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COMBINING HIGH RISK SCIENCE WITH AMBITIOUS SOCIAL AND ECONOMIC GOALS

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ABSTRACT

Great strides have been made during the past decade in understanding the interelatedness of human health, economic welfare and environmental quality. Among these is the certainty that improvements in health may be impeded or reversed by poverty and destruction of the natural resources that diverse biological species provide. The International Cooperative Biodiversity Groups (ICBG) represent an experimental effort supported by three agencies of the U.S. Government to integrate research in natural products drug discovery with efforts to build the scientific and economic capacity of developing countries as well as enhance the skills and incentives needed to conserve biological diversity. These groups are unique, public-private collaborations that have been carrying out interdisciplinary research and development projects for up to seven years in 12 countries in Latin America, Africa and Asia. In addition to research on species in 230 plant families and 25 arthropod orders, over 1400 individuals have received technical training, and potential therapies for several parasitic diseases, tuberculosis and crop diseases are in development. The ICBGs have also developed novel research and intellectual property agreements and have become important testing grounds in national and global discussions regarding access, informed consent and benefit-sharing associated with genetic resources.

Keywords: Drug discovery, economic development, biodiversity conservation, natural products, research, training, patents, traditional knowledge.

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INTRODUCTION

Can drug discovery research with natural products be conducted in such a way as to simultaneously promote human health, economic development, and conservation of biodiversity? The question is of much more than academic importance, for the three areas are integrally related. Natural products pharmaceutical and agricultural discovery depends on the existence of and access to diverse biota. However, many of the world's economies rely heavily on unsustainable uses of their natural resources. As a result, approximately 0.25 percent of the world's species of plants, animals, and microorganisms are lost to extinction every year due to tropical deforestation alone (Heywood & Watson,

Table 1. ICBG program goals.

Pharmaceutical and Agricultural Discovery – This goal covers the collection and extraction of raw materials, testing in a wide range of bioassays, chemical isolation, and pre-clinical evaluation of agents from natural sources to treat or prevent cancer, infectious diseases including AIDS, cardiovascular diseases, mental disorders, drug addiction, and other diseases, as well as a variety of crop plant and veterinary concerns.
Scientific and Economic Development – This is accomplished through scientific training and research capacity strengthening of host country institutions, and through equitable sharing of benefits that emerge from the research process and products with the host countries, groups, or organizations that facilitate the discovery process.
Conservation of Biodiversity – This goal encompasses creating incentives at all levels for the preservation of intact habitat; increasing the knowledge and skills upon which conservation activities depend; and developing long-term ecological and economic strategies to ensure more sustainable use of biodiversity.

1995). At present rates, it has been conservatively estimated that up to 10 percent of the world's species will be extinct within 25 years (Heywood & Watson, 1995), largely as a result of deforestation, urbanization, unsustainable agricultural and fishery practices, mining, and other economic processes that value only the bulk products of biodiversity (e.g., timber). In addition to losing the basis for many of the world's pharmaceuticals (Cragg, 1999; Grifo et al., 1997), we are likely to suffer many other impacts on human health, including loss of ecological equilibria that may regulate infectious disease dynamics, loss of diverse biological indicators of environmental quality, and even loss of models for biomedical research (Grifo & Rosenthal, 1997).

Because of the interdependence of natural products drug discovery, economic development and biodiversity conservation, new models for integrating these efforts are greatly needed (Schweitzer et al., 1991; Macilwain, 1998; Gollin, 1999). Our attempt to integrate pharmaceutical and agricultural discovery with economic development and biodiversity conservation is the essence of the experiment known as the International Cooperative Biodiversity Groups ICBG. The experiment takes the form of a six-year-old research and capacity building program funded by the National Institutes of Health (NIH), the National Science Foundation (NSF), and the Department of Agriculture (USDA). The ICBG program explicitly identifies three goals. The first is to improve human health through the discovery of new pharmaceutical, agricultural and veterinary agents to treat diseases of importance in both developed and developing countries. The second goal is to promote scientific and economic activity in less developed countries by sharing the benefits of the drug discovery and conservation research process and products. The third goal is to conserve biological diversity through understanding and valuation of diverse biological organisms and the development of local capacity to manage these natural resources (Table 1).

The popular conception of modern bioprospecting efforts is based on the notion that success toward the third goal, conservation, is dependent on major commercial success in drug discovery (Simpson et al., 1996; Pollack, 1999). (Note that here and henceforth, "drug discovery" is generally used as shorthand to include research toward pharmaceutical, crop protection and veterinary agents.) In that model, discovery of an important and profit-making drug will generate economic benefits that will in turn make conservation a viable economic action. However, drug discovery is a high-risk science. That is, a very small proportion of the research endeavors result in a major drug that will yield financial benefits to the research organizations and their partners. The ICBG program approaches bioprospecting in a more multi-dimensional way, such that progress in any one of the three goals ideally strengthens the efforts of the other two. By integrating research and development efforts toward all three objectives from the outset, the ICBG aims to make substantial and incremental contributions toward their achievement without pinning all hopes for success on the relatively low probability of producing a major pharmaceutical or agricultural product.

A BRIEF HISTORY OF THE INTERNATIONAL COOPERATIVE BIODIVERSITY GROUPS

The philosophy and basic operating principles of the ICBG program were originally developed at a 1991 international workshop on drug development, biodiversity conservation and economic growth (Schweitzer et al., 1991). The following year a joint Request For Applications (RFA) was released by NIH, NSF, and the U.S. Agency for International Development (USAID). The RFA solicited proposals to establish multidisciplinary groups to develop programs addressing the above described goals according to their specific scientific

Table 2. ICBG program summaries.

