CANCER FACTS

National Cancer Institute • National Institutes of Health
Department of Health and Human Services

Questions and Answers About NCI's Natural Products Branch

1. What is the Natural Products Branch and what are its goals?

The Natural Products Branch (NPB) of the National Cancer Institute's (NCI) Division of Cancer Treatment and Diagnosis is responsible for coordinating programs directed at the discovery and development of novel, naturally derived agents to treat cancer and AIDS. The NPB is responsible for: (1) acquiring crude biological materials of plant, marine, and microbial origin for NCI's drug screening programs; (2) coordinating research directed toward isolation of new agents; and (3) assisting in the large-scale production of new agents for preclinical and clinical development.

2. What is the Natural Products Repository?

Once a sample of an organism is collected, it is sent to the Natural Products Repository (NPR) at the Frederick Cancer Research and Development Center (FCRDC) in Frederick, Maryland. There, the sample is stored at -20 EC prior to extraction and further investigation. The repository also serves as a low-temperature storage facility for all natural product extracts.

3. How many samples does the repository possess?

Approximately 60,000 plant and marine organism samples have been collected. Each sample is extracted with an organic solvent and water to give two extracts. These extracts are divided further into two small vials and distributed in 96-well microtiter plates, which are sent out for screening. Together with microbial extracts, there are over 600,000 vials housed at the repository.

4. Who collects the samples?

Plant collections are carried out by three contractors. Each contractor has a specific collection region—the University of Illinois at Chicago obtains samples from Southeast Asia, the Missouri Botanical Garden is responsible for collecting in Africa (including Madagascar), and the Morton Arboretum in Lisle, Illinois, collects samples from the continental United States. Collections by the New York Botanical Garden from Central and South America were performed from 1986 to 1996, but samples are now obtained through direct collaboration with research organizations in the region. Five hundred samples are collected annually by each of the contractors operating in Southeast Asia and Africa, and 1000 samples are collected annually by the Morton Arboretum in the United States. Each sample is between 0.30 and 1 kilogram (kg) (dry weight), with different plant parts (bark, roots, leaves, fruits) constituting discrete samples. Contractors must submit detailed documentation for each sample—taxonomy, plant part, date and location of collection, habitat, and, if possible, medicinal uses and methods of preparation used by indigenous peoples.

Marine organisms are collected by the Coral Reef Research Foundation in the Indo-Pacific region. About 700 samples (between 0.5 and 1 kg) are collected each year, and full documentation is provided for each sample. Samples are frozen from the time of collection to the time of extraction.

Microbial cultivation is carried out by Science Applications International Corporation (SAIC) at NCI's Frederick Cancer Research and Development Center. In addition to regular contracts, the following collaborative studies have been established:

Collaborative Programs:

- The South American Organization for Anticancer Drug Development (SOAD) in Porto Alegre, Fundacao Oswaldo Cruz-FIOCRUZ in Rio de Janeiro, and the University Paulista in Sao Paulo investigate plants from Brazil.

- The Institute of Biological Diversity (INBio) in Costa Rica studies insects and plants.

- The Institute of Chemistry, National University of Mexico, studies medicinal plants.

- The Kunming Institute of Botany in China studies Chinese medicinal plants.

- The Korean Research Institute of Chemical Technology examines Korean medicinal plants.

- The H.E.J. Institute of Chemistry, University of Karachi, studies Pakistani plants.

- The University of Dhaka in Bangladesh studies plants and microbes.

- University of Panama studies Panamanian medicinal plants.
- Brigham Young University (Dr. Paul Cox) studies Polynesian medicinal plants.
- Tel Aviv University (Dr. Yoel Kashman) studies Red Sea marine invertebrates.
- The New Zealand National Institute of Water and Atmospheric Research studies marine organisms.
- The Cancer Research Center at the Russian Academy of Medical Sciences in Moscow studies Russian medicinal plants.
- The Zimbabwe National Traditional Healers Association and the University of Zimbabwe study Zimbabwean medicinal plants.
- The South African Council for Scientific and Industrial Research studies South African plants.

5. From which countries does NCI collect?

Because well over 50 percent of the estimated 250,000 plant species found on earth come from tropical forests, NCI concentrates on these regions. Plants have been collected from the African countries of Cameroon, the Central African Republic, Gabon, Ghana, Madagascar, and Tanzania. Collections are now concentrated in Madagascar, and collaborative programs have been established in South Africa and Zimbabwe.

In Central and South America, samples have been collected from Belize, Bolivia, Colombia, the Dominican Republic, Ecuador, Guatemala, Guyana, Honduras, Martinique, Paraguay, Peru, and Puerto Rico. The NCI has established collaborative programs in Brazil, Costa Rica, Mexico, and Panama. Southeast Asian collections have been performed in Bangladesh, Indonesia, Laos, Malaysia, Nepal, Pakistan, Papua New Guinea, the Philippines, Taiwan, Thailand, and Vietnam. Collaborative programs have been established in Bangladesh, China, Korea, and Pakistan. In each country, NCI contractors work in close collaboration with local botanical institutions.

