"Studies on Biodiversity of Vietnam and Laos" 1998−2005: Examining the Impact[#]

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The impact of the University of Illinois at Chicago-based Vietnam-Laos International Cooperative Biodiversity Group (ICBG) Program "Studies on Biodiversity of Vietnam and Laos", which has been in operation for the period of 1998−2005, touches on five major areas of endeavor: (a) biodiversity inventory and conservation; (b) studies on medicinal plants; (c) drug discovery and development; (d) economic development; and (e) issues on intellectual property rights and benefit sharing in natural products drug discovery and development. Highlights are presented and the significance is discussed.

Introduction

In 1992, the ICBG (International Cooperative Biodiversity Groups) program was established and administered by the Fogarty International Center (FIC) of the United States National Institutes of Health (NIH), in collaboration with the National Science Foundation (NSF) and the United States Department of Agriculture (USDA) (http://www.fic.nih.gov/programs/icbg.html). This program runs in a five-year cycle and went into operation in 1993, for the 1993−1998 cycle; in 1998, for the 1998−2003 cycle;[1−3] and in 2003, for the 2003−2008 cycle.

The ICBG program is a unique effort of the United States Government that addresses the interdependent issues of natural product drug discovery, biodiversity conservation, and sustainable economic growth. Its policy is based on the rationale that efforts to examine the medicinal potential of the earth's natural resources are urgently needed, since habitat destruction and diminishing biodiversity will make it increasingly difficult to do so in the future. If such an effort, usually termed "natural products drug discovery" or "bioprospecting", is undertaken in such a manner, so that local communities and other source country organizations can derive direct benefits from the effort and, ultimately, from their diverse biological resources, sharing of the financial and scientific benefits arising from the project may provide clear incentives for preservation and sustainable use of the biodiversity.[2−5]

The University of Illinois at Chicago-Based Vietnam-Laos ICBG: Studies on Biodiversity of Vietnam and Laos (1998−2003; 2003−2008)

Specific Objectives and Organizational Structure. In response to the 1997 Request for Application (RFA: TW-98-001) dated August 15, 1997,[6] a proposal to establish and implement an ICBG based at the University of Illinois at Chicago, at the PCRPS (Program for Collaborative Research in the Pharmaceutical Sciences), was submitted to the Fogarty International Center (FIC).[7] Funding for this project was awarded on September 29, 1998, covering the period of October 1, 1998, to September 30, 2003, to be referred to as Phase I. A re-competition in 2002 resulted in an award for the second phase (Phase II) of operation of the UIC ICBG, 2003−2008.[8] This ICBG, "Studies on Biodiversity of Vietnam and Laos", is also known as "UIC-based Vietnam-Laos ICBG" or, simply, UIC ICBG.

The Phase II UIC ICBG consists of a consortium formed by the University of Illinois at Chicago (UIC; the institutional and administrative base of this ICBG), Purdue University (West Lafayette, IN), Vietnamese Academy of Science and Technology (VAST; formerly, National Center for Science and Technology, Hanoi, Vietnam), Cuc Phuong National Park (CPNP; Ninh Binh, Vietnam), Traditional Medicine Research Center (TMRC; Vientiane, Laos), and Bristol-Myers Squibb (B-MS; Princeton, NJ). In Phase I, GlaxoSmithKline (GSK; Stevenage, UK) was our industrial partner. Within VAST, the units or institutes actually involved in the ICBG research are IBT (Institute of Biotechnology), ICH (Institute of Chemistry), and IEBR (Institute of Ecology and Biological Resources). Under special arrangement, the Laboratory of Mycobacteria of the Institute of Hygiene and Epidemiology in Hanoi collaborates in the project under the umbrella of the Institute of Biotechnology.

The specific aims of the Phase II UIC ICBG mirror those of the first cycle (1998−2003)[7,9] and may be stated as follows:

(i) To conduct a biotic survey and to implement biodiversity conservation effort at Cuc Phuong National Park, in Vietnam, and to carry out multifaceted studies on the medicinal plants of Laos.

a. In Vietnam, to prepare a manual for identification of the flowering plants of Cuc Phuong National Park; to establish a

[#] Dedicated to Dr. Norman R. Farnsworth of the University of Illinois at Chicago for his pioneering work on bioactive natural products.

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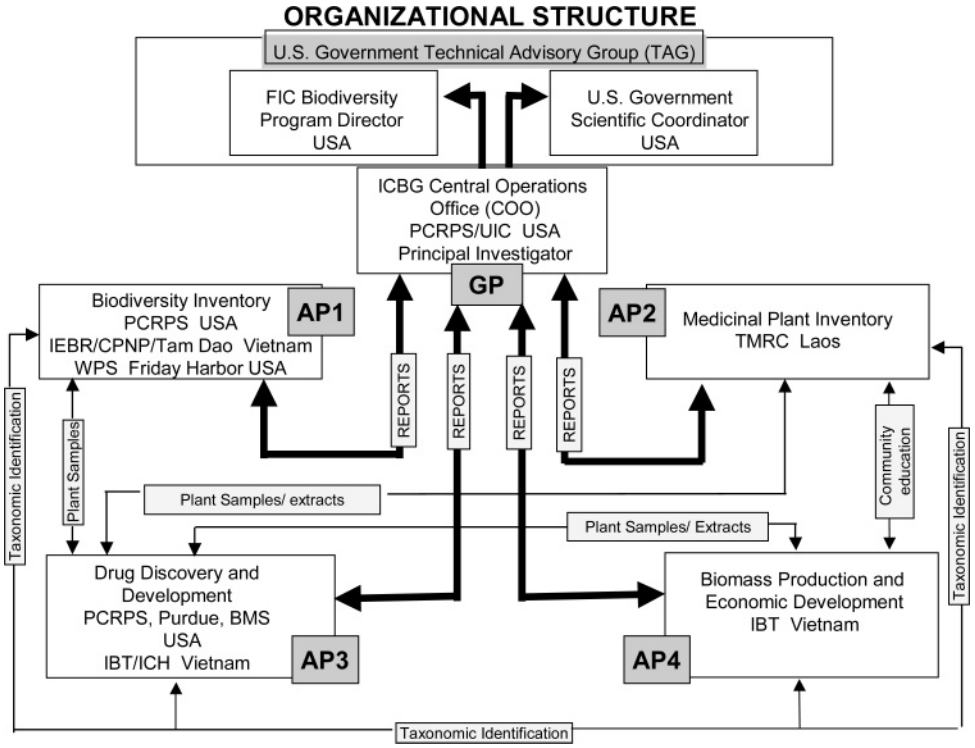


