

**COOPERATIVE RESEARCH AND DEVELOPMENT OPPORTUNITIES
WITH THE NATIONAL CANCER INSTITUTE**

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ABSTRACT

The Office of Technology Development (OTD) of the National Cancer Institute (NCI) is responsible for negotiating Cooperative Research and Development Agreements (CRADAs), whereby the knowledge resulting from NCI investigators' government-sponsored research is developed in collaboration with universities and/or industry into new products of importance for the diagnosis and treatment of cancer and acquired immunodeficiency syndrome (AIDS). The NCI has recently executed a unique "clinical trials" CRADA and is developing a model agreement based upon it for the development and commercialization of products for the diagnosis and treatment of cancer and AIDS. NCI drug screening, preclinical testing, clinical trials, and AIDS program capabilities form the basis for this new technology development/technology transfer vehicle. NCI's extensive drug screening program and "designer foods" program serve as potential sources of investigational new drugs (INDs) and cancer preventatives. Collaborations between NCI and pharmaceutical companies having the facilities, experience, and expertise necessary to develop INDs into approved drugs available to the public are being encouraged where the companies have proprietary rights to INDs, or where NCI has proprietary rights to INDs and invites companies to respond to a collaborator announcement published in the Federal Register. The joint efforts of the NCI and the chosen collaborator are designed to generate the data necessary to obtain pharmaceutical regulatory approval from the Food and Drug Administration (FDA) to market the drugs developed, and thereby make them available to health care providers for the diagnosis and treatment of cancer and AIDS.

INTRODUCTION

The Office of Technology Development is organizationally located in the Office of the Director of the National Cancer Institute. The National Cancer Institute is one of the thirteen Institutes of the National Institutes of Health. The National Institutes of Health is a part of the Public Health Service, which in turn is part of the Department of Health and Human Services.

The mission of the National Institutes of Health is to conduct biomedical and behavioral research into the treatment and control of disease, to positively benefit the health of the American people. As a main source of funding for medical research in the United States, the National Institutes of Health is a national resource for the evaluation of new disease therapies. Historically, the National Cancer Institute has been the most important effector in the discovery and development of new anticancer agents. More recently, the National Cancer Institute has also played a leading role in the discovery and development of anti-AIDS agents such as azidothymidine (AZT) and dideoxyinosine (ddI).

Cancer and AIDS research efforts at the National Cancer Institute are both basic and applied. Basic biomedical and molecular biology research being conducted include sequencing studies and studies of the molecular actions of drugs and mutagens. Applied diagnostic and treatment research being conducted includes: methods and materials to detect early cancer; methods and materials to detect human immunodeficiency virus (HIV) infection; and clinical trials to determine the efficacy of anti-cancer and anti-AIDS agents.

The Office of Technology Development serves as the National Cancer Institute's focal point for the implementation of the laws, policies, rules and regulations related to the implementation of the Federal Technology Transfer Act of 1986. The Office is responsible for the administration of activities related to collaborative agreements,

confidentiality agreements, material transfer agreements, inventions, patents, licensing and royalties. Office of Technology Development staff members provide advice, guidance and assistance to National Cancer Institute scientists and staff, and review and analyze planned agreements to ensure that they comport with applicable National Cancer Institute, National Institutes of Health, Public Health Service, and Department of Health and Human Services policy and procedures.

The Office of Technology Development interacts with several other National Institutes of Health technology transfer components. Among these are: the Patent Policy Board; the National Institutes of Health Office of Technology Transfer; the various Institute Technology Development Coordinators; and extramural components, including the Office of Extramural Programs. The Patent Policy Board oversees the technology transfer program for the Public Health Service, and makes policy recommendations to Public Health Service agency heads. The Office of Technology Transfer serves the following centralized functions for the National Institutes of Health: preparation, filing and prosecution of domestic and foreign patent applications, utilizing the services of its own Patent Branch, outside contract attorneys, and the National Technical Information Service; marketing and licensing of technology and inventions, either directly or through the Center for the Utilization of Federal Technology, Department of Commerce; and drafting of model agreements. Each of the Institutes of the National Institutes of Health has a Technology Development Coordinator who participates in the interactive stages of patent prosecution and licensing activities. Two Institutes also have established offices for the transfer of technology. The National Cancer Institute has established the Office of Technology Development; and the National Institute of Allergy and Infectious Diseases has established the Technology Transfer Branch. The extramural component includes grants, contracts, cooperative research and development agreements, informal clinical trial agreements, memoranda of understanding, and confidentiality agreements; for drug screening and discovery, and clinical trials with private industry. Through the office of Extramural Programs, grantee institutions report patentable inventions developed using Federal funds, and communicate the grantees' decisions regarding the assignment of rights to those inventions.

