Chapter 25

LINKING INSIGHTS FROM ECOLOGICAL RESEARCH WITH BIOPROSPECTING TO PROMOTE CONSERVATION, ENHANCE RESEARCH CAPACITY, AND PROVIDE ECONOMIC USES OF BIODIVERSITY

T.A. Kursar, T.L. Capson, L. Cubilla-Rios, D.A. Emmen, W. Gerwick, M.P. Gupta, M.V. Heller, K. McPhail, E. Ortega-Barría, D.I. Quiros, L.I. Romero, P.N. Solis, and P.D. Coley

OVERVIEW

Bioprospecting has frequently been cited as a sustainable use of biodiversity that should also provide a motivation for conservation. Nevertheless, in the tropical, biodiversity-rich regions of the world the level of bioprospecting is much below the potential, with the result that bioprospecting has had limited impact on conservation. Our group has developed a bioprospecting program in Panama that has addressed these critical issues. The program was initiated using the insights from 20 years of basic ecological research to enhance the likelihood of finding active compounds. In addition, instead of sending samples abroad, most of the research in our program is carried out in Panamanian laboratories. As a result, many young Panamanian scientists are trained. Through this and other mechanisms Panama receives immediate benefits from investigation into the uses of its biodiversity. Over the long term, such research may lead to intellectual property that assists with establishing new industry in Panama that is based upon sustainable uses of biodiversity. Additionally, we have linked our bioprospecting efforts to conservation via transparent communication about the program's use of biodiversity, resulting in a self-evident need to promote conservation. The Panama program has also made direct conservation efforts in a newly established protected area, Coiba National Park, an area in which we also collect. Hence, beginning with insights from ecological research, both conservation and sustainable development benefit from the enhanced bioprospecting effort that we have established in Panama.

THREATS TO BIODIVERSITY, BIOPROSPECTING, AND THE CONVENTION ON BIOLOGICAL DIVERSITY

Humans have greatly impacted earth's ecosystems, resulting in large and rapid changes. To date, human activity, including grazing, clearing for agriculture, and urban development, has extensively modified 35–50% of earth's land area, with the largest future impacts predicted to occur in the tropics (Ramankutty and Foley 1999, Tilman *et al.* 2001, Defries *et al.* 2002). Freshwater and marine ecosystems also are threatened (Jackson *et al.* 2001, Pauly *et al.* 2002, Rabalais *et al.* 2002). Many believe we are experiencing a major extinction crisis (Pimm *et al.* 1995). Exacerbating these environmental threats, the human population may grow by nearly 50% between 2000 and 2030, and resource use per capita is rising fast (Myers and Kent 2003). Given that diversity is concentrated in the tropics, it is likely that extinctions will be most frequent in the tropics. While conservation can potentially mitigate many of these problems, the extent and speed of conservation efforts may not be sufficient.

How can we better motivate conservation, especially in the developing countries of the tropics that harbor a large fraction of the world's biodiversity? Clearly, all appropriate conservation approaches should be applied with maximal effectiveness. Here we focus on a strategy often termed "use it or lose it." Put simply, if humans can obtain more value from habitat left in a natural state than from conversion for human uses, then economic forces can drive conservation. While "sustainable use," such as natural forest management, often leads to habitat degradation (Oates 1999, Terborgh 1999), other economic uses of biodiversity may prove easier to sustain. Particularly promising are medicinal and horticultural products, ecosystem services, ecotourism, and bioprospecting, the investigation of biodiversity as a source of useful medicines or genes (ten Kate and Laird 1999). For areas with high biodiversity, such as the tropics, bioprospecting may be an economic use of biodiversity that effectively promotes habitat protection.

Nevertheless, the utility of bioprospecting for providing benefits for developing countries and for enhancing the protection of their biodiversity has been controversial. This controversy results, in part, from changing perceptions on who owns and who should benefit from biodiversity. Between the 17th and early 20th centuries sovereign countries and colonial powers prohibited the export of viable seed or live plants of nutmeg, *Cinchona*, and coffee in order to retain the benefits of biodiversity. However, such efforts were not successful over the long term; there were many examples of "biopiracy" such as the smuggling of rubber seedlings out of Brazil and the subsequent establishment of lucrative rubber plantations in Southeast Asia (Balick and Cox 1996). During the 1970s and 1980s, a number of international conventions provided for biotic and open ocean resources as a common heritage of humanity and promoted their shared use (Gepts 2004).