Figure 1. Organizational structure of UIC ICBG, 2003−2008, showing lines of communication.

threatened plant rescue center; to implement a conservation education program at Cuc Phuong National Park; to transfer the GIS-based technology of biodiversity hotspot assessment to a Vietnamese scientist, using Tam Dao National Park as the study site; and to collect and identify plants as part of the continuing biodiversity inventory process.

b. In Laos, to carry out comparative ethnobotanical studies in selected ecogeographic zones of Laos; to undertake a traditional medicinal mapping project (TMMP), incorporating an innovative GIS technology component, as part of an effort in the protection of Lao Traditional Medicines; to consolidate all information acquired to date and communicate it to the scientific community; to upgrade and strengthen the Lao Medicinal Plant Database at TMRC; to take measures in the conservation of medicinal plants; to collect and identify plant samples (with a history of medicinal use) for drug testing and development.

(ii) To continue efforts to discover new biologically active molecules from plants of Cuc Phuong National Park, targeting the spermatophytes, pteridophytes, and bryophytes, and from medicinal plants of Laos, as possible candidates for drug development for therapies against malaria, AIDS, cancer, and tuberculosis.

(iii) To continue efforts to improve the standard of living of members of the communities who participate in the ICBG studies and to strengthen the human resources and the scientific infrastructure of host-country institutions of the UIC ICBG in Vietnam and Laos.

The above specific aims of the Phase II UIC ICBG are to be accomplished through the combined efforts of four Associate Programs: AP-1 (Associate Program 1), charged with biodiversity inventory and conservation and based in Vietnam (Ninh Binh/Cuc Phuong National Park; Hanoi/Institute of Ecology and Biological Resources) and Chicago (UIC-PCRPS-Field Museum); AP-2, charged with studies of medicinal plants of Laos and economic development and based in Laos (Vientiane/Traditional Medicine Research Center); AP-3, charged with drug discovery and development and based in Chicago (UIC-PCRPS), West Lafayette, Indiana (Purdue University), Princeton, New Jersey (BMS, industrial partner), and Hanoi, Vietnam (Institute of Chemistry); and AP-4, charged with biomass production and economic development, based in Hanoi, Vietnam (Institute of Biotechnology), and, in collaboration with the Laboratory of Mycobacteria of the Institute of Hygiene and Epidemiology (NIHE), to perform anti-TB assays. The complex and intertwining activities of the four Associate Programs are handled and coordinated by the ICBG Group Program (Central Operations Office) based at UIC-PCRPS in Chicago, where the UIC ICBG Principal Investigator (D.D.S.) is located (Figure 1).

Study Sites. The focus of biodiversity studies in Vietnam is the Cuc Phuong National Park (CPNP), a 22 000-hectare forest-covered limestone formation in northern Vietnam.[10,11] This park, which was officially recognized as a national park by the Vietnamese Government on July 7, 1962, is located at the intersection of three provinces (Ninh Binh, Thanh Hoa, and Hoa Binh), about 100 km southwest of Vietnam's capital city, Hanoi.[7,10−12] The focus of ICBG biodiversity studies in Laos is countrywide, but in particular, regions where Traditional Medicine Stations are located, with special emphasis on the inventory and collection of medicinal plants through field interviews with healers and with members of the general populations.[7,9]

Accomplishments

Seven years after the initiation of the UIC ICBG project, a number of significant accomplishments have been achieved that have impacted on scientific knowledge, communities, institutional infrastructure, human resources, and intellectual property policies on research on natural products, especially among our host-country institutions in Vietnam and Laos.

Biotic Survey and Biodiversity Conservation. In Vietnam, the book *Seed Plants of Cuc Phuong National Park−A Documented Checklist* was published in 2004,[13] providing the most complete data on our knowledge of the seed plants (gymnosperms and angiosperms) of Cuc Phuong National Park to date, and contributes significantly to our knowledge of the flora of Vietnam and Southeast Asia. In this book, 1922 species of angiosperms and four species of gymnosperms are catalogued, each documented by a series of voucher herbarium specimens. A previously published, *undocu-*

mented, inventory listed 1658 species of angiosperms and three species of gymnosperms.[14] Included in the additional number of species in the 2004 *Checklist* are numerous new distribution records of species and genera previously not known to occur in the Park [e.g., *Illigera parviflora* Dunn, Hernandiaceae; *Keenania tonkinensis* Drake, Rubiaceae; *Lysimachia insignis* Hemsl., Primulaceae; *Kadsura coccinea* (Lem.) A.C. Sm., Schisandraceae], even in Vietnam [e.g., *Phrynium hainanense* T.L. Wu & S.J. Chen, Marantaceae; *Nyctocalos cuspidatum* Miq., Bignoniaceae; *Anodendron howii* Tsiang, Apocynaceae],[15−18] and two genera and species of orchids new to science [*Vietorchis aurea* Aver. et Aver.; *Zeuxinella vietnamica* (Aver.) Aver.].[19] The data contained in this *Checklist* have also been made available globally (online), in the form of a web-based database *Atlas of Seed Plants of Cuc Phuong National Park* (http://fm2.fieldmuseum.org/plantatlas/). Currently, the atlas receives a worldwide exposure, in part through a link, which many institutions and online databases have placed on their websites (see Supporting Information).

