Biodiscovery Research in Panama: Linking Science, Technology, Human Health, and Conservation in the Host-Country Context

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In the context of searching for treatments for human disease from biological sources, 'bioprospecting' is generally associated with the process of exporting raw materials from a host country to an industrialized country where the subsequent steps of the drug-discovery process are carried out (Reid et al. 1993). Most of the literature on the subject, whether from a legal (Cabrera-Medaglia 2004a, 2004b), economic (Simpson et al. 1996, Vogel 1997), or general perspective (Reid et al. 1993, ten Kate and Laird 1999) envisions that the primary role of the host country is to provide to their partners from industrialized countries the necessary raw materials for drug-discovery research. In this model, biodiversity is essentially regarded as a commodity and the literature is dominated by the themes of access and benefit sharing (ABS).

In reality, contemporary natural products-based drug discovery is a research-driven process that is better described by the term 'biodiscovery'. There is a significant gap between a commodity such as an uncharacterized crude plant extract, usually with no commercial value or intellectual input, and a purified and characterized natural product with activity against an important disease, which can be universally recognized as intellectual property (IP), and in some cases, can be extremely valuable (Artuso 1997). The absence of any clear value for uncharacterized biological materials is in part responsible for the divergent views on what constitutes fair and equitable sharing of benefits, despite the fact that the Convention on Biological Diversity (CBD) was opened for signature in 1992 and the Global Environment Fund, the CBD's financial mechanism, had allocated a staggering US$3.86 billion to biodiversity in developing countries as of 2002 (ten Kate 2002). Regarding biodiversity as a commodity also overlooks or minimizes the fact that the drug-discovery process creates many opportunities for the substantial involvement of the host country and, with those opportunities, numerous benefits, as described below (Capson et al. 1996, Artuso 2002, Coley et al. 2003).

The International Cooperative Biodiversity Groups Program: A Unique Model for Natural Products-Based Drug Discovery

The International Cooperative Biodiversity Groups (ICBG) Program is a unique effort that addresses the interdependent issues of drug discovery, biodiversity conservation, and sustainable economic growth. The ICBG represents a novel experimental program that is one of the first large-scale attempts to design and execute such a multi-disciplinary approach to drug discovery (Rosenthal 1997, Rosenthal et al. 1999). Funding for the program is currently provided by the USA government's National Institutes of Health (NIH), the Biological Sciences Directorate of the National Science Foundation, and the Foreign Agriculture Service of the United States Department of Agriculture. The cooperating NIH components are the Fogarty International Center (FIC), the National Cancer Institute (NCI), 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 (Fogarty International Center 2006). The first awards were made in 1993, with new competitions in 1998, 2003, and 2005. There are currently seven active awards, including the Panama ICBG, which is described in this chapter.

Biodiscovery Research in a Post-CBD World: Circumstances That Influenced the Design of the Panama ICBG and its Contractual Arrangements

An Overview of the Drug-Discovery and Development Process

The stages in the use of natural products in the drug-discovery process have been explained in detail elsewhere (ten Kate and Laird 1999). For the purposes of the current discussion I will summarize three of those stages: (i) the collection of biological materials; (ii) the purification and characterization of the chemical compounds responsible for the biological activity of interest; and (iii) the development of promising candidates for the treatment of disease.

Collecting of Biological Materials

A variety of strategies have been employed for the collection of biological materials for drug discovery (ten Kate and Laird 1999). The random screening of plants, microorganisms, and marine biota sponsored by the NCI has led to the discovery of important agents for treating cancer (Hallock and Cragg 2003, Simmons et al. 2005). The use of traditional knowledge to guide collections for drug discovery has been the subject of a vast quantity of literature (see, for

example, Laird 2002, Ruiz et al. 2004). While successful in some cases (Cox 2001), it has generated enormous controversy in others (Dalton 2001, Larson-Guerra et al. 2004). Another collecting strategy relies on the use of ecological criteria for both marine (Paul and Puglisi 2004) and terrestrial collections (Coley et al. 2003) as described below for the Panama ICBG.

Bioassay-Guided Fractionation and the Isolation and Characterization of Compounds

Crude extracts, from both marine and terrestrial sources, are often subjected to a technique known as pre-fractionation, a preliminary purification procedure that increases the concentrations of active compounds and which removes the 'nuisance' compounds that sometimes provide false positives in biological assays (Abel et al. 2002). The partially purified fractions are then tested in biological assays in order to detect activity against the disease or pathogen of interest in an iterative process between the chemists carrying out the purification and the scientists that carry out the biological assays. The discrete chemical compounds derived from biological sources, referred to by chemists as 'natural products', are usually isolated and characterized in the laboratories of academic or pharmaceutical collaborators in industrialized countries. Ideally, the compounds isolated are novel chemical structures, not previously reported in the scientific literature. Academic biodiscovery programs in industrialized countries routinely reach this stage and receive government funding to support their research.[1]

This is a crucial step in the drug-discovery process because it results in the production of an entity that can be recognized as IP (Gollin 1994). While not inexpensive, the procedures for obtaining patent protection under these circumstances are well established (Gollin 2005).[2] If the chemical substance is patented, academic researchers are typically listed as inventors. The institution that owns the IP, for example, the inventor's employer, may choose to negotiate a licensing arrangement with a pharmaceutical partner. In some cases, when a compound of interest is isolated in collaboration between a pharmaceutical company and an academic partner, the share of the financial payments that the academic partner receives will depend upon their degree of involvement in the development of the invention. In any case, the academic partner, whether based in an industrialized or a developing country, benefits by playing a more significant role in the drug-discovery process. The pharmaceutical partner benefits by receiving a compound that is characterized chemically and with known biological properties.

Development of Promising Candidates for the Treatment of Disease

The preceding discussion focused on the discovery of candidates for the treatment of human disease. If a suitable candidate is discovered that meets the appropriate criteria for potency and selectivity, the purification is usually scaled up to afford larger quantities of the natural product and studies are often carried out in order to determine the relationship between structural elements of the compound and its biological activity (Koehn and Carter 2005). In some cases, a natural product may not require additional modification in order to be a clinically useful drug, as in the case of artemisinin, which is discussed below. In most cases, however, natural products are subjected to structural modification in order to increase potency and specificity or to develop analogs that are structurally less complex and more easily synthesized in the laboratory. The subsequent steps of preclinical and clinical evaluation are lengthy and expensive (The Economist 2005). The development of promising lead compounds is beyond the scope of traditional ICBG-supported research, but is nonetheless a highly desirable outcome for promising candidates that are discovered through the program.

Tracking of Samples Made Available for Biodiscovery Research

Arguments are occasionally made for the greater application of techniques such as chemotaxonomy or DNA fingerprinting in order to facilitate the tracking of samples that are made available for biodiscovery research and to ensure compliance by the users of those biological materials. These molecular and chemical techniques are routinely employed to establish taxonomic relationships between organisms (Thacker and Paul 2004). However, such techniques would add significantly to the costs of biodiscovery research in terms of labor, time, and money. Any successful drug-discovery initiative, whether commercial or nonprofit in nature, must screen significant numbers of extracts, fractions, and compounds in order to find a promising lead. It is essential to minimize time, costs, and labor invested in unsuccessful candidates in order to focus those resources on successful candidates. The application of techniques such as chemotaxonomy or DNA fingerprinting on samples entering into the drug-discovery process would have the effect of increasing the effort and expense invested in all extracts and compounds, the vast majority of which will not have useful properties for drug discovery. These issues are particularly important for nonprofit drug-discovery research for neglected diseases, where the absence of profit-generating medicines requires that the costs of

research be minimized. The overall effect would be to make natural products-based drug discovery less attractive than other techniques for treating disease.

The Benefits to the Host Country from Actively Participating in the Drug-Discovery Process

The importance of natural products for the treatment of diseases of both developing and industrialized countries, combined with the labor- and research-intensive nature of the drug-discovery process, creates opportunities for a more substantive involvement of the host-country partners in biodiscovery research. Instead of focusing primarily on the economic issues associated with drug discovery, such as milestone payments and royalties, all of which are highly uncertain (ten Kate and Laird 1999), more likely benefits include the strengthening of research programs for biodiscovery research in the host country. Economic models have been published that suggest that the value of biodiversity as a potential resource for 'biodiversity prospecting' is vanishingly small (Simpson et al. 1996, Craft and Simpson 2001). The underlying assumption in these models is that the value of a 'marginal' species is based upon its worth to pharmaceutical researchers. Their models assume that the role of the host country is limited to exporting unprocessed materials to industrialized partners. In reality, multinational pharmaceutical companies are generally not interested in paying for crude biological samples and are far more likely look to external sources for promising, well-characterized lead compounds. Therefore, unprocessed biological samples have no 'economic' value, marginal or otherwise, since there is no significant market.[3]

As discussed in detail below, the Panama ICBG provides an example in which the host country has benefited from investments in scientific infrastructure, the creation of research programs, the training of scientists, and the development of drug-discovery programs for diseases of importance to the host country. The combined investments of the Panama ICBG and the host-country government have resulted in high-quality scientific publications and IP whose authors are primarily Panamanian. While not all developing countries that wish to participate in international biodiscovery programs have circumstances that permit them to contribute to the drug-discovery process to the same degree as the host-country researchers in Panama, they can still benefit by participating in biodiscovery research. The following Papua New Guinea case study provides an informative contrast.

Case Study: The University of British Columbia and Papua New Guinea and the Development of the Hemiasterlins

The NCI's National Cooperative Drug Discovery Group (NCDDG) program, established in 1983, supports broad, multi-disciplinary approaches to the discovery of new, synthetic, or natural product-based anticancer drugs (see the chapter by Newman et al. in this volume, Hallock and Cragg 2003, Simmons et al. 2005). The hemiasterlins, sponge-derived tripeptides that inhibit cell growth by destabilizing microtubules (Andersen et al. 1997, Mitra and Sept 2004), were isolated as part of an NCDDG collaboration in Papua New Guinea by Raymond Andersen of the University of British Columbia (UBC), the project leader, working in a program led by Chris Ireland of the University of Utah. The entry of the hemiasterlins into clinical trials (Hallock and Cragg 2003) has resulted in milestone payments and a flow of revenues to Papua New Guinea that have been utilized to train students and enhance scientific infrastructure for biological research in the country. Ten laboratories have been built and renovated and stocked with equipment such as grinders, pH meters, balances, cabinets, and incubators. A fraction of the revenue is used to support graduate programs while another fraction supports a trust fund. One student is currently pursuing Ph.D. studies in Raymond Andersen's laboratory at UBC (T. Matainaho, pers. comm., 5 August 2005). The agreement negotiated between UBC and the government of Papua New Guinea called for the following division of revenues: one-third to the country of origin, one-third to the academic institutions involved, and one-third to the inventors. The one-third share to the institutions is further allocated according to the location of the inventors. Under such a scenario of equal numbers of inventors at UBC and the host-country institution, the host country would get one-third (33.3%) of the total automatically (the country-of-origin share), the host-country institution would get one-sixth (16.7%) of the total (half of the institutional share), and the host-country inventors would get one-sixth of the total (half of the inventor's share). The total transfer to the host country would be 66% of the total. Importantly, the agreements cover not just the original natural product lead compounds but also *any synthetic analog improvements that are made on the natural product lead structure*.

Despite the pioneering nature of this contractual arrangement and the benefits it has provided for the host country, it is largely unknown and has received little attention by policy experts. This example demonstrates that even when the host country does not have the capacity to perform biological assays and isolate the biologically active compounds, they can benefit by

participating in a collaborative effort that results in the production of discrete chemical compounds that constitute IP. The example above also illustrates the point that ownership of IP is not a necessary condition for receiving financial benefits from an invention. While the host country derives one-third of any revenues even if their role is only supplying the materials, if host-country participants are involved in the work that results in the generation of an invention, then that share increases, consistent with the notion of 'adding value', a concept that is highly relevant to the enterprise of drug discovery (Artuso 1997).

Commercial Versus Nonprofit: Two Paradigms for Developing New Medicines

The following discussion will consider two different paradigms for the development of candidates with the potential to treat disease. The first paradigm is the "commercial" model for drug discovery and which assumes that any medicine that is developed will be directed towards the diseases of wealthy countries and that the product will generate profits. This model dominates the discussions of ABS issues and biodiscovery research in general (see, for example, Simpson et al. 1996, Vogel 1997, ten Kate and Laird 1999, Cabrera-Medaglia 2004a, 2004b). The second paradigm is a "nonprofit" model for drug discovery for neglected diseases, i.e., diseases affecting poor populations in developing countries. In this model, the research is directed towards the needs of patients with minimal financial resources with the goal of making effective medicines available at the lowest possible price.

