National Cancer Institute

DIVISION OF CANCER TREATMENT AND DIAGNOSIS

PROGRAM ACCOMPLISHMENTS 2006

U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES

National Institutes
of Health

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FOREWORD

Cancer clinical research is changing, and a large part of the transformation is being spearheaded by the Division of Cancer Treatment and Diagnosis (DCTD), an extramural component of the National Cancer Institute (NCI) with the responsibility of overseeing much of NCI's infrastructure for clinical trials and drug development. I am pleased to provide you with this summary of accomplishments made possible by the many talented and dedicated staff members in programs throughout the division.

Dr. James H. Doroshow, Director, NCI Division of Cancer Treatment and Diagnosis.

Advances in molecular medicine have created new challenges for the design and conduct of cancer clinical trials. The National Cancer Advisory Board's Clinical Trials Working Group (CTWG) examined these challenges and, last year, issued 22 strategic initiatives to restructure the conduct of NCI-supported clinical trials so that new treatments reach patients with cancer more quickly. The CTWG endorsed team science in the broadest sense. This included the development of mechanisms to enhance the coordination of clinical, basic, and translational scientists in their efforts to improve molecular diagnostic and imaging techniques, as well as to increase the utility of novel targeted therapies. The success of the CTWG initiatives will require a significant commitment by all stakeholders in the clinical trials process to assist NCI in setting new policies, procedures, and standards and in guiding prioritization and decision-making.

DCTD will play a leading role in the implementation of the CTWG initiatives, with the goal of producing an integrated, responsive, efficient, and innovative clinical trials enterprise. The division will also assist the newly created NCI Coordinating Center for Clinical Trials as it assumes the day-to-day responsibilities for project management of the CTWG initiatives.

As part of the change process, DCTD and the Center for Cancer Research (CCR) are working in close collaboration to reinvigorate cancer drug development at NCI. Through a new, joint early therapeutics development program, extramural and intramural teams have prioritized a pipeline of NCI-driven targeted therapeutics for development. This program combines the strengths of DCTD's extensive expertise in anticancer drug development with CCR's dynamic in-house research and its location within new state-of-the-art facilities at the NIH Clinical Research Center. This collaboration will also utilize a recent guidance from the U.S. Food and Drug Administration concerning exploratory studies of investigational new drugs.

The implementation of CTWG initiatives, modernization and integration of cancer therapeutics development, and expansion of the pipeline of potential cancer therapies underscore NCI's position as a premier developer of novel cancer therapeutics and diagnostics.

Clinical trials performed using an exploratory investigational new drug (IND) will facilitate targeted therapies entering early phase evaluation where the target can be carefully monitored. The goal of this new guidance is to safely shorten the timeline for drug development. As part of the DCTD-CCR collaboration, novel agents for high-priority targets originating from academic and other extramural researchers will be eligible to take advantage of intramural resources.

Exploratory IND studies are ideal, as well, for imaging and other advanced technology applications aimed at developing clinically relevant assays of biomarkers that could help predict whether later-stage trials are likely to be successful. Biomarker assays can also assess the efficacy, mechanism of action, and toxicity of promising treatments. DCTD is also improving its capabilities to develop and validate pharmacodynamic markers. The division is developing standardized operating procedures for handling human tissue specimens and for pharmacodynamic assays. One major goal of this program is to incorporate molecular imaging techniques routinely into early therapeutics development; in particular, there will be a special emphasis on the development of novel imaging probes for monitoring new drug targeting to tumors and for determining the therapeutic benefit of the targeted therapy.

The goal is to produce a diverse portfolio of pharmacodynamic assays and imaging tools that are in the public domain. These complex tasks are time-consuming and expensive, and NCI is well suited to take on this enterprise. It is anticipated that this investment will reap many benefits by making a library of new molecular tools available to all researchers in the cancer research community to assess new targeted drugs and diagnostics.

These efforts also support an NCI-wide priority to better integrate preclinical and clinical research. In addition to partnering with intramural researchers in CCR, DCTD is working to link preclinical and clinical resources seamlessly within the division. This will support extramural trials of targeted therapies and foster better assimilation of molecular imaging and radiation techniques into therapeutics development. Teams of experts across NCI will unite to form integrated drug development teams. A joint CCR-DCTD drug development committee will oversee these teams, determine resource priorities, assess agent progress, identify gaps in the portfolio particularly suited to NCI drug development efforts, and evaluate new compounds for inclusion in the pipeline.

The steps being taken to implement the CTWG initiatives, modernize and integrate cancer therapeutics development using the exploratory IND and other approaches, and expand the pipeline of potential cancer therapies underscore NCI's position as a premier developer of novel cancer therapeutics and diagnostics.

DIVISION OF CANCER TREATMENT AND DIAGNOSIS

The Division of Cancer Treatment and Diagnosis collaborates with other National Cancer Institute components as the world's largest sponsor of clinical cancer research.

OVERVIEW

The Division of Cancer Treatment and Diagnosis (DCTD) collaborates with other National Cancer Institute (NCI) components as the world's largest sponsor of clinical cancer research.

The multidisciplinary staff members of DCTD identify the most promising areas of science and technology for development of better diagnostic and therapeutic interventions for patients with cancer. A roster listing full-time DCTD staff as well as contractors is appended to this report.

The division takes prospective detection and treatment leads, facilitates their paths to clinical application, and expedites the initial and subsequent large-scale testing of new agents and interventions in patients. By determining the highest priority questions that can be examined in the laboratory and through clinical trials, DCTD ensures that appropriate mechanisms and resources are available for the development of novel interventions for the wide range of cancers affecting children and adults.

Another major objective for the division is increasing the scientific depth at which new treatments are being evaluated while coordinating the administration and conduct of clinical trials with all other NCI components involved in the pursuit of clinical studies.

DCTD scientists support programs to pursue high-risk research that may yield great benefits for patients with cancer but may be too difficult or risky for industry or academia to undertake. This includes a particular emphasis on the development of unique molecular signatures for cancer and molecular assays and imaging techniques that will guide oncologic therapy in the future.

Dr. James H. Doroshow, Director

James H. Doroshow, M.D., FACP, has been the Director of the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), National Institutes of Health (NIH), since 2004. He fosters collaboration with other NCI divisions and offices, as well as extramural scientists and clinicians, patient advocates, and professional cancer organizations. He leads the DCTD professional staff, who represent a wide array of scientific specialties, to integrate their insights and skills into a cross-disciplinary, scientifically driven, cooperative research endeavor to discover and develop better diagnostic and therapeutic interventions for cancer.

Dr. Doroshow also oversees his own active laboratory program focusing on two lines of research: discovering the mechanisms that drive the anthracycline antibiotic cell death program and understanding the role of oxidative signals in the development and treatment of colon cancer.

From 1983 to 2004, Dr. Doroshow was the Associate Director for Clinical Research at the City of Hope's (COH) Comprehensive Cancer Center in Duarte, California; the Chairman of the COH Department of Medical Oncology and Therapeutics Research; and the Leader of the COH Cancer Center's Clinical and Experimental Therapeutics Program. Through these roles, he oversaw solid tumor therapeutic research, supervised a staff of 75 involved in investigating novel targeted agents and other therapies, and directed a program of clinical research that supported more than 150 concurrently active clinical trials. While at COH, he founded an early therapeutics consortium of three NCI-designated cancer centers in California funded by both NCI's phase I and II support grants. He was also the principal investigator for COH's membership in the Southwest Oncology Group (SWOG) and founding Chair of the SWOG Early Therapeutics Committee.

From the time he received his first research grant in 1980, Dr. Doroshow was funded continuously by NCI and NIH until moving to NCI in 2004. He is the author of more than 300 full-length publications in the areas of the molecular and clinical pharmacology of the anthracycline antibiotics, the role of oxidant stress in signal transduction, and novel therapeutic approaches to breast, gastrointestinal, lung, and gynecologic cancer. Dr. Doroshow is a senior editor of *Clinical Cancer Research*. He is a member of the editorial boards of *International Journal of Oncology, Technology in Cancer Research and Treatment,* and *Oncology*. He is also an associate editor for the widely used *Manual of Clinical Oncology* published by the International Union Against Cancer. Dr. Doroshow served from 1995 to 2001 as a member of the Subspecialty Board on Medical Oncology of the American Board of Internal Medicine, from 1999 to 2000 as Chair of NCI's Scientific Review Group A-Cancer Centers, and from 1990 to 1992 as Chair of the NIH Experimental Therapeutics II Study Section. He is currently a member of the U.S. Food and Drug Administration Oncologic Drugs Advisory Committee.

Dr. Doroshow received his bachelor's degree, magna cum laude, from Harvard College in 1969 and his medical degree, Alpha Omega Alpha, from Harvard Medical School in 1973. After completing an internship and residency at Massachusetts General Hospital in Boston, he spent three years (1975–1978) at NCI as a clinical associate. He is board-certified in internal medicine and medical oncology. Prior to joining COH in 1981, he held the position of Assistant Professor of Medicine in the Division of Medical Oncology at the University of Southern California School of Medicine in Los Angeles.

DCTD scientists support programs to pursue high-risk research that may yield great benefits for patients with cancer but may be too difficult or risky for industry or academia to undertake.

DCTD has six major programs that work together to bring unique molecules from the laboratory bench to the patient bedside:

- **Biometrics Research Branch (BRB)**—provides state-of-the-art statistical and biomathematical analyses for DCTD and other NCI components and performs research in the areas of statistical, mathematical, and computational sciences that is motivated and informed by real and important problems in current cancer research. Branch members provide leadership for the DCTD national research programs by formulating biomathematical approaches for analyzing genomic, proteomic, metabolomic, and other data emanating from the developmental therapeutics, diagnostics, imaging, radiation research, and clinical trials programs.
- **Cancer Diagnosis Program (CDP)**—strives to improve the diagnosis and assessment of cancer by effectively moving new scientific knowledge into clinical practice. This program stimulates, coordinates, and funds specimen resources, databases related to those specimens, and research on diagnostics and improved technologies to better characterize tumors, so that cancer patients and their physicians can have access to a broader range of diagnostic information as they make clinical decisions. The laboratory tools CDP develops also help to maximize the impact of cancer treatments.
- **Cancer Imaging Program (CIP)**—unites researchers in a team approach from disciplines as diverse as radiology, bioengineering, biology, chemistry, and physics. The program encourages researchers to integrate new imaging discoveries and developments into the study of cancer biology and into the clinical management of cancer and cancer risk. This translational research program is using new technologies to expand the role of imaging in noninvasive diagnosis, identification of disease subsets in patients, disease staging, and treatment monitoring. CIP supports and advises innovative developers in academia and private industry as they create the next generation of imaging technology, including molecular probes, optical technology devices, and new contrast agents.
- **Cancer Therapy Evaluation Program (CTEP**)—functions as NCI's primary clinical evaluator of new anticancer agents. Program staff members play a critical role in selecting promising agents to enter human clinical trials. In addition, the program evaluates new radiation and surgical methods, identifies biomolecular characteristics of malignant tumors that investigators may be able to exploit clinically, and administers the 11 cooperative research groups that unite researchers around the nation and the world in the pursuit of distinctive and effective new treatments for cancer. CTEP accomplishes its goals by administering, coordinating, and funding clinical trials, as well as sponsoring other research. The

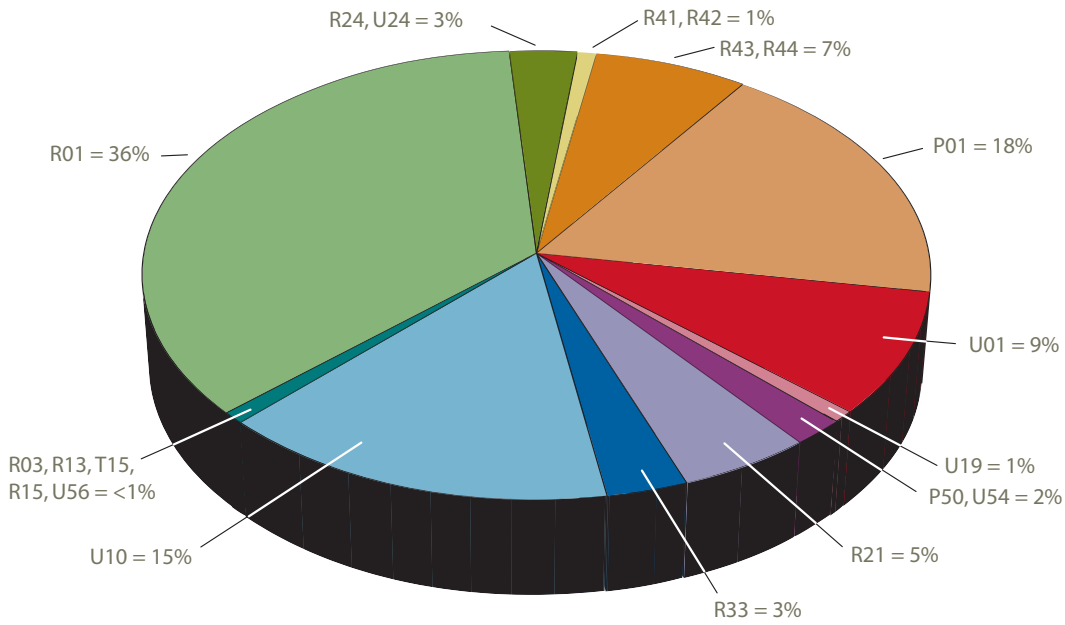
DCTD Management

program fosters collaborations within the cancer research community and works extensively with the pharmaceutical and biotechnology industries as well. CTEP also reaches out to patients and their advocates to help establish research priorities.

- **Developmental Therapeutics Program (DTP)**—serves as a vital resource in discovering potential cancer therapeutics and acquiring preclinical development information. The program provides research materials, including Web-accessible data and tools, vialed and plated compounds, tumor cells, and research animals, and manufactures new agents in bulk quantities for use in investigational new drug (IND)–directed studies. The program is playing a central role in new collaborations with the NCI Center for Cancer Research (CCR) to reinvigorate the cancer drug development pipeline, with the goal of significantly shortening the amount of time it takes to safely develop effective new treatments for patients with cancer.
- **Radiation Research Program (RRP)**—supports clinical research by providing expertise to investigators who perform novel radiotherapy research, assisting the radiotherapy research community in establishing priorities for the future direction of radiation research, providing medically underserved communities with access to radiotherapy, and evaluating the effectiveness of radiation research being conducted by NCI grantees. RRP also coordinates its activities with other radiation research programs at NCI, NIH, other federal agencies, and national and international research organizations. Additionally, RRP serves as a focal point for extramural investigators concerned with clinically related radiation research.

DCTD Research Grants

Percent of Grant Dollars Awarded by Mechanism*
Fiscal Year 2005



Grant Mechanisms

P01 = Research Program Project Grant
P50 = Specialized Center Grant
R01 = Research Project Grant
R03 = Small Research Grant
R13/T15 = Conference/Training Grant
R15 = Academic Research Enhancement Award (AREA)
R21 = Exploratory/Development Grant
R24 = Resource-Related Research Project
R33 = Phased Innovation Grant–Phase II
R41 = Small Business Technology Transfer (STTR) Grant–Phase I
R42 = Small Business Technology Transfer (STTR) Grant–Phase II
R43 = Small Business Innovation Research Grant (SBIR)–Phase I
R44 = Small Business Innovation Research Grant (SBIR)–Phase II
U01 = Research Project—Cooperative Agreement
U10 = Clinical Cooperative Groups
U19 = Research Program—Cooperative Agreement
U24 = Resource-Related Research Project—Cooperative Agreement
U54 = Specialized Center—Cooperative Agreement
U56 = Exploratory Grants—Cooperative Agreement

*Percentages may not total 100% due to rounding.

MAJOR ONGOING INITIATIVES AND ACCOMPLISHMENTS

As contributors to the goal of eliminating suffering and death due to cancer, DCTD staff members and their colleagues are reexamining discovery, development, and delivery of cancer therapeutics. What follows is a brief summation of some of the division's priorities as it hastens to find and develop more interventions tailored to the specific characteristics of a patient's cancer.

Restructuring NCI–Supported Clinical Trials

Between January 2004 and June 2005, the Clinical Trials Working Group (CTWG), a panel of 38 clinical trialists, advocates, and government representatives, conducted a transparent, inclusive evaluation of the cancer clinical trials process. The aim of the assessment was to improve efficiency, decrease redundancy and administrative burdens, and better coordinate activities to enhance the development and delivery of the best therapies to people with cancer. The CTWG's five-year improvement plan was approved for implementation by the National Cancer Advisory Board (NCAB) in June 2005. Dr. James Doroshow, DCTD director and CTWG chair, has begun the process of executing the CTWG recommendations.

A full six months ahead of schedule, a new NCI organizational structure, designed to oversee the Institute's entire clinical trials enterprise, was unveiled at the NCAB February 2006 meeting.

The structural components of the reorganization are the Clinical Trials Advisory Committee (CTAC), the Clinical Trials Operations Committee (CTOC), and the Coordinating Center for Clinical Trials (CCCT).

CTAC, the first new NCI advisory committee to the director approved in the past decade, will advise the NCI director on the Institute's clinical trials program and will include members of the NCAB as well as other NCI advisory boards and additional cancer clinical trials experts. CTAC will oversee implementation of CTWG initiatives, including a review of the system to evaluate and measure the effects of the implementation. CTAC also will provide advice on the use of correlative science funds, additional funding allotted to specific clinical trials for correlative science and quality-of-life studies.

CTOC, an internal NCI committee chaired by the NCI deputy director for clinical and translational sciences, includes the directors of every NCI division, branch, or center involved in clinical trials. Based in the NCI director's office, CTOC will coordinate clinical trials programs across NCI and will make recommendations to improve cost-effectiveness and reduce duplication and overlap among NCI components involved in clinical trials. CTOC will also evaluate new Requests for Applications and Program Announcements for clinical trials prior to review by the NCI Executive Committee.

CCCT will provide project management for the implementation of all CTWG initiatives. CCCT will support a number of significant activities, including coordinating new

Modern drug development techniques that employ imaging and other advances also make foreseeable the arrival of screening tools that could, early in the pathway, predict therapeutic or toxic activity in humans.

disease-specific steering committees for the prioritization of phase III trials, the investigational drug steering committee for phase I and II trials, and working groups that will develop critical new tools for clinical investigators, as well as measures to improve clinical trial operational efficiency.

Two disease-specific cancer steering committees have begun to take shape. In January and June 2006, respectively, the steering committees for gastrointestinal cancers and gynecologic malignancies held their first meetings.

DCTD Staff Members Add Expertise to the Translational Research Working Group

In 2005, following the success of the CTWG, a Translational Research Working Group (TRWG) was established to review NCI's current intramural and extramural translational research portfolio and to recommend ways to improve and integrate translational research efforts. The ultimate goal is to rapidly translate the scientific discoveries of the cancer community's many dedicated scientists into new interventions for preventing, diagnosing, and treating cancer.

The DCTD director and several associate directors from the division are participating in the TRWG process, which is set to make recommendations in early 2007.

Accelerating Cancer Drug Development

Despite increases in drug development expenditures in the public and private sectors during the 1990s, the number of new agents reaching human clinical trials has been decreasing. Even when compounds proceed to clinical testing, they often fail because of unexpected toxicities or lack of efficacy. The pathway from discovery of promising agents to delivery in the oncology clinic, though multifaceted and complex, may change due to improvements in our understanding of drug targeting at the molecular level. Modern drug development techniques that employ imaging and other advances also make foreseeable the arrival of screening tools that could, early in the pathway, predict therapeutic or toxic activity in humans. Such changes should shorten the amount of time it takes to bring useful new anticancer drugs to the patients who need them.

The following improvements in the use of DCTD resources have been made in the past year to accelerate drug development:

- DCTD and CCR have established a formal partnership to enhance pre-clinical and clinical drug testing
  - A joint pipeline of new agents is now being actively managed by DCTD and CCR
    - Decisions about what agents to develop are being made by a newly established **joint development committee**

- Molecules entering the pipeline will be managed by teams with members from both DCTD and CCR
- Joint drug development teams will be guided by a new DCTD **Developmental Therapeutics Project Management Office,** bringing a business-focused approach to tracking the progress of agents from discovery through early-phase clinical trial

- Together, DCTD and CCR investigators will utilize the recently announced Food and Drug Administration exploratory IND guidance to facilitate testing of targeted therapies in patients earlier in the drug development process so that informed decisions to proceed with or stop development can be made before expensive bulk drug formulation occurs. These studies will also take advantage of new advances in molecular imaging, which can help detect whether an agent being tested is reaching its target and having the desired effect.
  - Extramural drug developers, for the first time, will be offered opportunities to utilize CCR resources for clinical trial support. This mechanism will be employed for novel molecules or high-priority targets.

The National Clinical Target Validation Laboratory will develop and authenticate pharmacodynamic assays well in advance of human studies, so that they can be used in early phase trials to provide information about the safety and efficacy of the entities being tested.

- The DCTD **Developmental Therapeutics Project Management Office** will also lend project management assistance to advance the evaluation of targeted therapies being studied jointly by the DCTD Developmental Therapeutics and Cancer Therapy Evaluation Programs
- DCTD has initiated a new molecular toxicology laboratory that will develop novel approaches to toxicologic prediction using normal human tissues. This is concurrent with the new commitment by DCTD and CCR to combine resources to focus on developing predictive, preclinical molecular pharmacodynamic assays. These assays will support the clinical development of agents for which NCI holds the IND.
- The division has also expanded its capabilities to develop and standardize diagnostic imaging biomarkers in addition to pharmacodynamic assays. These processes will be aided by the development of new imaging tools and agents that can track molecular events in tumors and normal tissues. Once completed, the portfolio of biomarkers and assays will be made available to all interested cancer researchers. DCTD has identified several resources to help achieve this goal. Chief among them is the establishment by DCTD and CCR of a new **National Clinical Target Validation Laboratory** (NCTVL). This laboratory will develop and authenticate pharmacodynamic assays well in advance of human studies, so that they can be used in early phase trials to provide information about the safety and efficacy of the entities being tested.

BIOMETRIC RESEARCH BRANCH

Accomplishing research in the areas of statistical, mathematical, and computational sciences that is motivated and informed by real and important problems of current cancer research is the goal of the Biometric Research Branch.

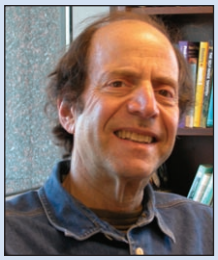
OVERVIEW

The Biometric Research Branch (BRB) is the statistical and biomathematical component of the Division of Cancer Treatment and Diagnosis (DCTD). BRB members provide statistical leadership for DCTD national research programs in clinical trials, developmental therapeutics, developmental diagnostics, diagnostic imaging, and statistical and computational genomics. During 2005, BRB consisted of 13 permanent doctoral-level research investigators supplemented by postdoctoral research fellows and guest researchers. Staff members have doctoral degrees and expertise in biostatistics, biomathematics, computational biology, and computer science.

The philosophy of BRB is to have the staff combine two functions: (1) collaboration and consultation with scientific administrators at DCTD and intramural investigators at the National Cancer Institute (NCI); (2) conduct of self-initiated research on topics important to cancer research and to the collaborative investigations. Combining these functions has enabled BRB to recruit and retain a very high-quality research staff, to provide the highest quality collaborative and consulting staff to DCTD and NCI scientists, and to accomplish research in the areas of statistical, mathematical, and computational sciences that is motivated and informed by real and important problems of current cancer research. BRB does not have a grant, cooperative agreement, or contract portfolio and does not sponsor or fund extramural research.

More information on many of the projects below can be found at: http://linus.nci.nih.gov/~brb/BRB-AnnualReport2005.pdf.

Dr. Richard Simon, Branch Chief



Richard Simon, Ph.D., is Chief of the DCTD Biometric Research Branch. Dr. Simon holds a doctoral degree in applied mathematics and computer science from Washington University in St. Louis, Missouri. He has been at the National Institutes of Health since 1969 and has developed many of the statistical methods used today in cancer clinical trials, including dynamically stratified randomization, optimal two-stage phase II designs, accelerated titration phase I designs, stochastic curtailment for futility monitoring, tests of qualitative treatment by patient covariate interactions, Bayesian subset analysis, and Bayesian designs for therapeutic equivalence (active control) trials. He has published more than 400 papers on the application of biostatistical methodology to biomedical research.

Dr. Simon is an elected member of the American Statistical Association, a member of the National Research Council Committee on Theoretical and Applied Statistics, and a former member of the Oncologic Drug Advisory Committee of the U.S. Food and Drug Administration. He is a pioneer in the use of data monitoring committees for cancer clinical trials.

In 1998, Dr. Simon established a multidisciplinary group of statistical, mathematical, computational, physical, and biological scientists to develop and apply methods for the application of genomic, gene expression, and other molecular data to cancer research. His group has developed expertise in the analysis of DNA microarray gene expression data; new methods for the planning and analysis of DNA microarray studies; and integrated software (BRB-ArrayTools) for the analysis of microarray data, with more than 5000 registered users in 62 countries (http://linus.nci.nih.gov/BRB-ArrayTools). He is the lead author of *Design and Analysis of DNA Microarray Investigations,* published by Springer. His group is also involved in development of methods for elucidating T-cell receptor binding rules based on combinatorial peptide library data, design of peptide vaccines, and development of models of oncogenesis for use in deep analysis of clinical trial results.

Cancer Therapy Evaluation Program

http://ctep.cancer.gov/

Collaborations with the Cancer Therapy Evaluation Program (CTEP) are primarily handled by Drs. Edward Korn, Larry Rubinstein, Boris Freidlin, and Sally Hunsberger. These collaborative activities include statistical review of all CTEP-sponsored clinical trials, service on Data Safety Monitoring Committees of the cooperative oncology groups, and participation in the design of clinical trials for the development and evaluation of investigational drugs. BRB statisticians collaborate with CTEP staff on a variety of topics involving the design and monitoring of clinical trials.

For example, BRB statisticians developed Early Stopping Guidelines for Slow Accruing Trials, and these guidelines are used to monitor accrual to CTEP cooperative group phase III trials. This allows early identification of the trials that are likely to fail to reach their objectives. The guidelines were developed and validated using the CTEP database containing 239 phase III cooperative group trials. Analyses were conducted with Dr. Seiichiro Yamamoto (chief statistician of the Japanese National Cancer Center) involving toxicity and efficacy of phase I drugs tested over the past decade under CTEP sponsorship. The collaboration involved staff from CTEP and the Clinical Bioethics Department within the National Institutes of Health (NIH).

BRB statisticians, in collaboration with CTEP, recently conducted a review of the use of accelerated titration designs in practice. The accelerated titration design is a novel design for phase I trials developed by BRB statisticians in collaboration with CTEP investigators. It permits more rapid dose escalation as well as dose titration within individual patients.

Cancer Diagnosis Program

http://www.cancerdiagnosis.nci.nih.gov/

Collaborations with the Cancer Diagnosis Program (CDP) are handled by Drs. Lisa McShane and Kevin Dobbin. Their activities include:

- Reviewing statistical aspects of research proposals, R21/R33 grants, cooperative group correlative science protocols, and requests for specimens from NCI-funded tissue resources. They also provide statistical expertise to scientific administrators in the monitoring and development of important NCI initiatives such as tissue resources, the Program for the Assessment of Clinical Cancer Tests (PACCT), and Strategic Partnering to Evaluate Cancer Signatures (SPECS).
- Providing statistical leadership for the establishment, maintenance, and utilization of CDP-funded tissue resources. Two pathologist concordance studies were conducted based on data from the Cooperative Breast Cancer Tissue Resource (CBCTR). BRB staff collaborated with four extramural groups in the NCI's Cooperative Prostate Cancer Tissue Resource to compare biological characteristics of prostate tumors in men with low diagnostic prostate-specific antigen (PSA) blood levels versus those with higher levels. The study identified

Microarrays are a powerful molecular analytical tool. BRB led a collaborative study showing that different laboratories using a common protocol can obtain consistent results.

a subgroup of patients in which low diagnostic PSA levels were associated with less aggressive tumors.

- Designing tissue microarrays for breast cancer, colon and rectal cancer, prostate cancer, as well as melanoma and designing studies for evaluating their quality.
- Serving on the DataMart Steering Committee. DataMart is a joint effort between NCI and the cooperative groups to establish a data repository of clinical trial data (including marker data) in order to allow more contemporaneous and frequent analyses of pooled breast cancer clinical trial research data.
- As a member of PACCT (http://www.cancerdiagnosis.nci.nih.gov/assessment/index.html), BRB provided NCI statistical leadership in developing major protocols involving multiple cooperative groups to evaluate predictive biomarkers. PACCT's first clinical trial is a prospective, randomized study designed to evaluate the use of a genomic test (the Oncotype DX® classifier) as a basis for determining treatment for breast cancer patients.

Director's Challenge Groups

http://www.cancerdiagnosis.nci.nih.gov/challenge/index.html

Traditionally, the classification of tumors has been based on morphology, or the tumor's structure, but morphological classification cannot accurately predict biological behavior, prognosis, or response to treatment. In 1998, the NCI Director issued an appeal, or Director's Challenge, called "Toward a Molecular Classification of Tumors," to urge the research community to revolutionize the classification of human tumors. Defining and understanding the changes associated with individual tumors can identify patient subsets and be used to tailor treatment regimens.

NCI Visuals Online, Bill Branson, photographer.

DNA microarray technology allows scientists to assess the level of expression of a large subset of the 100,000 human genes in a cell or tissue. This technology can quickly produce a snapshot of the genes that are active in a tumor cell, critical information in narrowing the precise molecular causes of a cancer.

Microarrays are a new and powerful molecular analytical tool that can help sort tumor characteristics, but until recently it was not known whether results achieved at one laboratory could be reliably compared with results obtained at other

BRB provides CCR researchers expertise in statistical design and analysis in their studies of neuro-oncology, urologic oncology, radiation oncology, metabolism, and cancer prevention.

laboratories. Dr. Kevin Dobbin, BRB, led a collaborative study involving four Director's Challenge groups that led to the first major published study of the comparability of gene expression microarray data produced at different laboratories. Indeed, different laboratories using a common protocol can obtain consistent results. The study also provided guidance for future large microarray studies involving multiple laboratories.

This project is also an example of NCI's interest in developing public/private partnerships. Affymetrix contributed some of the arrays for this comparison study and provided technical assistance to the four sites carrying out the study.

International Leukemia/Lymphoma Molecular Profiling Project

http://llmpp.nih.gov/lymphoma/

The Leukemia/Lymphoma Molecular Profiling Project (LLMPP) is a consortium of NCI intramural and extramural investigators who have pooled resources and talent to develop molecular classification of lymphomas. The consortium is led by Dr. Louis Staudt in the Molecular Biology of Lymphoid Malignancies Section of the NCI Center for Cancer Research (CCR). The large number of samples made available through this collaborative effort—substantially more than any single institution could have acquired—has allowed the researchers to draw reliable conclusions about how best to diagnose patients based on the molecular subtype of their disease. Dr. George Wright, BRB, serves as primary statistician for the many important publications of this group.

Center for Cancer Research

http://ccr.nci.nih.gov/

NCI's CCR is the largest component of the Institute's intramural research program. CCR investigators help translate new scientific discoveries into state-of-the-art diagnostic tools and therapies for cancer patients. BRB staff collaborate with CCR investigators in the areas of statistical genomics and biostatistics.