In 1992–1993 the Convention on Biological Diversity (CBD; Gollin 1993) reversed this trend by recognizing that nations have ownership of, and hence the right to control access to, their species ("genetic resources") and by requiring equitable sharing of the benefits derived from biodiversity. More recent international agreements have provided additional support for the new legal regime, one that researchers and industry presently abide by (Gollin 1999). A key component of the CBD that is not adequately appreciated provides that both developing and developed countries should facilitate the study of the uses of biodiversity. For example, the CBD indicates that each country should provide for appropriate access to biodiversity (Article 15) and that the developed countries allow for the transfer of technology (Article 16). In short, the CBD is a wide-ranging and expansive document that lays out a very broad perspective on the use of biodiversity. This ranges from guaranteeing nations sovereign rights over their biotic resources to stating that nations should "endeavour to create conditions to facilitate access to genetic resources for environmentally sound uses" as well as "develop and carry out scientific research based on genetic resources."

Given these provisions, many expected that the CBD would promote biodiversity research,

including bioprospecting, and would allow nations to capture the value of their biodiversity. In fact, many governments developed unrealistic expectations that have inhibited both basic and commercially oriented research on biodiversity (Grajal 1999, Gomez-Pompa 2004). This phenomenon resulted from the perception that biotic resources have a high value, even in a "raw," undeveloped state. In part these perceptions arose because in 1991, a 1.1 million dollar agreement between Merck and Costa Rica's National Biodiversity Institute (Aldhous 1991) fueled unrealistic hopes for substantial access payments to biodiversity-rich nations. Since then many of the academic studies and international conferences have dealt with legal issues such as defining prior informed consent for the use of traditional knowledge and specifying the nature of benefit sharing arrangements (CBD 2005). Inadequate attention has been paid to the equally important issues of promoting and streamlining scientific research on the uses of biodiversity. Furthermore, some countries have passed legislation that severely restricts basic research, such as the export of herbarium specimens as well as research by their own scientists on their own biodiversity (Grajal 1999, ten Kate and Laird 1999, p. 19). In addition, in biodiverse countries applied research by pharmaceutical and agricultural companies has been inhibited. Because the value of biotic resources can be realized only through research, the low investment in research has had the ironic effect of decreasing the value of biodiversity.

How can we return to the vision outlined in the CBD? How can we promote the study of the uses of biodiversity as well as link such studies with economic development and conservation? Prior to 1990 most bioprospecting arrangements involved shipping samples abroad with the expectation of receiving royalties or milestone payments. During the last 10 years, more emphasis has been placed on the provision of benefits that are derived from research (Laird and ten Kate 2002). Nevertheless, this approach to bioprospecting is in its infancy. In fact, no comprehensive programs to study the uses of biotic resources have been created in the biodiversity-rich countries of the world. This has left the bioprospecting-based argument, to conserve nature as a future source of medicines and genes, without any modern examples. A separate issue is that there is no inherent link between bioprospecting and conservation; in fact creating mechanisms by which bioprospecting directly promotes conservation has been elusive (Laird and ten Kate 2002). In this chapter we provide an overview of our Panama-based bioprospecting program, one that is attempting to address many of these issues (Kursar *et al.* 2006, 2007). In particular we focus on how ecological studies can assist biodiversity prospecting, and how such research can be linked to economic development as well as to conservation.

IS BIOPROSPECTING BENEFICIAL FOR DEVELOPING COUNTRIES?