In the commercial model for biodiscovery research, the pharmaceutical industry plays the leading role in the development of promising lead compounds and the high rate of compound attrition in the discovery and development process is compensated by a commercial return for those products that do reach clinical use. Although research is often conducted in-house, the pharmaceutical industry frequently looks to external sources for innovation and promising leads, such as the characterized natural products described in the preceding section (The Economist 2005). A recent analysis reported that it requires an average of 12 years to develop a drug from start to finish and at an average cost of somewhere between US$802 million and perhaps as high as $1.5 billion. For every 10,000 molecules screened, an average of 250 enter preclinical testing, 10 make it to clinical trials, and only one is approved (The Economist 2005). Accordingly, it is in the best interest of the pharmaceutical industry to minimize risk and work with materials, including natural products, that have been characterized biologically and chemically and that have a greater chance of becoming pharmaceutical agents. There are a number of natural

products that have entered clinical trials that were discovered through collaborations between academic researchers and pharmaceutical companies. Examples include discodermolide, isolated from the sponge *Discodermia dissoluta* by the Harbor Branch Oceanographic Institution (Sennet et al. 2002), the hemiasterlins, isolated from the sponges *Auletta* sp. and *Siphonochalina* spp. (Andersen et al. 1997), dolastatin 10, isolated most recently from a *Symploca* sp. cyanobacterium, and a host of other compounds (Hallock and Cragg 2003, Newman and Cragg 2004, Simmons et al. 2005).

The nonprofit model for drug discovery is applicable to the development of drugs to treat neglected diseases. Earlier perceptions were based on the assumption that these diseases were unprofitable and therefore unattractive to pharmaceutical companies. The landscape for neglected-disease drug-development has changed markedly since 2000 however, reflecting significant and fundamental structural changes (Moran 2005). There were 63 neglected-disease drug projects underway at the end of 2004, including two new drugs in the registration stage and 18 in clinical trials, half of which were in Phase III. The increase in activity is due in large part to "public-private partnerships" (PPPs), which are defined as public-health-driven not-for-profit organizations that drive neglected-disease drug development in collaboration with industry groups. As the PPPs conduct three-quarters of the known neglected-disease drug-discovery programs they have become the primary driving force behind the nonprofit model of drug discovery. Eighty percent of the PPP drug development activity is funded through private philanthropy (Moran 2005, Nature 2005b, Cohen 2006).

Multinational drug companies conduct half of the neglected-disease projects, either working through PPPs or working alone, but with the view of partnering at a subsequent stage (Moran 2005). The bulk of the research is conducted by four companies that have formally established neglected-disease divisions: GlaxoSmithKline, Novartis, AstraZeneca, and Sanofi-Aventis. In all cases, the companies are working on a noncommercial basis, meaning they are not motivated by commercial returns in neglected-disease markets, and they have agreed to provide products to patients in developing countries at nonprofit prices. The incentives for the multinational drug companies to participate in the neglected-disease market have been cited as: (i) enhancing their reputation due to their failure to address neglected diseases; (ii) corporate social responsibility and ethical concerns; and (iii) strategic concerns, such as positioning themselves in developing countries or having access to low-cost but highly skilled researchers.

The PPPs play a crucial role in facilitating the participation of multinational companies, which provide the technology in which they have invested for decades and their expertise in discovery, development, and distribution. Other important roles of the PPPs include: (i) integrating and coordinating the multiple industry, academic, and other partners in the drug-development pipeline; (ii) allocating public and philanthropic funds to the appropriate projects; (iii) managing neglected-disease drug portfolios; and (iv) their ability to lower costs by leveraging substantial in-kind resources and by excluding the costs of capital (Moran 2005).

Among the better known PPPs are the Medicines for Malaria Venture (MMV), a nonprofit organization created to discover, develop, and deliver new antimalarial drugs (Medicines for Malaria Venture 2006) and the Drugs for Neglected Diseases initiative, an independent, nonprofit drug development initiative that aims to develop new, improved, and field-relevant drugs for neglected diseases such as leishmaniasis, human African trypanosomiasis, Chagas' disease, and malaria (Drugs for Neglected Diseases Initiative 2006). The Institute for OneWorld Health is a nonprofit pharmaceutical company that directs a worldwide effort to uncover, research, and develop new medicines for neglected infectious diseases (Institute for OneWorld Health 2006). Academic consortia have also developed programs that have developed promising candidates for the treatment of the diseases of the developing world. For example, a consortium based at the University of North Carolina at Chapel Hill has developed a compound that is undergoing clinical trials against early stage sleeping sickness, uncomplicated malaria, and *Plasmodium jiroveci*-pneumonia (Werbovetz 2006).

Natural Products and Contemporary Drug Discovery

Natural products are unsurpassed for the variety and complexity of their chemical structures. Their chemical complexity is not the result of a random process but instead is the result of millions of years of selective pressure to develop molecular structures in response to intense interactions between species (Harborne 1993, Firn and Jones 2003). They are ideal for maximizing the success of screening for novel structures and for identifying previously unrecognized target proteins and molecular binding sites. Natural products are well recognized sources of new "lead" compounds, namely, chemical substances that have a different structure from existing treatments and which act by a different molecular mechanism. A well-known example is taxol, first isolated from the Pacific yew (*Taxus brevifolia*) from an NCI-sponsored

collection, which presented a novel mechanism for fighting cancer cells, namely interfering with the depolymerization of microtubules (Cragg and Newman 2005). New lead compounds are of paramount importance when addressing the issue of disease-causing pathogens that have become resistant to existing treatments, particularly relevant in the case of antibiotics (Levin 2004) and the treatment of tropical parasitic disease (Klausner and Alonso 2004). Discussed in greater detail below, the anti-malarial compound artemisinin, derived from the herb *Artemisia annua*, provided a new structural prototype for treating malaria (Vennerstrom et al. 2004).

Natural Products and the Pharmaceutical Industry

In their concise review of the importance of natural products to modern pharmaceutical research, Koehn and Carter (2005) reported that of the 877 small-molecule new chemical entities (NCEs)[4] introduced between 1981 and 2002, roughly half (49%) were natural products, semi-synthetic natural-product analogs, or synthetic compounds based upon natural-product structures. Natural products have also been invaluable tools for basic research, helping scientists decipher complex biochemical pathways (Clardy and Walsh 2004). Nevertheless, pharmaceutical research involving natural products has experienced a decline during the past two decades. The decline was attributed to the following factors: (i) the introduction of high throughput screening (HTS) against specific biological targets, a format inconsistent with the time-consuming nature of natural-products isolation; (ii) the development of combinatorial chemistry which produces large collections of synthetic structures; (iii) advances in molecular and cellular biology and genomics which increased the number of targets and decreased drug discovery timelines; (iv) a declining emphasis on infectious disease therapy, a traditional area of strength for natural products; and (v) the CBD and uncertainties with respect to collections of biological materials for drug discovery (Koehn and Carter 2005).

Nevertheless, emerging trends, coupled with unrealized expectations from current research and development (R&D) strategies, including combinatorial chemistry, are prompting a renewed interest in natural products as a source of chemical diversity and generation of novel lead compounds (Rouhi 2003, Clardy and Walsh 2004, Koehn and Carter 2005). This renewed interest is consistent with the difficulties experienced in recent years by the pharmaceutical companies in getting new drugs out of the pipelines and into the market (The Economist 2005). Nevertheless, it must be considered that the pharmaceutical industry has a broad variety of tools

at its disposal for drug discovery, and will rely on natural products only to the degree that they are available on practical terms.

To better appreciate the relative importance of natural products for the pharmaceutical industry, it is constructive to consider the success of a drug that was recently developed by Novartis to treat chronic myeloid leukemia (CML). CML is associated with a unique tyrosine kinase, a class of enzymes that play key roles in diverse biological processes such as growth, differentiation, metabolism, and programmed cell death and has been the subject of decades of basic biomedical research (Paul and Mukhopadhyay 2004). Based upon the knowledge obtained from the research on tyrosine kinases and the unique properties of the of the CML-associated enzyme, Novartis developed an inhibitor, imatinib mesylate, marketed as Gleevec[5], which produces marked responses in up to 90% of patients. The lengthy and expensive effort that culminated in the development of Gleevec benefited from a well-funded collaboration involving academia, government, and the pharmaceutical industry (Cortes and Kantarjian 2005). Gleevec is one of many examples of an effective therapeutic agent that is not based upon natural products, but rather a steadily growing understanding of complex biological processes, in this case, the role of the tyrosine kinase associated with CML. These developments suggest that natural products will have to be made available on competitive terms if they are to continue playing an important role in the treatment of diseases of importance to the industrialized world.

It is in the Best Interest of Researchers from Industrialized Countries to Play by the Rules

Gollin (1999) has described the incentives and disincentives for participants in biodiscovery research from industrialized countries to abide by international and national rules that regulate access to biological resources. The disincentives include: (i) potential patent disputes on inventions that are developed from materials that were not legally collected; (ii) the potential recovery of profits by the host country or person from inventions derived from illegally harvested materials; (iii) the reduced value of materials collected illegally; and (iv) the likelihood that the practitioner who does not collect samples legally or who fails to provide benefits will be denied access to biological samples in the future. Alternatively, the collector who plays by the rules is likely to benefit from continued access to biological materials and to benefit from the goodwill established in the process. From the perspective of the pharmaceutical company, given the extraordinary expenses associated with drug development that were described above, it

simply makes no sense to begin the lengthy and costly drug-discovery process with materials of an illegal or dubious origin.

The Industry Standard for Biodiscovery Research: Long-Term Relationships between Host-Country Participants and Well-Defined Contractual Agreements

As described above, the pharmaceutical industry routinely looks to external sources for innovations and compounds that can be 'in-licensed' from other sources, including natural products. There are numerous arrangements through which a pharmaceutical company can partner with commercial or academic collaborators (ten Kate and Laird 1999). In the case of contemporary USA government-sponsored biodiscovery research, a common arrangement involves a pharmaceutical company partner that works with a team of academic researchers that have a well-established relationship with a host country where collections of biological materials are carried out. Funding often comes from the NIH, for example, through the NCDDG program described above. A similar arrangement, described in detail below for the program in Panama, is utilized for the ICBG Programs. In both cases, participants from academic institutions are often responsible for establishing and maintaining the relationship with the host country. Virtually all of the host countries are signatories to the CBD and academic partners often have to invest years and considerable financial resources in order to establish a long-term and productive relationship. Just as described above for the pharmaceutical industry, it is in the best interest for the academic partners to play by the rules. Funding from the NIH requires the presence of transparent, coherent, and equitable contractual agreements with host-country partners (Rosenthal 1997, Rosenthal et al. 1999, Hallock and Cragg 2003). This is an important consideration when considering the argument, routinely heard, that academic and pharmaceutical researchers, once they find a promising lead, will then seek to source that material from another country with less-stringent requirements for access or where it can be found more cheaply (Vogel 1997).

In general, both academic and pharmaceutical participants benefit from stable, long-term relationships with host countries and it is not in the interest of the academic partner to 'burn bridges'. In the case of USA-based pharmaceutical companies, it is largely a moot point as they seldom have direct contact with the host country for collections. To be sure, from the perspective of USA-based academic and industrial collaborators, the relationships with host countries have evolved, in particular since the CBD came into effect. Just as host countries are grappling with

the issues of ABS, scientists from industrialized countries are attempting to cope with a changing set of expectations and regulations that can pose significant and sometimes insurmountable challenges. In some cases, researchers are unable to reach a satisfactory agreement and the research is either thwarted or terminated. As with any group of individuals, some researchers have higher standards than others, but the 'industry standard' has unmistakably been raised since the CBD entered into effect for all of the parties involved, including donors, academic scientists, and partners from the pharmaceutical industry, an important point for host-country participants and policy makers to take into account.

Drug Discovery for Diseases of Importance to Developing Countries

Most of the discussion on the use of genetic resources from developing countries for drug discovery focuses on economic uses. In a recent description of an international regime for ABS, Young (2004) writes "Investigations and workshops have demonstrated that most developing countries that attempt to develop ABS legislation have been preoccupied by potential profits." The implicit assumption is that biodiscovery research is directed towards drug discovery for diseases of importance to wealthy nations in which biodiversity is regarded as a commodity (i.e., the commercial model for drug discovery discussed above). Discussions on biodiscovery research frequently overlook the potential impact of the host country's biodiversity on diseases of importance to that country.

