

The US National Cancer Institute's Natural Products Repository; Origins and Utility

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5 Appendices

Appendix A

LETTER OF COLLECTION

Agreement Between

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

15 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
20 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
25 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
30 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
35 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
40 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
45 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

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50 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.

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

1) DTP/NCI will screen the extracts of all plants,
60 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.

65 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
70 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 compounds(s) responsible for the observed
75 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
80 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.

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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
90 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
95 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).

100 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
105 preclinical development, [SCO] and the DTP/NCI will discuss
participation by SCO scientists in the development of the
specific agent.

The DTP/NCI will make a sincere effort to transfer any
110 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.

115 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
120 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
125 with said NIH policy for any royalty-bearing license(s) for
these patent(s).

130 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.

135 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
140 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.

145 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
150 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
155 drug to the stage of marketing is a long term process which
may require 10-15 years.

160 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
165 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
170 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,
175 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
180 [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.

185 12) DTP/NCI will test any pure compounds
independently submitted by the [SCG or SCO] scientists for
antitumor activity, provided such compounds have not been
tested previously in the DTP/NCI screens. If significant
antitumor activity is detected, further development of the
190 compound may, as appropriate, be undertaken by DTP/NCI in
consultation with ~~[SCG]~~ and the [SCG or SCO].

Should an NCI/NIH patent on an agent derived from the
submitted compound(s) eventually be licensed to a
195 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
200 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.

13) DTP/NCI may send selected samples to other
205 organizations for investigation of their anti-cancer, anti-HIV
or other therapeutic potential. Such samples will be restricted
to those collected by NCI contractors unless specifically
authorized by the [SCG or SCO]. Any organization receiving
samples must agree to compensate the [SCG or SCO] and
210 individuals, as appropriate, in the same fashion as described
in Articles 8-10 above, notwithstanding anything to the
contrary in Article 11.

**B. The role of the Source Country Government ("SCG") or
Source Country Organization(s) ("SCO") in the collaboration
215 will include the following:**

1) The appropriate agency in [SCG or SCO] will
collaborate with Contractor in the collection of plants, micro-
organisms and marine macro-organisms, and will work with
Contractor to arrange the necessary permits to ensure the
220 timely collection and export of materials to DTP/NCI.

2) Should the appropriate agency in [SCG or SCO]
have any knowledge of the medicinal use of any plants,

micro-organisms and marine macro-organisms by the local
235 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
230 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
235 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
240 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
245 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
250 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
255 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)
260 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]:
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Andrew C. von Eschenbach, M.D. Name (typed):
Director, National Cancer Institute Title:
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Date Date
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mailing and contact address: mailing and contact address:
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Appendix B

MEMORANDUM OF UNDERSTANDING BETWEEN SOURCE COUNTRY ORGANIZATION (SCO)

AND
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THE DEVELOPMENTAL THERAPEUTICS PROGRAM DIVISION OF CANCER TREATMENT AND DIAGNOSIS NATIONAL CANCER INSTITUTE

295 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
300 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
305 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
310 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
315 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
320 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
325 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
330 [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].

335 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.

6) 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 technician(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.

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 parties. 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]: For the National Cancer Institute:

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

Date Date

mailing and contact address: mailing and contact address:
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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.

690 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 695 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.

700 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 705 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 710 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.

715 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 720 (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 725 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 SCO has had thirty (30) days following 730 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, 735 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.

740 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 745 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 750 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 755 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 760 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 765 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.

770 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 775 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 780 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 785 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 790 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 795 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.

800 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

805 “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)

810 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
815 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
820 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
825 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
830 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.

835 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
840 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.

845 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
850 Recipient and DTP/NCI), DTP/NCI will provide summary
screening data to the SCO.

855 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
860 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.

865 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
870 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
875 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
880 reflected in this document are truthful and accurate.

FOR RECIPIENT:

885 Date: _____

Applicant Investigator’s Signature / Title / Program

890 Date: _____

Signature for Recipient’s Authorizing Official
Name (Type or Print):
895 Title (Type or Print):

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

900 _____

Tel: _____

905 Fax: _____

910 **FOR THE NATIONAL CANCER INSTITUTE:**

915 Date: _____

Jerry E. Collins, Ph.D.
Associate Director, Developmental Therapeutics Program,
DCTD

920

Date: _____

Bjarne Gabrielsen, Ph.D., Senior Advisor, Drug Discovery /
Development, Technology Transfer Branch, NCI

Address correspondence related to this Agreement to:

NCI-Technology Transfer Branch
National Cancer Institute at Frederick (NCI-Frederick)
Fairview Center, Suite 500
1003 - W. 7th Street
Frederick, MD 21701
telephone: +301-846-5465, fax: +301-846-6820

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

1035 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,
1040 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:

1045 • **Vialed 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
1050 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)
1055 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
1060 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.**

1065 • 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).

1070 • 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.**
1075 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.

1080 • 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
1085 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.

1090 • 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
1095 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
1100 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
1105 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.
1110 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.

1115 • 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
1125 brief proposal (up to 5 pages) formatted as follows:

• Introduction.

• Research Hypothesis.

1130 • Screening Process, together with description of
characteristics of the screen.

• Personnel.

1135 • Organizational Research Capabilities.

Requests will normally be reviewed by staff from the NCI
Division of Cancer Treatment and Diagnosis (DCTD)
1140 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.

1145 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
1150 will be given to proposals related to cancer or AIDS, other
areas of research will be given consideration.

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

Repository Program. As of February, 1999, over 3,000 samples have been designated as active.

1270

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
1385 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:

1390 Dr. David Newman
Natural Products Branch
NCI-Frederick
Fairview Center, Room 206
P. O. Box B
1395 Frederick, MD 21702-1201

Phone: +301-846-5387

Fax: +301-846-6178

Email: dn22a@nih.gov

1400 The test results and requests for samples may be submitted to:
Mrs. Erma Brown at [<brown@dtpx2.ncifcrf.gov>](mailto:brown@dtpx2.ncifcrf.gov) or at the
address and contact numbers given above.
Requests must be copied to Dr. Newman at: dn22a@nih.gov