The US National Cancer Institute’s Natural Products Repository: Origins and Utility

Erma C. Brown* and David J. Newman**

Appendices

Appendix A

LETTER OF COLLECTION

Agreement Between

[Source Country Organization, SCO] and the Developmental Therapeutics Program Division of Cancer Treatment and Diagnosis National Cancer Institute

The Developmental Therapeutics Program (DTP), Division of Cancer Treatment and Diagnosis (“DCTD”), National Cancer Institute (NCI) is currently investigating plants, micro-organisms, and marine macro-organisms as potential sources of novel anticancer drugs. The DTP is the drug discovery program of the NCI which is an Institute of the National Institutes of Health (NIH), an arm of the Department of Health and Human Services (DHHS) of the United States Government. While investigating the potential of natural products in drug discovery and development, NCI wishes to promote the conservation and sustainable utility of biological diversity, and recognizes the need to compensate [Source Country, SC] organizations and peoples in the event of commercialization of a drug developed from an organism collected within their country’s borders.

As part of the drug discovery program, DTP has contracts with various organizations for the collection of plants, micro-organisms and marine macro-organisms worldwide. DTP has an interest in investigating plants, micro-organisms and marine macro-organisms from [Source Country], and wishes to collaborate with the [Source Country Government (SCG) or Source Country Organization(s) (SCO)] as appropriate in this investigation. The collection of plants, micro-organisms and marine macro-organisms will be within the framework of the collection contract between the NCI and the NCI Contractor [Contractor] which will collaborate with the appropriate agency in the [SCG or SCO]. The NCI will make sincere efforts to transfer knowledge, expertise, and technology related to drug discovery and development to the [appropriate Source Country Organization (SCO) in [Source Country] as the agent appointed by the [SCG or SCO], subject to the provision of mutually acceptable guarantees for the protection of intellectual property associated with any patented technology. The [SCG or SCO], in turn, desires to collaborate closely with the DTP/NCI in pursuit of the investigation of its plants, micro-organisms and marine macro-organisms, subject to the conditions and stipulations of this agreement.

A. The role of DTP, DCTD, NCI in the collaboration will include the following:

1) DTP/NCI will screen the extracts of all plants, micro-organisms and marine macro-organisms provided from [Source Country] for anticancer activity, and will provide the test results to [SCO] on an annual basis. Such results will be channelled via Contractor.

2) The parties will keep the test results and subsequently-developed data confidential until approved for publication by the parties. Before either party submits a paper or abstract containing test results for publication, the other party shall have 60 days to review and, as necessary file a sole or joint patent application in accordance with Article 6.

3) Any extracts exhibiting significant activity will be further studied by bioassay-guided fractionation in order to isolate the pure compound(s) responsible for the observed activity. Since the relevant bioassays are only available at DTP/NCI, such fractionation will be carried out in DTP/NCI laboratories. A suitably qualified scientist designated by [SCO] may participate in this process subject to the terms stated in Article 4. In addition, in the course of the contract period, DTP/NCI will assist the [SCO], thereby assisting the [Source Country], to develop the capacity to undertake drug discovery and development, including capabilities for the screening and isolation of active compounds from plants, micro-organisms and marine organisms.

4) Subject to the provision that suitable laboratory space and other necessary resources are available, DTP/NCI agrees to invite a senior technician or scientist designated by [SCO] to work in the laboratories of DTP/NCI or, if the parties agree, in laboratories using technology which would be useful in furthering work under this agreement. The duration of such visits would not exceed one year except by prior agreement between [SCO] and DTP/NCI. The designated visiting scientist(s) will be subject to provisions usually governing Guest Researchers at NIH. Salary and other conditions of exchange will be negotiated in good faith. Costs and other conditions of visits will also be negotiated in good faith prior to the arrival of the visiting scientist(s).

5) In the event of the isolation of a promising agent from a plant, micro-organism or marine macro-organism collected in [Source Country], further development of the agent will be undertaken by DTP/NCI in collaboration with [SCO]. Once an active agent is approved by the DTP/NCI for preclinical development, [SCO] and the DTP/NCI will discuss participation by SCO scientists in the development of the specific agent.

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The DTP/NCI will make a sincere effort to transfer any knowledge, expertise, and technology developed during such collaboration in the discovery and development process to [SCO], subject to the provision of mutually acceptable guarantees for the protection of intellectual property associated with any patented technology.

6) DTP/NCI/NIH will, as appropriate, seek patent protection on all inventions developed under this agreement by DTP/NCI employees alone or by DTP/NCI and [SCG or SCO] employees jointly, and will seek appropriate protection abroad, including in [Source Country], if appropriate. All resulting patent applications and patents shall be assigned to the U.S. Department of Health and Human Services and managed by NIH. Under current NIH policy, all inventors of such assigned patents may receive royalties in accordance with said NIH policy for any royalty-bearing license(s) for these patent(s).

7) All licenses granted on any patents resulting from this collaboration shall contain a clause referring to this agreement and shall indicate that the licensee has been apprised of this agreement.

8) Should an agent derived from an organism collected under the terms of this agreement eventually be licensed to a pharmaceutical company for production and marketing, DTP/NCI will request that NIH/OTT require the successful licensee to negotiate and enter into agreement(s) with the appropriate [SCG] agency(ies) or [SCO] within twelve (12) months from the execution of said license. This agreement(s) will address the concern on the part of the [SCG or SCO] that pertinent agencies, institutions and/or persons receive royalties and other forms of compensation, as appropriate.

9) The terms of Article 8 shall apply equally to inventions directed to a direct isolate from a natural product material, a product structurally based upon an isolate from the natural product material, a synthetic material for which the natural product material provided a key development lead, or a method of synthesis or use of any aforementioned isolate, product or material; though the percentage of royalties negotiated as payment might vary depending upon the relationship of the marketed drug to the originally isolated product. It is understood that the eventual development of a drug to the stage of marketing is a long term process which may require 10-15 years.