Most of the 7,500 plus medicines currently in development by biotech and pharmaceutical companies are for chronic diseases of wealthy nations, consistent with long-term administration and significant profits. Of the approximately 1,500 medicines launched over the past 30 years, fewer than 20 deal specifically with tropical disease (The Economist 2005). While there is an increasing awareness of the devastating impact of the diseases of the developing world (Gelb and Hol 2002, Sachs 2002, Klausner and Alonso 2004, Cross 2005) those needs are frequently absent in policy discussions on biodiscovery research, an omission that may have a significant impact on health in the developing world. As described above in the discussion on the nonprofit model for drug development, the outlook has improved markedly over the past few years for drug development for neglected diseases. It is now essential to now broaden the scope of debates on ABS to take those developments into account.

The Importance of Natural-Products Research for Tropical Parasitic Diseases

The impact of tropical protozoan diseases such as malaria, Chagas' disease, and leishmaniasis on the developing world is staggering: they collectively affect three billion people, most of whom survive on less than US$2 a day (Gelb and Hol 2002). For most diseases caused by tropical parasites, there are either no safe efficacious drugs or, as in the case of malaria, once-effective and affordable drugs are less widely used due to increased pathogen resistance to them (Klausner and Alonso 2004).

Each year 300 to 500 million new clinical cases of malaria are announced, although the actual impact of the disease may be significantly greater since many clinical events are never reported (Snow et al. 2005). A malaria vaccine has been a long-standing goal but there is little prospect of it becoming available within the next decade (Hemingway and Bates 2003). The cornerstone of malaria control worldwide remains effective and inexpensive drugs (Greenwood 2004) in which plant-derived natural products, or their derivatives, have played a central role. The quinoline antimalarials and related compounds such as chloroquine owe their origins to quinine, isolated from the bark of the Peruvian tree, *Cinchona ledgeriana* (Meshnick and Dobson 2001). Chloroquine has for decades been the primary chemotherapeutic means of malaria treatment and control, but resistance to the compound has developed on a global scale. Artemisinin has been used for 1,500 years in traditional Chinese herbal fever remedies and has received considerable attention in the scientific and health care communities (O'Neill 2004, Enserink 2005). Artemisinin-based combination therapies (ACTs), provide a rapid cure and are an immediate solution to the problem of drug resistance, but ACTs cost several times as much as existing drugs (Greenwood 2004). The first sign of resistance to artemisinin by *Plasmodium falciparum* was recently reported, highlighting the need to continue the search for more natural product-based breakthrough innovations (Jambou et al. 2005). An initiative supported by MMV has been successful in the development of synthetic compounds that are modeled after artemisinin and that may provide accessible and effective treatments (Vennerstrom et al. 2004).

Chagas' disease, or American trypanosomiasis, affects 16 to 18 million people, currently killing 10 to 20% of the people that it infects, and some 100 million, approximately 25% of the population of Latin America, are at risk of acquiring the disease (Gelb and Hol 2002). In the case of the leishmaniases (the collective diseases caused by the protozoan parasites of the genus *Leishmania*), an estimated 12 million people are infected worldwide, and 350 million live in

endemic areas at risk of acquiring the disease. There are no effective means of prevention and the control of *Leishmania* infections relies primarily on chemotherapy (Loiseau and Bories 2006). For visceral leishmaniasis, miltefosine has been registered for use in India (Gelb and Hol 2002) and the aminoglycoside, paromomycin, derived from the bacterium *Streptomyces rimosus*, has shown promising results in phase III clinical trials (Institute for OneWorld Health 2006). Nevertheless, there will remain a pressing need for new antileishmanials (Gelb and Hol 2002).

The tropical parasitic diseases discussed above, malaria, Chagas' disease, and leishmaniasis, have benefited from recent advances in medicine and molecular biology which will ultimately have an impact on the treatment of these diseases. The recent sequencing of the genomes of the parasites *Plasmodium falciparum* (a malaria-causing protozoan), *Trypanosoma cruzi*, *T. brucei*, and *Leishmania major* will facilitate the search for treatments for those diseases at least in part by defining new targets for therapeutic agents (Ash and Jasny 2005, Cross 2005). Nevertheless, there will remain a pressing need for new agents to interact with those targets, a need that the pharmaceutical industry alone is not likely to fulfill (Cross 2005), meaning that natural products are likely to continue to play a leading role.

The promising development of the nonprofit programs for drug discovery, discussed above, is likely to facilitate the development of novel treatments for neglected disease. But just as in the commercial model for drug discovery, the nonprofit model is absolutely dependent upon the discovery of novel lead compounds to enter the drug-discovery pipeline. As written in a recent article on drug development for neglected diseases "…if we are to effectively manage health outcomes in the long-term then we must also overcome drug resistance, which is a growing problem for many neglected diseases, including malaria, TB, leishmaniasis and sleeping sickness. To do so, we need to focus on 'breakthrough' innovation—that is, novel compounds with a novel mechanism of action against parasites and microbes" (Moran 2005). The diversity of structures of natural products has resulted in many 'breakthrough' innovations, and there are undoubtedly many remaining to be discovered.

Summary: Removing Access to Biodiversity is a Lose-Lose Proposition

As Cabrera-Medaglia (2004b) wrote, in describing Costa Rica's experience in developing ABS legislation, "Without access there is no benefit sharing." The lost benefits are not only economic but also include potential treatments for disease, especially those of importance to tropical countries and lost opportunities for strengthening host-country science programs. While there is

a renewed recognition of the importance of natural products in drug discovery in the pharmaceutical industry, that recognition is tempered by the enhanced difficulties, both real and perceived, in accessing biological resources from biologically diverse foreign countries (Koehn and Carter 2005). Drugs such as Gleevec are evidence that the pharmaceutical industry can draw upon a broad range of techniques to develop novel therapies that are independent of natural products, and the relative importance of those techniques will increase if access to biological resources in developing countries is made difficult or impossible. While state-of-the-art technology for drug discovery will continue to be directed towards diseases of importance to industrialized countries, the same trend is not likely to be seen for the diseases of the developing world. By restricting the drug-discovery pipeline for neglected diseases by hindering or preventing access to biological sources, the discovery of compounds such as artemisinin becomes far more unlikely, and the patients from the developing world that suffer from diseases such as malaria will bear most of the burden.

While difficult to quantify, the increasing difficulty for academic researchers to access biodiversity in tropical countries is having a significant impact on natural products-based drug discovery. The experience of Professor William Fenical from the Scripps Institution of Oceanography at the University of California at San Diego, a leading figure in the field of marine natural products chemistry, is informative. While his earlier research involved the use of marine invertebrates, increasingly difficult access to those organisms from other countries has led his program focus on actinomycetes that are cultured from marine sediments, often collected in USA territorial waters. Referring to policies adopted by certain host countries, he writes “In my opinion, restrictive governments have destroyed a huge amount of the opportunities for their scientists to receive education and collaboration abroad. True collaborations are, currently, almost nonexistent. The short-sighted view that someone, a foreigner, might make money has all but eliminated global, cooperative research in natural products chemistry.” (W. Fenical, pers. comm., 2 October 2005). The overall impact of this tendency is to exclude many biodiversity-rich countries from the drug-discovery process, effectively denying them the comparative advantage for biodiscovery research that their natural resources could otherwise provide.

Losing the Forest for the Trees? Tropical Biodiversity is a Disappearing Resource

At the same time that the increasingly restricted access to biological resources in the tropics is eliminating or discouraging biodiscovery research programs (Brush and Carrisoza 2004, Young

2004), the same biodiversity, both marine and terrestrial, is increasingly threatened. Humanity is rapidly destroying the terrestrial habitats that are the richest in number of species. Around two-thirds of all species occur in the tropics, largely in tropical humid forests (Pimm and Raven 2000). These forests originally covered between 14 million and 18 million square kilometers and around half of that remains. Much of the clearing of rainforests is recent and clearing now eliminates about 1 million square kilometers every 5 to 10 years. Burning and selective logging severely damage several times more than the area that is cleared (Pimm and Raven 2000).

Coral reefs are the most structurally complex and taxonomically diverse marine ecosystems, providing habitat for tens of thousands of associated fishes and invertebrates, but will not survive for more than a few decades unless they are promptly and massively protected from human exploitation over large spatial scales (Pandolfi et al. 2003). Among coral reefs, tropical reefs are major biodiversity hotspots and represent a high conservation priority (Roberts et al. 2002).

Given the scale of the threats to both terrestrial and marine habitats in the tropics and the rates at which habitats are being altered and destroyed, it is ironic that the majority of books and articles on the subject of biodiscovery emphasize ABS issues while often ignoring the fact that the very ecosystems from which the resources are derived are imperiled. In the context of drug discovery for human health, developing countries stand to lose the most as they lose the very species that contain potential treatments for disease. In the context of providing biological resources for international biodiscovery research, they are losing the very ecosystems that could provide them with a comparative advantage.

Biodiscovery Versus Conservation: A False Dichotomy

It is common to encounter in the policy-oriented literature on biodiscovery a perceived dichotomy between “sustainable development”, which is taken to mean “allowing access for bioprospecting” as opposed to “conservation”, which often implies “no access” (Ferreira-Miani 2004, Carrizosa 2004c). In all but the most extreme of cases, this is a false dichotomy. A concern that is frequently voiced is that of unsustainable harvesting of natural resources once a positive lead is identified and large quantities are required for commercial development. Three recent examples of compounds of interest to the pharmaceutical industry indicate more likely scenarios. Taxol, the well-documented anti-cancer compound originally isolated from the Pacific yew, is too complex to synthesize in a cost-effective manner. Once the potential demand for the

compound was clear, there was enormous incentive for the development of alternatives to isolation of the compound from the bark of the tree. As a result, a semi-synthetic route to taxol was developed that relies upon the elaboration of a relatively abundant precursor to taxol that is derived from the needles of the European yew, *Taxus baccata* (Cragg and Newman 2005). In the case of discodermolide, even to obtain the relatively small quantities necessary for Phase I clinical trials it was first necessary to obtain a synthetic source that did not require the isolation of the compound from the sponge (Freemantle 2004). As mentioned above, MMV-sponsored research has led to synthesis of chemical compounds that used artemisinin as a guide, but that have superior antimalarial properties (Vennerstrom et al. 2004). In summary, given the volumes of raw material that would be required to satisfy the market for any modern pharmaceutical agent originally found in organisms such as plants or marine invertebrates, it is exceedingly unlikely that the demand would be met by collections from its original source.[6] Accordingly, in any legitimate contemporary biodiscovery program, the concern that a commercial or academic partner could pose a threat to the resource is negligible and pales by comparison with the current destruction of tropical habitats described above.

In Costa Rica, ecotourism generates approximately US$1.5 billion per year (C.M. Rodríguez, pers. comm., 23 June 2005) and the country is considered to have a strong conservation ethic. Costa Rica is also the country that has participated in the greatest number of natural products-based drug-discovery programs: 15 approved projects since 1991 (Brush and Carrizosa 2004). That both activities should thrive in Costa Rica (at least until the passage of the Law of Biodiversity) suggests that the two are compatible and that biodiscovery research that is responsibly executed by any reasonable measure has no significant impact on biodiversity.

Contemporary Biodiscovery Research in Latin America

In order to put the Panama ICBG in the context of the current situation in Latin America, it is useful to compare selected approaches to ABS policies on regional and national levels. A detailed discussion of ABS policies in the Latin American countries included in the Pacific Rim can be found in Carrizosa et al. (2004). The Andean Community provides the only example of a regional approach to ABS regulation in Latin America (Ferreira-Miani 2004). Following the lead of the Andean Community, countries of the Central American region developed a draft protocol on “Access to genetic and biochemical resources and their associated knowledge” (Carrizosa

2004b). The example set by the Andean Community is widely cited in the policy-oriented literature as a model for addressing ABS issues in the context of the CBD (for example, ten Kate and Laird 1999, Barber et al. 2002, Carrizosa 2004b, Young 2004). On a national level, Costa Rica has by far the most extensive experience in dealing with ABS issues in Latin America and probably the world, and in 1998 adopted a Law of Biodiversity to regulate those activities (Young 2004, Cabrera-Medaglia 2004a). As a country that initially addressed ABS issues and biodiscovery research through contractual arrangements, and that now attempts to do that through national legislation, Costa Rica provides a useful case study for Latin America and other developing countries. Other countries in Central America, such as Nicaragua, have developed proposals for similar laws (Carrizosa 2004b). Under the ICBG Program a number of biodiscovery programs have been implemented in Latin America, including Peru (Lewis et al. 1999), Suriname (Kingston et al. 1999), and a single project incorporating Mexico, Argentina, and Chile (Timmerman et al. 1999).

