Chemical Prospecting: An Overview of the International Cooperative Biodiversity Groups Program

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Abstract

The International Cooperative Biodiversity Groups (ICBG) Program is an integrated conservation and development program which addresses the interdependent issues of biodiversity conservation, sustained economic growth, and human health in terms of drug discovery for diseases of concern to both developing and developed countries. The funding for this program is provided by the National Institutes of Health, National Science Foundation, and US Agency for International Development.

Because biological resources which benefit local communities are among those most likely to be preserved, chemical prospecting or more specifically, development of pharmaceuticals from natural products can be used to promote biological conservation by providing an economic return from sustainable use of the resources. A critical component of the supported activities is to ensure that equitable economic benefits from these discoveries accrue to the country of origin, community, group, or organization which facilitated the discovery of the natural product. This is being achieved through the use of novel contractual mechanisms among the members of each group.

Introduction

Projects linking conservation and development have evolved over the last two decades. Non-governmental organizations, multilateral and bilateral donors, and national governments have discovered the value of linking conservation to development. While parks and protected areas are an important component of any conservation plan, typically they cover only 4-10% of a nation's area. Integrated conservation and development projects (ICDP) potentially offer an opportunity for conservation solutions for all lands, while meeting basic human needs through economic development. The ICBG program is an example of an ICDP. Because it is an early example, a work in progress, it is an experiment from which we all should learn and to which we should all contribute through comments and constructive criticism.

An Overview of Drug Discovery Activity at the National Institutes of Health

Compounds from plants and animals have been a rich source of therapeutic agents throughout the ages. The International Cooperative Biodiversity Groups (ICBG) Program is one of many drug discovery efforts supported by the National Institutes of Health (NIH). A recently compiled NIH report on all its activities in regard to drugs and medical products derived from the natural world and its efforts in the protection of biological diversity revealed that in fiscal year 1993, twelve of NIH's Institutes, Centers, and Divisions (ICDs) funded biodiversity-related research (see Appendix A). Expenditures totalled nearly $60 million. The National Cancer Institute, the National Center for Research Resources, and the National Institute of Allergy and Infectious Diseases together accounted for 93 percent of the total.

Notable among these efforts are the National Cancer Institute's (NCI) multiple extramural and intramural drug discovery programs focusing on the discovery and development of new agents from natural products for the treatment of cancer and AIDS. High-throughput automated screening systems have been developed to assay for anti-cancer and anti-HIV activities in extracts prepared from a variety of plants marine organisms, and unicellualr organisms from 30 countries (Table 1). Approximately 50,000 organisms in the NCI Natural Products Repository are available to qualified researchers under materials transfer agreements. In return to access to the NPR, those receiving samples are required to follow NCI policies with respect to fair compensation to source countries. In addition through its extramural programs, NCI funds activities leading to the discovery of new drugs for cancer. NCI has also pioneered efforts to compensate countries contributing biological materials through the development of their "Letter of Intent" which has evolved into the legally much stronger "Letter of Collection". Several license agreements are being negotiated with source countries of naturally occurring biological materials discovered through NCI's programs.

The Origins of the International Cooperative Biodiversity Groups Program

In March of 1991, NIH, the National Science Foundation and the U.S. Agency for International Development sponsored a conference on Drug Development, Biological Diversity, and Economic Growth. In addition to the sponsoring agencies, government and technical experts from six developing countries richly endowed with biological diversity, participants included representatives from the pharmaceutical industry, experts in ethnobiology, traditional medicine, and intellectual property rights law. From their presentations and related workshop discussions there emerged a set of general principles and observations (see Appendix B). The three agencies based their discussions and development of a Memorandum of Understanding in the spring of 1992 and subsequent release of a Request for Applications (RFA) in June of 1992 on the workshop findings. The RFA invited applications for the establishment of International Cooperative Biodiversity Groups to address the interdependent issues of biodiversity conservation, sustained economic activity, and human health in terms of drug discovery for diseases of primary concern to developed and developing countries. Sixty-three letters of intent to submit an application were received in September followed by thirty-four applications in November. Applications included primary investigators and collaborators from 25 countries, 13 in Latin America and the Caribbean (LAC), 7 from Asia, 4 from Africa, and 1 from the Middle East. About half of the applications included a collaborator from LAC, a third from Asia, and about an eighth from Africa.