The model implicit in many bioprospecting arrangements has been that the source country provides biological materials and the developed country provides research. If a drug is commercialized, the source country would receive royalties. However, with a success rate of much less than 1 in 10,000 samples, royalties are a highly unlikely outcome (Principe 1991, McChesney 1996). Additionally, the time frame is long, perhaps 10–12 years from discovery to receiving benefits. This arrangement fails because neither bioprospecting nor conservation is promoted and because biodiversity-rich countries receive no immediate benefits. This model inhibits research on the beneficial uses of biodiversity and greatly weakens or invalidates the argument that biodiversity should be preserved because of future utility.

In order to create a bioprospecting program in which the source country receives immediate and tangible benefits, we have initiated a collaborative project based in Panama in which most of the drug discovery research is carried out in-country (Capson *et al.* 1996, Kursar *et al.* 1999). In this chapter, we describe our bioprospecting project which has been ongoing in Panama since 1995. Royalty agreements are in place with the Panamanian government. However, royalties are not the focus of the project. By conducting the research in Panama, the project provides guaranteed benefits even if a drug does not become commercialized.

THE PROCESS OF DRUG DISCOVERY RESEARCH

A key function of bioprospecting is to contribute some of the thousands of compounds that are discovered annually to have interesting structures or activities. A subset of these become new "lead compounds," that is, compounds that are promising enough to merit substantial investment and continued investigation. In a typical year, relatively few lead compounds are successful and become approved medicines. Hence, the drug discovery process can be thought of as a pyramid having a very broad base that is composed of thousands of compounds with new activities, with many of these derived from bioprospecting (Principe 1991, McChesney 1996). Higher on the pyramid are many fewer lead compounds and only 20–30 of these make it to market annually. Even though the discoveries of many research groups encompass interesting structures or activities that do not become medicines, such compounds represent the essential, initial steps of the drug discovery process. Recently it has been estimated that a third of new drugs, and perhaps more, including many of the most innovative medicines, are derived from research in academia, government, or small biotech companies (Angell 2004). Tens of billions of dollars are spent annually to support this research. Furthermore, nature is still a productive source of new medicines. Taken together, these observations indicate that bioprospecting research conducted in academia or in small companies will continue to provide both jobs and promising lead compounds. Given that much of biodiversity lies in the developing world, what mechanisms will promote the funding of bioprospecting research in these regions?

THE INTERNATIONAL COOPERATIVE BIODIVERSITY GROUPS

In 1992 the United States government (National Institutes of Health, the National Science Foundation, and the US Department of Agriculture) initiated an imaginative and ambitious program, The International Cooperative Biodiversity Groups (ICBG), with the goals of combining drug discovery from natural products with biodiversity conservation, scientific capacity-building, and economic development (Rosenthal *et al.* 1999). The motivation for the program was derived from the concerns that were outlined above regarding threats to biodiversity and the slow pace of research on uses of biodiversity. In addition, the program inception was prompted by the recognition that improvements in human health and agricultural productivity historically have depended on access to biodiversity (Grifo and Rosenthal 1997). For example, discovery of taxol in the 1960s led scientists to uncover a previously undescribed mechanism of anti-cancer activity in 1979 (Horwitz 1992). These discoveries had considerable consequences, including the development of taxol as an effective anti-cancer treatment, new assays to detect other microtubule stabilizing agents and, quite recently, the discovery of additional anti-cancer drugs that work through the same mechanism (Mani *et al.* 2004). An agricultural example is the case of the then-new, high yield rice varieties that were protected from grassy stunt virus during the 1970s by breeding with a wild species of rice from India (Plucknett *et al.* 1987). Because of many similar successes, the collection and protection of crop germplasm for use in crop breeding remains a very high priority worldwide (Biodiversity International 2007).

In many regions of the world the future development of biodiversity-based research is threatened not only by the biodiversity losses already mentioned, but also by restraints on access to biodiversity and by weak scientific infrastructure. To address these issues an experimental approach was applied to the creation of new modes of accessing and using biodiversity in pharmaceutical and agricultural discovery. The ICBG program is based upon "biodiscovery partnerships" in which systematists, chemists, cell biologists, conservationists, and lawyers from academia, business, and government in the USA and in developing countries have succeeded in promoting biodiversity-based research by developing novel institutional and legal arrangements. These programs have been or currently are based in many countries, including Panama, Peru, Surinam, Madagascar, Cameroon/Nigeria, Vietnam/Laos,