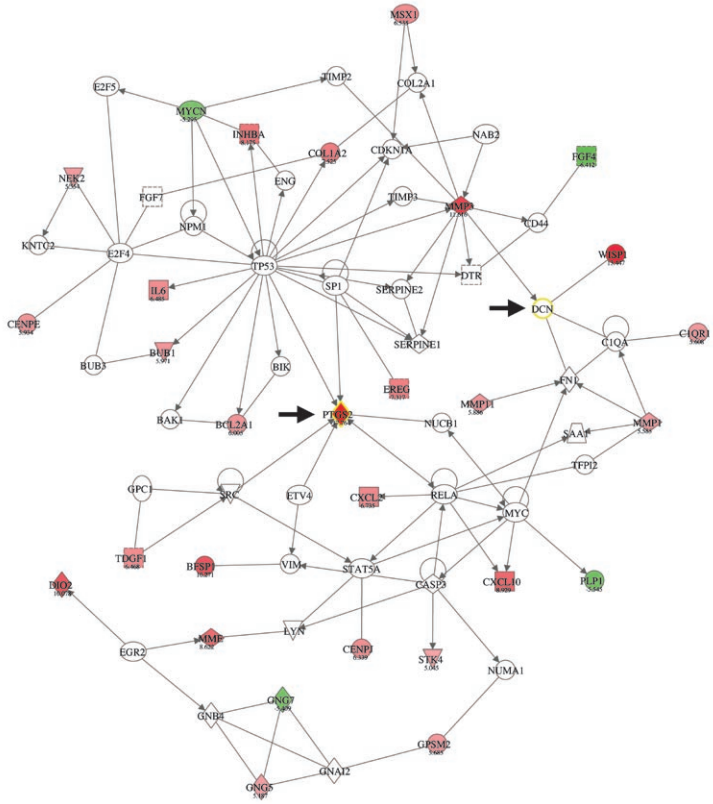
Dr. Paul Albert, BRB, serves as principal statistician for the CCR clinical studies in the areas of neuro-oncology, urologic oncology, radiation oncology, metabolism, and cancer prevention. He provides CCR researchers in these areas with access to statistical expertise in the design and analysis of their studies. These collaborations have in the past year included analysis of the Polyp Prevention Trial (resulted in four publications in 2005) and of the Women's Alcohol Study, a crossover study examining the effect of alcohol on hormones associated with cancer (resulted in three publications in 2005). In the area of radiation oncology, BRB and CCR researchers published six papers in 2005, and collaborations with the Urologic Oncology Branch led to an additional 2005 publication.

BRB staff also collaborate extensively with CCR investigators on the design and analysis of laboratory and clinical studies utilizing DNA microarrays. BRB staff members serve as principal statisticians for such studies. During the past year, these collaborations have included the following studies:

- Evaluation of two phosphorylation sites improves the prognostic

significance of Akt activation in NSCLC tumors. Collaboration of Drs. Joanna Shih, BRB, Jin Jen, CCR Laboratory of Population Genetics, and Phillip A. Dennis, CCR Cancer Therapeutics Branch.

- Ingenuity network assisted transcription profiling: identification of a new pharmacological mechanism for MK886. Collaboration of Drs. Shih, BRB, and Anatoly L. Mayburd, CCR Cell and Cancer Biology Branch.
- Desmoglein 3 as a prognostic indicator in lung cancer. Collaborators are Drs. Shih, BRB, and Jen.
- Cross-species comparisons of mouse mammary tumor models and human breast cancer by expression profiling: identification of luminal and basal phenotypes and a conserved gene signature discriminating estrogen-receptor-positive from estrogen-receptor-negative tumors. Collaboration of Drs. Shih and Jeff Green, CCR Laboratory of Cell Regulation and Carcinogenesis.
- Histological staining method preparatory to laser capture microdissection significantly affects detection of mRNAs in microarray hybridization. Collaboration of Drs. Shih and Frederic Mushinski, CCR Laboratory of Genetics.
- Identifying the sequential alterations of the genome, transcriptome, and proteome that define the transformation of normal colon epithelium and the progression from adenomas to invasive disease. Collaboration of Drs. Lisa McShane and Ed Korn, BRB, with Thomas Ried and others of the CCR Cancer Genomics Section of the Genetics Branch.
- Effectiveness of gene expression profiling for response prediction of rectal adenocarcinomas in preoperative chemoradiotherapy. Collaboration of Drs. Sudhir Varma and Richard Simon, BRB, with Ried and his colleagues.
- Selective utilization of the Wnt/b-catenin signaling pathway and aneuploidy-dependent massive deregulation of the cellular transcriptome in human rectal carcinomas. Collaboration of Drs. Varma and Simon, BRB, with Ried and colleagues.



Dr. Thomas Ried, CCR Genetics Branch.

Network mapping of genes involved in rectal tumorigenesis. Shades of red indicate genes with five-fold or greater expression in the tumors; shades of green indicate genes with a more than five-fold decrease in expression in the tumors relative to the normal rectal mucosa.

- Gene expression patterns and profile changes pre- and post-erlotinib treatment in patients with metastatic breast cancer. Collaboration of Drs. Simon, BRB, and Sandra Swain and others of the CCR Medical Oncology Branch.
- Response in gene expression profile to bevacizumab treatment in patients with inflammatory and locally advanced breast cancer. Collaboration of Drs. Simon and Swain.

Other Partnerships

Collaborations with the Cancer Imaging Program (CIP) (http://imaging.cancer.gov/) and the Developmental Therapeutics Program (DTP) (http://dtp.nci.nih.gov/) encompass an extensive and diverse mix of activities, including the design and analysis of major DCTD studies, protocol design and review, statistical advice to extramural investigators, and service on data monitoring committees. Collaborations with CIP are handled by Dr. Lori Dodd, and collaborations with DTP are handled by Dr. Larry Rubinstein. Dr. Rubinstein reviewed the reproducibility of the results of the NCI human tumor 60 cell line screen, and this review was utilized by the external committee that reviewed the performance of the screening system. Dr. Simon led a collaboration involving CTEP and DTP investigators to discover and develop specific inhibitors of the protein product of the mutant *BRAF* gene.

BRB staff collaborated with Dr. Allan Hildesheim of the NCI Division of Cancer Epidemiology and Genetics (DCEG) on the analysis of DNA microarry studies to elucidate the specific molecular events involved in nasopharyngeal oncogenesis as a result of Epstein-Barr virus infection.

Drs. Yingdong Zhao and Simon, BRB, have collaborated with Dr. Roland Martin and staff of the Laboratory of Neuroimmunology, National Institute of Neurological Disorders and Stroke (NINDS), NIH, to elucidate the basic mechanisms of T-cell immunity and the development of immunoinformatic methods for selecting molecular targets for therapeutic vaccines. This resulted in five published papers.

In collaboration with investigators from the Chinese Academy of Medical Sciences, a randomized factorial trial was conducted to evaluate two chemoprevention agents' ability to slow the rate of progression or increase the rate of regression of esophageal dysplasias. Dr. Korn, BRB, is the study statistician for this trial.

Co-Development of Diagnostics and Therapeutics: Using Biomarkers for Personalization of Treatment

During 2004, Dr. Simon published two papers that demonstrated the vast improvement in efficiency of randomized phase III trials that can be achieved from using a biomarker or genomic classifier to select patients likely to respond to the new treatment. In many cases, however, such classifiers are not available at the start of phase III trials. During 2005, Drs. Freidlin and Simon published a new phase III design that addressed this limitation. The design does not limit entry based on a biomarker but requires that tumor specimens be collected at the time of entry. At the end of the trial, outcomes for all patients on the new treatment are compared to those for all patients on the control. If the difference is significant at a level of 0.04 or better, results are taken to support approval of the new drug with a broad labeling indication. If not, then the specimens from the first half of patients randomized are used to develop a classifier of which patients appear to benefit from the new regimen. That classifier is then applied to the second half of the randomized patients, and those predicted to be sensitive to the new treatment are identified. If the outcomes for patients in that subset on the new treatment are significantly better than for the control patients in the subset and if the significance level is 0.01 or less, then the data are taken to support approval with a narrowed labeling indication for the new treatment.

Freidlin B, Simon R. Adaptive signature design: an adaptive clinical trial design for generating and prospectively testing a gene expression signature for sensitive patients. *Clin Cancer Res* 2005:11;7872–8.

Dr. Simon has interacted with scientists from industry and the Food and Drug Administration (FDA) in numerous scientific workshops and seminars to develop effective approaches to the development and evaluation of biomarker classifiers that identify patients who respond to particular therapeutics. In order to facilitate the application of this approach, Dr. Simon has established formal pharmacogenomic agreements with Johnson & Johnson Pharmaceutical Research & Development and Centicor.

Simon R. Roadmap for developing and validating therapeutically relevant genomic classifiers. *J Clin Oncol* 2005:23;7332–41.

Simon R, Wang SJ. Use of genomic signatures in therapeutics development in oncology and other diseases. *Pharmacogenomics J* (In press).

Trepicchio WL, Essayan D, Hall ST, Schechter G, Tezak Z, Wang SJ, Weinrich D, Simon R. Designing prospective clinical pharmacogenomic trials. Effective use of genomic biomarkers for use in clinical decision making. *Pharmacogenomics J* (In press).

Simon R. Validation of pharmacogenomic biomarker classifiers for treatment selection. *Dis Markers* (In press).

Simon R. A checklist for evaluating reports of expression profiling for treatment selection. *Clin Adv Hematol Oncol* (In press).

Simon R. Guidelines for the design of clinical studies for development and validation of therapeutically relevant biomarkers and biomarker based classification systems. In: *Biomarkers in Breast Cancer: Molecular Diagnostics for Predicting and Monitoring Therapeutic Effect.* Hayes DF, Gasparini G, eds. Totawa, NJ: Humana Press; 2005.

BRB staff developed a method for sample size planning of clinical studies with an objective to develop a predictor of outcome or predictor of phenotypic/genotypic class based on whole genome expression profiling.

Simon R. DNA microarrays for diagnostic and prognostic prediction. In: *Encyclopedia of Medical Genomics & Proteomics*. Fuchs J, Podda M, eds. New York: Marcel Dekker (In press).

Simon R. Development and validation of therapeutically relevant multi-gene biomarker classifiers. *J Natl Cancer Inst* 2005:97;866–7.

Simon R. An agenda for clinical trials: clinical trials in the genomic era. *Clin Trials* 2004:1; 468–70.

Methodology Development in Computational Cancer Biology and Statistical Genomics

Dr. Simon, in collaboration with Dr. Ruth Pfeiffer, DCEG Biostatistics Branch, and a postdoctoral fellow, Dr. Annette Molinaro, conducted research comparing a wide range of resampling methods for estimating prediction accuracy with high dimensional data such as from DNA microarrays. The results demonstrated that leave-one-out cross-validation is superior to split-sample validation or repeated split-sample validation, in contradiction to much of current conventional wisdom. Drs. Wenyu Jiang, a current postdoctoral fellow in BRB, and Simon have continued this research in conducting a study evaluating a wide variety of bootstrap resampling methods and found that many of the claims in the biostatistical literature concerning bootstrap methods are not applicable to high dimensional data problems. They developed a new adjusted bootstrap method that appears to be superior to previously reported methods. Drs. Varma and Simon have developed a method of optimizing classifier tuning parameters using resampling methods.

Molinaro AM, Simon R, Pfeiffer RM. Prediction error estimation: a comparison of resampling methods. *Bioinformatics* 2005:21;3301–7.

Jiang W, Simon R. A comparison of bootstrap methods and an adjusted bootstrap for estimating prediction error in microarray analysis. Submitted for publication.

Varma S, Simon R. Bias in error estimation when using cross-validation for model selection. *BMC Bioinformatics* (In press).

Drs. Alain Dupuy, a guest researcher from France, and Simon have reviewed all publications on whole-genome expression profiling of cancers that used patient outcome. They wrote a critical review of these publications and developed guidelines for use by authors, journal reviewers, and readers.

Dupuy A, Simon R. Critical review of published microarray studies for cancer outcome and guidelines on statistical analysis and reporting. Submitted for publication.

Pooling is often perceived as an efficient approach for microarray studies comparing gene expression between two classes because it may decrease the number of expensive microarray hybridizations required through reduction of the biological variability. BRB's Dr. McShane and collaborators conducted a microarray experiment using MCF-7 breast cancer cell line studied under two different experimental conditions for which the same number of independent pools as the number of individual samples was hybridized on Affymetrix GeneChips®. They showed the unexpected result that the number of probe sets found differentially expressed between treated and untreated cells when three individual samples per treatment class were hybridized on the GeneChips®

was about three times greater than that found using three independent pools per treatment class. Also, probe set-specific variability in pools was greater than that in individuals for more than 60 percent of the cases.

Lusa L, Cappelletti V, Gariboldi M, Ferrario C, DeCecco L, Reid JF, Toffanin S, Gallus G, McShane LM, Diadone MG, Pierotti MA. Caution regarding the utility of pooling samples in microarray experiments with cell lines. Submitted to *BioTechniques*.

BRB staff members Drs. Dobbin and Simon developed methods for planning sample size for studies whose objective is to identify genes that are differentially expressed among phenotypic or genotypic classes of tissue. They have considered how sample size depends on the microarray hybridization design utilized with dual label arrays and have considered a wide range of designs, including the common reference design, balanced block design, and loop design. They have also developed a method for sample size planning of clinical studies whose objective is to develop a predictor of outcome or predictor of phenotypic/genotypic class based on whole genome expression profiling.

Dobbin K, Simon R. Sample size determination in microarray experiments for class comparison and prognostic classification. *Biostatistics* 2005:6;27–38.

Dobbin K, Simon R. Sample size planning for developing classifiers using high dimensional DNA expression arrays. Submitted for publication.

Drs. Dobbin and Simon also studied the role of dye bias not removed by standard normalization methods. They corrected commonly held misconceptions about the implication of dye bias for the design

Affymetrix.

Affymetrix GeneChip® probe array.

of dual-label microarray studies and also corrected a statistical modeling flaw that had appeared in the literature that had led to erroneous conclusions about how to design and analyze microarray experiments.

Dobbin KK, Kawasaki ES, Petersen DW, Simon RM. Characterizing dye bias in microarray experiments. *Bioinformatics* 2005:21;2430–7.

Dobbin KK, Shih JH, Simon RM. Comment on "Evaluation of the gene-specific dye bias in cDNA microarray experiments." *Bioinformatics* 2005:21;2803–4.

Dobbin K, Simon R. Experimental design in expression profiling. In: *Encyclopedia of Genetics, Proteomics and Bioinformatics.* Jorde L, ed. New York: John Wiley & Sons; 2005.

The goal of many gene-expression microarray profiling clinical studies is to develop a multivariate classifier to predict patient disease outcome from a gene expression profile measured on some biological specimen from the patient. Techniques such as cross-validation or bootstrapping can be used in this setting to assess predictive power and, if applied correctly, can result in a less biased estimate of predictive accuracy of a classifier. However, some investigators have attempted to apply standard statistical inference procedures to assess the statistical significance of associations between true and cross-validated predicted outcomes.

Microarray Myths and Truths

Myths

- That the greatest challenge is managing the mass of microarray data.
- That pattern recognition or data mining is the most appropriate paradigm for the analysis of microarray data.
- That cluster analysis is the generally appropriate method of data analysis.
- That comparing tissues or experimental conditions is based on looking for red or green spots on a single array.
- That reference RNA for two-channel arrays must be biologically relevant.
- That multiple testing issues can be ignored without filling the literature with spurious results.
- That complex classification algorithms such as neural networks perform better than simpler methods for class prediction.
- That prepackaged analysis tools are a good substitute for collaboration with statistical scientists in complex problems.

Truths

- The greatest challenge is organizing and training for a more multidisciplinary approach to systems biology. The greatest specific challenge is good practice in design and analysis of microarray-based experiments.
- Pattern recognition and data mining are often what you do when you don't know what your objectives are. Effective microarray-based research requires clear objectives.
- Cluster analysis is useful for some types of studies, such as finding potentially coregulated genes. For most microarray studies, however, supervised methods of analysis are much more powerful.
- Comparing expression in two RNA samples tells you only about those samples and may relate more to sample handling and assay artifacts than to biology. Robust knowledge requires multiple samples that reflect biological variability.
- The reference RNA generally serves only to control variation in the size of corresponding spots on different arrays and variation in sample distribution over the slide.
- Comparing two classes of samples with regard to expression of 20,000 genes, one expects 1000 erroneous findings of genes that appear differentially expressed at the 5 percent significance level. This is true regardless of the correlation patterns of the genes. Eyeball analysis of multicolored image plots for genes that appear differentially expressed is no more reliable.
- "Artificial intelligence" sells to journal reviewers and institute leaders who cannot distinguish hype from substance when it comes to data analysis. But, comparative studies have shown that simpler methods work better for microarray problems in which the number of candidate predictors greatly exceeds the number of samples.
- Biologists need both good analysis tools and good statistical collaborators. Both are in short supply.

Dr. Richard Simon.

Naïve application of standard statistical inference procedures can result in errors.

Several BRB statisticians demonstrated that naïve application of standard statistical inference procedures to these measures of association can result in greatly inflated testing type I error rates and confidence intervals with poor coverage probabilities. These results suggest that some of the claims of exceptional prognostic classifier performance that have been reported in prominent biomedical journals in the past few years should be interpreted with great caution.

Lusa L, McShane LM, Radmacher MD, Shih JH, Wright GW, Simon R. Appropriateness of some resampling-based inference procedures for assessing performance of prognostic classifiers derived from microarray data. Revision under review with *Stat Med*.

Drs. Zhao, Li, and Simon developed a mixture model-based normalization method that adaptively identifies non-differentially expressed genes and thereby substantially improves normalization for dual-labeled arrays in settings where the assumptions of global normalization are problematic.

Zhao Y, Li MC, Simon R. An adaptive method for cDNA microarray normalization. *BMC Bioinformatics* 2005:6;28.

Clinical Trial Designs for the Development of Cytostatic Drugs

Many new anticancer agents being developed are not cytotoxic and, therefore, may not cause tumors to shrink appreciably. However, these agents may still offer significant clinical benefit to patients by delaying the progression of disease. Because standard phase I/II/III clinical trial development of agents depends on their ability to show activity in phase II trials by tumor shrinkage, new approaches are needed. BRB statisticians Drs. Hunsberger, Korn, and Rubinstein discuss and evaluate several new design approaches.

Korn EL, Rubinstein LV, Hunsberger SA, Pluda JM, Eisenhauer E, Arbuck SG. Clinical trial design for cytostatic agents and agents directed at novel molecular targets. In: *Strategies for Discovery and Clinical Testing of Novel Anticancer Agents.* Adjei AA, Buolamwini J, eds. New York: Elsevier; 2005.

Hunsberger S, Rubinstein LV, Dancey J, Korn EL Dose escalation trial designs based on a molecularly targeted endpoint. *Stat Med* 2005:24; 2171–81.

Drs. Freidlin and Simon evaluated two kinds of randomized designs for the early development of target-based cytostatic agents: randomized discontinuation and upfront randomization designs. They showed that the randomized discontinuation design is not as efficient as upfront randomization if treatment has a fixed effect on tumor growth rate or if treatment benefit is restricted to slower-growing tumors. The randomized discontinuation design can be advantageous if only a subset of patients, those expressing the molecular

In specific clinical situations… the interim release of data will not interfere with the final analysis of the trial but will potentially offer a significant benefit to the public.

target, is sensitive to the agent. To achieve efficiency, the design parameters must be carefully structured to provide adequate enrichment of the randomly assigned patients.

Freidlin B, Simon R. An evaluation of randomized discontinuation design. *J Clin Oncol* 2005:23;5094–8.

Surrogate Endpoints

In many clinical trials, it would be useful to have a surrogate endpoint that could be measured earlier or less invasively than the definitive endpoint. Three BRB statisticians—Drs. Korn, Albert, and McShane—described statistical methods for using the surrogate and definitive endpoint results from a series of previously completed trials to assess whether the surrogate endpoint could be used for a future trial.

Korn EL, Albert PS, McShane LM. Assessing surrogates as trial endpoints using mixed models (with discussion). *Stat Med* 2005:24;163–90.

Early Release of Interim Data in Randomized Clinical Trials

Standard data monitoring procedures for clinical trials only allow release of interim efficacy results at the end of the trial or earlier if the results have crossed a data monitoring boundary. Drs. Korn, Hunsberger, and Freidlin, BRB, in collaboration with Drs. Malcolm Smith and Jeffrey Abrams, CTEP, suggest specific clinical situations in which it might be preferable to release interim efficacy results even though no boundary has been crossed. The situations are such that the interim release of data will not interfere with the final analysis of the trial but will potentially offer a significant benefit to the public.

Korn EL, Hunsberger S, Freidlin B, Smith MA, Abrams JS. Preliminary data release for randomized clinical trials of noninferiority: a new proposal. *J Clin Oncol* 2005:23;5831–6.

Multiple Comparisons and Clinical Trials

Multiple comparison issues arise in clinical trials with subgroup analysis, multiple variables, interim monitoring, and data-driven choice of hypotheses. It has been suggested that a nonstandard type of analysis of clinical trial data ("likelihood-based methods") can eliminate the problems with multiple comparisons. Drs. Korn and Freidlin examine this proposition in detail and find it to be lacking.

Korn EL, Freidlin B. The likelihood as statistical evidence in multiple comparisons in clinical trials: no free lunch. *Biom J* (In press).

Sample Size Calculations for Trials with Historical Controls

In the 1980s, Dr. Simon and his colleagues showed that it was incorrect to ignore the variability of the historical control data when performing sample size calculations for trials using historical controls. More recently, BRB staff members have shown how these widely used methods from the 1980s can be improved upon.

Korn EL, Freidlin B. Conditional power calculations for clinical trials with historical controls. *Stat Med* (In press).

Rubinstein LV, Korn EL, Freidlin B, Hunsberger S, Ivy SP, Smith MA. Design issues of randomized phase II trials and a proposal for phase II screening trials. *J Clin Oncol* 2005:23;7199–206.

Evaluating Treatment Effects in the Presence of Competing Risks

Competing risks are often encountered in clinical research. For example, a cancer patient may experience local failure or distant failure, or die without recurrence. In comparing treatments, use of end-points based on the type of failure directly related to the treatment mechanism of action allows one to focus on the aspect of the disease targeted by treatment. Drs. Friedlin and Korn evaluate statistical methodology commonly used for testing failure-specific treatment effects. The article demonstrates that the cause-specific log-rank test is superior to the cumulative incidence-based approach.

Freidlin B, Korn EL. Testing treatment effects in the presence of competing risks. *Stat Med* 2005:24;1703–12.

Longitudinal Data Analysis

Drs. Albert and Hunsberger have continued a productive research program to develop new methods for the analysis of longitudinal data. Most of this work has been motivated by problems in analyzing repeated biomarker measurements over time. A new methodology for analyzing longitudinal data based on a serial dilution assay was applied to data from a clinical trial examining the effect of acupuncture on reducing nausea associated with breast cancer treatment.

Albert PS, Shen J. Modeling longitudinal semi-continuous emesis volume data with serial correlation in an acupuncture clinical trial. *J R Stat Soc Ser C Appl Stat* 2005:54;707–20.

Albert PS. On the interpretation of marginal inference with a mixture model for clustered semi-continuous data. *Biometrics* 2005:61; 879–80.

Albert PS. Hunsberger S. On analyzing circadian rhythm data using non-linear mixed models with harmonic terms. *Biometrics* 2005:61;1115–22.

Albert PS, Follmann DA. Random effects and latent process approaches for longitudinal binary data with missingness: with applications to the analysis of opiate clinical trial data. To appear in *Stat Methods Med Res.*

Evaluating Diagnostics in the Absence of a Gold Standard

In 2004, Drs. Dodd and Albert published a paper on potential problems from estimating the diagnostic error of binary tests without a gold standard using latent class modeling. They showed that these approaches are sensitive to the dependence structure between tests, yet it is generally nearly impossible to distinguish between competing models. In a follow-up paper, they examine the robustness of the estimation procedures when, in a fraction of cases, we observe the gold standard test. They propose semi-latent modeling approaches for this problem and show that, even with a small percentage of gold standard information, estimates of diagnostic error are insensitive to the assumed dependence structure between tests.

Albert PS, Dodd LA. Cautionary note on the robustness of latent class models for estimating diagnostic error without a gold standard. *Biometrics* 2004:60;427–35.

Albert PS, Dodd L. On estimating diagnostic accuracy from studies with multiple raters and partial gold standard evaluation. In revision at *J Am Stat Assoc.*

Albert PS. An imputation approach for estimating diagnostic accuracy from partially verified designs. Submitted to *Biometrics.*

Albert PS. Misclassification models. In: *Encyclopedia of Biostatistics.* 2nd ed. Armitage P, Colton T, eds. New York: John Wiley & Sons; 2005.

Smoothing-Based Approaches for Estimating the Risk of a Disease by Quantile-Categories of a Predictor Variable

When one collects data on a prospective cohort, the standard method is simply to categorize the key predictor variable by the empirical quartiles. One may then include indicator variables for these empirical quartile-categories as predictors, along with other covariates, in a generalized linear model (GLM), with the observed health status of each subject as the response. The standard GLM method, however, is relatively inefficient because it treats all observations that fall in the same quartile-category of the predictor variable identically, regardless of whether they lie in the center or near the boundaries of that category.

Alternatively, one may include the key predictor variable, along with other covariates, in a generalized additive model (GAM), again with the observed health status of each subject as the response. The alternative GAM method non-parametrically estimates the functional relationship between the key predictor variable and the response. One may then compute statistics of interest, such as proportions and odds ratios, from the fitted GAM equation using the empirical quartile-categories. Simulations show that both the GLM and GAM methods are nearly unbiased but that the latter method produces smaller variances and narrower bootstrap confidence intervals. This work by BRB's Dr. Albert was motivated by collaborative work on NCI's Polyp Prevention Trial.

Borkowf CB, Albert PS. Efficient estimation of risk of a disease by quantile-categories of a predictor variable using generalized additive models. *Stat Med* 2005:24;623–45.

In case-control studies of genetic epidemiology, participating subjects (probands) are often interviewed to collect detailed data about disease history and age-at-onset information in their family members. Genotype data are typically collected for the probands. In this article, Dr. Shih and collaborators consider an approach that utilizes family history data of the relatives. They used the methods for estimation of risk of breast cancer from *BRCA1/2* mutations using data from the Washington Ashkenazi Study.

Chatterjee N, Zeynep K, Shih JH, Gail M. Case-control and case-only designs with genotype and family history data: estimating relative-risk, familial aggregation and absolute risk. *Biometrics* [Epub Oct 20 2005].

Genomic Control for Association Studies under Various Genetic Models

Case-control studies are commonly used to study whether a candidate allele and a disease are associated. However, spurious association can arise due to population substructure or cryptic relatedness, which cause the variance of the trend test to increase. A novel genomic control approach had been developed to estimate the "variance inflation factor" using an additive genetic model. Dr. Freidlin and collaborators expand this approach to recessive and dominant genetic models. They also discuss appropriate uses for their method and the one derived for the additive model.

Zheng G, Freidlin B, Li ZH, Gastwirth GL. Genomic control for association studies under various genetic models. *Biometrics* 2005:61;187–93.

The case-cohort design is an efficient and economical design to study risk factors for infrequent disease in a large cohort. It involves the collection of covariate data from all failures ascertained throughout the entire cohort, and from the members of a random subcohort selected at the onset of follow-up. Dr. Shih develops case-cohort designs adapted to multivariate failure time data.

Lu S, Shih JH. Case-cohort designs and analysis of clustered failure time data. *Biometrics* (In press).

Dr. Shih also considered the problem of estimating covariate effects in the marginal Cox proportional hazard model and multilevel associations for child mortality data collected from a vitamin A supplementation trial in Nepal (Nepal Nutrition Intervention Project–Sarlahi, or NNIPS), where the data are clustered within households and villages. For this purpose, a class of multivariate survival models that can be represented by a function of marginal survival functions and accounts for hierarchical structure of clustering is exploited. Based on this class of models, an estimation strategy involving a within-cluster resampling procedure is proposed. The asymptotic theory for the proposed estimators is established, and the simulation study shows that the estimates are consistent. The analysis of the NNIPS study data shows that the association of mortality is much greater within households than within villages.

Shih JH, Lu S. Analysis of failure time data with multi-level clustering, with application to the child vitamin A supplementation trial in Nepal. Revision submitted to *Biometrics*.

Mathematical Modeling of Cancer Oncogenesis

Another BRB project, by Drs. Zhang and Simon, used age-incidence data to try to determine the number of rate-limiting events in breast cancer oncogenesis. They developed a model that incorporated the age-dependent dynamics of breast epithelium and clonal expansion of intermediate cells without the full complement of mutations required for an invasive tumor. They found that it was unlikely that there are more than three rate-limiting events in breast cancer oncogenesis occurring at a rate characteristic of point mutations in normal mammalian cells. The initial set of two or three mutational events appears to destabilize the genome and puts in place a process that

almost inevitably leads to an invasive tumor. They also analyzed similar age-incidence data for breast cancer in *BRCA1* and *BRCA2* mutation carriers and found results consistent with those for sporadic cases. Dr. Myong-Hee Sung, CCR Laboratory of Receptor Biology and Gene Expression, and Dr. Simon have extended this modeling work to colon cancer to elucidate the sequence of genetic changes that occur during oncogenesis and to identify the mechanisms most likely to be the targets of the rate-limiting oncogenic events.

Zhang X, Simon R. Estimating the number of rate-limiting genomic changes for human breast cancer. *Breast Cancer Res Treat* 2005:91;121–4.

Simon R, Zhang X. On the nature of carcinogenic events in patients carrying germline BRCA1 and BRCA2 mutations. Submitted for publication.

Sung MH, Simon R. Modeling tumorigenesis based on specific types of pathway de-regulation. Submitted for publication.

Immunoinformatics

Drs. Zhao and Simon have collaborated with Dr. Martin, NINDS, on a series of studies to clarify the molecular events in T-cell immune response to pathogens, in autoimmune processes, and in the development of statistical and computational methods for using genomic data and immunologic assays for the development of therapeutic vaccines.

Sospedra M, Muraro P, Stefanova I, Zhao Y, Chung K, Li Y, Hamashin C, Simon R, Mariuzza R, Pinilla C, Martin R. Promiscuous HLA restriction contributes to degenerate specificity of autoreactive CD4+ T cells. *J Immunol* (In press).

Sospedra M, Zhao Y, Hausen H, Muraro PA, Villiers EM, Pinilla C, Martin R. Arginine-enriched protein domains from the non-pathogenic Torque Teno Virus (TTV) and other common viruses trigger autoreactive T cells in multiple sclerosis. *PLoS Pathog* 2005:1;e41.

Markovic-Plese S, Hemmer B, Zhao Y, Simon R, Pinilla C, Martin R. High level of cross-reactivity in influenza virus hemagglutinin-specific CD4+ T-cell response: implications for the initiation of autoimmune response in multiple sclerosis. *J Neuroimmunol* 2005:169;31–8.

Venturini S, Allicotti G, Zhao Y, Simon R, Burton DR, Pinilla C, Poignard P. Identification of peptides from human pathogens able to cross-activate an HIV-1-gag specific CD4+ T cell clone. *Eur J Immunol* 2006:36;27–36.

Zhao Y, Sung MH, Simon R. Artificial intelligence methods for predicting T-cell epitopes. In: *Immunoinformatics: Predicting Immunogenicity in Silico. Methods in Molecular Biology.* Flower DR, ed. Totawa, NJ: Humana Press (In press).

Dr. Zhao has also collaborated with Dr. Francesco Marincola's laboratory in the Department of Transfusion Medicine of NIH on using HLA-binding data for the evaluation of platelet compatibility in 16 alloimmunized patients with aplastic anemia refractory to random donor platelet transfusions. They also used transcript expression profiling to identify cancer-specific markers that could be used broadly to increase the sensitivity and accuracy of cancer diagnosis and early detection of cancer recurrence.

Nambiar A, Duquesnoy R, Adams S, Zhao Y, Oblitas J, Leitman S, Stroncek D, Marincola F. HLAMatchmaker-driven analysis of responses to HLA-typed platelet transfusions in alloimmunized thrombocytopenic patients. *Blood* 2006:107;1680–7.

Basil CF, Zhao Y, Zavaglia K, Jin P, Panelli MC, Voiculescu S, Mandruzzato S, Lee HM, Seliger B, Freedman RS, Taylor PR, Hu N, Zanovello P, Marincola FM, Wang E. Common cancer biomarkers for colon, melanoma, ovarian and esophageal tumors. *Cancer Res* (In press).

TOOLS, PRODUCTS, AND RESOURCES

BRB-ArrayTools

http://linus.nci.nih.gov/BRB-ArrayTools.html

BRB-ArrayTools is comprehensive software developed by Dr. Simon that is widely recognized as the most statistically sound package available for the analysis of DNA microarray data. The package is implemented as an Excel add-in so that it has an interface that is familiar to scientists, and it has a flexible data import function that supports the use of data from all current expression platforms.