Years active	Project title	Group leader/AP leader	Institution
1993–1998	**Biodiversity Utilization in Madagascar and Suriname**	**David G.I. Kingston**	**Virginia Polytechnic Institute and State University**
1998–2002	AP-1 Botany and Systematics	James Miller	Missouri Botanical Garden
	AP-2 Ethnobotany, Conservation, and Development	Russell A. Mittermeier	Conservation International
	AP-3 Ethnobotany, Sample Processing & Phytomedicine Development	Rabodo Adriantsiferana	Centre National d'Application et des Recherches Pharmaceutiques (Madagascar)
	AP-4 Sample Processing and Antimicrobial Drug Discovery	Jan Wisse	Bedrijf Geneesmiddelen Voorziening Suriname
	AP-5 Drug Discovery from Surinamese and Madagascan Plants	J.J. Kim Wright	Bristol-Meyers Squibb Pharmaceutical Research Institute
	AP-6 Natural Products as Agrochemical Agents	B. Cliff Gerwick	DowElanco Agrosciences
	AP-7 Rain Forest Natural Products as Anticancer and Other Agents	David G.I. Kingston	Virginia Tech
1994–2000	**Peruvian Medicinal Plant Sources of New Pharmaceuticals**	**Walter H. Lewis**	**Washington University (St. Louis)**
	AP-1 Plant Ethnomedicine	Walter H. Lewis	Washington University
	AP-2 Biotic Inventories and Conservation	Gerardo Lamas	San Marcos University (Lima)
	AP-3 Medically Significant Plants in the Tropics	Abraham Vaisberg	Universidad Peruana Cayetano Heredia (Lima)
	AP-4 Phytochemistry	Dave Corley/Margaret Wideman	Searle-Monsanto Co.
	Collaboration with Indigenous Peoples	Cesar Sarasara	Confederation of Amazonian Nationalities of Peru
1993–1998	**Chemical Prospecting in a Costa Rican Conservation Area**	**Jerrold Meinwald**	**Cornell University**
	AP–1 Ecology, Systematics, Bioprospecting & Training	Ana Sittenfeld	INBio (Costa Rica)
		Giselle Tamayo	University of Costa Rica
	AP-2 Chemistry and Chemical Ecology	Jerrold Meinwald	Cornell University
	AP-3 Drug Discovery and Development	Dinesh Vyas	Bristol-Myers Squibb
1994–1998	**Drug Development and Conservation of Biodiversity in West and Central Africa**	**Brian G. Schuster**	**Walter Reed Army Institute of Research (WRAIR)**
1998–2002	AP-1 Biodiversity Inventory and Monitoring, Conservation and Training	Elizabeth Losos	Center for Tropical Forest Science, Smithsonian
	AP-2 Phytochemistry and Africa-based Bioassays, and PhytomedicineDevelopment	Johnson Ayafor	University of Dschang (Cameroon)
	AP-3 Antimalaria Drug Discovery and Development	Wilbur Milhous	WRAIR
	AP-4 Antiparasitic Drug Discovery and Development	Joan Jackson	WRAIR
	AP-5 Ethnobiology, Socio-Economic Value Assessment and Community-Based Conservation Projects	Maurice Iwu	Bioresources Development and Conservation Programme
	AP-6 Non-Parasitic Drug Discovery and Development	Brian Schuster	WRAIR
1993–1998	**Bioactive Agents from Dryland Biodiversity of Latin America**	**Barbara Timmermann**	**University of Arizona**
1998–2002	AP-1 Inventory, Ethnobotany and Conservation	Enrique Suarez	Instituto Nacional de Tecnologia Agropec. (Argentina)
		Gloria Montenegro	Pontifica Universidad Catolica de Chile (Chile)
		Robert Bye	Universidad Nacional Autonoma de Mexico (Mexico)
	AP-2 Drug Discovery	Barbara Timmermann	University of Arizona
	AP-3 Information Management, Dissemination, and Related Training	Barbara Hutchinson	University of Arizona
1998–2002	**Drug Discovery and Biodiversity Among the Maya of Mexico**	**Brent Berlin**	**University of Georgia**
	AP-1 Drug Discovery and Pharmaceutical Development	David Puett	University of Georgia
		Robert Nash	Molecular Nature Ltd. (UK)

Table 2 continues

Table 2. (cont.)

Years active	Project title	Group leader/AP leader	Institution
	AP-2 Medical Ethnobiology and Biodiversity Inventory	Brent Berlin Eloise Ann Berlin	University of Georgia
	AP-3 Conservation, Sustained Harvest and Economic Growth	Luis Garcia-Barrios Jose Carlos Fernandez	El Colegio de la Frontera Sur (ECOSUR)
1998–2002	**Ecologically Guided Bioprospecting in Panama**	**Phyllis Coley**	**Smithsonian Tropical Research Institute**
	AP-1 Collections, Coordination and Data Management	Phyllis Coley	Smithsonian Tropical Research Institute
		Todd Capson	Smithsonian Tropical Research Institute
		Thomas Kursar	Smithsonian Tropical Research Institute
	AP-2 Panama-based screening, isolation and characterization of biologically active natural products	Mahabir Gupta	University of Panama, School of Pharmacy
	AP-3 Screening biological material for activity against tropical disease agents	Eduardo Ortega-Barria	Gorgas Memorial Institute of Health Research
	AP-4 Biological Inventories	Don Windsor	Smithsonian Tropical Research Institute
	AP-5 Pharmaceutical and Agricultural Discovery and Development	Leslie Harrison	Monsanto
	AP-6 Conservation and Ethnobotany	Manuel Ramirez	Conservation International
1998–2002	**Biodiversity of Vietnam and Laos**	**Djaja D. Soejarto**	**University of Illinois at Chicago**
	AP-1 Inventory and Conservation of Cuc Phuong National Park	Djaja D. Soejarto	University of Illinois at Chicago
	AP-2 Lao Medicinal Plants as Potential source of New Medicines	Boun Hoong Southavong	Research Institute for Medicinal Plants (Laos)
	AP-3 Drug Discovery from Plants of Vietnam and Laos for AIDS and Malaria Therapies	John M. Pezzuto	University of Illinois at Chicago
	AP-4 Biomass Production and Economic Development	Le Thi Xuan	National Center for Natural Sciences and Technology (Vietnam)
	AP-5 Drug Discovery and Development	Melanie O'Neill	Glaxo Wellcome (UK)

interests and bio/cultural/economic context (NIH, NSF, USAID, 1992). The National Cooperative Drug Discovery Groups, funded by the National Cancer Institute, provided a structural model for large multi-component projects including public-private partnership. Initial awards were made in 1993 and 1994, and totaled $2.4 million in 1994. Budgetary stresses and personnel changes at USAID resulted in that agency's decision to discontinue funding participation in the program in 1995. However, funding levels were maintained as the other agencies increased their support.