Another significant accomplishment in Vietnam has been the completion and publication of the GIS (Geographic Information System)-based biodiversity assessment on the vegetation cover of Cuc Phuong National Park, wherein 45 "plant diversity hotspots" are recognized.[10] A ground-based inventory of tree species diversity in these hotspots based on 0.1-hectare plots has confirmed the concept and existence of these plant diversity hotspots. The results of this ground-truth study are being published elsewhere. The original idea of this GIS analysis was to identify areas within the park that may harbor high concentrations of plant species, where we should target our drug discovery collection, to maximize the taxonomic diversity of the plant samples collected. To an extent this was implemented. Beyond drug discovery collection, it was found that species richness and diversity among hotspots was not identical, but that each hotspot appears to have its own floristic composition. This finding, together with a change detection analyses of the Cuc Phuong vegetation cover, by comparing satellite imagery of 1992 against that of 2000, using GIS technology, has helped Cuc Phuong National Park identify critical areas within the park that need protection as a result of advancing human pressure, especially agricultural activities. Some of these areas that are situated near the park's boundaries embrace locations that have been identified as plant diversity hotspots. Thus, the argument for promoting the application of these plant diversity hotspots as a tool in conservation is based on factual information that forest changes and agricultural encroachment on the park did occur. Left uncontrolled, agricultural advancement may eventually wipe out the existence of one or more hotspots, and extinguish plant species unique to that hotspot, before we know of their existence there. Whether these plant diversity hotspots also harbor high concentrations of other organism species, including insect species, amphibians, reptiles, microbes, etc., requires further studies to provide the answer. Among actions the Park has taken in applying the concept of biotic richness and plant diversity hotspots are the training of the rangers in understanding the concept, in recognizing the physical locations of these plant diversity hotspots, and in locating them on the ground using a GPS (Geographic Positioning System) instrument. The Park, with funding from the ICBG program, starting in 2003, also implemented a Conservation Awareness Program (CAP), initially with the assistance of ENV (Education for Nature Vietnam) (http://www.envietnam.org/index.html), a Vietnam-based environmental education-focused local NGO (nongovernmental organization). CAP educates the younger members of the Cuc Phuong communities (especially school children) and raises awareness among adult members of the communities on the importance of conserving the Park's biodiversity. At present, CAP is a program that is ongoing at Cuc Phuong National Park, run by Cuc Phuong National Park's own staff. Daily activities of the CAP staff include running conservation clubs (local school students in the buffer zone of the park), village programs (adult-focused at locations around the park), student visits (to get local school students to learn about the park during their visits), puppet shows (with a biodiversity conservation story line), teacher visits (to get local teachers more involved in the conservation awareness program), teacher training, environment competititon, CAP staff training, and summer program. This program will be sustained in the future.

The results of the ICBG research on biotic inventory and biodiversity conservation at Cuc Phuong National Park also led to the establishment in 2004 of a "Threatened Plant Rescue Center" (TPRC) located near the Park's headquarters close to the Park entrance. The purpose of this facility is to preserve endangered and endemic (13 species), vulnerable (18 species), and rare (46 species) plant species found in the Park[20] by placing them in an easily accessible and manageable location for study. This ex situ collection represents a living gene bank that may serve as a resource for conservation and economic development initiatives. It is planned to expand the living collection to include rare and threatened plants of Vietnam.

Plant tissue culture is being used to produce biomass[21a,b] of species targeted for planting at TPRC, both for purposes of biological evaluation and to support the conservation effort in the Park by increasing the species population of endemic, endangered, vulnerable, and rare species. It is also intended to promote economic development among communities in the ICBG research site by helping members of the community generate income from distributed starter plants, in cases of economically valuable species. An experiment utilizing an economically valuable food plant species, *Melientha suavis* Pierre (Opiliaceae), is being implemented.

In Laos, through the effort of the Laos-based ICBG team, and as a result of the generosity of the people of the village of Somsavath of the Paksan District (Bolikhamsay Province), a 26-hectare Medicinal Plant Preserve was established. The legal document that recognizes this forested land as a preserve was decreed by the Paksan District Governor on July 26, 2004. The Decree states that the designated forested land is to be used for educational and research purposes on the study of medicinal plants, particularly those found on this site, for the benefits of medicine in the future, and that the Forestry Division of the District has to implement this Decree in accordance with the Forestry Law, namely, preserving the land and the biodiversity within. Work on full taxonomic and medicinal plant field inventory and literature searches on the potential medicinal importance of plants in this preserve are ongoing.

Ethnobotanical Studies and the Protection of Traditional Medical Knowledge. In Laos, ethnobotanical field interviews were performed throughout the country, but primarily among healers and members of communities in areas where a Traditional Medicine Station (TMS) is located. The TMS is a provincial facility established by the Provincial Health Office, in consultation with the Traditional Medicine Research Center (TMRC) under the mandate of the Ministry of Health of Laos, to support the work of TMRC in the promotion and popularization of traditional medicines of Laos. Of the 18 provinces, there were 10 TMS units, each located in one province and associated with a provincial Traditional Medicine Hospital, at the initiation of the ICBG project (1998). Today, there are 13 TMSs, three of which were established by the initiative of TMRC during our Phase I operation through the ICBG support. For reasons of distance and logistics, and due to existing good local facilities, fieldwork carried out by the TMRC ICBG team in three TMS areas has been especially extensive, namely, in the Oudomxai (northern), Bolikhamsay (central), and Champasak (southern) provinces. Human subject research aspects of the protocol used in this work (field ethnobotanical studies) were approved by the UIC Institutional Review Board (IRB), as to informed consent of interview subjects, interview methods, documentation, and safety and protection of human research subjects (UIC IRB Research

Protocols H-97-1056 and 2003-0636, subject to annual review and renewal).