The Peer Review of these applications in March of 1993 is worth mentioning because of its multidisciplinary nature. Reviewers came from universities, museums, pharmaceutical companies, the World Bank, and environmental non-profits with backgrounds in natural products chemistry, intellectual property rights law, systematics, ecology, ethnobiology, and international development. In addition, the Advisory Board of the Fogarty International Center, the administrators of the program, and a Technical Advisory Group made up of representatives of the three agencies also reviewed the proposals and participated in the selection process.

It is important to note that this review was based on the responsiveness of each application to the goals and priorities outlined in the very detailed and lengthy RFA. There was a very strong desire of three agencies for a balanced portfolio in terms of geography, industrial partners, target study organisms, diseases, etc. The composition of the final portfolio reflects this together with the desire to fund those applications which were most responsive to the goals and priorities outlined in the RFA.

The awarding of 5 Cooperative Agreements were announced in December of 1993. Each award is 5 years in duration and has an annual budget of approximately $450-475,000. Each ICBG constitutes a cooperative agreement with the U.S. Government. Cooperative agreements differ from grants and contracts in that sponsoring government agencies have substantial programmatic involvement in achieving the goals and objectives of the project. In the ICBGs this is accomplished through the designation of a Government Scientific Coordinator for each project who has scientific oversight responsibility and is assisted by an advisory committee consisting of staff in relevant technical fields from the participating agencies. There is no intent, real or implied, for government staff to direct group activities

or to limit the freedom or scientific investigators. Rather the Government Scientific Advisory Committee for each group serve as a resource and act in an advisory capacity.

Program Goals

The ICBG program has three inter-related goals reflecting the tri-agency support for the program: biodiversity conservation; sustainable economic activity; and drug discovery. The ICBG Program accomplishes this by linking developing country organizations and indigenous peoples with U.S. academic and industry partners for the purpose of developing and implementing innovative strategies for the conservation and sustainable management of biological diversity through economic returns from the screening of medicinal and other organisms for compounds active against both developing and developed country diseases, agricultural and veterinary purposes, and in some instances parallel development of medicinal or other products for host country markets.

CONSERVE BIOLOGICAL DIVERSITY

This goal encompasses the creation of incentives at all levels for the preservation of intact habitat; increasing the knowledge base upon which conservation activities are based; and development of long-term ecological and economic strategies to ensure more sustainable harvesting of targeted organisms and conservation of habitat. Programs undertake implementation of strategies to support the selection and acquisition of natural resources and novel agents, including the use of ethnobiological studies and approaches to working with traditional cultures and their knowledge of traditional medicine. Programs incorporate systematists, ecologists, and anthropologists in integrative surveys of a developing country's biological diversity. Programs develop collection practices compatible with conserving biodiversity. Production and documentation of all collected material in the form of published works, and/or databases, reporting specific locality and all features of biology relevant to standard botanical and zoological collections is an important aspect of the inventory work. Programs assure accessibility of inventory data to all individuals, including those not associated with the ICBG, by housing catalogues and databases in public institutions (such as universities and national museums) and, when databases are kept on computer systems in private institutions, by including in publications specific references to these databases.

DISCOVERY OF PHARMACEUTICALS FROM NATURAL PRODUCTS

This includes the preparation of crude materials for testing against diseases; isolation, and evaluation preclinically of agents from natural sources to treat or prevent cancer, infectious diseases including AIDS, cardiovascular diseases, malaria, mental disorders, parasitic infections, and other diseases. Medical conditions of primary concern to developing countries are important components of every ICBG. It should be noted that studies required for the later stages of drug development (e.g. formulation development, classical toxicology, etc.) and the conduct of clinical trials are beyond the scope of this program.

PROMOTION OF SUSTAINABLE ECONOMIC ACTIVITY IN DEVELOPING COUNTRIES

Benefit-sharing agreements incorporating the use of novel contractual or other legal mechanisms to ensure an equitable financial return to the host country, group or organization which facilitated the discovery of the natural product are at the core of achieving this goal and will be dealt with in more detail below. In addition, support for research training targeted toward the needs of the developing country or other countries represented within the Group fulfill this goal. Examples of relevant areas of training could include systematics, ethnobiology, ethnomedicine, chemistry, cell biology, biotechnology, or production methods and quality control in pharmaceutical development.