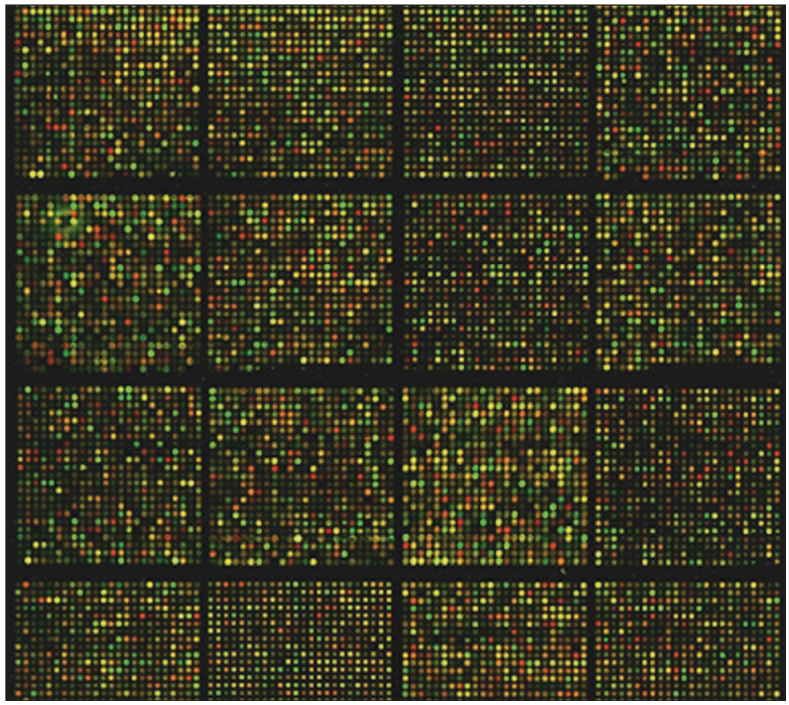
The computations are performed by sophisticated and powerful analytics external to Excel but invisible to the user. BRB-ArrayTools serves as a tool for instructing users on effective and valid methods for the analysis of their data. The existing suite of tools is continually updated as new methods of analysis and elucidation of pathway annotation are developed.

The program may be used for noncommercial purposes free of charge. BRB-ArrayTools software may be downloaded from BRB's Website. BRB-ArrayTools has 5125 registered users in 1026 laboratories in 62 countries and logs more than 90 new registrations per month. It is a successful experiment in using software to empower biomedical scientists to take advantage of DNA microarray software. Dr. Simon received the NIH Director's Award in 2005 for this work. The software is programmed and maintained under a contract with SRA International and the EMMES Corporation.

Gene Expression Data Sets

http://linus.nci.nih.gov/~brb/DataArchive.html

BRB has developed a data archive of publicly available gene expression datasets and corresponding clinical data for published human cancer gene expression profiling studies. The data are stored as BRB-ArrayTools project folders. This makes it easy for BRB-ArrayTools users to make their data publicly available, and it enables other clinical and biological investigators to easily download and start analyzing published data utilizing the most statistically powerful methods available. The archive currently contains data from 24 major studies of human cancer.

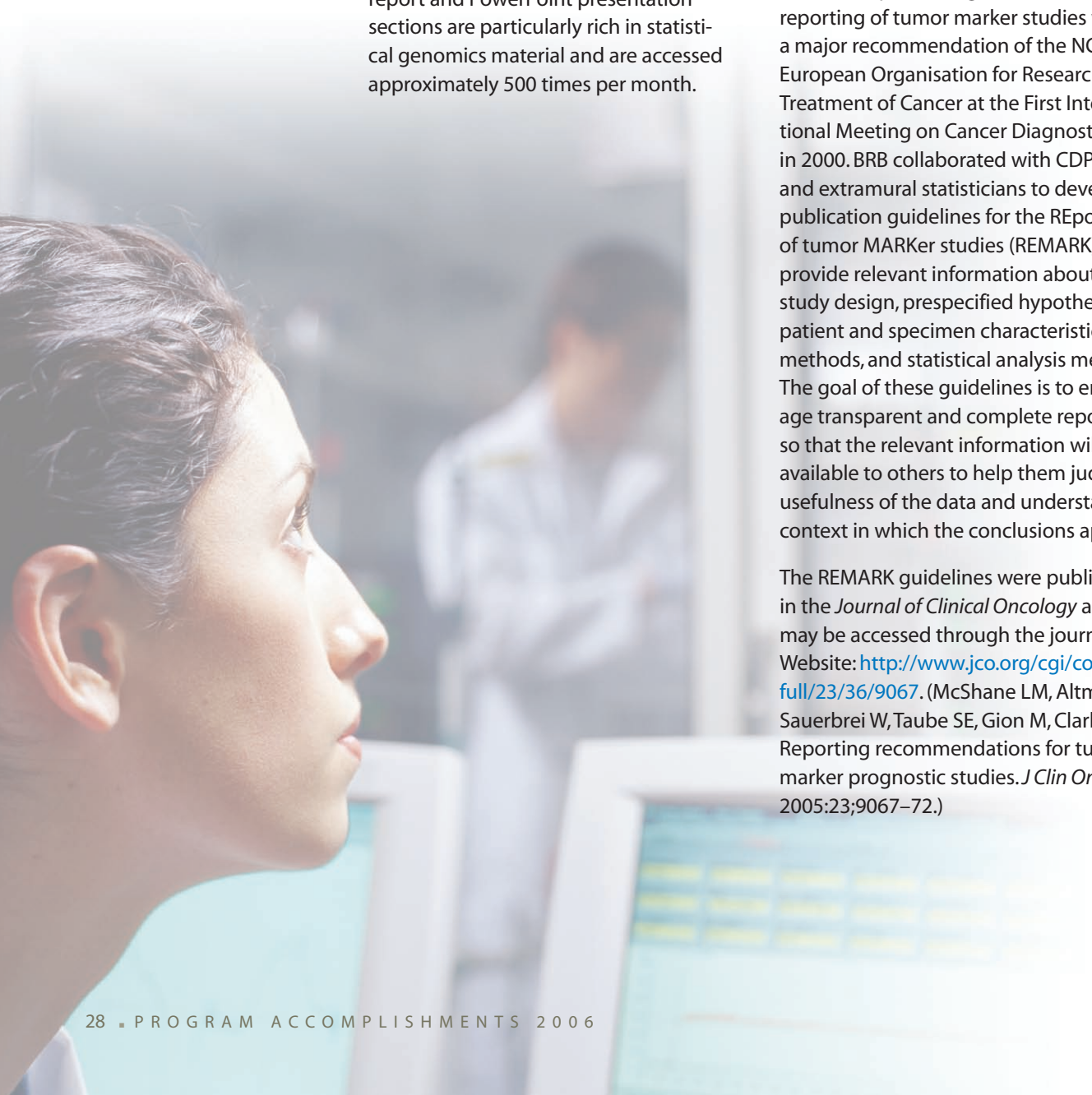


NCI Visuals Online, Dr. Jason Kang, photographer.

Software and Technical Report Archive

http://linus.nci.nih.gov/brb

The BRB Website contains other software, such as software for the generation of optimal and minimax two-stage phase II clinical trial designs and software for managing dose administration for patients on accelerated titration design phase I designs. The Website also contains technical reports and PowerPoint presentations of talks given by BRB staff. The technical report and PowerPoint presentation sections are particularly rich in statistical genomics material and are accessed approximately 500 times per month.



Guidelines for Tumor Biomarker Studies

Despite years of research and hundreds of reports on tumor markers in oncology, the number of markers that have emerged as clinically useful is pitifully small. Often, initial studies of a marker show great promise, but subsequent studies on the same or related markers yield inconsistent conclusions or stand in direct contradiction to the promising results.

The development of guidelines for the reporting of tumor marker studies was a major recommendation of the NCI-European Organisation for Research and Treatment of Cancer at the First International Meeting on Cancer Diagnostics in 2000. BRB collaborated with CDP staff and extramural statisticians to develop publication guidelines for the REporting of tumor MARKer studies (REMARK) to provide relevant information about the study design, prespecified hypotheses, patient and specimen characteristics, assay methods, and statistical analysis methods. The goal of these guidelines is to encourage transparent and complete reporting so that the relevant information will be available to others to help them judge the usefulness of the data and understand the context in which the conclusions apply.

The REMARK guidelines were published in the *Journal of Clinical Oncology* and may be accessed through the journal's Website: http://www.jco.org/cgi/content/full/23/36/9067. (McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM. Reporting recommendations for tumor marker prognostic studies. *J Clin Oncol* 2005:23;9067–72.)

CANCER DIAGNOSIS PROGRAM

The Cancer Diagnosis Program strives to improve the diagnosis and assessment of cancer by effectively moving new scientific advances into clinical practice.

OVERVIEW

The Cancer Diagnosis Program (CDP) strives to improve the diagnosis and assessment of cancer by effectively moving new scientific advances into clinical practice. The program stimulates, coordinates, and funds resources and research on diagnostics and improved technologies to better characterize cancers in order to develop information that can aid cancer patients and their physicians in clinical decision-making.

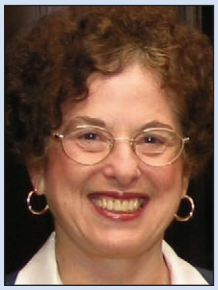
CDP supports research at medical centers, hospitals, businesses, and universities throughout the United States, Canada, and other countries.

CDP is divided into three branches:

- Diagnostic Biomarkers and Technology Branch
- Resources Development Branch
- Diagnostics Evaluation Branch

CDP, often in cooperation with other programs of the National Cancer Institute (NCI), offers a range of initiatives that encourage and support research in cancer diagnostics and related development of technology and specimen resources. CDP administered approximately 400 funded grants in 2005.

Dr. Sheila Taube, Associate Director



Sheila Taube, Ph.D., has served as Associate Director of the DCTD Cancer Diagnosis Program (CDP) since 1997. Under Dr. Taube's leadership, CDP has launched the Program for the Assessment of Clinical Cancer Tests (PACCT), which is designed to ensure efficient and effective translation of new knowledge and technology related to cancer diagnosis into clinical practice. The first prospective trial of a molecular signature for risk of recurrence in early stage breast cancer, the TAILORx trial, was developed as part of PACCT and opened in 2006.

Prior to serving as Associate Director of CDP, Dr. Taube was program director for biochemistry and then Chief of the NCI Cancer Diagnosis Branch, the predecessor of the Cancer Diagnosis Program. In the Cancer Diagnosis Branch, Dr. Taube was instrumental in developing programs to use molecular technologies for cancer diagnosis.

Dr. Taube serves on the American Society of Clinical Oncology's Expert Panel to develop practice guidelines for the use of tumor markers for breast and colorectal cancer. She also contributed to a seminal paper in the *Journal of the National Cancer Institute* on the methodology of evaluating prognostic markers and co-edited a special issue of *Seminars in Oncology* devoted to tumor marker development. Dr. Taube collaborated with the Receptor and Biomarkers Group of the European Organisation for Research and Treatment of Cancer (EORTC) to launch the biannual series of international meetings called "Molecular Markers for Cancer: From Discovery to Clinical Practice." In 2004, Dr. Taube and colleagues developed the syllabus for a short course for industry, "From Hypothesis to Product: An EORTC-NCI Diagnostics Development Tutorial." In 2005, Dr. Taube and colleagues published three separate articles about PACCT and personalized medicine.

Dr. Taube received her bachelor's degree in biology from Brandeis University and her doctorate in microbiology from the University of Pittsburgh School of Medicine. Following postdoctoral work at Yale University, she joined the faculty of the University of Connecticut Medical School, where she used a viral system to investigate cell membrane protein processing.

Program for the Assessment of Clinical Cancer Tests

http://www.cancerdiagnosis.nci.nih.gov/assessment/index.html

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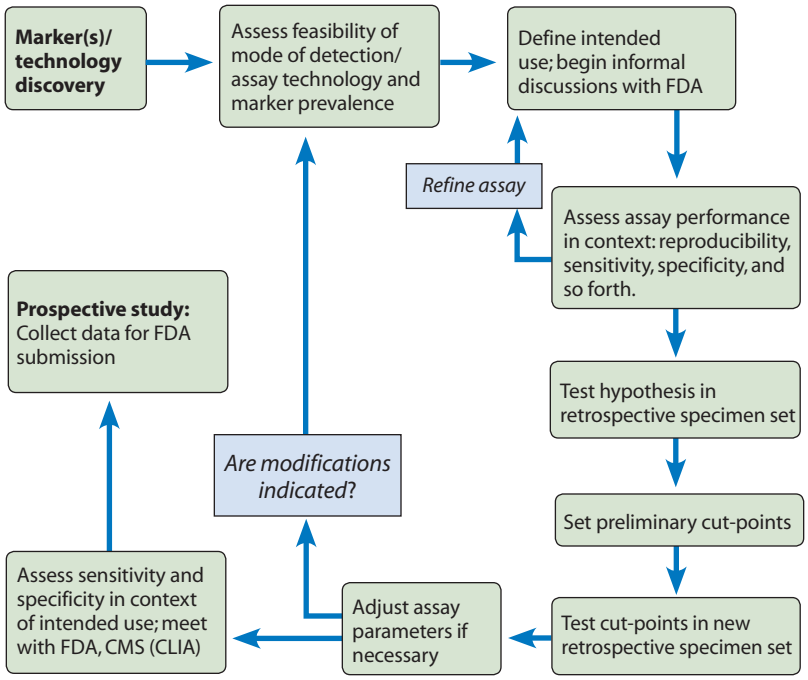
Many decisions relating to cancer patient management depend on information derived from clinical laboratory tests. Significant research and development are involved in producing a test that is reliable enough for routine clinical use. CDP launched the Program for the Assessment of Clinical Cancer Tests (PACCT) in 2000 to develop a process for moving the advances in new technologies and new understanding of cancer biology more efficiently and effectively into clinical practice.

Biomarker Development Process



A primary goal of PACCT is to develop more informative laboratory tools to help maximize the impact of cancer treatments. PACCT focuses on developing tests for cancer diagnosis, prognosis, and prediction of response to therapy. Its activities also include the generation of reference sets of clinical specimens, which are available to academic and industry researchers working to evaluate new markers and validate the utility of some known markers and tests.

PACCT is guided by a multidisciplinary strategy group, which developed criteria for assessing which markers are ready for further development. The strategy group comprises scientists from academia, as well as Food and Drug Administration (FDA) and NCI staff with expertise in clinical oncology, pathology, basic cancer biology, diagnostics technology and assay development, clinical trials methodology, and statistics.

The strategy group establishes working groups to address critical clinical problems in specific tumors. The Breast Cancer Working Group's efforts have led to the Trial Assigning IndividuaLized Options for Treatment (TAILORx), which is assessing the clinical utility of a new prognostic tool based on analysis of molecular signatures. The Colon Cancer Working Group is focusing on assay standardization and validation issues. Its goal is to validate tests to determine whether it is possible to identify a subgroup of patients with stage II colon cancer at sufficiently high risk to benefit from adjuvant chemotherapy. Working groups have recently been convened to address difficult clinical issues in prostate and lung cancer.

Trial Assigning Individualized Options for Treatment

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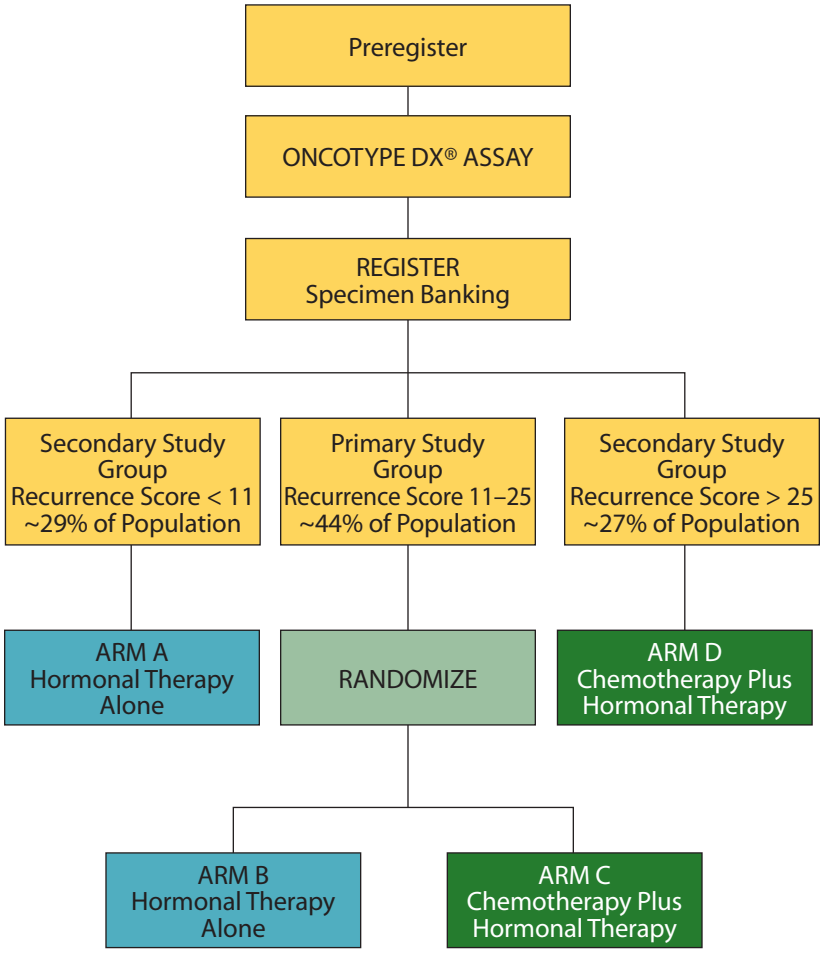
Breast cancer stamp sales by the U.S. Postal Service are playing a critical role in making a new, groundbreaking treatment trial possible by providing a portion of the funding for TAILORx. Without this support, the trial would not have been funded. TAILORx, the first trial launched by PACCT, will pioneer the integration of molecular diagnostics into clinical decision-making for breast cancer. The trial will test whether a set of expressed genes that have been shown to be associated with risk of recurrence in women with node-negative, hormone-receptor–positive breast cancer can be used to assign patients to the most appropriate and effective treatment. The signature to be tested is the 21-gene Oncotype DX® panel developed by Genomic Health in collaboration with the NCI cooperative group, National Surgical Adjuvant Breast and Bowel Project (NSABP). Details of the Oncotype DX® test were reported in the articles listed below.

The trial is being carried out as a collaboration of CDP, the Cancer Therapy Evaluation Program (CTEP), and all of the NCI clinical cooperative groups that perform breast cancer studies.

Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner FL, Walker MG, Watson D, Park T, Hiller W, Fisher ER, Wickerham DL, Bryant J, Wolmark N. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004:351;2817–26.

Paik S, Shak S, Tang G, Kim C, Joo H, Baker J, Cronin M, Watson D, Bryant J, Costantino J, Wolmark N. Expression of the 21 genes in the recurrence score assay and prediction of clinical benefit from tamoxifen in NSABP study B-14 and chemotherapy in NSABP study B-20. Presented at: 27th Annual San Antonio Breast Cancer Symposium. December 8–11, 2004. San Antonio, TX. Abstract #24.

TAILORx Schema



The Strategic Partnering to Evaluate Cancer Signatures program supports research that bridges the gap between the discovery of molecular signatures and their integration into clinical practice.

Strategic Partnering to Evaluate Cancer Signatures

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The Strategic Partnering to Evaluate Cancer Signatures (SPECS) program consists of six grants that support multi-institutional, multidisciplinary research teams. The SPECS program leverages NCI's investment in cancer clinical trials, cancer centers, NCI intramural programs, and the Specialized Programs of Research Excellence (SPORE) program. The projects include collaborations with biotechnology companies, community hospitals, national laboratories, and academic institutions in the United States, Canada, and Europe.

The SPECS initiative supports six large collaborative research groups that are exploring how information derived from comprehensive molecular analyses can be used to impact the care of cancer patients and ultimately improve outcomes. SPECS supports research that bridges the gap between the discovery of molecular signatures and their integration into clinical practice. Investigators are refining and confirming both genomic and proteomic signatures that have already been shown to address clinical needs or questions. They are defining the critical components of the signatures and developing robust assays for measuring those components in the clinical setting. They will confirm that the modified signatures provide reproducible, reliable information that can potentially inform clinical decision-making. It is anticipated that the signatures developed in SPECS will lead to assays that are ready for validation in prospective clinical trials.

Strategic Partnering to Evaluate Cancer Signatures Projects

Children's Hospital, Los Angeles, CA
http://researchportfolio.cancer.gov/projectdetail.jsp?ProjectID=92113

Principal Investigator:
Dr. Timothy J. Triche

This project will refine and validate molecular signatures that provide a more accurate diagnosis and more accurately predict clinical behavior of common childhood sarcomas.

University of California, Irvine, CA
http://researchportfolio.cancer.gov/projectdetail.jsp?ProjectID=92128

Principal Investigator:
Dr. Dan Mercola

This project will refine and validate molecular signatures that predict relapse in prostate cancer patients and distinguish indolent disease from disease that will progress.

University of Nebraska Medical Center, Omaha, NE
http://researchportfolio.cancer.gov/projectdetail.jsp?ProjectID=92117

Principal Investigator:
Dr. Wing C. Chan

This project will refine and validate diagnostic and prognostic molecular signatures for the major subclasses of non-Hodgkin's lymphoma using the LymphDX chip that was developed for the project by Affymetrix.

University of New Mexico, Albuquerque, NM
http://researchportfolio.cancer.gov/projectdetail.jsp?ProjectID=88797

Principal Investigator:
Dr. Cheryl L. Willman

This project will refine and confirm molecular signatures that improve risk classification, outcome prediction, therapeutic response, and risk of relapse in pediatric and adult acute lymphocytic leukemia.

Vanderbilt-Ingram Cancer Center, Nashville, TN
http://researchportfolio.cancer.gov/projectdetail.jsp?ProjectID=92112

Principal Investigator:
Dr. David P. Carbone

This project will refine and evaluate molecular signatures in lung cancer, including serum proteomic signatures that differentiate patients with cancer from those without disease, and provide signatures that predict risk of recurrence following surgery.

Washington University in St. Louis, MO
http://researchportfolio.cancer.gov/projectdetail.jsp?ProjectID=92110

Principal Investigator:
Dr. Matthew J. Ellis

This project will refine and validate molecular signatures that identify five subtypes of breast tumors using quantitative polymerase chain reaction to measure signatures in fixed tissues.

Phased Application Awards in Cancer Prognosis and Prediction

Program Announcement:
PA-04-102: http://grants.nih.gov/grants/guide/pa-files/PA-04-102.html
(expiration date 11/2/2006)

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James V. Tricoli, Ph.D.
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An increasing number of publications have described new molecules, new patterns of gene expression, and new aspects of tumor cell growth that seem to be correlated with known prognostic factors. However, studies that go beyond the exploratory stage of developing a new diagnostic test require large numbers of patient samples with associated clinical data. They also need an efficient assay technique and a great deal of statistical input. Such tools could improve clinical decision-making in the care of cancer patients.

This CDP-sponsored program is accelerating the translation of new discoveries into clinical practice by allowing investigators to use new diagnostic strategies to solve clinical problems. By providing up to five years of support for a first phase grant (R21) for technical development and a second phase grant (R33) for application and evaluation of clinical utility, CDP will enable investigators to evaluate the utility and pilot the application of new strategies for determining prognosis or predicting response to therapy.

Exploratory Studies in Cancer Detection, Diagnosis, and Prognosis

Program Announcement:
PA-05-165: http://grants.nih.gov/grants/guide/pa-files/PA-05-165.html
(expiration date 11/2/2008)

Contact:
James V. Tricoli, Ph.D.
301-496-1591, tricolij@mail.nih.gov

Advances in the understanding of basic cancer biology and the development of powerful molecular technologies are leading to the identification of many new abnormalities in precancerous and cancer cells. New biomarkers and laboratory assays are needed to screen patients for cancer and assess their risk. These biomarkers could also be used to assess disease prognosis and response to cancer treatments, especially new treatments.

The major goal of this CDP initiative is to promote the initial evaluation of new molecular or cellular characteristics of premalignant cells or tumors or the development of assays that will be useful for cancer detection, diagnosis, and prognosis. Using the exploratory/developmental grant (R21) mechanism, this initiative will provide up to two years of support for translational studies that identify promising new means for cancer detection and diagnosis and provide the initial, critical information needed to decide whether potential clinical utility justifies further investment.

CDP is homing in on clinical correlative or mechanistic studies that will be useful for cancer risk assessment, early detection, and prognosis, as well as predicting responses to therapy and prevention interventions.

Correlative Studies with Specimens from Multisite Trials

Program Announcements:
PA-05-062: http://grants.nih.gov/grants/guide/pa-files/PA-05-062.html *(expiration date 3/2/2008)* and **PA-06-296**: http://grants.nih.gov/grants/guide/pa-files/PA-06-296.html *(expiration date 3/2/2008)*

Contact:
Heng Xie, M.D., M.P.H.
301-496-8866, xiehe@mail.nih.gov

Over the past five years, NCI has sponsored more than 1500 clinical trials, including cancer treatment and prevention trials. More than 200,000 cancer patients have participated in these trials. CDP, in collaboration with other NCI programs, is tapping into the wealth of tumor specimens and accompanying information about patients that is available through these myriad trials. The tumor specimens can be used to evaluate and possibly validate diagnostic and prognostic biomarkers. They can be used to evaluate molecules and proteins relating to cell cycle or intracellular signal transduction pathways, as well as to provide informative molecular profiles relevant to cancer intervention and progression. These extremely valuable resources offer a tremendous opportunity to identify new mechanisms and develop more effective cancer interventions at a molecular level. The next step is to conduct clinical translational research on promising predictive and prognostic tumor markers.

This funding opportunity will use the R01 investigator-initiated research grant mechanism to support clinical correlative studies on large, multi-institutional clinical trials to validate promising tumor markers and the exploratory/pilot grant mechanism (R21) to support pilot exploratory studies. Because the nature and scope of the proposed research will vary, the size and duration of the awards will also vary, although funding under the R21 mechanism is limited to two years. Through these grants, CDP is encouraging researchers to take advantage of newly developed technologies and existing tumor specimens. By fostering collaborations among basic researchers, scientists working in private industry, and clinical investigators, CDP is homing in on clinical correlative or mechanistic studies that will be useful for cancer risk assessment, early detection, and prognosis, as well as predicting responses to therapy and prevention interventions.

PARTNERSHIPS AND COLLABORATIONS

European Organisation for Research and Treatment of Cancer

http://www.eortc.be

CDP has led an NCI collaboration with EORTC to convene the NCI/EORTC biannual meetings on molecular diagnostics. At the first meeting, held in Denmark in 2000, four international working groups were established. One of the working groups focused on development of guidelines for information that should be included in all publications about tumor markers. These recommendations were recently published simultaneously in several major scientific journals.

U.S. Food and Drug Administration

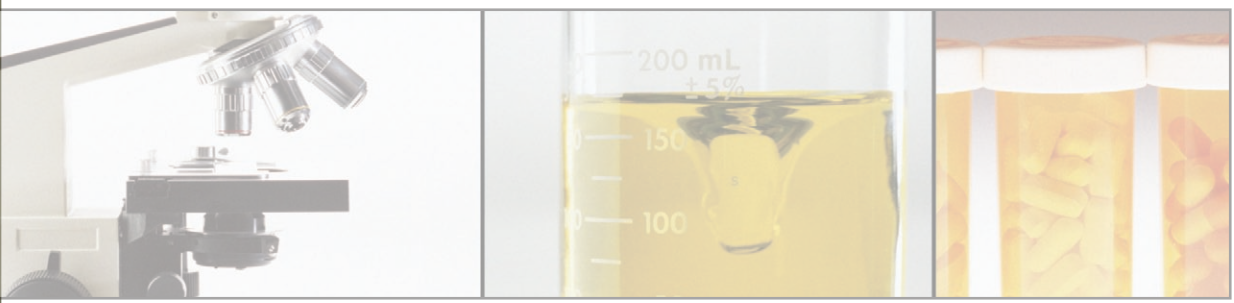
http://www.fda.gov

Through an agreement with the FDA, a CDP staff member has a joint appointment with NCI and FDA. This person has primary responsibility as a program director managing a portfolio of technology development and proteomics grants in the CDP Diagnostic Biomarkers and Technology Branch. At FDA, the staff person runs a laboratory that is carrying out research on microarray methods (a powerful technology that allows simultaneous measurement of expression levels for up to tens of thousands of genes) for detecting food-borne pathogens. The technology used at FDA is complementary to the technologies being used to detect molecular changes in cancer at NCI. The staff person also serves as a liaison between NCI and FDA on issues related to technology applications.

National Institute of Standards and Technology, FDA, and College of American Pathologists

http://www.nist.gov
http://www.fda.gov
http://cap.org

Overexpression of the *Her2* gene plays a pivotal role in oncogenesis, progression, and metastasis of breast cancer tumors. *Her2* testing is used to decide whether a patient with breast cancer is likely to benefit from treatment with trastuzumab after her surgery. CDP cosponsored a workshop on the need for reference material to ensure the reliability of *Her2* testing.



As a result of the workshop, the National Institute of Standards and Technology (NIST) agreed to produce a NIST-certifiable standard and a commercially developed standard for use in all *Her2* testing. Workshop participants agreed that all *Her2* testing must be done on samples fixed only in 10 percent buffered formalin, as specified in the FDA-approved testing methods. Finally, they decided to plan strategies to educate pathologists, clinicians, and laboratories about the need for and use of standards. A joint meeting of the American Society of Clinical Oncology and the College of American Pathologists in 2006 will finalize practice guidelines for *Her2* testing in clinical practice.

Melanoma Research Foundation

http://www.melanoma.org

Skin cancers are the most common of all cancers. One in five Americans will develop skin cancer in their lifetime. Although molecular profiling data to help identify biomarkers for early detection are collected for solid tumors such as those associated with breast and colon cancers, similar approaches in the field of skin cancer research are lagging behind.

The lack of high-quality tissue resources is a major barrier in identifying and validating biomarkers for disease management. CDP and the Melanoma Research Foundation convened melanoma research experts in February 2004 to identify areas of common interest and suggest new research resources for melanoma diagnosis and prognosis. As a result of the workshop, CDP provided supplemental funding to six institutions for tissue collection to be used to develop tissue microarrays (TMAs). NCI has produced a progression TMA that will be available to the melanoma community in 2006.

More than 50 prominent melanoma researchers met in October 2005 for the Resources for Melanoma Research Workshop, which was cosponsored by CDP, the skin cancer SPORE program at NCI, and the Melanoma Research Foundation. Researchers and clinicians from the major U.S. melanoma research centers discussed recent advances in biomarkers for diagnosis, prognosis, and prediction. Participants agreed that establishing a melanoma TMA bank would aid biomarker development. This bank will include the TMAs developed as a result of the first meeting and by the SPORE program. CDP will coordinate this activity to provide these valuable resources to the melanoma research community.

CDP is also involved in NCI melanoma focus groups in conjunction with the Melanoma Research Foundation and melanoma community investigators. These groups are identifying and coming to consensus on the directions needed to make progress in melanoma research. It is anticipated that another meeting will take place in 2007.

National Human Genome Research Institute

http://www.genome.gov

As a result of a collaboration with NCI scientists, the National Human Genome Research Institute exported TMA technology to NCI. With the support of CDP,

several types of cancer TMAs have been constructed and are now available to the cancer research community.

National Institute of Neurological Disorders and Stroke and Cancer Biomedical Informatics Grid

http://rembrandt.nci.nih.gov
https://cabig.nci.nih.gov

The REpository of Molecular BRAin Neoplasia DaTa (REMBRANDT) is a public database that was developed as a partnership of CDP staff, NCI intramural investigators, NCI's Cancer Biomedical Informatics Grid (caBIG), and investigators in the National Institute of Neurological Disorders and Stroke (NINDS). REMBRANDT will house biological and clinical data from several thousand primary brain tumors for a variety of purposes, including the development of novel molecular classification systems. This effort is an important step toward an era of individualized cancer treatment based on the molecular genetics of each patient's tumor. REMBRANDT will house two sets of valuable data.

The first set of data will come from the prospective Glioma Molecular Diagnostic Initiative (GMDI) study, which is collecting tumor specimens from patients enrolled in NCI-sponsored clinical trials. GMDI will generate data from the tumors on gene expression, chromosomal alterations, and presence of single nucleotide polymorphisms, as well as proteomic data from patient serum.

The second type of REMBRANDT data will be a wide array of molecular and genetic information regarding all types of primary brain tumors generated by NCI-funded investigators. REMBRANDT will allow huge amounts of disparate data types to be housed in a single place and will also supply the bioinformatics tools critically necessary for the useful analyses of such data.

NCI's caBIG is providing a library of tools and resources to REMBRANDT to facilitate integrative analysis from bench to bedside and back.

