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ORIGINAL PAPER

Linking bioprospecting with sustainable development and conservation: the Panama case

Thomas A. Kursar · Catherina C. Caballero-George · Todd L. Capson · Luis Cubilla-Rios · William H. Gerwick · Maria V. Heller · Alicia Ibañez · Roger G. Linington · Kerry L. McPhail · Eduardo Ortega-Barría · Luz I. Romero · P. D. Coley

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Abstract The limited international resources for economic aid and conservation can only mitigate poverty and losses of biodiversity. Hence, developing nations must establish the capacity to resolve their problems. Additionally, policy-makers and donors need to obtain scientific input on issues such as global change and ecosystem services. We propose that for nations rich in biodiversity, ecosystem services derived from bioprospecting, or drug discovery, could contribute to economic development. In the case where unstudied samples are shipped abroad for research, the chances of obtaining royalties are infinitesimally small. Therefore developing nations will only realize benefits from bioprospecting through in-country research on their own biodiversity. Policy-makers and donors have failed to appreciate the value of this approach. In order to provide an example of the inherent links

T. A. Kursar (✉) · P. D. Coley
Department of Biology, University of Utah, 257 South 1400 East, Salt Lake City, UT 84112-0840, USA
e-mail: kursar@biology.utah.edu

T. A. Kursar · C. C. Caballero-George · T. L. Capson · W. H. Gerwick · M. V. Heller · A. Ibañez · P. D. Coley
Smithsonian Tropical Research Institute, Panama City, Republic of Panama

L. Cubilla-Rios
Department of Chemistry, University of Panama, Panama City, Republic of Panama

W. H. Gerwick · R. G. Linington
Scripps Institution of Oceanography, La Jolla, CA, USA

R. G. Linington · E. Ortega-Barría · L. I. Romero
Institute of Advanced Scientific Research and High Technology, Panama City, Republic of Panama

K. L. McPhail
College of Pharmacy, Oregon State University, Corvallis, OR, USA

Present Address:
M. V. Heller
Secretaría Nacional de Ciencia, Tecnología e Innovación (SENACYT), Clayton, Ancon
Republic of Panama

between conservation and sustainable economic development, we initiated a drug discovery effort in Panama that emphasizes local benefit. As much of the drug discovery process as possible is conducted in Panamanian laboratories, providing jobs dependent on intact biodiversity and enhancing local research and training. In short, research, plus the spin-offs from research, provide immediate and long-lasting benefits to Panama. The connection between conservation and development has been highlighted in publicity about the project in Panama's urban media. This provides a constructive alternative to the perception the among the urban populace that economic development inevitably competes with conservation. In summary, our program uses biodiversity to promote human health as well as to support research capacity, economic development and conservation within Panama. The program provides an example of the widely recognized but little developed concept of bioprospecting research as an ecosystem service.

Keywords Bioprospecting · Chagas' disease · Convention on biological diversity · Ecosystem services · ICBG · Leishmaniasis · Malaria · Panama · Policy-makers · Sustainable development

Introduction

The high and increasing human population combined with the rapidly increasing standard of living in some parts of the world will make ever more demands on natural resources (Myers and Kent 2003). Future loss or degradation of biodiversity could be severe (Ramankutty and Foley 1999; Tilman et al. 2001; Jackson et al. 2001a, b; Defries et al. 2002; Pauly et al. 2002; Rabalais et al. 2002). At the same time, human well being depends on the services provided by natural ecosystems. Because losses of biodiversity and increasing demands on ecosystem services are critical issues throughout the world, the need to promote conservation and also protect, or even enhance, ecosystem services has never been greater. It seems clear that these issues, though of worldwide importance, will have their biggest impacts in the developing world.

Among the mechanisms for addressing these issues, one important approach must be identifying and developing ecosystem services (Daily and Ellison 2002; Kremen 2005; Odling-Smee 2005; Sachs and Reid 2006). For this reason the UN initiated an evaluation of the state of the Earth's ecosystems, the Millenium Ecosystem Assessment, that emphasized bioprospecting and related disciplines as a key component of human well-being (Beattie et al. 2005). We employ the term bioprospecting both in the narrow sense, as the search for new medicines and genes from natural sources, as well as to refer to research efforts that encompass related disciplines (Kursar et al. 2006).

