**Appendix A**

## 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:**

- **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 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.

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
Chief, Natural Products Branch
NCI-FCRDC
Fairview Center, Room 206
P.O. Box B
Frederick, MD 21702-1201

Phone: 301-846-5387
Fax: 301-846-6178
Email: newmand@mail.nih.gov

Requests for samples may be transmitted electronically to:

Mrs. Erma Brown at the address and phone/fax numbers given above, or by Email at browne@dtpepn.nci.nih.gov

Requests must be copied to Dr. Newman at:

newmand@mail.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.

**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 decides not to 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:

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Frederick, MD 21702-1201

Phone: 301-846-5387
Fax: 301-846-6178
Email: newmand@mail.nih.gov

Test results and requests for samples may be submitted to:
Mrs. Erma Brown at the address and phone/fax numbers given above, or by Email at
browne@dtpepn.nci.nih.gov

Requests must be copied to Dr. Newman at:
newmand@mail.nih.gov