10) In obtaining licensees, the DTP/NCI/NIH will require the license applicant to seek as its first source of supply the natural products from [Source Country]. If no appropriate licensee is found that will use natural products available from [Source Country], or if the [SCG] or [SCO] as appropriate, or its suppliers cannot provide adequate amounts of raw materials at a mutually agreeable fair price, the licensee will be required to pay to the [SCG] or [SCO] as appropriate, compensation (to be negotiated) to be used for expenses associated with cultivation of medicinal organisms that are endangered or for other appropriate conservation measures. These terms will also apply in the event that the licensee begins to market a synthetic material for which a material from [Source Country] provided a key development lead.

11) Article 10 shall not apply to organisms which are freely available from different countries (i.e., common weeds, agricultural crops, ornamental plants, fouling organisms) unless information indicating a particular use of the organism (e.g., medicinal, pesticidal) was provided by local residents to guide the collection of such an organism from [Source Country], or unless other justification acceptable to both the [SCG or SCO] and the DTP/NCI is provided. In the case where an organism is freely available from different countries, but a phenotype producing an active agent is found only in [Source Country], Article 10 shall apply.
micro-organisms and marine macro-organisms by the local population or traditional healers, this information will be used to guide the collection of plants, micro-organisms or marine macro-organisms on a priority basis where possible. Details of the methods of administration (e.g., hot infusion, etc.) used by the traditional healers will be provided where applicable to enable suitable extracts to be made. All such information will be kept confidential by DTP/NCI until both parties agree to publication.

The permission of the traditional healer or community will be sought before publication of their information, and proper acknowledgment will be made of their contribution.

3) The appropriate agency in [SCG or SCO] and Contractor will collaborate in the provision of further quantities of active raw material if required for development studies.

4) In the event of large amounts of raw material being required for production, the appropriate agency of the [SCG or SCO] and Contractor will investigate the mass propagation of the material in [Source Country]. Consideration should also be given to sustainable harvest of the material while conserving the biological diversity of the region, and involvement of the local population in the planning and implementation stages.

5) [SCG or SCG] and SCO scientists and their collaborators may screen additional samples of the same raw materials for other biological activities and develop them for such purposes independently of this agreement.

This agreement shall be valid as of the date of the final authorized signature below for an initial period of five (5) years, after which it can be renewed by mutual agreement. It may be amended at any time subject to the written agreement of both parties. Copies of such amendments will be kept on file at both of the addresses indicated below.

For the National Cancer Institute: For [SCI] or [SCO]:

Andrew C. von Eschenbach, M.D. Name (typed):
Director, National Cancer Institute Title:

Date Date

mailing and contact address: mailing and contact address:

Technology Transfer Branch NCI at Frederick Fairview Center, Suite 502 1003 - W. 7th Street
Frederick, Maryland 21701-8512, U.S.A.

Telephone: +301-846-5465 Facsimile: +301-846-6820

Appendix B

MEMORANDUM OF UNDERSTANDING BETWEEN SOURCE COUNTRY ORGANIZATION (SCO) AND THE DEVELOPMENTAL THERAPEUTICS PROGRAM DIVISION OF CANCER TREATMENT AND DIAGNOSIS NATIONAL CANCER INSTITUTE

The Developmental Therapeutics Program (DTP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is currently screening synthetic compounds and natural product materials derived from plants, marine macro-organisms and micro-organisms as potential sources of novel anticancer drugs. The DTP is the drug discovery program of the NCI which is an Institute of the National Institutes of Health (NIH), an arm of the Department of Health and Human Services (DHHS) of the United States Government. While investigating the potential of natural products in drug discovery and development, NCI wishes to promote the conservation and sustainable utility of biological diversity, and recognizes the need to compensate source country organizations and peoples in the event of commercialization of a drug developed from an organism collected within their countries’ borders.

DTP/NCI has an interest in investigating plants, terrestrial and marine micro-organisms and marine macro-organisms from [Source Country] and wishes to collaborate with the [Source Country Organization, SCO] in this investigation. DTP/NCI will make sincere efforts to transfer knowledge, expertise, and technology related to drug discovery and development to [SCO] in [Source Country, SC] (as the agent appointed by the [Source Country Government], subject to the provision of mutually acceptable guarantees for the protection of intellectual property associated with any patented technology. [SCO], in turn, desires to collaborate closely with the DTP/NCI in pursuit of the investigation of [Source Country]'s plants, terrestrial and marine micro-organisms and marine macro-organisms and selected synthetic compounds subject to the following conditions and stipulations of this Memorandum of Understanding (MOU). [SCO] will perform the collection and processing of terrestrial plants, marine macro-organisms or micro-organisms as appropriate. It is understood that the [SCO] will be solely responsible for abiding by all source country’s access policies and requirements for prior informed consent in the performance of collections. The NCI bears no responsibility for any contravention of such policies by the [SCO].

1) On the basis of in-house screening results in its anticancer screens, [SCO] may select both synthetic
compounds and extracts of plants, marine macro-organisms and micro-organisms (subject to previously determined limits as to numbers per year) for anticancer testing at DTP/NCI. If suitable in-house screens are not available at [SCO], a list of available materials may be sent to DTP/NCI.

2) Prior to submission of the materials, [SCO] will send a data sheet, to be held in confidence by DTP/NCI, on each material so that DTP/NCI may check its databases for records of prior submission to DTP/NCI.

3) For pure compounds, the data sheet(s) will give pertinent available data as to chemical constitution, structure, available biological data including in-house screening results, solubility, toxicity and any precautions which need to be followed in handling, storage and shipping.

For crude extracts, data will be provided as to the source organism taxonomy, location and date of collection, any hazards associated with the organism, available biological data and any known medicinal uses of the organism/extracts.