In many instances research training is supported through a fellowship which may be linked to degree-earning programs. Types of training include, but are not limited to: 1) practical and applied short-term courses or workshops; 2) course work, laboratory, or field training in essential research skills; and 3)

fellowships for degree candidates or post-doctoral trainees to conduct research related to the goals of the Group. While the primary goal of training is to acquire research skills needed to accomplish the goals of this program, and not to obtain a formal degree, in selected cases, training support has been provided for tuition, stipend, travel, and other expenses of formal, degree-earning programs.

Programs assist in improving the scientific infrastructure within the participating developing country(ies) where the biodiversity resources are found. Infrastructure support includes assistance for herbaria, museums, and laboratories, the supply of necessary equipment in these facilities, and the enhancement of collecting and screening capabilities in the host country. Limited renovation of existing facilities, but not construction of new facilities, is supported.

The goals of the program are broad and limited only by the creativity of the Groups in making use of 1) the rich diversity of biological entities with pharmacological potential to be found in nature, many providing host defenses against infectious disease, parasitism, or predation; 2) the wealth of knowledge held by traditional cultures where medicinal potential can most likely be realized; 3) recent advances in understanding the social, economic, and political causes of biodiversity loss; 4) new methods of sustainable resource management and use; and, 5) innovative analyses of biological resources and biogeographic patterns.

Individuals with expertise in diverse areas such as economics, sociology, and various disciplines of biological and physical sciences, including many who may not have collaborated in programs of this type, are active participants. In addition to being multidisciplinary, the Groups are international in scope with participation of developing country institutions as full intellectual partners.

Intellectual Property Rights

The ICBG program raises novel legal issues that link ordinarily distinct legal fields, such as environmental and intellectual property law. The following general principles for the treatment of legal issues relevant to the ICBG Program have been derived from the RFA issued in November, 1991 by NIH on behalf of the three agencies funding the program. All of the ICBG benefits-sharing agreements address each of these key issues and outline each group's plans for addressing them.

Conventional Intellectual Property Rights (IPR)

It is normally presumed that protection of IPR through some legal mechanism is necessary for the dissemination and transfer of findings through commercialization. Agreements demonstrate an awarness of the different types of IPR available at different stages of product development and for different types of products. For instance, in R&D stages that are too early for patenting, trade secret protection may be applicable in some countries. Even at the end product stage, patents may not be available (because they are not permitted for that type of product under national law, or because the product is a natural compound or plant instead of an invention, or because the innovation is too incremental to count as a patentable invention). In that case, agreements demonstrate awareness of alternatives such as trade secret protection or petty patenting, if available. Finally, it is conceivable if not likely that the way in which traditional knowledge is related to the product could justify trademark protection for some aspect of indigenous culture.

The laws of many developing countries do not permit patent protection for pharmaceuticals as well as products in certain other sectors. If the drug development or marketing will be done in a developing country, this lack of protection is considered. Similarly, patent laws are not internationally consistent in their treatment of the rights of the first applicant vs the discoverer of a patentable entity. Agreements safeguard against these differences.

Accrual of economic benefits and protection should apply equally to instances where the invention is the actual isolated product, or where the invention is a product structurally based on the isolated natural

product (ie. where the natural product provides the lead for development of the invention). Similarly, accrual of benefits and protection should apply equally to organisms collected directly and all other organisms collected with these organisms. For example, an the activity of an extract taken from a vascular plant might actually be due to an associated micro-organism.

Benefits-Sharing agreements provide compensation to institutions in source countries. Agreements outline plans for distribution of the benefits obtained from final products, including IPR protection. These plans provide for the following:

- Equitable distribution of benefits to all those who contribute to product development, whether they are members of the consortium or not, including research institutions and indigenous people in all countries who provide useful traditional knowledge.
- Flow-back of economic benefits to the area in which the source plant or animal was found, in such a way that they at least indirectly promote conservation of biological diversity (although the type of benefits must be chosen through discussions with indigenous and local people).
- Justification for selection of recipients of benefits (or for exclusion of other potential recipients).
- Appropriate structuring of economic benefits, e.g. trust funds managed by community or joint community-project boards rather than cash payments to a single authority or individual may be more effective in support of conservation, and for administration of services like health or education. Note that direct cash compensation may even have injurious effects on non-money economies.
- Design of adequate contracts. Agreements should be among commercial drug developers, source country and US research institutions, and the indigenous people whose knowledge is commercialized.
- Inclusion in contract between drug company and other partners of methods for monitoring R&D to track drug leads derived from samples provided under the contract.
- In instances where one party does not wish to pursue the development of a discovery, clear designation of the rights of all other signatories should be outlined.
- Ideally, compensation begins flowing early in the contract)through an initial payment, payments for samples delivered, or both)in order to provide short term conservation incentives.

