

Electronic Supplementary Material

Strategies for the discovery of potential anticancer agents from plants collected from Southeast Asian tropical rainforests as a case study

Esperanza J. Carcache de Blanco,^a Ermias Mekuria Addo,^a H. Liva Rakotondraibe,^a
Djaja D. Soejarto,^{b,c} A. Douglas Kinghorn^{*a}

^a *Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210, United States. E-mail: kinghorn.4@osu.edu*

^b *Department of Pharmaceutical Sciences, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612, United States*

^c *Science and Education, Field Museum, Chicago, IL 60605, United States*

Covering up to 2023

**AN AGREEMENT BETWEEN
THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOIS
AND THE INSTITUTE OF ECOLOGY AND BIOLOGICAL RESOURCES OF THE
VIETNAMESE ACADEMY OF SCIENCE AND TECHNOLOGY**

The Board of Trustees of the University of Illinois, a body corporate and politic of the State of Illinois, United States of America, on behalf of its campus in Chicago, Illinois ("UIC"), and The Director of the Institute of Ecology and Biological Resources of the Vietnamese Academy of Science and Technology ("IEBR"), located in the sovereign nation of Vietnam (jointly "the Parties"), form this Agreement to establish joint research as follows.

This Agreement is non-binding in that the research programs described below are dependent upon first obtaining funding from outside sponsors. Without such funding, the promises contained herein to conduct such programs shall not be binding upon either institution. This Agreement is binding in that if any such funded programs do occur, then the other provisions of this Agreement, Parts VI-XI, shall be binding upon both UIC and the IEBR as they may be applicable.

PART I – SCOPE OF THE COOPERATION

Joint programming shall include any research program of either institution, as may be desirable and feasible to the Parties, that fosters and develops the cooperative relationship described herein. Each institution shall contribute research, and other related activities. Areas of cooperation will include, but are not limited to, the following:

1. Exchanges of scientific personnel;
2. Jointly conducted research activities;
3. Attendance and participation in seminars and scientific meetings;
4. Other projects of mutual interest to the parties

Plans and budgets for such programs shall be mutually agreed upon in writing by both institutions prior to initiating a program. Where feasible, such programs shall be negotiated on an annual basis. Each institution shall designate a Liaison Officer to develop programs. Approval for all programs shall be contingent upon the availability of funds and the formal approval of the Board of Trustees of the University of Illinois and The Director of the Institute of Ecology and Biological Resources.

PART II – JOINT RESEARCH PROGRAMS

IEBR is a research institution under the Vietnamese Academy of Science and Technology located in Hanoi, with a mission to study the biological diversity of Vietnam in its entirety, including biotic survey, conservation, and potential economic value. UIC's Program for Collaborative Research in the Pharmaceutical Sciences (PCRPS) has been involved in the search for natural products derived from plants for more than 30 years. PCRPS wishes to carry out research on vegetal biodiversity of Vietnam in collaboration with scientists and professionals of

IEBR-VAST, with the objective of discovering biologically active compounds suitable for development as new medicines. A detailed description of the fields of research, research plan, and research objectives (“Research”) is attached as Appendix A.

The Parties affirm the importance of publishing new scientific ideas and advances. Each Party shall have the right to copyright and publish the results of Research in scientific journals and conferences. No publication generated from Research shall include any restrictions whatsoever on the use of such publication by either Party. Nothing in this Agreement shall be interpreted as having the effect of preventing or delaying the publication of Research findings, except for such reasonable delays as may be required for the purpose of obtaining patent protection, as more particularly described in Part VI.

PART III – UIC RESPONSIBILITIES

1. To undertake extraction and biological assays against disease target to be mutually agreed on, and to carry out more in-depth studies, including chemical isolation and structure elucidation of compounds judged as promising or novel, in the laboratories of UIC and other partner institutions.
2. File IP protection on any new discoveries and follow through their development.
3. If feasible, arrange for selected scientists from The Institute of Ecology and Biological Resources-VAST (IEBR-VAST) to participate as part of their research training activities at the UIC-PCRPS, under mutually agreeable terms, provided that funding is available for that purpose.
4. Provide results of bioassays and chemical isolation studies of plant extracts collected in Vietnam under this agreement, prepared at UIC or other partner institutions.
5. Provide literature data from NAPRALERT database, as desired.
6. Curate voucher herbarium specimens related to project activities described in Appendix A.

