Appendix 2

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. <u>THIS RESEARCH MATERIAL MAY NOT BE USED IN HUMAN SUBJECTS</u>. 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 SCO 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 <u>first</u> 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 Collins, Ph.D.
Associate Director, Developmental Therapeutics Program,
DCTD

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: _____

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