Disclosure to and Consent of Indigenous or Traditional Sources

Basic fairness requires that any arrangements for the use of traditional knowledge or the taking of samples or larger-scale harvesting from local people's lands should be based on full disclosure and on informed consent. The best practice is to negotiate written agreements with local people before collecting begins, especially if collecting is based on ethnobotanical methods. Codes of conduct developed by professional societies and the FAO have been both relevant, and helpful. Consent may still be an issue even if traditional knowledge is not used; random sampling still involves entry onto land that may be owned by indigenous peoples, and the taking of natural resources there.

The duty of disclosure and the need for consent go beyond mere compliance with existing laws, and is based on the highest standards (looking to the specifics of professional codes and developing general principles such as those found in the Draft Declaration on the Rights of Indigenous Peoples or the Convention on Biological Diversity). Nevertheless, proposed activities conform to applicable national and local laws protecting indigenous land rights and governing business with indigenous people.

Indigenous Concepts of Intellectual Property.

If indigenous people's knowledge is used in collecting, investigators make sure that they respect any indigenous concepts of intellectual property)i.e. they disclose their plans, and if indigenous authorities object that sacred knowledge or substances should not be made public or should not be commercialized, the objections are respected and attempts are made to resolve this issue as early as possible.

Public Access v. Proprietary Information.

Agreements anticipate the tension between the traditional scientific ethic of public access to information, and the understandable desire of commercial partners for confidentiality of information with potential commercial value pending protection through patenting.

Compliance With Environmental Laws.

An essential goal of the project is to develop models for *sustainable* commercial use of biodiversity-rich ecosystems. Every agreement acknowledges this goal and explains how it will be attained. At the very least, projects are designed so that cataloguing, collecting, harvesting and other activities comply with applicable domestic and international environmental laws, such as laws on plant conservation, endangered species)both CITES and domestic)and environmental assessment (if applicable to project activities). Mechanisms for monitoring the biological and other impacts of project activities are being developed in many projects and overall for the entire program. Agreements with public authorities or other landowners collecting within certain territory, agreements specify that activities will be done sustainably and in compliance with environmental laws. Although the initial sampling for analysis is unlikely to have significant environmental impact, later recollection may. And if a product is derived from a sample there is always the potential for commercial harvesting, and hence for over-exploitation. Agreements include plans for continued supply of plant materials in a sustainable manner from signatory countries and sources whenever possible.

Resources Returning To Developing Country Partners

Examples of Contributions from Pharmaceutical Companies include screening for therapeutic potential, training opportunities, equipment donations, fees for samples and up-front Payments, percentage of royalties from the sales of products developed through ICBG program, and inclusion of indigenous or local people as inventors on patents.

Examples of contributions from ICBG program funds include focus on search for therapeutics for developing country diseases, training opportunities, infrastructure development, and equipment purchases.

Overview of the Five Awards

BIODIVERSITY UTILIZATION AND CONSERVATION IN TROPICAL AMERICA

The objective of this ICBG is to stimulate biodiversity conservation in Suriname by demonstrating the value of biodiversity to the Surinamese people. To meet this objective, this ICBG, led by Dr. David Kingston of Virginia Polytechnic Institute and State University (Virginia Tech) will work with Conservation International (CI), CI-Surinam, Missouri Botanical Garden, Bristol-Myers Squibb Pharmaceutical Research Institute (BMS), the National Herbarium of Suriname, and Bedrijf Geneesmiddelen Voorziening Suriname (BGVS). Each organization will contribute its own expertise in an effort to examine potential medicinal agents from the Surinamese rainforest and initiate a program of educational and extension activities throughout the country.

Working in collaboration with the National Herbarium of Suriname, the Missouri Botanical Garden will collect rainforest plants in Suriname. BGVS will remove extracts from these plants and ship them to BMS for screening for drug potential. Researchers at BGVS, BMS, or at Virginia Tech will fractionate and identify active compounds from extracts which show promise. Once the bioactive compounds are obtained in pure form, their structures will be determined using state-of-the-art chemical and physical methods. Patenting, licensing, and division of royalties will be determined by conditions set forth in the benefits sharing agreement among all members of the group. Data generated by the interactions of these

diverse collaborators will be used by MBG and CI to examine the rationale for ethnobotanical selection of plant material as a potential source of new medicines.

