

Michael Banks, Caroline Bissada, Peyman Eghtesadi Araghi (Lead Author and Lead member), Elva Escobar-Briones, Françoise Gaill, S. Kim Juniper, Ahmed Kawser, Ellen Kenchington, Nigel Preston, Gabriele Procaccini, Nagappa Ramaiah, Jake Rice (Co-Lead member) Alex Rogers, Wouter Rommens, Zheng Senlin and Michael Thorndyke

The natural environment has long been a source of inspiration for new drugs and other products of biotechnology. Until relatively recently, the terrestrial environment, in particular, has been the primary source of genetic material and natural products at the centre of major new developments in biotechnology, including new drugs. Examples of natural products used in drug development include the anti-malarial drug quinine isolated from the bark of the *Chinchona*, the analgesics codeine and morphine from *Papaver somniferum* latex, and antibiotics such as penicillins and tetracyclines from strains of *Penicillium* sp. and *Streptomyces* sp. The terrestrial environment contains far more known species of plants and animals than are at present known in the oceans (Hendricks et al., 2006; Mora et al. 2011), and has contributed greatly to the development of new biotechnologies, and new drugs in particular (Molinski et al., 2009; Arrieta et al., 2010; Leal et al., 2012). Yet there are many reasons to expect that the marine environment should represent a rich reservoir of novel genetic material and natural products, particularly those derived from animals and their microbiomes. Covering more than 70 per cent of the planet, and constituting 95 per cent of the volume of the biosphere, the oceans are home to a greater diversity of major animal groups (phyla) than the terrestrial environment (34 of 36 known phyla are found in the oceans *versus* 17 found on land). Most marine organisms have a large dispersal potential, either through the movement of adults, or through the dispersal of larvae by ocean circulation, potentially crossing hundreds to thousands of kilometres during their development. It is thus likely for many species that the same genomic background could be sampled both within several exclusive economic zones (EEZs) and in areas beyond national jurisdiction (ABNJ).

The study and utilization of marine genetic resources is a fairly recent human activity and, compared to the terrestrial environment, examples are relatively few and scattered

offshore oceanic areas beyond national jurisdiction (ABNJ) are, by comparison, poorly documented. The growing appreciation of the diversity and novelty of life in the oceans that has emerged from the results of programs such as the Census of Marine Life, and

However, only in the last decade have these research efforts resulted in the production of a first generation of drugs from the sea into clinical trials. N

The antifoulant and marine adhesives industries have a long history. The costs of biofouling to the fleets around the world are estimated to run into 100 million US dollars each year. Many biocidal antifoulants are now banned (e.g., copper-based paints) because of their direct toxicity to marine organisms. Tributyl tin-based products, once used extensively, are now banned because of their now well-known impact on sex determination in marine molluscs and other organisms. Naturally derived antifoulants include enzymes, antimicrobials, biomimetics such as novel topographies, and natural chemical signals

and Sorcerer II (www.jcvi.org/cms/research/projects/gos/overview/) to conduct ocean basin-scale surveys of planktonic microorganisms. Further offshore sampling of deep-water organisms and the seabed requires an offshore-capable ship (defined here as greater than 60 metres in length) and in most cases a specialized research vessel. Operating costs for these larger vessels are typically greater than 25 000 United States dollars per day. At first glance, basic capability to engage in MGRs research appears to be fairly widespread among nations. The International Research Vessel database (www.researchvessels.org) lists 271 vessels greater than 60 metres in length available in more than 40 countries. However, the majority of these vessels belong to a few developed countries, as shown in Figure 1 (Juniper, 2013)

globally, such as the USA, Canada, the UK, France, the Russian Federation, Japan and most recently China, India and South Korea (Juniper, 2013). ROVs can also be chartered

countries account for 90 per cent of filed gene patents, with 70 per cent from the top three (Arnaud-Haond et al. 2011). Relatively new approaches, such as microbial metagenomics, also require sophisticated bio-informatics tools and training and these are most accessible in developed countries. Nevertheless, some (growing?) capabilities in bio-informatics and genomics exist in developing countries, particularly in the health and agricultural science sectors, and these skills could be adapted and applied to the exploitation of MGRs.

(e.g., through the identification, isolation, cloning, and expression of genes involved in the production of the chemicals), but also to the discovery of novel sources of molecular diversity (e.g., through the identification of genes and biosynthetic pathways from uncultured microorganisms; Bull et al., 2000).