Chile/Argentina, Mexico, Papua New Guinea, Costa Rica, Peru, and Uzbekistan/Kyrgyzstan (Rosenthal *et al.* 1999, Fogarty International Center 2005). They include collections of plants, algae, microbes, and invertebrates, a wide variety of bioassays, and the isolation and structural elucidation of active compounds. The ICBG program emphasizes the training of young scientists, the enhancement of research capacity, and the promotion of conservation, particularly in developing countries. The emphasis of the Panama ICBG, the focus of this chapter, has been to assure that Panama receives immediate benefits from bioprospecting and to link bioprospecting with conservation and sustainable development.

THE USE OF ECOLOGICAL INSIGHT IN BIOPROSPECTING IN THE PANAMA ICBG

Finding compounds that lead to marketable drugs is a highly unlikely process. Although many programs make random collections, using biological insight could enhance discovery. The Panama ICBG has used over 20 years of basic research on plant–herbivore interactions to guide our collections. The research suggested that young leaves are very dependent on chemical defenses whereas mature leaves depend more on toughness (Kursar and Coley 2003). We tested this and related ecological hypotheses by making extracts from fresh young and mature leaves and comparing their activities in bioassays. We found that 10.0% of the extracts from young leaves were highly active in anti-cancer assays while only 4.5% of the extracts from mature leaves were active. The National Cancer Institute has tested hundreds of thousands of samples, primarily dried, mature leaves, and found activity in only 4.3% (Figure 25.1). Extracts from young leaves also were more active in bioassays for activity against Chagas' disease, malaria, and HIV (Coley *et al.* 2003). Out of 23 species from which active compounds were purified, 10 species had compounds of interest only in the young leaves. Four species had some compounds of interest in the young leaves and other compounds in the mature leaves. For another 10 species most of the compounds of interest were found in both

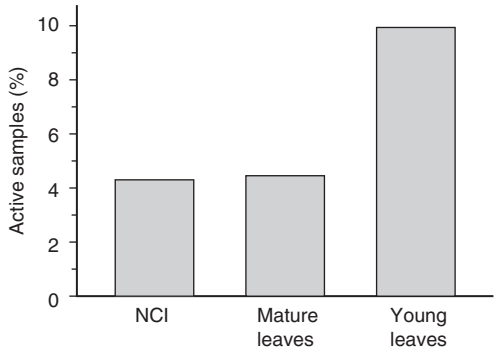

Figure 25.1 Comparison of the activity against cancer bioassays of samples from the National Cancer Institute (NCI) and the Panama ICBG. For the NCI data, about 114,000 extracts prepared during 1961–1980 from 25,000 to 35,000 species were measured for activity against lung (H-460), breast (MCF-7), and central nervous system (SF-268) cancer cell lines. NCI scored samples as "confirmed active" based upon an *in vivo* assay for anti-leukemia activity along with an *in vitro* assay for anti-mitotic activity (Suffness and Douros 1982). In our study, extracts were scored active if growth relative to the controls was inhibited by 50% or more at an extract concentration of $\leq 20\ \mu g$ of extract per ml (data from Gupta, Solis, and co-workers; bioassay methods described in Coley *et al.* 2003).

the young and mature leaves. In general, more interesting compounds were found in the young leaves, such as those isolated from *Myrospermum frutescens* and *Guatteria* spp. (Mendoza *et al.* 2003, 2004, Montenegro *et al.* 2003, Correa *et al.* 2006).