The Office of Technology Development was established as the result of a series of legislative enactments that were designed to transfer Federal technology to industry, to state and local governments, and to universities. Among these legislative enactments are: Federal patent law; the Bayh-Dole Patent and Trademark Act of 1980; the Stevenson-Wydler Technology Innovation Act of 1980; the Federal Technology Transfer Act of 1986; and Executive Order 125991 of 1987. Federal patent law (35 U. S. C. at §§ 200-212) authorizes the licensing of Government-owned patent rights. Under it, "... Each Federal agency is authorized to ... grant non-exclusive, exclusive, or partially exclusive licenses under federally owned patent applications, patents, or other forms of protection obtained, royalty-free or for royalties or other consideration, and on such terms and conditions, including the grant of a license of the rights of enforcement pursuant to the provisions of chapter 29 of this title as determined appropriate in the public interest;" The Bayh-Dole Act of 1980 allows nonprofit organizations and small business to retain rights to inventions (patents) or other intellectual property (trademarks, copyrights) developed under Federal grant or contract funding. This Act has been amended to allow Federal laboratories operated by nonprofit organizations to similarly retain intellectual property rights and commercialize Federally sponsored inventions. The Stevenson-Wydler Technology Innovation Act of 1980 establishes the policy that it is the duty of each Federal laboratory to transfer Federal technology to industry, to state and local governments, and to universities. However, it was not until the passage of the Technology Transfer of 1986, that Federal laboratories had effective incentives to encourage both the Federal scientists and collaborators in the state, local and private sectors to participate and accomplish this goal.

The Federal Technology Transfer Act (15 U.S.C. § 3710, "Utilization of Federal Technology") of 1986 amended the Stevenson-Wydler Technology Innovation Act of 1980 to authorized Federal laboratories to enter into Cooperative Research and Development Agreements (CRADAs), and to grant intellectual property rights in advance to collaborators for inventions made in whole or in part by Federal employees under the CRADA. The Federal Technology Transfer Act requires that agencies establish cash award programs for inventors and non-inventors for their contributions to technology transfer, and that laboratory directors recognize the competitive advantage Congress intended technology transfer to grant United States business. A 1989 amendment to the Federal Technology Transfer Act authorizes government-owned, contractor-operated (GOCO) facilities to enter into CRADAs so that technology developed for the government by private parties can also be transferred. Executive Order 12591 of April 10, 1987, "Facilitating Access to Science and Technology", orders Federal laboratories to transfer new knowledge from the research laboratories to universities and to the private sector (to "privatize" Federal research inventions), assisting

them in the development of new products and processes, thereby broadening our national technology base, and strengthening United States manufacturers' competitive position in the international economic arena.

Legislation is pending that would further enable technology transfer from the Federal sector. Currently, Federal employees are prohibited from copyrighting any work developed as part of their official duties. Under consideration is the protection by copyright of computer software and other material developed by Federal employees under a CRADA.

MODEL COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT AND RELATED POLICY

The National Institutes of Health/Alcohol, Drug Abuse and Mental Health Administration (NIH/ADAMHA) Model Cooperative Research and Development Agreement is a contractual mechanism for technology transfer, under which information and materials are exchanged between collaborators. The Articles and Appendices of the NIH/ADAMHA Model Agreement are as follows, with National Cancer Institute additions indicated:

Article 1.	Introduction
Article 2.	Definitions
Article 3.	Cooperative Research
Article 4.	Reports
Article 5.	Financial and Staffing Obligations
Article 6.	Title to Property
Article 7.	Intellectual Property Rights and Applications
Article 8.	Licensing
Article 9.	Proprietary Rights and Publication*
Article 10.	Representations and Warranties**
Article 11.	Termination
Article 12.	Disputes
Article 13.	Liability
Article 14.	Miscellaneous
Article 15.	Duration of Agreement
Appendix A	NIH/ADAMHA Policy Statement on CRADAs and Intellectual Property Licensing
Appendix B	Research Plan
Appendix C	Financial and Staffing Contributions of the Parties
Appendix D	Exceptions or Modifications to this CRADA

* NCI adds "Intellectual Contributions of the Parties" to this Article

** NCI adds "Potential Patentability of Subject Inventions" to this Article

Several NIH/ADAMHA policy considerations impact upon the terms agreed to by the Government under a CRADA. National Cancer Institute investigators are free to choose their research topics, provided their choices are consistent with the mission of the Institute and the program of their particular laboratories. This research freedom cannot be constrained by the conditions of a CRADA or a related licensing agreement. Nor can the scientists' participation in a cooperative research plan restrict his ability to disseminate research results freely in both publications and public fora. Provision is made for reasonable delays in this dissemination only for the purpose of filing patent application(s), which filing is, in fact, encouraged.