6.4 “Omics” Tools

Recent breakthroughs in marine metagenomics are paving the way for a new era of molecular marine research. Metagenomic studies of marine life are yielding new insights into ocean biodiversity and the functioning of marine ecosystems; for the first time we can explore ecological interrelationships at the gene level. The first study of this type, led by the J. Craig Venter Institute, used these tools to survey marine microbial diversity, discovering thousands of new species, millions of new genes and thousands of new protein families. A seminal 2004 paper described how the analysis of 200 litres of surface water from the Sargasso Sea enabled the identification of about 1,800 genomic microbial species and 1.2 million unknown genes using an environmental metagenomic shotgun approach (Venter et al., 2004). This work led to other marine metagenomic studies, such as those reviewed by Gilbert and Dupont (2011) that show how massive sequencing of environmental samples can lead to the discovery of extraordinary microbial biodiversity and to the unravelling of important components of the pathways of phosphorus, sulphur, and nitrogen cycling. These powerful molecular tools are enabling a new “study it all approach” to discovering organismal, genetic, biomolecular and metabolic diversity in the oceans at an accelerated pace, as exemplified by the recent round-the-world Tara expedition (Ainsworth, 2013) that returned over 25,000 samples of water column organisms for intensive molecular analysis with so-called ‘omics’ tools.

Climate change and ocean acidification are widely recognized as increasing threats to marine ecosystems impacting growth, survival, reproduction, and many other phenotypic features of all marine organisms, leading to changes in species abundances and distribution. Many key marine invertebrates, including crabs, echinoderms and molluscs often have equally if not more complex life histories with several, vulnerable, free-swimming planktonic stages before they metamorphose and settle to their adult benthic form. These sophisticated morphological and physiological processes are underpinned by complex gene regulatory networks and genomic pathways (Gilbert, 2013). This is significant because although it is now increasingly clear that predicted climate change events will affect marine biota, it is also now clear that several key organisms exhibit a valuable plasticity in the face of environmental stresses and challenges (Byrne and Przeslawski, 2013; Chan et al., 2015a, b; Dorey et al., 2013; Harley

et al., 2006; Merila and Hendry, 2014; Reusch, 2014; Stumpp et al., 2011a, b; 2012; Thor and Dupont, 2015). Understanding and exploring this potential will be vital if we are to identify resilient and potentially phenotypically plastic populations. Identification of the genetic bases of this plasticity will be an important resource to the future of exploited marine species in a changing ocean.

The commercial utilization of MGRs had very modest beginnings in the 20th century, particularly when measured against the estimated potential of the great diversity of species and biomolecules in the sea. More promisingly, the past decade has seen the commercialization of the first drugs derived from marine organisms, and considerable growth in nutraceutical and other non-medical uses of marine natural products. This past decade has also seen an astounding increase in our capacity to discover novel marine organisms and biomolecules and understand the genomic basis of life in the oceans. New technologies are fostering a new wave of optimism about the commercial potential of MGRs that is influencing funding priorities for marine research and has led to the emergence of futuristic terms, such as 'blue growth' and the 'knowledge-based blue economy of tomorrow'. Much of the capacity for discovery and commercialization of MGRs remains in the hands of a few developed countries. Much of the genetic diversity in our seas and oceans remains unknown and relatively unexplored; yet more potential is to be realized, particularly in the context of climate change. While this chapter has emphasized the commercial utilization of marine genetic resources, there are strong arguments to be made for the value to societies and ecosystems of simply protecting and conserving marine genetic resources (e.g. Pearce and Moran, 1994).

Ainsworth, C. (2013). Systems ecology: Biology on the high seas. *Nature* 501, 20–23
doi:10.1038/501020a.

Arnaud-Haond, S., Arrieta J.M., and Duarte, C.M. (2011). Marine biodiversity and gene patents. *Science* 331, 1521-1522, doi: 10.1126/science.1200783.

Arnaud-Haond, S., Arrieta J.M., and Duarte, C.M. (2010). What lies beneath: Conserving the oceans' genetic resources.

Brock, T.D. (1997). The value of basic research: Discovery of *Thermus aquaticus* and other extreme thermophiles. *Genetics* 146, 1207-1210.

Broggiato, S., Arnaud-Haond, S., Chiarolla, C., and Greiber, T. (2014). Fair and equitable sharing of benefits from the utilization of marine genetic resources in areas beyond national jurisdiction. *Marine Policy* 46, 101-110.