In 1997, after almost four years of effort, the funding agencies asked a small interdisciplinary group of experts to evaluate the progress and utility of the program in the context of the rapidly changing scientific and social environment of drug discovery and biodiversity conservation. The panel strongly endorsed the concept of the program and made a number of specific suggestions for improving it, including broadening the scope of research to include agricultural agents and phytomedicines (Albers-Schonberg et al., 1997). A second competition of the program (NIH, NSF, USDA, 1998) incorporated the advice of the panel and resulted in a second cycle of five-year awards, including three incumbent projects and three new ones (Table 2). The total budget for the ICBG program in 1999 was $3.7 million, including contributions from all collaborating partners. In this second cycle the funding agencies are the NIH, the NSF and the Foreign Agricultural Service (FAS) of the USDA. The program is administered by the Fogarty International Center of the NIH, and the other participating NIH organizations are the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, the National Institute of Mental Health, the National Institute on Drug Abuse, and the National Heart, Lung, and Blood Institute.

OVERVIEW OF ICBG PROJECTS

The eight programs that have been or are currently funded are outlined in Table 2, and each is described in detail in the other papers in this volume by the investigators themselves. Following the requirements in the RFA, each ICBG addresses the three goals outlined above, and specifically must include substantial and novel efforts in natural products drug discovery, biological inventory, research capacity-building, and benefit-sharing. At least one of the Associate Programs (projects) must be based in and led by a developing country organization. In addition to these requirements several other commonalities among the Groups have emerged. All have done at least some work with terrestrial plants (mostly in and from tropical forests), all conduct research in multiple disease areas simultaneously, most have some ethnomedical component to their field efforts, and most include collaboration with at least one industrial partner that finances its own research and development activities.

Beyond these similarities, a diversity of approaches, focuses, and strengths are seen among the eight cooperative groups. Together they encompass researchers from over 35 organizations in 12 countries on four different continents (see Table 2). One project is working entirely in arid and semi-arid landscapes (University of Arizona-Latin America ICBG). One has been focused primarily on arthropods both for inventory and as a source of novel compounds (Cornell-Costa Rica ICBG). The field efforts of two groups (Smithsonian-Panama and Cornell-Costa Rica ICBGs) are driven primarily by ecological cues regarding chemistry. One project has no industrial partner (WRAIR-West Africa Group), in part reflecting its principal focus on parasitic diseases for which there is little industrial interest. Another is working with a relatively small drug discovery company, rather than a major pharmaceutical corporation (University of Georgia-Maya Group). While most have knowledge and interests that overlap, the Group Leaders include three chemists (Kingston, Meinwald, Timmermann), a physician (Schuster), an ecologist (Coley), an anthropologist (Berlin), a plant taxonomist (Soejarto), and an ethnobotanist (Lewis). These specialties reflect only a fraction of the diverse expertise and approaches represented in the projects.

ACTIVITIES AND ACCOMPLISHMENTS

Drug Discovery Research

The primary effort of most groups is the collection, cataloguing and screening of diverse biota for activity against a range of diseases, followed by chemical identification and modification of active agents. Together the groups have collected over 11,000 samples from approximately 5,800 species of plants, 550 insects, and over 500 fungi. The family level diversity of collections has been reasonably high. While 5,800 species of vascular plants is a small fraction of the 320,000 named species (Heywood & Watson, 1995), these collections have sampled over half (see Table 3) of the 386 angiosperm families (Cronquist, 1988). Furthermore, five gymnosperm families, 11 fern families, the occa-

Table 3. Family or order of specimens evaluated by ICBGs.

PLANTS

Dicotyledons (185 families)
Acanthaceae
Actinidiaceae
Aextoxicaceae
Aizoaceae
Alangiaceae
Amaranthaceae
Anacardiaceae
Anisophylleaceae
Annonaceae
Apiaceae
Apocynaceae
Aquifoliaceae
Araliaceae
Aristolochiaceae
Asclepiadaceae
Asteraceae
Balanophoraceae
Balsaminaceae
Basellaceae
Begoniaceae
Berberidaceae
Bignoniaceae
Bixaceae
Bombacaceae
Boraginaceae
Brassicaceae
Brunelliaceae
Buddlejaceae
Buettneriaceae
Burseraceae
Cactaceae
Caesalpiniaceae
Calyceraceae
Campanulaceae
Capparidaceae
Caprifoliaceae
Caricaceae
Caryocaraceae
Caryophyllaceae
Cecropiaceae
Celastraceae
Chenopodiaceae
Chloranthaceae
Chrysobalanaceae
Clethraceae
Clusiaceae
Cochlospermaceae
Combretaceae
Connaraceae
Convolvulaceae
Crassulaceae
Cucurbitaceae
Cunoniaceae
Cyrillaceae
Davalliaceae
Dichapetalaceae
Dilleniaceae
Dipterocarpaceae
Ebenaceae
Elaeagnaceae
Elaeocarpaceae
Ericaceae
Erythroxylaceae
Escalloniaceae
Eucryphiaceae
Euphorbiaceae
Fabaceae
Fagaceae
Flacourtiaceae
Fouquieriaceae
Frankeniaceae
Gentianaceae
Gesneriaceae
Grossulariaceae
Gunneraceae
Guttiferae
Halophytaceae
Haloragidaceae
Hamamelidaceae
Hernandiaceae
Hippocrateaceae
Hoplestigmataceae
Humiriaceae
Hydnoraceae
Hydrangeaceae
Hydrophyllaceae
Hypericaceae
Icacinaceae
Irvingiaceae
Julianiaceae
Krameriaceae
Lamiaceae
Lauraceae
Lecythidaceae
Ledocarpaceae
Leeaceae
Lepidobotryaceae
Linaceae
Loasaceae
Loganiaceae
Loranthaceae
Lythraceae
Magnoliaceae
Malesherbiaceae
Malpighiaceae
Malvaceae
Marcgraviaceae
Martyniaceae
Medusandraceae
Melastomataceae
Meliaceae
Menispermaceae
Menyanthaceae
Mimosaceae
Misodendraceae
Monimiaceae
Moraceae
Myristicaceae
Myrsinaceae
Myrtaceae
Nolanaceae
Nyctaginaceae
Nympheaceae
Ochnaceae
Octoknemataceae
Olacaceae
Oleaceae
Onagraceae
Opiliaceae
Oxalidaceae
Pandaceae
Papaveraceae
Papilionaceae
Passifloraceae
Pedaliaceae
Phytolaccaceae
Piperaceae
Plantaginaceae
Plumbaginaceae
Polemoniaceae
Polygalaceae
Polygonaceae
Portulacaceae
Primulaceae
Proteaceae
Quiinaceae
Ranunculaceae
Rhamnaceae
Rhizophoraceae
Rosaceae
Rubiaceae
Rutaceae
Sabiaceae
Salicaceae
Santalaceae
Sapindaceae
Sapotaceae
Saururaceae
Saxifragaceae
Scrophulariaceae
Scytopetalaceae
Simaroubaceae
Solanaceae
Sonneratiaceae
Staphyleaceae
Sterculiaceae
Symplocaceae
Ternstroemiaceae
Theaceae
Theophrastaceae
Thymeleaceae
Tiliaceae
Trigoniaceae
Tropaeolaceae
Turneraceae
Ulmaceae
Urticaceae
Valerianaceae
Verbenaceae
Violaceae
Vitaceae
Vivianiaceae
Vochysiaceae
Winteraceae
Zygophyllaceae

