Report of a Special Panel of Experts on the International Cooperative Biodiversity Groups (ICBG)

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In 1992, four Federal agencies combined efforts to launch the International Cooperative Biodiversity Groups (ICBG) Program. Acting together, the agencies sought to respond to scientific and public concern about three interdependent issues: conservation of biodiversity among the world's plant and animal resources, sustained economic growth for developing countries, and discovery and development of pharmaceuticals from natural products to improve human health. The agencies sponsoring the program are the National Institutes of Health (NIH), including the National Cancer Institute (NCI), National Institute of Allergy and Infectious Diseases (NIAID), and Fogarty International Center (FIC); the National Institute of Mental Health (NIMH), which subsequently became part of the NIH; the National Science Foundation (NSF); and the U.S. Agency for International Development (USAID). The FIC both administers the program and contributes resources to it.

The ICBG Program supports awards for up to 5 years made to the institution of the principal investigator (group leader) for an ICBG group. Group leaders may be located in a public or private nonprofit institution, government or governmental agency, or a foreign nonprofit organization, and the group leader's institution must be located in the United States or a developing country participating in the group. Applications are reviewed competitively at the NIH. Awards are made as Cooperative Agreements, allowing the sponsoring agencies to participate in the scientific and technical management of each group's program. During the past 4 years, the sponsoring agencies have funded five program awards.

In preparation for a second 5-year funding cycle, the FIC convened a panel of six experts on February 27-28, 1997, to review the ICBG Program and to make recommendations for improving the design and potential impact of the program. This document is the panel's report and contains the panel's recommendations for the evolving ICBG Program.

The review panel was chaired by Dr. George Albers-Schonberg, Executive Director, Natural Products Chemistry (retired), Merck Sharp and Dohme. Other panel members were Dr. Mikhail Antoun, University of Puerto Rico; Dr. John Burley, Arnold Arboretum, Harvard University; Dr. Anil Gupta, Indian Institute of Management; and Dr. Claudia Sobrevila, The World Bank. (The panel roster and agenda are provided in Attachments A and B, respectively.)

THE PANEL'S REVIEW

For the panel's meeting, the FIC asked the panel to address eight focus questions. These questions are as follows (the full text is given in Attachment C):

- What should be the relationship between and the relative weight of the three goals of the program: drug discovery, conservation of biodiversity, and economic development?
- Should the research and development focus of the program be expanded beyond pharmaceuticals to include related endeavors?
- How might future drug discovery efforts make best use of recent advances in the science as well as the resources of biological diversity and traditional knowledge?
- How should the program treat intellectual property rights (IPR) and benefit-sharing issues?
- Should balance among geographic regions be a criterion in the review and funding decisions of the agencies?
- What should be the appropriate balance of training in the ICBG?
- What lessons have we learned from the "demonstration" or outreach aspects of the program?
- Are there any significant concerns regarding the overall merit of renewing the ICBG Program?

Before addressing these questions specifically, the panel members heard presentations from FIC staff, program directors, and Government sponsors. Dr. Philip Schambra, Director, FIC, presented the charge to the panel, and FIC staff gave an overview of the program. Dr. George Albers-Schonberg commented on important considerations for the future of biodiversity prospecting and elaborated on the process and promise of drug discovery. The group leaders of each ICBG program described their program's goals, activities, organization, and progress. Representatives from five Government partners (NSF and four NIH components) commented on future priorities.

The panel considered all of this information, as well as written materials provided previously by the FIC, in its discussions, which began at the end of the first day and continued through the next morning. Panel members prepared written drafts in response to the eight questions which were used by the chair to report the panel's findings at the end of the meeting. After the meeting, the chair wrote the panel's final report in consultation with the panel members.

THE ICBG PROGRAM: OVERVIEW

Objectives and Goals

The four objectives of the ICBG Program, set forth in the first Request for Applications (RFA) issued in 1992, are to:

- "Discover, isolate, and evaluate preclinically, agents from natural sources to treat or prevent cancer, infectious diseases, including AIDS, cardiovascular diseases, mental disorders, and other diseases or medical conditions of primary concern to developing countries

- "Undertake inventories of biological diversity and develop collection practices compatible with conserving biodiversity, and produce documentation of all collected material in the form of museum catalogues, published works, and/or databases, reporting specific locality and all features of biology relevant to standard botanical and zoological conditions; 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

- "Support research training targeted toward the needs of the developing country or other countries represented within the [ICBG] group and related to the scope of work of the RFA, and to augment field experience and training of U.S. scientists in areas of knowledge unique to the developing country...

- "Assist in improving the scientific infrastructure within the participating developing country(ies) where the biodiversity resources are found...."

The intent of the sponsoring agencies is to establish multidisciplinary programs involving the active and substantial participation of scientists and institutions from the U.S. and developing countries. The overall aim is "to promote the conservation of biological diversity through the discovery of bioactive agents from natural products, and to ensure that equitable economic benefits from these discoveries accrue to the country of origin." The three key goals of the program are to:

- Conserve biological diversity

- Discover pharmaceuticals from natural sources

- Promote sustained economic activity in developing countries.

Research training and infrastructure development are important components of each of these elements, as is assurance of IPR and equitable sharing of benefits. The sponsoring agencies asked the ICBG groups to address a set of general IPR principles in their negotiations among the collaborating partners. These principles urge utilization

of conventional IPR protection, specification of benefits and compensation to the source countries, disclosure to and consent of indigenous (local) or traditional sources, respect for local concepts of intellectual property, planning for the resolution of disputes about public access versus proprietary information, and compliance with environmental laws.

Because of the wide interest in the ICBG Program and the large number of applications received in response to the first RFA, the FIC, in collaboration with NSF, subsequently initiated a second, smaller program to support Bioprospecting Opportunity Awards (BOAs). Small-grant BOA awards support international drug research and discovery (bioprospecting). Eligible applicants must already have an NSF grant for survey, inventory, or other biodiversity-related research. Four BOA awards are currently funded for research in Panama and Costa Rica (two awards) and on the international seas.

ICBG Program Descriptions

Of the five ICBG programs established since 1992, three were funded beginning in 1993 and two were funded beginning in 1994. Each award was made for 5 years, with costs ranging from $320,000 to $575,000 each year. The awards are funded by the FIC from moneys contributed by the three sponsoring agencies (NIH, NSF, USAID).

Each program is directed by a group leader from a U.S. research institution and involves multiple collaborating partners. The U.S. grantee institutions are Virginia Polytechnic Institute and State University, Washington University, Cornell University, Walter Reed Army Institute of Research, and the University of Arizona. Collaborating partners include local peoples, institutions, and universities in developing countries; other U.S. research institutions; non-governmental organizations active in conservation or economic development; plant-collecting organizations, such as museums, herbaria, or botanical gardens; and major pharmaceutical companies. Programs are subdivided into associate programs that emphasize different elements of the overall program.

Four of the current programs are based in Latin America, and one is based in Africa. The programs differ in geographic areas, program emphases, and resources. A brief description of each is given below.