The goal of our group of investigators in Panama is to demonstrate that, for nations rich in biodiversity, the research and activities associated with bioprospecting are an untapped form of ecosystem service that can provide scientific and sustainable economic development as well as promote conservation. The search for medicines and genes from nature has been promoted as a non-destructive use of habitat that promotes human health as well as supports economic development and conservation. Nevertheless, to date this has provided only minor improvements in development and conservation because, in the biodiversity-rich, developing world, little such research is carried out. A well-known example of this approach is the 1991 Merck-INBIO agreement in Costa Rica (Aldhous 1991) and, more recently, similar commercial agreements in Brazil (Neto and Dickson 1999; Willis 2006). In principal, bioprospecting research carried out on a large scale in laboratories based in developing countries would represent a "new" ecosystem service (ten Kate and Laird 1999). Nevertheless, this remains to be demonstrated and it is this challenge that the Panama project seeks to address.

Bioprospecting as a research discipline

Bioprospecting is the discovery from natural sources of medicines or genes of use for human health, agriculture, industry or other applications (ten Kate and Laird 1999). It is widely recognized that medicines can be developed using modern technology. Less appreciated is that improvements in human health and agricultural productivity also depend on access to biodiversity (Grifo and Rosenthal 1997). Overall, the percentage of new medicines derived from natural products, in excess of 35%, remained constant during 1981–2002 (Grifo and Newman 1997; Newman et al. 2003; Koehn and Carter 2005), suggesting that this rate of success will continue. Although we do not have exact figures, it is highly unlikely that one third of drug discovery research is invested in studies of natural products. In other words, despite under-investment in natural products, such research may be exceedingly productive.

Medicines derived from nature, or "natural products", can have mechanisms of action that are novel, that is, previously unknown to science. For example, the discovery of taxol in the 1960's 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). Natural products derived from fungi, FK506 and cyclosporin, played a similar, key role in the development of the immune suppressors that revolutionized organ transplantation (Rosen and Schreiber 1992). Consequently, natural products can lead to the discovery of novel molecular targets, which in turn creates opportunities for additional innovations. Such discoveries also may lead to sophisticated efforts at the commercial synthesis of analogs having equal or greater efficacy (Paterson and Anderson 2005).

An agricultural example is the case of high yield rice varieties that were protected from grassy stunt virus during the 1970's by breeding with a wild species of rice from India (Plucknett et al. 1987). Because of numerous similar successes, the collection and protection of crop germplasm for use in crop breeding remains a very high priority worldwide (CGIAR 2007). Hence biodiversity, by providing natural products and genes as ecosystem services, is the foundation of discoveries that are vital to human well-being.

Bioprospecting research as an ecosystem service

Ecosystem services include direct benefits such as wood and water obtained from intact or well managed biodiversity. Ecosystem services also refers to benefits, such as health or economic, which are mediated through the creation of new industry, including ecotourism and research activities such as bioprospecting. Clearly these provide benefits that would be absent were ecosystems not protected. Additionally, these uses of ecosystems are not destructive. Since bioprospecting research and its associated activities provide benefits that are dependent upon intact ecosystems, bioprospecting is widely recognized, at least in principal, as an ecosystem service. In addition to the benefits from research, new medicines are derived from nature. Clearly, products from nature that improve human health represent an important service (similar to clean water) provided by intact ecosystems. Hence, the research and the actual discoveries from bioprospecting both represent valued ecosystem services.

Nevertheless, within the developing world, the research-based, economic benefits described in this paper do not actually provide a substantial ecosystem service. For example, although exact figures are not available, there is little doubt that expenditures in the developing world on ecotourism dwarf those for bioprospecting. As a consequence, in practical terms, the benefits associated with research on useful genes and chemicals in nature contribute little to habitat protection. We believe that policy-makers, donors and governments need to see practical demonstrations of the links between biodiversity and health as well as between biodiversity and economic development.