4) DTP will inform [SCO] which of the materials are new to the program, and such materials will be shipped to DTP for screening. DTP will provide a record of the accession number for the materials. Quantities of materials required for initial testing are 5 mg for pure compounds and 10 mg for crude extracts.

5) a) Data provided by [SCO] will be considered as confidential information of [SCO], if so labeled, and will be held confidentially by DTP/NCI, unless the data are otherwise available from public sources. No confidential information of [SCO] will be kept in files open to the public either by DTP/NCI, testing laboratories, or data processing facilities, all of which are U.S. government contractors. Only those employees directly engaged in the operation of DTP/NCI will have access to the files of information regarding the source and nature of confidential materials, unless the release of data about the materials is required under law or by court order. In the event of expiration of this agreement, the confidentiality of data provided by the [SCO] will be maintained.

b) All test results will be provided to [SCO] as soon as they are available, but not later than 270 days (nine months) from the date of receipt of the sample. If available, in vitro test results will be delivered within 90 days from receipt of the sample. [SCO] will be informed in writing of any delays beyond this period (270 days) together with an explanation of the reason(s) for delay.

c) Unless the release of test results is required under law or by court order, the parties will keep the test results and subsequently-developed data confidential until published in accordance with Article 15 or until corresponding patent applications are filed in accordance with Article 9.

Any extracts exhibiting significant activity will be further studied by bioassay-guided fractionation in order to isolate the pure compound(s) responsible for the observed activity. Such fractionation will be carried out in [SCO] laboratories. If [SCO] has no available bioassay, DTP/NCI may assist [SCO] to establish the necessary bioassay systems subject to the availability of the necessary resources. Alternatively, or in addition, suitably qualified designated [SCO] scientists may be sent to DTP/NCI for the isolation studies subject to the terms stated below in Article 7. In addition, DTP/NCI may assist the [SCO], thereby assisting the [Source Country], to develop the capacity to undertake drug discovery and development, including capabilities for the screening and isolation of active compounds from terrestrial and marine organisms.

7) Subject to the provision that suitable laboratory space and other necessary resources are available, DTP/NCI agrees to consider inviting senior technican(s) and/or scientist(s) designated by [SCO] to work in the laboratories of DTP/NCI or, if the parties agree, in laboratories using technology which would be useful in furthering work under this MOU. The duration of such visits would not exceed one year except by prior agreement between [SCO] and DTP/NCI. The designated visiting scientist(s) will be subject to provisions usually governing Guest Researchers at NIH. Cost-sharing and other conditions of visits will be negotiated in good faith prior to the arrival of the visiting scientist(s).

8) In the event that an agent isolated and purified from materials provided by [SCO], and/or a synthetic compound provided by [SCO] meets the criteria established by the Drug Development Group (DDG) of NCI’s DCTD (DTP’s parent organization), which would include, but not be limited to, in vivo activity in rodent models, further development of the agent may be undertaken by DTP/NCI in agreement with the [SCO]. Further development of the specific agent may include but not be limited to analog development through medicinal and/or combinatorial chemistry, formulation, pharmacology and/or toxicology studies. Once an active agent is approved by DTP/NCI for preclinical development (i.e., has passed the DDG at Stage IIA), DTP/NCI may collaborate with [SCO] scientists in the development of the specific agent.

9) Both [SCO] and DTP/NCI recognize that inventorship will be determined under patent law. DTP/NCI/NIH and [SCO] will, as appropriate, jointly seek patent protection on all inventions developed jointly under this MOU by DTP/NCI and [SCO] employees, and will seek appropriate protection abroad, including in [Source Country], if appropriate. Application for patent protection on inventions made by [SCO] employees alone will be the responsibility of [SCO]. Application for patent protection on inventions made by DTP/NCI employees alone will be the responsibility of DTP/NCI.

With respect only to those compounds that have been determined to possess such significant anti-cancer potential as to be scheduled for clinical trials by DCTD, the U.S.
Government shall have a royalty-free, irrevocable, nonexclusive license to manufacture and/or use by or for the U.S. Government the invention(s) claimed in any patents that [SCO] may have or may obtain on such compounds or on a process for use of such compounds. However, this license will apply only to [SCO] patents that rely upon data generated by DTP/NCI or DTP/NCI testing laboratories. This license shall be only for medical research purposes related to or connected with the therapy of cancer. The term "medical research purposes" as used herein shall not include treatment of patients outside of clinical trials or commercial distribution of the compounds.

10) DTP/NCI will make a sincere effort to transfer any knowledge, expertise, and technology developed during such collaboration in the discovery and development process to [SCO], subject to the provision of mutually acceptable guarantees for the protection of intellectual property associated with any patented technology.

11) All licenses granted on any patents arising from the collaboration conducted under the terms of this MOU shall contain a clause referring to this MOU and shall indicate that the licensee has been apprised of this MOU.

12) Should an NCI/NIH patent on an agent discovered under this collaboration eventually be licensed to a pharmaceutical company for production and marketing, DTP/NCI will request that NIH/OTT require the licensee to negotiate and enter into agreement(s) with [SCO] and/or an appropriate [Source Country] Government agency(ies) within twelve (12) months from the execution of said license. The agreement(s) will address the concern on the part of the [Source Country] government that pertinent agencies, institutions and/or persons receive royalties and other forms of compensation, as appropriate.

Such terms will apply equally to inventions directed to a direct isolate from a natural product material, a product structurally based upon an isolate from the natural product material, a synthetic material for which the natural product material provided a key development lead, a derivative of a synthetic compound provided by [Source Country] or [SCO], or a method of synthesis or use of any aforementioned isolate, product, material or derivative; though the percentage of royalties negotiated as payment might vary depending upon the relationship of the marketed drug to the originally isolated product. It is understood that the eventual development of a drug to the stage of marketing is a long term process which may require 10-15 years.