Based upon our ecological studies we predicted that, comparing the young leaves of different species, the speed of leaf expansion would show a negative correlation with activity. In short, some species invest less in secondary metabolites during leaf development and depend on rapid expansion to minimize the window when leaves are vulnerable to herbivores (Aide and Londoño 1989). In order to expand rapidly, they allocate resources from chloroplast development to growth, so the young leaves appear white or light green (Kursar and Coley 1992a–c). We classify this as an "escape" syndrome (Kursar and Coley 2003). In contrast, other species follow a "defense" syndrome in which they expand

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leaves more slowly, invest in effective secondary metabolites throughout development, and green normally (Coley *et al.* 2005). Although investment in secondary metabolites appears linked to expansion rate, expansion rate is not easy to assess rapidly in the field. Instead, we hypothesized that the extent of chloroplast development, or the "greenness" of a leaf, might be a rapid visual clue to the level of chemical defense and hence activity in our bioassays (Coley *et al.* 2003). Although extracts from green young leaves were more active than light green or white leaves, leaf color was not significant (non-parametric analysis of variance, $P = 0.16$; Coley *et al.* 2003). Thus, our data did not warrant focusing collection efforts only on young green leaves.

We also predicted that shade-tolerant species, because they are adapted to lower resource environments, should be better defended than species that require high light for establishment (Coley 1983, Coley *et al.* 2003). In fact, extracts from mature leaves of shade species were significantly more active than those from gap-requiring species (Coley *et al.* 2003). Although we would not predict a priori that growth form should influence chemical defense, it has been suggested that epiphytes (Bennett 1992) or lianas (Hegarty *et al.* 1991, Phillips 1991) should be active. We found no significant effect of growth form on activity among shrubs, trees, herbs, ferns, lianas, vines, and epiphytes (Coley *et al.* 2003). However, palms were less active, perhaps due to a greater reliance on toughness.

THE SCIENTIFIC OUTPUT OF THE PANAMA ICBG

The Panama ICBG group has collected over 1500 species of plants, made over 1000 isolates of endophytic fungi as well as collected dozens of cyanobacteria and marine invertebrates. Using ICBG funds, two laboratories were set up in Panama and several existing laboratories in Panama were enhanced. The project also acquired the first nuclear magnetic resonance (NMR) facility in Panama (Bruker Avance 300 MHz). This infrastructure has supported the isolation and structure elucidation of over 50 compounds with medicinally relevant activities, primarily from plants. These represent the majority of the published studies of the uses of Panama's biodiversity in which all or nearly all of the elucidation of the chemical structure and the development of the medicinal bioassays has been accomplished in Panama-based laboratories.

Plants have been an excellent source of anticancer compounds (Cragg *et al.* 1993) and a major biotic resource accessed by the ICBG. Since the 1970s Dr M.P. Gupta and more recently Dr P.N. Solis (Faculty of Pharmacy, University of Panama) have carried out bioassay-guided purification of active molecules from plants. As part of the ICBG they established the first cytotoxicity, or cell-based, anti-cancer assay in Panama and isolated 40 anti-cancer compounds, 13 of which are new to science (Hussein *et al.* 2003a,b, 2004, 2005).

Drs Ortega-Barría and Romero have developed *in vitro* bioassays for testing the activity of extracts and compounds against tropical diseases, including Chagas' disease, leishmaniasis, and malaria (Williams *et al.* 2003). These assays do not use radioactivity and are more appropriate for developing nations. The malaria assay, based upon a DNA-sensitive fluorometric probe, uses no radioactive reagents and is particularly novel (Corbett *et al.* 2004). The assay has been patented (Ortega-Barría *et al.* 2005) and scientists from Bolivia, Madagascar, and Peru have come to Panama to learn the fluorescent bioassay method.

Agricultural products, such as pesticides, also are relevant for bioprospecting. Aphids and whiteflies may constitute the worst agricultural pests in the tropics (Oerke and Dehne 1997). Drs Quiros and Emmen in the Department of Zoology at the University of Panama developed a method for the rapid, efficient assay of plant extracts for activity against aphids in a 96-well microtiter plate format as well as an improved whitefly assay.