The new molecular glioma classification system that will result from GMDI and REMBRANDT will be biologically based, giving insight into the pathology of glioma cells and helping physicians predict responsiveness to specific therapies. The research community will be able to access REMBRANDT resources through an NCI-developed Web portal.

Reporting Recommendations for Tumor Marker Prognostic Studies

The strategy group of PACCT and an NCI-EORTC working group collaboration have developed a set of guidelines, REporting recommendations for tumor MARKer prognostic studies REMARK, for reporting tumor marker studies. The article describing the guidelines was accepted for simultaneous publication in five high-impact journals in August 2005. The guidelines include a checklist of the information that all publications on tumor marker studies should include so that scientists can interpret and critically evaluate the results. This checklist is designed to ensure that reports of marker studies specify the study hypothesis, how the study was designed to test the hypothesis, how the specimens were analyzed, and how the data were analyzed. These recommendations will help researchers understand what will be needed for publication of tumor marker studies, and this should lead to the design of better studies. The recommendations will also help journal reviewers ensure the publication of interpretable and useful studies.

McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM. Reporting recommendations for tumor marker prognostic studies. *J Clin Oncol* 2005:23;9067–72.

McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM; Statistics Subcommittee of the NCI-EORTC Working Group on Cancer Diagnostics. REporting recommendations for tumor MARKer prognostic studies (REMARK). *Nat Clin Pract Oncol* 2005:2;416–22.

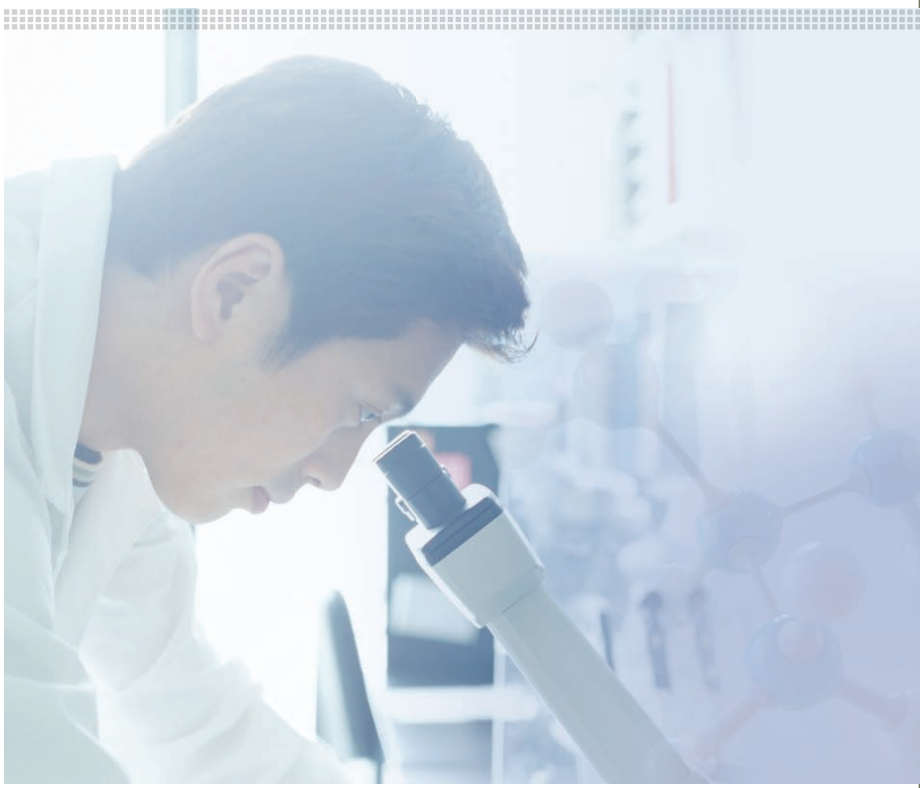
McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM; Statistics Subcommittee of the NCI-EORTC Working Group on Cancer Diagnostics. REporting recommendations for tumour MARKer prognostic studies (REMARK). *Br J Cancer* 2005:93;387–91.

McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM; Statistics Subcommittee of the NCI-EORTC Working Group on Cancer Diagnostics. Reporting recommendations for tumor marker prognostic studies (REMARK). *J Natl Cancer Inst* 2005:97;1180–4.

McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM; Statistics Subcommittee of the NCI-EORTC Working Group on Cancer Diagnostics. REporting recommendations for tumour MARKer prognostic studies (REMARK). *Eur J Cancer* 2005:41;1690–6.

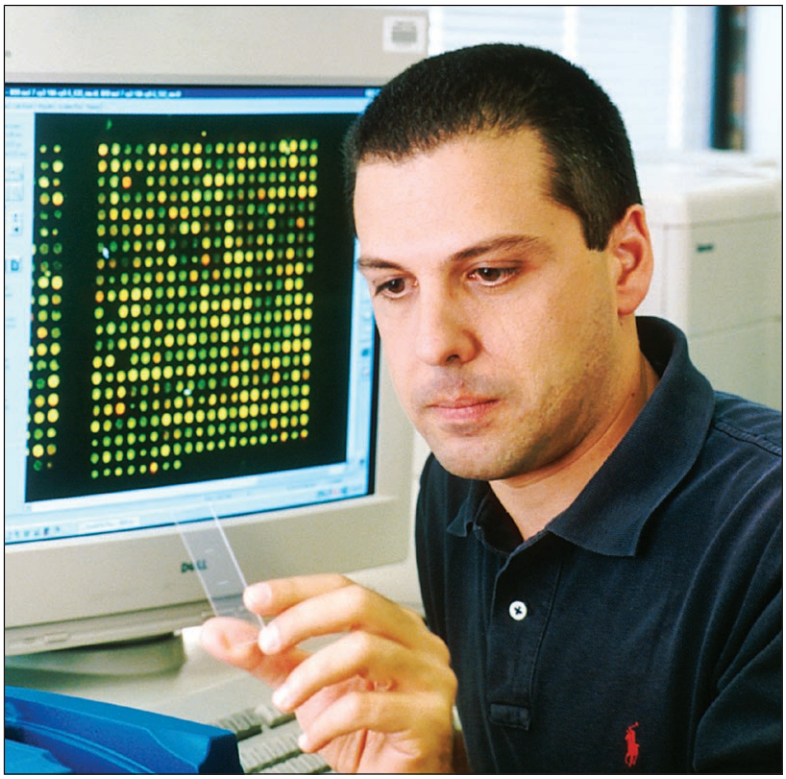
Comparable Cancer Gene Expression Data from Several Laboratories

Large studies are critical to bringing the results of gene expression studies into clinical practice. For these studies to be conducted, microarray data from different laboratories must be comparable and reproducible. A CDP statistician working



A CDP statistician working with academic collaborators showed that under properly controlled conditions, it is possible to perform complete tumor microarray analysis at several independent laboratories for a single study.

with academic collaborators showed that under properly controlled conditions, it is possible to perform complete tumor microarray analysis at several independent laboratories for a single study. The investigators assessed the comparability of data from four laboratories that are conducting a large microarray profiling confirmation project in lung cancer. To test the feasibility of combining data across laboratories, the authors analyzed frozen tumor tissues, cell lines, and purified RNA at each of the four laboratories. The laboratories used the same protocol for all of the tissue-processing steps, RNA extraction, and microarray analysis. The investigators observed high within-laboratory and between-laboratory correlations on the purified RNA samples, cell lines, and frozen tumor tissues. Correlations within laboratories were only slightly stronger than between laboratories.



Courtesy of NCI Visuals Online, Bill Branson, photographer.

Dobbin KK, Beer DG, Meyerson M, Yeatman TJ, Gerald WL, Jacobson JW, Conley B, Buetow KH, Heiskanen M, Simon RM, Minna JD, Girard L, Misek DE, Taylor JM, Hanash S, Naoki K, Hayes DN, Ladd-Acosta C, Enkemann SA, Viale A, Giordano TJ. Interlaboratory comparability study of cancer gene expression analysis using oligonucleotide microarrays. *Clin Cancer Res* 2005:11;565–72.

Models for Diagnostic and Predictive Biomarker Development and Validation

CDP staff have worked with academic investigators through PACCT to develop strategies for effective development and validation of diagnostic and predictive biomarkers. CDP staff communicate these strategies to the cancer research community through a series of public presentations and publications in order to facilitate more effective development of clinical tests. In combination with the REMARK guidelines, these publications have the potential to improve the quality of studies carried out to demonstrate a biomarker's potential clinical utility.

Jessup JM, Lively TG, Taube SE. Program for the Assessment of Clinical Cancer Tests (PACCT): implementing promising assays into clinical practice. *Expert Rev Mol Diagn* 2005:5;271–3.

Taube SE, Abrams, JS. Program for the Assessment of Clinical Cancer Tests (PACCT): assisting the development of tailored cancer therapy. *Personalized Med* 2005:2;363–9.

Taube SE, Jacobson, JW, Lively TG. Cancer diagnostics: decision criteria for marker utilization in the clinic. *Am J Pharmacogenomics* 2005:5; 357–64.

Advice and Resources for Cancer Diagnostics Researchers

http://www.cancerdiagnosis.nci.nih.gov/diagnostics/advice.html

This page on the CDP Website addresses such topics as what makes a marker useful, who should be on the research team, and publication guidelines. This site also lists literature resources for marker development methods.

Human Tissue Specimen Resources

http://www-cdp.ims.nci.nih.gov/resources.html

The Resources Development Branch (RDB) of CDP stimulates, develops, and supports human tissue specimen resources to ensure availability of the tissue specimens needed to facilitate basic and translational cancer research. The branch provides information on legal and ethical issues and human subjects policy as they apply to human specimen resources.

Access to high-quality tissue specimens and clinical and outcome data is critical to continued scientific progress. RDB monitors changes in scientific needs for tissue specimen resources and acts to ensure that changing needs for specimens can be met in a timely manner.

RDB supports the collection and storage of high-quality, well-annotated human specimens collected from patients in NCI-funded, phase III clinical treatment trials. This support ensures that the tissue banks of NCI's cooperative groups implement best practices, such as common data structures and standardized collection and storage practices. A common application process for using the specimens will improve access to specimens by the broader research community. Available information will include appropriate patient demographic, clinical, outcome, and treatment data. These activities are overseen by a Steering Committee formed from the cooperative groups.

The following tissue resources are available from CDP:

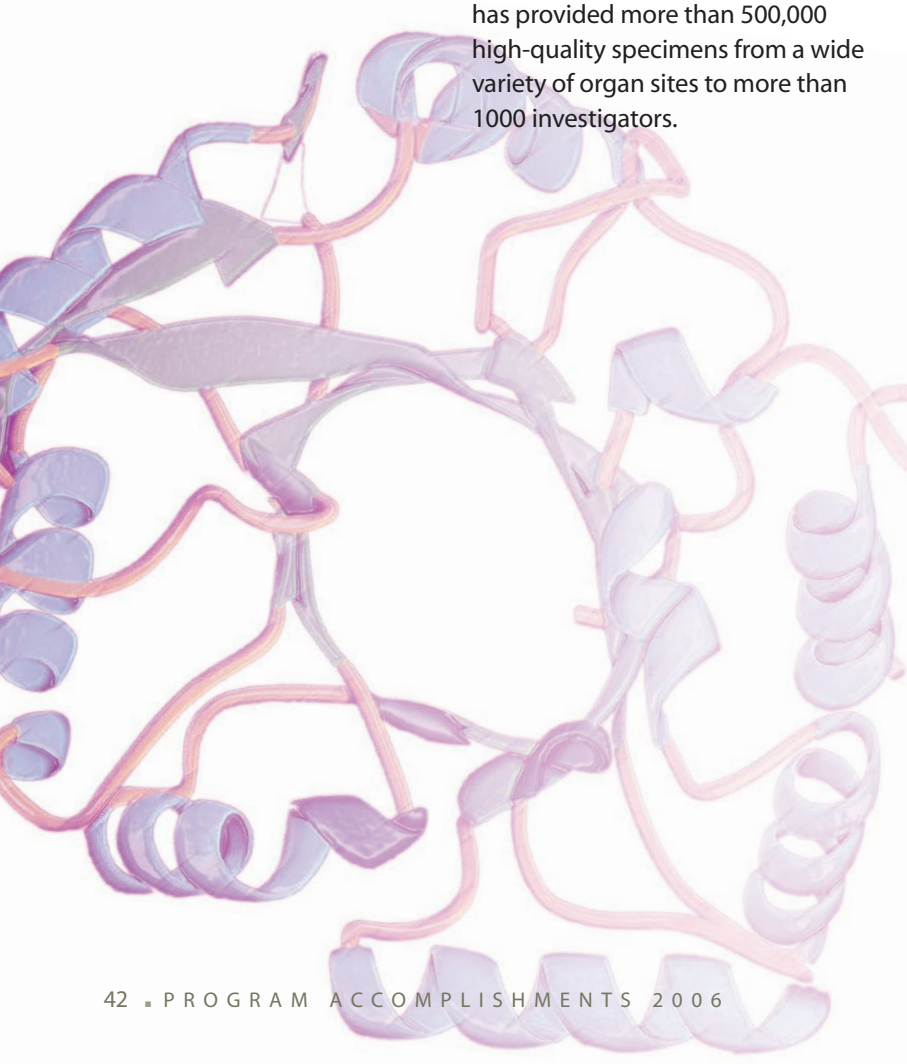
- **Cooperative Breast Cancer Tissue Resource (CBCTR)**
  http://cbctr.nci.nih.gov

  CBCTR supplies researchers with primary breast cancer tissues and associated clinical data. This valuable collection facilitates large studies that need archival tissue with clinical and outcome data. The CBCTR Website features an online database that investigators can search to identify the number of available breast cancer samples that meet their research requirements.
- **Cooperative Prostate Cancer Tissue Resource (CPCTR)**
  http://cpctr.cancer.gov/index.html

  CPCTR provides researchers with primary prostate cancer tissues and associated clinical data. This valuable collection facilitates large studies that need archival tissue with clinical and outcome data. The CPCTR Website features an online database that investigators can search to identify the number of available prostate cancer samples that meet their research requirements.

- **Cooperative Human Tissue Network (CHTN)**
  http://www-chtn.ims.nci.nih.gov

  CHTN provides biomedical researchers with access to human tissues. Six regional member institutions coordinate the collection and distribution of tissues across the United States and Canada. In addition to normal, benign, and malignant tissues, the resource offers tissues from patients with other diseases such as ulcerative colitis. Trained personnel coordinate the retrieval, preservation, and delivery of specimens obtained from surgical resections and autopsies. Since its establishment in 1987, CHTN has provided more than 500,000 high-quality specimens from a wide variety of organ sites to more than 1000 investigators.



- **The NCI Clinical Trials Cooperative Groups** have banked tumor specimens from large numbers of uniformly treated cancer patients with a variety of malignancies. Each group has a review process for research proposals. If proposals receive favorable reviews, specimens with clinical, treatment, and outcome data can be made available to researchers through collaborative arrangements. These banked specimens are most useful for clinical correlative studies on uniformly treated patient populations. Interested investigators may visit the NCI Specimen Resource Locator Website (http://pluto3.nci.nih.gov/tissue/default.htm) or contact the Tissue Expediter at tissexp@mail.nih.gov.

Reporting Studies of Tumor Markers

http://www.cancerdiagnosis.nci.nih.gov/assessment/progress/remark.html

The REMARK guidelines resulted from a collaboration of a PACCT strategy group and an NCI-EORTC working group. REMARK includes information that should be reported in all publications about tumor markers. These recommendations were published simultaneously in *British Journal of Cancer, European Journal of Cancer, Journal of Clinical Oncology, Journal of the National Cancer Institute,* and *Nature Clinical Practice Oncology.*

The recommendations are available on the CDP Website to help the research community and members of journal editorial boards ensure that more complete information is included in publications about prognostic markers.

The guidelines help researchers evaluate whether markers or assays are ready for use in clinical settings.

The recommendations are organized according to a format typical of articles appearing in biomedical journals, corresponding to the introduction, materials and methods, results, and discussion sections.

Repository of Molecular Brain Neoplasia Data Brain Tumor Repository

http://rembrandt-db.nci.nih.gov/rembrandt/login.jsp

REMBRANDT is a national database of several thousand primary brain tumors. It focuses on innovation, model building, and validation based on the correlation of diverse data types. An in-depth, multiplatform query in REMBRANDT can yield such findings as the existence of a particular genetic marker in all tumors and its relationship to a specific tumor suppressor gene. Researchers can use REMBRANDT to explore how genetic changes correlate with a patient's response to therapy and overall survival within given age groups, geographical locations, and ethnicities. The database will ultimately be fully open and accessible to all investigators, both intramural and extramural.

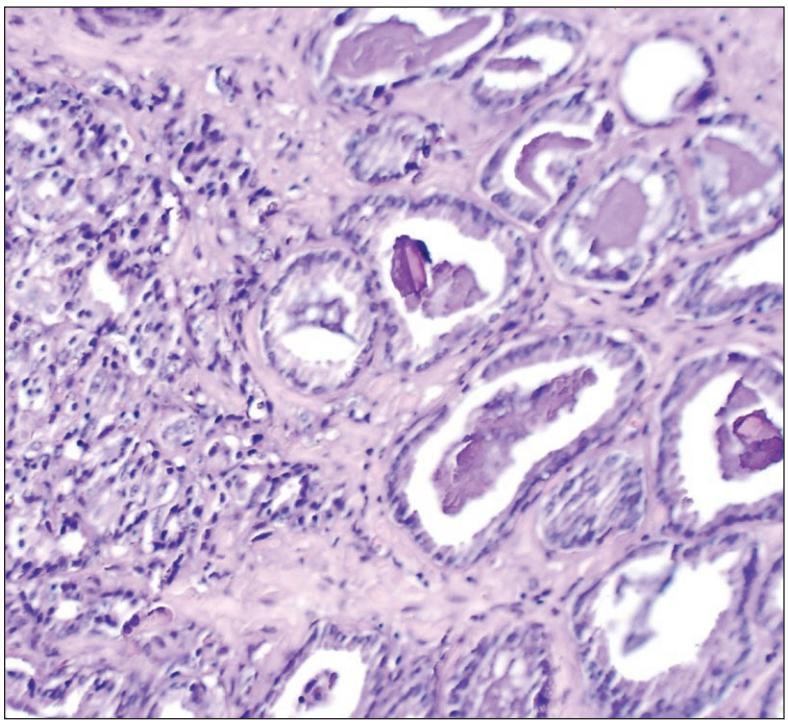
Guidelines for Marker Development

http://www.cancerdiagnosis.nci.nih.gov/assessment/progress/markerdev.html

A researcher, when undertaking identification of a potentially useful marker, must consider such questions as:

- Is there a biological rationale for this marker?
- Is there an assay system available that is working in at least one laboratory with reasonable reproducibility?
- Has the marker been examined in normal as well as abnormal/diseased tissue?
- Can a patient population be defined for which this marker may have utility? What is an expected range for the prevalence of this marker in populations of potential interest?
- Can the marker be measured in the types of specimens that will generally be available?

To assist researchers who are considering whether to proceed with development



NCI Visuals Online, Dr. Otis Brawley, photographer.

Histological slide showing prostate cancer.

Progress in many areas of cancer research depends on the availability of human specimens for research. A CDP research initiative, the Shared Pathology Informatics Network (SPIN), makes existing archived pathology specimens and their associated clinical data more accessible.

of a marker, the CDP-supported PACCT strategy group developed draft guidelines, which are available on the Web. The guidelines help researchers evaluate whether markers or assays are ready for use in clinical settings. It should be possible to determine what further steps need to be taken by critically examining available data. Some of this information has been incorporated into a journal article: Hammond ME, Taube SE. Issues and barriers to development of clinically useful tumor markers: a development pathway proposal. *Semin Oncol* 2002:29;213–21.

Shared Pathology Informatics Network

http://spin.nci.nih.gov

Progress in many areas of cancer research depends on the availability of human specimens for research. A CDP research initiative, the Shared Pathology Informatics Network (SPIN), makes existing archived pathology specimens and their associated clinical data more accessible.

The goals of SPIN are to develop and test a Web-based model system to access pathology and other clinical information linked to tissue specimens from multiple existing databases. Two funded SPIN consortia have developed a query system that can find cases matching specified criteria from archived information on more than a million cases in 10 to 15 separate databases and return the response in minutes. The systems automatically strip the records of identifiers to protect the confidentiality of patients whose records are searched. SPIN is also developing computerized systems to extract information from the text portions of pathology reports and code the information.

Tissue Expediter

http://www.cancerdiagnosis.nci.nih.gov/specimens/finding.html#expediter

The Tissue Expediter is a CDP scientist assigned to identify sources of human tissue specimens and help researchers locate the tissue and related data that they need. The Tissue Expediter (tissexp@mail.nih.gov) has contacts in the resources community who can rapidly identify sources to meet investigator needs. The Tissue Expediter can also help researchers identify potential collaborators.

CANCER IMAGING PROGRAM

The role of imaging in cancer research is changing, and the Cancer Imaging Program is a catalyst for this transformation.

OVERVIEW

The Cancer Imaging Program (CIP) of the Division of Cancer Treatment and Diagnosis (DCTD) is an innovative biomedical program that encourages collaboration among experts in basic, translational, and clinical research to advance the understanding of cancer imaging and to create better diagnosis and treatment options for patients.

The role of imaging in cancer research is changing, and CIP is a catalyst for this transformation. Instead of the past focus on getting clearer and more detailed anatomic pictures of organs and tissues, the primary new thrust is on functional or molecular imaging, which visualizes the physiological, cellular, or molecular processes in living tissues as they take place. In the next decade, CIP-sponsored research will not only contribute to the basic understanding of various cancers, but will enhance imaging's clinical role in noninvasive diagnosis, identification of disease subsets in patients, disease staging, and treatment monitoring.

CIP unites in a team approach researchers from disciplines as diverse as radiology, bioengineering, biology, chemistry, computer science, and physics. The program encourages researchers to integrate and apply new imaging discoveries and developments to the study of cancer biology and to the clinical management of cancer and cancer risk. Originally formed as the

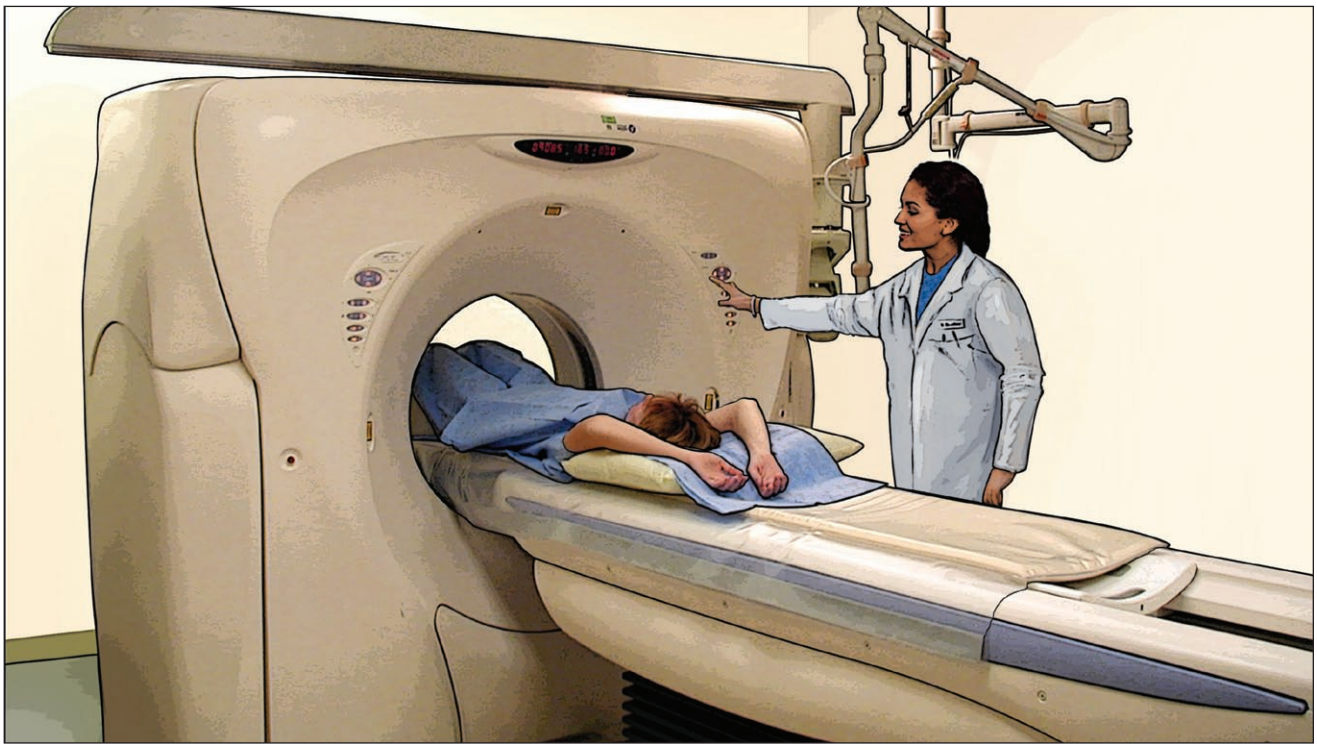
Dr. Daniel C. Sullivan, Associate Director

Daniel Sullivan, M.D., has had a distinguished career in the field of radiology, with more than 70 publications in peer-reviewed journals. His areas of clinical and research expertise are nuclear medicine and breast imaging, and he holds certifications in diagnostic and nuclear radiology from the American Board of Radiology.

Dr. Sullivan joined the DCTD Cancer Imaging Program as its Associate Director in 1997. He currently heads the NCI-Food and Drug Administration (FDA) Interagency Oncology Task Force, the NCI-Centers for Medicare & Medicaid Services (CMS) Interagency Task Force Imaging Subcommittee, and the NCI Imaging Integration and Implementation (I2) Team. He is also a member of the NCI-CMS Interagency Task Force, the NCI Bioinformatics I2 Team, the NCI Translational Research Working Group, the NIH Multiple Principal Investigator Committee, the NIH Bioengineering Consortium, and the NIH Molecular Libraries and Molecular Imaging Roadmap Steering Committee. Dr. Sullivan is a member of the editorial board of the *Journal of the Academy of Molecular Imaging*.

Dr. Sullivan received an A.B. in 1966 from Brown University and an M.D. in 1970 from the University of Vermont College of Medicine. From 1970 to 1977, he held several postdoctoral training and fellowship appointments at the Bethesda Naval Hospital and Yale-New Haven Hospital. From 1977 to 1997, he held faculty positions at Yale Medical School, Duke University Medical Center, and University of Pennsylvania Medical Center. In 1996, he was a member of the Project Hope Assessment Team that coordinated breast cancer detection and treatment in Poland.

CIP supports and advises innovative developers in academia and private industry as they create the next generation of imaging technology, including molecular probes, optical technology devices, and new contrast agents.



NCI Visuals Online, Terese Winslow, artist.

Diagnostic Imaging Program in 1996, CIP divides its staff and administered grants among four branches:

- Diagnostic Imaging Branch
- Molecular Imaging Branch
- Image-Guided Intervention Branch
- Imaging Technology Development Branch

CIP supports and advises innovative developers in academia and private industry as they create the next generation of imaging technology, including molecular probes, optical technology devices, and new contrast agents.

As part of its cutting-edge program, CIP plays a critical role in the activities of the National Institutes of Health (NIH) and the National Cancer Institute (NCI) related to emerging technologies, such as nanotechnology, proteomics, and high-throughput screening. In addition to funding projects in key areas, CIP supports researchers by providing pooled resources and developing protocols that encourage the sharing of data, samples, and results. CIP's portfolio included 347 funded grants during fiscal year 2005.

National Lung Screening Trial

http://www.cancer.gov/nlst

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About six out of 10 people with lung cancer die within a year of finding out that they have the disease. To determine whether screening people with either spiral computed tomography (CT) or chest X-ray before they have symptoms could reduce deaths from lung cancer, NCI launched the National Lung Screening Trial (NLST)—the largest lung cancer screening study ever undertaken. The study, begun in 2002, completed its challenging recruitment goal of 50,000 current and former smokers in 18 months, which was six months ahead of schedule.

Spiral CT, a technology introduced in the 1990s, uses X-rays to scan the entire chest in about 15 to 25 seconds. A computer creates images from the scan, assembling them into a three-dimensional model of the lungs. More than half of the hospitals in the United States own spiral CT machines and routinely use them for staging lung and other cancers, that is, determining how advanced the cancer is after diagnosis.

Both chest X-rays and spiral CT scans have been used to find lung cancer early. Spiral CT can detect smaller lung abnormalities, including cancers, than chest X-ray. Finding and treating these smaller abnormalities may reduce lung cancer deaths. But it may not. It could turn out that screening with spiral CT will result in more intrusive diagnostic and therapeutic procedures without reducing lung cancer deaths. Answering this question is the goal of NLST.

CIP, through its cooperative imaging group American College of Radiology Imaging Network (ACRIN), is funding 23 sites throughout the country participating in NLST. In this study, to conclude in 2009, CIP is collaborating with the NCI Division of Cancer Prevention, which marshaled its large nationwide network of screening researchers to recruit thousands of participants throughout the United States. In addition to performing the screening study, ACRIN sites will collect blood, urine, and sputum samples, which may one day prove useful in early detection of lung cancer. ACRIN sites will also evaluate quality-of-life issues, assess the cost-effectiveness of both methods, and determine the impact on smoking cessation of screening by spiral CT compared to chest X-ray.

National Computed Tomography Colonography Trial

http://imaging.cancer.gov/clinicaltrials/screening

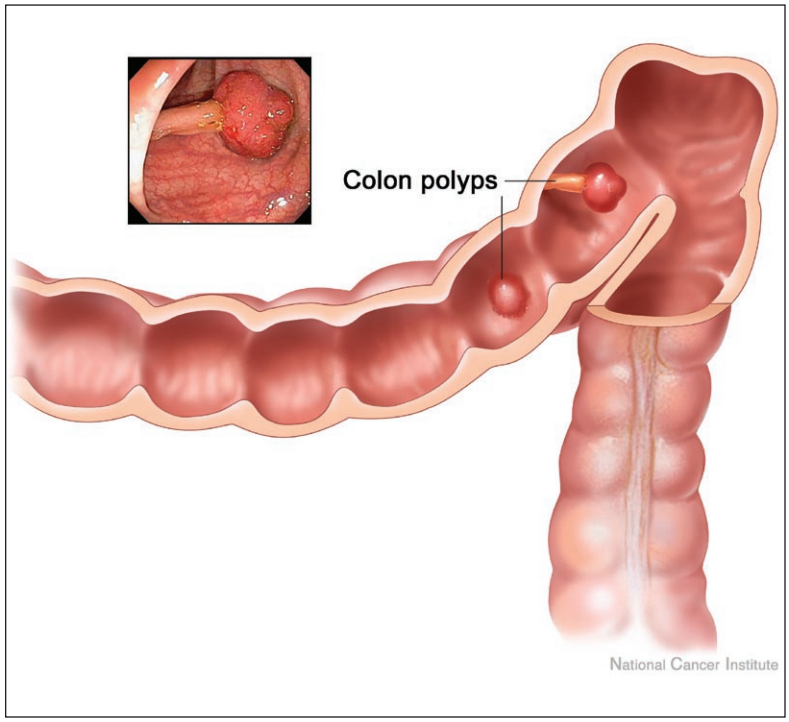
Principal Investigator:
C. Daniel Johnson, M.D., Mayo Clinic

Approximately 145,290 Americans will be diagnosed with colorectal cancer in 2006. This is the second most common cause of cancer death in the United States. As most colon cancers develop from polyps, detection and removal of these polyps can prevent cancer. When colon cancer is detected in its early stages, the survival rate is 90 percent. Though there are several approved screening tests for colon cancer, including colonoscopy, many people

have never been screened or are screened inconsistently. The reasons are multifaceted, including insurance coverage, access to screening, and patient discomfort during or before screening procedures.

Traditional, or optical, colonoscopy is an examination of the entire colon (large bowel) using a lighted instrument called a colonoscope, which is inserted through the rectum while the patient is sedated or under anesthesia. Potential risks of colonoscopy include bleeding and puncturing of the lining of the colon. A new form of colonoscopy, called CT colonography and commonly known as virtual colonoscopy, allows physicians to use cutting-edge imaging technology to produce three-dimensional X-ray images of the colon without probing inside the body. This minimally invasive technique requires less time than traditional colonoscopy, does not necessitate sedation, and is less expensive—all characteristics that may entice people to be screened for colon cancer.