13) In obtaining licensees, DTP/NCI/NIH will require the applicant for license to seek as its first source of supply the natural products available from [Source Country]. If no appropriate licensee is found who will use natural products available from [Source Country], or if [SCO] or their suppliers cannot provide adequate quantities of raw materials at a mutually agreeable fair price, the licensee will be required to pay to the [Source Country] Government or [SCO] as appropriate, compensation (to be negotiated) to be used for expenses associated with cultivation of medicinal organisms that are endangered or for other appropriate conservation measures. These terms will also apply in the event that the licensee begins to market a synthetic material for which a material from [Source Country] provided a key development lead.

14) Article 13 shall not apply to organisms which are freely available from different countries (i.e., common weeds, agricultural crops, ornamental plants, fouling organisms) unless information indicating a particular use of the organism (e.g., medicinal, pesticidal) was provided by local residents to guide the collection of such an organism from [Source Country], or unless other justification acceptable to both [SCO] and DTP/NCI is provided. In the case where an organism is freely available from different countries, but a phenotype producing an active agent is found only in [Source Country], Article 13 shall apply.

15) Publication of data resulting from the collaboration under this MOU will be undertaken at times determined by agreement between [SCO] and DTP/NCI. Before either party submits a paper or abstract for publication, the other party shall have sixty (60) days to review and as necessary, file a patent application in accordance with Article 9.

16) It is the intention of NCI that [SCO] not be liable to DTP/NCI for any claims or damages arising from NCI's use of the material provided by [SCO]; however, no indemnification for any loss, damage, or liability is intended or provided by any party under this MOU. Each party shall be liable for any loss, claim, damage or liability, that said party incurs, as a result of said party's activities under this MOU, except that the NCI, as an agency of the United States, assumes liability only to the extent as provided under the Federal Tort Claim Act (28 U.S.C. § 171).

DTP/NCI and its relevant contractors will not distribute materials provided by [SCO] to other organizations without written authorization from [SCO]. However, should [SCO] wish to consider collaboration with organizations selected by NCI for distribution of materials acquired through NCI collection contracts, DTP/NCI will establish contact between such organizations and [SCO].

18) [SCO] scientists and their collaborators may screen additional samples of the same materials for other biological activities and develop them for such purposes independently of this MOU.

With the exception of Articles 1-4 and 6, all other Articles shall survive the expiration of this Agreement or its termination by the [Source Country] or [SCO]. Subsequent compounds and/or extracts may be submitted under the appropriate DTP/NCI mechanism and agreement.

19) This MOU shall be valid as of the date of the final authorized signature below for an initial period of five (5) years, after
which, it can be renewed by mutual agreement. It may be
amended at any time subject to the written agreement of both
dispatch. Copies of such amendments will be kept on file at
both of the addresses indicated below. [SCO] and DTP/NCI
are confident that this MOU will lay the basis for a mutually
successful cooperation in discovering and developing new
therapies in the treatment of cancer.

For the [SCO]:

Andrew C. von Eschenbach, M.D.
Director, National Cancer Institute

For the National Cancer Institute:

Andrew C. von Eschenbach, M.D.
Director, National Cancer Institute

Appendix C

Model Agreement First Approved: May 22, 1989
Last Revised and Approved by TTB/NCI and DCTD/NCI:
October 29, 1999

Natural Products Branch
Developmental Therapeutics Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
National Institutes of Health

NATURAL PRODUCTS REPOSITORY MATERIAL
TRANSFER AGREEMENT

This Material Transfer Agreement ("MTA") has been adopted
for use by the National Institutes of Health ("NIH") and
revised for use in the Natural Products Branch ("NPB") of the
Developmental Therapeutics Program (DTP), of the Division
of Cancer Treatment and Diagnosis ("DCTD"), of the
National Cancer Institute ("NCI") of the NIH for all transfers
of research materials ("Research Material") from the Natural
Products Repository ("NPR") of NPB, DTP, DCTD, NCI.

The NPR represents a resource of natural products (e.g., plant
extracts, microbial cultures, etc.) which are being used for the
discovery and development of new agents for the treatment
and prevention of cancer and AIDS. These Research
Materials have been collected from one or more Source
Countries, generally in collaboration with one or more Source
Country Organizations. ("Source Country Organization" or
"SCO" is defined as a governmental entity of a country from
which the Research Material was obtained or an appropriate
organization affiliated with the Source Country with authority
to provide the Research Material to NCI.) NCI wishes to
promote the use of this national resource by other
organizations involved in the discovery of bioactive agents of
relevance to the NCI mission, and will provide limited
quantities of Research Materials from the NPR to selected
qualified research organizations for such purposes, under the
selection criteria and procedures set forth in Appendix A.

This MTA specifies the conditions under which NCI will
transfer samples to successful applicant investigators. In the
event an applicant is successful, this MTA represents the
terms of agreement between NCI and the applicant investigator's institution [hereinafter referred to as "Recipient," except that "Recipient" will refer to the investigator as an individual if he or she is unaffiliated with an institution].

Specifically:

1. NCI shall disclose to Recipient Confidential
Information on the Research Materials currently available
from the NPR solely for the purpose of and in sufficient detail
to enable Recipient to identify and select specific Research
Materials for evaluation as described in Recipient's proposal
to NPB, DTP and approved by the DTP Committee on Natural
Products Repository Access on ____________.

Alternatively, Recipient may specify immediately below the
types of Research Materials it would like to access from the
NPB:

However, Recipient will not have access to Research
Materials in the Active Repository (i.e., materials that are or
recently have been the subject of investigation by NCI
scientists), nor will it be informed about what materials are in
the Active Repository, unless Recipient agrees to the special
terms appearing on Page 6 of this Agreement.