6. Does the Natural Products Branch have policies for international collaboration and compensation?

The NCI is very aware of the contributions made by various countries around the world in permitting the evaluation of their natural resources for anticancer and anti-AIDS activity. The contractors collecting samples for NCI collaborate closely with source country institutions. The results of anticancer and anti-AIDS testing of samples from a source country are provided to that country's scientific community. Scientists of source countries are invited to NCI laboratories to collaborate in the study of active samples collected in their countries or gain experience in NCI screening methods. The NCI funds these visits and provides technical training lasting up to 12 months, and also promotes

technology transfer. Should a drug from a particular country advance to commercial use, NCI will require the pharmaceutical company marketing the drug to negotiate, directly with the country, terms of compensation to that country.

7. What is the history of the Natural Products Branch?

In the 1950s, scientists discovered two plant-derived antileukemic agents, vinblastine and vincristine, and isolated podophyllotoxin, which was modified by a pharmaceutical company to the clinically useful anticancer agents, etoposide and teniposide. These discoveries prompted NCI to collaborate with the Department of Agriculture in the systematic collection and screening of plants for antitumor activity. This program was initiated in 1960; spanning the next 22 years, over 35,000 plant samples were collected, and researchers tested over 114,000 plant extracts. In addition, over 18,000 extracts of marine organisms were tested between 1975 and 1982. The NCI also collaborated closely with the pharmaceutical industry in the testing of over 180,000 microbial extracts. Apart from the discovery of the plant-derived agents Taxol® (paclitaxel) and camptothecin, few of these natural products showed potential for human use, so NCI discontinued natural product collections in 1982. However, with the advent of new screening techniques, NCI developed a new natural products acquisition program in 1986. In September 1986, the rejuvenated program awarded contracts for the collection of plants in tropical and subtropical regions worldwide, and for marine organisms in the Indo-Pacific region. In addition to the search for antitumor agents, NCI initiated a program to find natural products for the treatment of AIDS in 1988.

8. What is the process a specimen goes through once it is collected?

a. **Collection**: Upon collection, a sample is assigned a unique NCI collection number, expressed in the form of a barcode label, which is attached to the sample bag in the field. Five voucher specimens of each product are prepared. One is donated to the national herbarium or marine organism depository in the country of collection, and another is deposited with the Smithsonian Institution's Museum of Natural History in Washington, D.C. Plant products are dried and shipped by air freight. Marine products are shipped frozen. Once the plant specimen arrives at NPR, it is stored at -20 EC for 48 hours to kill unwanted pests and pathogens.

b. **Extraction**: After freezing, plants are brought to the extraction laboratory where they are ground and sequentially extracted with a methanol/dichloromethane mixture and water. Frozen marine samples are ground in a large meat grinder, immersed in water, and centrifuged to separate the aqueous extract. The residual sample is freeze-dried and extracted with a methanol/dichloromethane mixture to provide an organic extract.

c. **Screening**: The extracts are tested *in vitro* for selective cytotoxicity against panels of human cancer cell lines—including leukemia, lung, colon, central nervous system, melanoma, ovarian, breast, prostate, and renal cancers. Up to

early 1997, *in vitro* anti-HIV activity was assessed against virus-infected human lymphoblastoid cells.

d. **Isolation**: Extracts showing significant selective cytotoxicity are provided to qualified research groups, including the NCI Laboratory for Drug Discovery Research and Development through the Active Repository Program. Chemists isolate the active chemicals and determine their structures. Novel active chemicals, which show sufficient activity against cancer, are advanced to preclinical development.

9. What is the microbial collection?

Along with plants and marine life, NPB is interested in microorganisms and how they can be used to fight cancer and AIDS. Scientists at the University of Miami have isolated protists—unicellular organisms—from water and soil samples, while researchers at SAIC, FCRDC, acquire fungi from collections all over the world. One such collection is the American Type Culture Collection in Manassas, Virginia, which serves as a major repository for microbial cultures.

Once the microorganism is cultivated, it goes through processing similar to that of plant and marine samples. The sample is extracted with water and organic solvents and is screened for cytotoxicity and anti-HIV activity. A number of cancer drugs derived from microorganisms are used today in chemotherapy: adriamycin, bleomycin, and mitomycin, to name a few.

10. What are the Active and Open Repository Programs?

The Natural Products Repository (NPR) of extracts is a unique and valuable resource for the discovery of potential new drugs to combat the full range of human diseases. In recognition of this potential, the NCI has developed policies for the distribution of these extracts to qualified organizations for further study, subject to the signing of a legally-binding Material Transfer Agreement (MTA), which protects the rights of all parties, particularly those of the countries of origin of the natural source materials (plants and marine organisms). Since 1992, extracts lacking significant activity in the NCI human cancer cell line screen have been made available through the open repository program to organizations for testing in screens pertaining to activity against cancer, AIDS, and related opportunistic infections, as well as diseases of concern to developing countries (e.g., malaria, parasitic diseases). The extension of this program to organizations testing against all human diseases was implemented in 1999. Since late 1997, extracts showing significant activity in the NCI human cancer cell line screen have been made available, through the Active Repository Program, to organizations for testing in screens related to cancer.