As a result of four years of effort, data on more than 600 flowering plant species that are used in traditional therapies in Laos were gathered, comprising 655 entries in the Lao Medicinal Plant Database (LMPD) housed at TMRC. Together with data gathered through other efforts, more than 1000 species of medicinal plants of Laos, comprising 1211 entries, are represented in the LMPD, a database that is intended to serve as the clearinghouse for traditional medicinal plant information of Laos. Each entry represents a record of collection (interview). Besides ethnomedical data, more than 1000 voucher herbarium specimens are deposited at the Herbarium of TMRC as the physical documentation of the ICBG-funded ethnobotanical interviews. As part of the ICBG setup, taxonomic identification of these voucher specimens was performed initially at the Herbarium of TMRC, then at the Herbarium of the Institute of Ecology and Biological Resources of the Vietnamese Academy of Science and Technology (Hanoi, Vietnam) and at the Herbarium of the Field Museum (Chicago, IL). A portion of these ethnobotanical data has been analyzed.[22]

The Lao Medicinal Plant Database (LMPD) is the basis of the ICBG-sponsored effort to map the traditional medicinal plant uses throughout Laos, a project referred to as TMMP (Traditional Medicine Mapping Project). Initially, only data derived from the ICBG-sponsored fieldwork are mapped, but eventually also from data in the LMPD derived from other sources, including data from the old palm-leaf scripts.[23] These records of ancient traditional medicine uses of plants were deposited in many temples throughout Laos, but today they have been assembled in a single place, the National Library of Laos, in the form of microfilm. The purpose of the ongoing TMMP is to contextualize all ethnobotanical/ethnomedical information (ecological, biological, taxonomic, ethnomedicinal, and geographic) in a coherent, holistic fashion into map layers, which can be combined using GIS software. Both LMPD and the results of TMMP will eventually serve to provide support to and allow TMRC scientists to design and implement effort in the protection of the Traditional Medicines of Laos.[24]

In Vietnam, a field interview-based ethnobotanical inventory of medicinal plants used by the Muong ethnic communities, who live in villages surrounding Cuc Phuong National Park, was also performed during Phase I of the UIC-based Vietnam-Laos ICBG. A total of 394 plant species, used in over 200 traditional prescriptions for treating 19 different disease categories, were documented. A book (in English) on the medicinal plants of the Muong people is in preparation, while an illustrated playing-card style booklet (in Vietnamese), intended for members of the community, has been published.[25] Aside from the book, the Vietnam ICBG project under the leadership of the AP-4 team, and in collaboration with the Cuc Phuong Commune People's Committee, established an Ethnobotanical Garden, containing more than 70 species of medicinal plants, to preserve the medicinal plant knowledge of the Cuc Phuong healers and communities, while also serving as a ready source of medicinal plant material for the Cuc Phuong Commune.

Drug Discovery and Development. The raw material for the drug discovery and development endeavor of the UIC-based Vietnam-Laos ICBG is sourced through two approaches: (a) the biodiversity-based or the "random" collection-based approach, from plants of Cuc Phuong National Park; (b) the ethnobotany-based approach, primarily through field interviews performed throughout Laos as described above and, during Phase I, also through field interviews performed with the ethnic Muong at Cuc Phuong Commune.[7,9] During Phase I, a plant collection permit in Vietnam was issued by the Ministry of Agriculture and Rural Development (MARD) through a letter dated September 15, 1998, Ref. No. 3551/BNN/KHCN, and from the Cuc Phuong National Park, through a letter dated September 16, 1998. In Laos, a permit was issued by the Department of Forestry of the Ministry of Agriculture and Rural Development (MARD) dated September 18, 1998. In Phase II, a plant collection permit in Vietnam was issued by MARD (Permit No. 683 QD/BNN-HTQT) dated March 3, 2004, while in Laos, a permit was issued by the Ministry of Agriculture and Forestry (MAF) (Permit No. 0158/2004 dated January 27, 2004).

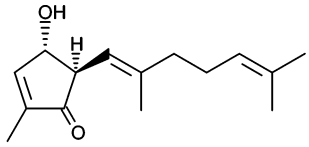
By August 2005, a cumulative total of 3556 angiosperm plant samples, stem bark, root, fruit, combined leaf and twig, etc., each 100−500 g dry weight, comprising approximately 900 species of angiosperms, and 42 pteridophyte samples (42 species) had been collected from Cuc Phuong National Park through a biodiversity-based approach. Through the ethnobotany-based approach, 420 plant samples (about 420 angiosperm species) had been collected from Vietnam, and 655 plant samples (about 600 species, mostly angiosperms) had been collected from Laos. A total of 142 re-collections (3−6 kg dry weight) (approximately 110 species) of samples had been completed from Cuc Phuong National Park, and 52 re-collections of samples based on ethnobotanical interviews (from Laos and Vietnam) had also been re-collected. The following major angiosperm families have been well sampled from Vietnam; namely, 50% or more of the species belonging to each of these families occurring at Cuc Phuong National Park have been sampled: Lauraceae (93%), Sapindaceae (90%), Araliaceae (81%), Annonaceae (74%), Rutaceae (72%), Moraceae (71%), Rosaceae (62%), Verbenaceae (57%), Meliaceae (56%), Euphorbiaceae (54%), Leguminosae (50%) (Supporting Information). Of these families, novel and biologically active compounds have been isolated from the Lauraceae, Rutaceae, and Moraceae (see below). Families with more than 15 species at CPNP and not adequately sampled include Orchidaceae (1%; only one of 69 species sampled), Cyperaceae (5%), Gramineae (12%), Acanthaceae (21%), Urticaceae (22%), Compositae (26%), Labiatae (31%), and Sterculiaceae (31%) (Supporting Information). No new or biologically active compounds have been isolated from members of these families. On the other hand, a number of minor families, Dipterocarpaceae (four species sampled of five recorded at Cuc Phuong National Park), Loganiaceae (four species sampled of four in the family), Burseraceae (seven species sampled of eight in the family), and Tiliaceae (six species sampled of eight in the family), have yielded new, biologically active compounds.[26a−d] Presently, analyses on the overall novelty of plant species collected at Cuc Phuong National Park in terms of their potential in harboring new biologically active compounds are being performed, through search of data in the NAPRALERT database (http://info.cas.org/ONLINE/DBSS/napralertss.html and http://www.uic.edu/pharmacy/depts/pmch/napralert/). Preliminary examination indicated that the greater proportion of plant species collected at Cuc Phuong National Park does not appear in the NAPRALERT database plant list.

