Photos courtesy of Diversa Corp.

Bioprospecting — the exploration and sampling of biodiversity for commercial and industrial purposes — holds substantial promise for the development of new compounds for consumer goods, public health, and energy and environmental uses. Proteins from deep seabed marine life, for example, could provide novel antifreezes for food and automotive products, and thermal vent microorganisms possess enzymes naturally optimized for the extreme conditions of various manufacturing processes.

Yet this positive exploitation of natural resources is not without potential ethical, technological, and politicosociocultural challenges. The use of these resources can call into question the very purpose of biotechnology and its ultimate effects on human society.

A Point of View article on p. 252 argues that commercial use of natural resources must respect indigenous lands and cultures. Diversa Corporation offers a model for ethical and successful bioprospecting collaboration with international regions (p. 255). And a comprehensive excerpt from a United Nations–Institute of Advanced Studies report (p. 250) outlines key considerations for bioprospecting of the deep seabed.

Respectful and intelligent application of diversity-based biotechnologies will ensure the maximal and exciting human benefits harnessed from global resources for greatest international good.

Bioprospecting ethics & benefits

A model for effective benefit-sharing

Leif P. Christoffersen and Eric J. Mathur

Abstract

The Convention on Biological Diversity (CBD) entered into force in 1993, yet challenges and misunderstandings related to the search for new biological products and applications still exist. Diversa Corporation (San Diego, California) has developed a framework model for engaging in ethical bioprospecting in which participating countries, institutions, and corporate stakeholders all benefit, with minimal conflict or disagreement. This model involves securing legal access and providing equitable benefits for access to both terrestrial and marine biodiversity. Moreover, Diversa has developed products that have resulted in some of the first royalties ever paid from such bioprospecting activities. These products are not only generated through strong ethical principles, such as Prior Informed Consent (PIC) and equitable benefit-sharing, but they also play a role in reducing pollution. This paper provides important insights into how bioprospecting can lead to economic, scientific, and environmental benefits.

Bioprospecting defined

A common perception is that bioprospecting is a new science linked to modern biotechnology. The fact is that humankind has been studying, manipulating, and exploiting natural diversity ever since the emergence of *Homo sapiens* over 150,000 years ago.[1] Our early ancestors explored biodiversity and learned how to derive benefits from nature. Early bioprospecting led to the improvement of methods for growing food, building shelters, and maintaining health. Modern-day bioprospecting is simply an extension of our long history of exploring nature to improve our quality of life. Bioprospecting is defined as the exploration of biodiversity for commercially valuable genetic and biochemical resources and should result in the protection of wild lands and wildlife, through funding of conservation activities. Furthermore, bioprospecting should bolster economic and conservation goals underpinning medical and agricultural advances needed to combat disease and sustain a growing human population.

Life science corporations and academic institutes frequently engage in bioprospecting to explore and discover biological molecules for commercial applications. Today, the market size for products and applications derived from bioprospecting is estimated to be US$500–800 billion per annum. Yet the (equitable) sharing of revenues from the source nations from which these products were derived remains a rare occurrence. Interestingly, pharmaceutical products represent only about half of the revenues generated from bioprospecting, so one cannot discount the industrial and agricultural sectors in terms of impacting global benefit-sharing.[2]

In contrast to bioprospecting, the unauthorized and uncompensated taking/stealing of genetic or biological resources is referred to as "biopiracy".[3] Critics and opponents of bioprospecting broadly invoke the term "biopiracy" to describe all discoveries from biological diversity, because they believe that any commercial exploitation of nature is unethical and should be considered illegal.