- "Biodiversity Utilization and Conservation in Tropical America." Geographic area: Suriname rainforest. Program emphases: examination of potential medicinal agents from the rainforest, initiation of educational and extension activities in Suriname, search for nonmedicinal forest products for sustainable harvest, training in land management. Resources: rainforest flora.

- "Peruvian Medicinal Plant Sources of New Pharmaceuticals." Geographic area: Andean tropical rainforest. Program emphases: survey of tropical flora and fauna in northeast Andes, examination of the efficacy of traditional medicines and the health status of the Peruvian people of the northeast Andes, investigation of methods of sustainable harvest of medicinal plants for local markets. Resources: rainforest flora.

- "Chemical Prospecting in a Costa Rican Conservation Area." Geographic area: dry tropical forests of the Guanacaste Conservation Area. Program emphases: examination of forest insects and related species; contribution to the National Biodiversity Inventory in Costa Rica; building of the Costa Rican capacity for extract preparation; training in tropical ecology, chemical prospecting, natural products chemistry, and screening techniques; identification of natural products for further study. Resources: insects and related species from dry tropical forests.

- "Drug Development and Biodiversity Conservation in Africa." Geographic area: rainforests of Cameroon and Nigeria. Program emphases: evaluation of rainforest plants as cures for parasitic diseases, research on forest dynamics to understand the effect of sustainable harvest and cultivation of important medicinal plants, training of West Africans in natural products chemistry and tropical ecology. Resources: rainforest plants.

- "Bioactive Agents from Dryland Plants of Latin America." Geographic area: arid and semi-arid land in Argentina, Chile, and Mexico. Program emphases: discovery and development of pharmaceuticals and crop protection agents; training of Latin Americans in extraction, isolation, and identification of natural products and in growing, large-scale extraction, and processing of plant materials; creation of a bilingual biological, chemical, geographic, and bibliographic database. Resources: arid and semi-arid land plants.

The names of the investigators and institutions participating in these programs are given in Attachment D.

Successes and Opportunities

Even in such a short time, the ICBG programs have achieved some important successes. The programs have provided short-term training for more than 425 individuals and extended field, laboratory, and museum training for more than 120 individuals. Consistent with the terms of the Request for Applications, the programs have emphasized the development of basic technical capacity of host-country participants. This training has benefited both U.S. and host-country individuals, including technicians, bachelor-degree students, graduate students, and postgraduate investigators. Three individuals have received degrees (1 Ph.D., 2 M.Sc.) based in part on this training. These training efforts are important for enhancing the scientific infrastructure of developing countries and for promoting linkages between U.S. and host-country scientists and institutions.

The ICBG programs are contributing to infrastructure development in other ways as well. The groups are providing vehicles, computers, laboratory equipment, and supplies to host institutions to support the collection, processing, classification, testing, and storage of species and samples.

The programs have made progress toward drug discovery. Investigators have collected about 4,000 species, and initial screening, conducted in U.S. and host-country

institutions, has been completed on more than 7,000 samples. Through this screening, investigators have identified more than 140 samples for further investigation, have requested recollection of more than 170 samples, and have identified more than 35 priority leads. One group has discovered 3 novel compounds, isolated 10 bioactive compounds, and synthesized 5 analogs for further investigation. All five programs are developing critical biological information.

The programs also are contributing to scientific databases and communications, which will heighten recognition and help ensure conservation of the world's biodiversity. Investigators in each group have prepared, submitted for publication, or published a number of papers, abstract, or book chapters on biodiversity, natural products chemistry, or pertinent policy issues. One investigator is completing a multi-volume book on local, knowledge-based medicine (sometimes referred to as ethnomedicine). Group investigators also have participated in public workshops and on panels at scientific meetings. In addition, the groups have created more than 10 new databases that make geographic, biodiversity, and natural products information broadly available to the public. Also available to the public are nine new software programs for accessing and utilizing these databases.

In some host countries, the ICBG programs have stimulated the host government's interest in and policies for biodiversity conservation. Some also have stalled exploitation of the local environment for short-term economic gains (e.g., through deforestation, mining). To enhance local peoples' opportunities for sustainable economic development and support for biodiversity conservation, some groups have begun to embrace activities, such as eco-tourism and marketing of local crafts, as short-term incentives to help sustain longer-term conservation and drug discovery efforts.

In sum, the ICBG Program has served, and can continue to serve, as a national and international model of interdisciplinary collaboration among multiple funding agencies, multiple collaborating partners, and the United States and developing countries. The ICBG groups are generating important lessons on financial, administrative, and legal aspects of such collaborations, orchestration of agreements between mutually benefiting partners and with local groups, protection of IPR and equitable benefit sharing between scientists and institutions in industrialized and developing countries, integration of modern drug discovery methods with traditional and contemporary local botanical and medicinal approaches, cost-effective strategies for studying and conserving biodiversity, political and socioeconomic aspects of conservation, and sociological aspects of international research.

These lessons also suggest many opportunities for future research and training activities. Maintaining the flexibility of the ICBG Program to allow different groups in different areas to pursue the same goals in different ways will be critical. Sharing of information and lessons learned among the groups will be important as the ICBG Program continues to evolve over the next 5 years. The exchange of information will be especially important for devising new strategies and incentives to stimulate interrelated and strengthened efforts to meet the three goals of the program.

CONCLUSIONS AND RECOMMENDATIONS

The mutually dependent goals of the ICBG Program are to: (a) improve world health by discovering important drugs from natural products, (b) conserve the diversity of the world's biological resources and ecological settings that are the source of these products by promoting the sustainable use of resources in healthy environments, and (c) foster economic growth in developing countries that contain these resources by strengthening their pharmaceutical research capacity and infrastructure, promoting public health, and ensuring income from medicines that are discovered. The most diverse biological resources are generally found in developing countries located near the equator. Improved health and economic growth can be a powerful incentive for conserving these nations' biological diversity.

The review panel unanimously agrees with the concept of this very important, cost-effective program and urges that the program be continued through at least another 5-year funding cycle. Each of the current ICBGs have made remarkable progress, and each should have an opportunity to build on its successes. The experiences gained during the first 4 years of the present funding cycle also provide a solid base for gradually expanding the overall program to enable additional investigators to participate.

Additional funding will be needed to support expansion of the ICBG Program to include new investigators and new activities. Current funding levels are minimal. As noted by the principal investigators of the five ongoing ICBG programs, funds are not currently available for preparatory and negotiating efforts, which may last 6 months, or for projects that could yield short-term benefits. The review panel encourages the ICBG sponsors to seek additional funding for the program.

In response to the focus questions listed in Attachment C, the review panel makes seven specific recommendations. These recommendations, and the rationale supporting the recommendations, are presented on the following pages.

Goals of the Program

Recommendation 1:

Integration of drug discovery, conservation of biodiversity, and economic development into one program is a very important concept of the ICBG Program and should be continued. Economic development is, and should continue to be, a key link between the other two goals; it would be greatly strengthened by long-term support from USAID or other development organizations. Because major drug discoveries potentially can generate substantial benefits for host countries over the long term and because the possibility of these discoveries is a strong motivating factor for conservation efforts, additional financial incentives are needed to stimulate drug discoveries.