The Panama ICBG

To show the inherent connections between both conservation and sustainable economic development, we initiated a drug discovery effort in Panama that emphasizes local benefit. It is not realistic to expect to receive local benefits that are derived from royalties since the probability that a discovery would make it to market is exceedingly small. In fact, biodiversity as a source of compounds and genes realizes its greatest value only as a result of research. Funds spent by academic, philanthropic and governmental institutions and pharmaceutical companies on research related to the discovery of medicines probably exceed 50 billion dollars per year (Agnew 2000; Morel et al. 2005). Nearly all of these funds are spent in developed countries. In our program, as much of the drug discovery process as possible is conducted in Panamanian laboratories, providing jobs dependent on intact biodiversity, enhancing local research and educational capabilities and training students by providing hands-on research experience. In short, the participation of Panama in the research process, plus the spin-offs from research, represent the benefits to Panama (Capson et al. 1996; Kursar et al. 1999; Laird and ten Kate 2002).

The project, termed International Cooperative Biodiversity Groups (ICBG), is funded by the National Institutes of Health, the US National Science Foundation and the US Department of Agriculture from 1998–2008 (Rosenthal et al. 1999; Rosenthal and Katz 2004). This was preceded, in 1995–1998, by a pilot project funded by the US National Science Foundation, the Huntsman Cancer Institute at the University of Utah, and Panama's Fundacion Natura and, prior to that, by over 15 years of basic ecological research at STRI (Kursar and Coley 2003).

The ICBG program consists of collections, assay of samples for activity against specific disease targets and the purification of active compounds (Table 1). The collections program, based at the Smithsonian Tropical Research Institute in Panama City, currently focuses on plants, endophytic fungi, marine cyanobacteria and macroalgae, corals and sponges. Samples are collected in Panama's protected areas; extracts are prepared and submitted for bioassay. Bioassays are carried out at Panama's national laboratories, the Institute of Advanced Scientific Research and High Technology (INDICASAT, for the acronym in Spanish). The active components are purified in laboratories at the University

Table 1 Organization of the Panama ICBG

Function	Institution	Leaders	Assistants, undergraduates[a]
Administrative functions			
Lead institution	STRI	W. Gerwick	0
Legal negotiations	STRI	All, by concensus	0
Patenting	STRI, INDICASAT, Oregon	Inventors	0
Publicity and outreach efforts	All	All	0
Research and conservation functions			
Collections, culturing of fungi	STRI	T. Kursar, P. Coley, C. Caballero-George	5
Bioassays	INDICASAT	E. Ortega-Barría, L. Romero, D. Kyle[b]	6
Purification and structure elucidation	University of Panama	L. Cubilla-Rios	5
Purification and structure elucidation	INDICASAT	R. Linington, M. Balanus[c]	2
Purification and structure elucidation	Scripps	W. Gerwick	1
Purification and structure elucidation	Oregon	K. McPhail	2
Conservation initiatives	STRI	T. Capson, A. Ibañez	2
Pursuit of leads	All	All	0

[a] The number of non-Ph.D. scientists employed by the project. Students who do research for their undergraduate theses number many more

[b] Department of Global Health, School of Public Health, University of South Florida

[c] As of this writing, R. Linington is based at Scripps and another Ph.D. chemist, Dr. Marcy Balanus, is based at INDICASAT

of Panama, INDICASAT, Scripps Institution of Oceanography and Oregon State University.