For example, there was a bill introduced into the Hawaii State Legislature to place a moratorium on bioprospecting, which was driven largely by concerns about conflict with Native Hawaiian culture. Although the bill did not pass, various stakeholders are continuing to address these concerns in an effort to propose a more sound and rational policy for access to Hawaii's unique biological resources.[4-6] This policy should recognize the fact that the majority of bioprospecting activities do not rely on the use of indigenous knowledge. Activities that do involve the use of indigenous knowledge should only be conducted with the expressed permission (PIC) of the host culture community.[7]

Some companies and academic institutions collect biological samples without obtaining PIC, legal permits, and without establishing mechanisms for benefit-sharing. This careless practice was widespread among biotechnology and drug discovery companies prior to the enactment of the CBD in 1993.[8] The CBD grants each nation sovereign rights to its own genetic and biochemical resources. Thus, gone are the days when companies would send their scientists to foreign countries to collect biological samples, bring them back to their lab-

oratories, and develop commercial products with no intention of returning any benefits to the source nation or community.

A landmark example of biopiracy took place in Norway during 1969 when a microbiologist from Ciba Geigy collected soil samples while on vacation in the Hardangervidda mountains. The samples were subsequently brought back to the Ciba Geigy labs in Switzerland where they were used to develop the drug cyclosporin A, a drug used to prevent infections from organ transplants. This blockbuster drug generates over $1 billion dollars in annual sales. However, since no formal permits or benefit-sharing arrangements were agreed upon, Norway does not receive any royalties from this dramatic commercial success.[9] With the CBD now ratified by 188 nations and the continuing development and implementation of new laws and regulations governing access and benefit-sharing, biopiracy is now illegal in many countries.[10]

By supporting sustainable development and global conservation of biodiversity through bioprospecting framework agreements, Diversa Corporation has worked to become a recognized leader in ethical bioprospecting. The basic premises of the company's bioprospecting program are consistent with and fully supportive of the objectives of the CBD[11]; they recognize the conditions set forth by Article 15 of the CBD[12]; and comply with the Bonn Guidelines on access to genetic resources and the fair and equitable sharing of benefits arising from their utilization that were developed by an expert panel created and supported by the CBD.[13]

Obtaining PIC and legal rights to collect samples through the establishment of bioprospecting framework collaborations are prerequisites before any samples can be shipped to Diversalaboratories. The nuances and legal details of the framework relationships are complex. Diversa consults with the particular National Focal Point concerned as much as possible to ensure complete compliance and support in securing permits or other forms of authorization from govern-

The deep submergence vehicle ALVIN from the US Navy and operated by Woods Hole Oceanographic Institute provided Diversa with hydrothermal vent chimney samples from which archaeal genes were cloned to develop the industrial enzyme Ultra-Thin™.
Photo courtesy of Woods Hole Oceanographic Institution

ment authorities and encourages biodiversity collaborators to communicate closely with the National Focal Point as well.[14]

These mutually beneficial bioprospecting collaborations have enabled Diversa to secure legal rights to collect genetic resources in a manner that exceeds norms of ethical business practices from the following locations around the world: Antarctica, Alaska, Australia, Bermuda, Costa Rica, Ghana, Hawaii, Iceland, Indonesia, Kenya, Meadowlands (New Jersey), Puerto Rico, Russia, San Diego Zoo's Center for Research on Endangered Species, South Africa, and Yellowstone National Park (*see Figure 1, Methods article, "A biodiversity-based approach to developing performance enzymes," p. 283*). Diversa establishes and manages these research collaborations by offering its collaborators fair and equitable benefit-sharing arrangements that include milestone payments, royalties, technology transfer, training workshops to facilitate capacity building, donation of supplies and equipment, and financial support (such as annual payments or per-sample fees).[15] Moreover, in many cases, collaborations have also resulted in peer-reviewed publications, research grants, and the development of products which have triggered milestone and royalty payments to Diversa collaborators. In Costa Rica, among the country's international bioprospecting collaborators over the past 15 years, including Merck and GlaxoSmithKline, Diversa was the first to pay royalties to the National Biodiversity Institute (INBio).[16]