All five of the ongoing ICBG programs exhibit solid relationships between the U.S. and host-country partners, at several levels, and the host countries are receiving a range of benefits. Although no drug has been discovered yet, the partners are collecting and extracting samples and have identified a number of drug "leads" that merit followup. Program staff report local cultivation of medicinal plants; improved, sustainable agriculture; and moderation of the number of timber concessions granted. They are developing inventories of local biodiversity, assessing the values of forests, renovating herbaria, conducting workshops, and training local scientists. As an indication of the success of these initial ICBG efforts, several countries intend to use the ICBG Program as a model for their own future programs.

Until major drug discoveries can support the many development and conservation efforts that are being pursued, however, participation by USAID or other development donor organizations is highly desirable. To create maximum synergy among the three goals of the ICBG Program, sufficient incentives must be provided to host countries to develop and implement policies favoring long-term conservation and sustainable use of their biodiverse resources.

In addition, ICBG groups must focus on the transfer of information, technology, and skills required to develop future benefits that will meet the needs and interests of host countries. Participating companies and other organizations should be encouraged to invest in appropriate scientific infrastructure and human resources in host countries that could lead to, for example, the capacity to develop drugs from natural products and other local resources to treat tropical diseases of local importance that would not otherwise attract the attention of the international pharmaceutical industry. As already demonstrated, ICBG resources can serve as an important leverage for obtaining complementary investments in economic development in host countries.

As the ICBG Program enters the next 5 years, it should build on the investments already made and give incentives to ongoing programs to continue their work. During the past 4 years, all five programs have overcome very significant startup problems, such as establishing communications and trust with host-country personnel, ensuring the collaboration of universities in host countries, and obtaining local government permits.

Realistically assessing the research progress that has been made is now timely, and a mechanism for reviewing progress on a continuing basis should be developed. Based on these assessments, successful ICBG strategies could be identified and supported with additional incentive awards, while less successful strategies could be rethought. To ensure the continued participation of ICBG partners, the review mechanisms and process must preserve, without exception, the confidentiality of all proprietary information, such as chemical structures and biological data, and must not jeopardize the patentability of discoveries.

Research and Development Focus

Recommendation 2:

The research and development focus of the ICBG Program should be expanded beyond pharmaceuticals to include projects that deliver nearer-term benefits to local communities and institutions. Possible areas for expansion include agricultural products (e.g., natural pesticides, herbicides, growth regulators), veterinary medicines, cosmetics, fragrances, and natural dyes. Of direct interest to developing countries may be insect products (e.g., sex attractants) that target insect vectors of tropical parasitic diseases. Other nontimber-forest products such as fruits or ecotourism activities may not generally be appropriate because they would divert the special scientific expertise of ICBG principal investigators and because they can best be developed by established conservation organizations. However, specific projects must be considered and evaluated on a case-by-case basis.

The screening for natural products has been a source of very important drugs even as other powerful discovery methods have become available. Examples of the drugs obtained from natural products include (a) cyclosporin, which made possible modern organ transplantation; (b) ACE inhibitors, which are based on snake venom and are used to control high blood pressure; (c) cholesterol-lowering drugs, which are unmodified or slightly modified natural products; (d) ivermectin, a major drug for treating veterinary parasitic infections which has the potential of eradicating river blindness, a tropical human parasitic disease that affects 80 million people worldwide; (e) the new protease inhibitors for human immunodeficiency virus (HIV) infection, which are based on a microbial product discovered 25 years ago; and (f) taxol, the newest powerful anticancer agent, which is derived from the Pacific Yew tree.

Although natural products are the basis for these and other major drugs, the process of drug discovery is much more difficult and unpredictable than most persons imagine. Development and government approval of new drugs are lengthy processes, requiring, for example, about 12 years in the United States. Realization of significant royalties from drug discoveries also is slow. In addition, drugs that can generate major royalties are those that are used to treat diseases that are prevalent in industrialized countries; the incentive for developing countries to compete in the discovery of these drugs is small.

For these reasons, the review panel recommends that the ICBG Program be expanded to include optional research objectives, as identified above, that may have a more predictable and earlier chance of success and that are of more immediate interest and benefit to host countries. Expansion of the program in these areas will prevent disillusionment with the longer-term process of drug discovery.

These nearer-term projects, however, must embrace the three long-term objectives of the ICBG Program: drug discovery, conservation of biodiversity, and economic development. Drug discovery, in this sense, is both a goal and a means. That is, discovery of products for treating tropical parasitic diseases, for example, can contribute to economic development in a major way, not only by generating payments and

royalties but also by eradicating disease and freeing enormous human resources for productive endeavors. As constructed, the ICBG Program can become a productive development program.

Economic development must continue to include institution building. By developing and strengthening local institutions and by training local people in biodiversity conservation and sustainable use of resources, the potential for overextraction can be minimized. Similarly, the strengthening of biomedical research institutions will contribute to all three program goals. ICBG participants are encouraged to monitor the sustainability and diversity of the environment being studied. A broad, ecological approach is needed to ensure biodiversity conservation for the long term. Social scientists, who have expertise in institutional development, community organization, and cultural values, have contributed important perspectives to the program; their insights will continue to be needed in the future.

Research Advances and Resources

Recommendation 3:

To make best use of current scientific advances as well as biological resources and traditional and contemporary knowledge, ICBG programs are encouraged to concentrate on plants that are selected based on botanical strategies and on local knowledge; to include selections of microorganisms and insects; to use state-of-the-art screening and confirmatory assays; and to evaluate "leads" fully. Samples should be screened in different assays in many target areas by different organizations in academia, industry, and participating Government laboratories to maximize the chances of uncovering new leads from a given species and to utilize fully the information gained from samples.

Successful discovery of drugs from natural products depends on optimal selection of organisms to be tested; use of a variety of biochemically relevant screening assays; clinical evaluation of local, knowledge-based medicines and practices; and the willingness of partners to invest in thorough exploration of the medicinal and chemical aspects of identified leads. Each of these factors is addressed separately below.

Optimal Selection of Organisms

Scientists currently estimate that the total number of species of flora and fauna on earth is between 10 million and 50 million. However, only about 1.5 million species have been described scientifically and named by taxonomists. Of these, about 250,000 are vascular (higher) plants. Estimates of the total number of insects vary from 5 million to 30 million and even higher. The total number of species of fungi and nematodes is not known, and some taxonomists predict that it may be as large or larger than the number of insects. The total number of microorganisms is completely unknown and is a scientific "black hole." By broad selection and screening of plants, microorganisms, and

insects, ICBG scientists can contribute to scientific knowledge in general as well as drug discovery.