It is not yet known, however, whether CT colonography is as effective as traditional colonoscopy in detecting polyps and cancer. As leaders in evaluating new imaging technologies, CIP and ACRIN initiated the National CT Colonography Trial at 15 sites across North America. ACRIN, a national network of radiologists funded by CIP, is coordinating the study, which has recruited more than half the 2300 individuals needed for the trial since it opened in February 2005.



NCI Visuals Online, Terese Winslow, artist.

Colon polyps; shows two polyps (one flat and one pedunculated) inside the colon. Inset shows photo of a pedunculated polyp.

Industry-Academic Partnerships for Development of Biomedical Imaging Systems and Methods that Are Cancer-Specific

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The initiative fosters partnerships between academic researchers and industry by providing two-year "seed" grants for collaborative *in vivo* imaging research and for projects to help validate new approaches to improve early detection, screening, diagnosis, image-guided interventions, and assessment of response to therapy.

New projects will include creation of a research network to address such issues as how to measure drug response using noninvasive imaging methods.

Because most clinical imaging work depends on commercially available imaging devices, CIP aims to ensure that commercial technology developers have access to the expertise of academic researchers. These partnerships help to ensure that new platforms and projects are robust and mature, making it more likely that the innovations will be incorporated into NCI and privately funded clinical trials and clinical investigations. By supporting high-risk/high-reward projects, grants in this program support new uses or devices for imaging that industry would not otherwise explore.

About 10 partnerships were funded under a program announcement PAR-03-157 (http://grants.nih.gov/grants/guide/pa-files/PAR-03-157.html), which closed in November 2004. One partnership is addressing the use of sonography to visualize lymph nodes, and another is testing a type of magnetic resonance imaging (MRI) known as magnetic resonance spectroscopic imaging (MRSI) to noninvasively look at changes in the chemical composition of tumor tissues and thus monitor the effectiveness of radiation treatment. These two projects involve existing technologies that have not been validated for use on these particular oncology problems.

Because of its success, CIP expects to issue a new announcement related to this program in summer 2006 that will give successful partnerships five years to build on their collaborations. New projects will include creation of a research network to address such issues as how to measure drug response using noninvasive imaging methods.

NCI Integration and Implementation (I2) Teams for Imaging and Lung Cancer

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Early in 2003, the NCI director announced a Challenge Goal to the Nation—to eliminate the suffering and death due to cancer by 2015. Reaching this goal will require an integrative approach to cancer research. New paradigms of collaboration will mean new ways of thinking about how to do science. This new culture will require the creation of an environment conducive to change, the merging of old disciplines, and the development of new ones.

To stimulate needed change, NCI has developed Integration and Implementation (I2) Teams for bioinformatics and imaging and one related specifically to lung cancer. CIP staff members participate in all the groups but are playing key leadership roles in the latter two groups. I2 Teams seek to fill in scientific gaps by pursuing projects that are not being supported by peer-reviewed grants and those that are not being developed by the private sector. The teams use a model borrowed from the business community to formulate business plans for their areas that include trans-NCI goals and metrics.

The NCI-wide goals of the I2 Imaging Teams are to:

- Increase the number of imaging tests qualified as biomarkers for therapy development

Optical molecular imaging is one of the fastest growing imaging modalities for cancer research. Establishing the network during the early phase of technology development will bring the different communities together to accelerate translation toward delivery of these technologies.

- Support development and delivery of image-guided interventions
- Accelerate the delivery of new imaging agents and technology for research and clinical use
- Improve imaging informatics infrastructure
- Advance the role of imaging to detect and treat preneoplastic lesions
- Improve understanding of communications between cancer cells and their environment

Lung cancer was chosen as an I2 Team emphasis because of the inescapable facts that five-year lung cancer survival rates have improved only modestly over the past three decades, that only a fraction of lung cancers are diagnosed at an early stage, and that even the most intensive smoking cessation programs succeed less than 25 percent of the time. Therefore, merely doing more of the same—even with higher levels of funding support—would be unlikely to dramatically improve the status quo.

In 2005, the Lung Cancer I2 Team—composed of NCI staff and extramural researchers under the leadership of Dr. Margaret Spitz of the M.D. Anderson Cancer Center—issued a set of recommendations to accelerate and expand efforts against lung cancer by focusing on strategies with enormous opportunity and potentially high returns. The recommendations focus on critical strategies that together serve as a pathway toward the 2015 goal, not by incorporating incremental strategies, but rather by focusing on transformational strategies.

The team envisions a strategic role for imaging in improving early detection of lung cancer and precancerous conditions, thereby improving the likelihood of cure. The team's plan highlights the need for effective and validated early detection techniques. It builds upon various lung-specific projects of existing *in vivo* imaging initiatives to achieve objectives related to lung cancer at substantial cost savings.

Additionally, the Lung Cancer I2 Team proposes to advance the science of imaging response assessment with molecular imaging technologies that directly reflect response to targeted therapies. The team also envisions a role for CIP in providing uniform, high-quality imaging acquisition, quality control, and analysis and creation of a lung cancer imaging meta-directory within the conduct of clinical trials.

Network for Translational Research: Optical Imaging

http://imaging.cancer.gov/programsandresources/specializedinitiatives/ntroi

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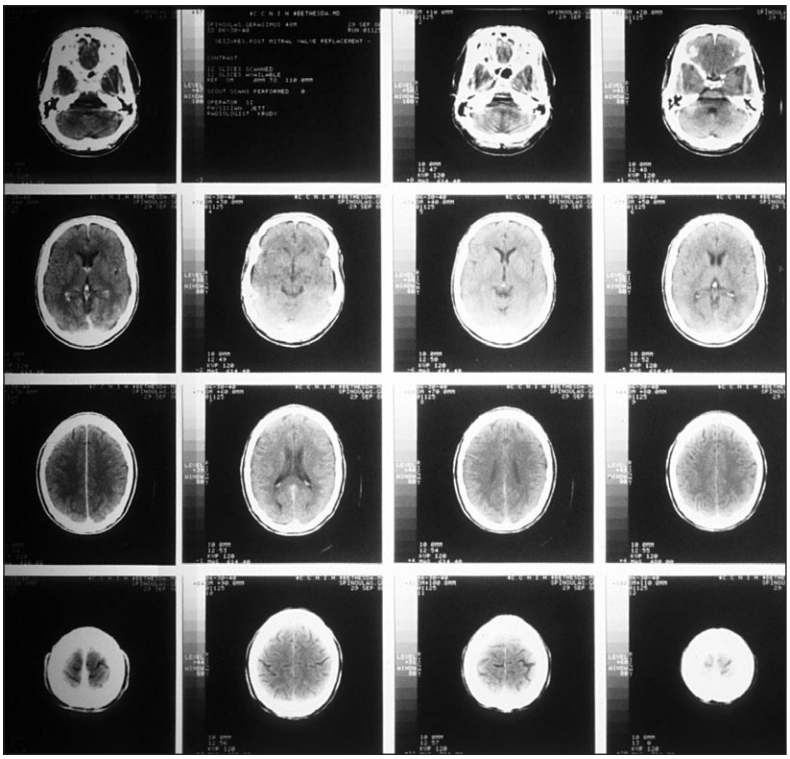
The Network for Translational Research in Optical Imaging (NTROI) was implemented in September 2003 as a demonstration project to show that technological innovations developed under CIP grants could benefit from coordinated attention to the processes of validation and translation toward clinical use. The intent of this program is to address the fact that too many medical inventions fail to progress

beyond prototypes. The area of optical imaging and spectroscopy was chosen for the pilot effort because this technology has recently generated multiple new imaging and spectroscopic modes. The use of non-ionizing radiation offers a huge capacity to capture *in vivo* information on the status of tissue and cellular physiology and pathology (molecular imaging). Multiple technologies in the area are approaching or at the threshold of clinical translation.

The NTROI network develops consensus processes for translational research in optical imaging, including optimizing emerging optical imaging systems, targeted or activatible probes, and methods for validation. Long-term goals of the program include development and delivery of common or similar platforms for measuring and extracting quantitative signatures from endogenous molecules or molecular probes that are cancer-specific. Use of combined signatures will improve sensitivity and specificity, particularly for early cancer detection, cancer diagnosis, treatment, and measurement of response to therapy.

A Network Steering Committee (SC) of team principal investigators and key co-investigators also includes scientific observers from the Food and Drug Administration, National Science Foundation, and National Institute of Standards and Technology to encourage a more seamless and timely process for regulatory approval of optical imaging methods.

Optical molecular imaging is one of the fastest growing imaging modalities for cancer research. Establishing the network during the early phase of technology development will bring the different communities together to accelerate translation toward delivery of these technologies. The request for applications (RFA) published in August 2002 yielded 17 applications, with total collaborating investigators exceeding 700, and resulted in four funded U54 Cooperative Agreements—Specialized Research Resource Centers.



NCI Visuals Online, Linda Bartlett, photographer.

Small Animal Imaging Resource Programs

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Small animal models, particularly genetically engineered mice, are increasingly recognized as powerful discovery prototypes in cancer research. Imaging techniques are an important tool for providing data about biological processes *in vivo,* and they can be performed repetitively in the same animal. However, not every researcher can afford the expensive imaging equipment needed to perform *in vivo* studies.

NCI Visuals Online.

To make imaging tools available to a greater pool of researchers, CIP created the Small Animal Imaging Resource Program (SAIRP). To increase the efficiency and synergy among basic, clinical, and translational cancer researchers, this initiative supports:

- Multiple imaging technologies for small animals, emphasizing technologies that can provide information *in vivo*
- Research and development on innovative new imaging technologies appropriate for small animals
- Assistance with small animal anesthesia and care, and advice on the optimal use of animals in imaging experiments

CIP has funded 10 SAIRPs under RFA-CA-07-004 (http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-004.html), which was re-released in February 2006. These small animal resources focus on different topics. For example, one SAIRP at Massachusetts General Hospital established a shared resource for the New England region, which is supporting more than 10 grants from different institutions and two local mouse model consortia. Technology development is directed towards optimizing and adapting new imaging technologies, validating new imaging approaches, and correlating structural and functional information.

At Stanford University, SAIRP funding is being used to establish a shared small-animal imaging facility to enable investigators to evaluate the efficacy of combination drug therapies and novel immune cell therapies in treating various

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types of tumor cells at different disease stages. CIP anticipates a recompetition in fiscal year 2007 for five of the 10 SAIRPs. As a result of this recompetition, CIP expects to fund eight five-year SAIRPs using the U24 cooperative agreement mechanism, bringing the total number of NCI-funded SAIRPs to 13.

In Vivo Cellular and Molecular Imaging Centers

http://imaging.cancer.gov/programsandresources/specializedinitiatives/icmics

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In Vivo Cellular and Molecular Imaging Center (ICMIC) grants bring together interdisciplinary scientific teams to lead cutting-edge cancer molecular imaging research in P50 center grants that last five years. The initiative focuses on human disease and exclusively supports translational research. ICMICs provide unique core facilities to support oncology imaging research, flexibility to respond to exciting pilot research opportunities, and interdisciplinary career development opportunities for the young investigators who will be tomorrow's innovators. The program promotes coordination, interrelationships, and scientific synergy among research components and resources, leading to highly integrated imaging centers.

CIP is currently supporting eight ICMICs pursuant to a program announcement (http://grants1.nih.gov/grants/guide/pa-files/PAR-04-069.html) that closed last year. However, CIP reissued a program announcement for ICMIC applications in spring 2006.

CURRENT FUNDING OPPORTUNITIES

Clinical Cancer Therapy and Prevention Research

Program Announcement:
PA-04-046: http://grants.nih.gov/grants/guide/pa-files/PA-04-046.html
(expiration date extended to 11/2/2006)

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CIP supports translational clinical studies and encourages investigators to conduct trials that will move discoveries and advances in basic biology and drug development to the patient's bedside. This initiative, which supports R01 grants to individual investigators for up to five years, encompasses a full range of therapeutic and preventive studies that employ single therapies as well as combinations that can include conventional (drugs, radiation, surgery) or unconventional (dietary supplements, bioactive food components, hypothermia, and hyperthermia) elements.

This initiative also supports programs in molecular profiling, as well as correlative studies that have been linked to therapeutic and preventive trials.

In Vivo Cancer Imaging Exploratory/ Developmental Grants

Program Announcement:
PA-04-045: http://grants.nih.gov/grants/guide/pa-files/PA-04-045.html
(expiration date extended to 11/2/2006)

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301-435-9024, am187k@nih.gov

Innovative *in vivo* cancer imaging applications have an expanding potential to improve the detection and diagnosis of cancer and alter the clinical management of cancer patients. This CIP initiative provides investigators at all career levels with a level of funding adequate for the initial feasibility testing of high-risk/high-impact cancer imaging concepts and generation of experimental preliminary data. Investigators from other scientific disciplines who wish to apply and integrate new imaging reagents and technologies in unique ways are also eligible for this R21 exploratory/developmental grant program, which provides nonrenewable funding for up to two years.

This CIP program has been available to investigators since 1999 and was recently approved for an additional three-year reissuance. Each release of this continuing series of announcements has responded to changes in the field of imaging. In the newest announcement, additional emphasis is placed on the development and application of imaging agents and methodologies to monitor response to therapy.

The CIP projects funded through this mechanism have precedent-setting potential in new areas of *in vivo* cancer imaging.

This program has supported research at every end of the discovery-development-delivery continuum for imaging—from the synthesis and early development of novel imaging agents to development of cutting-edge imaging hardware and software and a number of pilot-phase clinical studies. Topics have included innovative *in vivo* cancer imaging technologies, novel agents to detect cancerous and precancerous processes, methods to display and analyze *in vivo* images, and image-guided treatments of cancer.

A review of 95 grants funded in fiscal years 1999 through 2003 reveals that 32, or 34 percent, have successfully transitioned to larger NIH-funded programs.

Novel Technologies for *In Vivo* Imaging

Program Announcements:
PA-06-045: http://grants.nih.gov/grants/guide/pa-files/PA-06-045.html (STTR) and **PA-06-046**: http://grants.nih.gov/grants/guide/pa-files/PA-06-046.html (SBIR) and **PA-04-095**: http://grants.nih.gov/grants/guide/pa-files/PA-04-095.html *(expiration date 11/2/2006)*

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Three program announcements comprise the CIP initiative Novel Technologies for *In Vivo* Imaging. Two are open to U.S. small business applicants, PA-06-045 for STTR and PA-06-046 for SBIR. The third, PA-04-095, uses the R21/R33 grant mechanism. It is modeled on the SBIR/STTR Fast Track, but unlike the Fast Track, it is open to all applicants. All three program announcements encourage the development and delivery of imaging tools and related resources to support biomedical imaging for cancer and other diseases. One motivation is to facilitate multidisciplinary development of novel imaging technologies for risk assessment, early detection, screening, diagnosis, and treatment. The program also supports limited evaluation studies that show proof-of-concept and clinical functionality.

Another motivation for these program announcements is shared with the NIH-wide Bioengineering Consortium (BECON) committee's efforts with the Bioengineering Research Partnership (BRP) and Bioengineering Research Grant (BRG) R01 program announcements. BECON, with CIP participation, seeks to expand acceptance of engineering's design-driven, problem-solving approaches as a reasonable addition to the hypothesis-driven and mechanistic paradigms already well established in most R01 study sections.

Quick-Trials for Imaging and Image-Guided Interventions: Exploratory Grants

Program Announcement:
PAR-05-114: http://grants.nih.gov/grants/guide/pa-files/PAR-05-114.html
(expiration date 4/10/2008)

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NCI's significant investment of resources in imaging has stimulated considerable additional research activity in developing new devices, methodologies, and imaging agents. Consequently, many new methods in cancer imaging and image-guided intervention are at the preclinical stage of development. For these methods to move into the clinic, they need to be further developed and then validated in a clinical setting.

This CIP initiative supports early clinical trials of novel imaging agents and phase I studies of image-guided interventions. These trials, which are developmental R21 grants funded for two years, will ensure safety and efficacy and establish treatment parameters.

A Small Business Innovation Research/Small Business Technology Transfer (SBIR/STTR) Initiative for Image-Guided Cancer Interventions

Program Announcements:
PA-06-032: http://grants.nih.gov/grants/guide/pa-files/PA-06-032.html (SBIR) and
PA-06-031: http://grants.nih.gov/grants/guide/pa-files/PA-06-031.html (STTR)
(expiration date 11/2/2006)

Contact:
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301-451-2651, farahank@mail.nih.gov

This program is designed to stimulate a systems approach for integration and clinical testing of image-guided intervention technologies for the treatment of cancer. Through this initiative, CIP is fostering partnerships between small businesses that develop the component technologies and major imaging companies that provide the imaging platforms. These partnerships will be valuable both for developing new products and for evaluating their use in patients. Joint ventures are likely to help small companies leverage their expertise and pool their resources.

This is a reissue of PA-04-063 (http://grants.nih.gov/grants/guide/pa-files/PA-04-063.html), which was previously released in February 2004 and now is divided into separate announcements for SBIR and STTR funding mechanisms. Applications for this initiative may be submitted for support as Phase I, Phase II, or Fast Track grants.

Advanced Magnetics, Inc.
http://www.advancedmagnetics.com

NCI, through CIP, holds clinical trials agreements with Advanced Magnetics, Inc., to study two novel nanoparticle magnetic resonance contrast agents, ferumoxytol and ferumoxtran-10 (Combidex®), which were developed by the company. An exploratory clinical trial with ferumoxytol in patients with brain cancer was completed in 2005, and another exploratory clinical trial is ongoing in patients with prostate and breast cancer. CIP has also initiated a phase II study evaluating the role of ferumoxtran-10 in detecting tumor spread in axillary lymph nodes. A multicenter trial with ferumoxtran-10 for staging patients with cervical cancer is in the final stages of planning and is expected to commence in 2006.

American Cancer Society
http://www.cancer.org

The American Cancer Society (ACS), a nationwide, community-based voluntary health organization with more than 3400 local offices throughout the United States, has worked in partnership with CIP on several initiatives. For example, ACS helped with NLST, a trial supported by CIP and the NCI Division of Cancer Prevention, by recruiting nearly 50,000 current or former smokers in just 18 months. ACS is currently assisting CIP with recruitment of patients for the National CT Colonography Trial, which needs the participation of more than 2300 Americans who already anticipate having a screening colonoscopy.

American College of Radiology
http://www.acr.org

The 30,000 members of the American College of Radiology (ACR) include radiologists, radiation oncologists, medical physicists, interventional radiologists, and nuclear medicine physicians. CIP is working with this organization to address a factor that can limit the value of imaging in clinical trials: a lack of consistency in protocols across multiple study sites. Together, CIP and ACR are developing guidelines for acquiring images from each type of tool, starting with CT, to maximize imaging efficacy for clinical trials.

In addition, CIP has leveraged the resources of ACR by initiating and supporting ACRIN (www.acrin.org) clinical trials of diagnostic imaging and image-guided technologies. ACRIN's trials, which include NLST and the National CT Colonography Trial, address the major applications of imaging to cancer care, including screening, diagnosis and staging, image-guided treatment, and measuring response to treatment. ACRIN's trials are designed to help worthwhile technologies reach clinical practice more quickly, and the research network collaborates with patient advocacy groups, foundations, and representatives of industry and insurers to meet this goal.

Association of American Cancer Institutes

http://www.aaci-cancer.org

The Association of American Cancer Institutes (AACI) established the Cancer Imaging Initiative to explore how cancer centers can partner more effectively with NCI, private industry, and other cancer research entities to develop new research and clinical trials opportunities in imaging.

AACI partnered with ACRIN, a cooperative group supported by CIP, to cosponsor a special imaging workshop for cancer center directors and chairs of radiology departments. This workshop identified barriers to productive collaboration by the two groups and developed recommendations to promote imaging studies in cancer research. In response to one of these recommendations, CIP developed Imaging Response Assessment Teams (IRATs), comprising radiologists and imaging scientists, to participate in the initial design of therapy-based clinical trials. A particular focus is to advance imaging as a means of assessing response to therapy, particularly by applying imaging endpoints in clinical trials.

The first IRATs were formed in 2005 at eight NCI-designated cancer centers and will be funded for three years. Once they have participated in their first round of trials, they will begin to disseminate their methods and successes with IRATs at other institutions.

Foundation for the National Institutes of Health

http://www.fnih.org/

NCI is working closely with the Foundation for the National Institutes of Health (FNIH), which facilitates public-private partnerships of all sizes and configurations, in a collaboration to encourage the rapid development of more advanced medical imaging software tools. Directed by CIP, the Imaging Database Resources Initiative (IDRI) is designed to rapidly create a public database of lung CT and X-ray images that can be used by industry to optimize and evaluate computer-aided diagnostic products in the clinical management of lung cancer. This focused demonstration project expands on NCI's Lung Imaging Database Consortium (LIDC) and draws on resources from the CIP-cosponsored NLST.

IDRI is part of CIP efforts to speed the development and dissemination of quantitative informatics tools for imaging and integration of other patient data for clinical decision-making. This initiative will help enable the use of molecular imaging and other molecular-based methods for patient-specific diagnosis and assessment of therapy response.

Eight medical imaging companies are participating in the two-year initiative: AGFA HealthCare, Eastman Kodak Company, Fuji Photo Film Company, General Electric Company, iCAD, Inc., Philips Medical Systems, Riverain Medical, and Siemens Medical Solutions.

General Electric Healthcare

http://www.gehealthcare.com/usen/index.html

NCI, through CIP, has entered into an agreement with General Electric Healthcare to develop the radiopharmaceutical imaging agent F-18 fluorodeoxythymidine for use with positron emission tomography (PET) in clinical trials. This agreement may serve as a template for similar projects. NCI and FDA are also working together to evaluate other approaches to implementing regulatory requirements governing the use of imaging agents.

National Institute of Biomedical Imaging and Bioengineering and the Radiological Society of North America

http://www.nibib.nih.gov/publicPage.cfm?pageID=639

http://www.rsna.org/

CIP is collaborating with the Radiological Society of North America (RSNA), the NCI Center for Bioinformatics, and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) on a pilot project called the Reference Image Database to Evaluate Response to Therapy in Lung Cancer (RIDER).

RIDER, which is part of the larger LIDC initiative (http://imaging.cancer.gov/reportsandpublications/ReportsandPresentations/LungImaging), aims to produce a reference database for researchers, allowing them to develop software and other tools to address the problems of cancer detection, characterization, and response to therapy. This collaborative effort is reducing barriers to research by generating publicly available image databases, with the first prototypes being related to the imaging of lung cancer.

The RIDER pilot project thus far has resulted in an initial Web-accessible resource (http://imaging.nci.nih.gov/i3/) of serial CT data compatible with the NCI Cancer Biomedical Informatics Grid (caBIG). The proposed expansion of the RIDER project will initially include image and related metadata collected from imaging modalities such as X-ray CT and PET/CT as applied to lung cancer, collected from a wide range of both NCI- and industry-supported drug trials. One important industry goal of this resource is to attempt to accelerate FDA approval and the Centers for Medicare & Medicaid Services (CMS) reimbursement of software tools.

RIDER is striving to accomplish all its goals using open-source coding so that researchers can tailor applications to meet their individual specifications and mesh with other applications.

Food and Drug Administration and Centers for Medicare & Medicaid Services

http://www.fda.gov
http://www.cms.hhs.gov

The National Forum on Biomedical Imaging in Oncology (NFBIO) was created in 1999 to facilitate partnerships between researchers, the imaging industry, and government agencies. The goal is to address new biomedical opportunities and challenges in oncology and to focus on the regulatory, coverage, and reimbursement issues for established technologies to improve patient diagnosis and care. The forums are cosponsored by NCI, the National Electrical Manufacturers Association (NEMA), FDA, and CMS. The sixth NFBIO took place April 7–8, 2005, and focused on quantitative oncologic imaging. The speakers' presentations and other information are available on the NFBIO Website: http://imaging.cancer.gov/NewsAndMeetings/meetings.

Some Technologies Presented to the Interagency Council on Biomedical Imaging in Oncology in the Pas

1. Computed tomography (CT) and combination instrumentation
2. Magnetic resonance imaging (MRI)/magnetic resonance spectroscopy (MRS)—various instrument strengths from 1.5 to 12 Tesla
3. Ultrasound
4. Optical imaging
5. Nuclear medicine, both single-photon and positron emission tomography
6. Molecular imaging agents
7. Image-guided therapy

The Interagency Council on Biomedical Imaging in Oncology (ICBIO), with its next meeting set for October 17, 2006, brings representatives of NCI, FDA, and CMS together with technology developers to expedite the launch of new imaging products. The council's representatives provide advice on the spectrum of scientific, regulatory, and reimbursement issues related to developing an imaging device or technology. Any business or academic investigator who develops a technology relevant to biomedical imaging in cancer may submit a request. Investigators typically meet with the council for approximately one hour for an informal and confidential discussion. More information is available on the council's Website: http://imaging.cancer.gov/programsandresources/specializedinitiatives/ICBIO.

CIP and FDA have an interagency agreement to develop databases for evaluating image-processing methods for cancer screening, diagnosis, and treatment. The collaboration seeks to develop:

- Criteria to design and populate proposed image databases for the evaluation of computer-aided diagnosis and related processing methods
- Statistical methods to determine the size and content of the proposed image databases and permit the comparison of image processing or computer-aided diagnosis methods
- Statistical methodology for evaluating performance of computer-aided diagnosis and image-processing methods

Digital Mammograms May Benefit Some Women: Results from the Digital Mammographic Imaging Screening Trial

http://www.cancer.gov/dmist

As part of its role to evaluate new imaging technologies, CIP funded the Digital Mammographic Imaging Screening Trial (DMIST) to determine whether digital mammography is as good as, or better than, conventional screen-film mammography in detecting breast cancer, the second most common cancer among U.S. women.

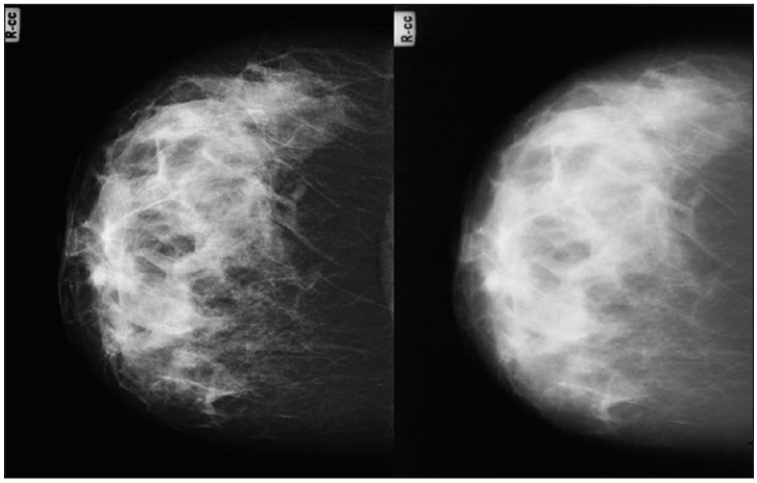
Although only approximately 8 percent of breast imaging units in the United States provide digital mammography, the technology is becoming more common. One of the concerns surrounding greater use of digital mammography is its cost, with digital systems currently costing approximately 1.5 to 4 times more than film systems. Digital mammography may offer advantages over conventional mammography because:

- The images can be stored and retrieved electronically, making long-distance consultations with other mammography specialists easier
- The images can be electronically adjusted by the radiologist, and subtle differences between tissues may be noted
- Digital mammography may reduce the number of necessary follow-up procedures

Standard film mammography has been used for more than 35 years and is very effective, but it is less sensitive for women who have dense breasts, a population at higher risk for breast cancer. Prior studies suggest that approximately 10 to 20 percent of breast cancers detected by breast self-examination or physical examination are not visible by film mammography.

Until DMIST, there were only some limited studies that showed no significant difference in the performance of digital mammography vs. film mammography. DMIST was purposively designed to measure relatively small, but potentially clinically important, differences in diagnostic accuracy between digital and film mammography.

DMIST researchers are also assessing the relative cost-effectiveness of both technologies and their effect on patient quality of life. The American College of Radiology Imaging Network (ACRIN), a research network funded by CIP, is conducting the study.



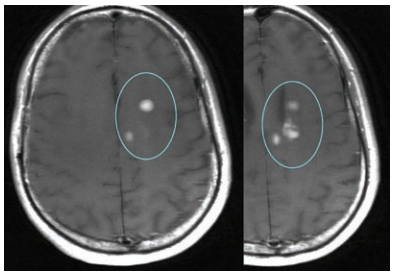
University of North Carolina Lineberger Comprehensive Cancer Center.

A comparison of digital and film mammography (left: digital; right: film). The questionable area, just below the nipple, is more easily visible in the digital image.

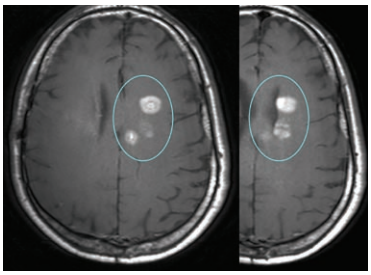
Digital mammography images can be electronically adjusted by the radiologist, and subtle differences between tissues may be noted.

In 2005, results from DMIST showed no difference in detecting breast cancer for the general population of women in the trial. However, women with dense breasts, who are pre- or perimenopausal (women who had a last menstrual period within 12 months of their mammograms), or who are younger than age 50 may benefit from having a digital rather than a film mammogram. The results were reported September 16 in a special online publication of the *New England Journal of Medicine* and at the 2005 annual meeting of ACRIN.

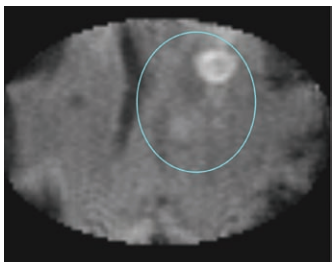
The results of this large clinical trial of about 50,000 women, led by Drs. Etta D. Pisano, University of North Carolina at Chapel Hill, and Edward Hendrick, Northwestern University, will give clinicians better guidance and greater choice in deciding which women would benefit most from various forms of mammography.



30 minutes after gadolinium



24 hours after ferumoxytol



MRI in the operating room
26 hours after ferumoxytol

Magnetic resonance images of a patient with high-grade brain tumors. The ferumoxytol shows larger areas of the three tumors and can also be seen on a special magnetic resonance machine used in the operating room without giving more contrast agent. The larger target volume of the tumors at surgery and the persistent enhancement allows the surgeon to see if all the tumor has been removed during the operation.

Dr. Edward A. Neuwelt, Oregon Health & Science University.

Pisano ED, Gatsonis C, Hendrick E, Yaffe M, Baum JK, Acharyya S, Conant EF, Fajardo LL, Bassett L, D'Orsi C, Jong R, Rebner M; Digital Mammographic Imaging Screening Trial (DMIST) Investigators Group. Diagnostic performance of digital versus film mammography for breast-cancer screening. *N Engl J Med* 2005:353;1773–83.

Pilot Study Evaluates Use of Ferumoxytol in Magnetic Resonance Studies of Brain Tumors

A CIP-funded pilot study at Oregon Health & Science University is investigating the potential role of ferumoxytol in the evaluation of malignant brain tumors. Ferumoxytol is an iron oxide nanoparticle that targets phagocytic cells and can be used for MRI of pathology that has a significant phagocytic component. The investigators compared ferumoxytol imaging, perfusion, and magnetic resonance angiography (MRA) with gadolinium imaging. The results from this pilot study of 12 patients with brain tumors indicated that, after administration of ferumoxytol, the tumors were detectable on magnetic resonance studies at various field strengths, including an intraoperative 0.15-Tesla magnet. In addition, there was less early leakage out of the blood vessels after injection of ferumoxytol in comparison to gadolinium. Further investigations are required to evaluate whether magnetic resonance studies with ferumoxytol would be superior or complementary to studies with gadolinium for assessing tumor perfusion and predicting tumor response to therapy.

Neuwelt EA, Várallyay CG, Manninger S, Solymosi D, Haluska M, Hunt MA, Nesbit G, Stevens A, Jerosch-Herold M, Jacobs PM, Hoffman JM. Potential of ferumoxytol nanoparticle in MR imaging, perfusion, and angiography of CNS malignancy. Manuscript in preparation.