Drs L. Cubilla and L. Romero submitted a patent application for aporphine alkaloids from young leaves of two species of *Guatteria* (Annonaceae) that have high *in vitro* toxicity against *Leishmania mexicana* (leishmaniasis) but 65-fold lower toxicity to the human host cell

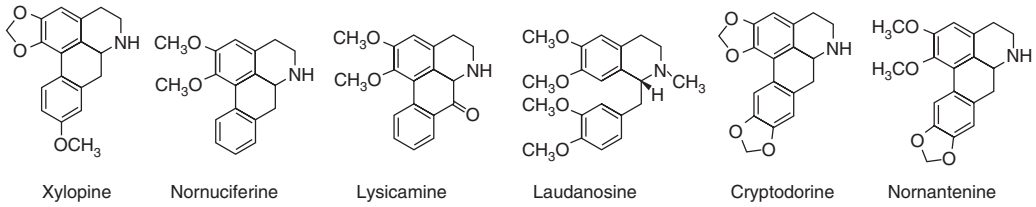

Figure 25.2 Six aporphine alkaloids isolated from crude extracts of *Guatteria amplifolia* and *G. dumetorum* and purified based upon their *in vitro* activity against *Leishmania mexicana* (Montenegro *et al.* 2003).

(Figure 25.2; Montenegro *et al.* 2003, Rios *et al.* 2004). These compounds are sufficiently promising that they should be evaluated at the next level, for safety and efficacy in a vertebrate (mouse) model.

COMBINING BIOPROSPECTING WITH TECHNOLOGY TRANSFER AND TRAINING IN THE PANAMA ICBG

The Panama ICBG is based at the Smithsonian Tropical Research Institute (STRI), the University of Panama, and the Institute of Advanced Scientific Investigations and High Technology Services or INDICASAT, all in Panama City, as well as at US universities. The sophisticated scientific, communications, and administrative infrastructure provided by STRI has been essential for meeting project goals of technology transfer and training in Panamanian laboratories. The factor that most limits research in biodiversity-rich countries is the development of laboratories that publish in international journals. The technology transfer and training with the Panama ICBG has been recognized within Panama and also internationally as a model program (Dalton 2004, *The Economist* 2005). With funding of about $500,000 per year, the Panama ICBG has contributed substantially towards enhancing infrastructure, provided research opportunities for eight Panamanian laboratory leaders, and given research experience to over 70 young scientists. Twenty are working on BS degrees in Panama, 12 on MS degrees within Panama, and 12 have moved to other countries for MS and PhD studies. Informal comparisons suggest that in many developing countries students have few opportunities to participate in research on the uses of their own biodiversity.

LINKING BIOPROSPECTING WITH ECONOMIC DEVELOPMENT

In the context of bioprospecting we define economic development to mean enhanced research. At a minimum developing countries should expect bioprospecting to provide new jobs. A vigorous and productive bioprospecting program also will provide developing country researchers with intellectual property, such as novel, active compounds or genes. In developed countries intellectual property can be the basis for creating new companies. In principle, the same process should operate in developing countries. Based upon the substantial amount of funding expended for pharmaceutical and biomedical research, this expectation is quite reasonable. Annual spending by the largest pharmaceutical companies on research is estimated at 27–43 billion dollars worldwide (Agnew 2000). Additional research funds are expended by government (e.g., National Institutes of Health), non-profit institutions (e.g., Howard Hughes Foundation, Medicines for Malaria Venture, Institute for OneWorld Health), and many small companies (Morel *et al.* 2005). About one third of total research in the large pharmaceutical companies (9–14 billion dollars) is similar to the initial steps of bioprospecting (ten Kate and Laird 1999). These include the discovery of active compounds through bioassay, purification, and structure elucidation, their modification

to enhance activity, and their testing in vertebrate models. These all are currently employed in the Panama ICBG and can be carried out in most developing countries. Expending a small fraction of total funding on biodiversity-based research in developing countries would have a substantial economic impact in most countries.

Pharmaceutical companies regularly collaborate with academia and small companies in developed countries. To what extent has bioprospecting in developing countries promoted growth in their economies? While some bioprospecting activity has been carried out in developing countries, extension of the model described above to biodiversity-rich countries has been slow. In other words, developing country scientists have not participated in the more advanced stages of bioprospecting research and few researchers have used biodiversity-based intellectual property in order to attract funding and establish biotechnology companies in developing countries. Serious barriers remain to be overcome in order to meet these goals.

WHAT ARE THE OBSTACLES AND THE SOLUTIONS FOR REALIZING ECONOMIC AND SCIENTIFIC DEVELOPMENT THROUGH BIOPROSPECTING?