Plants. For many years, the National Cancer Institute has been screening plants as a productive source of tissue-specific cytotoxic compounds that can be used for treating cancer. Screening of plants for other therapeutic uses, which was reinstated about 10 years ago, has been less successful. Collection and preparation of suitable extractions for screening is a slow process, resulting in a small number of samples available for screening. To overcome these limitations, the criteria for selecting species must be optimized, the resupply of species must be secured and accelerated, and extraction and testing methods must be miniaturized in order to save samples and time.

Reasonable and productive strategies for selecting plants for screening are (a) a broad-based taxonomic approach, consisting of initial surveys of the entire plant kingdom, followed by more intensive examination of promising genera or families; (b) utilization of local traditional and contemporary knowledge about available plants; and (c) a stratified, random, sampling approach that captures the widest range of taxonomic, geographic, ecological, and population-level genetic diversity. Ecological relationships may provide important clues.

Stratified, random sampling is likely to be the most productive broad-based approach because it allows for serendipitous discoveries that may not be made when pursuing a more structured approach. Random sampling also enables investigators to focus on specimens that are flowering and fruiting at a given time (usually less than 30 percent of the species in any one tropical area); taxonomic identifications are more reliable when they are based on flowering or fruiting plants.

Broad-based sampling is important also for another reason. To assess the drug potential of a taxonomic group and because of the wide chemical diversity within plant families and genera, a considerable number of species must be sampled for each group. This effort is manageable and, contrary to random collection, will yield systematic information that becomes very valuable as more species are sampled. Only a small percentage of the earth's flora has been investigated chemically.

Local knowledge about plants, and traditions in using these plants, are important criteria for selecting organisms to sample. The biochemical mechanisms of action of botanical drugs used by local populations can be difficult and costly to determine, but determination of these mechanisms is nonetheless necessary. However, the mechanisms of action and potential for long-term toxicity must be determined before they can be evaluated clinically, especially for long-term use (e.g., for treating ailments affecting elderly persons). The use of traditional and contemporary knowledge-based medicines without prior toxicology studies does not establish their clinical safety and efficacy.

Microorganisms. In addition to screening plants, the ICBG Program should include screening of microorganisms. Industry laboratories have focused much of their efforts in

natural products on various microorganisms as sources of new compounds, especially eubacteria and fungi. The opportunities for discovering drugs based on organisms are enormous. Organisms exhibit a great diversity in the structures of their secondary metabolites, they include a very large number of species, and they are associated with specific ecological sites.

Insects. Insects produce chemicals that are highly specific for their species and targets. Because of the vast number of insects, a major challenge is the development of strategies for selecting species for screening. It may be productive to utilize the biology of insects, in particular, in the search for products that target insect vectors of tropical parasitic diseases.

Selection of Screening Assays

Screening assays can be highly focused biochemical assays that target a single enzyme or receptor; "pathway" assays that screen entire sequences of biochemical reactions; or in vivo assays. The assays used in the ICBG Program should be state-of-the-art.

Biochemical Assays. Modern pharmaceutical researchers favor biochemical assays that are targeted precisely to specific cells or cell components. These assays allow researchers to know the mechanism of action of a drug before developing the drug, thus minimizing potential side effects that would otherwise not be observed until the chemically optimized drug is tested in expensive toxicology studies and clinical trials.

With the biotechnology tools available today, researchers can analyze in increasingly greater detail the processes and molecular mechanisms inside cells that offer potential targets for highly specific medicines. With these tools, they also can often determine in advance whether a drug's interference with a specific biochemical event can be effective therapeutically. Sometimes these assays can be constructed as pathway assays, which offer a larger window of opportunity for discoveries.

Advances in biotechnology also have made human proteins readily available. In the past, only animal enzymes or receptors were available for screening assays and testing of structural modifications. Many drug candidates that looked promising in these assays were later found to be ineffective in clinical trials.

In Vivo Assays. In contrast to biochemical assays, in vivo assays usually do not have sufficient capacity for primary screening and are likely to result in the discovery of compounds whose mechanism of action is not known. Like local, knowledge-based medicines, they can lead to the discovery of new, therapeutically useful mechanisms. However, elucidation and evaluation of these mechanisms can be difficult and costly. In vivo assays must be strongly justified ethically whenever used. For screening purposes, they are generally not practical; for preclinical evaluations, they are indispensable.

Preparation of Extracts. Proper preparation of extracts for screening is as important as using state-of-the-art assays. Pure synthetic compounds are used in most screening laboratories in industry. Because natural product extracts can contain hundreds of chemical entities, many of which can interfere with target proteins, the strategies for preparing samples must be discussed in detail among all ICBG partners, including the collaborating testing laboratories. The strategies selected must then be strictly followed.

Evaluation of Local, Knowledge-Based Medicines and Practices

In addition to screening for natural products, evaluation of the medicines and healing practices already used by local groups could lead to important discoveries and insights. These medicines and practices need to be evaluated rigorously by multidisciplinary teams of medical practitioners, epidemiologists, researchers, and social scientists.

The potential gains from such studies have already been demonstrated. In one ICBG program, for example, an herb that was proven to have therapeutic benefit in a local setting did not exhibit effectiveness in the laboratory until the researchers incorporated local healers' method of delivery (oral ingestion) into their testing procedures. This experience indicates the benefits of combining biochemical screening strategies with an assessment of local, knowledge-based medicines and healing practices. In-country workshops that include local healers and ICBG research teams could foster broader understanding of all aspects of drug discovery.

Thorough Exploration of Leads

Open eyes, an open mind, and luck play an enormous role in discovering new drugs. The attention to local healers' practices, described above, is one example. Another example is the discovery of Calanolide A, a new anti-HIV compound that researchers are beginning to test in clinical trials. This compound is derived from a plant collected in Sarawak 10 years ago. The plant was collected spontaneously and probably would have been overlooked if the researchers had been following a strict, structured sampling protocol. Intelligence, imagination, and persistence are some of the essential ingredients for drug discovery. As techniques for biochemical screening become ever more rapid and technologically advanced (e.g., high-throughput screening), investigators' intuitions and their commitment to exploring all leads thoroughly will be critical to the success of the ICBG Program.

Testing Samples Thoroughly. One aspect of this commitment is the need to test samples thoroughly. Because of proprietary interests, pharmaceutical companies do not like to disclose details of their assays, yet they can provide sufficient information to establish that samples are being tested thoroughly and valid data are being generated. By encouraging technically strong U.S. laboratories, both public and private, and the World Health Organization (WHO), for example, to participate in the ICBG Program, the sponsors can ensure that state-of-the-art methods are being used and are being used properly.

High-throughput screening can quickly exhaust the largest supply of synthetic compounds that a pharmaceutical company has available. If this happens, the company will likely discontinue the assay. A long-term commitment, however, is needed for the screening for natural products. Prospective partners, including industry partners, should discuss this potential conflict and agree on the logistics needed to ensure thorough testing of samples.