Recipient agrees to accept the Confidential Information and
employ all reasonable efforts to maintain the Confidential
Information secret and confidential, such efforts to be no less
than the degree of care employed by Recipient to preserve and
safeguard Recipient's own confidential information. The
Confidential Information shall not be disclosed, revealed or
given to anyone except employees of Recipient who shall
have a need to have Confidential Information in connection
with Recipient's evaluation, and who have entered into a
secrecy agreement with Recipient (or are covered by a secrecy
obligation to Recipient) under which such employees are
required to maintain confidential and secure the proprietary
Information of Recipient. Furthermore, such employees shall
be advised by Recipient of the confidential nature of the
Confidential Information and of their obligation to treat the
Confidential Information accordingly.

It is hereby acknowledged by NCI that Recipient shall incur
no liability merely for examining and considering the
Confidential Information; however, Recipient agrees that it will not use the Confidential Information for any purpose except as set forth herein.

2. NCI agrees to transfer to Recipient for evaluation specific crude extracts listed in the Confidential Information, upon request by Recipient and approval by NPB, DTP. An electronic record of the specific extracts provided will be kept by the NPB and will be updated as Research Materials are provided to Recipient. This electronic record will serve as an appendix to this agreement. A written copy of this record will be provided on a periodic basis or upon request to the Recipient.

3. THIS RESEARCH MATERIAL MAY NOT BE USED IN HUMAN SUBJECTS. This Research Material will only be used for research purposes by Recipient under suitable containment conditions. Exchange of samples among collaborating organizations or individuals not party to this MTA may occur only upon execution of a copy of this MTA by each such collaborator. This Research Material will not be used for commercial purposes such as production or sale. A commercialization license may be required for commercial use of the Research Material. Recipient agrees to comply with all Federal rules and regulations applicable to the Research Project and the handling of the Research Material.

4. In all oral presentations or written publications concerning the Research Project, Recipient will acknowledge the contribution of NCI, as well as the SCO and any other appropriate organizations or individuals as identified by NCI, unless requested otherwise. To the extent permitted by law, Recipient agrees to treat in confidence, for a period of three (3) years from the date of its disclosure, any and all of NCI's written information about this Research Material that is stamped "CONFIDENTIAL" except for information that was previously known to Recipient or that is or becomes publicly available or which is disclosed to Recipient without a confidentiality obligation. Recipient may publish or otherwise publicly disclose the results of the Research Project. However, if NCI has given CONFIDENTIAL information to Recipient, such publication or public disclosure may be made only after the SOC has had thirty (30) days following notification by the NPB to review the proposed disclosure, except in the event that a shortened time period is required pursuant to a court order or request under the Freedom of Information Act, 5 U.S.C. 522. Recipient agrees to inform the NPB, under reasonable reporting requirements, of the intent, progress, results and additional research plans for the use of the Research Material. NCI agrees to reciprocally maintain information Recipient identifies as “CONFIDENTIAL” under the terms set forth above.

5. This Research Material represents a significant investment on the part of NCI and is considered proprietary to NCI. Recipient agrees to retain control over this Research Material, and further agrees not to transfer the Research Material to others not under Recipient’s supervision without advance written approval of NCI. The execution by others of an MTA such as this, as described in Article 3 above, would constitute one form of such approval. NCI reserves the right to distribute the Research Material to others and to use it for its own purposes. When the Research Project is completed, or three (3) years have elapsed, whichever occurs last, the Research Material will be destroyed or disposed of as mutually agreed by NCI and Recipient.

6. This Research Material is provided as a service to the research community. IT IS BEING SUPPLIED TO RECIPIENT WITH NO WARRANTIES, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. NCI makes no representations that the use of the Research Material will not infringe any patent or proprietary rights of third parties.

7. Recipient agrees to pay all reasonable costs for the preparation, handling and shipment of this Research Material to Recipient. Further, Recipient agrees that all samples of Research Material will be provided contingent on the availability of a sufficient supply of Research Material, but in no case will samples be provided that adversely affect the research programs of NCI.

8. NCI shall retain title to the Research Material, per se, and any patent or other intellectual property rights in inventions by its employees in the course of the Research project. Furthermore, Recipient agrees that any intellectual property rights in inventions made by the employees, agents or contractors of the Recipient will vest by operation of inventorship as determined under appropriate patent statutes in the controlling jurisdiction(s). Recipient agrees not to claim, infer, or imply Government endorsement of the Research Project, the institution or personnel conducting the Research Project, or any resulting commercial product(s). Recipient agrees to hold the United States harmless and to indemnify the Government for all liabilities, demands, damages, expenses and losses arising out of Recipient's use for any purpose of the Research Material.

9. Recipient acknowledges that NCI may have obtained the Research Materials from the SCO under a Letter of Collection (“LOC”) agreement stipulating that NIH will require any commercial licensee of an invention by NCI personnel derived from the Research Material (whether the invention is directed to a direct isolate from the Research Material, a product structurally based upon an isolate from the Research Material, a synthetic material for which the Research Material provided a key development lead, or a method of synthesis or use of any aforementioned isolate, product or material) to enter into an agreement that addresses the mutual concerns of NIH’s licensee and SCO, respectively.