Lung Imaging Database Consortium

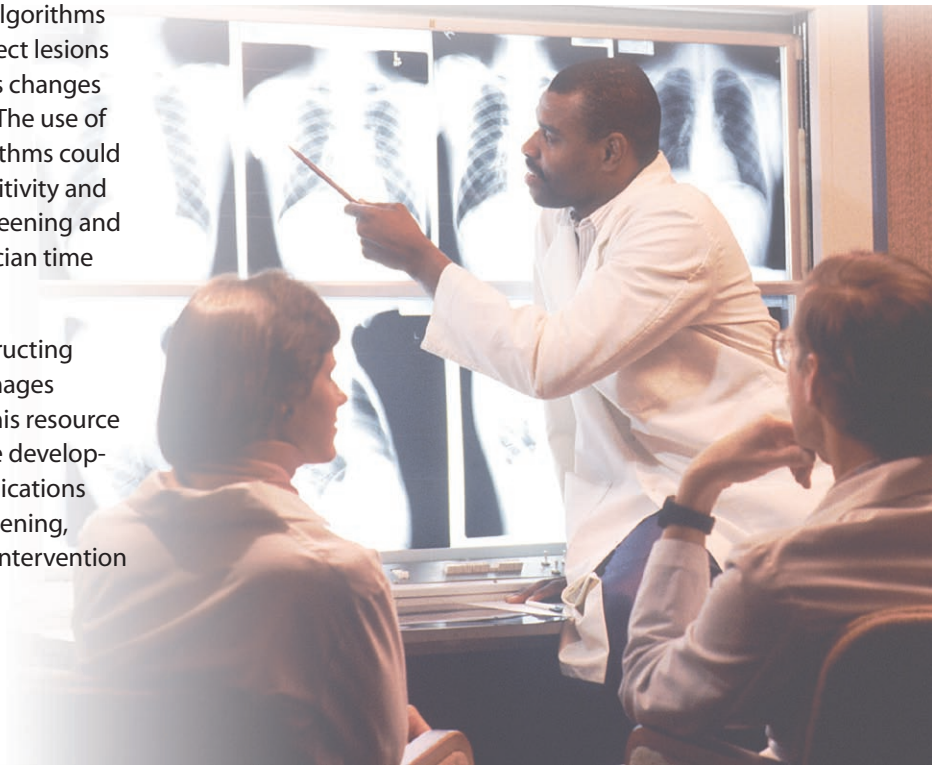
http://imaging.cancer.gov/reportsandpublications/reportsandpresentations/firstdataset

The Lung Imaging Database Consortium (LIDC), funded by CIP, comprises five institutions that are developing consensus guidelines and metrics for the use of spiral CT lung images.

Preliminary clinical studies show that spiral CT scanning of the lungs could play a role in improving early detection of lung cancer in high-risk individuals. However, more clinical data are needed before public health recommendations can be made for population-based spiral CT screening. Image-processing algorithms have the potential to help detect lesions in spiral CT scans and to assess changes in lesions on serial CT studies. The use of such computer-assisted algorithms could significantly enhance the sensitivity and specificity of spiral CT lung screening and lower costs by reducing physician time needed for interpretation.

LIDC is in the process of constructing a database of spiral CT lung images as a test-bed and showcase. This resource will stimulate further database development and thus accelerate applications of imaging to lung cancer screening, diagnosis, and image-guided intervention and treatment.

The database has wide utility as a research, teaching, and training resource. Already available on the LIDC Website via FTP download are two lung cancer cases with CT scans performed at multiple time points during treatment. Nodule markings are contained in .xml files accompanying the scans. More data sets will be presented in the future. Also available is the first data set, containing images of 23 nodules and a boundary definition of the nodules from a screening and diagnostic caseload. This preliminary database may prove to be useful for the evaluation of image segmentation methods. LIDC has plans to provide the final database of 400 cases in summer 2006.



NCI Visuals Online, Bill Branson, photographer.

Virtual Colonoscopy Training Collection

http://nova.nlm.nih.gov/wramc

CIP offers a virtual colonoscopy image database from the National CT Colonography Trial that can be downloaded for training, research, or development of computer-aided diagnostic applications for enhancing or interpreting images. This project is a collaboration with the Walter Reed Army Medical Center Virtual Colonoscopy Center and the NIH National Library of Medicine.

The images comprising the database are DICOM-compliant, meaning that they adhere to standards for Digital Imaging and Communications in Medicine developed jointly by ACR and NEMA.

NCI Visuals Online, Bill Branson, photographer.

This database currently provides 52 complete cases (26 with polyps) consisting of three-dimensional CT data, several two-dimensional images, pathology reports, virtual and optical colonoscopy reports, and optical colonoscopy video.

National Forum on Biomedical Imaging in Oncology

http://imaging.cancer.gov/NewsAndMeetings/meetings

The National Forum on Biomedical Imaging in Oncology (NFBIO), cosponsored by NCI, NEMA, FDA, and CMS, facilitates partnerships between researchers, the imaging industry, and government agencies. The goal is to address new biomedical opportunities and challenges in oncology and to focus on the regulatory, coverage, and reimbursement issues for established technologies to improve patient diagnosis and care. The two-day meeting concentrates on a different topic each time it is held. Planning is under way for a 2007 meeting.

Interagency Council on Biomedical Imaging in Oncology

http://imaging.cancer.gov/programsandresources/specializedinitiatives/ICBIO

In informal, confidential meetings, the Interagency Council on Biomedical Imaging in Oncology (ICBIO) brings representatives of NCI, FDA, and CMS together with technology developers. Developers receive advice from a multiagency perspective on the spectrum of scientific, regulatory, and reimbursement issues related to commercializing new imaging devices or technologies.

CANCER THERAPY EVALUATION PROGRAM

The Cancer Therapy Evaluation Program fosters collaborations within the cancer clinical research community and works extensively with the pharmaceutical and biotechnology industries.

OVERVIEW

The death rate from all cancers combined has been decreasing in the United States since 1991, and since 2003 the decrease has been large enough to outpace the growth and aging of the population, reducing the actual number of cancer deaths—a remarkable turn in the decades-long fight against cancer.

This milestone has been achieved, in part, because therapeutic and preventive interventions to fight cancer are working. One key to the success of these interventions is that they were tested rigorously in the clinic. Clinical trials are the mechanism for testing new approaches for cancer prevention, diagnosis, and treatment. More than 1500 NCI-sponsored clinical trials are conducted annually, and some 900 treatment trials are sponsored by the Cancer Therapy Evaluation Program (CTEP) within the Division of Cancer Treatment and Diagnosis (DCTD).

CTEP is organized into nine offices and branches:

- Office of the Associate Director
- Clinical Grants and Contracts Branch
- Clinical Investigations Branch
- Clinical Trials Monitoring Branch
- Investigational Drug Branch
- Pharmaceutical Management Branch
- Protocol and Information Office
- Regulatory Affairs Branch
- Office of AIDS Malignancy Program

Not only does CTEP identify promising agents for evaluation, but also it identifies biomolecular characteristics of malignant

Dr. Michaele C. Christian, Associate Director

Michaele Chamblee Christian, M.D., was appointed Associate Director of the Cancer Therapy Evaluation Program of DCTD in 1997. She previously worked in the Investigational Drug Branch overseeing the clinical development of novel anticancer drugs. In 1995, she established NCI's Clinical Trials Monitoring Branch, which oversees quality assurance and compliance for hundreds of NCI clinical trials.

Dr. Christian received her M.D. from Georgetown University School of Medicine, graduating summa cum laude. Additionally, she completed residency training in internal medicine and fellowships in hematology and oncology at Georgetown. Among numerous awards, Dr. Christian received the Kober Award for highest academic achievement and was elected to Alpha Omega Alpha medical honor society. Her research interests include early therapeutics development, ovarian cancer treatment, clinical trial design, and enhancing participation of underrepresented populations in clinical trials.

Dr. Christian is often asked to speak about new opportunities in clinical research, including accelerating bench to bedside or practical translational research, using clinical trials networks to address broader transdisciplinary research questions, and the growing use of international collaborations to conduct research that addresses global medical needs.

Not only does CTEP identify promising agents for evaluation, but also it identifies biomolecular characteristics of malignant tumors that investigators may be able to exploit clinically.

NCI Visuals Online.

CTEP houses NCI's primary program for evaluating new anticancer treatments. It also provides and tracks experimental agents for clinical trials run by other NCI components. During fiscal year 2005, CTEP:

- Managed 942 active clinical trials
- Supervised 127 active Investigational New Drugs (INDs)
- Oversaw the recruitment of nearly 31,000 patients to CTEP-sponsored clinical trials

tumors that investigators may be able to exploit clinically. CTEP accomplishes its goals by administering, coordinating, and funding clinical trials, as well as sponsoring other clinical research. The program fosters collaborations within the cancer research community and works extensively with the pharmaceutical and biotechnology industries. CTEP also reaches out to patients and advocates to help establish research priorities. The program administered 399 grants in 2005 and played a role in 942 open clinical trials.

Combining Targeted Therapies and the Critical Molecular Pathways Project

A high priority for CTEP has been combining molecularly targeted agents to achieve optimal treatment effects. To that end, CTEP has initiated a proof-of-principle project called Critical Molecular Pathways to define a series of clinical trials to evaluate the concept of enhanced activity with rational molecular combinations. CTEP has also initiated other combination trials of targeted agents.

CTEP staff are seeing proof of principle in the remarkable antitumor activity of novel agents in properly selected patients whose tumors express or are driven by the relevant molecular targets. Researchers have entered a period of great promise in therapeutics development as a result of advances in understanding the molecular biology of the cancer cell, cell signaling pathways, and abnormal processes associated with the malignant phenotype.

Intellectual Property Rights

CTEP also has developed standard clauses concerning intellectual property, which will allow drugs from two different companies to be combined in a clinical trial in a way that will preserve the interests of each company while allowing this critical research to move forward. Intellectual property and liability concerns can slow progress in developing trials with agents from more than one company, either in trials with multiple single agent arms or those testing combination regimens. CTEP has played an important role in facilitating collaborations within the private sector without the need for additional bargaining between the parties. CTEP developed standard language now used in all agreements with industry concerning how data are to be shared and how companies may benefit from any invention that may arise using drug combinations.

Both the scientific and regulatory components of CTEP have worked aggressively to move combination therapies forward. Clinical trials are being conducted in several tumor types, including renal cell carcinoma, melanoma, glioblastoma, and cancers of the lung, ovary, pancreas, head and neck, colon, and breast.

Clinical Trials Cooperative Group Program

http://ctep.cancer.gov/resources/coop2.html

CTEP supports 11 organizations conducting cancer treatment trials through the Clinical Trials Cooperative Group Program. Emphasis is placed on the development and conduct of large, multicenter, randomized phase III studies. Although the program's mission encompasses a wide variety of investigational efforts, the cooperative groups do not replace funding mechanisms for more narrowly focused research project grants, such as RO1 and PO1 grants or U01 and U19 cooperative agreements.

Cooperative groups consist of networks of researchers who develop and conduct cancer treatment clinical trials.

Through the Children's Oncology Group's network of member institutions, children with cancer, regardless of where they live, can access state-of-the-art therapies and the collective expertise of world-renowned pediatric specialists.

The Clinical Trials Cooperative Group Program reaches scientists and patients throughout the nation:

- In 2005, of all the new patients accrued to CTEP-sponsored trials, about 27,000 entered into cooperative group studies
- 12,000 new patients are evaluated in correlative laboratory studies each year, and many times that number receive follow-up evaluations
- Thousands of investigators participate in cooperative group protocols

Each cooperative group receives support so that it can generate trials compatible with its particular areas of interest and expertise. Unlike most other NIH cooperative clinical trials efforts, the cooperative groups' funding is not linked to a specific clinical trial.

CTEP uses the U10 mechanism to fund more than 160 cooperative agreements with the following groups:

- American College of Surgeons Oncology Group (ACOSOG)
- Cancer and Leukemia Group B (CALGB)
- Children's Oncology Group (COG)
- Eastern Cooperative Oncology Group (ECOG)
- European Organisation for Research and Treatment of Cancer (EORTC)
- Gynecologic Oncology Group (GOG)
- National Cancer Institute of Canada (NCIC)
- National Surgical Adjuvant Breast and Bowel Project (NSABP)
- North Central Cancer Treatment Group (NCCTG)
- Radiation Therapy Oncology Group (RTOG)
- Southwest Oncology Group (SWOG)

Pediatric Clinical Trials Cooperative Groups and Consortia

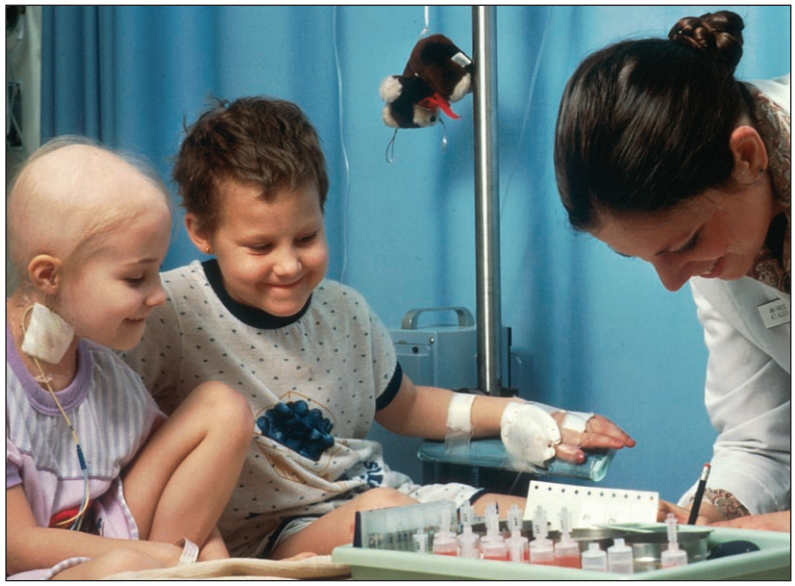
http://ctep.cancer.gov/resources/child.html

CTEP-sponsored pediatric trials are conducted primarily by the Children's Oncology Group (COG), its phase I Consortium, the Pediatric Oncology Branch of the NCI Center for Cancer Research (CCR), the New Approaches to Neuroblastoma Therapy (NANT) Consortium, and the Pediatric Brain Tumor Consortium. CTEP also supports a limited number of pediatric clinical trials through P01 program project grants and through the conventional NCI investigator-initiated research funding, such as R01s.

- **The Children's Oncology Group (COG):** COG is supported by CTEP and conducts clinical trials devoted exclusively to children and adolescents with cancer and develops and coordinates cancer clinical trials at more than 200 member institutions, which include cancer centers of all major universities and teaching hospitals throughout the United States and Canada, as well as sites in Europe and Australia. COG members include more than 5000 cancer researchers dedicated to saving the lives of children with cancer. Through the COG network of member institutions, children with cancer, regardless of where they live, can access state-of-the-art therapies and the collective expertise of world-renowned pediatric specialists.
- **The Children's Oncology Group (COG) Phase I/Pilot Consortium:** The consortium's primary objective is to expeditiously develop and implement

pediatric phase I and pilot studies, thus facilitating the integration of advances in cancer biology and therapy into the treatment of childhood cancer. The consortium includes approximately 20 institutions. Pharmacokinetic and biological correlative studies are key components of the consortium's phase I trials and are increasingly important for new agents with specific molecular targets. The consortium conducts pilot studies of promising multi-agent regimens. These studies are an important step in the integration of new agents into the therapy of specific childhood cancers and require careful monitoring for toxicity and safety. After their initial evaluation for safety in children by the consortium, agents and regimens can be studied within the larger group of COG institutions to determine their role in the treatment of specific childhood cancers.

- **New Approaches to Neuroblastoma Therapy (NANT) Consortium:** This collaborative group brings together university and children's hospitals to test promising new therapies and combination therapies for high-risk neuroblastoma. The group is closely linked with laboratory programs developing novel therapies for high-risk neuroblastoma. The group conducts limited clinical trials, with the goal that promising therapies will be tested nationally.
- **Pediatric Brain Tumor Consortium (PBTC):** This group's primary objective is to rapidly conduct phase I and II clinical evaluations of new therapeutic drugs, intrathecal agents, delivery technologies, biological therapies, and radiation treatment strategies for children 0–21 years of age with primary central nervous system tumors. The PBTC consists of nine leading academic institutions that have extensive experience with tumors of the brain that develop during childhood. Another objective of the PBTC is to develop and coordinate innovative neuroimaging techniques.
- **Pediatric Preclinical Testing Program:** The Pediatric Preclinical Testing Program assists clinical researchers in selecting study agents and combination therapies that are most likely to be effective for childhood solid tumors and leukemias. Some correlations have been observed between preclinical antitumor activity of agents tested in pediatric tumor models and clinical activity for these same agents. Although these examples support the potential predictive value of preclinical models, validation of the models across a broader range



NCI Visuals Online, Bill Branson, photographer.

of pediatric cancers and therapeutic agents is needed. In 2005, plans were made to test 12 new agents against a molecularly characterized panel of childhood cancers each year.

Office of AIDS Malignancy Program

http://ctep.cancer.gov/resources/aidsmalignancy

The Office of AIDS Malignancy Program is designed to support extramural HIV and AIDS malignancy research. The office coordinates all AIDS and AIDS oncology efforts across NCI, including the development of extramural initiatives and AIDS co-funding agreements. Projects being managed include the AIDS and Cancer Specimen Resource, the Women's Interagency HIV Study, the Multicenter AIDS cohort study, and the AIDS International Training and Research Program. The office works closely with the Centers for AIDS Research (CFAR) at NIH, providing administrative and research support for AIDS research projects.

The programs emphasize the importance of collaboration between disciplines and between basic and clinical investigators, of research in which laboratory discoveries are translated into clinical practice, and of research on prevention and behavioral change.

Improving the Clinical Trials System

In addition to implementing recommendations of the Clinical Trials Working Group (http://integratedtrials.nci.nih.gov/), CTEP is making other changes to accelerate the development of new interventions.

CTEP has established the following priorities:

- Accelerating therapeutics development by:
  - Speeding the concept approval process by meeting with cooperative group phase III investigators, as well as partners within the Food and Drug Administration (FDA) and industry, to resolve clinical trial issues in a rapidly scheduled joint meeting and discussion process rather than in a time-consuming iterative review process
  - Decreasing the time from concept approval to protocol implementation by developing joint Protocol Development Teams with the cooperative groups
- Increasing the transparency and expertise of the CTEP review process by engaging external scientists and advocates in the review of all concepts for phase III trials
- Expanding access to clinical trials through continued growth of the Cancer Trials Support Unit (www.ctsu.org)
- Continuing improvement of the informatics infrastructure that supports clinical trials by continuing development of clinical trials standards, including the common toxicity criteria and common data elements, and by the development and pilot implementation of a remote data capture system for the collection of clinical trial data

The following is a list of high-priority trials sponsored by CTEP. They address renal cell cancer, chronic myelogenous leukemia, glioma, and melanoma.

A Randomized, Double-Blind Phase III Trial of Adjuvant Sunitinib versus Sorafenib versus Placebo in Patients with Resected Renal Cell Carcinoma

There is currently no known effective adjuvant therapy for patients with localized kidney cancer; those who undergo resection remain at risk for relapse. This CTEP-sponsored trial, begun in 2006, represents the first randomized phase III renal adjuvant study in over a decade. It involves the cooperation of two competing pharmaceutical companies—Bayer and Pfizer—in the phase III evaluation of recently approved agents with documented renal carcinoma activity.

Sorafenib and sunitinib, agents that inhibit the formation of tumor blood vessels among other things, were approved by FDA in late 2005 and early 2006, respectively. Intermediate and high-risk renal cell carcinoma patients whose cancerous kidneys have been removed will be accrued to the study and randomized to three treatment arms (sorafenib, sunitinib, or placebo) for 54 weeks. The trial will include translational studies that may identify molecular profiles associated with response. This trial will collect and store kidney tissue removed at surgery.

The trial is slated to open in the first quarter of 2006, within a few months of the drugs' approval by FDA for treatment of advanced renal cancer.

A Phase IIb Study of Molecular Responses to Imatinib, at Standard or Increased Doses, or Dasatinib for Previously Untreated Patients with Chronic Myelogenous Leukemia (CML) in Chronic Phase

http://www.cancer.gov/clinicaltrials/SWOG-S0325

Contacts:
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This trial, a Southwest Oncology Group study financed by CTEP and known as S0325, will assess the activity of dasatinib, a promising new oral targeted therapy in

the front line treatment of chronic myelogenous leukemia (CML). Dasatinib has been shown to be effective in CML patients who are resistant or refractory to imatinib. The study is designed with three arms including imatinib treatment at standard and increased doses. Results of the trial may influence the standard of care for CML patients and will provide insights into trial designs for future CML studies that may include combinations of dasatinib and imatinib.

Phase II Pilot Trial of Sorafenib Plus Interferon Alpha-2b in Metastatic Renal Cell Cancer

http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=398171&version=HealthProfessional&protocolsearchid=2210776

This early phase trial, known as DUMC-6258-04-9R0 and being conducted by Duke University and University of North Carolina investigators under CTEP sponsorship, is assessing a combination regimen of two active agents—sorafenib and interferon (INF)—against renal cell carcinoma. The combination rationale was based on the potential for sorafenib-induced potentiation of INF-mediated antiangiogenic and antiproliferative activity. The objective response rate (34 percent) noted in this limited patient cohort represents a significant improvement over single-agent sorafenib (2 percent) or INF (< 10 percent) and may have a beneficial effect on progression-free survival and possibly overall survival in patients. This and other combination strategies involving sorafenib that CTEP is using may lead to significant dividends with respect to identifying promising new therapies for renal cell cancer.

Targeted Therapy Combinations in Glioma, Melanoma, and Renal Cell Cancer

CTEP has initiated about a dozen early phase trials testing various novel combinations of targeted agents for the treatment of three tumor types—glioma, melanoma, and renal cell cancer. The doublet combinations encompass a variety of strategies to intersect signaling via interruption of horizontal or vertical signaling pathways as well as incorporating antiangiogenesis therapies that have proven successful in the treatment of solid tumors. These studies will provide significant insights into the efficacy and potential toxicities of targeted agent combinations; as part of this initiative, a translational studies program is being implemented that will collect samples from patients entered in these trials.

It is clear that the development of better cancer therapeutics has improved the prognosis and quality of life for those who are diagnosed with cancer. During the early 1950s, the overall cure rate for cancer was 33 percent. In 1976, half of all cancer patients survived more than five years after diagnosis. In 2005, closer to two-thirds are alive five years after they learn they have cancer. The NCI's goal is to reduce further the cancer-related suffering and death by 2015, and CTEP is well suited to help achieve this goal.

Clinical Cancer Therapy and Prevention Research

Program Announcement:
PA-04-046: http://grants.nih.gov/grants/guide/pa-files/PA-04-046.html
(expiration date 11/2/2006)

Contact:
Roy Wu, M.D.
301-496-8866, wur@ctep.nci.nih.gov

This CTEP announcement will provide selected investigators with up to five years of support for new intervention studies and trials. At present, the traditional R01 research grant mechanism is underutilized by clinical investigators who perform translational research. CTEP has responded to this research gap by putting in place grants using the R01 mechanism to support translational clinical studies and trials. This initiative will encourage clinical investigators to conduct clinical therapeutic and preventive studies and trials that can move preclinical discoveries and advances in basic biology and drug development into the clinic.

Correlative Studies Using Specimens from Multi-Institutional Treatment and Prevention Trials

Program Announcement:
PA-05-062: http://grants.nih.gov/grants/guide/pa-files/pa-05-062.html
(expiration date 3/2/2008)

Contact:
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301-496-8866, wur@ctep.nci.nih.gov

CTEP, along with the Cancer Diagnosis Program (CDP) and the Cancer Biomarkers Research Group (CBRG), cooperatively sponsors this funding opportunity to support correlative studies that use tumor specimens collected during multi-institutional clinical trials. This funding opportunity uses the R21 and R01 award mechanisms.

Investigators who apply for funding should propose correlative studies that use trial-related tumor specimens to compare genetic variations and molecular changes and to monitor drug resistance, therapeutic effectiveness, and patient outcomes. These studies should evaluate new cancer interventions by using these tumor tissue resources and accumulated clinical trial results for better cancer risk assessment, early detection, and prediction of response to various cancer therapies and prevention strategies.

Continuing progress in basic cancer research and drug development has led to discoveries of new agents and approaches for molecular targeting in novel cancer therapies.

Quick-Trials for Novel Cancer Therapies: Exploratory Grants

Program Announcement:
PAR-04-155: http://grants.nih.gov/grants/guide/pa-files/par-04-155.html
(expiration date 12/10/2007)

Contact:
Roy Wu, M.D.
301-496-8866, wur@ctep.nci.nih.gov

Continuing progress in basic cancer research and drug development has led to discoveries of new agents and approaches for molecular targeting in novel cancer therapies. These new agents and approaches suppress tumor growth through various mechanisms, such as cell cycle control, activation of tumor suppressor genes, essential signal pathway blockage, tumor vaccines, and tumor microenvironment modification.

Some of these novel approaches and agents are ready to be tested in the clinic with new tools and laboratory analyses that allow investigators to ascertain how specific targets are affected by therapy. CTEP, through this initiative, known as Quick-Trials because projects will be funded using the developmental R21 grant mechanism, seeks to rapidly translate these exciting discoveries into clinical practice by providing investigators with rapid access to support for pilot, phase I, and phase II clinical trials as well as support for patient monitoring and laboratory studies linked to a cancer clinical trial.

Exploratory Investigational New Drug Studies

Exploratory IND studies, which are also called phase 0 trials, will facilitate targeted therapies being tested in patients earlier in the drug development process. These trials are an integral part of the new joint early therapeutics development program, the latest collaborative effort between DCTD and CCR. This initiative uses pharmacokinetic and pharmacodynamic principles to streamline the development of novel cancer therapeutics by rapidly screening new drugs in humans before making a commitment in time and resources to a full therapeutic development plan.

CTEP investigators provide clinical trial expertise, a national clinical development infrastructure, and a relationship with pharmaceutical companies to the new exploratory IND trials. These studies will perform first-in-human, or mini-, trials that will validate the initial scientific rationale of a new drug by gathering pharmacological data directly from human volunteer patients. CTEP's role will be to provide the clinical development. Other DCTD programs also are involved in this joint venture, including the Developmental Therapeutics Program, the Cancer Diagnosis Program, the Cancer Imaging Program, and the Radiation Research Program.

Industry Collaborations

CTEP is in a unique position to facilitate nonclinical and clinical studies involving combinations of investigational anticancer treatments, especially when the agents are developed by more than one pharmaceutical company. At present, CTEP has more than 150 active INDs, and almost 100 of these are being co-developed with members of industry.

Industry Collaborators	Agent Name
Abbott Laboratories	A-861695 (NSC#737664)
Aeterna Laboratories	AE-941 shark cartilage extract (NSC#706456)
AOI Pharmaceuticals	KRX-0401 (Perifosine®) (NSC#639966) O-6-benzylguanine (NSC#637037)
AstraZeneca Pharmaceuticals LP	AZD0530 AZD2171 (NSC#732208) Anastrozole Fulvestrant (Faslodex®) (NSC#719276) AZD1839 (gefitinib, Iressa®) (NSC#715055)
Bayer Corporation	BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate) (NSC#724772)
Berlex, Inc.	Alemtuzumab (Campath®) (NSC#715969) Granulocyte-macrophage colony-stimulating factor (GM-CSF)

Industry Collaborators	Agent Name
Biogen Idec	Rituximab monoclonal antibody C2B8 anti-CD20, chimeric (Rituxan®) (NSC#687451) In2B8/Y2B8 radiolabeling kit (ibritumomab tiuxetan, Zevalin®) (NSC#710085)
BioNumerik Pharmaceuticals, Inc.	BNP7787 (Tavocept®) (NSC#716976)
BioVest International, Inc.	Lymphoma Ig vaccine-KLH (NSC#659770)
Bristol-Myers Squibb	BMS-214662 farnesyltransferase inhibitor (NSC#710086) BMS-275291 (MMPI) (NSC#713763) BMS-354825 (NSC#732517) BMS-247550 (epothilone B) (NSC#710428) XK469
Celgene Corporation	CC-5013 (lenalidomide, Revlimid®) (NSC#703813) Thalidomide (Thalomid®) (NSC#66847)
Collgard Biopharmaceuticals, Ltd.	Halofuginone, intravenous solution
CuraGen	PXD101 (NSC#726630)
Eisai, Inc.	E7389 (halichondrin B analog) (NSC#707389)
Elsohly Laboratories, Inc.	Artemisinin
EMD Pharmaceuticals	EMD 273063 (hu14.18-IL-2 fusion protein) (NSC#721298)
EntreMed, Inc.	2-methoxyestradiol (NSC#659853)
Exelixis, Inc.	XL119 (becatecarin, rebeccamycin analog) (NSC#655649)
F. Hoffmann-La Roche, Ltd.	All-trans retinoic acid
GeminX Biotechnologies	GX015-070 (NSC#729280)
Genentech, Inc.	Bevacizumab (Avastin®) (NSC#704865) Trastuzumab (Herceptin®) (NSC#688097)
Genta, Inc.	G3139 (oblimersen, Genasense®) (NSC#683428)
GlaxoSmithKline	506U78 (nelabarine) (NSC#686673) GW572016 (lapatinib) (NSC#727989) GW786034 (NSC#737754) SB-715992 (ispinesib) (NSC#727990) Topotecan (Hycamtin®) (NSC#609699)
Gloucester Pharmaceuticals, Inc.	FK228 (depsipeptide) (NSC#630176)
ImClone Systems, Inc.	Cetuximab C225 chimeric monoclonal antibody (Erbitux®) (NSC#714692)
Infinity Pharmaceuticals	IPI-609
Introgen Therapeutics, Inc.	Adeno-p53 (Ad5CMV-p53); Advexin® (NSC#683550)
Ipsen	SJG-136 (NSC#694501)
Ishihara Sangyo Kaisha, Ltd.	Benzoylphenylurea (BPU) (NSC#639829)

Industry Collaborators	Agent Name
Johnson & Johnson	R115777 (tipifarnib, Zarnestra®) (NSC#702818)
Kosan Biosciences, Inc.	17-AAG (NSC#330507) 17-DMAG (NSC#707545)
Kyowa Pharmaceuticals, Inc.	UCN-01 (NSC#638850)
Lorus Therapeutics, Inc.	GTI-2040 (NSC#722929)
Medarex, Inc.	Anti-CTLA4 antibody
MedImmune, Inc.	MEDI-522 (Vitaxin®) (NSC#719850)
Merck and Company, Inc.	Suberoylanilide hydroxamic acid (SAHA, vorinostat) (NSC#701852)
Merck KGaA	EMD 121974 (cilengitide) (NSC#707544)
MGI Pharma, Inc.	Decitabine (5-aza-2'-deoxycytidine) (NSC#127716) MGI-114 (irofulven) (NSC#683863)
Millennium Pharmaceuticals, Inc.	MLN 518 (NSC#726292) PS-341 (bortezomib, Velcade®) (NSC#681239)
Novartis	STI571 (imatinib, Gleevec®) (NSC#716051) Zoledronic acid (Zometa®) (NSC#721517)
Oncolytics Biotech, Inc.	Reolysin® human reovirus formulation (NSC#729968)
Ortho Biotech	Liposome encapsulated doxorubicin (Doxil®) (NSC#620212) Orthoclone OKT®3 (muromonab-CD3) (NSC#618843)
OSI Pharmaceutical, Inc.	OSI-774 (erlotinib, Tarceva®) (NSC#718781)
Pfizer	Exemestane (Aromasin®) (NSC#713563) SU11248 (sunitinib, Sutent®) Irinotecan (CPT-11, Camptosar®) (NSC#616348)
Pharmacyclics, Inc.	Motexafin gadolinium (Xcytrin®) (NSC#695238) Motexafin lutetium (NSC#695239)
Pharmion Corporation	Azacitidine (Vidaza®) (NSC#102816)
PowderJect	gp100 cDNA /gold (plasmid vector pWRG1644) (NSC#708477)
Praecis Pharmaceuticals	PPI-2458 (fumagillin analog) (NSC#720735)
Protherics, Inc.	Carboxypeptidase G2 (CAMR) (NSC#641273)
Reata Pharmaceuticals, Inc.	CDDO (NSC#711193)
Roche Laboratories	Capecitabine (Xeloda®) (NSC#712807)
Sanofi-Aventis	Flavopiridol (alvocidib) (NSC#649890) Tirapazamine (NSC#130181) VEGF-Trap® (NSC#724770) Oxaliplatin (Eloxatin®) (NSC#266046)
Schering AG	MS-275 (NSC#706995)

Industry Collaborators	Agent Name
Schering OY	Clodronate (Bonefos®) (NSC#713466)
Schering-Plough Corporation	Interferon alfa-2b (Intron-A®) (NSC#377523)
Searle	SC-55494 (Synthokine®)
Seattle Genetics	SGN-30 anti-CD30 monoclonal antibody (NSC#731636)
Therion Biologics Corporation	rF-TRICOM (recombinant fowlpox-TRICOM) (NSC#710658) rF-B7.1 (recombinant fowlpox-B7.1) (NSC#679008)
TopoTarget	PXD 101 (NSC#726630)
Vaccine Company	Proteinase 3:PR1 peptide (NSC#698102)
Vion Pharmaceuticals, Inc.	Triapine® ribonucleotide reductase inhibitor (NSC#663249)
Wyeth Pharmaceuticals	CCI-779 (rapamycin analog) (NSC#683864)
Total: 62 Collaborators	**Total: 91 Agents**

Trastuzumab Combined with Chemotherapy Improves Disease-Free Survival for Patients with Early-Stage Breast Cancer

The combination of the targeted agent trastuzumab (Herceptin®) and standard chemotherapy cuts the risk of *Her2*-positive breast cancer recurrence by more than half compared with chemotherapy alone. The result comes from two large, CTEP-sponsored, randomized trials testing, as adjuvant therapy, a trastuzumab/chemotherapy combination against chemotherapy alone in women with invasive, early stage, *Her2*-positive breast cancer.