Sharing Samples. Samples of extracts of plants or other organisms that are being tested may have a wide spectrum of potential activity. Researchers can enhance the likelihood of discovering new drugs from these products by sharing samples with other partners and by testing the same samples repeatedly for different activity. Pharmaceutical companies, however, prefer, understandably, to gain exclusive and unlimited testing rights for products of interest. As long as the availability of new species is not limited, companies may be willing to hold exclusive testing rights for defined categories of applications for a limited period of time, after which all rights would revert to the source country. This compromise would allow another company or laboratory to test the same species simultaneously for different applications.

Defining Leads. The screening of extracts is characterized by the discovery of many biologically active compounds but only a few authentic "leads." Whether an active compound is a lead depends on its chemical structure and the biological properties of the pure compound and not necessarily on structural novelty. Known compounds can have interesting and unexpected biological properties. Investigators must apply "dereplication" methods with great care to eliminate known structures; if they use dereplication procedures in haste, they could easily overlook minor structural novelties that may indicate a promising and patentable discovery.

The criteria used for determining the promise of leads may very well differ among industry, academia, and developing country partners. Participating pharmaceutical companies should be committed to the thorough evaluation of potentially interesting compounds and to the attempted development of all leads. The collaboration agreement should specify that these companies must satisfactorily explain to the other partners their reasons for abandoning a lead and should state the rights and options of the other partners in such cases.

<u>Intellectual Property and Benefit Sharing</u>

Recommendation 4:

In the next RFA, the ICBG sponsors should clarify and refine the terms of IPR and the principles of benefit-sharing, while allowing principal investigators to maintain the widest range of options to meet local needs. Sponsors also should clarify the differences between patent rights and benefit sharing. ICBG agreements should be carefully drafted to specify all rights and obligations of all ICBG partners, partners' rights to second-generation inventions, and the full range of contributions by all partners. Agreements should be developed in consultation with professional legal counsel for all partners.

The validity of IPR pertaining to traditional knowledge and the validity of ownership of natural resources, according to international law, are now acknowledged widely in industrialized countries. Current discussions now focus on practical questions about appropriate benefits to developing countries or communities whose natural resources and traditional knowledge are being studied or utilized by industrialized countries. Each developing country or community participating in the ICBG Program presents a different situation and different needs that must be accommodated.

Key issues pertain to patents and benefit sharing. The granting and ownership of patents is governed by patent laws that are recognized internationally. Benefit sharing is a more complex topic because benefits are manyfold, difficult to quantify, and vary with each situation. Both of these topics are immensely important to pharmaceutical companies as well as other ICBG partners.

Patents. The role of patents intellectually and in creating profitable products is often misunderstood. Patents convey ownership of an invention or discovery, but not necessarily the value of what is owned. They are legal instruments for protecting inventions, for a limited number of years, against unauthorized use of the patented information. In the case of drugs, development and clinical trials consume about one-half of a patent's duration.

The availability of patents is intended to stimulate innovation. Trivial modifications of an invention that add no improvement to the invention cannot be patented. Improvements can be patented and may render an invention obsolete long before its patent expires. This possibility encourages both original inventors and competitors to search for improvements. For an ICBG, holding a patent on a new natural product or on a new use of a known natural product is not sufficient; the ICBG will lose all benefits from an invention if a competitor successfully improves on it.

Individual inventors are the original owners of their patents. Inventorship cannot be changed, but inventors can assign their rights to another person or organization that has the requisite legal and scientific knowledge and capability to obtain and defend the patent.

Benefit Sharing. The legal aspects of benefit sharing are a separate issue and are not governed by patent law. Benefits to ICBG inventors and contributors, and especially to the developing country partner, can and should be defined in a legally binding agreement signed by all partners, including the designated or assigned owners or licensees of a patent. Because the commercialized version of an invention may differ from the original invention and may have different inventorship, agreements should specify the extent to which improvements and second-generation products entitle the original inventors and contributors, or countries, to benefits. International law gives countries sovereignty over their natural resources. The specific beneficiaries within a country may be designated by national and local laws and should be identified in harmony with the principles of the program.

Financial benefits. Within the ICBG Program, financial benefits are among the most important and most immediate benefits to be gained from discovering drugs and/or developing other, near-term products. These financial benefits, which are distributed as agreed upon by the collaborating partners, include:

- Royalties from the sale of drugs and other products
- Up-front payments based on the potential commercialization of products
- Other payments linked to the accomplishment of milestones
- Contributions by participating industries and local governments
- Venture capital, risk funds, and trust funds obtained from interested parties
- Additional support from USAID, The World Bank, foundations, and other donor organizations.

Realization of financial benefits depends on the participation of experienced partners and may be constrained by the highly competitive nature of pharmaceutical research. A key aspect, however, is the recognition of IPRs based on ownership of natural resources and traditional knowledge. Fairness in recognizing these rights is fundamental to achieving the economic development goal of the ICBG Program and, consequently, the conservation goal.

Other benefits. Many significant benefits other than the discovery of drugs and other products may accrue during an ICBG collaboration. Some of these benefits, as reported by ICBG principal investigators and others, are listed below. Other benefits also are possible.

Rights and Standards

Specific property rights for individuals and communities
Time limits on licensees' exclusive testing rights
Established payment standards

Infrastructure Development

Establishment of laboratories
Establishment and updating of national herbaria
Training of scientists, managers, and staff
Access to databases, other expertise, and other information
Capacity building through technology transfer
Control over local resources
Allotment of land and equipment for further experimentation and innovation
Recognition of individuals and communities with fellowships, awards, grants, and honors
Revitalization of networks of local healers and preservation of healers' knowledge
Strengthening of education programs, health services, and other infrastructure, especially in poor, very remote areas

Resource Assessment

- Assessment of the breadth and value of an area's biological resources, including its landscape and habitat and the genetic diversity, abundance, and density of species
- Assessment of the value of medicinal plants, locally and in industrialized countries
- Development of databases containing local knowledge of indigenous plants, nontimber-forest products, and novel uses of biodiversity
- Dissemination of conservation information and experiences

Education and Research

- Education on biodiversity in schools and herbaria
- Monitoring of threatened species
- Linkage with U.S. organizations (e.g., NIH, NSF, U.S. Department of Agriculture, Federal laboratories) and non-U.S. organizations (e.g., WHO
- Research on tropical diseases
- Continuing collection, screening, and pharmacological assessment of flora and fauna
- Interaction among local agriculture communities, specialists from industrialized countries, and industry

Management and Information

- Development of negotiating skills for achieving equitable agreements
- Access to pertinent information through reports and briefings from ICBGs and other groups
- Training in the management of local endeavors
- Training in disengagement strategies

Technical Assistance

- Analysis and documentation of biodiversity resources
- Modification of timber concession policies
- Assistance in development of sustainable agriculture
- Exchange of information on experiences with sustainable use of biodiversity.