Under a CRADA there is an exchange between the collaborators of intellectual and/or technical resources that are not otherwise reasonably available. Provision is made for personnel, services, facilities and equipment to be exchanged between the collaborator and the National Cancer Institute. Funds may flow from the collaborator to the National Cancer Institute; however, in no case may funds flow from the National Cancer Institute to the collaborator.

The CRADA collaborator is chosen on the basis of scientific expertise and commercialization capabilities. When the Government has the intellectual lead, a Federal Register notification may be appropriate. NIH/ADAMHA will give special consideration to entering into CRADAs with small business firms and consortia involving small business firms. Further, preference will be given to businesses located in the United States, or which agree to manufacture substantially in the United States products which embody inventions developed under CRADAs.

Proprietary information may be exchanged and maintained as confidential under a CRADA, since Freedom of Information does not require the release of "trade secrets and commercial or financial information ... [that] are privileged and confidential". Secrecy is routinely maintained under National Cancer Institute drug screening programs and during the Food and Drug Administration regulatory approval process. Proprietary information under CRADAs is maintained as confidential as long as is necessary to accomplish the research plan. However, in no case will secrecy be maintained once an invention has been patented.

The time-limited right to exclude others from making, using, or selling an invention, which is conveyed by a license is used as an incentive for collaborators to invest in product development under a CRADA. Time-limited options to negotiate non-exclusive, partially exclusive, or exclusive licenses may be granted in advance to CRADA collaborators. When granting licenses to inventions developed wholly by NIH/ADAMHA investigators or jointly with a collaborator under a CRADA, the Government retains a nonexclusive, irrevocable, paid-up license to practice the invention or to have the invention practiced throughout the world by or on behalf of the U.S. Government. The Government also requires the grant of a research license for inventions made wholly by a collaborator under a CRADA. Further, NIH/ADAMHA reserve the right under any license granted to the collaborator, to grant research licenses to third parties.

Requests for exclusive commercialization licenses must include a development and commercialization plan. After an exclusive license is granted, reports on progress toward utilization of the invention are required. NIH/ADAMHA reserves the right to grant several, separate exclusive licenses in various fields of use. Exclusive licenses will have "best effort" clauses, and may be terminated when a licensee is not actively engaged in an effort to produce product, or a licensee cannot meet market demand. Exclusive licensees must not unreasonably deny requests for sublicense in unused fields of use, or requests for cross license rights from future CRADA collaborators when derivative rights are necessary for a CRADA to go forward, and the exclusive licensee has been given a reasonable opportunity to be a party to the CRADA.

A pricing clause will be found in every CRADA since policy states that "DHHS has a concern that there be a reasonable relationship between the pricing of a licensed product, the public investment in that product, and the health and safety needs of the public. Accordingly, exclusive commercialization licenses granted for NIH/ADAMHA intellectual property rights may require that this relationship be supported by reasonable evidence."

COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENTS FOR THE CLINICAL DEVELOPMENT OF ANTI-CANCER AND/OR ANTI-AIDS AGENTS

When a compound is discovered or developed by the National Cancer Institute that shows promise as an anti-cancer or an anti-AIDS agent, the involvement of a private firm is sought, since the National Cancer Institute does not take drugs to market. The early involvement of a pharmaceutical firm permits substantial cost sharing between the Government and the private sector, and can speed the commercial availability of effective agents. Industry is asked to invest its resources to bring an agent from the discovery stage through subsequent development, clinical trials, regulatory approvals, and ultimately into commercial production. An exclusive license may be granted to the industrial collaborator in cases where substantial additional risk, time and cost must be undertaken prior to successful commercialization. An option to negotiate such a license may be granted in advance under a CRADA for the clinical development of an agent.

Under a CRADA for the clinical development of an agent, national, multicenter clinical trials in various research settings, and trials in combination with other agents, can be planned and coordinated. Efforts to investigate and evaluate alternative sources of the agent can also be planned and coordinated.