The products produced by Diversa are often beneficial to the environment, frequently reducing the levels of toxic chemicals released into the biosphere. For example, Luminase™ is an enzyme product developed for use in the pulp and paper industry. Luminase is used in a biobleaching step prior to the chlorine dioxide treatment in the bleaching stage of pulp processing. Biobleaching with Luminase reduces the cost of pulp processing by both minimizing the use of toxic chemicals and the expense associated with disposal of harsh chemical wastes.[17] Diversa's Luminase product was developed from an environmental sample collected from the Uzon Caldera in Kamchatka, Russia, through support from the US Department of Energy's Initiative for Proliferation Prevention.[18] Very recently, sales of this product triggered royalty payments to Diversa's Russian bioprospecting partners.

Marine environments are a significant focus of Diversa's bioprospecting program. To collect samples from shallow marine ecosystems, Diversa employs its own staff and biodiversity partners who scuba dive to collect samples. Partnerships with the University of Hawaii, Bermuda Biological Station for Research, and Tropical GenoDiversities in Puerto Rico are aimed at collecting and processing samples of sponges, sediments, and soft corals primarily within territorial seas. In all cases, Diversa has facilitated the initiation of a process to seek and acquire legal rights to such sample collections in a manner that complies with local laws and that leads to prior informed consent. Sponges and soft corals are of particular interest since estimates suggest that as much as 50% of sea sponge dry weight may consist of bacteria.[19] Sponges are sessile marine metazoans which have co-evolved for over 700 million years with symbiotic bacteria. In many cases, these symbiont-host relationships have resulted in the creation of chemical arsenals that protect the sponges from fungal and other marine pathogens. These chemical compounds are of interest to companies searching for new pharmaceutical leads including anti-infectives and small molecule immune modulators. Diversa's proprietary technologies enable the collection of very small samples that are then used to create metagenome (environmental) libraries that can be propagated in the laboratory and used for screening over a long period of time, which reduces the impact on the environment *(see Methods article, p.)*.

Deep Ocean Expeditions, another biodiversity collaborator for Diversa, supports this low-environmental-impact approach. Deep Ocean Expeditions operates two MIR manned submersibles designed to dive to a maximum depth of 6,000 meters, facilitating access to 98% of the world's oceans.[20] Diversa has also worked with Woods Hole Oceanographic Institute (WHOI), which operates the US Navy-owned Deep Submergence Vehicle, ALVIN, as a national oceanographic facility. The ALVIN can dive to a depth of 4,500 meters.[21] Through these partnerships, Diversa has acquired small samples from international seas that are outside the jurisdiction of territorial seas (or so-called Exclusive Economic Zone, or EEZ).[22] Diversa developed the enzyme product Ultra-Thin™ from a sample collected by the Alvin from a black smoker chimney in a Pacific Ocean hydrothermal field at a depth of roughly 2,700 meters. Ultra-Thin is designed to improve the efficiency and economics of ethanol production from starch, operating at a higher temperature and lower pH than other commercially available enzymes. The Ultra-Thin enzyme, marketed in collaboration with Valley Research (South Bend, Indiana), is an alpha-amylase designed to provide ethanol producers with improved liquefaction performance. This enzyme works in concert with other enzymes to convert the starch present in corn into fermentable sugars for production of ethanol or other value-added products, such as high fructose corn sweetener.[23]

While Ultra-Thin was developed from a sample aquired outside the EEZ, bioprospecting in international seas is still in its infancy. The Institute of Advanced Studies of the United Nations University think tank (UNU-IAS) has stimulated an important debate on the management of equitable access to genetic resources found in international waters through its report, *Bioprospecting of genetic*

resources in the deep seabed: Scientific, legal, and policy aspects (see p. 260). The report has led to a number of commentaries, discussions, and proposals on how best to share benefits from commercialization of products derived from genetic resources collected in the deep seabed, outside national boundaries.