Trastuzumab, manufactured by Genentech, Inc., specifically targets the HER2 protein, which is overexpressed in approximately 20 to 30 percent of breast cancers. *Her2*-positive tumors are not only more aggressive than tumors that do not overproduce HER2 protein, but also they are more likely to recur. Trastuzumab is approved by FDA for use in women with *Her2*-positive metastatic breast cancer. These are the first trials to show a benefit for trastuzumab as breast cancer adjuvant therapy.

Additional analyses will allow the trial leaders to perform a more thorough risk/benefit analysis. In the interim analysis, the likelihood of congestive heart failure (CHF) in women receiving the trastuzumab/chemotherapy combination was increased by 3 to 4 percent, compared with a less than 1 percent CHF rate in those treated with chemotherapy alone.

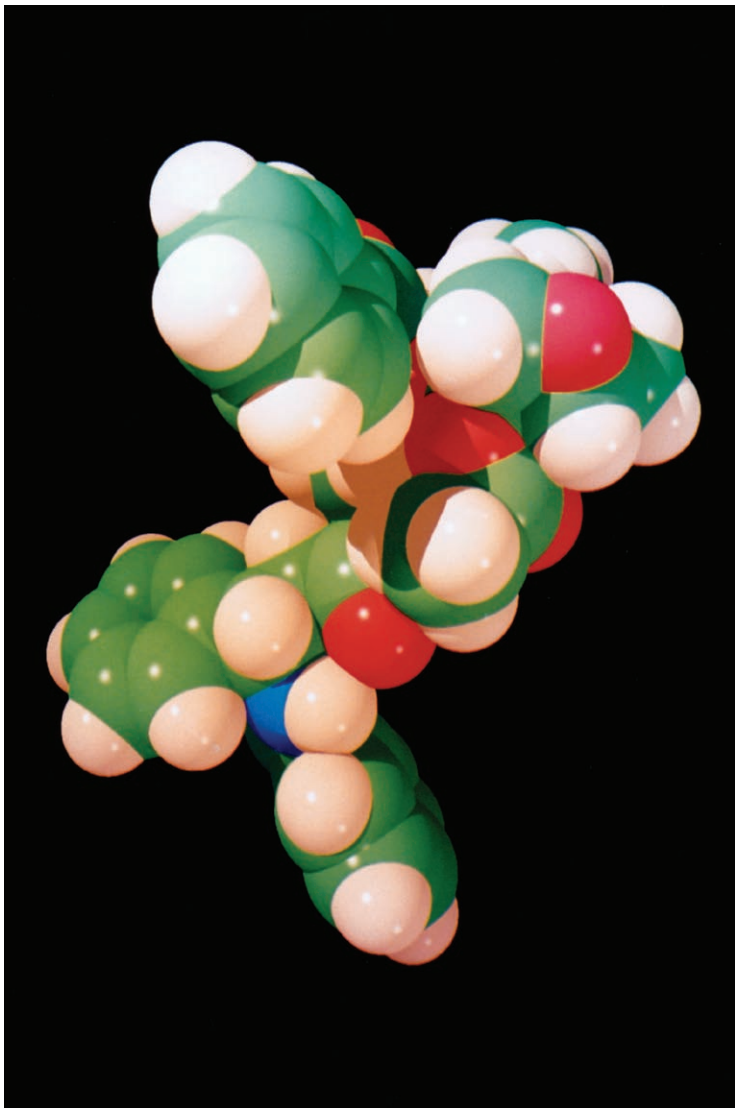
Romond EH, Perez EA, Bryant J, Suman V, Geyer CE, Davidson N, Tan-Chiu E, Martino S, Swain SM, Kaufman P, Fehrenbacher L, Pisansky T, Vogel V, Kutteh LA, Yothers G, Visscher D, Brown AM, Jenkins R, Seay TE, Mamounas E, Abrams J, Wolmark N. Joint analysis of NSABP-B-31 and NCCTG-N9831. Presented at: Advances in Monoclonal Antibody Therapy for Breast Cancer Scientific Symposium, ASCO Annual Meeting. May 13–17, 2005. Orlando, FL.

Oncotype DX® Test Predicts Breast Cancer Recurrence Risk and Chemotherapy Benefit

Results from several studies validate that a new test can predict the risk of breast cancer recurrence in a sizable group of patients; the studies also appear to identify which of those patients will benefit most from chemotherapy. The studies were heralded by researchers as an important moment in the move toward individualized cancer care. Central to the investigations is a test, Oncotype DX®, which analyzes the expression of a 21-gene panel in biopsy samples from women with estrogen-dependent, lymph-node negative breast cancer, which accounts for more than 50,000 breast cancer cases in the United States each year.

Confirmation of earlier data on the ability of the assay—developed by Genomic Health, Inc., which, along with CTEP and the DCTD Cancer Diagnosis Program, funded some of the studies—to accurately predict recurrence risk was

The Oncotype DX® assay is considered a breakthrough because it can be used on tumor specimens that are fixed and embedded in paraffin.



NCI Visuals Online, George McGregor, photographer.

A space-filling model of a paclitaxel (Taxol®) molecule. A CTEP-sponsored study showed that when paclitaxel is combined with the antiangiogenesis drug bevacizumab, the progression of breast cancer is slowed.

needed. What was lacking, some breast cancer researchers had argued, was data on whether the assay could forecast chemotherapy benefit, which would help guide treatment decisions.

An analysis of biopsy samples from patients in the tamoxifen plus chemotherapy arm of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-20 study using the assay, Oncotype DX®, appears to answer that question. Patients with high recurrence scores on the assay (31 or higher on a 0 to 100 scale) had a significant benefit from chemotherapy (27.6 percent absolute increase in distant relapse-free-survival at 10 years). Patients with low recurrence scores (18 or lower), on the other hand, essentially received no benefit from chemotherapy. According to these results, about one-quarter of patients with node-negative, estrogen receptor-positive breast cancer are at high risk for recurrence and would benefit from chemotherapy in addition to tamoxifen, while about half of patients are at low risk and would not.

Other studies using Oncotype DX® on archival samples from NSABP showed that the actual breast cancer recurrence rate was 6.8 percent at 10 years in patients with low recurrence scores, 14.3 percent in the intermediate-score group, and 30 percent in the high-score group.

The Oncotype DX® assay is considered a breakthrough because it can be used on tumor specimens that are fixed and embedded in paraffin. This has been

technically difficult to do because RNA is altered when stored in this fashion. Researchers at Genomic Health, Inc., however, developed a method for performing genetic analyses that allows use of the altered RNA, making testing of patient samples readily accessible to clinicians in all settings. Currently, the California-based company is the only facility licensed to perform the test.

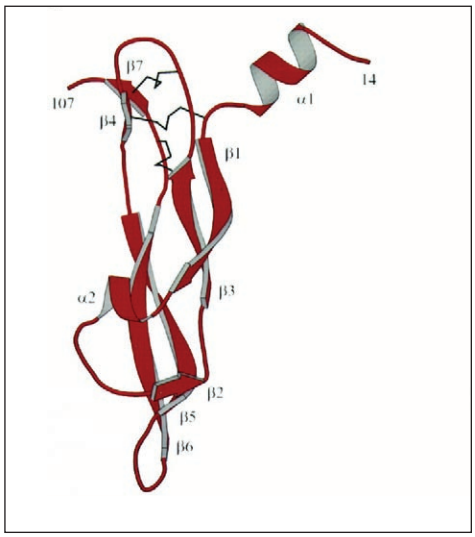
DCTD will conduct a major randomized, prospective clinical trial involving all the clinical trials groups that study breast cancer. The trial will use Oncotype DX® to identify patients with recurrence scores in the intermediate range to determine whether they would benefit from chemotherapy.

Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner FL, Walker MG, Watson D, Park T, Hiller W, Fisher ER, Wickerham DL, Bryant J, Wolmark N. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004:351;2817–26.

Paik S, Shak S, Tang G, Kim C, Joo H, Baker J, Cronin M, Watson D, Bryant J, Costantino J, Wolmark N. Expression of the 21 genes in the recurrence score assay and prediction of clinical benefit from tamoxifen in NSABP study B-14 and chemotherapy in NSABP study B-20. Presented at: 27th Annual San Antonio Breast Cancer Symposium. December 8–11, 2004. San Antonio, TX. Abstract #24.

Benefit of Antiangiogenic Therapy in Patients with Breast Cancer

Recent clinical trials have shown that antiangiogenesis drugs—those that inhibit blood vessel growth—can slow progression of colon and lung cancers. Recent preliminary results from a CTEP-sponsored study reveal that the antiangiogenesis drug bevacizumab (Avastin®) has the same effect on recurrent or metastatic breast cancers when combined with the chemotherapy drug paclitaxel (Taxol®).



Proc Natl Acad Sci USA *1997;94;7192–7. Figure 1.*

The receptor-binding domain of VEGF. Bevacizumab works by blocking VEGF.

This study is the first to find a benefit of antiangiogenic therapy in patients with breast cancer and represents a major advance in the treatment of patients with metastatic disease. These results come from the Eastern Cooperative Oncology Group clinical trial E2100, which studied 722 women.

Bevacizumab is a humanized monoclonal antibody approved by FDA to treat metastatic colorectal cancer when combined with chemotherapy. It works by blocking a tumor-released molecule called vascular endothelial growth factor (VEGF). The drug is manufactured by Genentech, Inc., and

provided for use in this clinical trial through a Cooperative Research and Development Agreement with CTEP.

Women in the E2100 trial were randomized to receive paclitaxel either alone or in combination with bevacizumab. On average, those who received the combination saw no worsening of their disease for four months longer than those who received only the paclitaxel.

Miller KD, Wang M, Gralow J, Dickler M, Cobleigh MA, Perez EA, Shenkier TN, Davidson NE. Bevacizumab (anti-angiogenesis) in locally recurrent/metastatic breast cancer. Presented at: Advances in Monoclonal Antibody Therapy for Breast Cancer Scientific Symposium, ASCO Annual Meeting. May 13–17, 2005. Orlando, FL.

Paclitaxel after Doxorubicin Plus Cyclophosphamide as Adjuvant Chemotherapy for Node-Positive Breast Cancer Increases Disease-Free Survival

A primary aim of the CTEP-sponsored National Surgical Adjuvant Breast and Bowel Project trial NSABP B-28 was to determine whether four cycles of adjuvant paclitaxel after four cycles of adjuvant doxorubicin/cyclophosphamide (AC) prolongs disease-free survival (DFS) and overall survival (OS) compared with four cycles of AC alone in patients with resected operable breast cancer and histologically positive axillary nodes. Paclitaxel received following AC significantly reduced the risk of recurrence by 17 percent; DFS at five years was 76 percent for patients randomly assigned to AC followed by paclitaxel compared with 72 percent for those randomly assigned to AC.

Improvement in OS was small and not statistically significant. The addition of paclitaxel to AC resulted in significant improvement in DFS but no significant improvement in OS with acceptable toxicity. Paclitaxel administered sequentially after AC offers a DFS advantage in node-positive breast cancer.

Mamounas EP, Bryant J, Lembersky B, Fehrenbacher L, Sedlacek SM, Fisher B, Wickerham DL, Yothers G, Soran A, Wolmark N. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. *J Clin Oncol* 2005:23;3686–96.

Mamounas E, Bryant JL, Lembersky BC, Fehrenbacher L, Sedlacek SM, Fisher B, Wickerham DL, Yothers G, Soran A, Wolmark N. Paclitaxel (T) following doxorubicin/cyclophosphamide (AC) as adjuvant chemotherapy for node-positive breast cancer: results for NSABP-B-28 (meeting abstract). *Proc Am Soc Clin Oncol* 2003:22;4 (A12).

Letrozole Following Tamoxifen as Extended Adjuvant Therapy in Receptor-Positive Breast Cancer Improves DFS

Despite the proven benefits of tamoxifen therapy, women who have been treated with five years of tamoxifen subsequently experience substantial rates of both new primary tumors and relapses at all sites. The Community Clinical Oncology Program (CCOP) MA.17 trial was designed to determine whether extended adjuvant therapy with the aromatase inhibitor letrozole after tamoxifen reduces the risk of such late recurrences.

In 2003, after preliminary data showed improved DFS among women with estrogen receptor–positive breast cancer

who received letrozole versus placebo following five years of adjuvant tamoxifen, results from the MA.17 clinical trial were announced a year ahead of schedule. At that time, participants in the placebo group were unblinded and offered letrozole. In September 2005, the study team released a more detailed analysis of the drug's efficacy and toxicity up to the time of unblinding.

The updated data from 5170 postmenopausal patients show that after four years of follow-up, 94.4 percent of women who received letrozole survived without disease recurrence, compared with 89.8 percent of those who received the placebo. In general, women who received letrozole and women who took the placebo saw no difference in OS, though the drug did seem to improve overall survival among a subset of women who had positive axillary lymph nodes, as well as those who had taken tamoxifen for more than five years. Letrozole after tamoxifen is well tolerated, but toxic side effects of concern included those related to bone metabolism and cardiovascular disease. However, bone fractures and cardiovascular events occurred equally between the two study groups.

Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, Castiglione M, Tu D, Shepherd LE, Pritchard KI, Livingston RB, Davidson NE, Norton L, Perez EA, Abrams JS, Cameron DA, Palmer MJ, Pater JL. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005:97;1262–71.

Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, Castiglione M, Tu D, Shepherd LE, Pritchard KI, Livingston RB, Davidson NE, Norton L, Perez EA, Abrams JS, Therasse P, Palmer MJ, Pater JL. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003:349;1793–802.

Paclitaxel-Carboplatin-Bevacizumab Represents New Treatment Standard for Metastatic Non-Squamous Non-Small Cell Lung Cancer

A CTEP-sponsored phase III study in patients with advanced non-squamous, non-small cell lung cancer (NSCLC) showed that adding bevacizumab to standard chemotherapy for patients with NSCLC provides a statistically and clinically significant survival advantage with tolerable toxicity.

The study, known as E4599, involved randomizing 842 patients to one of two treatment arms. One patient group received standard treatment—six cycles of paclitaxel and carboplatin. The second group received the same six-cycle chemotherapy regimen with the addition of bevacizumab, followed by bevacizumab alone until disease progression.

Patients who received bevacizumab in combination with standard chemotherapy had a median OS of 12.5 months, compared to patients treated with the standard chemotherapy alone, who had a median survival of 10.2 months. This finding sets a new treatment standard in this population of patients with metastatic NSCLC.

Sandler AB, Gray R, Brahmer J, Dowlati A, Schiller JH, Perry MC, Johnson DH. Randomized phase II/III trial of paclitaxel (P) plus carboplatin (C)

with or without bevacizumab (NSC # 704865) in patients with advanced non-squamous non-small cell lung cancer (NSCLC): an Eastern Cooperative Oncology Group (ECOG) Trial - E4599. *Proc Am Soc Clin Oncol* 2005:23;1090S.

Adding Bevacizumab to Oxaliplatin-Based Chemotherapy Prolongs Survival for Previously Treated Patients with Advanced Colorectal Cancer

Colorectal cancer is the third most common cancer in both men and women in the United States. An estimated 55,170 deaths from colorectal cancer will occur in 2006, accounting for about 10 percent of all cancer deaths in the nation. A recent phase III study, sponsored by CTEP and performed by the Eastern Cooperative Oncology Group, examined high-dose bevacizumab given either alone or in combination with FOLFOX4, an oxaliplatin-based chemotherapy regimen, compared to FOLFOX4 alone, in patients with previously treated advanced colorectal cancer.

A total of 829 patients, all of whom previously had received a fluorouracil-based chemotherapy and irinotecan, were enrolled in the study from November 2001 to April 2003. The bevacizumab-alone arm of the study was closed in March 2003 on the recommendation of the Data Monitoring Committee when review of early results suggested OS for patients in that group might be lower than that of patients treated in the other two groups.

Updated efficacy results from this trial, presented at the 2005 annual meeting of the American Society of Clinical Oncology, demonstrated that high-dose bevacizumab in combination with an oxaliplatin-based chemotherapy regimen is well tolerated and improves OS and progression-free survival in previously treated patients with advanced colorectal cancer.

The bevacizumab/FOLFOX4 approach is now being tested in the adjuvant (postsurgical) setting for colon cancer.

Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, Schwartz MA, Benson AB. High-dose bevacizumab improves survival when combined with FOLFOX4 in previously treated advanced colorectal cancer: results from the Eastern Cooperative Oncology Group (ECOG) study E3200. *Proc Am Soc Clin Oncol* 2005:23;1S.

Oxaliplatin in Combination with a Bolus 5-Fluorouracil/Leucovorin Regimen Reduces Recurrence in Early Stage Colon Cancer

Multiple randomized trials over the last three decades have validated the use of systemic therapy to prolong survival for patients with stage III colon cancer. In one recent study, the CCOP sponsored MOSAIC, a large, randomized clinical trial, which demonstrated that oxaliplatin, when combined with infusional 5-fluorouracil (5-FU) and leucovorin (LV), increased the three-year DFS for patients with early-stage colon cancer compared to standard therapy 5-FU/LV alone. The MOSAIC trial, however, did not address whether oxaliplatin in combination with bolus 5-FU and

Perioperative recovery was faster in the laparoscopic-surgery group than in the open-colectomy group, as reflected by shorter hospital stays and briefer use of parenteral narcotics and oral analgesics.

LV, a less burdensome treatment regimen, would lead to the same improvement in three-year DFS.

Following MOSAIC, CTEP sponsored a trial known as NSABP C-07, which was a randomized prospective study designed to determine whether bolus 5-FU/LV plus oxaliplatin (FLOX) would increase three-year DFS compared to a bolus schedule of 5-FU/LV alone.

More than 2400 patients with early-stage colon cancer were randomized to receive either bolus 5-FU/LV or FLOX. The primary endpoint was DFS. Events were defined as first recurrence, second primary cancer, or death. The median follow-up for patients who were still alive was 34 months. Three-year DFS was 76.5 percent for the group of patients who received FLOX and 71.6 percent for the group who received bolus 5-FU/LV.

The addition of oxaliplatin to weekly bolus 5-FU/LV significantly improved three-year DFS in patients with stage II and III colon cancer. The NSABP C-07 trial confirmed and extended the results of the MOSAIC trial by demonstrating that oxaliplatin in combination with a bolus schedule of 5-FU/LV resulted in a similar benefit for patients with early-stage colon cancer.

Wolmark N, Wieand HS, Kuebler JP, Colangelo L, Smith RE. A phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: results of NSABP Protocol C-07. *Proc Am Soc Clin Oncol* 2005:23;246S.

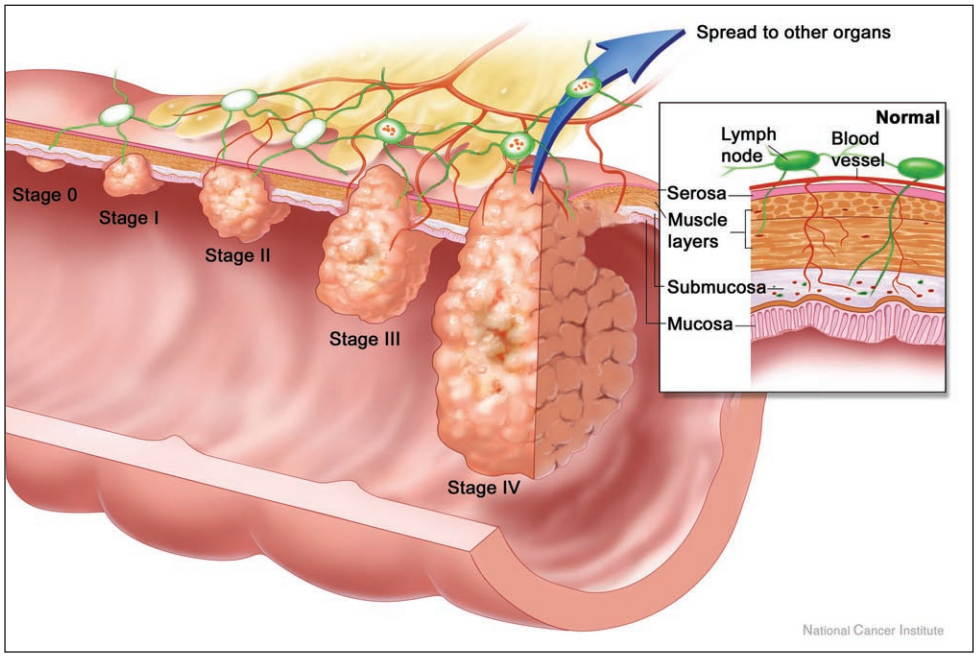
Laparoscopic Colectomy Is an Acceptable Alternative to Open Colectomy for Colon Cancer

The Clinical Outcomes of Surgical Therapy Study Group, through the CTEP clinical trials cooperative groups, conducted a trial at 48 institutions that randomly assigned 872 patients with adenocarcinoma of the colon to undergo traditional open or laparoscopically assisted colectomy performed by credentialed surgeons.

This prospective, randomized trial found that laparoscopic colectomy was a safe alternative to open colectomy for patients with curable colon cancer. The primary endpoint of the study was time to tumor recurrence. Based on a median follow-up of 4.4 years, the rates of tumor recurrence at three years were similar in the two groups—16 percent among patients in the group that underwent laparoscopic surgery and 18 percent among patients who received traditional surgery. There was no significant difference between groups in the time to recurrence or OS for patients with any stage of cancer.

Perioperative recovery was faster in the laparoscopic-surgery group than in the open-colectomy group, as reflected by shorter hospital stays and briefer use of parenteral narcotics and oral analgesics.

Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med* 2004:350;2050–9.



NCI Visuals Online, Terese Winslow, artist.

Colon cancer: Stage 0, Stage I, Stage II, Stage III, and Stage IV. Inset shows serosa, muscle, submucosa and mucosa layers of the colon wall, lymph nodes, and blood vessels.

Oxaliplatin-Based Regimen Permits Successful Resection of Metastatic Colorectal Cancer

A subset of patients with inoperable metastatic colorectal cancer in a study led by the North Central Cancer Treatment Group, N9741, showed that chemotherapy with fluorouracil (5-FU), oxaliplatin, and irinotecan combinations shrunk tumors enough to allow surgical removal of their metastatic disease. 5-FU, oxaliplatin, and irinotecan combinations improve time-to-tumor progression (TTP), objective response, and OS in patients with metastatic colorectal cancer.

Resection of metastatic disease after chemotherapy is possible in a small but important subset of patients with metastatic colorectal cancer, particularly after receiving an oxaliplatin-based chemotherapy regimen, with encouraging OS and TTP observed in these highly selected patients.

Delaunoit T, Alberts SR, Sargent DJ, Green E, Goldberg RM, Krook J, Fuchs C, Ramanathan RK, Williamson SK, Morton RF, Findlay BP. Chemotherapy permits resection of metastatic colorectal cancer: experience from Intergroup N9741. *Ann Oncol* 2005:16;425–9.

Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts SR. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004:22;23–30.

Delaunoit T, Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Findlay BP, Thomas SP, Salim M, Schaefer PL, Stella PJ, Green E, Mailliard JA. Mortality associated with daily bolus 5-fluorouracil/leucovorin administered in combination with either irinotecan or oxaliplatin: results from Intergroup Trial N9741. *Cancer* 2004:101;2170–6.

Rothenberg ML, Meropol NJ, Poplin EA, Van Cutsem E, Wadler S. Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. *J Clin Oncol* 2001:19;3801–7.

Continuous-Infusion Fluorouracil Diminishes Severe Toxicity but Does Not Improve DFS or OS in Adjuvant Treatment of Stage III and High-Risk Stage II Colon Cancer

Modest toxicity and possibly enhanced activity make continuous-infusion fluorouracil (CIFU) an attractive alternative to fluorouracil plus leucovorin (FU/LV) for the adjuvant treatment of colorectal cancer. CTEP sponsored SWOG to perform SWOG-9415 to compare the efficacy of CIFU plus levamisole to FU/LV plus levamisole in the adjuvant treatment of high-risk Dukes' B2 and C1 or C2 colon cancer. At least one grade 4 toxicity occurred in 39 percent of patients receiving FU/LV and 5 percent of patients receiving CIFU. However, almost twice as many patients receiving CIFU discontinued therapy early compared with those receiving FU/LV.

The five-year OS was 70 percent for FU/LV and 69 percent for CIFU. The corresponding five-year DFS was 61 percent and 63 percent, respectively. CIFU had less severe toxicity but did not improve DFS or OS in comparison with bolus FU/LV.

Poplin EA, Benedetti JK, Estes NC, Haller DG, Mayer RJ, Goldberg RM, Weiss GR, Rivkin SE, Macdonald JS. Phase III Southwest Oncology Group 9415/Intergroup 0153 randomized trial of fluorouracil, leucovorin, and levamisole versus fluorouracil continuous infusion and levamisole for adjuvant treatment of stage III and high-risk stage II colon cancer. *J Clin Oncol* 2005:23;1819–25.

Meta-analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol* 1998:16;301–8.

Sentinel Nodes Predict Survival for Melanoma Patients

Treatment of patients with primary cutaneous melanoma and clinically normal regional lymph nodes has been controversial. Melanoma is more likely to be fatal if it has spread to the nearby lymph nodes. Nevertheless, only 20 percent of melanoma patients turn out to have cancerous lymph nodes; removing all of them as a matter of course can cause significant complications. In this study, a minimally invasive technique called lymphatic mapping and sentinel-node biopsy (LM/SNB)—which looks for cancer in a few nodes first—was better than a watch-and-wait approach in helping melanoma patients whose cancer had spread to the lymph nodes to live longer.

Between 1994 and 2002, the research team enrolled 2001 patients with stage I melanoma in the United States, Europe, and Australia. The patients were randomly assigned to one of two groups. One group (the watch-and-wait group) had surgery to remove the melanoma followed by

Lymphatic mapping and sentinel-node biopsy are rapidly leading to changes in the standard of care for melanoma patients.

regular checkups to look for lymph-node swelling. If spread was detected, patients then underwent surgery to remove all the nearby lymph nodes.

The second group had surgery to remove the melanoma plus LM/SNB to look for cancer in the sentinel nodes. In patients whose sentinel nodes contained cancer, all the nearby lymph nodes were removed soon after sentinel node removal. Patients whose sentinel nodes were cancer-free received no further treatment.

When looking at all patients enrolled in the study—those in the LM/SNB group and those in the watch-and-wait group, regardless of whether cancer was ultimately found in their lymph nodes—patients treated with LM/SNB were 26 percent less likely to have a recurrence of melanoma after five years than those treated with the watch-and-wait approach. Follow-up of study patients will continue for another five years.

A significant survival advantage was seen when looking only at the 20 percent of patients in the study whose lymph nodes were found to have cancer. Among these patients, 71 percent of those treated with LM/SNB and immediate lymph-node removal were alive at five years, compared with 53 percent of those in the watch-and-wait group.

LM/SNB is rapidly leading to changes in the standard of care for melanoma patients.

A follow-up study, MSLT-II, will determine whether complete removal of the regional lymph nodes is of therapeutic benefit in patients with lymph node metastases identified by LM/SNB.

Morton DL, Cochran AJ, Thompson JF, Elashoff R, Essner R, Glass EC, Mozzillo N, Nieweg OE, Roses DF, Hoekstra HJ, Karakousis CP, Reintgen DS, Coventry BJ, Wang HJ; the Multicenter Selective Lymphadenectomy Trial Group. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. *Ann Surg* 2005:242;302–13.

Cisplatin Plus Topotecan Gives Patients with Advanced Cervical Cancer More Time

Women with advanced or recurrent cervical cancer who were treated with a combination of cisplatin (Platinol®) and topotecan (Hycamtin®) lived a few months longer and went longer without their disease progressing than patients who received cisplatin alone. The additional toxicity did not significantly affect their quality of life compared with the cisplatin-only patients.

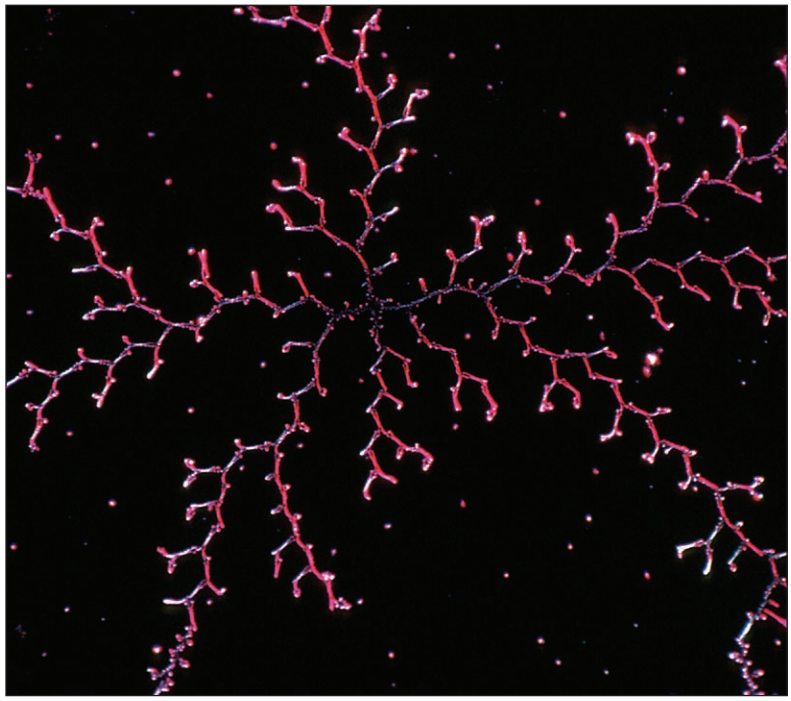
This is the first randomized phase III trial to demonstrate a statistically significant survival advantage for combination chemotherapy in patients with advanced or recurrent cervical cancer.

Between June 1999 and September 2002, researchers enrolled 356 women with advanced (stage IVB) recurrent or persistent cervical cancer, for whom curative surgery and radiation therapy were not suitable. The women were randomly assigned to one of three groups in the CTEP-funded trial run by the Gynecologic Oncology Group and known as GOG 179.

One group of 147 patients received a combination of cisplatin plus topotecan; a second group of 146 patients received cisplatin alone; and 63 patients received a four-drug combination regimen known as MVAC, which includes cisplatin. The MVAC arm of the trial was closed in July 2001 after an unacceptable number of deaths. The trial continued with the other two arms and the MVAC results were excluded from the final analysis.

Thirty-six months after the start of the trial, 129 patients in the cisplatin-only group and 118 patients in the combination group had died. Patients receiving the combination treatment had a statistically significant longer median survival of 9.4 months, compared to 6.5 months for cisplatin alone. The median time until disease progressed was also significantly lengthened in the combination group: 4.6 months compared to 2.9 months in the cisplatin-only group. This means that the risk of both death and disease progression was cut by 24 percent for patients receiving the topotecan plus cisplatin combination.

Fourteen patients in the combination arm saw all evidence of their cancer disappear for at least four weeks, compared to four in the cisplatin-only arm. Another 22 patients in the combination arm had a major improvement in the disease for at least four weeks, compared to 14 in the cisplatin-only arm.