PART IV – RESPONSIBILITIES OF THE INSTITUTE OF ECOLOGY AND BIOLOGICAL RESOURCES

1. To procure source plant materials for this collaborative research through field collection expedition by staff of IEBR-VAST or jointly with staff of UIC-PCRPS within Vietnam’s territory. To the extent possible, expedite government permits, and other permits related to international agreement on biodiversity, and documentation needed for the collection and shipment of plant materials to UIC. Such expediting includes clearance and payment of all export and import duties, where applicable.
2. Work closely with the UIC scientists to achieve the goals of this Agreement.
3. Exchange the results of its research with members of the UIC research team.
4. Assist UIC in determining inventorship for patent purposes, including providing legal

documentation from inventors, if patent protection is appropriate.

5. Facilitate local transportation needs of personnel, in accordance with program activities.
6. Curate voucher herbarium specimens related to project activities described in Appendix A.

PART V – JOINT RESPONSIBILITIES

1. Continue to seek external funding to support Research, including fieldwork to collect plants, extract plant samples, conduct bioassays of extracts, and isolate active compounds from plants. Each institution shall contribute by helping to identify and cultivate potential sponsors, design project plans and budgets, and write grant proposals.
2. Designate coordinators who will be responsible for guiding the progress of this Agreement and maintaining all communications between the institutions.
3. Select qualified junior scientists for training either at the IEBR or in the U.S. in fields of Research.

PART VI – INTELLECTUAL PROPERTY RIGHTS

The agreement of the Parties regarding new inventions originating from Research and any intellectual property rights therein follows below.

1. **Ownership of Intellectual Property.** Each Party's ownership share of intellectual property arising from the Research shall be based upon its:
 - a. Inventive contributions to the Research ;
 - b. Institutional policies on inventions and intellectual property
2. **Technology Transfer.** UIC will be the "Lead Party," and thus have overall responsibility for the administration, marketing, licensing and/or commercialization of the results of the Research. UIC shall file, prosecute and maintain patent applications or other intellectual property protection as it determines appropriate for the Research results, and shall keep the IEBR informed of all relevant information and progress regarding intellectual property protection and technology commercialization.
3. **Income Distribution.** Unless otherwise mutually agreed between the Parties, UIC shall distribute the income received from technology/patent licensing. Such income shall be distributed as shown in Appendix B and as follows:
 - a. UIC shall first deduct direct out-of-pocket costs (e.g., non-reimbursed patent expenses, technology development costs, consultants, etc.) incurred to protect the intellectual property, and second, deduct overhead costs of 15% of the total income to arrive at the total net income.

- b. UIC will distribute *net income* as follows:
 - 51% to IEBR
 - 49% to UIC
- c. Each Party shall be responsible for distributing its share of net revenue to its inventor employees, or others as may be determined by each Party.

PART VII – TRANSFERS OF BIOLOGICAL MATERIALS

These paragraphs will govern the exchange of all biological materials transferred under this Agreement.

1. For purposes of this Part VII:
 - a. “Material” means any biological material of a plant, animal, microorganism or other origin, containing units of heredity, and any progeny, unmodified derivatives, or modifications thereof.
 - b. “Provider” means the provider of Material, including a person, institution, organization or country, who will transfer custody of a genetic resource, including populations of both wild and domesticated species, according to the principles of the Convention of Biological Diversity.
2. The IEBR shall designate a management committee as its representative for the purposes of Materials transfers. The committee may be composed of representatives from the IEBR staff/scientists, a technology transfer program, or other similar group. The committee shall be responsible for ensuring that all laws and procedures relating to the exchange of biological material are satisfactorily observed. The committee shall make reasonable efforts to inform individual researchers of such laws and procedures. In the alternative, if the IEBR does not designate a committee or other authorized representative, the IEBR Director shall be responsible for ensuring all laws and procedures are observed as provided in the Agreement.
3. Materials, including any modifications thereof, wherever located, shall at all times be the property of the Provider and shall not be used by, or transferred to, third parties without the knowledge, consent and written authorization of the IEBR. The ownership of any new intellectual property derived from Materials shall be governed by the terms of Part VI of this Agreement.
4. The Parties shall not transfer Materials to any third party without the approval of the other.
5. The Parties shall execute a separate MTA document for each transfer of Material, particularly describing the nature of the Material, the rights and obligations of the recipient, and the duration of the transfer.
6. All Materials will be used only for research purposes described in this Agreement. Materials may be used for other, non-conforming uses only with the permission of the IEBR, which permission shall not be unreasonably withheld. However, commercial uses of Materials may only be granted by the IEBR, and may be withheld for any reason.