Regional Approaches to Regulating Access to Biological Resources in Latin America: Decision 391 of the Cartagena Agreement

Decision 391 of the Cartagena Agreement of the Andean Pact Countries was adopted in 1996 by the Andean countries of Bolivia, Ecuador, Venezuela, Colombia, and Peru (Isaza Casas 1999, Ferreira-Miani 2004). The law was drafted in response to several factors: the "the need to develop legislation to protect genetic resources in order to gain control over the inventions derived from them", the fact that Andean countries share significant biodiversity, a perceived sense of urgency to approve a decision to regulate ABS issues, and the 'green gold' perception that their biological resources were extremely valuable economically and would yield an immediate return (Ferreira-Miani 2004). The range of materials whose access is regulated by Decision 391 is broad, and includes genetic resources, derivative products, intangible components (e.g., traditional knowledge), *ex situ* and *in situ* collections (native and domestic) and their derivatives indigenous to each member country, and even migratory species which can be found in the countries.[7] The inclusion of *ex situ* collections means that botanical collections, seed banks, zoos, breeding centers, botanical gardens, aquariums, tissue banks, collections in natural history museums, herbaria, and other settings are incorporated, whether located in the host country or elsewhere (Ferreira-Miani 2004). Decision 391 covers a broad range of activities including "research, bioprospecting, conservation, industrial application, or commercial profit,

among others" (Ferreira-Miani 2004). Once approved under the Cartagena Agreement of the Andean Pact Countries, Decision 391 became binding and it was automatically integrated into national legislation. In practice, however, it has been necessary for each country to adopt specific policies in order to incorporate Decision 391 into national contexts (Carrizosa 2004b).

In Colombia, Decision 391 constitutes the main legal framework for access to genetic resources. Due to the broad range of activities that fall under the scope of the agreement and the ambiguity of certain definitions, even routine transactions such as transferring botanical vouchers may fall under the agreement. Commenting on the Colombian experience in dealing with the agreement, Ferreira-Miani (2004) wrote "Decision 391 presents ambiguities that have prevented not only its implementation at a national and regional level, but has also prevented the advancement of science and the involvement of traditional communities in access and benefit-sharing projects." Independent cases in Venezuela and Ecuador resulted in one-year moratoriums on the transfer of botanical vouchers, both of which were attributed to Decision 391 (Grajal 1999).

Overall there has been little implementation of Decision 391. Between July 1996 and July 2001, Venezuela, Ecuador, Bolivia, and Peru received 26 applications, only one of which was approved, but not a single access contract had been signed as of January 2004. One exception has been Venezuela, which has invoked Decision 391 to facilitate access to 12 noncommercial projects requiring access to biological resources (Carrizosa 2004b). In Colombia, potential applicants either do not understand the decision or they ignore it, perceiving it as an obstacle to research. The absence of a more participatory consultation during the drafting and the lack of adequate technical, scientific, and economic experience were cited as some of the factors influencing the outcome of Decision 391 (Carrizosa 2004c, Ferreira-Miani 2004). This has resulted in "a net loss of opportunities for the sustainable use of biological resources" (Ferreira-Miani 2004).

National Approaches to Regulating Access to Biological Resources in Latin America: Costa Rica

A total of 15 international agreements have been negotiated by Costa Rica's National Biodiversity Institute (INBio), the best known of which is the contractual agreement between Merck Pharmaceutical and Costa Rica. Signed in 1991, this was the country's first agreement under which biological samples were provided to a company for pharmaceutical and veterinary

purposes (Reid et al. 1993, Cabrera-Medaglia 2004a). Adopted before the CBD was opened for signature, the first contract resulted in a two-year research and sampling payment of US$1.135 million to Costa Rica. It was cited as "a watershed in the history of biodiversity prospecting" and received worldwide attention (Reid et al. 1993). It was renewed three times before expiring in 1999.

The policy-oriented literature on biodiscovery is replete with references to the Merck-INBio agreement (see, for example, Reid et al. 1993, ten Kate and Laird 1999, Laird and Lisinge 2002). Combined with the perception of the enormous wealth generated by pharmaceutical companies (ten Kate and Laird 1999), the Merck-INBio agreement fueled expectations, in Latin America and elsewhere, that biodiversity is a commodity for which industrialized countries should pay, and are willing to do so. While the details of the working arrangements between INBio and its pharmaceutical partners have not been made public (confidentiality is a standard practice), the literature suggests that INBio's business model has relied primarily on the collection of biological samples and preparation of extracts which were then made available for industrial partners (Artuso 2002). None of the agreements entered into by INBio have generated royalty payments (Young 2004), but the benefits that Costa Rica has derived through this experience are evident and include monetary payment for samples, technology transfer, equipment, training for scientists, experience in negotiations, and a better understanding for the potential commercial uses of biodiversity (Artuso 2002, Cabrera-Medaglia 2004a). Sixteen years later it is now more clear than ever that the Merck-INBio situation was the exception to the rule and, in part, a product of Costa Rica's biological, political, and social environment (Reid et al. 1993, Young 2004).

Costa Rica is the only country in the region that has a national law (Law of Biodiversity, adopted in 1998) that seeks to regulate "access to genetic material, biochemical resources and traditional knowledge" (Cabrera-Medaglia 2004a). The legislation was designed to implement the CBD in Costa Rica and its goals are to promote the conservation and sustainable use of biodiversity and to ensure the equitable sharing of benefits. The details of the law as well as the process and context of its development have been described in detail by Cabrera-Medaglia (2004b). The Law of Biodiversity is designed to regulate "specifically the use, management, associated knowledge and distribution of benefits and costs derived from the utilization of the elements of biodiversity". Despite the fact that the Law of Biodiversity was adopted in 1998, its

application and implementation in key areas still remains to be determined. An act to declare the law unconstitutional was brought by the Attorney General's Office at the request of Costa Rica's own Ministry of Environment and Energy. The challenge is based upon the duties of an office created by the Law of Biodiversity, the Commission of the Management of Biodiversity (CONAGEBIO), which include the formulation of biodiversity and ABS policies and the management of public funds (Cabrera-Medaglia 2004a, Carrizosa 2004c).

The law has several significant difficulties including the lack of clarity and the presence of provisions that may actually prevent access. As of 2004, because of the act on unconstitutionality filed against the law, it has not been implemented (Cabrera-Medaglia 2004a). The outcome was reflected by a "legislative process [which] revealed a lack of technical expertise from certain sectors such as academic, rural, political and entrepreneurial groups, some of which used the opportunity to make political rather than technical statements" (Carrizosa 2004c). The time constraints imposed by the Parliamentary procedures for the approval of legislation prevented a full discussion of some of the most controversial and relevant aspects of the law, begging the question as to whether the legislative process is the appropriate venue for host countries to develop regulations for biodiscovery research. Overall, if the Law of Biodiversity is ever implemented, there are elements of the law that "suggest a difficult future for bioprospectors" (Cabrera-Medaglia 2004b). Scientists attempting to work under the Law of Biodiversity should be concerned since the "regulatory authorities tend to be suspicious and try to impose strong control mechanisms in order to avoid past injustices. Suspicion and mistrust appear to be the main motivators behind this tendency." (Cabrera-Medaglia 2004b).

As the country that some consider to have the most successful ABS system (Young 2004), and the greatest experience with international biodiscovery programs, Costa Rica is perhaps the best available test case for comparing the benefits of a contract-based approach to developing ABS procedures versus national legislation. As Brush and Carrizosa (2004) conclude "the case of Costa Rica suggests that success in the implementation of ABS policy is best achieved in a decentralized system with flexible norms of negotiating benefits, a simple system whereby the entity empowered to grant access negotiates directly with the organization seeking access and where the number of parties involved in the negotiation and permitting process is minimized".

Putting the Cart before the Horse: Regulations to Implement the CBD are Hindering all Access to Biodiversity, Stifling Opportunities from which Host Countries Could Gain Experience

Article 15 of the CBD stipulates "Each Contracting Party shall endeavor to create conditions to facilitate access to genetic resources for environmentally sound uses by other Contracting Parties and not to impose restrictions that run counter to this objective". While "the principles of the CBD are finding their way into national laws and policies" (ten Kate 2002), those principles are not being implemented uniformly. The ABS laws and policies developed under the CBD have created a complex scenario for access and exchange of biological resources (Carrizosa 2004b). Referring to the CBD, Jon Daly, a curator of Amazonian botany at the New York Botanical Garden commented, "Something that was well intentioned and needed has been taken to an illogical extreme." (Revkin 2002). In the entire Pacific Rim region, national ABS laws and policies have approved 15 projects in Costa Rica, three in Mexico, two in the Philippines, one in Samoa, and one in the USA (Brush and Carrizosa 2004). Taking into account that all 15 projects approved in Costa Rica occurred *outside* of the Law of Biodiversity and that the three programs in Mexico have been terminated, the trend is clear. The absence of any approved, commercial biodiscovery projects in the Andean countries regulated under Decision 391, a region that may collectively harbor the largest proportion of the world's biodiversity, shows the same tendency (Grajal 1999).

A recent study of the Pacific Rim countries indicated that "the most successful bioprospecting projects were established outside of focused national frameworks corresponding to the CBD" (Brush and Carrizosa 2004) and that "In synthesis ABS laws and policies developed under the umbrella of the CBD have created a complex and comprehensive scenario for exchange of genetic resources." (Carrizosa 2004b). If the CBD is to have its intended effect of creating conditions to "facilitate access to genetic resources for environmentally sound uses", the evidence to date suggests that a far greater effort must be made to accommodate the needs of the practitioners that seek to access biological resources.

Contracts as Tools for Building Bridges between the Participants in Biodiscovery Research

The preceding discussion provides examples of the operational and conceptual difficulties in implementing a functional ABS system under a centralized system of laws and policies. Given that biodiscovery is a research-intensive process and that the research programs are inherently

variable and dynamic, it is clear that more flexible legal devices are required if biodiscovery research programs that are international in scope are to succeed. During the development of the contractual agreements for the Panama ICBG, described below, it was found that the process of drafting legal agreements was a valuable experience for the parties involved, providing the opportunity to clarify misunderstandings, resolve differences, and define shared objectives, all in the context of a document that is legally enforceable. Alternatively, when there are fundamental differences between parties that are considering working together, the process of drafting an agreement makes those differences clear. The current difficulties in establishing biodiscovery research programs in Latin America suggest that more flexible and straightforward policies should be considered by host countries. Contractual agreements may be the most appropriate mechanism for providing control over the access to biological resources while avoiding excessive restrictions and bureaucracy.

The Panama ICBG: Investing in the Host Country in Order to Maximize its Role in the Drug-Discovery Process and to Link the Research to Conservation

The overall goals of the Panama ICBG are to: (i) discover new lead compounds from Panamanian plants, algae, and marine invertebrates for the treatment of several tropical diseases and cancer; (ii) to carry out that research in a way that is inextricably connected to the development of scientific training, capacity building, and development of scientific infrastructure; (iii) to develop techniques that facilitate drug-discovery research in developing countries; and (iv) to develop programs that promote biodiversity conservation in a manner that strengthens host-country institutions. There have been two five-year cycles of funding for the Panama ICBG, the first from 1998 to 2003 and the second from 2003 to 2008.

Context of ABS Issues in Panama at the Beginning of the Panama ICBG

The Panama ICBG was initiated in 1998, shortly after the adoption of Decision 391 in 1996 and when substantial international attention was focused on Costa Rica's positive experience with INBio and its commercial collaborators. During the same period, the institution responsible for access and use of biological resources in Panama at that time, the National Institute for Natural Renewable Resources (INRENARE), was elevated in status from an 'Institute' to an 'Authority', now known as the National Authority of the Environment (ANAM, Autoridad Nacional del Ambiente). The law which created ANAM and which defines its responsibilities is Law 41 of

1998, the General Law of the Environment (GLE) (La Asamblea Legislativa 1998). ANAM is represented before the Executive Branch by the Ministry of Economy and Finance. The GLE defines "Prospecting or Biological Exploration" as "The exploration of natural wild areas in the search of species, genes or chemical substances from biological resources, in order to obtain medicinal, biotechnological or other products."

