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Biodiscovery in US Federal Waters

David J. Newman, D.Phil.
Natural Products Branch
DTP, DCTD, NCI

The following is a series of background comments that will complement the actual 10 minute presentation. That presentation will be 10 slides and the comments below are designed to expand upon the topics though they do not track exactly with the slides.

What is meant by the term, "Biodiscovery"?

I have chosen to use this term rather than the more hackneyed term, "Bioprospecting" because it encompasses all types of scientific work on marine invertebrates, algae and microbes, from taxonomic censuses through to materials that might well be of use as either directly or as leads to agricultural, aquacultural, veterinary and human-directed pharmaceuticals and food.

I am deliberately avoiding the fin-fish aspect of any of the work, other than when there is evidence of a fish feeding deterrent, and then the interest is in the deterring agent.

Why use "invasive techniques" such as collections ?

There is effectively no way of looking at a marine ecosystem and being able to pinpoint that a particular invertebrate, alga and/or microbe is either producing or is capable of producing an agent that might be of utility. One can observe obvious signs such as a mobile nudibranch that is not eaten by organisms higher up the food chain, the lack of predation on a given algal genus when others nearby are being actively grazed upon, or contact inhibition between two sponges on a coral face. Although all of these are indicators of some form of chemical defence, they are not in of themselves, leads that can be used immediately.

In the terrestrial environment, an analogy would be the early observation that chrysanthemums were not attacked by some insect species which led later to the use of the petals as a potential insecticide and then the ultimate isolation and further work on of the chemical class known as the pyrethrins.

Why involve the NIH/NCI ?

One of the major sources of funding in the US for work on biodiscovery related to human diseases is the National Institutes of Health, and in particular, the National Cancer Institute, through both direct "investigator-initiated grants" and also through three very effective other mechanisms: *viz*

1. The direct marine and plant collections overseen by the Natural Products Branch (and the subsequent investigations by scientists all over the World).

2. The National Cooperative Natural Product Drug Discovery Groups (NCNPDDGs) administered by the DTP's Grants and Contract Branch; many of whom use collections from #1 to supplement their own work. There are also spin-offs of this program related to microbial biosynthesis mechanisms (*c.f.* later).

3. The International Cooperative Biodiversity Groups (administered by the Fogarty International Center at NIH) and based upon the model of the NCNPDDGs. Some of these groups also make use of part of the collections in #1.

Other US government agencies also support work in the marine biodiscovery field, from the basic work funded by the NSF in many marine fields to the very important "translational funding" provided by the DoC's SeaGrant program. Except for some of the grants funded under SeaGrant, and now a very interesting but restricted program from the DoI's Minerals Management Service, the grants are all designed to answer specific fundamental questions in marine biology.

However, the only group tasked with collections under direct, ecologically conserved and controlled conditions are the collections performed under # 1 above by the competitively awarded shallow-water marine collection program of the NCI. These collections have been made, effectively between the tropics, since 1987. In the early program, collections were made in the Caribbean, some of the waters around Florida and some in the Gulf of Mexico, but the vast majority of collection have been made in Indo-Pacific, in Australia, New Zealand and in particular, in the island nation of Belau (Palau in the Western Caroline Islands).

Due to the NCI collection activities, Palau has what is probably the best described taxonomic database in the World for a single country.

Protections.

All collections are made with the express permission of the Countries in whose territorial waters we collect, whether or not the NCI's Letter of Collection (LOC), which predates the Convention on Biodiversity (CBD) by four years, has been signed.

This document contains language that requires that if any material coming from an organism collected in the source country is later licenced for development of a commercial agent (in this case, a human use pharmaceutical, but in principle, any product), the source country MUST be involved in the development of the agent, and suitable recompense made if it becomes a commercial product. Even if no LOC is signed due to a variety of reasons, usually related to a lack of a suitable source country agency, all collections are made as though it has been and all requirements are enforced.

This particular document (the LOC) has become a basis (though heavily modified) for a number of biodiscovery agreements in other countries, examples being the agreements between the Australian Institute of Marine Sciences (AIMS) and the State of Queensland, for work in Queensland's state waters, with the work that AIMS is permitted to perform in the Great Barrier

Reef (GBRPA), and a Memorandum of Understanding (MOU) based on the LOC between AIMS and the NCI that will allow joint investigations of the potential in Australia after a nine year hiatus.

What is the potential in US Federal Waters for such work?

Specific Suggestions (Invertebrates).

If one can use the AIMS/GBR relationship as an example, where AIMS is permitted to perform scientific work in selected, controlled areas of the GBR with benefit-sharing arrangements if anything commercially profitable comes from such research (in addition to the basic scientific knowledge), then I would suggest that there could be a very close parallel in the case of the US.

