents a real stumbling block in the pathway from enzyme to market. In another scenario, a company may be willing to pay for the commercialization and exploitation of the enzyme. In this instance there is a need for a benchmark calculation to estimate, on average, the cost of enzymes for multiple applications. This would help academic groups to establish a starting point for discussions with companies from different sectors in terms of payment.

“There is a need for a benchmark calculation to estimate, on average, the cost of enzymes for multiple applications to facilitate discussions between academia and industry.”

Sampling -
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THE WAY FORWARD: CONCLUSIONS AND RECOMMENDATIONS

INMARE is an exemplar of how European collaborations can fast-track innovations in industrially relevant research and development. The project has exceeded its own expectations, developing innovative high-throughput screening and processing methodologies and generating novel enzyme collections, the use of which can and will drastically shorten the laborious industrial enzyme screening and optimisation steps. In less than three years, the INMARE partnership has catalogued and characterised the widest collection of marine genomic and metagenomic enzymes worldwide, some of which currently outperform the best commercial prototypes.

Horizon 2020[6] is the financial instrument implementing the Innovation Union[7] and is *'a means to drive economic growth and create jobs*'. Projects funded under Horizon 2020, such as INMARE, generally incorporate public sector science actors and commercial enterprises. There is no doubt that the collaborative, multi-partner, public-private nature of these projects contributes to their success in advancing the state-of-the-art and in developing new products and prototypes.

Large mixed-partner-type consortia can also create difficulties in terms of sharing biological and data resources, managing intellectual property and realising value creation. Much can be learned from the challenges that these projects encounter in achieving their aims and objectives. Projects should be encouraged to communicate these challenges to their funding body (or project officer) so that they can be addressed in future calls. This may requirea confidential and informal post-project forum, to allow partners to discuss these.

A significant stumbling block that remains in these collaborative biotechnology projects is the ambiguity around Access and Benefit-Sharing (ABS) regulations. Numerous marine research initiatives, funded at national, regional and European level have supported extensive sampling campaigns both within and beyond European territorial waters. Many of these samples are stored in repositories around Europe but are effectively unusable for research and development because of the difficulty in ascertaining applicable ABS obligations. Samples and derivatives pass through a long pipeline of processes, often in different laboratories, in different countries. This creates a confusing and off-putting prospect for potential commercialization of an end-product. More ABS support and tools are needed to create clarity for scientists, in particular academic researchers. Networks such as EMBRC (European Marine Biological Resource Centre) are making strides in this direction, but again are limited by the lack of ABS information available.

The issue of scale-up of bioprocesses from lab scale to the scale required for industrial processes was highlighted as a remaining scientific challenge by INMARE partners. Whilst this may be a critical issue for industry, it may not be seen as sufficiently interesting scientifically for academic partners to work in this area, given pressures to publish and do novel research with limited funding sources. This can lead to academics pursuing other avenues of research and so an important bottle-neck in the pipeline remains. It is important that innovation funding calls identify real-life challenges so that critical issues can be addressed.

Communication and dissemination of project outputs is an important requirement of EU funded projects such as INMARE, in order to justify the public funding. It can be difficult to generate media interest in a project when there are very few outputs and findings in the early

6. https://ec.europa.eu/programmes/horizon2020/

7. https://ec.europa.eu/info/research-and-innovation/strategy/goals-research-and-innovation-policy/innovation-union_en

stages of the project. It is important to focus on ensuring that, at all stages of the project, knowledge transfer is effected, to ensure that new knowledge is being taken up and used by the appropriate actor, be they another scientist, a policy maker, commercial enterprise or member of the general public. This allows projects to show *'tangible proof that collaborative research adds value'*. For projects where the the pipeline to impact is longer (such as is typical in biodioscovery projects like INMARE), a longer term post-project review of the outputs could be more effective in demonstrating true value creation, but this would require investment by the funding bodies in ex-post evaluations.

It is a fact that marine biodiversity holds great promise for the discovery of enzymes and bioactive molecules, with marine microorganisms estimated to have a 100 times higher potential for the discovery of anti-tumour drugs than soil microoganisms. Despite this potential, marine biodiversity remains largely unexplored, mainly due to the costs and time associated to exploratory research vessel cruises and subsequent steps. Projects like INMARE, and their forerunners, including MAMBA, MicroB3 and PharmaSea, to name but a few, have made huge strides in sampling and exploring the bioactive potential of marine biodiversity.

In four years, building on the work of their successors, INMARE has developed novel technologies in data mining, bioinformatics prediction, high-throughput screening and expression platforms. These technologies, together with the amassed knowledge on biochemical characterization, structural elucidation and biocatalysis will accelerate enzyme and bioactive discovery, making current pipelines more resource-efficient and increasing success rates. Proof of this is demonstrated by INMARE's own outputs.

Within the project's four-year lifespan, INMARE has screened samples from 187 geographically distinct sites resulting in a collection of over 1000 active enzymes, of which 15 are promiscuous enzyme candidates. These have led to the identification of novel lead structures and products, including both polymer degrading and pharmaceutically relevant enantioselective hydrolases. All of this work has been captured in over 60 peer reviewed publications and has resulted in 4 patents and the establishment of one start-up company. This represents a substantial achievement and impact for a single collaborative project.

INMARE has clearly demonstrated the importance and effectiveness of European collaboration by academia and industry and the role of the European Union's Horizon 2020 Research and Innovation Programme in fast-tracking innovation.

FUTURE RESEARCH PRIORITIES IN ENZYME BIODISCOVER

1. Implementation of a biocatalytic process requires scale-up and process development with robust enzymes capable of withstanding high temperatures and, in particular, high concentrations of organic solvents. There is a need to identify key paramters allowing a proper scale up from mL-scale reactors to L- and cubic-m scales. This work is regarded as less 'interesting' scientificallty and, as such, does not receive high levels of financial support.

2. Biocatalytic models using industrially relevant substrates to compare potential biocatalysts from different research groups must be developed.

3. Develoment of high throughput analytical tools are required to efficiently identify the most promising biocatalyst(s) and to provide essential kinetic data.

4. INMARE results should be used to define enzyme chassis that can provide suitable starting points from which to engineer enzymes with high enantioselectivity or substrate promiscuity.

5. Methods pipelines should be developed to identify enzymes with useful properties from metagenomic DNA sequiences

6. IT solutions and database approaches are needed to manage large and very diverse data, to make them available and manageable for project partners with differing needs.

INMARE CONSORTIUM

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