Monocotyledons (26)
Agavaceae
Alstroemeriaceae
Amaryllidaceae
Araceae
Arecaceae
Bromeliaceae
Cannaceae
Commelinaceae
Costaceae
Cyclanthaceae
Cyperaceae
Dioscoreaceae
Haemadoraceae
Heliconiaceae
Iridaceae
Liliaceae
Marantaceae
Musaceae
Orchidaceae
Palmae
Poaceae
Pontederiaceae
Rapateaceae
Smilacaceae
Stemonaceae
Zingiberaceae

Mosses (1)
Sphagnaceae

Ferns (and fern allies) (11)
Adiantaceae
Cyatheaceae
Equisetaceae
Hymenophyllaceae
Lycopodiaceae
Salviniaceae
Plagiopteridaceae
Polypodiaceae
Schizeaceae
Selaginellaceae
Thelypteridaceae

Gymnosperms (5)
Cupressaceae
Ephedraceae
Gnetaceae
Podocarpaceae
Taxodiaceae

Algae
Cyanophyta

Arthropod orders (25)
Araneae
Blattodea
Coleoptera
Dermaptera
Diptera
Hemiptera
Homoptera
Hymenoptera
Isopoda
Isoptera
Iulida
Lepidoptera
Mantodea
Megaloptera
Odonata
Orthoptera
Neuroptera
Phasmatodea
Phalangida
Opiliones
Polydesmida
Scorpione
Thysanoptera
Trichoptera
Uropygi

Table 4. ICBG therapeutic research areas.

Therapeutic area	Principal investigator/ICBG							
	Berlin Mayan Mexico	Coley Panama	Kingston Suriname/ Madagascar	Lewis Peru	Meinwald Costa Rica	Schuster West Africa	Soejarto Vietnam/ Laos	Timmermann Arid Lands
Bacterial	•	•		•	•	•		•
Diarrhea	•			•				
Viral	•	•	•		•	•		•
Fungal	•		•		•	•		
Inflammation			•	•	•			•
HIV/AIDS	•	•	•			•	•	
Cancer	•	•	•	•	•	•	•	•
Cardiovascular	•		•	•	•			•
Central Nervous System	•		•	•	•	•	•	•
Contraception	•							•
Cryptosporidiosis				•				
Immunology	•		•	•	•			•
Leishmania		•		•		•		
Malaria	•	•	•	•	•	•	•	
Obesity/Diabetes			•	•				•
Osteoporosis								•
Toxoplasma				•				
Trypanosomes		•				•		
Tuberculosis	•			•		•		•
Phytomedicine	•		•			•		
Agricultural – Fungi	•		•			•		•
Agricultural – Insects	•	•	•					•
Agricultural – Nematodes			•					•
Agricultural – Weeds	•		•					•
Animal Health			•					•

Table 5. ICBG principles for the treatment of intellectual property.[a]

Protection of inventions using patents or other legal mechanisms.
Clear designation of the rights and responsibilities of all partners.
Sharing of benefits with the appropriate source country parties.
Disclosure and consent of indigenous or other local stewards.
Information flow that balances proprietary, collaborative and public needs.
Respect for and compliance with relevant national and international laws, conventions and other standards.

[a]For the complete text detailing these principles and suggestions for their implementation see the Request for Applications that structures the program (NIH, NSF, USDA, 1998).

sional alga or moss, and arthropods from 19 orders have also been examined (Table 3).

Each Group works in multiple therapeutic areas (Table 4). Almost all of the Groups have some effort in cancer and in malaria. Cancer is generally a research area for the industrial partners and some academic labs, while malaria research is at present entirely the domain of academic and government labs. Most Groups also target a variety of infectious diseases. Four Groups have some work in agricultural areas, including veterinary medicines and insect, weed, nematode, and fungal pest control, predominantly through the industrial partners. With eight Groups running assays in multiple labs and multiple therapeutic areas, it is estimated that over 200,000 assays have been run over the six-year life span of the project. The largest portion of these represent mechanism-based assays in high-throughput systems carried out by the industrial partners.

At least 260 compounds of interest have been isolated over the past six years. Of these, approximately 50 are novel. While compounds have been studied in animal models in at least six therapeutic areas, none to date has reached clinical trials. Approximately 25 compounds are considered active leads. These are mostly compounds with anti-infective, anti-parasitic, and anti-cancer properties. Currently, the most promising of these leads are in analog development programs for potential as malaria, leishmaniasis, tuberculosis, and crop protection agents.

Beyond identifying new and potentially useful compounds, the projects have contributed to the science of natural products collection, extraction, isolation and analysis. The papers in this volume describe a diversity of approaches that are tailored to the particular circumstances of the habitats, organisms and interests and capacities of the organizations involved. The Latin America ICBG has identified useful compounds from a

little known source, floral pollen (Valcic et al., 1998). The Costa Rica ICBG has identified a number of important lessons relating to the collection and chemical analysis of arthropods (Sittenfeld et al., 2000). The ICBGs have also made important contributions to major reference works on ethnomedicine and chemistry (see for example Lewis et al., 1998).

Research Capacity Building

Training and the installation of technology, including equipment and assays, represent a significant investment of ICBG efforts. Since 1993, over 1400 individuals from 12 countries have received formal training through the program. Over 90 percent of these trainees represent developing country participants. They include Bachelor's, Master's, doctoral students and post-doctoral fellows, as well as technicians, non-scientific community residents, and others. Approximately 80 of the trainees have been enrolled in long-term degree-earning programs. The vast majority of others have participated in short-term training efforts such as workshops (1–7 days) and limited duration visits (3 weeks to 6 months) to participating laboratories.

Training topics include almost every aspect of ICBG drug discovery work, including plant collection and drying in the field, extraction, testing, compound isolation, identification and modification, database development and maintenance, use of Geographic Information Systems, contract development, and understanding of intellectual property rights. Numerous training events have also focused on other elements of ICBG work, including conservation and restoration, pollination biology, cell and tissue culture, taxonomy, ethnobotany, plant anatomy, agroecology, curatorial methods, grassroots community organization, and commercial production of medicinal plants.