According to Article 71, "ANAM is the competent authority, as established in the present law and its implementation, to establish norms and regulations and control access and use of biogenetic resources in general, with the exception of human species, respecting the rights of intellectual property. To comply with this function, legal instruments or economic mechanisms shall be developed and introduced. The right to use natural resources does not allow its owners to use the genetic resources contained within them." Also relevant to the Panama ICBG is the country's system of protected areas. Article 66 of the GLE established a National System of Protected Areas (SINAP) made up of all of the protected areas established by laws, decrees, resolutions, or municipal agreements, all of which are regulated by ANAM. Article 94 of Chapter 10, entitled "Coastal-marine and Wetland Resources", establishes that the use, management, and conservation of coastal-marine resources shall be subject to the regulations issued by the Panama Maritime Authority. Significantly, "In the case of Protected Areas with coastal-marine resources under the jurisdiction of ANAM, regulations shall be issued by that authority". Accordingly, the most obvious course of action for biodiscovery research in Panama was to establish a contractual agreement with ANAM that is consistent with the CBD and the GLE, the terms of which are described below.

Overview of the Panama ICBG Drug-Discovery Process

Perhaps the greatest distinction of the Panama ICBG compared to the majority of natural products-based drug-discovery programs is the degree to which the host country plays an essential role in the drug-discovery process (Capson et al. 1996, Kursar et al. 1999, Coley et al. 2003). Departing from the traditional model in which the primary role of the host country is to provide the raw materials for drug discovery to collaborators in industrialized countries, the program has placed a major emphasis on strengthening scientific research capacity in Panama by complementary investments in the training of young scientists, in the creation of research opportunities for scientists in Panama, and in scientific infrastructure. The program has placed a premium on transferring, developing, and implementing technology that is practical for

developing countries. The Panama ICBG utilizes an extended network of collaborators from academic institutions and the pharmaceutical industry in the USA, allowing the project to: (i) broaden the scope of the research by incorporating techniques and expertise not otherwise available; (ii) focus resources and strengths on well-defined immediate and long-term objectives that can be practically implemented in Panama; and (iii) provide first-class training opportunities for Panamanian students and researchers.

Conceptually, the drug-discovery component of the Panama ICBG is similar to many biodiscovery programs based in industrialized countries: the scientists involved in the program are involved in the collections of biological materials, bioassays and bioassay-guided fractionation, resulting in the discovery of discrete chemical compounds, preferably novel, and with activity against a clinically or economically important disease. The model is identical to that described above that resulted in the discovery of discodermolide (Sennet et al. 2002), dolastatin-10 (Simmons et al. 2005), and the hemiasterlins (Andersen et al. 1997). In this model, the scientists that played a key role in the discovery are recognized as 'inventors' of any IP that is generated. In this case of the Panama ICBG, the inventors are primarily the host-country scientists.

Associate Programs in the Panama ICBG

There are currently six institutions involved in the Panama ICBG, which participate in a total of four Associate Programs and an administrative entity based in Panama known as Central Operations. The programs are based in Panama and the USA. Central Operations, based at the Smithsonian Tropical Research Institute (STRI) is responsible for the drafting of legal agreements for the ICBG, coordination with the Panamanian government, and ensuring a consistent flow of samples and data and other administrative responsibilities. Associate Program 1, coordinated through STRI, is responsible for coordination, administration, collections of plants, cultivation of endophytic fungi, and extraction. Associate Program 2 conducts assessments of bioactivity against parasites and cancer, and is currently carried out in the laboratories of the Institute of Advanced Scientific Research and High Technology Services (INDICASAT) and the Novartis Institutes for Biomedical Research (NIBR). Efforts are currently underway to incorporate Dow AgroSciences into Associate Program 2. Associate Program 3 is carried out at Oregon State University, the Scripps Institution of Oceanography, INDICASAT, and the University of Panama. This Associate Program carries out the fractionation and structural

elucidation of the biologically active components from cyanobacteria, plants, and endophytic fungi. The roles of Associate Program 4 are to link the drug-discovery activities of the Panama ICBG with biodiversity conservation, to isolate and characterize marine natural products from marine invertebrates, and to carry out research and conservation activities in the Coiba National Park, as described below.

Organisms Collected by the Panama ICBG

The collecting strategy for the first five-year cycle of the program involved terrestrial plants. The plant collecting efforts focused on young leaves, based on the theory that young leaves, being subjected to greater levels of herbivory than mature leaves, have higher levels of secondary metabolites (Coley et al. 2003). The materials collected are subjected to biological assays in the INDICASAT laboratories (described below) and additional collections are made only when the combination of results from biological assays and scientific literature suggests that recollections are warranted. A biological assay-driven process was used to select plants for subsequent studies, leading to the identification of a number of chemical compounds with significant activity against cancer (Hussein et al. 2003, 2004, 2005, Rodríguez et al. 2003), leishmaniasis (Montenegro et al. 2003), and Chagas' disease (Torres-Mendoza et al. 2003, 2004, Chérigo et al. 2005). Nevertheless, the bioassay-driven purification process often led to plant species and genera that had already been the studies of numerous investigations, minimizing the possibility of isolating novel lead compounds, a major goal of natural products-based drug discovery. Accordingly, for the second five-year cycle, less-studied organisms more likely to yield novel biologically active compounds were incorporated. For terrestrial collections, the emphasis has shifted from plants to endophytic fungi, microorganisms that live within the tissue of living plants and which are relatively unstudied as potential sources of novel natural products (Strobel et al. 2004).

Marine organisms have also been incorporated into the Panama ICBG, principally cyanobacteria and soft corals, both of which are rich sources of biologically active natural products (Paul and Puglisi 2004). Most recently marine actinomycetes, a well-known source of biologically active metabolites (Magarvey et al. 2004), have been incorporated. Cyanobacteria have been among the richest aquatic or marine sources of new clinical candidates for the treatment of cancer, the best-known example of which is dolastatin 10, a potent anticancer compound which is currently in Phase II clinical trials (Simmons et al. 2005). Collections are carried out only by experts in their respective fields, ensuring that the collections have no

significant biological impact, a particularly important consideration in the case of organisms such as corals (Guzman et al. 2004). To date, publications have been generated from studies of soft corals (Gutiérrez et al. 2004, 2005b, 2006) and sponges (Gutiérrez et al. 2005a) and, most recently, from cyanobacteria (Simmons et al. 2006).

Disease Targets Selected by the Panama ICBG: Technology Transfer and Development for Bioassays

An essential and unique element of the Panama ICBG is the ability to carry out a range of biological assays in the host country. The Panama-based bioassays allow the program a degree of autonomy and productivity that would not otherwise be available, and easily justify the significant investment in time and money necessary to establish and maintain them. Academic collaborations played an important role in the establishment of the bioassays in Panama. A suite of bioassays for diseases of importance to both industrialized countries as well as developing countries was selected in order to enhance the impact of the program and to increase the probability of finding natural products of interest. The choice of bioassays has also been dictated by the cost, practicality, reliability, and interest in avoiding the use of radioactive isotopes. From the beginning, the Panama ICBG benefited from the participation of experts in tropical parasitic diseases, which was essential for the development of the tropical disease bioassays. During the first five-year cycle, the bioassay targets included cancer, HIV, the parasites responsible for leishmaniasis, Chagas' disease and malaria, and the agricultural pest, whitefly (*Bemisia tabaci*). The HIV bioassay was established in collaboration with the NCI AIDS Drug Screening and Development Laboratory and utilized a non-infectious strain of HIV that can be used in standard laboratory facilities (Kiser et al. 1996). The assay for HIV proved to be costly and labor intensive and was eventually abandoned. Efforts to develop a bioassay based upon the whitefly were unsuccessful, and it was not included in the second five-year cycle.

Drug Discovery for Cancer

The bioassays established in collaboration with the NCI and include breast, lung, and central nervous system cell lines (Monks et al. 1991). The NCI provided the cell lines and the non-infectious HIV bioassay described above at no cost and helped organize a workshop in Panama on their use. The NCI routinely sponsors visits by scientists by collaborating host countries to participate in collaborative research and training opportunities (Hallock and Cragg 2003) and did

so in the case of the Panama ICBG. The colorimetric bioassay used with the tumor cell lines measures cell death and thus provides a measure of the cytotoxicity of the test substance. The cell line and assays were initially established in the Center for Pharmacognostic Research on the Panamanian Flora (CIFLORPAN) at the University of Panama. For the second five-year cycle, the cancer cell line assay was transferred to INDICASAT, which is now responsible for all of the Panama-based biological assays. The tumor cell lines have been used to characterize a variety of cytotoxic compounds, all derived from plants (Hussein et al. 2003, 2004, 2005, Rodríguez et al. 2003).

Collaboration with the Novartis Institutes for Biomedical Research

Another key element to the anticancer drug-discovery component is provided by the collaboration with NIBR. During the first five-year cycle, negotiations with the Monsanto Corporation were prolonged and ultimately unsuccessful. With initial assistance from the NCI, the NIBR joined the Panama ICBG, and the collaboration has continued through the second five-year cycle. The primary benefit of the NIBR collaboration is the access to their mechanism-based oncology bioassay program that relies upon state-of-the-art knowledge of cancer cell biology along with HTS to find mechanism-based anticancer lead compounds. The mechanism-based anticancer assays are the ideal complement to the whole-cell assays described in the previous section and which are performed in Panama. The cell line assays provide a general indication of cytotoxicity to the tumor cell lines without providing specific information about how the test substances may work. By contrast, the mechanism-based bioassays provide information about specific targets within cancer cells. The sensitivity of the NIBR HTS bioassays to compounds such as tannins often result in false positives and requires that all crude samples first undergo a pre-fractionation protocol as described in the earlier section "*Bioassay-Guided Fractionation and the Isolation and Characterization of Compounds*".

Drug Discovery for Malaria

The establishment of a permanent culture of the malaria-causing parasite, *Plasmodium falciparum,* and the development of an efficient and cost-effective anti-plasmodial bioassay that does not require the use of radioactive isotopes has been one of the single largest investments in time and financial resources for the Panama ICBG. Collaborators from the Walter Reed Army Institute of Research and the General Clinical Research Center at the University of California at

San Francisco played crucial roles in training of a Panamanian researcher in the cultivation of *P. falciparum.* The standard bioassay for screening potential drugs for antiplasmodial activity is a radioactivity-based method that relies upon the incorporation of [^{3}H]hypoxanthine into the parasite's DNA in order to measure parasitic replication in erythrocytes (Corbett et al. 2004). The method is sensitive and it can be used to screen a large number of compounds, but employs hazardous radioactive materials that require special facilities and procedures.

Accordingly INDICASAT researchers developed an alternative method of testing *Plasmodium* susceptibility to potential antimalarial agents that utilizes PicoGreen®, an ultrasensitive fluorescent nucleic acid stain which enables the detection of exceedingly small quantities of double-stranded DNA with a moderately priced microfluorimeter. The assay takes advantage of the fact that the erythrocytes in which the parasites are cultivated have no DNA, and therefore do not interfere with the analysis of parasitic DNA. The development of a novel, straightforward, efficient, and accurate method for the detection of potential antimalarial agents based upon a fluorimetric technique marks a significant accomplishment for the INDICASAT laboratories and the Panama ICBG (Corbett et al. 2004). The development of a microfluorimetric method is likely to find wide application, especially in other developing nations that also contend with logistical problems when using radioactive isotopes. To date, INDICASAT scientists have trained researchers from Madagascar and Bolivia in the cultivation the parasite and the use of the fluorescent bioassay technique. The Malagasy scientists are associated with a Madagascar-based ICBG program and the FIC of the NIH provided the funds necessary for their training in Panama (D.G.I. Kingston, pers. comm., 2 February 2006). The bioassay technique was the subject of a provisional patent whose authors were participants in the Panama ICBG, but was provided at no cost and without restrictions to the Malagasy scientists.[8]

Drug Discovery for Leishmaniasis

There are significant problems associated with the development of an effective chemotherapeutic agent for leishmaniasis, among them the need to target the relatively insensitive intracellular (amastigote) form of the parasite (Croft and Yardley 2002). Initially work employed the extracellular (promastigote) form of the parasite *Leishmania mexicana* since it is the form of the parasite most easily grown *in vitro* and it can be cultured in well-defined media in the absence of a host cell. A novel colorimetric assay was developed in the INDICASAT laboratories for the promastigote form (Williams et al. 2003) and was used by University of Panama-based

participants to identify anti-leishmanial compounds in plants (Montenegro et al. 2003). The amastigote form of the parasite multiplies inside the host macrophages and is responsible for the disease manifestations in humans and should be the target of any novel treatment (Bates et al. 1992, Croft and Yardley 2002). Accordingly, INDICASAT researchers subsequently developed a novel microfluorimetric assay for the intracellular form of the parasite that employs PicoGreen®, which forms a fluorescent complex with the parasitic DNA as described above for the anti-plasmodial assay. As the parasites are grown in a cell-free environment there is no potential interference with cellular DNA and growth is measured with an inexpensive microfluorimeter in 96-well plates, a methodology similar to the anti-plasmodial bioassay described below. The Panama ICBG continues to search for compounds active against leishmaniasis. It is hoped that the genome sequence for *Leishmania major* will reveal new drug targets and facilitate the search for urgently needed treatments for the leishmaniases.