7. The Parties shall be responsible for enforcing the terms of this Part VII with all their employees, agents or students to whom Materials may come into possession. No such person may make available Materials or related information to any third party or any person not under the Parties' direct control.
8. Inventions which are derived in whole or in part from the use of Materials shall be assigned as provided in Part VI.
9. Unless otherwise agreed, MTA's executed under paragraph 5 above will terminate with the termination of this Agreement.
10. Materials may have latent characteristics that are unknown, unexpected, or difficult to determine, and which may be potentially hazardous. Thus, neither Party makes any warranties, express or implied, as to the safety, quality, viability or purity of the material, or merchantability or fitness for any particular purpose.

PART VIII – DISPUTE RESOLUTION

Any dispute, controversy or claim arising under, out of or relating to this contract and any subsequent amendments of this contract, including, without limitation, its formation, validity, binding effect, interpretation, performance, breach or termination, as well as non-contractual claims, shall first be negotiated amicably by representatives of the Parties. If such negotiation fails or continues without settlement for 180 days, either Party may invoke arbitration.

The place of arbitration shall be designated by the Party against whom arbitration is asserted.

PART IX – RENEWAL AND AMENDMENT

This Agreement becomes effective upon the date the last signature is affixed below and shall have a duration of 5 (five) years thereafter. This Agreement may be renewed or amended by mutual written agreement of each signatory institution.

PART X – TERMINATION

This Agreement may be terminated by either Party for any reason upon ninety (90) days prior written notice to the other. The Parties agree that, to the extent practicable, upon notice of termination they will allow researchers sufficient time and resources to wind up ongoing work. No termination shall affect the obligations of either institution under Part VI, Intellectual Property, Part VII, Transfers of Biological Materials, and Part VIII, Dispute Resolution.

PART XI - MISCELLANEOUS

This Agreement is binding upon both Parties, their affiliates, employees, agents, and associated entities. This Agreement replaces any previous agreements or understandings, oral or written, between UIC and the IEBR. This Agreement shall be executed in five originals. Faxed signed copies of this Agreement and duly executed amendments, renewals or notices sent via fax shall be treated as originals and valid for all purposes.

IN WITNESS WHEREOF, the parties hereto have offered their signatures:

THE BOARD OF TRUSTEES OF
THE UNIVERSITY OF ILLINOIS

THE DIRECTOR OF THE INSTITUTE
OF ECOLOGY AND BIOLOGICAL
RESOURCES

Walter K. Knorr, Comptroller

Date

Le Xuan Canh

Date

Michele M. Thompson, Secretary

Date

APPENDIX A
RESEARCH PLAN

**COLLABORATIVE RESEARCH ON ANTICANCER EVALUATION OF
NATIVE PLANTS OF VIETNAM**

Background (Research field)

Under Grant # 1 P01 CA125066-01A1 (2007-05653; “*Discovery of Anticancer Agents of Diverse Natural Origin*”; PI: A.D. Kinghorn), UIC-PCRPS (Program 2 of this project) undertakes research to acquire, evaluate, and isolate compounds from cyanobacteria materials, and acquire plant materials for biological evaluation and chemical isolation studies, to discover biologically active molecules as potential candidates for development for anticancer therapy.

The Program for Collaborative Research in the Pharmaceutical Sciences (PCRPS) of the University of Illinois at Chicago (UIC-PCRPS), Chicago, Illinois, USA and the Institute of Ecology and Biological Resources of the Vietnamese Academy of Science and Technology (IEBR-VAST), Hanoi, Vietnam, wish to collaborate in the research effort of Project # 1 P01 CA125066-01A1.

Research Objective

UIC-PCRPS and IEBR will undertake joint research to discover anticancer agents from the vegetal biodiversity of Vietnam, as a component of Project # 1-P01-CA125066-01A-1. Research activities will include biological assays of extracts of terrestrial plants and cyanobacterial materials at UIC and at other institution members of Project # 1-P01-CA125066-01A-1, followed by chemical isolation of active compounds, in the event of active test results, and compound development, and sourcing of terrestrial plant and cyanobacterial materials from Vietnam by IEBR.