Even if the Research Materials were not obtained under such an LOC agreement, as an agency of the U.S. Government, NCI complies with the U.S. Government’s policy to follow the principles articulated in the United Nations Convention on Biological Diversity (“U.N. CBD”). The U.N. CBD calls for
“sharing in a fair and equitable way the results of research and development and the benefits arising from the commercial and other utilization of genetic resources with the [source country] providing such resources.” (U.N. CBD; Article 15.7)

In order to abide by these principles and address the interests of SCO, Recipient further agrees that, should an invention derived from the Research Material eventually be developed and marketed by the Recipient, or licensed by Recipient to a company or other institution for development and commercialization (whether the invention is directed to a direct isolate from the Research Material, a product structurally based upon an isolate from the Research Material, a synthetic material for which the Research Material provided a key development lead, or a method of synthesis or use of any aforementioned isolate, product or material), Recipient or Recipient’s Licensee(s) will negotiate and enter into an agreement with the appropriate SCO. This agreement between the Recipient and/or Recipient’s Licensee(s) and SCO will address the mutual concerns of both parties. Recipient agrees that negotiations between either Recipient or Recipient's Licensee(s) and the SCO must commence prior to the start of clinical development studies that are conducted, directed or sponsored by either Recipient or Recipient's Licensee(s). Negotiations must be completed and an agreement executed prior to the commercial sale of an agent structurally based or isolated from the Research Material. This agreement relating to the agent must be binding upon SCO, Recipient and any Licensee(s) or assignees of Recipient with respect to any intellectual property rights relating to the agent.

Recipient will seek to utilize the Source Country as its first source of supply and/or cultivation for raw (natural product) materials required for the manufacture of an agent (regardless of whether the agent is an isolated natural product or is structurally based thereon) if such material can be made available in quantities and quality sufficient for use by the Recipient at a mutually agreeable fair price. If such material must be cultivated, recipient agrees to seek to utilize Source Country as its first source of such cultivation efforts.

10. In addition to the reporting requirements under Article 4, Recipient will provide screening results on the Research Material to NPB, DTP. Following removal of identified proprietary information (jointly defined by Recipient and DTP/NCI), DTP/NCI will provide summary screening data to the SCO.

11. NCI can promise an option to license intellectual property rights only under a Cooperative Research and Development Agreement (CRADA). If Recipient desires prospective license rights to inventions derived from Research Material made in whole or part by NCI employees, a formal CRADA must be negotiated. For general inquiries regarding CRADAs or NCI technology transfer policies, contact the NCI Technology Transfer Branch at (301)-846-5465.

12. This MTA shall be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

13. This Materials Transfer Agreement between NCI and the Recipient will be effective when signed by all parties. By signing this MTA, the Recipient acknowledges that it has received and read a copy of the policy statement on Distribution of Materials from the Natural Products Repository, which is attached as Appendix A.

14. The provisions of this Agreement are severable. If any item or provision of this Agreement shall to any extent be invalid or unenforceable, the remainder of this Agreement shall not be affected thereby, and each item and provision of this Agreement shall be valid and shall be enforced to the fullest extent permitted by law. The undersigned expressly certifies or affirms that the contents of any statements made or reflected in this document are truthful and accurate.

FOR RECIPIENT:

Date: __________
__________________
Applicant Investigator’s Signature / Title / Program

Date: __________
__________________
Signature for Recipient’s Authorizing Official
Name (Type or Print):
Title (Type or Print):

Recipient’s Address for Correspondence Related to this Agreement to:

__________________
Tel: __________
Fax: __________

FOR THE NATIONAL CANCER INSTITUTE:

Date: __________
__________________
Jerry E. Collins, Ph.D.
Associate Director, Developmental Therapeutics Program, DCTD
SPECIAL ADDITIONAL PROVISIONS THAT APPLY TO SAMPLES FROM THE ACTIVE REPOSITORY

In the case of applications for access to Research Material from the Active Repository (i.e., materials that are or recently have been the subject of investigation by NCI scientists), Recipient recognizes that such materials are of current interest to NCI and that there has been intellectual input by NCI scientists into the screening, and in many cases further analysis and development, of such materials. Recipient therefore agrees that the use of the Research Material constitutes a form of collaboration with NCI’s Natural Products Branch or other designated NCI facility, as appropriate. Recipient further agrees to comply with the provisions set forth hereunder, so that the isolation, purification and testing of the Research Material will be closely coordinated with NCI’s efforts to ensure that pure isolates from such Research Material may be further developed in an efficient manner and in cooperation with the NCI.

In particular, Recipient agrees to report in a timely fashion to NCI the identity and nature of any isolates, including identified compounds or combinations of compounds, derived from the Research Material; as well as any processes for making or using such isolates. In addition, Recipient agrees to report to the NCI Technology Transfer Branch (see the address on the Signature Page) Recipient’s intention to file patent applications on any inventions developed from the use of Research Material and to negotiate in good faith a Confidentiality Disclosure Agreement with NCI under which NCI/DTP and Recipient will exchange information regarding their respective research and development efforts to ensure that Recipient’s and NCI’s interests in Research Material may be respectively, and where appropriate jointly, protected.

Recipient understands that a limited number of samples from the Active Repository (generally no more than twenty) can be made available at any one time under any single Agreement. Recipient agrees that once it has completed analysis of a sample, it will return any and all remaining sample to NPB, DTP. At any time following Recipient’s receipt of the first group of samples, DTP has the right to make access to additional samples from DTP repositories contingent upon Recipient’s entering into a Cooperative Research and Development Agreement (CRADA) with NCI to ensure that Recipient’s and NCI’s respective development efforts are coordinated.

Recipient’s signatures on below signify agreement to these special provisions regarding access to Research Material from the Active Repository. Access to Research Material from the Active Repository will not be granted without such agreement.

Signature of Recipient’s investigator signifying agreement to the Special Provisions governing access to samples from the Active Repository:

_________________________

Date: __________________

Signature of Recipient’s authorizing official signifying agreement to the Special Provisions governing access to samples from the Active Repository:

_________________________

Date: __________________

(MTA) Appendix A

Original, December 13, 1991
Last Revised by DTP/NCI October 29, 1999

POLICY FOR THE DISTRIBUTION OF MATERIALS FROM THE NATURAL PRODUCTS REPOSITORY

The Natural Products Repository (NPR) of the National Cancer Institute’s (NCI) Developmental Therapeutics Program (DTP) represents a unique resource in terms of both the magnitude and diversity of materials that might be utilized for the discovery and development of new agents for cancer, HIV/AIDS, and other diseases, as well as for other meritorious research endeavors. As a national resource, it is incumbent on the NCI to assure that it is utilized to the greatest extent for the public good.