Laboratory testing for anti-HIV and antimalarial activities is performed at UIC in Chicago; cytotoxicity assays against cancer cell lines were performed at UIC during Phase I, but at Purdue University in Phase II. Although an anti-TB assay was performed at the laboratory of the Institute of Tuberculosis Research (ITR) at UIC during Phase I, in Phase II, following the training of Vietnam-based TB specialists by our UIC-based TB scientist, a screening assay was performed at the Laboratory of Mycobacteria of the National Institute of Hygiene and Epidemiology (NIHE), Hanoi. The antimalarial assay was performed at UIC. The methods used in the screening of extracts for anti-HIV, cytotoxicity, antimalarial, and anti-TB activities have been described in previous articles.[7,9,27,28]

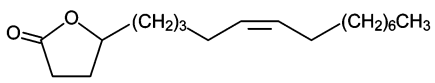
By August 2005, extracts of 2309 samples (comprising more than 600 species) had been assayed in our infectious disease assays and tumor cell line panel. From 22 of the re-collected samples (see above), 249 pure natural products of varying degrees of structural complexity and/or biological activity were isolated from plant leads, identified on the basis of their anti-HIV, antimalaria, antituberculosis, or anticancer activities. Aside from the discovery of biologically active compounds, our studies have contributed significantly

to the knowledge of natural products chemistry with 82 new secondary metabolites, including the novel litseane sesquiterpene carbon skeleton from *Litsea verticillata* Hance (Lauraceae).[29] The large percentage (ca. 33%) of our isolates that are new compounds may well be the result of a rigorous prioritization system based primarily on preexisting biological and chemical information on both the plant genus and species in question. This literature-based dereplication strategy is effectively coupled with resources and expertise available in an academic setting to achieve a dynamic level of productivity in the discovery of new bioactive compounds. The chemical diversity of these new natural products includes alkaloids and amides, macrocyclic compounds, lignans, neolignans, butenolides, phenylpropanoids, steroids, and terpenoids.

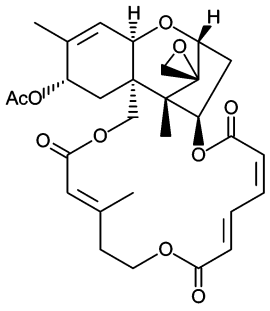
A total of 103 compounds, including 50 new substances, were found to possess varying degrees of biological activity. Examples of these compounds include eight novel anti-HIV litseane sesquiterpenes (e.g., litseaverticillol A, **1**) from the combined leaves and twigs of *Litsea verticillata*,[30a] the antimalarial active macrocyclic trichothecene sesquiterpenoid (verrucarin L acetate, **2**) from the leaves and stem bark of *Ficus fistulosa* Reinw. ex Bl. (Moraceae),[31a] and the anti-TB active fatty acid lactone (micromolide), (−)-*Z*-9-octadecene-4-olide (**3**), the alkaloid lansine, and a number of carbazoles, from the stem bark of *Micromelum hirsutum* Merr. (Rutaceae).[32] The anti-HIV litseanes showed inhibitory activity against HIV-1 replication in the HOG.R5 system with IC_{50} values ranging from 8 to 58 μM. To improve the anti-HIV activity of the litseanes, a synthetic study of new litseane derivatives is being conducted in collaboration with Greek scientists, who have recently completed total synthesis of the litseanes.[30b−d] Verrucarin L acetate, a trichothecene sesquiterpene, was isolated as a potent antimalarial agent from *F. fistulosa*. Trichothecenes are established mycotoxins,[31b] and selected members of this group of compounds have been reported to exist in higher plants such as in *Baccharis cordifolia* DC. (Asteraceae).[31c] The isolation of verrucarin L acetate from the extract of *F. fistulosa* most probably suggests the involvement of pathogenic fungi in the plant material collected for this work.



1. Litseaverticillol A
IC_{50} = 56.2 μM (SI = 2.6)



3. Micromolide
MIC = 5.4 μM (SI = 63)
EC_{99} = 20.0 μM (macrophage assay)



2. Verrucarin L acetate
IC_{50} = 1.1 nM (D6, *Plasmodium falciparum*, SI = 158)
IC_{50} = 1.3 nM (W2, *P. falciparum*, SI = 135)

Trichothecenes are potent inhibitors of protein synthesis[31d] that presumably exert their antimalarial effects via identical mechanisms.[31e] Micromolide showed potent in vitro anti-TB activity against H37Rv (MIC = 5.4 μM) and a selectivity index (SI) of 63 and exhibited activity against the Erdman strain of *M. tuberculosis* in a J774 mouse macrophage model (EC_{99} = 20.0 μM).[32] Lansine and 3-formyl-6-methoxycarbazole are less active, with MIC = 59.3 and 69.3 μM, respectively, but the lesser anti-TB activity of these latter compounds and of four other closely related carbazoles from this plant, coupled with the lack of cytotoxicity of all six carbazoles, suggests that anti-TB potency could be enhanced without a significant increase in mammalian cell cytotoxicity. SAR of both compound classes is currently being explored via the generation of analogues and bioassays.

Of the approximately 600 flowering plant species (655 plant samples) collected in Laos through the ethnobotanical approach, two species [*Asparagus cochinchinensis* (Lour.) Merr., Asparagaceae; *Nauclea orientalis* (L.) L., Rubiaceae] yielded biologically active, novel compounds (anti-HIV from *A. cochinchinensis*; antimalarial from *N. orientalis*), but no ethnopharmacological correlation was found between the history of medicinal use, as stated in the field interviews, and the biological activity of the compounds isolated.[33a−c]

Economic Development. Two aspects of economic development activities have been implemented. The *first* is capacity building and institutional infrastructure strengthening of ICBG partners in Vietnam and in Laos, and the *second* is improvement of the living conditions of members of the communities where UIC ICBG operates, through various actions and reciprocity measures.