Associated with training and research efforts, a substantial amount of equipment and infrastructure enhancement for both U.S. and developing country institutions is carried out by the Groups. Through the ICBGs and their industrial collaborators, developing country scientific organizations have received items such as updated computers and software, Geographic Positioning Systems, HPLC equipment, rotovaporators, fume hoods, vehicles, microscopes, bar code readers, herbarium cabinets, greenhouse supplies, laboratory glassware and safety equipment. Participating community organizations also receive other simple but important contributions such as water tanks, fencing for gardens, shade cloth, boats, refrigerators, building enhancements or travel finance.

Conservation and Economic Development

Several types of ICBG activities promote conservation and development. They include training personnel and research capacity enhancement at host country institutions, scientific research in support of biodiversity management, in-situ and ex-situ conservation projects, environmental education, and policy analysis. These are described below.

1) The capacity-building efforts have been characterized above. With better trained and equipped staff, as well as experience with non-destructive uses of biodiversity, developing country institutions involved in natural resource management will be better prepared to make informed decisions on important and pressing concerns such as logging or mining concessions or agricultural development projects. For example, the Suriname ICBG, through the Missouri Botanical Garden and Conservation International, has enhanced the facilities for preserving plant specimens and managing data at the National Herbarium as well as the associated technical skills of both Herbarium staff and the National Forest Service. Increased capacity to identify and monitor regions of high biodiversity will help these and other Surinamese institutions assess the advisability and nature of commercial logging concessions that are under consideration by the government (Kingston et al., 2000).
2) Conservation is also advanced through scientific investigation that directly provides taxonomic, ecological and economic data that are useful in managing natural resources. Here we describe a few illustrative examples among the many supported by the ICBG program. The forest dynamics and inventory plots of the West Africa ICBG in Cameroon (Schuster et al., 2000) provide information that will be useful in assessing long-term trends of reproduction and survivorship in tropical forests under threat. Studies that yield understanding of the patterns of feeding, distribution and migration of butterflies and other insects help us to identify areas and periods of high diversity for collection, and to project the impacts of development programs in a given site (Lamas, 1997; Janzen & Gauld, 1997). Studies of morphological and anatomical predictors of plant tolerance to tissue harvesting (see for example Montenegro et al., 1999) are useful to sustainable collections of medicinal plants. Socio-economic assessment of the value of biodiversity for local medicines and other non-timber forest products (West Africa ICBG,

Suriname-Madagascar ICBG) can provide important information for local and national decisions regarding natural resource use.

3) Ex-situ conservation in botanical gardens and seed banks will be an increasingly important resource for conservation as natural habitats are destroyed by development and other processes. Most of the ICBGs have made significant contributions to these efforts in established host country institutions, such as the Botanical Garden of the National University of Mexico as well as U.S. institutions, and several have started smaller medicinal plant gardens in communities, parks, and at universities.
4) The ICBG is, in part, an integrated conservation and development program (ICDP) (Alpert, 1995). That is, conservation of biodiversity is an expected outcome of development efforts that create an opportunity, means, and incentive to change patterns of resource use. In this framework, conservation-promoting activities are those that build scientific, commercial, and legal capacity, those that educate resource users and regulators about the alternatives to unsustainable practices, and finally, those that provide financial or other benefits to stakeholders in ways that may influence relevant behavior. Financial benefits that are relevant are all those that are a result of the project, including near-term compensation, milestones or royalties that may come from commercial partners in relation to research activities and any commercial products that emerge. Due to the research focus of the ICBG program, local commercial use of biodiversity that generates significant near term income for local populations has been a more limited feature of the program to date than classic ICDPs usually promote. However, most of the Groups are supporting projects such as development of traditional woodcraft enterprises (Suriname), propagation of ornamental plants (Mayan Mexico), and propagation of plants for widely sold herbal remedies (West Africa, Vietnam, Mexico, Peru). Almost all of the projects have provided income to community members as compensation for their time and skill expended as participants in the research and training efforts of the projects.

As the expected outcome of the integrated conservation and development approach is a shift in attitude and behavior by landowners, policy makers, and others who affect natural resource use, it is often difficult to tie specific events that occur on a national or regional level to the efforts of any individual project. However, one important example of this 'incentive/example' effect on conservation is the role of the Suriname ICBG in the recent establishment of the Central Suriname Reserve, a four million acre preserve of interior rainforest (Kingston et al., 2000).

5) All of the above-described contributions to conservation require dissemination of findings and outreach to other scientists, governments, and communities to be effective. All of the Groups have made numerous presentations and publications on the 'process' elements of their programs including partnership structures (see for example Kingston et al., 1999; Timmermann, 1997) and contractual arrangements (Iwu, 1996; Iwu & Laird, 1995), and the potential for economic use of preserved landscapes (Janzen, 1999). Outreach efforts such as environmental education are in themselves important means of advancing conservation. Several of the projects as well as the government funding agencies have held international conferences related to sustainable use of biodiversity and bioprospecting (see for example Timmermann & Montenegro, 1997; Iwu et al., 1997; Grifo & Rosenthal, 1997). Perhaps the most important long-term investment is education of grade school children upon whom future decisions regarding resource use will depend. The Costa Rica, Arid Lands, Panama and Mayan Mexico, ICBGs have been very active with children and youth groups in this regard.

U.N. Convention on Biological Diversity

The United Nations Convention on Biological Diversity (CBD) emerged from the same ferment of ideas, programs, and policy actions in the early part of the 1990's that gave rise to the ICBG. The CBD was launched in Rio de Janeiro in 1992; it entered into force the following year, and currently there are 176 parties to the treaty (for more information and list of parties see *http://www.biodiv.org/conv/background.html*). The United States became a signatory to the CBD under President Clinton in 1993, but the U.S. Senate has yet to ratify it. The treaty has radically and permanently altered the political landscape for access to sources of natural products for drug discovery (Gollin, 1999). The CBD states that national governments have authority to determine access to their genetic resources, and calls on governments to provide for conservation, sustainable use and equitable sharing of the benefits from commercial use of those resources.