Drug Discovery for Chagas' Disease

To search for compounds active against *Trypanosoma cruzi*, the INDICASAT laboratories employ a colorimetric bioassay that utilizes a recombinant strain of the parasite that expresses the *Escherichia coli* ß-galactosidase gene (Buckner et al. 1996). Initially, a technique to evaluate the extracellular (epimastigote) form of the *T. cruzi* parasite was employed since the growth requirements and conditions of the culture are relatively straightforward. INDICASAT researchers have since established a bioassay with the more clinically relevant intracellular (amastigote) form that is now used routinely to evaluate potential anti-trypanosomal compounds. The colorimetric assay and the recombinant parasite were developed at the University of Washington and made available to INDICASAT researchers at no cost. The assay is performed in a 96-well plate and parasite growth is easily and accurately quantitated with a routine microplate reader. Chemists at the University of Panama utilized these bioassays to characterize novel compounds from plants with activity against the disease-causing parasite (Torres Mendoza et al. 2003, 2004). The recent sequencing of the genome of *T. cruzi* promises to open up a plethora of new drug targets (Cross 2005) but, as in the case of leishmaniases, there will remain a crucial need to isolate new lead compounds to test against those targets (Croft et al. 2005).

General Investments in Infrastructure and in Research Programs

During the first five-year cycle, the Panama ICBG supported, in whole or in part, three research programs at the University of Panama and a research program responsible for the bioassays of tropical parasites. The latter program was initially part of the Gorgas Memorial Institute and is now located at INDICASAT. Two of the research programs that were created during the first five-year cycle continue to receive support during the second cycle of funding, namely a laboratory involved in the bioassay-guided fractionation of natural products (Montenegro et al. 2003, Torres-Mendoza 2003, 2004) and the bioassay component of the INDICASAT laboratories (Williams et al. 2003, Corbett et al. 2004). Equipment purchases for Panama-based laboratories include high-pressure liquid chromatographs (HPLCs), fume hoods (for working with organic solvents and hazardous substances), microscopes, rotary evaporators, computers, laminar flow hoods (for working in sterile conditions), chromatography supplies, and other supplies. Another significant investment supported primarily by the Panama ICBG was a 300 MHz Bruker Avance NMR spectrometer which is housed at STRI. Independently, the National Secretary for Science, Technology, and Innovation (SENACYT) has made significant investments in scientific infrastructure and equipment in INDICASAT, which consists of a large, modern complex of offices, laboratories, and library facilities. The combined investments of the Panama ICBG and its host-country partner institutions have made a fundamental difference in the ability of Panamanian scientists to carry out biodiscovery research.

The Training of Students and Creation of Research Opportunities in the Panama ICBG

The other pillar of host-country investment for the Panama ICBG has been in the training of students and the creation of research opportunities for Panamanian scientists. A total of 84 Panamanian students, scientists, and technicians have passed through the Panama ICBG practicing disciplines that include botany, natural products chemistry, molecular biology, parasitology, virology, and microbiology, performing the majority of the work essential to the program including plant collections, natural products chemistry, biological assays, and database management. Many of the students and young scientists have used the Panama ICBG as a springboard to graduate school. At this writing, 14 Panamanians are pursuing or have completed M.Sc. theses outside of Panama and three are pursuing Ph.D. degrees, two were recently accepted into Ph.D. programs in Europe, and one recent Ph.D. was awarded a full postdoctoral

scholarship to study at the Scripps Institution of Oceanography. The number of trained students is the most significant legacy of the Panama ICBG and is the ideal complement to the investments in infrastructure discussed above.

The Panama ICBG and Traditional Knowledge

The first five-year cycle of the Panama ICBG included a program with the Naso indigenous group from northwestern Panama with the purpose of helping preserve their traditional ethnobotanical knowledge of medicinal plants. The program involved three groups of Naso students and teachers, one teacher per group and a total of 18 students, and ran for over three years. The program was terminated when most of the traditional knowledge of the Naso had been documented. The recorded information is the sole property of the Naso and was never studied or copied by any non-Naso participant in the Panama ICBG. While the agreement between ANAM and STRI for the Panama ICBG contemplated the possible use of traditional knowledge, the Naso's ethnobotanical knowledge was never utilized to guide plant collections. While there are several ICBG programs that have successfully used traditional knowledge to guide plant collections (Kingston et al. 1999, Soejarto et al. 2004), the experience of an ICBG program based in Chiapas, Mexico, led to the conclusion that the potential risk of negative publicity associated with the use of traditional knowledge was too great (Berlin et al. 1999). Known as the Mayan ICBG and initiated in 1998, the organizers went to extraordinary lengths to inform local participants of the nature of the research and of the potential benefits, including improvements in health care and an enhanced capability to use and conserve their disappearing biological resources and associated traditional knowledge (Rosenthal 2002). Nevertheless, the program was the subject of extraordinary negative publicity and was closed in October 2001 (Dalton 2001, Larson-Guerra et al. 2004). The negative publicity surrounding the Mayan ICBG has undoubtedly had a chilling effect on many legitimate biodiscovery programs (Rosenthal 2002).

Biodiversity Conservation Component of the Panama ICBG

Public Outreach

Since the Panama ICBG's inception, program participants have engaged in over 200 outreach efforts that emphasize the link between biodiversity and human health and the benefits that the country has received by investments in scientific infrastructure, the training of students and the

creation of research opportunities for local scientists. Many of the outreach activities were associated with the Coiba National Park as discussed below.

Collections in Protected Areas and Collaboration with ANAM

ANAM is responsible for the management of Panama's extensive system of 41 protected areas, both marine and terrestrial, that collectively encompass 19.5% of the national territory. All collections of plants and marine organisms have been made in protected areas. The relationship is mutually beneficial for ANAM and the Panama ICBG in the following ways: (i) the Panama ICBG benefits from clearly defined terms of access to national territory under the sole jurisdiction of ANAM; (ii) the materials collected are subjected to the terms of the ANAM-STRI Agreement procedures; (iii) collections are made in areas that receive protection by the host country; and (iv) the Panama ICBG-sponsored research provides valuable information to ANAM about the area's biological diversity through its biodiversity inventory activities. For terrestrial plants, since the beginning of the program in 1998, a total of 3,099 samples have been collected from 1,877 species, representing 786 genera and 178 families. In addition to providing access to biodiversity inventories of its collections, the Panama ICBG developed in collaboration with ANAM a digital interface for preparing all permits utilized by the institution. Created at the request of ANAM's National Director for Natural Patrimony and designed by a systems analyst working for the Panama ICBG, the system facilitates all permit-mediated transactions, including concessions, scientific research, exports of biological materials, and determination of whether a given species is listed on the CITES database of endangered species. The Panama ICBG provided a computer that serves as an internal server, allowing the use of the system by ANAM personnel from anywhere in its administrative center.

The Coiba National Park: Providing Scientific Input to Strengthen Protected Areas

In the second five-year cycle of the Panama ICBG, one of the four Associate Programs, titled "Conservation, outreach and biodiversity inventory in Panama", was explicitly designed to link the drug-discovery activities of the Panama ICBG with substantive conservation measures and to develop and implement initiatives to promote the protection of the Coiba National Park. Located off the southwest coast of Panama in the Gulf of Chiriquí (Guzmán et al. 2004) and comprising an area of 2,700 km^2, the Coiba National Park includes a marine area of 2,165 km^2 and an insular area 535 km^2. It is located within the Tropical Eastern Pacific (TEP), a unique tropical marine

region, one of the most isolated regions in the world's oceans, which has probably the highest rate of endemism of any equivalent region in the world. The Gulf of Chiriquí belongs to the section of the TEP with the greatest biological value (Sealy and Bustamente 1999). As a consequence, no other continental-shore marine park could do as much for marine conservation in the entire TEP as the Coiba National Park and its adjacent buffer zone of 1,600 km^2 (ANAM 2005). Coiba Island is located in the center of the park. With an area of 503 km^2, it is the largest tropical island on the continental shore of the Pacific coast of the Americas. Coiba Island retains 85% of its original primary forest, which harbors numerous endemic species and subspecies (Ibáñez 2001, Guzmán et al. 2004).

The Panama ICBG led an initiative to compile the existing information about the Coiba National Park and to conduct surveys with local fishermen in order to understand their fishing practices, perceptions about conservation of the park, and socioeconomic conditions. The information obtained on the park was presented to government officials and the public at large during a lengthy debate to establish the park by law (it was previously established by a weaker Executive Decree). One of the more effective arguments for the park's protection was the potential for scientific research; both basic research as well as biodiscovery, pointing out that the unique marine and terrestrial ecosystems constitute "living libraries" for natural products-based drug discovery. Legislation was adopted for the Coiba National Park on July of 2004, the first law of its kind for the Republic of Panama (ANAM 2005). Starting in November of 2002, Panama ICBG members worked closely with ANAM to have the Coiba National Park inscribed into UNESCO's list of World Heritage Sites. In July of 2005, the Coiba National Park was formally inscribed, one of approximately 160 World Heritage Sites worldwide. The Panama ICBG is providing funding and personnel for the first complete botanical survey of the islands of the Coiba National Park. Preliminary studies of the flora of Coiba Island resulted in the discovery of a new genus (*Desmotes* in the family Rutaceae), endemic to Coiba, along with three endemic species (Ibáñez 2001). The interior section of the island is largely unexplored and will likely yield additional endemic taxa. All data from the Panama ICBG-sponsored botanical survey of the Coiba National Park will be made available to ANAM, which is in the process of developing a new management plan for the park. Panama ICBG support has also provided support for taxonomic research in the Coiba National Park's marine environment. Partial support for a sponge taxonomist resulted in the identification of a new species of sponge, *Aplysina*

chiriquensis, from the park (Diaz et al. 2005). To counter the difficulty in obtaining funds for botanical surveys or taxonomic research in general (Wheeler et al. 2004), biodiscovery research can help provide the badly needed financial support.

Conclusion: Linking Biodiscovery Research to Biodiversity Conservation

It has proved challenging to explicitly link biodiscovery research to the conservation of biodiversity. This is due in part to the nature of conservation work: success does not usually result in a concrete ‘product' but is rather a combination of actions, attitudes, and regulations that promote the protection of a given area or species within that area. It is widely recognized that there are insufficient funds necessary to protect all of the world’s threatened species, in either terrestrial or marine habitats (Myers et al. 2000, Roberts et al. 2002). Accordingly it is crucial to explore mechanisms whereby funds available for complementary activities, such as biodiscovery research, can promote biodiversity conservation. Biodiscovery research is one of several vehicles through which a biodiverse country can capitalize upon its natural heritage, using it as a comparative advantage to attract funds to strengthen host-country research programs. When employment and educational opportunities are linked to biodiversity, an ineluctable consequence is an enhanced appreciation for biodiversity. Under appropriate circumstances a direct link between human health and biodiversity can be made, as described above for the Coiba National Park. Cabrera-Medaglia (2004b) indicated that in the case of Costa Rica, the fraction of money from drug discovery is significantly less than that derived from tourism activities. But ecotourism does not train scientists, provide investments for scientific infrastructure, or provide future treatments for diseases whose impact is greatest in the developing world. In any event, the Costa Rica example clearly demonstrates that both enterprises are compatible if not complementary. To dismiss the potential impact of biodiscovery research on biodiversity conservation by virtue of a “pharmaceutical researcher’s willingness to pay for biodiversity as an input into commercial products” (Simpson et al. 1996) assumes that the role of the host country is limited to providing biological resources as a commodity and ignores the potential benefits to be gained by its participating as a partner in biodiscovery research.