Two programs for access to the NPR have been established:

• The Open Repository Program.
• The Active Repository Program.

OPEN REPOSITORY PROGRAM
This program was established in 1992 to enable the extramural community to investigate NPR materials, not currently under active investigation at the NCI, as potential sources of agents for the treatment of cancer, AIDS, opportunistic infections, and diseases of concern to the Countries of Origin of the materials. In 1999, the scope of investigation was expanded to include all human diseases.

Distribution of Materials:

- **Vialled Samples**: Samples (25 mg), identified by a code number and by taxonomy to family level, may be shipped to a recipient at a maximum rate of 500 per month (this rate may be accelerated if a formal CRADA is in place). Particular genera and/or species within a family, or samples from specified Countries of Origin, may be included or excluded, as far as possible, from shipments if requested.

- **Plated Samples**: Samples may also be shipped to a recipient in 96-well polypropylene (15mg or 500ug per well) or polystyrene (50ug per well) plates; there is no restriction on the rate of shipment of plated samples. No initial exclusivity will be granted to the extracts, nor will any information other than the type and source of the extracts on a particular plate be provided (i.e., plate # contains 88 organic plant extracts at 50ug per well in lanes 2 through 12). Plates may also contain samples from the Active Repository Program; such extracts will only be available to investigators qualified for access to the Active Repository Program. Identical plates may be sent to multiple investigators.

- An exclusivity period of 3 months is granted for testing of the materials, after which the test results are submitted to the DTP Natural Products Branch (NPB).

- On identification of active extracts, investigators will communicate with NPB directly by e-mail or fax, and will be informed whether or not the active materials are available.

- **Investigators will have active samples reserved for further investigation on a first-come first-served basis.** Where more than one investigator observes activity for a particular extract, it will be reserved for the first investigator to report activity, and a waiting list of other interested investigators will be established.

- Extracts will not be available if they are under active study (on reserve) in either the Open Repository Program (maximum of 6 months exclusivity) or Active Repository Program (up to 15 months exclusivity with the possibility of extension, if necessary).

- Once the relevant extract is released by the first investigator, it will be shipped to the next in line on the waiting list.

- A further supply of any active materials (75-100 mg), together with the rest of the taxonomy and relevant collection data, are provided.

- A further 3 months exclusivity is granted to permit secondary testing and/or initial isolation of the active agents. At the end of this time the recipient will inform NPB of its discoveries and its level of interest.

- **The maximum period of exclusivity on any extract is 6 months.**

- At the end of the 6 month period from the initial receipt of the material, NPB will inform the Countries of Origin of the materials of the results obtained, using language agreed to in advance by the recipient.

- The Countries of Origin will be given the name of the recipient organization, and will be informed that the organization will contact them if further material is required. Acquisition of further material will normally be the responsibility of the recipient organization working through the original collector (if possible) and the relevant Source Country permitting agency.

- Since it is the responsibility of the NCI to ensure that the conditions of the Material Transfer Agreement (MTA) are maintained during this and subsequent stages of development, NPB will maintain interaction with the recipient organization and the Countries of Origin.

**Requests for Access**

Requests for NPR materials will be accepted from research organizations and individual investigators in the form of a brief proposal (up to 5 pages) formatted as follows:

- **Introduction.**

- **Research Hypothesis.**

- **Screening Process,** together with description of characteristics of the screen.

- **Personnel.**

- **Organizational Research Capabilities.**

Requests will normally be reviewed by staff from the NCI Division of Cancer Treatment and Diagnosis (DCTD) appointed by the Director, DCTD. Ad hoc members from outside the Division, Institute, or NIH may be appointed as needed, while ensuring appropriate confidentiality of information provided in the proposal.

The review will consider primarily the scientific merit of the proposal related to the screening target for drug discovery, and the applicant’s chemical and pharmaceutical expertise for adequate follow-up on the natural products supplied from the NPR. Although preference will be given to proposals related to cancer or AIDS, other areas of research will be given consideration.

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Supplementary Material (ESI) for Journal of Environmental Monitoring

Countries of Origin of the materials. In 1999, the scope of investigation was expanded to include all human diseases.
The Committee to review applications for access to the Natural Products Repository will accept and review proposals on a continuing basis. This schedule is subject to change depending on the volume of applications.

Conditions of Access

The staff of the Natural Products Branch will be administratively responsible for the operation of this program. Successful applicants will subsequently deal directly with the Branch to request material and report scientific results.

Organizations and individual investigators whose applications are approved will be provided selected samples under the terms of a Material Transfer Agreement (to which this Policy Statement is attached), which has been modified from the standard Public Health Service (PHS) agreement to meet the specific needs of this program. Important aspects of this agreement are:

- Recipients must agree to protect the interests of the Countries of Origin providing the materials to NCI.
- The NCI will retain ownership of the material per se. Such ownership is separate from intellectual property rights.
- The recipient will pay the "out-of-pocket" costs of preparing and shipping samples.
- In no case will a sample be provided that depletes the supply of that material or otherwise affects adversely NCI's own efforts.
- Unused samples will be disposed of in a manner to be agreed on by both parties.
- A reporting procedure will be established to assure that NCI is kept informed of the usage of Research Materials. To this end, recipients are encouraged to contact the NPB as early as possible once a particular extract has proven to be of interest in order that suitable arrangements for further development may be agreed upon by all parties. These may include full taxonomic identification; provision of more extracted Research Material; aid in obtaining raw material via the then current Collection Contractors; or the negotiation of a formal Cooperative Research and Development Agreement (CRADA).
- Research results derived from this Research Material will be transmitted in a timely manner to the NCI.
- A summary of the screening results relating to the Research Material and any purified natural products will be provided to the relevant organizations in the Countries of Origin.
- Safeguards will be installed to prevent disclosure of proprietary information during this interchange.
- As part of this interchange of information, if a research organization has been identified within the Country of Origin that is actively pursuing studies in the relevant scientific area, then the recipient will be informed with the aim of facilitating collaborative studies.
- All test information from NCI that is provided to recipient, collector, and the Country of Origin government or an appropriate organization within the Country of Origin is to be maintained as “CONFIDENTIAL” with any publication delayed until DTP authorizes release to outside parties.
- The NCI will not grant unlimited access to Research Materials within the repository. The selection of samples will be determined by the NCI after discussion with the recipient, and the size of samples will be limited to that required for primary and limited secondary testing in the recipient's screens.
- Large amounts of raw material required for follow-up isolation and development of active agents will generally be obtained by recipients at their own expense and in accordance with established agreements among NCI, its collecting agents and the Source Country Organization. In specific cases, however the NCI may agree to participate with the investigator(s) in the recollection process to procure additional raw and/or Research Material if the initial findings are of substantial scientific interest to the program.

Further technical information may be obtained from:

Dr. David Newman
Natural Products Branch
NCI-Frederick
Fairview Center, Room 206
P. O. Box B
Frederick, MD 21702-1201
Phone: +301-846-5387
Fax: +301-846-6178
Email: dn22a@nih.gov

Test results and requests for samples may be submitted to:

Mrs. Erma Brown at <brown@dtpax2.ncifcrf.gov> or at the address and contact numbers given above.

Requests must be copied to Dr. Newman at:
<dn22a@nih.gov>

ACTIVE REPOSITORY PROGRAM

This program has been established to permit qualified U.S. investigators access to materials active in the 60 cell line anti-tumor screen, in addition to those falling into the Open
Qualifications for Access

• U. S.-based investigators whose screening activities have been peer-reviewed by suitable bodies (e.g., U. S. Government funding agencies, the American Cancer Society and other comparable U. S. funding organizations). Such investigators will provide current grant number(s).

• U. S. chartered organizations whose screening activities have not been peer-reviewed. Such organizations will submit short proposals for review as discussed under "Requests for Access" in the section on the Open Repository Program.

• Organizations based in Countries of Origin that have participated in NCI collection programs. Such organizations have access to extracts of organisms collected in their own countries.

All investigators and organizations requesting access to the Active Repository Program will be asked to provide the following information:

• A brief description of their assays and their relevance to cancer.

• A description of the expertise in chemistry available for bioassay-guided isolation studies.

• The types of extracts desired for testing (one or more of marine or terrestrial plants or marine invertebrates).

Distribution of Materials

• Upon signing of the special terms appearing on page 6 of the Material Transfer Agreement (to which this policy statement is attached), NPB will provide investigators with electronic media containing details of all materials available (full taxonomy and anti-cancer screening data sets composed of single- and multi-dose tests, together with mean graphs).

• Investigators may choose up to 20 samples for further study.

• 25 mg of each selected sample will be provided for investigators to determine if their assays will detect the activities.

• Plated Samples: Investigators receiving plated samples through the Open Repository Program may identify extracts restricted to the Active Repository Program. Such extracts may be made available to the investigators providing they qualify for access to the Active Repository, and subject to the 20 sample restriction mentioned above.

• On identification of active extracts, investigators will communicate with NPB directly by e-mail or fax, and will be informed whether or not the active materials are available.

• Investigators will have active samples reserved for further investigation on a first-come first-served basis. Where more than one investigator observes activity for a particular extract, it will be reserved for the first investigator to report activity, and a waiting list of other interested investigators will be established.

• A three month exclusivity period will be granted from the date of receipt of the samples during which time the investigators will inform NPB whether their assays are effective.

• Materials for further investigation may be obtained as follows:

  • Grantees, non-profit organizations and small businesses (that meet SBIR criteria): NPB will provide further materials in negotiated amounts.

  • For-profit organizations not qualifying as small businesses under SBIR regulations will be responsible for the acquisition of further material, working in collaboration with the original collector (if possible), and the Country of Origin as stipulated in Article 9 of the MTA.

  • A further exclusivity period of one year from the time of receipt of the second amount of material will be given to perform bioassay-guided isolation of the active agents. If necessary this period may be extended after review of progress by NPB and the investigator.

• The 20 samples are on a rotating basis. When the investigator decide not pursue further research on a sample, or identifies the active agent(s) in a sample, the remainder of that particular sample will be returned to NPB within five working days of reclassification.

• For each sample reclassified as being of no further interest to the investigator, one new sample may be requested. No more than 20 samples from the Active Repository Program may be held at one time.

• NCI will be kept informed of the progress of the investigations, and will help in the development of any agents meeting the approval criteria of the DCTD Drug Development Committee.

• Since it is the responsibility of the NCI to see that the conditions of the MTA are maintained during this and subsequent stages of development, NPB will maintain interaction with the investigators and the relevant Countries of Origin.

Conditions of Access
The same conditions of access as apply to the Open Repository Program (vide infra) generally apply to the Active Repository Program, except for differences specified under the Distribution of Materials. Further technical information may be obtained from:

Dr. David Newman
Natural Products Branch
NCI-Frederick
Fairview Center, Room 206
P. O. Box B
Frederick, MD 21702-1201

Phone: +301-846-5387
Fax: +301-846-6178
Email: dn22a@nih.gov

The test results and requests for samples may be submitted to:
Mrs. Erma Brown at <brown@dtpax2.ncifcrf.gov> or at the address and contact numbers given above.
Requests must be copied to Dr. Newman at: dn22a@nih.gov