In addition to standard CRADA provisions, a CRADA for the clinical development of an anti-cancer or anti-AIDS agent may also contain terms regarding:

The formation and functioning of a Clinical Research Team, or Steering Committee

Provision for supply of drug up to New Drug Application (NDA) filing, including amounts for compassionate use

Provision for Investigational New Drug Application (IND) sponsorship, and for cross-referencing of INDs

Summary of completed and ongoing preclinical and clinical testing and data

Provision for data collection

Provision for New Drug Application (NDA) filing

Provision of support staff for Group C distribution

Conveyance of orphan drug status

License of pre-dating compounds or methods of use apart from CRADA

Publication clause: "Nothing shall prevent the timely publication of the results of clinical trials or pre-clinical research."

A recently executed example of a CRADA for Clinical Development is one for the clinical development of taxol. Taxol is a promising new drug for the treatment of refractory ovarian cancer. Taxol was discovered during the NCI-sponsored screening of extracts of over 35,000 plant species. It is a natural product that is in short supply. In return for the significant financial investment of procuring sufficient taxol for clinical trials, and for exploring alternative natural and synthetic sources, and for prosecuting the NDA, the collaborator has been given exclusive access to the clinical data, and conveyance of the orphan drug status that was granted taxol by the FDA. This is an unusual CRADA, since taxol is not patented, and other companies are, therefore, free to work on taxol, as well as its analogues.

NCI'S UNIQUE RESEARCH CAPABILITIES

NCI has research capabilities uniquely suited to cooperative research for the clinical development of anticancer and anti-AIDS agents. NCI has the largest staff and funding among the Institutes of the National Institutes of Health, and possesses unique capabilities in support of clinical development efforts. NCI's drug screening and development programs include acquisition and synthesis of novel compounds, *in vitro* screening, *in vivo* assays, preclinical testing, clinical trials, and AIDS program capabilities.

NCI's Clinical Therapy Evaluation Program (CTEP), within the Division of Cancer Treatment, is researching the uses of therapeutic compounds supplied by intramural as well as extramural researchers and pharmaceutical companies. CTEP designs and implements the development plans for new agents; it files INDs with FDA, permitting DCT to act as a drug sponsor; and it is responsible for the contracts and cooperative agreements under which most clinical testing takes place. Through grants, contracts and cooperative agreements, NCI funds a large, multicenter clinical trials network, including cooperative groups, new drug development contractors, and other investigators at cancer centers and university hospitals. More than 500 investigators and approximately 500 institutions are involved; and over 100 compounds are currently in various stages of clinical testing.

NCI oversees the only Government Owned Contractor Operated (GOCO) facility at NIH, at the Frederick Cancer Research and Development Center (NCI-FCRDC). Five separate NCI-FCRDC contract operations provide: basic research, operations and technical support, computer services, library services, and animal production. The following NCI Divisions have intramural, extramural and clinical activities at NCI-FCRDC: the Division of Cancer Etiology (DCE); the Division of Cancer Treatment (DCT, including the Developmental Therapeutics Program and Biological Response Modifiers Program); the Division of Cancer Biology, Diagnosis and Centers (DCBDC), and the Division of Cancer Prevention and Control (DCPC). GOCO contractors at NCI-FCRDC are engaged in basic research into the causes and biology of cancer, and furnish the following technical support services: support for new DCT programs for *in vitro* screening of antitumor and anti-AIDS compounds, including the development of large-scale natural products extraction capability; support for the Biological Response Modifiers Program's experimental clinical trials at a nearby outpatient facility and an inpatient capability located at a local hospital; support for AIDS vaccine development program efforts at NCI-FCRDC and an outside subcontract network; repositories for cell lines, natural product compounds, and other research materials; managing the NCI Supercomputer Center, with special emphasis on mathematical biology in biomedical research.

NCI's Cancer Network includes: Cancer Information Service (CIS), a national toll-free telephone service that provides immediate answers to cancer-related questions from cancer patients, families, the public, and health professionals; Cancer Centers, a program of cancer research centers across the country which significantly contributes to progress in basic research, clinical studies, and cancer prevention and control; Community Clinical Oncology Program (CCOP), a program affording community physicians and their patients the opportunity to participate in NCI-approved cancer treatment and cancer prevention and control clinical trials; Physicians Data Query (PDQ), an on-line computer system that provides state-of-the-art information on cancer detection, diagnosis and treatment; Cooperative Group Outreach Program (CGOP), designed to increase patient enrollment in clinical trials and to upgrade the skills of community physicians and other health professionals; Surveillance, Epidemiology, and End Results (SEER) Program, population-based cancer registries that permit monitoring of cancer incidence, mortality and survival, and is a key tool for assessing progress against cancer.