The long-term viability of the ICBG Program depends on careful, realistic assessment of all the benefits likely to accrue to all partners and fair, appropriate assignment and distribution of these benefits. The experience gained during the past 4 years reinforces the importance of listening and attending to all concerns when establishing and implementing ICBG programs. For programs to flourish, the interests of university and industry scientists in both industrialized and host countries and of local healers and communities must continue to be recognized. When evaluating programs, the level of reciprocity and measures of accountability should be included among the indicators of

success. Improvements in economic development and conservation of biodiversity are as essential as the discovery of new drugs. To maximize achievements toward these ICBG goals and the benefits accruing to all partners, ICBG participants are encouraged to seek additional funding from other bilateral and multilateral programs of conservation and development.

Balance Among Geographic Regions

Recommendation 5:

Requiring geographic diversity among or within ICBG programs as a strategy for optimizing the overall program is discouraged. Competition and duplication of effort among ICBGs in individual areas or smaller countries should be avoided. However, under some circumstances, well-organized collaborative programs could have important advantages. An individual ICBG program must provide strong scientific justification and evidence that it has the administrative capacity for working in different areas or countries simultaneously. Overall merit must continue to be the primary criterion for selecting awardees.

Geographic diversification among ICBG programs is generally desirable, but should not be a requirement of the overall program. As a condition for funding, diversity of geographic location can be counterproductive. Important considerations for identifying areas of interest include their value for biodiversity conservation, the potential to arrest environmental destruction of rich ecological niches, the diversity of the habitat, evidence of local medicinal knowledge, and the availability of local expertise in using resources in a sustainable manner. Considerations such as these are more indicative of the potential for success than simply geographic diversity.

Within one ICBG program, the advantages of operating in several countries simultaneously are likely to be outweighed by the increased administrative burdens (e.g., in program management and logistics). Diversification also could dissociate efforts from rewards, resulting in loss of synergy among the three ICBG goals or inability to attain a critical mass of expertise in one geographic area. In contrast, the concentration of an ICBG program within one geographic area favors synergy, makes re-collection of species easier for followup studies, helps focus incentives for conservation (which are probably strongest in areas where land tenure is common), and fosters establishment of strong personal ties with local people in host countries.

The benefits of geographic concentration, however, may be outweighed by a better selection of species in a large(r) geographic area. If a researcher is conducting an initial overview of the taxonomy in an area or is selecting specific medicinal plants, the number of interesting species in one contained area may be limiting. In these instances, collections in several geographic areas and under different climatic conditions may be advantageous. However, if a researcher is interested only in obtaining a number of randomly collected species or in studying ecological relationships in very defined habitats, a more limited area will likely contain the variety of species needed.

A principal investigator's personal scientific objectives for a ICBG program also must be considered. In general, decisions about the geographic spread within an ICBG program should be made by that program's principal investigator as long as the main criterion of overall merit is satisfied.

Training

Recommendation 6:

Extraordinary efforts should be made to train scientists at all levels to conduct modern pharmaceutical research in host countries. Training and other capacity-building efforts in host countries should move rapidly beyond collection of plants, development of inventories, and preparation of extracts to all phases of research, including design of assays, performance of chemistry studies, and management of databases. Training should be provided at all levels of expertise and must be structured according to the capacity of the host country to absorb new technologies. Training also should be provided to enhance administrative and negotiation skills, which are critical for establishing and maintaining partnerships.

Establishing technologically advanced laboratories in developing countries will be cost effective only after a critical mass of scientists has been trained. Even then, continued material and moral support will be needed to enable these scientists to work productively under potentially very difficult conditions and to discourage them from emigrating to countries that are more technologically advanced. This type of capacity building cannot be achieved at once, but only incrementally. More than any of the other benefits of an ICBG partnership, however, training is the necessary condition for economic development and, ultimately, the success of the overall ICBG Program.

Scientific training alone will not suffice. Administrative skills are needed for ensuring sound research management. These skills also will be useful for conceiving and negotiating new types of relationships with institutions and corporations in industrialized countries as sophisticated laboratories become viable in developing countries.

Training of host-country individuals, scientifically and administratively at all levels, and involvement of host-country scientists in all phases of research, from designing projects to publishing results, should continue to be emphasized in the ICBG programs. An evaluation of ongoing training efforts could indicate different training strategies or new training components that would strengthen the ICBGs' capacity-building efforts. In addition, the development of consortia or networks among individuals and institutions benefiting from ICBG training could foster a useful exchange of information, experiences, and lessons learned across all ICBG programs.

Demonstration and Outreach

Recommendation 7:

Dissemination of goals, designs, and results is an important feature of the ICBG Program. Individual ICBG programs should share as much information as possible among themselves and with other interested parties. At all times, the ICBG groups should communicate clearly and specifically their near- and long-term objectives and the probabilities and types of benefits likely to emerge from their efforts. The information shared within and among the groups and with the broader international community should include descriptions of specific efforts and lessons learned. This information should be communicated through local scientific institutions, schools, networks of healers, the Internet, print publications, and other media.

The ICBG Program, by combining drug discovery, biodiversity conservation, and economic development, is a courageous and imaginative concept that attracts much hope. The complex of divergent, seemingly contradictory, and yet interdependent objectives presents demanding challenges for managers centrally and in the field.

The concept is nevertheless realistic. Without strict rules and with great flexibility, managers and researchers have adapted the concept to very different conditions--biological, cultural, political--and to individual scientific interests and styles. At the same time, they have complied with the provisions of the Convention on Biological Diversity, including those pertaining to international cooperation (Article 5); conservation and sustainable use of biodiversity (Articles 6 and 10); inventory and monitoring of biodiversity (Article 7); in situ conservation (Article 8) and ex situ conservation (Article 9); provision of economic and social incentives (Article 11); establishment and maintenance of research and training programs (Article 12); public education and awareness of the importance of biodiversity (Article 13); minimization of adverse environmental impact (Article 14); negotiated access to genetic resources (Article 15); access to and transfer of technology (Article 16); international exchange of information (Article 17); technical and scientific cooperation (Article 17); and provision of additional financial resources (Article 20).

Some of the key lessons learned from the five current ICBGs are highlighted below. These relate to the role of drug discovery, the importance of formal agreements, support for preparatory efforts, interaction with local communities, collaborations in conservation, forging partnerships with industry, monitoring and evaluation, funding, and dissemination of information.

Drug Discovery. Important new drugs, which can generate substantial royalties for conservation and development, are rare discoveries, however, and other, short-term benefits are needed if the ICBG concept is to survive. The addition of such new projects necessarily creates great, new challenges. Drug discovery, however, will continue to be the potentially most powerful "engine" for the program. For this reason, the possibility of incorporating appropriate financial incentives to stimulate drug discoveries should be explored.

Formal Agreements. ICBG collaborations must continue to be based on legally binding agreements. These agreements should be negotiated carefully and thoroughly and should comply with the terms and the spirit of the Convention on Biological Diversity.

Preparatory Efforts. When considering a collaboration, and at the earliest stage possible, potential partners should select the most capable and committed collaborators and should establish "open channels" to governments, community leaders, and local experts. Before permissions are sought from host governments and tribal authorities, the potential benefits of conserving natural resources should be mutually understood by the partners, and information on the prospective value of the resources should be obtained and provided. The time and resources needed to support these preparatory efforts, which consume an estimated 6 months, should be included in the ICBG charters and grants.

