Report of the Workshop on Bioprospecting in the High Seas

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A group of delegates met at the University of Otago in Dunedin to discuss bioprospecting in the high seas. The objective of the meeting was to identify and discuss the nature of current activities, including sustainability, limits to growth, timelines, regulatory requirements and potential environmental consequences. The program and the list of participants are attached as Appendix I and 2 respectively.

OVERVIEW OF PRESENTATIONS

Science

Research scientists working on sponges, microorganisms and fish gave an overview of their experiences with regard to sample collection, laboratory investigation, findings and knowledge of the bioprospecting industry.

The group heard that the oceans are the largest ecosystems on earth with immense biodiversity already known and thousands of new species being discovered as marine scientific research intensifies. Novel marine biodiversity is concentrated most specifically in four areas or *hot spots*: coral and temperate reefs, seamounts, hydrothermal vents and abyssal slopes and plains. These concentrations are largely untouched, despite being highly sought after by scientists, governments and companies that have speculated about the immeasurable pharmaceutical potential of novel structures. However, each of the *hot spots* also has idiosyncrasies that make it particularly vulnerable to other ocean uses such as trawl fishing.

Case studies of work in progress highlighted the nature of some current activities. A compound, IPL576,092 based on the sponge steroid *contignasterol*, completed US Phase I trials as an asthma drug in 2000. Cytotoxins from deep-water sponges found on the Chatham Rise 400 km off the New Zealand coast are also under investigation. Other work in progress involves the *Conus* venoms (the source of the first of the modern marine-based drugs and cytotoxic organic extracts); cold adapted enzymes from deep sea microbial extremophiles in the Southern Ocean and deep sea extreme environments such as hydrothermal vents; and genes for "anti-freeze" proteins from fish (Southern Ocean). The difficulties with assay and the long time frame of investigation of potential leads were explained. In the case of fish proteins, for example, it was noted that the proteins could be replicated from genetically modified organisms and did not require the direct harvesting of fish. In a similar fashion, most bacteria can be cultured. Sponges have historically been harvested, but it is also possible to culture them under certain conditions in a natural environment.

Potential applications from marine-sourced material include:

- Pharmaceuticals
- Enzymes
- Cryoprotectants
- Cosmaceuticals
- Fine chemicals
- Agrichemicals
- Bioremediators
- Nutraceuticals

Industry

A study of small-molecule new chemicals introduced globally as drugs between 1981-2002 showed that 61% can be traced to, or were inspired by, natural products (Newman et al 2003a). This figure rose to 80% in the year 2002-2003. Compounds from natural products are considered to be more agreeable to consumers and two-thirds of the anti-cancer drugs, for example, are derived from both terrestrial and marine natural products. Marine-sourced material (eg. from sea water/sediment) has a higher chance of a successful commercial *hit* because of its mega-diversity (using the formula: samples x biodiversity x assays = probability of a hit).

The USA National Cancer Institute (NCI) was one of the first organisations to begin systematic large scale collection of marine invertebrates and in the mid-1980s formal collection programs were initiated to protect access to the original material (Newman et al 2003b). The cost of sample collection, laboratory investigation and further downstream processing is very high, and there is only an estimated 1:50 chance of successfully producing a marketable product beyond a pre-clinical lead. For example, one kilogram of shallow water marine invertebrate collected, prepared for sampling, identified and transported costs approximately US$1,000 per sample. From the one-kilogram sample, only approximately 20-50 grams of liquid and 4-15 grams of organic material will be extracted, costing approximately US$200 per sample. Subsequent testing (in the 60 cell line screen, for example) may cost as much as US$300 per sample. If all associated costs (laboratory staff and equipment, for example) are included, the total rises to tens of thousands of dollars per sample. However only about 10% of samples are eventually determined to be 'active' (these figures refer to shallow water collections. Newman et al 2003b).

Sampling from shallow water is economically more viable than from the deep-sea, from which specimens may be difficult to retrieve. Early NCI collection programs used submersibles and ROVs, but the cost was too high and their deep-sea program was suspended. Others have had more success. Harbour Branch Oceanographic Institution does use manned submersibles and have successfully synthesised a molecule, *discodermolide*, from a previously undescribed deep-sea sponge. Another compound, *halichondrin B*, has also been isolated from a sponge species by a New Zealand joint venture. In the latter case, one metric tonne of sponge was harvested, which yielded 300 mg of pure *halichondrin B*. This process cost approximately US$500,000 (Newman et al 2003b:5-7).

The schema below represents the NCI approach to the processes of biological prospecting.