The rapid and substantial successes of fields such as genetics and cell biology, as well as their ability to attract funding, can be assigned in large part to the premium placed on collaboration and on the sharing of materials and techniques among competing laboratories (Edwards 2004). Thus, bioprospecting will be most competitive where an open, dynamic research environment is created. Nevertheless, a barrier to collaboration is the tendency of some to view bioprospecting as a confidential activity. As far as possible, the Panama ICBG maintains open access, sharing materials and techniques.

Another barrier to collaboration is the difficulty of entering into legal agreements with academic and pharmaceutical collaborators. Lack of experience and restrictive regulations, leading to very slow and expensive legal processes, probably blocks many bioprospecting projects. At present sufficient experience exists worldwide such that, in principle, developing countries could be provided with legal advice that is consistent with the CBD, protects the interests of all sides, and also allows negotiations to be completed rapidly. A key recommendation would be the creation of institutions which provide such assistance (e.g., Public Interest Intellectual Property Advisors, Inc. 2005).

Another limitation is that very few of the thousands of active compounds discovered in academic laboratories and published each year are investigated for safety and efficacy in vertebrate models. In effect, the research process ends before the utility of these compounds has been determined. This lack is especially critical in the case of tropical diseases; 3 billion people live in affected areas and no safe and effective treatments are available (Trouiller *et al.* 2001, Gelb and Hol 2002). By working with vertebrate models, researchers would more effectively address the need for new treatments as well as establish more substantial intellectual property.

A major barrier to linking bioprospecting to economic development is that laboratories in the developing world often are not internationally competitive. This key step, enhancing in-country scientific training, infrastructure, funding, and institutional capacity, deserves to be a focus of development efforts (Kettler and Modi 2001, Annan 2003, Holmgren and Schnitzer 2004). In order to attract established scientists or highly qualified postdoctoral associates from developed countries, it is essential to arrange not just space and set-up funds, but also a secure option for such scientists to return to an institution in the USA or Europe should they choose to do so. Once such laboratories are established in-country, they can pursue additional research funds.

In general, funding to developing country researchers should be provided on a competitive basis, with researchers and their institutions held accountable for the use of funds and productivity evaluated as part of the competitive process. Accountability should be a centerpiece since indiscriminate support by donors can impede scientific development.

Another obstacle is the failure to appreciate the breadth of bioprospecting-related research. Narrowly defined, bioprospecting includes only collections, bioassay, and natural products chemistry, ending with the publication of novel, active compounds. In fact, chemically based interactions among organisms, particularly for tropical animals, microbes, and plants, is a vastly understudied area that could be the basis for vigorous and exciting research programs. Studies of mechanisms of action, biosynthesis, and chemical modification of active compounds followed by retesting would involve researchers from genetics to neurobiology to organic synthetic chemistry. Other important areas include agricultural applications, the safety and efficacy of medicinal plants as well as the traditional areas of biodiversity research such as ecology and systematics.

LINKING BIOPROSPECTING WITH CONSERVATION IN THE PANAMA ICBG

While excellent conservation efforts originate from large organizations that are based in developed countries, more conservation initiatives within developing countries are needed. Clearly there is a great need to develop an in-country conservation ethic. In particular, urbanites are an increasingly important fraction of the population in developing countries, with an estimated increase in Latin America and the Caribbean, for example, of 42% to 85% during the period 1950–2030 (United Nations 2003). We must address the need for conservation tools that effectively engage these citizens, especially the urban-based businesses, governments, and universities (Aide and Grau 2004). Our experience has been that bioprospecting provides a Panamanian voice in support of conservation, one that is especially unique and powerful since it originates in the urban areas.

The first link with conservation must be to assure that biodiversity-rich countries receive immediate economic benefits from bioprospecting. We argue that research must be viewed as the primary economic benefit of bioprospecting. In essence research on biodiversity provides jobs, training opportunities for young scientists, and could lead to the creation of new industries.