Creating a key link between Suriname's forest people and their industrial partners, C.I. will be responsible for the documentation of ethnobotanical usage of rainforest plants. C.I. will also launch its "Shaman's Apprentice" programs within the study villages to ensure that ethnobotanical knowledge is passed on to the younger generation.

To increase the economic value of the forest in the near future, ICBG partners will also search for non-medicinal forest products which can be sustainably harvested in the short-run. Forest products sold in local markets can generate significant income for the communities that harvest them, providing a powerful incentive for conservation and sustainable development.

The project will also work with Surinamese people who do not live in the forests. Efforts to build a conservation ethic in the urban population include training in both ethnobotanical field techniques and in advanced surveying technologies. This building of local capacity not only contributes to the project's environmental education goals, it also helps the Surinamese manage their natural resource more efficiently.

PERUVIAN MEDICINAL PLANT SOURCES OF NEW PHARMACEUTICALS

The ICBG led by Dr. Walter Lewis at Washington University in St. Louis proposes a multidisciplinary program combining conservation of biological diversity with sustained economic management of medicinal plants needed for the discovery and development of pharmaceuticals to improve human health. A major goal of this group is to determine the health status of Aguaruna and Huambisa people in the northeastern Andes, to learn what traditional medicines are being used to treat their illnesses, and to determine how comprehensively these medicinal plants keep these people healthy. To accomplish these goals, Washington University is collaborating with the Natural History Museum and the Cayetano University both in Lima, Peru and Missouri Botanical Garden and Monsanto Company in St. Louis. Dr. Lewis' group has initiated a research program in the northeastern Andean tropical rainforest of Peru, an area known for its high but endangered biodiversity, and rich in ethnobotanical knowledge.

Plants which have been used medicinally by people in Peru and elsewhere in South America for generations to treat a broad range of illnesses are being collected. Primary screens are conducted to test for activity against a number of infective agents, including respiratory viruses, herpes viruses, pathogenic yeasts, and tuberculosis. When crude extracts show promise in primary and secondary screens, further studies are initiated. An important contribution is the identification and initiate cultivation of those medicinal plants needed in research development and for commercial use. Use of marginal lands and sustainable and environmentally friendly cultivation methods designed to reduce demand on forests for the supply of these important plants are used.

Other aspects of the ICBG are to collect, identify, and curate specimens of plants and selected groups of animals, in order to characterize the species richness of the northeastern Andean slopes of Peru. Investigators at the Natural History Museum will provide lists of potentially useful species of plants and animals which may be harvested and ranched in sustainable ways by the local population, thus combining conservation of natural resources with economic improvement of the area.

A final objective is to assess the effectiveness and safety of plants used by traditional medicine practitioners through testing for three conditions: tumors, leishmaniasis, and diarrheal diseases. Promising leads for new drugs with anti-infective and anti-inflammation activity are also isolated and identified.

CHEMICAL PROSPECTING IN A COSTA RICAN CONSERVATION AREA

Cornell University, in cooperation with the Instituto Nacional de Biodiversidad (INBio) of Costa Rica and Bristol-Myers Squibb Pharmaceutical Research Institute (BMS) has developed a program that looks at tropical insects and related species as potential sources of new drugs against a wide range of diseases. While insects are well known to utilize a wide variety of secondary metabolites as defensive agents, venoms, and pheromones, they have received much less attention than plants, microbes, or marine organisms as potential sources of useful pharmaceutical agents.

The INBio team headed by Dr. Ana Sittenfeld, with Dr. Daniel H. Janzen of the University of Pennsylvania providing ecological expertise, coordinates the collection of biological materials from the Guanacaste Conservation Area, a dry tropical forest in northwestern Costa Rica. INBio, a non-profit organization devoted to the goal of conserving and developing Costa Rica's biologically diverse national conservation areas through sustainable use, trains Costa Ricans to conduct field and drug discovery studies. INBio scientists prepare extracts from biological materials, and in collaboration with the University of Costa Rica, carry out an anti-malarial screening program. Additionally, through agreements with Bristol-Myers Squibb and Cornell that ensure that a portion of any resulting benefits flow back into the country, INBio hopes to show that sustainable use of wildland biodiversity can contribute to biodiversity conservation and economic development.