Unfortunately, despite the profound conceptual shift in treatment of genetic resources that the CBD signifies, the treaty provides little guidance to governments or private organizations on how to implement this new paradigm. Elaboration of a model system to implement access and benefit-sharing policies has been elusive, even seven years after the treaty entered into force. In part, this is due to the complexity of the scientific, legal and commercial elements of the model. To make matters worse, suspicion, resentment, and misunderstanding, fueled by colonial history and the politics of trade and intellectual property rights, have frequently brought discussion of the issues to a standoff in both multilateral and project-specific fora.

The ICBG program has had both the privilege and challenge of being one of the first large-scale and coordinated efforts to implement the access and benefit-sharing objectives of the CBD in specific projects. The Groups have generally had to develop their access and benefit-sharing policies and agreements in the complete absence of any regulatory guidance beyond the general framework of the CBD (Macilwain, 1998) and the principles of the ICBG program (originally outlined in Schweitzer et al., 1991 and further developed in NIH, 1998). Because of the relative success the ICBG program has had in this challenging environment, the program and the specific projects discussed in this volume have frequently been examined in the context of treaty proceedings as a model for the balancing act that the CBD creates.

Due to the congruence of the philosophy of the ICBG program with the principles of the CBD, people frequently ask about the relationship of the program to the treaty. In particular, individuals from developing countries find it difficult to understand how the U.S. Government can fund such a program when it is not a party to the Convention. The simplest response is that few people in the U.S. Government disagree with the objectives of the CBD – conservation, sustainable use, and equitable sharing of benefits. Ratification of the treaty by the U.S. Senate has been held up by concerns among some members of that body regarding how these important objectives may be implemented in the U.N. process. The ICBG program is a research and development effort, separate from the political treaty process, that approaches this trio of objectives in a practical manner that promotes scientific growth and is compatible with existing legal frameworks, including the CBD, the Trade Related Intellectual Property Rights agreement (TRIPS) and contract law.

Many countries, including Mexico, Argentina, Chile, Peru, and Suriname, have treated the ICBGs as testing grounds for their developing policies on access and benefit-sharing for genetic resources. While this has occasionally produced frustration for the investigators and has been a significant rate-limiting factor in some projects, overall we consider it to be a positive role for the program. We believe that the projects have offered concrete experiences for governments and a variety of resulting lessons. Some examples of these lessons, as we interpret them, include: 1) while business and legal issues are ever-present, bioprospecting is essentially a research process and will function best when treated in that context; 2) "one size fits all" approaches are impractical, and elaborate and inflexible access regulations in this diverse and changing field may hurt the interests of both providers and users of genetic materials; 3) a diversity of benefits may be available through such collaborations, and while biodiversity is of global value, monetary benefits from any specific project may be unpredictable.

In summary, in the first six years of the program, the ICBGs have: 1) discovered numerous bioactive compounds, some of which are leads of significant continuing interest; 2) enhanced the technical capacity of over a thousand developing country participants and their associated institutions; 3) contributed to the scientific and policy process of conservation; 4) provided important models for governments and other organizations for collaborative research that supports multiple objectives, including those of the Convention on Biological Diversity.

This last accomplishment is perhaps the single most significant contribution of the program to date. The ICBG has pioneered the development of models for non-traditional international partnerships of universities, companies, and government and community organizations. It has shown that such organizations may work collaboratively to achieve their own objectives and contribute to larger goals. Over the last several years the funding agencies have received hundreds of queries and requests for guidance in this area from governments, universities, companies, multi-lateral banks, foundations, conservation organizations, and others. The investigators have undoubtedly received many as well. From the standpoint of the funding agencies, it has also provided a model for collaboration on complementary goals that could not be supported by one agency alone. The demand for ways to achieve the integration of goals that the ICBG represents is huge, while the examples of such integration are very few.

The projects have received much attention for the intellectual property and benefit-sharing aspects of

their collaborations. While very important and significant accomplishments, these formal agreements are only a part of very complex set of professional relationships that govern the operations of these non-traditional collaborations. The papers in this volume provide more information on the other aspects of program design and operation. Strong leadership and a great deal of patience and trust among participants are required to sort out issues of sharing data, sharing samples, publishing results, distributing financial and research resources, as well as planning research and development activities.

Even in the relatively narrow context of biomedical research needs, it is critical that we do not underestimate the value of this product of the program – models for collaboration. Drug discovery from natural products, as well as a wide range of biomedical research topics on physiology, genetics, and behavior depend on access to tens of thousands of different organisms that may occur in very isolated places around the world. Beyond plants, access to diverse populations of biomedical study organisms, including sulfur bacteria, endophytic fungi, nematodes, grasshoppers, coral reef sponges, sea cucumbers, dolphins and chimpanzees, to name a few, is increasingly threatened not only by the rapid disappearance of these organisms, but also by changing attitudes and suspicions about their use. The research community needs to demonstrate that this work can be done in a flexible and accommodating manner that recognizes the environmental and socioeconomic context in which these organisms exist, or we will lose access to them in the near term through politics, and eventually to extinction. It is in recognition of this imperative that some commentators have pointed to the ICBG program as one of the best opportunities to find a constructive path toward resolution of the apparently opposing points-of-view associated with prospecting for drugs and crop protection agents in biodiversity-rich developing countries (Nature, 1998).

SOME LESSONS LEARNED

The combined efforts of a diverse group of investigators and their collaborators over the past six years have yielded a number of valuable lessons, as seen from the perspective of the funding agencies. Some of these lessons have been discussed elsewhere (see Baker et al., 1995; Schweitzer et al., 1991; Grifo, 1996; Grifo & Downes, 1996; Rosenthal, 1997a,b). Below we summarize some observations that have not received substantial discussion in other ICBG publications. These relate to research productivity, sharing of data, the role of plants and ethnomedical knowledge, expectations of benefits, and patents associated with biodiversity and traditional knowledge.

Research Productivity

One of the central hypotheses of the ICBG experiment is that combining the diverse goals of pharmaceutical and agricultural research, economic development and biodiversity conservation will lead to synergistic outcomes. It is indisputable that attempting to carry out the high-risk (low probability) research of drug discovery is slowed down by multiplying demands on the research budget and process. As with almost any broadly interdisciplinary program in its early to mid-term stage, the achievements in any component are less than they might be if the entire project were to concentrate on that one area. This reality occasionally frustrates the supporters of one objective or another of the program.

However, the sum total of the program's efforts across the full range of objectives may already be much greater than that attainable by separate efforts. For example, expeditions for field collections in bulk for drug discovery typically require different equipment, scheduling and other logistical elements than those ideally employed for expeditions focused on biological inventory. Hence, several Groups have found that these are best accomplished in temporally separated efforts. However, within one Group's activities, each type of expedition informs the other regarding locations, field conditions, and unusual species clusters. The combination of two related, but different types of expeditions may often lead to higher quality and more efficient work for both. Similar observations have been made about chemistry and bioassay research in relation to careful inventory and taxonomic research.