RESEARCH INITIATIVES WITHIN THE DIVISIONS OF THE NATIONAL CANCER INSTITUTE

Research initiatives within the Divisions of the National Cancer Institute of interest to potential CRADA collaborators are as follows. Research initiatives within the Division of Cancer Etiology (DCE) include dietary mutagen studies, and an investigation of the relationship between human papilloma viruses and cancer risk. Within the Division of Cancer Biology, Diagnosis and Centers (DCBDC), new discoveries are providing new strategies for potentially inhibiting cancer invasion metastasis formation and growth. Using a panel of about 60 human tumor cell lines, the Division of Cancer Treatment (DCT) is routinely screening about 20,000 synthetic compounds and natural products extracts annually for anti-cancer activity. Screening of potential anti-AIDS drugs also has been carried out in HIV-infected cells at a rate of about 20,000 synthetic compounds and natural products extracts annually. DCT's research activities also include: clinical strategies to overcome multi-drug resistance; human gene therapy; clinical development of taxol; adoptive immunotherapy; and tumor suppressor genes.

NCI PRECLINICAL AND CLINICAL TREATMENT RESEARCH EFFORTS

Pharmaceutical industry interactions with NCI for the testing and joint development of agents are possible at all stages of antitumor screening, preclinical toxicology, and clinical testing.

NCI's preclinical research efforts include new drug discovery through natural product screening and rational drug design; and the preclinical discovery and development of biological response modifiers, including such research areas as monoclonal antibodies, cell-mediated cytotoxic therapy, targeting of growth factor oncogenes and tumor-tumor suppressor genes, and hematopoietic growth factors

NCI's clinical research efforts include: enhancement of the effectiveness of chemotherapy; immunotherapy; gene therapy; differentiation therapy; radiation oncology; diagnostic imaging; and clinical trials, including investigational drug and chemoprevention trials.

RECENT/CURRENT NATIONAL CANCER INSTITUTE CRADAS

AIDS Vaccine Development: HIV gp160

Generation and Characterization of Monoclonal Antibodies to Carcinoma Associated Antigens

Retroviral-Mediated Transfer for AIDS Therapy

Retroviral-Mediated Gene Transfer into Bone Marrow Cells and T and B Lymphocytes

Research in the Field of Early Detection of Lung Cancer

Evaluation of cDNA Clones Related to Cancer Metastases

Transforming Growth Factor- α /Pseudomonas Exotoxin Hybrid Proteins

Cytokines for Enhancing Drug Delivery and Pharmacologic Action

Clinical Development of Taxol

Interleukin-2/Pseudomonas Exotoxin

Development of Methods for PCR Amplification of DNA Sequences Directly from Clinical Specimens

Human Cytochrome p-450 cDNA Expression and Mutagenesis

Clinical Development of PALA

Testing of Antigens for Improvement of IL-2 Therapy

Immunoglobulin and Immunotoxin Therapeutics for HIV Infections and AIDS

The Function of Two Novel, Inducible Proteins Secreted by Activated T Cells

Novel CD4 Targeted Anti-HIV Agents

Construction of a Multiwell Cell Settling Chamber

AIDS Vaccine

Single Chain Bispecific Antibody

Hair Follicle Cell Biology, Biochemistry and Molecular Biology

Human Papillomavirus (HPV) Infection and Cervical Dysplasia

Development of Nontoxic Aqueous Chemiluminescent Systems for Use in Photodynamic Therapy

RECENT/CURRENT NCI CRADA COLLABORATORS

Abbott Laboratories/Johns Hopkins University

American Cyanamid Company

Amgen Incorporated

Bristol-Myers Squibb

Cetus Corporation

Creative BioMolecules

Dow Chemical

Genetic Therapy, Inc.

Gentest Corporation

Hoffmann-LaRoche

Immuno-U.S.

Integrated Genetics

Lofstrand Labs

Merck

Molecular Oncology

Molecular Vaccines

Neuro Probe, Inc.

Sandoz Forschungsinstitut

U.S. Bioscience

Upjohn Company

Virogenetics