53EMC3.00006(po)3Tw40.319.29d(0)-d2 Td(-/TT0 1 Tf0 Tc 2(1)-111)312 Td(o3.0.036;c(us -1.)re())

- conservation of hydrothermal vents. *Conservation Biology* 25, 214-222, doi: 10.1111/j.1523-1739.2010.01642.x.
- Guerard, F., Decourcelle, N., Sabourin, C., Floch-Laizet C., Le Grel, L., Le Floch, P., Gourlay, F., Le Delezir, R., Jaouen, P. and Bourseau, P. (2010). Recent developments of marine ingredients for food and nutraceutical applications: a review. *Journal des Sciences Halieutique et Aquatique* 2, 21-27.
- Harley, C.D.G., Randall Hughes, A., Hultgren, K.M., Miner, B.G., Sorte, C.J.B., Thornber, C.S., Laura, F. Rodriguez, C.S., Lars, Tomanek L., and Williams, S.L., (2006). The impacts of climate change in coastal marine systems. *Ecology Letters* 9, 228-41.
- Hendriks, E., Duarte, C.M. and Heip, C.H.R. (2006). Biodiversity research still grounded. *Science* 312, 1715.
- Hendriks, I.E. and Duarte, C.M. (2008). Allocation of effort and balances in biodiversity research. *Journal of Experimental Marine Biology and Ecology* 360, 15-29, C.

Mattila, P., Korpela, J., Tenkanen, T., and Pitkanen, K. (1991) Fidelity of DNA synthesis by the *Thermococcus litoralis* DNA polymerase - An extremely heat-stable enzyme with proof-reading activity. *Nucleic Acids Research* 19: 4967-4973.

Mayer, A.M.S. et al. (2010). The odyssey of marine pharmaceuticals: a current pipeline perspective. *Trends in Pharmacological Sciences* 31, 255–265.
doi:10.1016/j.tips.2010.02.005

Merila, J. and Hendry, A.P. (2013). Climate change, adaptation, and phenotypic plasticity: the problem and the evidence. *Evolutionary Applications* 7 1-14.

Mizuki, K., Iwahashi, K., Murata, N., Ikeda, M., Nakai, Y., Yoneyama, H., Harusawa, S., and Usami, Y. (2014). ~~OSIDESEVE~~ -Pericosine E. *Organic Letters* 2014 16 (14), 3760-3763. doi 10.1021/ol501631r.

Molinski, T.F., Dalisay, D.S., Lievens, S.L. and Saludes, J.P. (2009). Drug development from marine natural products. *Nature Reviews Drug Discovery* 8, 69-85,
doi:10.1038/nrd2487.

Mora, C., Tittensor, D.P., Adl, S., Simpson, A.G.B., Worm, B. (2011). How Many Species Are There on Earth and in the Ocean? *PLoS Biol* 9(8): e1001127.
doi:10.1371/journal.pbio.1001127.

Newman, D.J. and Cragg, G.M. (2012) Meeting the supply needs of marine natural products. pp. 1285-1313 in E. Fattorusso, W. H. Gerwick, O. Tagliatela-Scafati (eds.) *Handbook of Marine Natural Products*. Springer Dordrecht, Heidelberg, New York, London. DOI: 10.1007/978-90-481-3834-0.

Ngo, D.-H., Wijesekara, I., Vo, T.-S., Ta Q.V., and Kim, S.-K. (2011). Marine food-derived d c functional ingredients (potent antioxidant) in the food industry. *Food Funct* 2(1): 1-10
doi:10.1039/c1fo20001a

- Stumpp, M., Wren, J., Melzner, F., Thorndyke, M.C. and Dupont, S. (2011b). CO₂-induced seawater acidification impacts sea urchin larval development I: Elevated metabolic rates decrease scope for growth and induce developmental delay. *Comparative Biochemistry and Physiology. A, Molecular & Integrative Physiology* 160, 331–340.
- Stumpp, M., Hu, M.Y., Melzner, F., Gutowska, M., Dorey, N., Himmerkusa, N., Holtmann, W.C., Dupont, S.T., Thorndyke, M.C. and M. Bleich. (2012). Acidified seawater impacts sea urchin larvae pH regulatory systems relevant for calcification. *Proceedings of the National Academy of Sciences of the United States of America* 109, 18192–18197.
- Thor, P. and Dupont, S., (2015). Transgenerational effects alleviate severe fecundity loss during ocean acidification in a ubiquitous planktonic Copepod. *Global Change Biology*, doi: 10.1111/gcb.12815.
- Venter, J.C. et al. (2004). Environmental genome shotgun sequencing of the Sargasso Sea. *Science*, 304: 66-74.
- Vidanarachchi, J.K., Kurukulasuriya, M.S., Malshani Samaraweera A. and Silva, K.F. (2012). Applications of marine nutraceuticals in dairy products. *Adv. Food Nutr. Res.* 65: 457-478.
- Wilde, V.L., Morris, J.C. and Phillips, A.J. (2012). Marine Natural Products Synthesis. Pp. 601-673 in E. Fattorusso, W. H. Gerwick, O. Taglialatela-Scafati (eds.) *Handbook of Marine Natural Products*. Springer Dordrecht, Heidelberg, New York, London. DOI: 10.1007/978-90-481-3834-0.