Access and Benefit-Sharing Contracts Utilized by the Panama ICBG

First-Generation Access and Benefit-Sharing Contracts for the Panama ICBG: The Hub and Spoke Model

As described above, access and use of biological diversity in Panama is currently defined by the GLE (Law 41 of 1998). Accordingly, a suite of legal agreements for the Panama ICBG were developed that met the following basic requirements: (i) consistency with the spirit and letter of the GLE and the CBD; (ii) a model that anticipated the substantive development of the host country in biodiscovery research; (iii) equitable benefit sharing for all of the partners concerned; (iv) clearly defined provisions for the collection and transfer of biological samples; (v) clearly written and easily understood; and (vi) practical to implement. Material Transfer Agreement (MTA) templates that were developed elsewhere were initially explored (Putterman 1996), but it was decided to develop *sui generis* contracts that could be tailored for the circumstances in Panama. Many of the standard contractual elements ('legal boilerplate') that are present in the legal agreements of the Panama ICBG have been published elsewhere (Gollin 2002a).[9]

The Panama ICBG currently operates with a series of coordinated two-party agreements. The main advantage of this arrangement, known as the "hub and spoke model" (Gollin 2002b), is that bilaterial agreements are easier to negotiate and to change if the parties or terms change during the life of the agreement. As the recipient of the ICBG Program award and as a consequence of the program's original design, including the contractual arrangements, STRI is the "hub" institution. Ensuring consistency between the different agreements proved to be straightforward and imposed no significant burden during the negotiations or during the implementation of the program. There are three primary disadvantages of this model: (i) the hub institution must carry the burden of the negotiation and coordination between the contracts (Gollin 2002b); (ii) by negotiating bilateral agreements, one loses the opportunities to have all of the parties work together and simultaneously; and (iii) any one of the parties in a two-party agreement is more vulnerable to criticism than if there were a consortium of institutions involved.

Elements of the ANAM-STRI Agreement for the Panama ICBG

Beyond the provisions of the GLE, the primary legal framework for the Panama ICBG was established by the agreement between ANAM and STRI (ANAM-STRI Agreement). All

subsequent two-party agreements negotiated for the program are consistent with the terms of this agreement (Capson 2002a, Gollin 2002a).

Key Concepts and Definitions Specified in the Agreement

While the agreement does not cite any articles of the CBD in particular, the ANAM-STRI Agreement explicitly acknowledges its consistency with the CBD. Standard concepts such as access fees (i.e., fees paid by an industrial collaborator, often annually, that are independent of any funds from the development or commercialization of any product) (ten Kate and Laird 1999), intellectual property, milestone payments, and net revenue were explicitly defined. The definition of "Materials" is broad in order to ensure that any biological materials collected, even inadvertently, falls under the terms of the agreement (e.g., microbes). Materials are defined as "Any biological substance, either in whole or in part, which is collected under this Agreement. Examples include, but are not limited to, plants, insects, microbes, and uncharacterized organisms such as microbial life present in samples or parasites transferred adventitiously, and extracts, derivatives and preparations thereof."

In defining "Derivatives", the intention was that any chemical compound derived from Materials, *as well as any informational content that those compounds may contain*, are subject to the terms of the ANAM-STRI Agreement. Derivatives are defined as "Any discrete chemical compound that has been obtained from Material, an analog of such a compound, a synthetic counterpart to such compound, a variant that is structurally based on the compound or that is otherwise produced using in substantial part information contained in, or conveyed by, the Material, and genetic material able to express such compounds." If a pharmaceutical agent is developed from material originally collected by the Panama ICBG, even if it is entirely synthetic, it is still subject to the terms of the ANAM-STRI Agreement.

The ANAM-STRI Agreement specifies that collaborations between STRI and each collaborator shall be formalized through an individual agreement, a copy of which shall be made available to ANAM. Institutions that collaborate with STRI for the Panama ICBG are classified as Industrial Collaborators, Noncommercial Collaborators, or Panamanian Collaborators. Noncommercial Collaborators are defined as "Any public institution, scientific or research institution or a not-for-profit organization working in collaboration with STRI as part of the ICBG". During the first five-year cycle, non-Panamanian academic collaborators played essential roles in the Panama ICBG through technology transfer and training of students, but they

were not involved in research activities involving the use of biological materials. Panamanian Collaborators are a subset of Noncommercial Collaborators that are based in Panama. As described above, researchers in Panama-based institutions played the primary roles in the research activities and were the only institutions included in revenue-sharing provisions. As described below in the section "*Evolution of the Panama ICBG"*, that situation has changed. While ANAM's permission is not required for STRI to enter into collaborative agreements for the Panama ICBG, in practice, for each Industrial Collaborator that is incorporated into the Panama ICBG, ANAM's recognition is obtained in writing. Significantly, ANAM has the final word in these arrangements as they approve the export of each sample sent outside of Panama for the Panama ICBG.

Procedures for the Collection and Testing of Biological Materials

In particular, STRI agrees to minimize environmental impacts while collecting biological materials and to avoid the collection of any materials known to be rare or endangered. STRI also pledges to solicit permission for any recollections of a quantity greater than 100 grams dry weight. Standard ANAM collecting permits are utilized by the Panama ICBG for the collection of both marine and terrestrial samples.

The Use of Traditional Knowledge

The ANAM-STRI Agreement stipulates that collections based on traditional knowledge would only occur "with the express prior written consent of the appropriate competent governing authorities, where such a governing authority exists, and in a manner that ensures the equitable sharing of benefits that arise from traditional knowledge". The contract stipulates that "institutions or organizations offering traditional knowledge, such groups, institutions or organizations may participate as Panamanian Collaborators", meaning that representatives of groups offering traditional knowledge would participate in the Panama ICBG with the same status as the Panamanian Collaborators participating from Panamanian academic or governmental institutions. For reasons described above, the Panama ICBG has never utilized traditional knowledge to guide the collection of biological materials for drug discovery.

Procedures for Obtaining ANAM's Authorization for Use, Transfer, and Export of Biological Materials

The intention of this clause was to streamline procedures for the authorization to use, transfer, and export the biological materials collected under the ANAM-STRI Agreement. Once material was 'authorized', STRI would be able to use the material for research, transfer materials within Panama, and export the biological materials to collaborators outside the country, without the need to obtain additional authorization from ANAM. This provision would have applied only to the Panama ICBG and would have added a novel administrative procedure for ANAM in addition to creating a new category of biological materials. This procedure proved impractical and, by mutual agreement, conventional ANAM permits for exporting biological materials have been used. The materials that are exported are indicated by their scientific names (when known) and each carries a unique code.

Establishment of an Environmental Trust Fund

The ANAM-STRI agreement anticipates the establishment of an Environmental Trust Fund, designated by mutual agreement between ANAM and STRI, "for the purpose of biodiversity conservation and to support sustainable uses of biodiversity, including biodiversity prospecting, in the Republic of Panama" (Capson 2002b). The fund is to be administered by a local foundation, *Fundación Natura*, whose mission is "to promote natural resource management in Panama, particularly through the financing of projects that promote the conservation of biological diversity, environmental protection and sustainable development in Panama, and by strengthening the capacity of the institutions and organizations that implement those projects" (Fundación Natura 2006). Specifically, the trust fund would be used to "support projects, studies, institutions and individuals that promote the understanding, conservation, protection and/or sustainable use of biological diversity throughout the Republic of Panama". The recipients of grants from this fund will include nongovernmental organizations and individuals. Since there has been no money from either access fees or from the development of any compound developed by the Panama ICBG to date, the fund has not been established. However in light of the probable incorporation of Dow AgroSciences into the Panama ICBG, which will result in the generation of access fees, it is anticipated that the fund will be established in 2007.

Distribution of Net Revenue and Access Fees

This clause in the ANAM-STRI Agreement describes the distribution of revenues among the Panama-based institutions of the Panama ICBG. The largest share of any revenue (30%) would flow to the Environmental Trust Fund, the second largest share (20%) would flow to a fund managed by ANAM, and the remaining 50% would be split in equal shares among the Panama-based Collaborators to the Panama ICBG (as defined above), irrespective of their relative contribution to any invention that generated the intellectual property. The latter provision was designed to promote a spirit of collaboration among Panama-based researchers in which information, data, and ideas are freely shared. As the revenues derived from Access Fees were expected to be relatively small (e.g., US$25,000 to 40,000) they are divided between fewer participants, namely, the Environmental Trust Fund (40%), ANAM (30%), and STRI (30%) with the stipulation that the latter portion be spent "to support research and conservation activities in the Republic of Panama".

Management of Intellectual Property

It was originally envisioned that STRI would manage the IP generated by STRI and its Panamanian Collaborators associated with the Panama ICBG. The motive was one of expediency: it was anticipated that it would be far easier for one institution to manage IP for the program than multiple institutions. The ANAM-STRI Agreement stipulates: "It is contemplated that STRI shall own IP, or manage IP shared with Non-Commercial Collaborators, including the obligation to incur expenses for the filing and maintenance of patents, and responsibility for licensing Intellectual Property to provide revenues." In practice, this clause was sometimes misconstrued to mean that STRI shall uniquely 'own' all of the IP associated with the Panama ICBG (in fact, the IP generated to date through the Panama ICBG has been shared between investigators from STRI and Panama-based institutions). Contractual agreements drafted in the future for the Panama ICBG are likely to specify that ownership and management of IP shall be decided collectively by all of the institutions involved in the generation of the invention.

The Influence of Science and Technology on Contract Negotiations

As a research-driven program, the application and development of the necessary and appropriate technology for the Panama ICBG has played a major role in the design and implementation of the program, including the contracts that were negotiated between the participating parties. For

example, the contractual arrangements between STRI and the Panamanian research institutions involved in the program took into account the techniques that could be performed in Panama for the *in vitro* testing of biological materials for antiparasitic and anticancer properties and the isolation and characterization of biologically active chemical compounds. In the contract between STRI and the University of Panama, the parties commit to the training of Panamanian university level students and postdoctoral scientists, including "the use of biological assays, data analysis, methods of analysis and purification of proteins and organic compounds, and other applicable scientific methods and techniques". The language in the ANAM-STRI Agreement is consistent with the contracts between STRI and its Panama-based academic collaborators, and recognizes that STRI will commit to "transfer knowledge, expertise, technology and materials" related to the research activities described above. In some cases, the contemporary technology necessary for the Panama ICBG was unavailable for practical or proprietary reasons, for example, the screening methodologies utilized by NIBR, and contracts were developed that permitted their incorporation into the Panama ICBG under well-defined terms.

The design of the program anticipated that host-country participants would generate publications and IP. Accordingly, all of the contractual agreements for the Panama ICBG address the ownership and management of IP and recognize the willingness of the participants to work cooperatively to publish the results of the research. The significant role of host-country scientists in the Panama ICBG, which is reflected in all of the contractual arrangements for the program, has had a fundamental impact of the way the program has been perceived by government officials, scientists, students, and the public at large, a perception from which the program has consistently benefited.

The Essential Role of USA- and Europe-Based Academic and Governmental Collaborators for Technology Transfer and Development for the Panama ICBG

During both five-year cycles of the Panama ICBG, academic collaborators have played crucial roles in the transfer of materials and technology and by providing training opportunities. Examples of biological materials obtained through collaborations include the cancer cell lines (Monks et al. 1991), the non-infective HIV assay (Kiser et al. 1996), the recombinant *Trypanosoma cruzi* parasite that expresses the *Escherichia coli* ß-galactosidase gene (Buckner et al. 1996), and strains of the *Leishmania* sp. parasite. Most of the cell lines and parasites are proprietary and made available through MTAs. During the first five-year cycle of the Panama

ICBG, Panamanian scientists trained in laboratories in Mexico, Spain, and the USA in a range of techniques including the bioassay-guided isolation and characterization of natural products with activity against cancer cell lines or tropical parasites and the cultivation of the malarial parasite. Without this transfer of technology and the availability of proprietary materials and training opportunities, the program would not have much of its current Panama-based research capability. During the second five-year cycle, the program has relied less on transfers of technology and materials, but continues to benefit from training opportunities in the USA.

Evolution of the Panama ICBG

As could be expected of any complex and multi-institutional biodiscovery program, the Panama ICBG has evolved over the past seven years. The overall program goals remain the same but the program has grown more focused by eliminating elements that were either unsuccessful or peripheral to the basic mission of drug discovery and conservation. Collections of biological materials now include organisms that are more likely to yield novel biologically active compounds, for both marine (cyanobacteria and soft corals) and terrestrial (endophytic fungi) collections. Accordingly, the reliance on terrestrial plants has decreased. While maintaining a focus on research, capacity building, and biodiversity conservation in Panama, the program has benefited from the involvement of established marine natural products chemists from the Scripps Institution of Oceanography, increasing the level of sophistication of the chemistry component and bringing the expertise of decades of research in multi-institutional, international drug-discovery research.

While the first generation of legal agreements for the Panama ICBG utilized the hub-and-spoke model, the subsequent round of agreements is likely to incorporate elements of the 'consortium' contractual model, the advantages of which were discussed above. The experience gained by the earlier contractual arrangements will be incorporated into the next round of agreements. As described below in the section "*The Changing Landscape for Biodiscovery Research in Panama*", ANAM plans to implement a new set of ABS regulations in the near future. Those regulations will affect all of the contracts associated with the Panama ICBG in ways that are unclear at this writing.