In addition to the indirect link between economic benefits from the Panama ICBG's studies of the uses of biodiversity, other ICBG efforts have promoted conservation. All of the investigators involved in the project have worked to create a link between bioprospecting and conservation. Members of the Panama ICBG, from the principal investigators to assistants, give up to 100 talks annually to students at schools, to the public in small towns, to the business community, to government officials, and to visitors from outside of Panama. These can be powerful since they are Panamanians giving talks to their countrymen about discoveries from their biodiversity, as well as the value of and threats to Panama's biodiversity. In addition, the newspapers and television frequently report on the Panama ICBG. These efforts have created wide public awareness of the Panama ICBG's bioprospecting efforts, giving the project a high degree of transparency. Legal agreements that provide for nearly all benefits, such as royalties, to return to Panama also meet the need for equitable sharing of benefits, as defined in the CBD, and enhance local support for the project. Efforts at transparency, the provision of immediate benefits, and equitable legal agreements promote the perception that Panama's biodiversity has direct value to Panama.

Many of these conservation efforts can be viewed as indirect, making it difficult to quantify their conservation impact. Nevertheless, if ecotourism can motivate conservation, as clearly is the case in Costa Rica, the same outcome can be foreseen for bioprospecting. Hence, we believe such efforts do have an impact and, just as conservation should be an integral aspect of ecotourism, conservation should be part of bioprospecting. Bioprospecting also has direct effects on conservation since researchers in parks and reserves have in many cases made important contributions to habitat protection. In particular, Dr Todd Capson, a chemist, pioneered a novel approach in which an ICBG scientist worked actively in conservation. He provided scientific support for the establishment of Coiba National Park, a spectacular marine and terrestrial park. Rather than representing a conservation organization or

conservation biology, Dr Capson represented the interests of an applied project that is recognized within Panama for the economic and other benefits it provides. To our knowledge, Dr Capson's initiative was the first application of this highly effective conservation strategy.

THE FUTURE OF BIOPROSPECTING RESEARCH

Any discussion of bioprospecting must touch on the issue of fear of biopiracy. To what extent should the goals and organization of bioprospecting projects be determined by biopiracy issues? Due to these concerns the Panama ICBG has not worked with indigenous groups and campesinos. In our view, the absence of a single authority and the consequent uncertain legal relationships among these groups create the possibility of biopiracy claims (Dalton 2001). Otherwise our experience has been that charges of biopiracy have not taken hold. From its inception, the Panama program has focused on the concept of providing immediate benefits that would link bioprospecting, economic development, and conservation. Similarly constituted ICBG projects have been politically acceptable in other countries (Kingston *et al.* 1999, Schuster *et al.* 1999, Soejarto *et al.* 1999).

Bioprospecting continues to play an important role in the discovery of novel, active compounds. Recent experience demonstrates that natural products research continues to complement the drug discovery research of medicinal chemists and cell biologists. We define natural products to include compounds derived from plants, fungi, bacteria, corals, sponges and other invertebrate animals, and vertebrate venoms but to exclude compounds that are based upon human physiology such as interferon and testosterone. Despite the fact that all of the available analyses combine both classes of compounds, it is clear that natural products, as we have defined them, contribute considerably to new medicines. The percentage of new medicines derived from natural products, in excess of 35%, remained constant during the period 1981–2002 (Grifo and Newman 1997, Newman *et al.* 2003, Koehn and Carter 2005), suggesting that this rate of success will continue. Many of these have mechanisms of action that are novel and not previously discovered. Consequently, natural products also lead to the discovery of novel molecular targets, creating opportunities for additional innovations. Another reason that natural products research will retain its value is that new medicines will be needed due to pathogen resistance, the spread or evolution of new diseases, the failure of vaccine or public health measures to control disease, and the societal expectation that medical care should improve. Thus bioprospecting has great potential to contribute to human health. Clearly, many developing countries could carry out much exciting, high quality research on the uses of their own biodiversity that provides in-country training in laboratories and contributes to human health, economic development, and conservation. Nevertheless, new laboratories, cross-disciplinary collaborations, and a dynamic research environment must be established in more developing countries before the promise of bioprospecting can be fulfilled.

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