Within the USA's (Federal) territorial waters, there are areas that have been set aside as (Federal) Marine Preserves (FMP). These are formally similar to the Australian Great Barrier Reef Park Authority and what I am suggesting is the following:

> NCI's contract marine collectors, the Coral Reef Research Foundation, which is a California Non-Profit and is based in Palau was recently (2/2002) awarded another 5 year contract to provide taxonomically identified marine invertebrates to the NCI for investigation of their pharmacological potential. In this contract, as distinct from the two previous 5 year ones that they satisfactorily completed, they have a consortium of groups working with them as sub-contractors.
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> One of these is a small, but experienced marine group based in the Florida Keys and they will be providing samples from areas of the US, but not including Federal preserves. Since NPB/NCI can directly control this group, the suggestion is that they be permitted to thoroughly survey and collect in an ecologically sensitive manner, up to one kilogram wet weight of selected marine invertebrates from, initially a small defined area (I hectare or less) of the Florida Marine preserve. This would be a pilot study with full taxonomic, GPS and photographic data being returned to the "Park Authority".
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> Effectively, the Agency/Marine Preserve would be considered to be equivalent to a "source country" and all the requirements in the LOC would apply. If satisfactorily completed, then other FMPs can become part of the projected program.
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> This has been a very effective mechanism for another program that we have had running for many years with the USDA's Foreign Weed Research Group whereby we isolate and investigate microbes from their sources.

Specific Suggestions (Microbially-Directed Studies).

Another aspect which is of great potential use, would be to permit, under NCI's supervision, selected grantees to take very small samples of the flora and fauna from the "defined area" in order to isolate and use the microbial flora and in particular, the "meta-genome" of the organisms involved. This has immense potential from both a basic science and applied science perspective.

The reason for this is that the most unstudied, but most biologically diverse area in the World is not the invertebrate fauna or the plant flora as is usually mentioned, but the microbial flora that is both free-living and an essential part of these organisms.

As mentioned frequently by the Director of NSF (Dr. Rita Colwell) during her days at the University of Maryland and at the Center Of Marine Biotechnology in Baltimore, less than 1% of the microbes that can be seen microscopically in seawater can be cultured using current techniques. Using genomic extraction techniques, investigators have shown using genomic taxonomic analyses that the microbes that can be cultured are definitely not representative of those that are present; with many more families being currently uncultured than are culturable.

However, techniques are now available that permit the use in a number of cases of the biosynthetic genomic machinery from as yet uncultured microbes. This opens up immense possibilities in leads to novel agents in agriculture to human use drugs and requires less than 10 grams of sample, one time!

> Thus another suggestion would be that researchers who are recipients of competitively funded US gov't grants dealing with this type of research, would be permitted to remove very small quantities (10 g or less) of invertebrates and/or soil samples from the same "plots" that the Coral Reef collectors are using. These collections would be under similar rules as the larger scale samples.

Benefits.

Initially, the FMP would have an inventory of a very specific reef, with *in situ* photographs and GPS coordinates. This could be repeated at suitable intervals (and extended if desired) and would be at no cost to the FMP. If anything came from the invertebrate samples in a pharmacologic or agricultural sense, then the FMP and hence the US gov't would be a direct beneficiary, with downstream potential for mariculture/aquaculture etc.

Timing, Costs & Administration.

Since this would be part and parcel of an existing US gov't program (under NCI), no extra organization/funds would be required. Effectively all that is required is permission to proceed.

Since NPB/DTP has marine collectors effectively on site and funded, the initial work on marine invertebrates could commence **within a month or so of the go signal**. Mechanisms are already in place (see http://dtp.nci.nih.gov) to prepare, screen and develop any materials that are of interest from a human use perspective. For other areas (agricultural etc.) contact personnel are known in a variety of organizations. Administration would simply be part of the on-going program.

In the case of the microbial area, Since the Grants and Contracts branch of NCI's DTP is currently administering some pilot scientific programs in this area, and NCI/NIH is funding a

number of such basic investigations, all administrative infrastructure is already present**. As above, what is needed is permission to proceed**.

This work could dovetail nicely with other on-going programs at NSF and DoC as the MNP area could be used as a laboratory area in which to perform specific marine biological experiments built upon the data generated in the initial trials as they would be published in due course.

Downside.

The concept of "controlled access" could be anathema to some NGOs. However, we are not suggesting in any way stopping access to the area in any way for National Park-related activities. This "controlled access/removal" would be for the removal of small amounts of invertebrates and microbes by qualified scientists with an overall benefit to the FMP (initially scientific and perhaps monetary in due course) and ultimately the Nation.

Extra Information.

In addition to the above notes, a CD has been provided to the commission that has on it copies of the following:

1. The NCI's Letter of Collection.
2. A paper covering the use of the LOC as a method for recompense to source countries.
3. A report to the CBD's COP covering the discovery and development of two drug leads from nature by the NCI.
4. A listing of chemical agents from marine sources that are currently in clinical trials or approaching clinical trials in cancer and other selected diseases.
5. A relatively recent scientific review that shows the influence of compounds from natural sources as leads to ethical drugs.