In principle, many classes of organisms can be accessed and tested for bioactivity. In practice, the choice of which groups to collect in the Panama ICBG was based upon the available local and international expertise. The strategy at the initiation of the collections program used the insights from 20 years of basic, ecological research to enhance the likelihood of finding medicinally useful chemical compounds. Ecologists recognize that chemical interactions among organisms represent the basis for key ecosystem functions. Nevertheless, the nature of the chemical interactions is poorly understood. Investigation into the defenses used by tropical rainforest plants to protect their leaves against insects and pathogens, indicated that for plant tissues going through development, such as expanding leaves, chemistry should be the primary defense against herbivorous animals (Kursar and Coley 2003). It was predicted that young leaves should be an untapped source of active compounds, some of which could have medicinal uses (Kursar et al. 1999). These ecological ideas have successfully guided the collection of chemically active plant samples (Coley et al. 2003). Hence the ecological component of the Panama ICBG has demonstrated that basic research can be a powerful mechanism for guiding biodiscovery research.

The research effort provides benefits to Panama

We argue that countries should minimize the constraints on, and even promote, basic research while at the same time regulating, but not inhibiting, research that could have commercial applications. A fundamental premise of our project is that research having commercial potential should be promoted in manner that ensures that Panamanian scientists, based in Panama, play a central role in research on the uses of their own biodiversity. In doing so, they receive immediate, substantial and lasting benefits in terms of greatly enhanced scientific training and economic development, as well as provide an incentive for conservation (Capson et al. 1996; Kettler and Modi 2001; Annan 2003; Coley et al. 2003; Holmgren and Schnitzer 2004; Kursar et al. 2007). A model for this approach is the project's bioassay laboratory based in Panama's research laboratories, INDICASAT. This laboratory tests samples in assays for anti-cancer activity using three cancer cell lines. (These were originally established at CIFLORPAN, University of Panama, with the assistance of the US National Cancer Institute).

Additionally, Drs. Ortega-Barría and Romero at the INDICASAT laboratories have developed a series of assays that permit samples to be tested for activity against leishmaniasis, malaria and Chagas' disease (American trypanosomiasis). The need for new medicines for these diseases is especially critical; three billion people live in affected areas and no safe and effective treatments are available (Trouiller et al. 2001; Gelb and Hol 2002). The assays for these three diseases have been modified such that they use reagents and technologies that are available in Panama and other developing countries (Williams et al. 2003). The traditional anti-malaria assays used radioactivity, making their use impractical in a majority of developing countries. At the outset of the Panama ICBG program, 1998–2002, INDICASAT developed an anti-malaria assay which takes advantage of the absence of a nucleus and DNA in the red blood cell within which the parasite lives. The quantity of parasite, and hence parasite growth, is detected using a DNA-sensitive fluorescent probe (Corbett et al. 2004). The assay has been patented (Ortega-Barría et al. 2005) and scientists from Bolivia, Madagascar and Peru have traveled to Panama to learn the method. Laboratories at the University of Panama as well as those in Puerto Rico and Spain have used this assay to evaluate the activity of new natural products (Wei et al. 2004; Gutiérrez et al. 2005a, b; Ospina et al. 2005)

Chemical studies of plants, carried out at the University of Panama, were guided by ecological hypotheses about young leaves (Kursar et al. 1999). As part of the ICBG, Drs. Gupta and Solis, who had carried out bioassay-guided purification of active molecules from plants at the University of Panama beginning in the 1970's, established the first cytotoxicity (or whole cell) anticancer assay in Panama and isolated 40 anticancer compounds, 13 of which are new to science (Hussein et al. 2003a, b, 2004, 2005). In additional studies at the University of Panama by Cubilla and co-workers, out of 23 plant species from which compounds of medicinal interest have been purified by the Panama group, 14 species had compounds of interest only or primarily in the young leaves. In fact, the young leaves were the source for some of the most interesting compounds isolated by the program (from *Myrospermum frutescens*; Torres-Mendoza et al. 2003, 2004) and the only source for the most medicinally useful compounds isolated by the program, the anti-leishmanial compounds from *Guatteria* spp. (Montenegro et al. 2003; Correa et al. 2006).