Of course, a long-term synergy we hope to see is in the relationship between increased scientific and economic capacity, new incentives for conservation, and the long-term availability of diverse natural sources of bioactive molecules for health and agricultural applications. We hope that assessing the productivity of the ICBGs at that level will be tractable a few years from now.

Data-Sharing

Sharing research results among these non-traditional partners is crucial to successful work, yet it has been a greater challenge than many may have predicted. Companies are typically concerned that their competitive

edge will be compromised if proprietary bioassays and related methodology, as well as the nature of any specific leads or the financial terms of an agreement, are shared readily with parties peripheral to this work. Furthermore, the unfamiliar objectives and conduct of conservationists, indigenous groups, and others raises concerns that their needs for secrecy will not be respected.

Similarly, host country governments and communities frequently would like to have withheld identities and localities of species being collected, not only from non-participants, but also from the collaborating companies, in order to maintain their control over sources of the natural products. Furthermore, conservation interests are potentially compromised by publishing data on valuable species. For instance, there is concern that making information widely available on the biological activity of a given species will stimulate unauthorized and unsustainable harvesting.

Lastly, there are concerns that returning in vitro results on bioactivity of plant species to communities without accompanying clinical data on safety may lead to changes in traditional uses of the plants in ways that could compromise the health of local peoples. Given the current growth in use of botanical remedies, these last two issues, overharvesting and healthcare applications, are not trivial concerns. Despite these concerns, it is increasingly clear to the ICBGs that without free flow of information among the partners the complementarity of their efforts is greatly reduced. Each Group has struggled to overcome these barriers to communication and each has chosen to tackle the issues on a case by case basis. Many of the barriers based on suspicion are overcome as partners begin to know and trust each other and learn more about how the information is used, how it is maintained, and by whom.

The Role of Ethnomedical Knowledge

The linkage of research efforts to community development in the ICBG program concept has resulted in a predominant focus on terrestrial plants and a high profile role of indigenous ethnomedical knowledge. The use of ethnomedical information has been varied, as has the relative productivity of the leads it has provided (see Kingston et al., 2000; Lewis et al., 2000; Schuster et al., 2000). One early lesson is that while such information is of interest to most academic and industrial drug discovery scientists, it is difficult to effectively integrate ethnomedical knowledge into the large-scale high-throughput systems commonly used by the industrial partners. In part, this is due to the requirement of industrial systems to quickly identify pharmacologically pure compounds with high levels of very specific targeted biological activity. Traditional knowledge may be more often useful in academic environments, government labs and with companies that have flexible systems that can be easily customized to take advantage of the information (Rosenthal & Callahan, in preparation).

Heightened Expectations and Financial Benefits

The paradox of bioprospecting is that successful translation of research efforts into conservation incentives is based, in part, on enhancing the perception among policy makers and resource owners and users of the value of biodiversity. However, unrealistic expectations are difficult to avoid and are frequently a barrier to implementation. In order to balance this paradox, most ICBGs attempt to be very clear with host country collaborators and regulators about the low probability of major pharmaceutical drugs emerging from any one project, but do everything they can to provide tangible near term benefits of the sort described above and elsewhere (Reid et al., 1993; Iwu, 1996; Rosenthal, 1997a) to host country organizations and communities.

Patents, Biodiversity, and Traditional Knowledge

In the current legal and commercial environment, patents on natural product derivatives are basic to the research and development paradigm of private companies and thus essential to the development of most pharmaceutical and agricultural products. Without legal protection for 'inventions', companies typically will not make the multi-million dollar investment required to bring a derivative to late development, clinical trials, and ultimately to market (ten Kate & Laird, 1999; Artuso, 1997). However, advances in biotechnology and their commercial applications have raised a variety of difficult issues, including the morality of patents relating to life-forms and the lack of legal protection for biodiversity and traditional knowledge that may contribute to an invention. Controversy around the nature and role of patents grows from a number of sources. There are genuine philosophical objections to granting monopolies on the uses and products of biodiversity by some. Similarly, there are concerns that the scope of biotechnology patents is expanding with potentially negative impacts such as the hindering of future research. Others argue that there is an unjust imbalance between the expansive patent rights available for biotechnological inventions and the lack of incentives available to those conserving biodiversity and associated traditional knowledge that may serve as an important resource enabling those inventions. At the same time, some of the

controversy reflects confusion regarding what rights patents actually confer. Concerns about the relationship of Intellectual Property Rights to biodiversity and traditional knowledge are much broader than that directly relevant to the ICBGs. It is beyond the scope of this paper to provide in depth analysis on the subject. Rather, we attempt here to identify the general approach the ICBG program has taken and a couple of the lessons that have emerged from this approach.

The ICBGs have attempted to balance the critical role of patents in drug development with the need to protect the rights of host country organizations, communities and individuals using an explicit set of principles for conduct of research and development of contractual agreements among the parties in a Group. These principles are detailed in the Request for Applications of the program (NIH, NSF, USDA, 1998) and briefly enumerated in Table 5. Each ICBG implements these principles regarding intellectual property, informed consent and benefit sharing in the manner most appropriate to the nature of their collaboration and the legal and social environment in which they work.

While the legal and philosophical discussion around 'patenting life' (see for example Wagner, 1987) is an important backdrop to many of the issues in this area, patenting an actual organism has not occurred as a result of ICBG partnerships to date, and is unlikely to be a significant element in the future. In the context of natural products research for discovery of pharmaceuticals and crop protection agents, patents on living organisms are relatively uncommon. More commonly, patents are related to the technological advances embodied in the isolation and modification of useful chemical derivatives and analogs of compounds originally isolated from a plant, animal, or microorganism for specific identified uses. In fact, a *naturally-occurring* organism cannot itself be legally patented in the United States (35 U.S. Code § 101). This distinction has sometimes been reassuring to ICBG project participants and observers who have philosophical concerns about patents relating to living organisms. However, researchers should be conscious of the fact that the distinction between owning the rights to an intellectual advance derived from the study of an organism, and owning the rights to an organism itself (Wagner, 1987; Gollin, 1994) is a relatively nuanced one that may often be unsatisfying to non-specialists or those who have broad moral objections in this area.