Community Interaction. No unrealistic promises should be made to convince host communities and governments to participate in an ICBG program or to ease the attainment of grants or export permits. Communities are an integral part of the program, and their concerns and interests should be heeded. The input and involvement of communities and local experts are critical and do not end when necessary permits are obtained. A cohesive, successful program is based on strong personal ties and mutual trust. Building such a program can be particularly challenging when the ICBG operates over a very large area or even in more than one country.

Conservation Efforts. Experience also suggests that ICBG investigators should not attempt to establish new conservation programs but to collaborate with an already existing, capable organization in the host country. In addition, investigators should be aware that sustainable management of resources is not necessarily an approach developed or taught by industrialized countries. Local expertise must be sought, evaluated, and supported. ICBG programs can perform an important function by disseminating information about conservation methods to other areas and countries.

Partnerships With Industry. Forging close collaborations with, and commitments by, industry partners may not be easy. The criteria for electing to develop a compound may differ among the industry, university, and host-country partners. Such potential differences should be anticipated, addressed, and resolved as early as possible in the collaboration. Particular attention must be paid to rapid communications and turnaround of data.

Monitoring and Evaluation. All ICBG programs should include monitoring and evaluation systems for measuring the progress of each project and of the overall program. These systems, and the review processes they embrace, must be confidential. If industry partners do not have complete confidence in the confidentiality of these systems and processes, they will not disclose important information and, possibly, not even enter into a partnership.

Progress in a natural products program cannot be assessed adequately or accurately until the program has been operating for at least 5 years. A key aspect of the ICBG Program, discovery of a viable drug candidate, can take considerably longer than 5 years to show results. Organizations that could provide consultants for reviewing and refining the program include the U.S. Department of Agriculture, Oak Ridge Laboratory, Lawrence Berkeley Laboratory, and NIH's Office of Alternative Medicine.

Information Dissemination. Information about the ICBG Program should be disseminated widely and frequently to all ICBG partners, host countries, and other interested parties. This dissemination would enhance awareness of the program and its potential benefits, demonstrate the partners' and sponsors' commitment to the ICBG goals, and help create a synergy of effort among groups and organizations active in drug discovery, biodiversity conservation, and economic development of developing countries. Information that could be shared easily includes:

- Local knowledge about uses of biodiversity
- Local knowledge about sustainable agriculture
- Restoration of depleted species to their habitats
- Potential benefits of the program
- Realistic expectations of the program
- Models of international cooperation and collaboration involving public and private sectors
- Lists of potentially endangered species
- Productive negotiating positions
- Local and international markets.

Special effort is needed to prepare and disseminate this information in the local languages of the communities participating in the ICBG programs. Measures of the learning that takes place at all levels could be identified, communicated, and assessed periodically. This investment in knowledge transfer will enhance informed consent and negotiating processes. Involvement of community, national, and international organizations in these activities is desirable.

Annual meetings of the ICBG partners also are very important for formally and informally exchanging ideas, information, and program results. Scientists, administrators, and government officials should be invited to attend these meetings.

Overall Merit of Renewing the ICBG Program

The ICBG Program, already promising, will benefit from incorporation of the lessons learned over the past 4 years and the panel's recommendations for the next 5 years. The program can serve as a model of cooperation in which mutual interests and expectations are clearly acknowledged between countries in the northern and southern hemispheres and between countries within the southern hemisphere.

The FIC's leading role in the program reflects the central role of drug discovery and world health in the program. Over the next 5 years, the importance of discovering new drugs to improve the health of all peoples cannot be overstated, and work in this area must be complemented by, and integrated with, conservation and economic development efforts. The ICBG Program has made a strong start at advancing these goals. This panel recommends that the ICBG sponsors refine the program as recommended in this report and seek additional funding to meet the challenges of the next 5 years.

ATTACHMENTS

Attachment A

INTERNATIONAL COOPERATIVE BIODIVERSITY GROUPS (ICBG) PROGRAM REVIEW PANEL

Dr. George Albers-Schonberg (co-chair)
Executive Director (retired)
Natural Products Chemistry
Merck Sharp and Dohme
Princeton, New Jersey

Dr. Christine Padoch (co-chair)*
Institute of Economic Botany
New York Botanical Garden
Bronx, New York

Dr. Mikhail D. Antoun
School of Pharmacy
University of Puerto Rico
San Juan, Puerto Rico

Dr. Anil Gupta
Centre for Management in Agriculture
Indian Institute of Management
Vastrapur, Ahmedabad

Dr. John Burley
Harvard University Herbaria
Cambridge, Massachusetts

Dr. Claudia Sobrevila**
The World Bank
Washington, D.C.

* Invited to serve as co-chair but unable to attend because of illness.
** Presently at Conservation International, Washington, D.C.

Attachment B

INTERNATIONAL COOPERATIVE BIODIVERSITY GROUPS (ICBG) PROGRAM REVIEW

AGENDA

FEBRUARY 27-28, 1997

Lawton Chiles International House (Bldg. 16)

National Institutes of Health (NIH)

Bethesda, MD

February 27

8:30	Opening and Introduction	Co-Chairs
-	Charge to Panel	Dr. Philip Schambra
-	Overview of ICBG Program	Dr. Joshua Rosenthal
-	Discussion	Co-Chairs
9:30	Important Considerations for the Future of Biodiversity Prospecting	Co-Chairs
-	Integrated Conservation and Development	Dr. Christine Padoch*
-	Drug Discovery	Dr. George Albers-Schonberg
9:50	ICBG Presentations	-
	Chile, Argentina, Mexico	Dr. Barbara Timmermann
10:15	Break	-
10:45	Suriname	Dr. David Kingston and Ms. Lisa Famolare
-	Costa Rica	Dr. Jerrold Meinwald and Dr. Joseph O'Sullivan
-	Peru	Dr. Walter Lewis
	Cameroon and Nigeria	Dr. Brian Schuster and Dr. Maurice Iwu
12:35	Lunch	-
1:35	Government Partners - Future Priorities:	-

-	NCI	Dr. Gordon Cragg
-	NIAID	Dr. Alex Fairfield
-	NIMH	Dr. Linda Brady
-	FIC	Dr. Kenneth Bridbord
-	NSF	Dr. James Rodman
-	USAID	Mr. Franklin Moore*
2:10	Discussion	-
3:00	Break	-
3:30	Deliberations (Closed sessions) Adjournment at discretion of Co-Chairs	-

February 28

9:00	Deliberations: Preparation of Recommendations and Draft Report	-
11:00	Presentation of Recommendations	Co-Chairs
12:30	Adjourn	-

*Unable to attend

Attachment C

INTERNATIONAL COOPERATIVE BIODIVERSITY GROUPS PROGRAM REVIEW

FOCUS QUESTIONS TO PANEL

- **What should be the relationship between and relative weight of the three goals of the program: drug discovery, conservation of biodiversity, and economic development?**

The original RFA framed the program as an integrated conservation and development effort based upon the search for novel therapeutic agents and emphasized that all three goals should be addressed by each group. In this initial phase the efforts of the five groups have been dominated by research and training associated with drug discovery and biological inventory, and development and refinement of novel partnerships. Is integration of these three goals a productive approach?