Yet the amount of research that takes place in international waters is incredibly small. According to the Ocean Biogeographic Information System, a project of the Census of Marine Life, 90% of all marine research records are based on activities conducted at a depth of 200 meters or less. Another 9% is conducted at a depth of between 200 and a little more than 1,000 meters.[24] This suggests that at least 99% of all research activities take place within territorial seas.

Furthermore, there are only 5 manned submersibles that can travel to depths below 3,000 meters and there is only one ROV submersible built to withstand dives of up to 7,000 meters, and few that travel below 3,000 meters. The ROVs that are used for laying cable have a 6,000-meter depth limit, covering roughly 98% of ocean floors.[25] Most of these ROVs are neither set up nor employed to engage in bioprospecting activities. Thus, at present, the negative impact associated with bioprospectors searching international seas is negligible. Fortunately, in this case, there is still time to develop a bioprospecting framework that could receive international support and acceptance to help mitigate future negative impacts as the intensity of deep seabed marine research increases. The debate started by the UNU-IAS is a step in the right direction and should be supported by all scientists engaged in research activities in international seas.

It is worthwhile to mention that many countries are extending their "national use" limits. In essence, this expands nations' EEZ based on efforts to delineate geographic boundaries of their respective continental shelves that extend beyond the existing 200 nautical miles to a maximum of 350 nautical miles.[26] Therefore, an intensive scramble is under way to map these geographical delineations. This would effectively reduce the area of International Waters and thus facilitate greater protection and management of marine research activities in a manner that protects marine biodiversity for future generations.

However, a more pressing concern related to bioprospecting on both land and in the sea relates to facilitating greater compliance to new legal frameworks inspired by the CBD to govern access and benefit-sharing associated with biodiversity. Corporations and academic institutions must become proactive and support the goals and objectives of the CBD, working within these newly established regulations and laws. Some scientists and scholars criticize the CBD for an inefficient, ineffective bureaucracy at national levels. Others believe the CBD has only served to create impediments toward the advancement of science; in some cases, these criticisms may be valid. For example, several legal frameworks created in South America have dramatically reduced the number of bioprospecting and life science research projects funded within South American countries. The Philippines has recently reduced the number of bureaucratic steps for securing approval for initiating bioprospecting projects, thereby intending to facilitate greater access to its biodiversity; yet many believe that the process remains too cumbersome.[27] Nations that develop burdensome bureaucratic bioprospecting legal frameworks do not help to facilitate compliance with and support for the CBD.

On the other hand, many other nations have managed to develop

Diversa scientists collecting geothermal sediment samples in the Uzon Caldera, Kamchatka, Russia. Samples collected from this site resulted in the discovery of the gene used in development of the Luminase™ pulp biobleaching enzyme. Photo ©Frans Lanting

effective systems for facilitating access to their biodiversity and have created appropriate mechanisms for reasonable benefit-sharing. Notable leaders in biodiversity and bioprospecting management include Costa Rica and Kenya. Such countries experience pressures to demonstrate that their conservation activities provide more than a thriving ecotourism industry. Accordingly, bioprospectors and the life science community need to become more supportive and enter into legal framework agreements that will ultimately result in the development of royalty-bearing products, thus providing an additional value for their biodiversity conservation investments. The best way to protect an environment is to show it has value.

Ultimately, not only will the countries providing the genetic diversity receive benefit, but so will the scientists within the life science community by protecting their discoveries from claims and accusations of unethical research practices. Legal access framework agreements also give confidence to third party industrial collaborators that their research activities will not be exposed to such accusations. This model of a more ethical approach also creates a clear paper trail to the legal origin of discovery. During the past 11 years, Diversa has discovered thousands of novel enzymes and developed an array of products that have not only generated financial benefits for Diversa, but also for its bioprospecting and industrial/pharmaceutical collaborators. Although this bioprospecting framework model requires patience, time, and effort, it is well worth the investment, both ethically and economically.

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