A more common concern for the ICBGs has been the view that patents on technological advances derived from the study of biological organisms represent unfair expropriation of the rights of source countries and communities (Shiva, 1997). The basis for this view is the belief that the existing Intellectual Property Rights system is inherently biased against less technologically advanced societies, affording little opportunity to protect their contributions of biodiversity and traditional knowledge to patented inventions (Posey & Dutfield, 1996). It is, in part, to provide for and define this protection that the ICBGs and other modern bioprospecting ventures have relied on contractual agreements, frequently referred to Access and Benefit-sharing Agreements. These agreements typically define, among other things, the objectives of the partnership, terms of material transfer, the rights and responsibilities of the collaborating organizations, and the types and amounts of benefits to be shared. For further discussion of these agreements see the other chapters in this volume and Rosenthal (1997a). The ICBG agreements, while imperfect documents, have become important models for what can be achieved to meet the needs of host countries and communities in an international partnership.

Perhaps even more complex than the rights over biological materials and their products is the contribution of traditional knowledge to the invention process. Significant anxiety exists among traditional peoples and others that, even when benefits are defined, patents relating to such knowledge may rob these people of credit for their innovations and infringe on their ability to carry out traditional practices and make innovations based on that knowledge. The ICBGs have attempted to formally recognize the value of this knowledge, protect the rights of the providers, and compensate them for the use of the information. The policy of the ICBG program is that when traditional ethnomedical knowledge is involved in a patentable invention, if the traditional knowledge provider cannot be recognized as an inventor, the contribution should be treated as valuable 'know how' and the contribution should be credited in any related publications and in the patent as prior art, and the providers should be compensated for their contributions, as appropriate. Prior art citations formalize the contribution of such knowledge but do not claim any monopoly rights to its use. The absence of important prior art citations may constitute grounds to deny or invalidate a patent.

ICBG experiences have shown that the possibility of patents on new derivative products emerging from a research effort is not generally a significant barrier to development of a partnership. In discussions with host country organizations and traditional peoples, it is critical to clarify that it is unlikely that such patents will either infringe upon or affirm their own rights to use

their tangible and intangible resources in both traditional and in truly innovative ways. Recent U.S. Patent Office rulings on patents on Turmeric (Gollin, 1999) and Ayahuasca (Wiser, 1999; Science, 1999) provide relevant evidence that patent claims that are not truly novel can be overturned, although it can be difficult and expensive to identify and challenge such patents. Anxiety over the implications of patents is frequently diminished once this is understood, and once the importance of legal protection of inventions for the drug development process is communicated. At the same time, protecting local rights to use of components of biodiversity or traditional knowledge remains an important and valid concern. It may often be necessary to develop specific language in a contractual agreement that guarantees such rights and defines potential boundaries for commercial and other uses of these resources. In addition to defining compensation for use of the information, it may be important to outline commitments by academic and commercial partners to avoid legal or commercial practices that would interfere with local practices and innovations related to the knowledge that is shared. All of the ICBGs that utilize ethnomedicinal knowledge provide for compensation to providers. In one Group (Peru ICBG) a specific Know-How License was negotiated between the collaborating indigenous groups and the commercial partner to address a number of such issues (Lewis et al., 2000).

FUTURE OUTLOOK

There continues to be great interest in bioprospecting from the academic, industrial, and conservation communities, as well as the general public, and there have been significant results in the ICBG program to date. However, it is still too early to say how much bioprospecting can contribute to conservation and economic development, and whether the ICBG approach is the best one to integrate drug discovery, economic development and biodiversity conservation. Bioprospecting is fundamentally tied to scientific interest and commercial success of natural product derivatives. In the rapidly changing and complex world of drug discovery, the perceived value of natural products seems to wax and wane every few years with the entrance of a new technology and the time since a major new natural product drug has hit the market. Combinatorial chemistry is the latest perceived replacement for natural products (Service, 1996; Service, 1999). However, the very limited number of important leads that combinatorial chemistry has provided to date (Lahana, 1999) has led some scientists and organizations to seek means of integrating this technology and rational drug design with natural products leads in order to gain the best results (see for example Nicolaou et al., 1998).

Bioprospecting ventures have had ups and downs recently. The high profile efforts of Shaman Pharmaceuticals took a significant downturn this past year as the company abandoned pharmaceutical development to pursue marketing of botanicals. This took place when, contrary to the expectations of Shaman scientists and management, the FDA ruled that the number of patients in the phase III trials of their anti-viral agent SP-303 had to be doubled after the first 400 cases were reviewed (S. King, pers. comm.). This turn of events was viewed by some (The Economist, 1999), probably unfairly, as a statement on the value of natural products and ethnomedical knowledge for drug discovery today. Providing some evidence to the contrary, Glaxo Wellcome recently signed a major agreement with a Brazilian company, Extracta, to receive a wide variety of plant, animal, and microorganism samples for screening, some with ethnomedical knowledge (Bonalume Neto & Dickson, 1999).

The rise of botanical dietary supplements in the marketplace and the growing recognition of their continuing importance for healthcare in developing countries have contributed greatly to interest in biodiversity as a source of healthcare products. In recognition of the potential economic and health care benefits botanicals may offer to developing countries, several ICBGs (Africa, Mayan Mexico, Suriname-Madagascar Groups) have chosen to pursue work in this area and others are evaluating the possibility.

While plants are the major focus of the current ICBGs, fungal, bacterial, and algal microorganisms are a growing interest of several current Groups. Unfortunately, these organisms raise even greater anxiety among source country governments because they are frequently collected, transported, and maintained in living culture that can be replicated. Many governments view the need to return to the source for more material for development, as is frequently the case with plant-derived natural products, as an important control point for access.

Another potentially important source of novel bioactive molecules lies in marine and coastal biodiversity, such as that found in coral reefs. These are of great interest scientifically and are high priorities for conservation. However, no projects on these resources have competed successfully for ICBG funding to date. Both marine

organisms and terrestrial microorganisms would be a likely interest in any future competitions of the program.

The high risk efforts of drug discovery are the anchor for the ICBG program design. However, the development of an important drug may not be the ultimate benchmark of success for this multi-faceted program. For example, improved understanding of potential therapeutic mechanisms, establishment of associated conservation reserves, enhancement of scientific and economic capacity of developing country research organizations, and development of models of productive, equitable partnerships in international research are also important outcomes. To date, we at the funding agencies are very pleased with the progress of the program and look forward with great anticipation to future developments and the continuing evolution of the ICBG experiment.

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