The anti-leishmanial alkaloids from two species in the genus *Guatteria* (Annonaceae) are particularly interesting. These have up to 65-fold higher toxicity towards cells of the disease organisms, *Leishmania mexicana*, than towards human macrophages (the host cell of *L. mexicana*). Because this suggests that the *Guatteria* alkaloids hold therapeutic promise, they should be evaluated for safety and efficacy in a vertebrate (mouse) model. Additional studies in Spain have been made of compounds derived from corals, sponges (Gutiérrez et al. 2004, 2005a, b) and in Oregon, Scripps and INDICASAT on cyanobacteria (Simmons et al. 2006; Linington et al. 2007; McPhail et al. 2007).

Perhaps foremost among the benefits to accrue to Panama from the research in the ICBG program is training. For example, over a eight-year period our program has provided research experience for over 70 young scientists. Of these, 22 have continued their studies outside the country at the Masters, Ph.D., or postdoctoral level. Another outcome has been that two new entities in Panama, Panama's national research institute, INDICASAT, and the ICBG, both were strengthened synergistically due to the presence of added researchers and laboratories. Infrastructure improvements are one of the key contributions that the ICBG has made to Panama. For example, the program established the first nuclear magnetic resonance (NMR) instrument in Panama (Bruker Avance 300 MHz). This was later joined by a 400 MHz instrument and mass spectroscopy facilities at INDICASAT. It is difficult to emphasize the extent to which the ready access to NMR and mass spectroscopy instrumentation has promoted student training and speeded progress in the isolation and identification of medicinally relevant compounds. Good infrastructure also permits local scientists to fully benefit from their intellectual investments; rather than send samples outside the country, Panamanian scientists can lead each investigation to its logical endpoint.

How can benefits be provided on a large scale?

The training, infrastructure improvements and research results described above were produced with modest funds, about $500,000 per year. The approach described here meets a principal focus of policy-makers and international donors, that projects have an applied component and that they equip developing countries with the capacity to address their problems. Even though judicious investments worldwide in similar research could yield substantial rewards, a significant gap exists in the funding of such projects (Reid 2004).

The potential economic benefits of expanding programs such as this within the developing world are under-appreciated. Of the approximately 50 billion dollars spent annually worldwide on drug discovery research (Agnew 2000; Morel et al. 2005), it has been estimated that about one third of such funds are expended on the initial stages of research. In fact, on the order of a third of new drugs, including many of the most innovative medicines, may be derived from research in academia, the government or small biotech companies (Angell 2004). Research along these lines is carried out already by the Panama ICBG and similar programs could be initiated in other developing countries (ten Kate and Laird 1999).

The limiting factor to attracting research grants is establishing laboratories in developing countries that are competitive in the international arena. Should such laboratories be established, there is little doubt that, with the great biodiversity present in numerous countries, discoveries of important natural products would follow. In principle, such laboratories could follow the same pattern seen in the developed world and establish research-based companies. In short, large corporations choose to access new technology or research results by funding the discoverers to pursue their own findings. Interestingly, the number of small, research companies that are based in the developing world has been increasing. For example, between 1996 and 2002, R&D investments from transnational corporations to affiliates based in the developing world increased from 2% to 18% of total investment

(UNCTAD 2005, p. xxvi). In the case of pharmaceuticals and biotechnology, about 17% of their total, worldwide R&D is expended with affiliates or similar arrangements (UNCTAD 2005, p119–121). We conclude that developing countries have the potential to obtain much greater benefits from research focused on the uses of their own biodiversity.

Balancing the rural and urban interests in ecosystem services and conservation

Ecosystem services should provide benefits for rural people, particularly those residing within protected areas (Schwartzman et al. 2000). Nevertheless, studies of integrated conservation and development projects and community-based ecotourism suggest that meeting the twin goals of protecting the environment and providing rural benefits may be difficult (Newmark and Hough 2000; Kiss 2004; McShane and Wells 2004).

Equal in importance to the rural communities is the extent to which urban communities are engaged in and benefit from conservation. Increasingly, the dominant fraction of the citizens of developing countries will live in cities. For example, in Latin America and the Caribbean, for example, urbanites will increase from 42% in 1950 to an estimated 85% of the population in 2030 (Aide and Grau 2004; United Nations 2004). Cities are centers for decision-makers, including politicians, businesses, medical facilities and universities, and also for the majority of voters. Hence, it will be increasingly important to demonstrate the benefits of conservation to urban populations.