At Cornell, components of the program of research and training encompassing the fields of chemical ecology and chemistry are coordinated by Dr. Thomas Eisner who establishes criteria for selection of organisms for chemical study and designs and carries out bioassays leading to isolation of natural products from these organisms. Dr. Jon Clardy will bring his expertise in single crystal X-ray diffraction, one of the most powerful structural tools available, to the enterprise. Dr. Jerrold Meinwald and Dr. Athala Attigalle will carry out separations, structure proofs, and syntheses of compounds from insects. Visiting Costa Rican scientists and students receive training at Cornell in all of these areas.

BMS will receive extracts prepared at INBio and will carry out screening over a broad range of biological activities, including a search for anti-cancer, anti-infective, cardiovascular, central nervous system, and dermatological medicinal compounds. BMS also trains Costa Rican scientists at its labs.

DRUG DEVELOPMENT AND BIODIVERSITY CONSERVATION IN AFRICA

The Walter Reed Army Institute of Research, in cooperation with the University of Yaounde, Cameroon, the Smithsonian Institution, the Biodiversity Support Program, Shaman Pharmaceuticals and Bristol-Myers Squibb Pharmaceutical Research Institute, explores the rich biodiversity of the second largest continuous moist tropical forest in the world, as a source of new molecular leads for drug development and as an important economic resource for communities inhabiting the area. The strategy of this ICBG is to use data from field ethnobotanical and ethnomedical studies, plus existing chemotaxonomic and pharmacologic publications to generate a prioritized list of plants for investigation. This ethnographic approach is supplemented by a random mass screen in which targeted screens are used to evaluate a large quantity of additional biological samples. Active compounds identified in either system are isolated and characterized for further development.

The subject of study is the biologically diverse rainforest of Oban hills in southeastern Nigeria and the Korup forest range of Cameroon, over 2.8 million square kilometers in West and Central Africa. Group members from the Smithsonian Institution are installing a large-scale permanent forestry plot in the Korup National Park of Cameroon, for forest dynamics research. This provides assessment of the local abundance, distribution, and dynamics of trees and shrubs with medicinal properties and the feasibility of sustainable collection or harvest of these species from natural forest or of their plantation cultivation. Training is provided for Western African students and natural resource managers both through organized courses and through participation in the installation of the forest plot.

The traditional medical system in this area is still the prevalent form of medical care for the majority of people. A prioritized list of plants recommended for collection, and further study is generated using a strategy which combines the results of interviews with users of the traditional medicines, the evaluation of the ethnobotanical information, computerized literature search, and chemotaxonomic considerations.

Once collected, extracts of natural products will be evaluated for use against malaria, leishmaniasis, African sleeping sickness, and trichomonad infections to identify new antiparasitic chemotypes for development into orally active, readily available, safe and effective drugs.

BIOACTIVE AGENTS FROM DRYLAND PLANTS OF LATIN AMERICA

The objectives of this International Cooperative Biodiversity Group (ICBG) are to discover and develop pharmaceuticals and crop-protection agents from plants of arid and semi-arid ecosystems in Latin America and to promote sustained economic activity while conserving biological resources in these fragile environments. To meet these objectives, The University of Arizona is working with the Catholic University of Chile in Santiago, the National University of Patagonia and the Institute of Biological Resources (INTA), in Argentina, and the National University of Mexico (UNAM). In the U.S., Louisiana State University, Purdue University, and the Medical and Agricultural Research Divisions of American Cyanamid Company will be working with The University of Arizona.

Plants are collected from poorly known floristic areas in Mexico, Chile, and Argentina. The highest priority is given to plants that have a rich ethnobotanical background, thereby increasing the chances for potential drug use. The collections are chemically processed for a battery of biological testings in the U.S. These are conducted at American Cyanamid Company in a variety of in vitro screens. Therapeutic areas of potential target application include: medical areas: central nervous system; cardiovascular; intermediary metabolism; allergy/inflammation; gastrointestinal; cancer; anti-viral; and anti-bacterial; and agricultural applications in crop protection and animal health.

This group is also interested in the potential for commercial production of biologically active compounds which ultimately could result in the development of specialty cash crops for the country in which the compound originated. Both Latin American and North American graduate students and postdoctoral fellows are being trained in the isolation and identification of compounds, as well as the growing, large scale extraction, and processing of plant materials.