Further information on these programs may be found at http://dtp.nci.nih.gov on the NCI Developmental Therapeutics Program homepage.

11. What are the odds that a sample collected in the field will be an effective drug against cancer or AIDS?

Since 1960, only seven plant-derived anticancer drugs have received Food and Drug Administration (FDA) approval for commercial production: taxol, vinblastine, vincristine, topotecan (a camptothecin derivative), irinotecan, etoposide, and teniposide—the last two being semisynthetic derivatives of epipodophyllotoxin. According to NPB, each year scientists test about 20,000 extracts, and 98 percent of them do not show activity against cancer or AIDS. Since 1986, over 40,000 plant samples have been screened, but thus far only five chemicals showing significant activity against AIDS have been isolated. Three are currently in preclinical development. Before being considered for clinical trials in humans, these agents must show tolerable levels of toxicity in several animal models.

12. What are the most promising current natural products?

For AIDS, three agents are presently in preclinical or early clinical development.

- (+)-Calanolide A and (-)-Calanolide B (costatolide) are isolated from *Calophyllum lanigerum* and *Calophyllum teysmanii*, respectively, trees found in Sarawak, Malaysia.

Both these agents are licensed to Medichem, Inc., Chicago, which is developing them in collaboration with the Sarawak State Government through a joint company, Sarawak Medichem Pharmaceuticals, Inc. (+)-Calanolide A is currently in early clinical trials in the United States.

- Conocurovone, isolated from the shrub species, *Conospermum incurvum* (saltbush), found in Western Australia, has been licensed for development to AMRAD, a company based in Victoria, Australia.

In addition, michellamine B, from the leaves of *Ancistrocladus korupensis*, a vine found in the Korup rainforest region of southwest Cameroon, has undergone extensive preclinical study, but is considered too toxic for advancement to clinical trials. Prostratin, isolated from the wood of *Homolanthus nutans*, a tree found in Western Samoa, has been placed on low priority, largely due to its association with a class of compounds shown to be tumor promoters.

A tree native to China—*Camptotheca acuminata*—is the source of four promising anticancer drugs, two of which have been approved by the FDA.

- **Topotecan (Hycamtin®)**: Has been approved by the FDA for the treatment of ovarian and small cell lung cancers. It is currently in clinical trials, either alone or in combination with other anticancer drugs, for several types of cancer.

- **Irinotecan (CPT-11, Camptosar®)**: Has been approved by the FDA for the treatment of metastatic colorectal cancer. It is currently in clinical trials for a variety of cancers.

- **9AC (9-aminocamptothecin)**: Currently in clinical trials for several types of cancer, including ovarian and stomach cancers and T-cell lymphoma.

- **Camptothecin**: While no clinical trials are being performed in the United States, trials are ongoing in China.

Other plant-derived agents in clinical trials include homoharringtonine from the Chinese tree, *Cephalotaxus harringtonia*, perillyl alcohol, and flavopiridol, a totally synthetic compound based on a flavone isolated from *Dysoxylum binectiferum.*

The following agents are from marine sources and currently are in preclinical or clinical development to treat cancer.

- Dolastatin-10, isolated from the sea hare, *Dollabella auricularia*, is found in the Comoros Islands. It is in phase I and II clinical trials.

- Ecteinascidin 743, isolated from a tunicate, *Ecteinascidia turbinata*, is collected in the Caribbean. It is in phase I and II clinical trials in Europe.

- Bryostatin 1, isolated from the bryozoan, *Bugula neritina*, is collected off the coast of California. It is in phase I and II clinical trials.

- Halichondrin B, isolated from the sponge, *Lissodendoryx* species, is found in New Zealand. It is in preclinical development.

Several agents isolated from microbial sources, mainly *Streptomyces* species, are in preclinical or clinical development for the treatment of cancer.

- Rebeccamycin analog is in phase I and II clinical trials for several types of cancer, including lymphomas and neuroblastoma.

- COL-3 (a tetracycline analog) is in phase I and II clinical trials for advanced solid tumors.

- Bizelesin (a CC1065 analog) is in phase I clinical trials for patients with advanced cancers.

- UCN-01 (a staurosporine analog) is in phase I clinical trials for hematologic cancers and advanced solid tumors. Hematologic cancers are cancers of the blood or bone marrow, including leukemia and lymphoma.

- KRN5500 (a spicamycin analog) is in phase I clinical trials for solid tumors.

- 17-AAG (17 Allylamino-17-desmethoxy-geldanamycin) is in phase I clinical trials
- FR 901228 (a bicyclic depsipeptide) is in preclinical testing for hematologic cancers.

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Sources of National Cancer Institute Information

Cancer Information Service

Toll-free: 1–800–4–CANCER (1–800–422–6237)
TTY (for deaf and hard of hearing callers): 1–800–332–8615

NCI Online

Internet

Use http://cancer.gov to reach the NCI's Web site.

LiveHelp

Cancer Information Specialists offer online assistance through the *LiveHelp* link on the NCI's Web site.

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