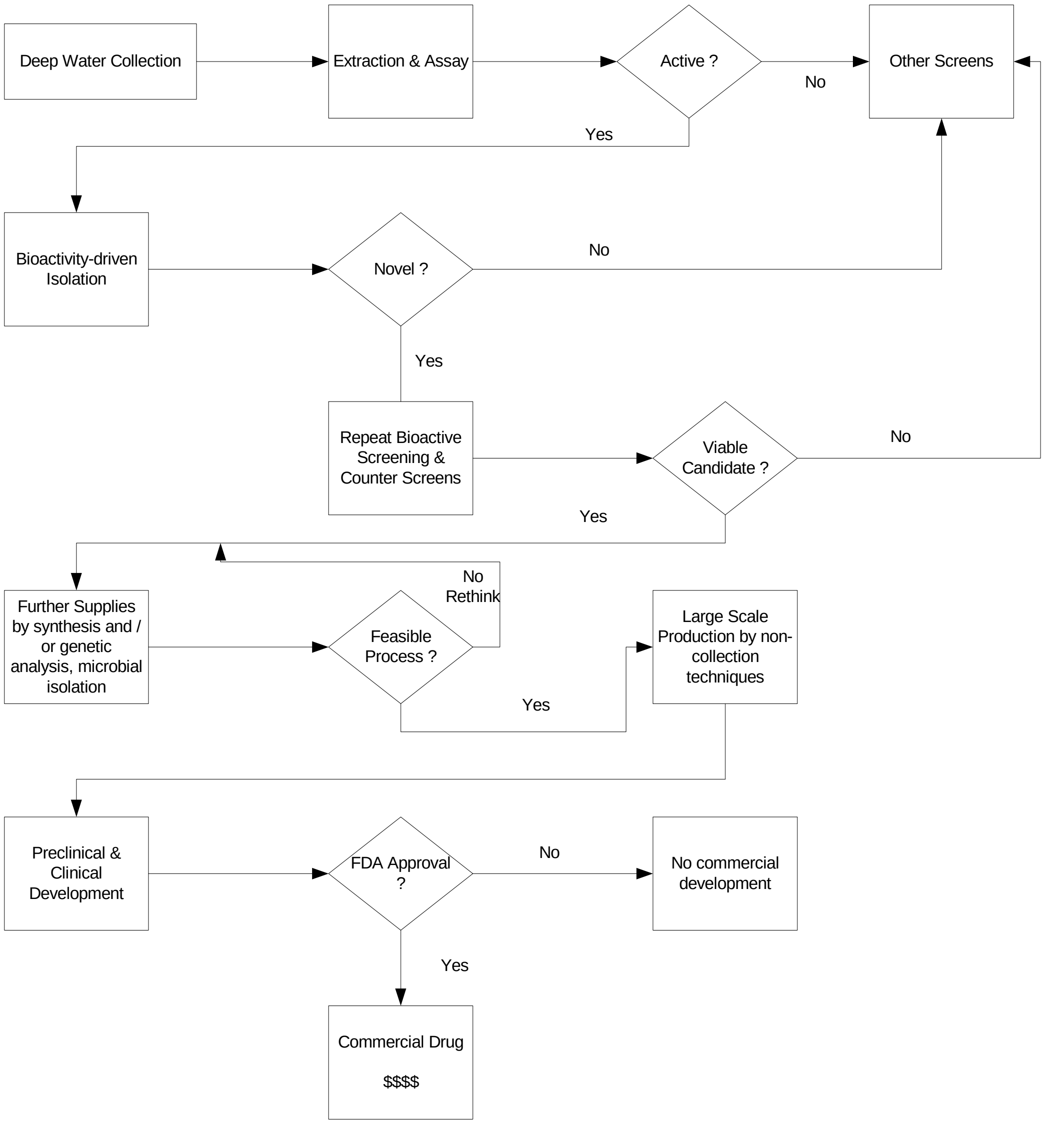

Figure 1: NCI schema of Bioprospecting Process (from Newman 2003b:12)

It is important to note that current US legislation prohibits government institutions from "encumbering a future invention" (Newman et al 2003b:4) therefore in terms of benefit sharing, they are prohibited from entering into royalty agreements in the phases of sample collection and testing. This may bring the government institutions into contravention of the Convention on Biological Diversity (CBD) if the US Government ratifies it. NCI approaches benefit sharing in a novel way, begun prior to the CBD but in many ways in conformity with the principles contained therein. It involves a 'letter of collection' agreement, which requires absolutely that any licencee of an NCI patent must involve the country of origin in the further development of the compound (Newman et al 2003b:4). Despite the argument that the acts of collection and routine testing of extracts are not inventions in themselves, institutions such as NCI cannot infringe US law by collecting in some countries where the CBD (and its royalty provisions) would apply. Another significant point is the fact that no sample collected by an NCI collector may be analysed by other researchers.

Ongoing access to material (ie. because it cannot be replicated in a laboratory or because further samples are sought) is of primary importance. Aquaculture and mariculture have both been used successfully in some cases (eg. shallow-water sponges).