In Vietnam, institutional capacity building through the strengthening of the human resources of the Vietnam Academy of Science and Technology (Institute of Ecology and Biological Resources, Institute of Biotechnology, and Institute of Chemistry), of Cuc Phuong National Park, and of National Institute of Hygiene and Epidemiology (NIHE) host institutions was implemented in various forms. The most notable has been short-term training activities (formal training, namely, in workshop or seminar settings, or informal, in joint activities during the implementation of research work, in the laboratories or in the field) of various levels of ICBG staff (laboratory assistants, junior and senior scientists), in which senior scientists provide the training to junior scientists, or interactions among senior scientists themselves on the application of new knowledge or new methodologies. This type of interaction occurred throughout the implementation of the UIC-Vietnam-Laos ICBG project, 1998−2005. The synergistic interactions built up and strengthened the capacity of all involved. Numerous formal and semiformal seminar-workshops were held in Hanoi and Cuc Phuong National Park facilities.

Another form of human resource strengthening has been the long-term training of junior and senior scientists in settings outside of Vietnam, both at the headquarters of the UIC ICBG, PCRPS-UIC, and at the Field Museum, the botanical research base of the UIC ICBG, under the guidance of UIC ICBG Chicago staff, as well as, informally, under the guidance of other botany staff of the Field Museum. Training was also undertaken in other foreign institutions, such as in France (Natural History Museum, Paris) and the People's Republic of China (Institute of Botany, Kunming). The training included database management, herbarium curation and management, advanced taxonomy, ethnobotany, biodiversity conservation, bioassay techniques (anti-TB, antimalaria, cytotoxicity, anti-HIV), bioassay-guided isolation, structure elucidation of active compounds, technology transfer, intellectual property management, research ethics (human subject protection), and traditional medicines development. A junior taxonomist from both the Institute of Ecology and Biological Resources (IEBR) and Cuc Phuong National Park (CPNP), a senior plant taxonomist from IEBR, a junior biologist from the Institute of Biotechnology (IBT), and two senior chemists

from the Institute of Chemistry (ICH) undertook long-term training in Chicago. Since their return from Chicago, all of them have undertaken research activities independently at their respective home institutions. These activities have been sustained to date. Three junior taxonomists obtained a M.Sc. degree in plant taxonomy at the Institute of Ecology and Biological Resources under the funding of the ICBG project, while one junior taxonomist is presently pursuing a M.Sc. degree in plant taxonomy and conservation at the University of Missouri at St. Louis with support, in part, by ICBG funding. Finally, the implementation of the use of NAPIS (Natural Products Information System, http://www.wps2.com/products.htm) presented the opportunity to UIC ICBG staff in Vietnam and Laos not only to learn the use of a complex database system but also to experience the day-to-day management and opportunity for the utilization of such a database, including the creation of reports (herbarium labels, NAPIS-formatted reports) and data mining. All UIC ICBG consortium members now prepare and submit reports to the Chicago-based NAPIS database manager as required by the project.

Infrastructure strengthening was implemented in the form of purchases of new field and laboratory equipment, materials, and supplies, as well as the acquisition of books important in the conduct of ICBG research. Numerous items were acquired. Notable among these were vehicles, herbarium cases and curatorial supplies, tissue culture setup and other equipment, chemistry laboratory equipment, computers, and cameras.

The most outstanding results of the infrastructure strengthening effort have been, *first*, the enhancement of the herbarium at IEBR, whereby the Vietnamese Academy of Science and Technology (VAST) was provided with additional office and laboratory space destined specifically for use by ICBG research personnel, and (ii) the establishment of the Herbarium of Cuc Phuong National Park (herbarium acronym: CPNP) as a botany research unit of the park. This new Cuc Phuong Herbarium has been included in the list of the Herbaria of the world (http://sciweb.nybg.org/science2/IndexHerbariorum.asp; http://207.156.243.8/emu/ih/herbarium.php?irn=124362; http://www.nybg.org/bsci/ih/ih.html). The CPNP Herbarium presently has 12 440 herbarium collection holdings, stored within 28 metal cases, about half of which represent new collections made under the ICBG funding. In fact, research for the book *Seed Plants of Cuc Phuong National Park*−*A Documented Checklist* (see above) was undertaken, in part, at the CPNP Herbarium. Research capability and activity will be sustained when the junior scientist of Cuc Phuong completes his M.Sc. degree and returns to Vietnam.

Another significant step is the enhancement of the tissue culture laboratory of Cuc Phuong National Park, the role of which is to strengthen the conservation initiatives of the Park. Thus, personnel of the plant tissue culture laboratories at CPNP is now collaborating closely with scientists at the Institute of Biotechnology in supporting the plant conservation effort of the park.

Support in terms of geographic information system (GIS) capabilities was provided to a scientist at Hanoi University Botany Department in the form of a capitalized GIS facility and training in satellite image processing and GIS grid analysis for delineation of "plant diversity hotspot" regions in Tam Dao and Cuc Phuong National Parks. The scientist trained in this GIS technology is now performing a follow-up ground-truth study at Tam Dao, to further the concept of the plant diversity hotspots in this park. Beyond Tam Dao, this scientist is expected to continue to apply the GIS technology he acquired in the performance of similar analyses of plant diversity hotspots in other national parks of Vietnam.

In Laos, as part of the institutional capacity building and infrastructure strengthening, personnel of the Traditional Medicine Research Center (TMRC) have had the opportunity to undertake training and upgrading of their knowledge, both in the United States at the University of Illinois at Chicago, the Field Museum of Natural History in Chicago, and the United States National Cancer Institute, and in various other foreign institutions, notably, in Vietnam, Thailand, Malaysia, Japan, and Korea, either through funds from the ICBG project or from funds received from other sources, for which the ICBG project served as a leverage. Training included expertise in plant taxonomy, herbarium curatorial techniques, database management, chemical isolation, ethnobotany, and traditional medicines development. On-site training at TMRC has also been implemented, in the form of workshops organized during visits of foreign scientists and experts and which included database building and management, ethnobotany field techniques and documentation, IP management, technology transfer, research ethics, and biodiversity conservation.