Issues concerning implications for biodiversity and sustained economic activity have been identified and strategies for minimizing negative impacts and defining and assuring local community benefits are being developed. These objectives encourage sharing of resources and knowledge and create the necessary framework for achieving the project's potential long-term conservation and health benefits. It also leaves a legacy on which to build responsible programs for the future. Biological, chemical, geographic, and bibliographic information on each species is included in a database in both English and Spanish.

Conclusions

Although the ICBG program is still quite young, there are useful observations that can be made based on our experiences thus far. The first is a matter of perspective. Bioprospecting, no matter how well done, cannot solve the biodiversity crisis, alleviate the complex of land tenure issues often at the root of the upheaval and loss of indigenous cultures, nor undo the scores of ills of international development. While not a panacea, it is, however, one of many important tools at our disposal to address these problems.

Another potential pitfall of bioprospecting is that its practioners fall into the traps exemplified in hundreds of years of colonial export of raw materials from developing countries without increasing their capacity to export developed products. The ICBG program and other bioprospecting efforts can address this concern in three ways. First they must paint a realistic picture of what the returns might be. Second they must be sensitive to the desires of countries to engage in bioprospecting. And third, they must through up-front

payments, equipment donations or other short-term funding significantly increase the in-country capacity for extraction, screening, isolation, and development of natural products. Expecting royalty payments to cover these expenditures is not realistic. By close attention to these issues bioprospecting can distinguish itself from other ongoing waves of resource exploitation in developing countries. Bioprospecting programs can benefit from diversification. Each collection, extract production, and associated data management represent a significant financial investment. Maximization of this investment is possible by negotiating for the right to allow various sectors of industry to screen extracts or collections for activity of use to them. It is also essential that the long-term storage of collections and extracts be considered. Unfortunately, in spite of our best efforts, much of what we screen today may be gone from the wild tomarrow. Like herbaria, museums and zoos, natural products storage facilities have an important role to play.

One of the factors in the success of the program are the largely unprecendented linkages between the private and public sector. Through the mediation, dissemination of information, and cooperation of both international and local NGOs, connections have been made between large multinational companies, academic institutions and local communities. In the ICBG program NGOs have been essential for the formation of such equitable relationships. These relationships of trust among NGOs and local and indigenous peoples are essential for the fair and equitable management of intellectual property, as well as seeing to a multitude of other concerns. Currently, it is far beyond the financial capacity or experience of most local or indigenous collaborators to manage this alone. At the same time, NGOs must actively work towards building the capacity amongst local and indigenous peoples to act alone, if that is what they desire.

Another important precedent set by the program is the support for and recognition of the crucial role of natural history collections in the US and abroad, in bioprospecting. These insititutions house, organize, and disseminate information without which bioprospecting could not happen. All projects involve collaborations with such institutions and the transfer of technology which allows them to design and implement information management systems which make data accessable in native languages to developing countries. These databases are important not only for what they tell us about the activity of each extract, but also for the negative results which they should include.

Much of the success of the ICBG program stems from the creativity of the applicants. This was possible because the program is based on awardee initiated and designed proposals, rather than the design of projects by either too few experts or experts too removed from each developing country scenario. In this way the process of concensus building among group members began long before any funding. Each funded application represented an intellectual partnership which began with its inception and continues throughout the project. This is ensured by the monitoring of each project through site visits, quarterly and annual written reports, and the welcoming of comments and questions by the government managers from all participants, not just the primary investigators. Along these same lines, the beauty of each benefits sharing agreement also stems from their individual design, rather than a top down approach which might stifle the ability of each group to negotiate for what it defines as a benefit.

Bioprospecting programs must realistically understand at the outset how much time and energy will go into their contractual agreements. There are three general mechanisms currently available. The first is to have a predesigned document that all participants must sign. The benefits of this approach are enourmous savings of time and legal and other expenses. Potentially, such an agreement could be very comprehensive and see to the rights of all involved parties very efficiently. Such an agreement cannot however, be an exact fit for all situations. The second option is to design agreements for each project. The advantages of this option are the specificity each agreement can convey, and the disadvantages are the months and expense of the negotiations necessary for the production of such an agreement. Programs at the NIH employ both of these approaches. The NCI Letter of Collection is a standard agreement while the ICBG program allowed applicants to design their own contractual arrangements according to a set of guidelines. Both work. A third hybrid approach, however, could prove to be the most useful. It might consist of a flexible model contract which incorporates the issues of concern to all parties, yet allows for their individual needs. In fact, this hybrid approach is what the ICBG contracts ended up employing by default. Nearly all the contracts are close approximations of the modal contract designed by

Downes et al in the World Resources Institute Bioprospecting book. Yet each agreement differs in many details. The program staff found this book exceedingly useful in educating awardees on contract negotiation.