Addition of New Disease Targets

INDICASAT researchers are working on the development of a novel fluorescence-based *in vitro* biological assay for detection of substances with activity against the dengue virus that can be performed in 96-well plates. The global prevalence of dengue has grown dramatically in recent decades: some 2.5 billion people are now at risk from dengue. An estimated 500,000 cases of dengue hemorrhagic fever, a potentially lethal complication, require hospitalization each year; many of these victims are children. There is no specific treatment for dengue fever (World Health Organization 2006).

The Changing Landscape for Biodiscovery Research in Panama

The landscape for scientific research within Panama has also evolved during the life of the Panama ICBG and will likely continue to do so. There is a clear recognition by members of the government, in particular SENACYT, that biological diversity that is accessible on practical and equitable terms provides Panama with a comparative advantage internationally for both basic and applied research, including biodiscovery. That research can, in turn, promote economic growth and help secure the country's health by finding treatments for diseases of national importance. The current SENACYT administration is actively pursuing a science and education agenda that continues to invest in scientific infrastructure by substantial increases in the number of grants for scientific research (the only peer-reviewed grants in the country) and by providing opportunities for graduate and postdoctoral scientists and education professionals at all levels to study abroad. Of the students and young scientists that are currently undergoing training outside of Panama, some are likely to pursue academic careers within Panama. Combined with scientists that have been trained overseas through the CIFLORPAN facilities at the University of Panama, they are likely to contribute to substantial changes in Panama's scientific landscape.

As described above, ANAM is responsible for developing the appropriate "legal instruments and/or economic mechanisms" in order to regulate and control the access and use of biological resources in Panama. At this writing, ANAM is in the process of developing regulations for those purposes. It is hoped that the experience obtained through the design and implementation of the Panama ICBG, by both practitioners of biodiscovery research and the officials that regulate those activities, will prove beneficial. Irrespective of the outcome of those regulations, due in part to the Panama ICBG, the environment in which the regulations are being developed is characterized by a significant degree of cooperation between academic and

governmental institutions within the country, in recognition of the fact that all of the institutions, and the constituencies that they serve, will be affected by the outcome.

South-South Technology Transfer

Pending the availability of additional funds, the South-South training component of the Panama ICBG will be enhanced, in particular with respect to biodiscovery research for treatments of tropical parasitic and viral disease. By providing training opportunities to developing country scientists, it is hoped that the program will help promote equitable biodiscovery research in countries where that research is either absent or significantly restricted. The collaboration between the ICBG programs in Panama and Madagascar, discussed above in the section "*Drug Discovery for Malaria*", provides a particularly relevant example of productive South-South training and technology transfer.

Conclusions

Panama provides an example of how a biodiversity-rich country can benefit by participating in biodiscovery research. Panama's participation in an international collaborative drug-discovery program helped contribute to the development of an integrated biodiscovery program that includes a guided collection strategy, a unique suite of bioassays, and the facilities and equipment that permit the bioassay-guided fractionation and characterization of compounds that are active against important disease targets. Funds from the Panama ICBG have been complemented by investments from the host-country government. The Panama ICBG has proved to be an excellent vehicle for training young scientists, who then use that experience to advance their scientific careers. In effect, Panama has leveraged its biodiversity under highly advantageous terms and invested in education and in the country's scientific infrastructure. Provided the program remains productive and internationally competitive, funds for the continuity of drug-discovery research are likely to come from any of a number of international funding agencies.

Applying the Experience in Panama in Other Settings

The biodiscovery program in Papua New Guinea (described as a case study in the section "*Case Study: The University of British Columbia and Papua New Guinea and the Development of the Hemiasterlins"*) provides an informative contrast. While Papua New Guinea is not currently in a

position to maintain the scientific apparatus present in Panama, by partnering with academic colleagues that can isolate and characterize biologically active natural products with the potential to treat disease, Papua New Guinea has received significant financial benefits that are being invested in the country's scientific infrastructure. The examples from Panama and Papua New Guinea share four important elements. First, both are heavily dependent upon international collaborations. Second, the drug-discovery programs involving both countries produce discrete chemical compounds that are chemically and biologically characterized. Both programs offer to their pharmaceutical partners a value-added product that can be recognized as IP and protected by international patents: the major difference is the degree of involvement of the academic partner from the developed country. Third, both programs were allowed to proceed in the absence of excessive national regulations that could have otherwise discouraged practitioners or potential donors. Fourth, the working relationships between the collaborating partners, including the pertinent government authorities, were transparently defined by contracts. Panama and Papua New Guinea differ significantly in terms of indigenous scientific capacity and the social and economic conditions that permit long-term scientific research, nevertheless, both countries have benefited by participatory biodiscovery research.

The other examples cited above provide informative comparisons but for different reasons. Costa Rica once utilized contractual models to regulate access to biological resources and to define the terms of biodiscovery programs, and is now attempting to do the same with national legislation. The regional and national legislation that regulates access to biological resources and biodiscovery research in Colombia has, in effect, created circumstances that are not conducive to participation in international biodiscovery research. In the context of Latin America, where the development of the functional legal and contractual mechanisms for biodiscovery research has created significant challenges, it is hoped that the experience in Panama will prove useful for both policy makers and researchers.

In other settings, the experience in Panama may prove most useful in the context of science and technology. In the case of Africa, as the world's poorest continent, a considerable amount of media attention in both the lay and scientific press has been directed towards the need to develop indigenous science and technology (Nature 2005a, 2005c). Policy and health care experts from Africa have indicated a number of areas that need to be strengthened, including the training of more scientists, the creation of solid institutions that ensure that scientists have

specific, well-resourced projects to work on, training programs, and collaborative research links across Africa and abroad that are rooted in African health problems. As described in the section "*Disease Targets Selected by the Panama ICBG: Technology Transfer and Development for Bioassays*" the participation in biodiscovery research provided the framework and financial means by which technology was transferred to Panama or developed by local scientists, most of which was directed towards diseases of great importance to the host country. The presence of that technology in Panama has played a major role in catalyzing research, investments, and the training of students. While Africa provides a unique, variable, and challenging set of circumstances, the experience in Panama suggests that biodiscovery research could play a role in the strengthening of science and technology on the continent.[10]

Biodiscovery Research at a Crossroads

There is a tremendous need to develop novel treatments for diseases of global importance and no shortage of disease threats on the horizon (Garrett 2005), all of which would benefit from novel treatments. Diseases and pathogens are capable of rapidly developing resistance to existing drugs (Garrett 1995, Normile 2005). As discussed above, the pharmaceutical industry is showing a renewed interest in natural products (Koehn and Carter 2005) and new partnerships have emerged for the treatment of neglected diseases that are providing substantial funding for research (Nature 2005b). Collectively, these trends suggest that there will be a consistent demand for biologically active natural products. In addition, barring any remarkable change in circumstances or practices in developing counties, the destruction of tropical habitats described above is likely to continue, suggesting that those countries that maintain intact tropical habitats will become even more valuable from the perspective of biodiscovery research.

Does the current international political climate suggest that biodiversity rich countries are willing to leverage their biological wealth for participation in biodiscovery research, even under optimal circumstances? Unfortunately, that does not appear to be the case. A recent study of the Pacific Rim countries concludes "...in the next ten years countries and bioprospectors will probably continue to experience many of the policy development and implementation obstacles, limitations, and problems described in this report" (Carrizosa 2004a). Since the CBD was opened for signature, there are many examples from which developing countries can draw upon should they choose to enter into equitable biodiscovery research programs. But policy makers must appreciate that biodiscovery is a research-driven endeavor that can only succeed in the presence

of flexible and clear ABS regulations. The benefits that host countries can receive from substantive participation in biodiscovery research are significant, but far more significant would be the discovery of treatments for diseases that are responsible for enormous human suffering in the developing world, trapping countries in a vicious cycle of poverty and ill health (Sachs 2002).

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[1] The process of isolating and characterizing natural products is expensive, time consuming, and labor intensive and may take years for a single complex and novel natural product. The economist Joseph Vogel has proposed that countries that are suppliers of the biological and chemical materials for biodiscovery research should form international cartels and that "revenues (from drug discovery) should be distributed among countries that could have provided the same chemical" (Vogel 1997). Such a model would require an accurate (or at least an estimate) of the host country's chemical diversity. Given that the estimates of the number of species on the planet vary by orders of magnitude (Wilson 1992), that a small fraction of those species been given scientific names, and that a far smaller fraction have been characterized for their chemical content, even a rough estimate of a host country's chemical diversity is logistically impossible. The "biological diversity cartels" discussed above would presumably use their strengthened bargaining position to demand royalties on the order of 15% from pharmaceutical companies (Vogel

1997). Suggesting royalties of this size is inconsistent with the economic realities of the drug-discovery industry and would serve only to render natural products at a distinct disadvantage to compounds developed from other sources.

[2] Assistance with IP management is available from the Public Interest Intellectual Property Advisors (PIIPA). PIIPA was established as "an independent international service and referral organization that can help fill the need for assistance by making the know-how of intellectual property professionals available to developing countries" (Gollin 2005, Public Interest Intellectual Property Advisors 2006).

[3] Other assumptions made by Simpson et al. (1996) are also inconsistent with contemporary biodiscovery research and undervalue the biological resources in biodiverse countries: (i) Their model considers extremely large numbers of samples for screening (e.g., up to 10 million). In reality, natural products chemistry is a time consuming and expensive task and chemists tend to focus on certain taxa that are known to be rich in biologically active natural products (e.g., plants, sponges, and cyanobacteria) and may manage to study only on the order of dozens of species in the context of an entire academic career. (ii) Their assumption that "all species within a particular taxon are 'equally different' is inaccurate. It is well known that certain species produce extraordinary numbers of natural products. For example, the cyanobacterium, *Lyngbya majuscula*, has yielded no fewer than 150 secondary metabolites (Tan et al. 2003), an extraordinary diversity even among the cyanobacteria, a well-known source of biologically active natural products. They are correct in their conclusion that their "simple model does not begin to do justice to the real-world complexities involved". Refinements of the model presented by Simpson et al. (1996) and published by Craft and Simpson (2001) suffer from the same assumption that there exists a market for unprocessed biological materials by the pharmaceutical industry.

[4] An NCE is a medication that contains an active ingredient that has not been previously approved for marketing in any form (Koehn and Carter 2005).

[5] While Gleevec was originally thought to bind to a single target, providing support for the single-target approach to drug discovery, subsequent research has shown that it may not be as specific as originally thought. It has been shown to target a platelet-derived growth factor (PDGF) receptor, and is active against a second rare cancer known as gastrointestinal stromal tumor. Researchers now think that too much specificity can be problematic and that drugs that bind to more than one target may provide a better approach for treating complex diseases (Frantz 2005).

[6] There are cases in which chemical compounds used by the pharmaceutical industry are derived directly from natural sources. From plants, examples include vincristine and vinblastine, derived from the Madagascar periwinkle, *Catharanthus roseus* (Rischer et al. 2006). In the case of marine invertebrates, the bryozoan, *Bugula nertina*, is a source of bryostatin 1, and *Lissodendoryx* sp., is a source of halichondrin B, both of which are obtained by farming (Faulkner 2000). As the case studies in this chapter involving Panama and Papua New Guinea describe, the contractual arrangements for the respective biodiscovery programs ensure that the host country will continue to receive benefits even if the commercially available product is not derived from the host country where the original collections occurred.

[7] As described by Carrizosa (2004b), procedures for the access and use of *ex situ* collections for biodiscovery research, whether established before or after the adoption of the CBD, are generally not clearly defined and the ownership of those *ex situ* collections is often controversial.

[8] The incentives for seeking provisional patent protection for the microfluorimetric method for antimalarial drug discovery were twofold. First, should the technique prove to be of commercial value, provisional patent protection ensures that mechanisms can be developed that will ensure that a fraction of any revenues that result will return to the Panama-based institutions that own the IP. Second, ownership of the IP ensures that the technique can be made available at no cost to developing country scientists, as in the case of the Madagascar ICBG.

[9] *Sui generis* contracts have been chosen by many investigators (Gollin 2002b). During the development of the agreements for the Panama ICBG, input was received from Michael Gollin of Venable LLP who ensured that the agreements were drafted in a manner that was enforceable, coherent, and internally consistent and that they contained the basic elements present in contractual agreements of this nature.

[10] Among the examples of successful research institutions in Africa are the Kenya Medical Research Institute and the Malaria Research Training Centre in Bamako, Mali (Butler 2004). The latter was cited as a successful grass-roots initiative directed towards research into malaria, which has been successful in training scientists and generating high-quality research.