Research Plan

A. Research to be performed by IEBR

1. IEBR scientists will perform field collection of samples of plants of Vietnam, alone or jointly with scientists from UIC, according to collection methods and schedules to be agreed between UIC-PCRPS and IEBR.
2. Terrestrial plants and cyanobacteria to be collected will be focused on species native to Vietnam, with endemic species having special interest; selection of species or genera will be guided by certain criteria to be developed by UIC-PCRPS scientists, that include review of the experimental literature, and review of data contained in the NAPRALERT database on natural products.
3. Each sample to be collected will be in the amount of 400-1000 g dry weight (seed plants) or smaller for cyanobacteria, for primary screening, and in the amount of 3-5 kg dry weight, in the event of recollection for chemical isolation studies.
4. In the event of recollection, the cost per sample will be negotiated and funded separately.
5. Each plant sample (primary collection or recollection) will be documented by fully prepared and labeled voucher herbarium specimens according to standard botanical collecting, and should include data on geographic coordinates, read preferably through the use of a GPS instrument.
6. Plant collection should take into consideration good collecting practices, protection of the species concerned, and the conservation of the forest resources and the biodiversity within.
7. Taxonomic identification of the plants collected will be performed at the herbarium of IEBR by

- taxonomists of this institution.
8. One set of herbarium specimens will be deposited in the IEBR herbarium, one set at the Herbarium of the Field Museum, Chicago, and one set to be sent to UIC for transmission to taxonomic specialists for assistance in taxonomic identification or confirmation of identification, in the event of a need.
 9. IEBR will ship plant samples and voucher herbarium specimens collected to UIC-PCRPS by air freight, and will expedite all the necessary paperwork for the shipment. Shipment should be addressed to: Dr. D. D. Soejarto, University of Illinois at Chicago, Pharmacognosy Field Station, Downers Grove, IL 60515 Tel.: (630) 740-6961/740-6960.
 10. IEBR will provide a written report to UIC-PCRPS on the outcome of its effort in the sourcing of the Vietnam's biodiversity.

B. Research to be performed by UIC-PCRPS

1. UIC-PCRPS will expedite the paperwork to receive shipment of plant materials shipped from IEBR.
2. UIC-PCRPS scientists will inventory plant samples received in a database to be developed at UIC, for sample tracking and accounting purposes.
3. Voucher herbarium specimens received will be sterilized, labeled, mounted on herbarium paper, and deposited at the John G. Searle Herbarium of the Field Museum, Chicago, which will be accessible for examination and studies by UIC and IEBR scientists, when required.
4. Additional set of voucher herbarium specimens will be sent by UIC-PCRPS to selected taxonomic specialists as necessary for assistance in taxonomic identification or confirmation of identification, in the event of a need. Where necessary, taxonomic identification or confirmation of identification of plants received will be performed at the Field Museum Herbarium.
5. Samples received will be extracted using organic solvents as established in the extraction protocol for Project # 1 P01 CA125066-01A1.
6. Extracts will be submitted to anticancer evaluation and chemical isolation studies at a laboratory designated for Project # 1 P01 CA125066-01A1.
7. UIC-PCRPS scientists in collaboration with consortium scientists in Project # 1 P01 CA125066-01A1 will perform biological evaluation of the extracts of plants collected in Vietnam, followed by chemical isolation studies of active species, and further development as potential drugs to treat cancer, if the results are promising.
8. In the event of promising compounds, a patent protection on the potential use of the compounds to treat cancer will be sought; in such an event, authorship of any patent to be filed with the US Patent Office will be determined in consultation with scientists at IEBR, taking into consideration the scientific contribution of each individual scientists involved.
9. In the event that no patent protection is justified, results of studies will be written as a scientific communication by UIC-PCRPS scientists in collaboration with other scientific personnel of Project # 1 P01 CA125066-01A1, to be published as a scientific contribution/paper in a peer-reviewed journal; in such a case, authorship of the paper will include collaborating scientists at IEBR who have contributed scientific input in the discovery.
10. UIC-PCRPS will provide report to the IEBR on the status and progress of the research periodically, based on an agreed time schedule.

C. Funding for the collaborative research

1. UIC-PCRPS, through funds from Grant # 1 P01 CA125066-01A1 will provide funding to IEBR for the field collection, identification, and shipment of the biodiversity source materials collected.
2. The amount of funding will be negotiated on a case-by-case basis, depending on whether a collection expedition is to be undertaken by Vietnamese scientists alone or whether collection

expedition is to be undertaken jointly between UIC scientists and IEBR scientists.

3. In the event of joint expedition, the cost of the expedition will be paid by the UIC expedition personnel. In such a case, fund in the amount of \$4,000 will be made available to IEBR to cover the cost to curate the voucher herbarium collections in deposit at IEBR.
4. In the event collection is performed by IEBR alone, fund will be transferred from UIC to IEBR through a standard UIC contractual agreement procedure.

APPENDIX B
ROYALTY AND FEE REVENUE SHARING MECHANISM