Thus, under ICBG support, TMRC has been able to upgrade its infrastructure to undertake research as defined in the specific objectives of this institution under the ICBG award. Infrastructure strengthening included the purchase and acquisition of two vehicles to conduct ethnobotanical fieldwork, upgrade of TMRC's research facilities, including enhancement of its Herbarium and medicinal plant display garden, and various other upgrades that allow Internet communications (e-mails), scientific presentations, medicinal plant processing, chemical extraction of plant materials, and strengthening of its laboratories to perform efficient multiple extractions of a large number of samples. The most important expertise acquired and sustained to date by the TMRC personnel in the ICBG project has been the upgrading of their ethnobotanical field interview methods and documentation, following a protocol and strict guidelines developed at UIC by the Chicago-based ICBG staff. Support to strengthen the TMRC infrastructure also leveraged a donation in the form of funds, personnel, and materials from the Vietnamese Embassy in Laos, for the establishment in January 2002 of a Traditional Medicine Clinic located inside the facilities of TMRC. Under the ICBG funding, starting in 2001, TMRC has been publishing biannually a *Bulletin of Lao Traditional Medicine* (in the Lao language) to inform the Lao public and traditional medicine practitioners in Laos on research at TMRC and on new research findings in the study of medicinal plants.

In Vietnam, community reciprocity efforts have included the enhancement of the Muong community's kindergarten building facilities, to provide a cleaner, healthier, and better learning environment to the preschoolers; provision of educational supplies to Cuc Phuong schools and plastic pipes to the commune for cleaner water; the implementation of periodic community education sessions at Cuc Phuong Commune, covering topics such as fruit trees for the garden, better agriculture on sloping lands, methods of cultivating new, improved crop plants, and importance and value of conserving Cuc Phuong biodiversity; and other projects. A microloan program was instituted, whereby each of the poorest families in the commune (identified by an Economic Development Village Board appointed by the UIC ICBG Principal Investigator) was provided no-interest, rotating loans (US $180−200) that enabled these families to acquire farm animals (particularly cows and water buffaloes) to help increase agricultural productivity and income (through breeding, dung production as a fertilizer), or other domestic animals or crop plant starters to improve their household economy. For the period 2000−2005, 45 families from the commune have benefited from the ICBG support (a US $8000 ICBG investment) through this program. Aside from improving household economy of the poor families, the microloan program has also helped reduce the human pressure on the Park's biodiversity, based on the review and evaluation of the program in a seminar held with the participation of members of the commune, local officials, and the Forest Protection Service of Cuc Phuong National Park (CPNP).

During Phase I, an Ethnobotanical Garden adjacent to the clinic of the Cuc Phuong Commune was established by the IBT-based ICBG team with the assistance of ICBG personnel from IEBR and CPNP; more than 70 traditional Muong medicinal plant species

were planted in the garden. In 2002, this garden was transferred to the clinic and the commune, for monitoring and use in community health care and educational activities, stressing the heritage and exploration of traditional medicine knowledge among Muong people in Cuc Phuong. The transfer was effected through a document signed by the Head of the Cuc Phuong People's Committee, the Head of Cuc Phuong Commune Clinic, and ICBG personnel. Since the beginning of Phase II, Institute of Biotechnology-based and Cuc Phuong-based ICBG personnel continued to provide assistance to the commune in the maintenance and growth of this garden (with more medicinal plant species), while also publicizing this educational facility to visitors to the Cuc Phuong National Park.

Community reciprocity efforts in Laos, the infrastructure and capacity building activities, included the provision of herbarium cases, cabinets, an electric grinder for plant samples, motorcycles, and other materials to a number of Traditional Medicine Stations and funds to attend training to upgrade knowledge on medicinal plants and traditional medicines. The amount of support provided to Traditional Medicine Stations' (TMSs') facilities in three provinces (Bolikhamsay, Oudomxai, Champasak) has been rather generous, since these TMSs serve as models for other TMSs. In parallel, three new TMSs (Luang Prabang, Luang Namtha, Xekong) were established with ICBG funding, to expand the health services of TMSs to communities, from 10 provinces at the start of the ICBG project (1998) to 13 provinces. Seminars addressed to traditional healers on "How to integrate traditional and modern medicine in the prevention and treatment of diseases" were held in selected TMSs by staff of the Traditional Medicine Research Center (TMRC).

During Phase I (1998−2003), TMRC ICBG staff worked to improve the standard of living of participating communities through community education, including supporting village meetings and seminars on primary health care and on the uses of plants for medicine. The personnel of TMRC also sponsored workshops, training sessions, and networking meetings for local healers at the provincial Traditional Medicine Stations (TMSs) they visited each year and at special events at the headquarters of TMRC. Under the support of the UIC ICBG, TMRC provided funds to some communities for, among other things, the improvement of local schools, local clinics, and the provision of basic medicines (aspirin, antibiotics) and school texts. For example, support was provided to Boun Tay Village (Pathomphon District, Champasak Province) for the purpose of repairing and enhancing the Traditional Medicine Hospital facilities of this village. The importance of this hospital, and of the ICBG support, may be appreciated by the fact that this hospital serves six other villages surrounding Boun Tay. Also in Champasak, support was provided to the primary school of Nonphachao Village (Phone Thong District) to repair the dilapidated school building. In Xayaboury Province, support was provided to repair the primary school building and facilities in the Xayaboury District, and to the Pagoda of Na Gnao Village, for the improvement of its Traditional Medicine Unit. Another example of support was provided for the upgrading of the medicinal plant garden of Na La Village. In Attapeu Province, Xaysettha District, Somkhot Village, tiles were purchased for repairing the roof of its school building.

This economic development support continued in Phase II and is expected to continue and to be sustained beyond the life of the ICBG project, through the establishment of the Laos Biodiversity Fund (LBF), approved by Ministerial Decree No. 2832/MOH dated December 30, 2003, of the Ministry of Health of Laos. The objectives of LBF are defined in the LBF's by-laws, as follows: (a) to promote economic development among Lao ethnic communities, especially those in ICBG study areas; (b) to promote research to value and to protect Lao traditional medicine; (c) to strengthen the capacity to conduct scientific and policy research and analysis on Lao biodiversity and protected areas; (d) to promote environmental education and to increase environmental awareness of Lao communities. LBF was established with an endowment of US $90 000 from the UIC ICBG, from compensation money provided by GlaxoSmithKline (GSK), an industrial partner of the UIC ICBG during Phase I (1998−2001). The business plan of LBF states that one to three "small" projects ($3000 or less) and one to three "large" projects ($5000) will be funded during its first year of operation. As of September 2005, nine project proposals (for a total of $30 500) had been submitted by various communities and entities for development and conservation effort. Of these proposals, three were funded, for a total of $9619. Meanwhile, the LBF business plan also calls for vigorous fund-raising, which would allow for LBF to support and to sustain the support of projects defined in its objectives, toward the future.