Industry presentations placed great emphasis on the odds of success, with a figure of approximately only 1-2% of preclinical *candidates* actually becoming commercially produced.

Law and Policy

Presentations were made giving an overview of international law and international obligations, protecting the biodiversity of hydrothermal vents and the unique situation in the Southern Ocean. Relevant laws include intellectual property laws, environmental protection and biodiversity conservation laws, the United Nations Convention on the Law of the Sea (LOSC) and Antarctic-specific laws.

Regarding patentable inventions (ie. products and processes that provide a technical solution to a technical problem), it was noted that patenting involves elements of novelty, inventive step and industrial applicability (or utility: ie. can be commercialised). A grey area within the law, however, is the patenting of living organisms and products of nature. Whilst products of nature are currently excluded, even minor modification that introduces the elements noted above may allow patenting to proceed. Patentable biotechnological inventions may include genetically modified plants, animals, and microorganisms, and isolated, synthetically produced, cells, proteins and genes of known function. Key points for discussion were the potential for conflict between sovereign rights over resources and patent rights over inventions; bioprospecting and biopiracy, traditional knowledge and novelty (eg. does traditional knowledge compromise the element of *novelty*?); and equitable access and benefit sharing (consistent with the Convention on Biological Diversity but see earlier note regarding US legislation).

With regard to hydrothermal vents, the applicable legal regime, if any, to monitor activities and provide protection and regulation will depend on the location of the vents. If they are located within territorial waters and exclusive economic zones (EEZs), coastal state jurisdiction prevails over access to and use of genetic resources. If they are located on the continental shelf beyond the EEZ, the coastal state can only regulate access to sedentary species. If hydrothermal vents are located outside national jurisdiction, access is largely free and unregulated except where states regulate the activities of their nationals, consistent with the Convention on Biological Diversity and other international law (see Leary 2003). Discussion ranged across broad areas of potential international regulation, including expanding the mandate of the International Seabed Authority to include the superjacent waters above the Area.

It was acknowledged that the Southern Ocean is a special case because of the overlap of international law and Antarctic-specific law, as well as the unproven nature of sovereignty over the continent and, thus, the marine areas. This complex case highlights how the traditional freedoms of the sea have been modified in the Antarctic. A regional fishery body - the Commission for the Conservation of Antarctic Marine Living Resources - regulates the conservation and rational use of all Antarctic marine living resources (not including whales and seals). Furthermore, an environmental protocol - the Madrid Protocol to the Antarctic Treaty - requires environmental evaluation of all activities in the Antarctic Treaty Area (ie. south of 60° South) prior to the operation being undertaken. Activities in this case include marine scientific research. The initial phase of bioprospecting (sample collection) would be unlikely to breach either of these arrangements, but large-scale collection through harvesting would require closer scrutiny.

Consideration was also given to the Southern Ocean as a global commons and its resources, the "common heritage of mankind", not unlike the situation with the deep sea bed of the high seas.

Case Studies

The first case study described the extent of some of the leads discovered by one institution - the Australian Institute of Marine Science (AIMS). The collection housed by AIMS includes 10,000 species of marine bacteria, fungi and microalgae and 12,000 species of invertebrate macroorganisms.

The presentation also introduced new terminology and a new concept: a dichotomy between *biodiscovery* (primary collection to find leads) and *bioprospecting* (looking for more of the lead material - re-collection).

Biodiscovery was considered to have the following practical applications, in addition to the ones listed above: seafood toxin testing, antifoulants, bioremediation, environmental monitoring and as research tools. The latter is a lucrative application, with some marine natural products valued extremely highly, eg. Neosaxitoxin derived *inter alia* from dinoflagellates, blue-green algae and toxic shellfish is valued at US$21,400 per milligram. In terms of supply, however, AIMS (citing Garson 1994) noted the following quantities of original material required to yield relative quantities of lead material:

ORIGINAL MATERIAL	QUANTITY YIELDED
450 kg acorn worms	1 mg cephalostatin
1,600 kg sea hares	10 mg dolastatin
2,400 kg sponge	<1 mg spongistatin
847 kg moray eel livers	.35 mg ciguatoxin

The table above highlights the importance of sustainable methods of wild harvest, chemical synthesis, aquaculture, cell and tissue culture and genetic splicing.

The AIMS presentation also considered Australian policy. Prior to 1994 the AIMS collections were undertaken in conformity with a scientific research permit and no benefit sharing was applied. Subsequent collections were subject to new permit conditions, which meant that new permits became more difficult to obtain in some jurisdictions and doubt was cast over the legal certainty of some existing collections. In addition, permit conditions restricted use. Benefit sharing also became difficult, with questions arising about a lack of process and legislative basis, who should be beneficiaries, and what exactly are the benefits? As a result, AIMS put in place best practice guidelines on these issues. In addition, the Queensland government (the Australian state in which AIMS is located) is introducing a

Biodiscovery Bill into Parliament, which will provide greater clarity as to the legal obligations in this area.