It is evident from the above discussion that bioprospecting is primarily a high technology, laboratory-based activity, with most of the benefits accruing to the urban areas. From an urban perspective, the funds expended on research to discover new uses for biodiversity provide diverse forms of economic development (similar to ecotourism). Additionally, as is widely recognized, the provision of new medicines from nature that improve human health represents a valued ecosystem service. Thus bioprospecting research, should it be established on a much larger scale than at present, would provide a new type of ecosystem service that benefits the critical, urban segment of the population. Perhaps applied bioprospecting research also would better motivate the rural and urban sectors of society to cooperate on conservation decisions.

Links between conservation and biopropsecting

Bioprospecting also should provide an incentive for conservation. Demonstrating that intact ecosystems have value should help to resolve the conflict, as perceived by urban citizens, the private sector and government, between conservation and the use of natural resources for development. In our experience bioprospecting provides a Panamanian voice in support of conservation, one that is especially unique and powerful since it originates in the urban areas. In fact 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 dozens of 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, Panama's newspapers and TV frequently report on the ICBG. The local and international reports have created wide public awareness of the Panama ICBG's bioprospecting efforts, giving the project a high degree of transparency. Additionally, transparency, the provision of immediate benefits and equitable legal agreements also demonstrate that biodiversity has direct value to Panamanian citizens. In summary, only the application of both rural and urban initiatives can provide a balanced conservation portfolio and bioprospecting can contribute in substantially to the urban component.

The Panama program also has made direct conservation efforts in a newly established protected area, Coiba National Park, a spectacular marine and terrestrial park and an area in which we collect. Dr. Todd Capson, a chemist, has pioneered a novel form of conservation initiative. Specifically, Dr. Capson worked actively for the establishment of Coiba NP and its recognition as a UNESCO World Heritage Site by mobilizing scientific support and demonstrating the economic utility of conserving the park's biotic resources. The significance of his efforts lies in the fact that, 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, one that should be applicable to most bioprospecting efforts.

Biopropsecting and the Convention on Biological Diversity

A final point regards the relationship of bioprospecting with the principles established in the Convention on Biological Diversity in 1992 (CBD). As is well known, the CBD gives countries sovereignty over their biodiversity along with the ability to regulate access to biodiversity (Gollin 1993, 1999; CBD 2003). Much less appreciated is the fact that the CBD also vigorously promotes the sharing of biotic resources, research capacity and the facilitation of studies on the uses of biodiversity in both developed and the developing world. For example, the CBD indicates that countries should provide for appropriate access to biodiversity (Article 15) and that the developed countries should transfer technology (Article 16). The CBD is in fact a wide-ranging and visionary document and states 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". As a consequence, a program such as that of the Panama ICBG that seeks to amplify the impact of bioprospecting research as an ecosystem service acts in full accord with the international principles established in the CBD.

Conclusion

The Panama ICBG began with insights from ecological research, established an effective research and training program in Panama and, finally, has had constructive impacts on both conservation and sustainable development. We believe that these approaches can complement other initiatives to enhance ecosystem services and rural development. Given that most people in the developing and developed world have a desire to promote biodiversity, it is relevant to ask whether similar efforts could succeed in other countries. Although many barriers exist to such an enterprise, similarly constituted ICBG projects have provided benefits in other developing countries (Kingston et al. 1999; Schuster et al. 1999; Soejarto et al. 1999).

We conclude that developing countries, should they be able to access international funds from governments, NGOs and pharmaceutical companies, can carry out high quality research on the uses of their own biodiversity, provide in-country scientific training and contribute to human health and economic development. Given such advances, scientists also would help to create new forms of ecosystem services that contribute to sustainable development and conservation. Nevertheless, because of the dearth of effective mechanisms for communicating scientific findings to the policy-makers and donors, the practical benefits of such contributions may not be realized. Clearly all parties must take the initiative to bridge the "science-policy divide" (Reid 2004).

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