Issues on Intellectual Property and Benefit Sharing. Central to the functioning and implementation of the UIC ICBG is a fully signed document, the Memorandum of Agreement (MOA) that binds the members of the consortium to work together and to share the benefits that may arise as a result of the cooperation. Analysis of the terms and conditions of the UIC ICBG MOA has been published,[34] and readers are referred to this paper for details.

The Phase I UIC ICBG MOA[34] spells out the obligations of each party and their joint obligations. These include issues on property rights and intellectual property rights for plant genetic material to be used in the studies, within the framework of the ICBG. All members agree that property of the plant genetic material (plant species) belongs to the country where that genetic material originates and that any discovery or invention that may arise as a result of research under the framework of the ICBG and new technology to be developed based on this genetic material should be protected and that the benefits of the discovery be shared in an equitable manner between the participating members. Benefit sharing also includes the assignment of authorship of publications and new technology that may result from the ICBG's efforts. GlaxoSmithKline waived its rights to any share of monetary benefits that may result from a royalty stream. The new Phase II UIC ICBG MOA retains all clauses of the Phase I MOA, with appropriate modifications on percentages of share by the ICBG institutions, because of an additional institutional expansion (Purdue University) in the membership of the consortium. In Phase II, like GSK, Bristol-Myers Squibb (BMS) waives the rights to a share of the royalty stream. One major difference between Phase II and Phase I MOAs is the recognition of each consortium member, including the industrial partner, BMS, in filing for an IP protection of new discoveries.

The importance of the UIC ICBG MOA goes beyond the ICBG. It has provided a model to our host country institutions in negotiating issues on IP and benefit sharing in international bioprospecting cooperation. It has also served as a platform for the University of Illinois at Chicago in revising intellectual property rights and benefit-sharing policy for biodiversity-based drug discovery and development research at UIC.[35] The UIC ICBG MOA represents a "flagship" agreement at UIC.

Discussion and Conclusion

The ICBG program is an experiment of the United States Government, a signatory of the 1992 Rio Convention on Biological Diversity, to implement the principles of this Convention, despite the fact that the U.S. Congress has not ratified the Convention (Parties to the Convention on Biological Diversity at http://www.biodiv.org/world/parties.asp).

The uniqueness of the ICBG lies in the effort to integrate drug discovery (valuation of economic potential), biodiversity conservation, and economic development, which is also the substance and objective of the CBD (Convention on Biological Diversity Article 1 at http://www.biodiv.org/convention/articles.asp). To implement such a program, members of an ICBG must abide by the principles of the CBD, which include (i) recognition of the sovereign rights

of States over their genetic resources; (ii) compliance with the requirement of obtaining informed consent in accessing the genetic resources; (iii) recognition and respect for the knowledge, innovations, and practices of indigenous and local communities embodying traditional lifestyles relevant for the conservation and sustainable use of biological diversity; (iv) compliance with the ethics of using and promoting such knowledge, innovations, and practices toward their wider application with the approval (informed consent) and involvement of the holders of such knowledge, innovations, and practices; and (v) sharing the benefits arising from the utilization of such knowledge, innovations, and practices in an equitable manner.

Through the observance and implementation of the above principles, the UIC ICBG has been able to achieve the objectives it set during the past seven years of operation. The impact of the accomplishments touches on five aspects: (a) biodiversity conservation; (b) study and protection of traditional medicinal knowledge; (c) drug discovery and development; (d) economic development; and (e) access and benefit sharing, including issues of intellectual property and intellectual property rights. In terms of long-term benefits, it is common knowledge that the chances of discovering new molecules that would make it into commercial production are very small; hence long-term benefits in the form of a share from a royalty stream may never be in sight. Therefore, the real-time benefits that accompany the research process, which can support the research itself, the capacity building and infrastructure strengthening of host country institutions, the improvement of the economic conditions of the communities, the biodiversity inventory and conservation, drug discovery endeavor, and the study of traditional medicinal plant knowledge, as implemented by this ICBG, ensure that the benefits and the impact of the collaborative arrangements are realized. In conclusion, it can be stated that the results and the accomplishments of the UIC-based Vietnam-Laos ICBG have had significant impact on the institutions, the community, and the pursuit of new knowledge.

The lesson learned from the experiences of this ICBG tells us that natural product drug discovery or bioprospecting is a highly complex, challenging endeavor. It requires the amalgamation of a broad spectrum of expertise: team scientific expertise (of all relevant disciplines), a good, comprehensive agreement (Memorandum of Agreement), consent to the access to genetic resources and indigenous medicinal knowledge, individual and group motivation, trust, and common sense. Within the context of an international setting, it requires a fluid communication between members of the consortium, in particular, between the U.S.-based Principal Investigator and overseas members of the consortium, both in person (periodic overseas travel and on-site group meetings) and through various media (phones, faxes, e-mails). Additionally, the UIC-based ICBG convenes a group meeting once a year in a rotating location, attended by all key investigators, the ICBG Program Director from the Fogarty International Center, and the Chairperson of the U.S. Government Advisory Committee. Finally, it goes without saying that one requirement for a drug-targeted bioprospecting project, an industrial partner, is a necessity, which will move a discovery into the pipeline toward commercial product.

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Supporting Information Available: Statistics on web visitors to *Atlas of Seed Plants of Cuc Phuong National Park* for the months of August−October 2005 were retrieved on November 18, 2005, together with the last 100 visitors as recorded on that date (November 18, 2005). The statistics for the months of November−December 2005 were retrieved on January 19, 2006, together with the last 100 visitors as recorded on this date (January 19, 2006). Statistics on major flowering plant families that have been sampled as part of the drug discovery effort of this ICBG project, based on data compiled in August 2005, are presented in Tables 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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