One last point concerning negotiation is the importance of each party, at the very begining of the discussions, defining their goals, needs and desires, as well as, what they believe are reasonable expectations of the other parties in writing. This may seem very simple and obvious, yet in the ICBG experience it was in several instances a difficult and often overlooked step. Early acquaintance with the diverse agendas of partners is an asset to any negotiation.

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TABLE I

Countries in which the National Cancer Institute has Active Collectiong Samples

Cameroon	Belize	Antarctica
Central African Republic	Bolivia	Australia
Gabon	Columbia	Indonesia
Ghana	Dominica	Malaysia
Madagascar	Ecuador	Nepal
Tanzania	Guatemala	New Zealand
Zaire	Honduras	Papua New Guinea
Zimbabwe	Martinique	Philippines
-	Paraguay	Sri Lanka
-	Peru	Taiwan
-	Puerto Rico	Thailand

APPENDIX A

National Institute of Health Institutes, Centers, and Divisions Funding Biodiversity Research

National Cancer Institute
National Center for Research Resources
National Institute of Allergy and Infectious Diseases
National Institute of Drug Abuse
National Institute of General Medical Sciences
National Institute of Mental Health
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Dental Research
National Institute of Environmental Health Sciences
National Heart, Lung, and Blood Institute
National Institute Child Health and Human Development
Office of Alternative Medicine

APPENDIX B

Principles from the National Institute of Health, National Science Foundation, US Agency for International Development sponsored workshop on"Drug Development, Biological Diversity, and Economic Growth".

General Principles

1. Equal partnership, cooperation, and fair compensation are the principles which should guide all multinational efforts to maintain and use sustainably biodiversity and traditional knowledge.
2. The maintenance of biological diversity and traditional knowledge can be viable only if it makes sense economically within the cultural, political, and developmental realities in countries where these resources occur. Special attention needs to be given to maintaining biological diversity in areas where other natural resources are being used.
3. Traditional knowledge is threatened and as valuable as biological diversity. Both resources deserve respect and must be concerned.
4. Traditional healers and indigenous peoples have valuable knowledge and important observational and analytical capabilities. These specialists may know almost all of the useful medicinal plants available in an ecosystem.
5. Efforts to develop drugs from medicinal plants should address diseases and health problems seen in developing countries as well as diseases which primarily affect developed countries' populations.

Compensation and Intellectual Property Rights

1. Intellectual property rights should be extended in some form to traditional knowledge, and mechanisms to provide appropriate protection and compensation are urgently needed.
2. Compensation for traditional knowledge, and mechanisms to provide appropriate protection and compensation are urgently needed.
3. Multinational corporations, anthropologists, botanists, and others involved in the use of natural products and traditional knowledge need to recognize their responsibility to provide reasonable compensation as an integral part of their business or research and development activities.

4. Intermediate compensation mechanisms and incentives need to be developed to bridge the 10-15 years between the identification of a potentially useful species and the production of a marketable and profitable drug from that species.

Training, Institution Building, and Information Dissemination

1. Enhancing capabilities for conservation and sustainable resources use through training should be a high priority. Any such training efforts should recognize and use existing local knowledge and capabilities, especially in relation to resource management and raw-materials processing.
2. Countries having varying capabilities to exploit and sustain their biological diversity and traditional knowledge resources; therefore there are different needs for external assistance and cooperation. In all cases, any existing indigenous capabilities should be strengthened so that solutions are developed which account for each developing country's unique circumstances.
3. Appropriate conservation and resource exploitation technologies and knowledge need to be transferred to developing countries through training, joint research, and other cooperative activities in resource cataloging, monitoring and use. Often countries rich in biological resources can learn from each others experiences to develop solutions suited to their circumstances.
4. Efforts to educate the public and decision makers are critically important to assure broad and effective recognition of the value of biological diversity and traditional knowledge in conservation and development.
5. An immediate priority need is for the completion of species and traditional knowledge inventories, which should include information dissemination. These inventories need to be developed using electronic databases with wide access.
6. Some countries need to develop further their traditional medicine quality control mechanisms and national capabilities to manage systems of production and distribution of traditional medicines.