The presentation on environmental aspects of bioprospecting acknowledged that many agencies expect environmental impact to occur with bioprospecting activities because historically, extracting resources from the oceans (especially fishing) has had environmental consequences. Conversely, the proponents would be inclined to see bioprospecting as posing no, or only slight, risk to the environment. It is likely that the proponents see their activities this way because they are comparing their level of activity with hyper-extractive fishing, for example. It was considered, however, that this generation of bioprospectors represent only the artisanal stage of the activity. All human activities related to ocean usage have impact. Those relating to bioprospecting will be relative to the location; the modes of transport, support and sample retrieval; the discard of unwanted material; and the nature of the target (ie. compare microorganisms with fish). The presumption that extraction of target taxa will have negligible impact is only a presumption.

There are considerable legal obligations arising from, *inter alia*, the LOSC and CBD for the protection and preservation of the marine environment, including conducting environmental evaluation of proposed activities. The take-home message was that the juridical picture is a complex one and is still evolving.

CRITICAL POINTS & CONCLUSIONS EMERGING FROM GENERAL DISCUSSION

Definitions

It became apparent from the outset that there were divergent interpretations of the critical language – “bioprospecting” and “high seas” – and, therefore, it was important to define the way in which the terms were used throughout the meeting.

- “High Seas” = LOSC definition, ie. maritime areas “outside national jurisdiction”. The group also included "the Area" (ie. the deep sea bed) and the sub-sea biosphere in its discussion. There was considerable discussion about the status of the Southern Ocean. Although there are similarities between the Southern Ocean and other high seas areas, the complex legal situation arising from unproven sovereignty means that the Southern Ocean is a special case subject also to the legal regimes established within the Antarctic Treaty System.

- There was no universally agreed definition of “bioprospecting” but rather it was viewed as a broad concept embracing a number of phases of research to investigate a region’s biodiversity and to collect samples of biological organisms. It was suggested that the definition be split into two discrete terms: “biodiscovery” = the first phase of scientific research into a region’s biodiversity, and “bioprospecting” = the second and subsequent phases of the re-collection of biological resources for the purposes of further investigation. It was noted that the distinction may, at times, be for expedience only and that the two classes of activity may have different objectives, different outcomes, and different requirements for permit conditions and environmental reporting, for example, attached to them.

Level of Activity & Future Potential

There is already a considerable amount of marine scientific research conducted in high seas areas, including biodiscovery, and this has the potential to expand into more substantial bioprospecting activities in the future. Biodiscovery activity can be both targeted (eg. at locations such as hydrothermal vents and seamounts, or events such as the death and decay of marine mammals) and serendipitous (eg. curiosity-driven marine scientific research, by-catch).

The rich biological diversity of the high seas has the potential to yield biological products of broad ranging applicability. In particular there are unique mega-diverse areas where the biodiversity is relatively untouched. Significantly, the ratio of potentially pharmaceutically useful compounds to compounds screened is higher in marine-sourced materials. There is, therefore, a higher probability of commercial success. However, marine research is expensive, and the high cost together with difficult technological challenges of retrieving material from the deep ocean, impose significant limitations on the industry.

Spin-offs

Spin-offs include dedicated technology that is required to assist in biodiscovery. It is important to note that technology developed from high seas experiences has much wider application.

Bioresource spin offs include:

- Contributions to the store of scientific knowledge about previously unexplored regions and taxa; and
- Identification of biodiversity *hot spots*, with new information contributing to the implementation of better management strategies.

Legal Status

Except in very general terms as prescribed in the LOSC and the CBD, biodiscovery and bioprospecting in the high seas is largely unregulated. Specifically there is no clear legal regime for:

- Environmental management
- Benefit sharing (who "owns" the resources?)
- Access

Patenting is the main avenue for securing economic benefit as a return for investment. But there is a dividing line between biodiscovery, bioprospecting and the requirement to share benefits from commercialisation.

Environmental Vulnerability

There is at present no evidence that biodiscovery and bioprospecting are having any greater impact on the marine environment than any other form of marine scientific research. Currently there are greater threats to high seas biodiversity from other activities such as various technical aspects of fishing and mining. However, a precautionary approach is indicated.

CONCLUDING REMARKS

In conclusion, three ways forward were advanced:

1. The approach to conditions for access and benefit sharing must be regionally and globally consistent;
2. Sample collection and associated activities must be sustainable and subject to environmental impact assessment; and
3. In lieu of economic benefit sharing, access to data, scientific knowledge and information that reveals intrinsic values may be considered appropriate alternatives.

The high seas is a global commons and it was considered that its biodiversity could, therefore, be considered "common heritage of mankind" in similar fashion to the mineral resources of the deep sea bed.

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