The role of USAID in a renewal of the ICBG program is as yet undefined. In light of this consideration future efforts may or may not include economic development as one of the principal and explicit goals. What effect would this adjustment have on the other long term goals and specific objectives of the program? How might we strengthen the promotion of drug discovery and the conservation of biodiversity correspondingly?

- **Should the research and development focus of the program be expanded beyond pharmaceuticals to include related endeavors?**

Development of herbal medicines and dietary supplements, natural products-based veterinary and crop protection agents, and biological control agents have all been identified as potentially valuable resources for sustainable utilization of biodiversity. Which, if any, of these additional research targets would be likely to enhance conservation and sustainable development objectives without causing the program to lose focus. Currently, development of herbal medicines and agro/veterinary agents are secondary components of two ICBGs.

- **How might future drug discovery efforts make best use of recent advances in the science as well as the resources of biological diversity and traditional knowledge?**

The foundation for the program is the recognition that natural products from diverse plants, animals and microorganisms have been the basis for, or involved in, the development of many of our pharmaceuticals. In addition, there has been a very strong interest in and considerable effort toward utilizing both modern and traditional knowledge of these organisms during the research process. The basis of this interest is the historical role modern and traditional knowledge have had in facilitating the research process, as well as the important conservation and development benefits that emerge from their study.

Since the program was designed, advances in chemistry and biochemistry, including combinatorial techniques, have generated a great deal of enthusiasm among some members of the research community. Accepting that the natural product often serves as the lead compound in the drug development process, to what extent are these advances likely to be part of future ICBG research? Is there a need to explicitly encourage their use?

- **How should the program treat intellectual property (IPR) and benefit-sharing issues?**

To date the government has treated IPR with a "program principles" approach because of the integral role that benefit sharing plays in the conservation and development objectives. That is, explicit but general principles regarding informed consent and benefit-sharing must be satisfied in order for groups to receive government funding. This approach represents an attempt to balance the limits of the statutory authority of the government over technology transfer and a conservation/development philosophy based upon local empowerment, capacity building and creation of incentives. Is this approach too intrusive, or not specific enough? If it is appropriate to refine the general principles, how might that best be accomplished?

- **Should balance among geographic regions be a criterion in the review and funding decisions of the agencies?**

Among ICBGs: On the basis of merit and secondary reviews of competitive applications four of the five ICBGs selected for awards are in Central and South America. Should the program attempt to diversify geographically in the second round, and if so how? Number, size and duration of awards may be relevant considerations, as well as the alternative model offered by the Bioprospecting Opportunity Awards (BOA).

Within ICBGs: Some groups have limited their work to relatively defined areas within a country while others are working in several countries simultaneously. Each approach has advantages and disadvantages. A very broad geographical range increases the species diversity with which they are able to work, but may limit the total support available to host country participants as well as the continuity of community level conservation and development activities. Should groups be encouraged to focus, or alternatively to broaden, the geographical extent of their efforts?

- **What should be the appropriate balance of training in the ICBG?**

Individuals receiving training are currently from both U.S. and host country academic origins, as well as from small towns and villages in host countries. Training includes areas of chemistry, ethnobotany, biological inventory, computer database development, and, less formally, contract law and negotiation. Trainees include post-doctoral researchers, graduate students, undergraduates and technicians in long and short term programs. Are we spread too thinly, and if so what should be our focus?

- **What lessons have we learned from the "demonstration" or outreach aspects of the program?**

Demonstrating to national governments and local communities that their biological diversity and associated traditional knowledge have potential commercial value, and establishing working models for how they may be used in a sustainable and equitable fashion have been important objectives of the program. Each of the groups has achieved positive results from these efforts. However, each of the groups has also had to contend with unrealistic expectations at the international, national and community levels of financial benefits from bioprospecting endeavors. Can this paradoxical issue be managed, and how might this be accomplished?

- **Are there any significant concerns regarding the overall merit of renewing the ICBG program?**

This program was initiated as an experimental effort and no commitment to continue funding beyond the first cycle has been made. On the basis of the progress made thus far, and accepting that all three of the program goals are long-term processes, most of the funding partners have expressed some interest in developing a second RFA. Are there any fundamental or compelling reasons why a program such as this should not continue in some form for a second funding cycle?

Attachment D

International Cooperative Biodiversity Groups - Investigators and Institutions

Principal Investigator/U.S. Institution HOST COUNTRY	Foreign Collaborating Investigators /Institutions	Domestic Collaborating Investigators/Institutions
David Kingston/ Virginia Polytechnic and State University SURINAME	Jan Wisse/ Bedrijf Geneesmidden Voorzenig Suriname Stan Malone/ Conservation International Suriname Marga Verkhoven/ University of Suriname Herbarium	Dinesh Vyas/Bristol-Myers Squibb Pharmaceutical Research Institute Russell Mittermeier/Conservation International Henk van der Werff/Missouri Botanical Garden
Walter Lewis/ Washington University PERU	Abraham Vaisberg/ Peruvian Cayetano Heredia University Gerardo Lamas/ San Marcos National University of Peru	David Corley/Monsanto-Searle Pharmaceutical Research Memory-Elvin Lewis/ Washington University
Jerrold Meinwald/ Cornell University COSTA RICA	Ana Sittenfeld/ National Biodiversity Institute of Costa Rica Giselle Tamayo/University of Costa Rica Misael Chinchilla/University of Costa Rica Olga Guerrero/ University of Costa Rica	Daniel Janzen/University of Pennsylvania-Guanacaste Conservation Area - Costa Rica Tom Eisner/Cornell University John Clardy/Cornell University Dinesh Vyas/Bristol-Myers Squibb Pharmaceutical Research Institute

Brian Schuster/ Walter Reed Army Institute of Research CAMEROON, NIGERIA	Johnson Ayafor/ University of Yaounde, Cameroon Maurice Iwu/ University of Nigeria, Nsukka Nicholas Songwe/ Institute for Agriculture Research, Cameroon Johnson Jato/ University Center for Health Sciences, Cameroon Ayoade Oduola/ College of Medicine, University of Ibadan, Nigeria	Joan Jackson/Walter Reed Army Institute of Research Elizabeth Losos/Smithsonian Institution
Barbara Timmermann/ University of Arizona CHILE, ARGENTINA, MEXICO	Robert Bye/ National Autonomous University of Mexico Gloria Montenegro/ Catholic University of Chile Enrique Suarez/National Institute of Agricultural Technology and Biotic Resources, Argentina Edgardo Saavedra/Patagonia University	Scott Franzblau/Louisiana State University Joseph Hoffman/University of Arizona William Maiese/Wyeth-Ayerst - American Cyanamid Co.