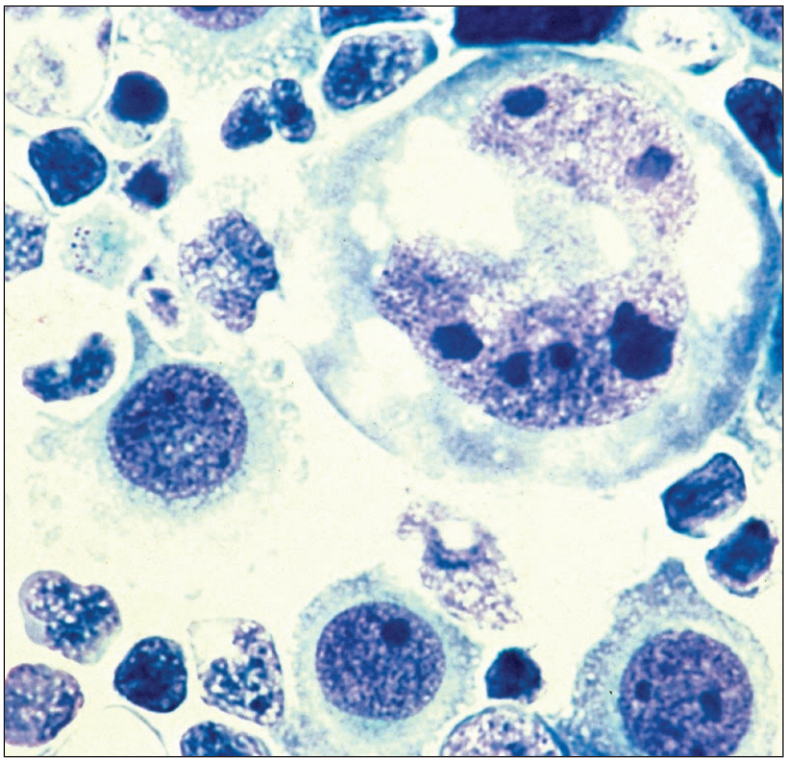


NCI Visuals Online, Larry Ostby, photographer.

Cisplatin crystals. The risk of both death and disease progression was cut by 24 percent for cervical cancer patients who received cisplatin plus topotecan.

Patients in the combination arm had significantly more adverse effects with their blood count and more infections than those taking cisplatin alone. However, when asked a variety of questions about pain and other symptoms associated with the chemotherapy regimen, patients in both groups rated their quality of life about the same.

Long HJ 3rd, Bundy BN, Grendys EC Jr, Benda JA, McMeekin DS, Sorosky J, Miller DS, Eaton LA, Fiorica JV. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. *J Clin Oncol* 2005:23;4626–33.



NCI Visuals Online.

Human lymphoma tumor cells.

Nelarabine Active in T-Cell Leukemia and Lymphoma

In late 2005, FDA approved nelarabine (Arranon®) to treat adults and children with T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL), and whose disease is refractory to or has relapsed following at least two chemotherapy regimens. Nelarabine, which was approved under an accelerated approval mechanism and also granted orphan drug status, is the first drug cleared for these rare indications; an estimated 500 patients per year have relapsed or refractory T-cell malignancies. FDA based the accelerated approval—which requires the drug's manufacturer, GlaxoSmithKline, to conduct additional studies to verify clinical benefit—on two CTEP-sponsored phase II clinical trials. The nelarabine phase II trial in children was conducted by the Children's Oncology Group (COG), whereas the trial in adults was led by the Cancer and Leukemia Group B, in conjunction with the Southwest Oncology Group. In both trials, complete responses were observed in approximately 20 percent of patients. Median OS was 21 weeks in adults and 13 weeks in children. The post-approval study will be a CTEP-funded phase III trial conducted by COG and will include event-free survival at four years as an endpoint.

A COG-conducted pilot study is testing nelarabine upfront in patients with T-ALL or T-LBL who are at increased risk for relapse. This trial recently closed to accrual.

Berg SL, Blaney SM, Devidas M, Lampkin TA, Murgo A, Bernstein M, Billett A, Kurtzberg J, Reaman G, Gaynon P, Whitlock J, Krailo M, Harris MB; Children's Oncology Group. Phase II study of nelarabine (compound 506U78) in children and young adults with refractory T-cell malignancies: a report from the Children's Oncology Group. *J Clin Oncol* 2005:23;3376–82.

Adoptive Immunotherapy Makes Mismatched Hematopoietic Stem Cell Transplantation Possible

Blood or marrow stem cell transplants (BMT) from a donor can cure patients with hematologic malignancies who are not cured by chemotherapy alone. The

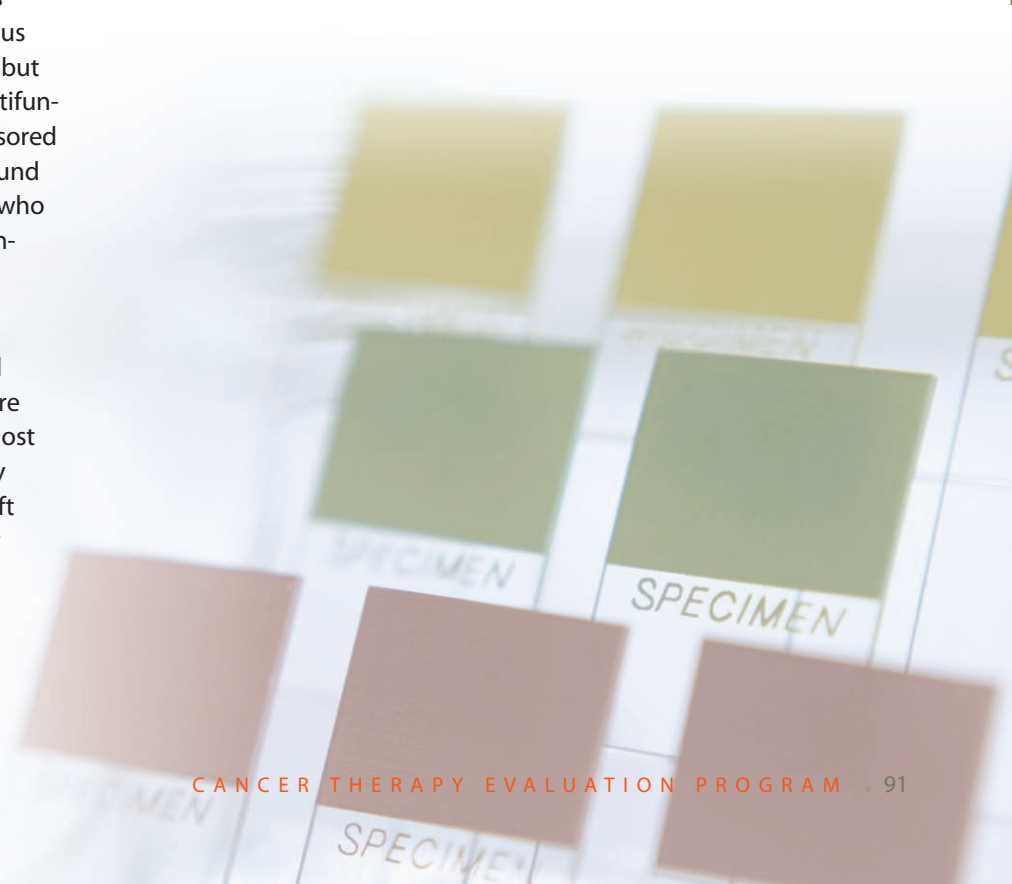
best donor is matched at all six human leukocyte antigens (HLA). Matched siblings make the best donors because they also have a similar genetic background to the patient. Unfortunately, only about 25 percent of patients have a matched sibling donor. In other cases, unrelated donors from the national donor registry are often used. Using three of six HLA-mismatched relatives as donors would save considerable time searching for and verifying the donor, almost everyone would have a donor, and more patients might get to transplant. Unfortunately, the technique used to prevent rejection and graft-versus-host disease in three of six HLA-mismatched transplants also prevents reemergence of the patient's immune system. Patients often die of invasive fungal or viral infections.

Italian investigators funded by NCI developed a method to culture donor cells to remove donor anti-patient cells, thus preventing graft-versus-host disease but leaving the donors with their own antifungal and antiviral cells. In a CTEP-sponsored randomized trial, the investigators found that the immune profiles of patients who received pathogen-specific cells (compared to non-infused patients) were more robust and recovered faster.

Another important aspect of this trial is that immunosuppressive drugs were not needed to prevent graft-versus-host disease. That was done by extensively depleting the donor T cells in the graft before transplant. Overall, 15 of 46, or 33 percent, were event-free survivors (patients did not relapse or die of infection) compared to 50 percent of immunotherapy-treated patients. Median follow-up was two years.

The CTEP grantees who pioneered this methodology understand that in order for it to become widely adopted, it must be reproducible, economical, and practical. Studies in the United States soon will be under way to verify the results.

Perruccio K, Tosti A, Burchielli E, Topini F, Ruggeri L, Carotti A, Capanni M, Urbani E, Mancusi A, Aversa F, Martelli MF, Romani L, Velardi A. Transferring functional immune responses to pathogens after haploidentical hematopoietic transplantation. *Blood* 2005:106;4397–406.



Cancer Trials Support Unit
http://www.ctsu.org

The Cancer Trials Support Unit (CTSU) is designed to streamline and centralize many administrative, financial, and data collection tasks associated with clinical trials. The CTSU provides participating physicians with a single access point to NCI's phase III clinical trials system, facilitating access to protocols, training, and educational information. Highlights of the fully developed system will include:

- Increased physician and patient access to NCI-sponsored clinical trials
- Streamlined and standardized trial data collection and reporting
- Reduced regulatory/administrative burdens on investigators participating in NCI-sponsored cooperative group clinical trials (phases I–III)

In addition to all cooperative group members, the CTSU is now open to physicians and institutions in the United States who are not affiliated with a cooperative group. It supports a national network of physicians participating in NCI-sponsored phase III cancer treatment trials.

Patient Information about NCI Clinical Trials

Finding Clinical Trials
http://www.cancer.gov/clinicaltrials/findtrials

This link provides a detailed yet simple guide entitled "How to Find a Cancer Treatment Trial," which helps patients to:

- Gather the information they need to search for a cancer treatment clinical trial
- Identify a wide variety of sources that list clinical trials
- Learn about clinical trials that are of potential benefit to them
- Ask questions that will help them decide whether or not to participate in a particular trial

Searching for NCI-Sponsored Clinical Trials
http://www.cancer.gov/clinicaltrials/

This is the entry to the database for patients of NCI-sponsored clinical trials. A search form for the database is provided, and an advanced-search feature is also available.

Tracking Clinical Trial Results
http://www.cancer.gov/clinicaltrials/results/

This link provides the means for monitoring progress in cancer care by providing summaries of recently released results from cancer clinical trials that may affect medical care. The summaries are listed in reverse chronological order. Navigation

tools allow searching by keyword or type of cancer. The site also includes links to other patient information materials.

ClinicalTrials.gov
http://clinicaltrials.gov

This Website provides regularly updated information about federally and privately supported clinical research in human volunteers. It includes all diseases and gives information about a trial's purpose, who may participate, locations, and phone numbers for more details.

Community Clinical Oncology Program
http://www.cancer.gov/prevention/ccop

The Community Clinical Oncology Program (CCOP), administered by the NCI Division of Cancer Prevention, is a comprehensive clinical trial mechanism for disseminating the latest cancer prevention and treatment research findings to the community level. A third of all patients accrued to all NCI treatment trials and prevention trials are enrolled at CCOP sites.

Created in 1983, the program works in tandem with CTEP to enable patients and physicians to participate in clinical trials at 61 major research centers in 34 states, the District of Columbia, and Puerto Rico.

In 2005, 50 CCOPs and 13 minority-based CCOPs across the country received funding for participation in NCI-approved trials. Altogether, the program comprises 3645 participating physicians and 415 participating hospitals working on more than 300 active treatment trials and more than 70 active prevention and control trials.

CTEP's Online Resources for Investigators
http://ctep.cancer.gov/resources/index.html

CTEP offers investigators online resources for submitting data and reports, conducting research, and accessing reference materials:

- *Investigators' Handbook* (http://ctep.cancer.gov/handbook/index.html): Offers practical information for oncologists, nurses, pharmacists, research administrators, and data managers about policies and procedures of DCTD with respect to the clinical use of its investigational agents, as well as guidance on protocol writing and submissions, reporting requirements, and agent accountability
- *Common Terminology Criteria for Adverse Events (CTCAE) v2.0 and v3.0:* Standards used to grade, assign attribution, and report adverse effects experienced by patients in clinical trials
- *Adverse Event Expedited Reporting System (AdEERS):* NCI's Web-based system for submitting expedited reports for serious or unexpected events that occur during a clinical trial
- *Common Data Elements (CDE) Dictionary:* A dictionary of terms that are used when collecting patient information for clinical trials or cancer care
- *Clinical Data Update System (CDUS):* The mechanism used when submitting specified data for CTEP-approved clinical trials

- *Clinical Trials Monitoring Branch—Auditing Information System (CTMB-AIS):* A Web-based information system that permits online submission of data collected during quality assurance audits of CTEP-sponsored cooperative group clinical trials

CTEP Online Resources for Industry Collaborators

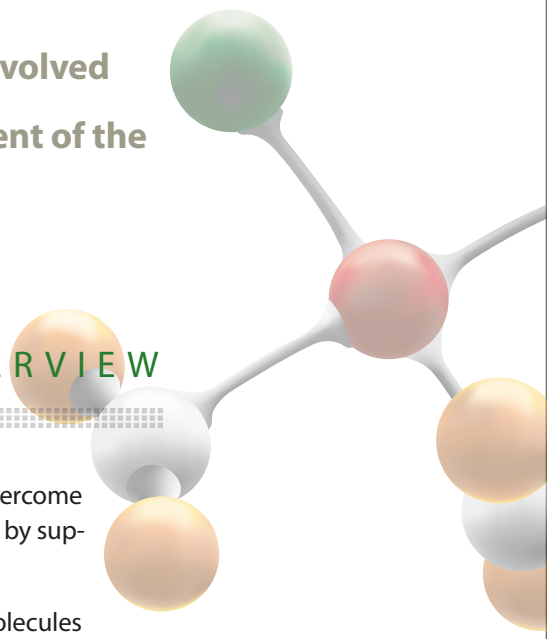
http://ctep.cancer.gov/industry/

CTEP offers a unique combination of resources and expertise to assist industry collaborators in clinical development of new therapeutic agents and the ability to evaluate investigational agents in a wide variety of tumor types and disease settings. This section of the CTEP Website provides information regarding the process for co-developing an investigational anticancer agent with NCI, for example:

- *NCI Standard Protocol Language for Collaborative Agreements:* NCI/DCTD standard language to be incorporated into all protocols involving agent(s) covered by a clinical trials agreement (CTA) or a cooperative research and development agreement (CRADA)
- *CTEP Interaction with Industry:* Provides information regarding the process for co-developing an investigational anticancer agent with NCI and provides links to other online resources to assist with technology development, clinical development resources, and small business research funding
- *Model Agreements:* A collection of 14 model documents in Microsoft Word for use by industry collaborators
- *NCI/Cooperative Group/Industry Relationship Guidelines:* Background information on government-industry collaboration and technology transfer for research involving one or more investigational agents that are proprietary to a pharmaceutical or a biotech company
- *Intellectual Property Option Policy:* A description of the policy governing intellectual property rights and proprietary data protections under government-industry collaborations
- *CTEP Pharmacogenomics Guidelines:* CTEP's guidelines for investigators and pharmaceutical/biotechnology companies concerning the conduct of pharmacogenetics protocols linked to CTEP-sponsored clinical trials

DEVELOPMENTAL THERAPEUTICS PROGRAM

The Developmental Therapeutics Program has been involved in the discovery or development of more than 70 percent of the anticancer therapeutics on the market today.



OVERVIEW

The Developmental Therapeutics Program (DTP) has played an intimate role in the discovery or development of 40 U.S.-licensed chemotherapeutic agents, with the rest coming directly from the pharmaceutical industry.

DTP's roster of drug success stories is impressive. On that list is paclitaxel (Taxol®), one of the most widely prescribed anticancer drugs on the market. Paclitaxel, a natural product, was first harvested by researchers working under a joint U.S. Department of Agriculture-National Cancer Institute (NCI) grant. It was a DTP contractor who formulated the drug for use in clinical trials. Bortezomib (Velcade®) is another DTP success story. In cooperation with its commercial sponsor, bortezomib was screened and formulated by DTP. Approved by the FDA in 2003, it was the first treatment in more than a decade to be approved for patients with multiple myeloma.

DTP has been involved in the discovery or development of more than 70 percent of the anticancer therapeutics on the market today. Although many academic and private-industry laboratories also are focused on drug discovery, financial and technical burdens as well as lack of funding and infrastructure present barriers that may keep promising therapeutics from reaching patients. DTP helps to overcome therapeutic development barriers by supporting high-risk projects.

In keeping with its goal to turn molecules into medicine for the public health, DTP, created by Congress in 1955 as the Cancer Chemotherapy National Service Center, serves as a vital resource in acquiring preclinical information; providing research materials, including Web-accessible data and tools, vialed and plated compounds, tumor cells, and animals; and providing bulk drugs for investigational new drug (IND)–directed studies.

Dr. Jerry M. Collins, Associate Director

Jerry M. Collins, Ph.D., is an internationally recognized pharmacologist. He has been closely associated with NCI's drug development efforts for more than 25 years, first as an NCI intramural investigator and then as the Chief of the Pharmacokinetics Section. From 1988 until 2005, Dr. Collins served as the Director of the FDA's Laboratory of Clinical Pharmacology, where he headed the development of new methods to facilitate research on human tissue metabolism to create an *in vitro* model to reduce adverse drug reactions. Dr. Collins was named Associate Director of the DCTD Developmental Therapeutics Program in September 2005.

Dr. Collins' areas of expertise are clinical pharmacology, the application of pharmacokinetic and pharmacodynamic (PK/PD) principles to cancer research, and increasing biomarker efficacy with positron emission tomography.

Dr. Collins received his bachelor's degree from Drexel University and his master's and doctoral degrees from the University of Pennsylvania. He is the author or co-author of more than 170 articles and holds eight patents.

DTP's staff and administered grants are divided among nine components:

- Biological Resources Branch
- Biological Testing Branch
- Drug Synthesis and Chemistry Branch
- Grants and Contracts Operations Branch
- Information Technology Branch
- Natural Products Branch
- Pharmaceutical Resources Branch
- Screening Technology Branch
- Toxicology and Pharmacology Branch

In 2005, DTP administered 581 investigator-initiated, peer-reviewed grants.

Approved Cancer Treatment Drugs Developed with DTP Involvement

2004	Erbitux® (NSC 632307)
2003	Velcade® (NSC 681239)
1998	Ontak® (NSC 697979)
1996	Gliadel® (NSC 714372) Topotecan (NSC 609699)
1995	All-t-retinoic acid (NSC 122758)
1992	Chlorodeoxyadenosine (NSC 105014) Taxol® (NSC 125973) Teniposide (NSC 122819)
1991	Fludarabine Phosphate (NSC 312887) Pentostatin (NSC 218321)
1990	Hexamethylmelamine (NSC 13875) Levamisole (NSC 177023)
1989	Carboplatin (NSC 241240)
1988	Ifosfamide (NSC 109724)
1987	Mitoxantrone (NSC 301739)
1983	Etoposide (NSC 141540)
1982	Streptozotocin (NSC 85998)
1979	Daunorubicin (NSC 82151)
1978	cis-Platinum (NSC 119875)
1977	BCNU (NSC 409962)
1976	CCNU (NSC 9037)
1975	Dacarbazine (NSC 45388)
1974	Doxorubicin (NSC 123127) Mitomycin C (NSC 26980)
1973	Bleomycin (NSC 125066)
1970	FUDR (NSC 27640) Mithramycin (NSC 24559) o-p'-DDD (NSC 38721)
1969	Ara-C (NSC 63878) Procarbazine (NSC 77213)
1967	Hydroxyurea (NSC 32065)
1966	Pipobroman (NSC 25154) Thioguanine (NSC 752)
1964	Melphalan (NSC 8806) Actinomycin D (NSC 3053)
1963	Vincristine (NSC 67574)
1962	Fluorouracil (NSC 19893)
1961	Vinblastine (NSC 49842)
1959	Cyclophosphamide (NSC 26271) Thiotepa (NSC 6396)
1957	Chlorambucil (NSC 3088)

Joint Early Therapeutics Development Program

The Division of Cancer Treatment and Diagnosis (DCTD) is reexamining its discovery and development paradigm. Pharmacokinetic and pharmacodynamically (PK/PD)–guided clinical trials are being emphasized in conjunction with assays of specific molecular targets. Such studies are already used to examine the biological effects of drugs in animals and humans. By studying PK/PD responses, researchers will be better able to administer the appropriate dose to achieve the desired therapeutic response with a minimum risk of toxic effects.

A new collaborative effort between the DTP drug developers in DCTD and the programs and clinicians at the Center for Cancer Research (CCR), called the joint early therapeutics development program, uses PK/PD principles to streamline the development of novel cancer therapeutics. This initiative builds on CCR's strengths in integrated research and its clinical program, as well as DCTD's expertise in drug development and its relationships with pharmaceutical companies. The goal is to shorten the drug development timeline for new molecular entities and cytotoxic agents by rapidly screening new drugs in humans before making a commitment in time and resources to a full therapeutic development plan.

In 2005, this new initiative began to take shape. DTP's Toxicology and Pharmacology Branch identified laboratory resources required to support the program and is working to expand capacities to perform PD assays, *in vitro* toxicity analysis, and virus toxicity testing. DTP also is augmenting its animal model efficacy program. A National Clinical Target Validation Laboratory was established within the Toxicology and Pharmacology Branch to assess the pharmacodynamic effects of therapeutics on cellular targets, perform target validation assays, and evaluate the consequences of anticancer drugs on patients in early clinical trials.

Exploratory Investigational New Drug Studies

The joint early therapeutics development program will utilize a recent guidance from the Food and Drug Administration (FDA) concerning exploratory studies of INDs. Exploratory IND studies, which are also called phase 0 trials, will facilitate targeted therapies being tested in patients earlier in the drug development process. This will allow informed decisions to proceed or stop with that particular drug's development before expensive bulk drug formulation and other steps such as additional preclinical toxicology occur. New advances in imaging technologies, which can help detect whether an agent being tested is reaching its target and producing the desired effect, will also be employed.

A unique aspect of the program is that extramural drug developers, for the first time, will be offered opportunities to utilize CCR resources for clinical trials support. Candidate compounds for exploratory IND studies may come from intramural, extramural, academic NCI-funded, or industry laboratories. Consideration will be given to novel small molecules, antibodies, or peptide

therapeutics. Proposed exploratory INDs may start by obtaining PK data suggesting that appropriate drug levels in plasma and tumor can be achieved. Next, PD studies exploring how the agent affects its proposed target *in vivo* would be appropriate.

Exploratory IND studies embody the ideal drug development scenario required to conduct a limited, single-dose PK/PD dose-escalation study in humans. In such trials, researchers perform real-time PK/PD studies to guide dose escalation instead of escalation to maximum tolerated dose as is now the norm in phase I trials. This approach is essential for patient safety in early human clinical trials.

The distinctive features of phase 0 studies are:

- First-in-human, with single or combination drugs
- Molecules from CCR, academia, small biotech
- Small patient numbers (6–10); joint CCR-DCTD clinical trial effort performed in the Clinical Research Center
- Provide PK/PD data to support rapid future dose escalation based on extensive preclinical toxicology and target effect studies
- Initial target assay development and drug/target assessments (primary and surrogate, imaging and molecular expression)
- Preliminary toxicity evaluation in humans
- Inform subsequent broad phase I/II trials
- High throughput of trials, each completed in three to six months

Joint Development Committee

A joint development committee (JDC) has been created by DCTD and CCR to coordinate the joint early therapeutics development program and the exploratory IND efforts. This committee is charged with determining overall project priorities, allocating resources, and providing product development teams with guidance and feedback monthly.

The expansion of the DTP Toxicology and Pharmacology Branch to include a National Clinical Target Validation Laboratory will provide an essential support mechanism for the Institute's national therapeutics development effort.

Developmental Therapeutics Project Management Office

Compounds entering the joint early therapeutics development program will be managed by project teams with members from both DCTD and CCR. A new Developmental Therapeutics Project Management Office will employ a business-focused approach for tracking the advancement of agents from discovery through completion.

The office will track compounds in exploratory IND studies as well as those targeted therapies being supported by collaborations between DTP and the DCTD Cancer Therapy Evaluation Program (CTEP).

Establishment of a National Clinical Target Validation Laboratory

To address the mechanistic gap that occurs because of difficulties in determining the effect of a therapeutic intervention on its putative site of action in patients, in 2005, the DTP Toxicology and Pharmacology Branch was expanded to include NCTVL. This laboratory will elucidate novel methodologies in target tissues specifically applicable to human cancer clinical trials. These methodologies will demonstrate the therapeutic effects of small molecule anticancer agents on specific cellular pathways of interest. The advantages of this crucial endeavor, which will utilize the unparalleled resources of NCI to provide an essential support mechanism for the Institute's national therapeutics development effort, are:

- Provision directly to the intramural and extramural cancer therapeutics and cancer prevention communities of a resource to develop and perform validated procedures on tumor or surrogate tissues for the evaluation of molecularly targeted therapies. These procedures will be exported to the extramural cancer clinical research community as part of NCI's current early therapeutics development program, as well as to the NCI's intramural program, speeding the completion of translational clinical investigations nationwide. NCTVL will utilize small and difficult-to-obtain patient specimens, in advance of patient entry into clinical trials, to develop quality-controlled methodologies for correlative clinical investigations essential to the evaluation of therapeutics efficacy. The laboratory will serve a central core function, performing target validation assays for patients treated within CCR as well as for patient samples from NCI-funded extramural investigators lacking the expertise or facilities to perform such assays.
- Development of procedures allowing extramural investigators with ongoing clinical trials that are part of the current NCI-funded phase I and II program, Cancer Centers, Specialized Programs of Research Excellence (SPOREs), or the cooperative groups to utilize NCI laboratory or clinical resources for the evaluation of molecular targets critical to the completion of their studies. Investigators will access resources through direct patient referral to CCR or by obtaining DCTD support for the development of correlative laboratory procedures for their own investigations.

Drug Discovery

International Cooperative Biodiversity Groups

http://www.fic.nih.gov/programs/research_grants/icbg/index.htm

Contact:
Bruce Butrum
301-496-1670, butrumb@mail.nih.gov

Natural products are a leading source of therapeutics—anticancer agents included. For instance, some 60 to 65 percent of all anticancer drugs are derived from natural products. Additionally, sales figures from 2003 show that for all drug sales of more than $1 billion, purely synthetic therapies comprise only 20 percent of the market.

The International Cooperative Biodiversity Groups (ICBG) program addresses the interdependent issues of drug discovery, biodiversity conservation, and sustainable economic growth. Funding awarded under a program announcement (http://grants2.nih.gov/grants/guide/rfa-files/RFA-TW-04-004.html), which expired in February 2006, is supporting groups that are conducting research on using nature's diverse resources for drug development, but this research also is focused on maintaining biodiversity and promoting economic growth in countries that have potentially natural-sourced drugs.

Since awards were first made in 1992, ICBGs have conducted research in nine countries in Latin America, Africa, Southeast and Central Asia, and the Pacific Islands. Some 5000 species of plants, animals, and fungi have been collected to examine biological activity in 19 different therapeutic areas. Numerous publications in chemistry, biodiversity policy, conservation, and ethnobiology have emerged from the funded investigators, and several novel compounds have been discovered.

Funding for this program has been provided by nine components of the National Institutes of Health (NIH), the Biological Sciences Directorate of the National Science Foundation, and the Foreign Agriculture Service and Forest Service of the U.S. Department of Agriculture. The cooperating NIH components are the Fogarty International Center; NCI; National Institute of Allergy and Infectious Diseases; National Institute of Mental Health; National Institute on Drug Abuse; National Heart, Lung, and Blood Institute; National Center for Complementary and Alternative Medicine; Office of Dietary Supplements; and National Institute of General Medical Sciences.

No new applications for this program are being accepted at this time.

Rapid Access to NCI Discovery Resources—for Academics

http://dtp.nci.nih.gov/docs/rand/rand_index.html

Contact:
R·A·N·D
Office of the DTP Associate Director
301-496-8720, rand@dtpax2.ncifcrf.gov

The process of creating an effective, molecularly targeted cancer drug begins with basic research and the search for chemical compounds with potential anticancer properties and molecules within cancer cells and their surroundings that might provide targets for cancer interventions.

Natural products are a leading source of therapeutics—anticancer agents included. For instance, some 60 to 65 percent of all anticancer drugs are derived from natural products.

In 2001, NCI began Rapid Access to NCI Discovery Resources, or *R·A·N·D*, a program to provide DTP resources to academics in the earliest stages of finding promising therapeutics.

Recent advances in chemistry, molecular biology, bioinformatics, and high-throughput screening methods have increased the number of agents that can be screened and studied, but often require a large investment in equipment that most academics cannot afford. With the help of *R·A·N·D*, DTP hopes to accelerate the rate at which new compounds are studied for fighting cancer. Examples of preclinical discovery tasks that DTP can provide through *R·A·N·D* include, but are not limited to:

- Recombinant production and characterization of molecular target proteins
- Development and implementation of high-throughput screening assays
- Chemical synthesis for library generation, structure-activity studies, and lead optimization
- Bioassay-directed natural product isolation and characterization
- Early formulation, as well as pharmacokinetic, pharmacology, and toxicology studies

R·A·N·D is not a mechanism for obtaining grants. To access the laboratory-based services of the *R·A·N·D* program, academic researchers can submit applications to DTP twice a year, on April 1 and October 1. The applications, which provide a detailed summary of the proposed project, are reviewed by a panel of extramural experts who assess the strength of the hypothesis, novelty, and cost-benefit ratio. Once an application is accepted, *R·A·N·D* services are performed at no cost to the investigator by DTP laboratories. All output from the project is returned to the originator for further investigation.

Among the recipients of *R·A·N·D* services is Dr. Robert Silverman, Cleveland Clinic Foundation, whose research group is developing an assay suitable for high-throughput testing to aid in the discovery of a novel drug for late-stage prostate cancer. DTP will test compounds and perform computer-assisted analysis of the molecular targets. Dr. Nicholas Farrell, Virginia Commonwealth University, also benefited from *R·A·N·D* services after the program synthesized a potential anticancer compound for ovarian cancer and non-small cell lung cancer in sufficient quantities for his group to conduct pharmacokinetic studies.

Drug Discovery and Development Initiative

National Cooperative Drug Discovery Group Program—for Academics and Industry

http://dtp.nci.nih.gov/branches/gcob/gcob_web3.html

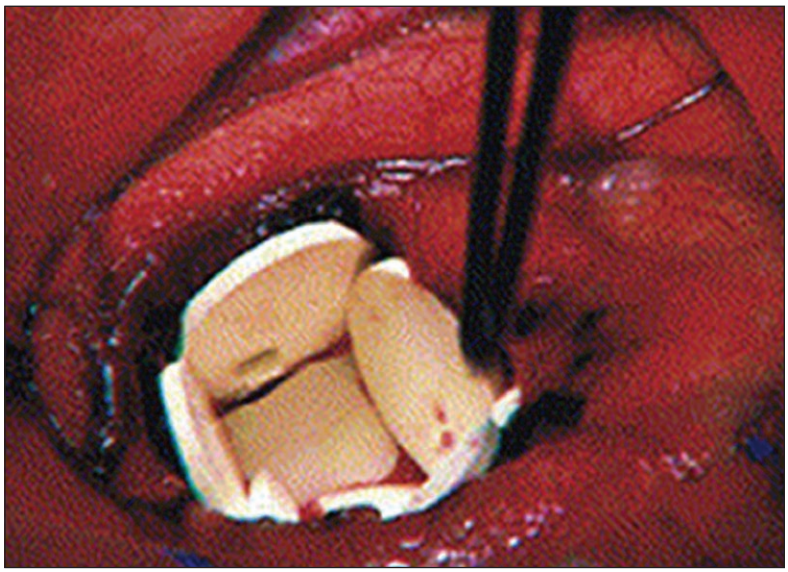
Contact:
Mary K. Wolpert, Ph.D.
301-496-8783, wolpertm@exchange.nih.gov

DTP's National Cooperative Drug Discovery Group (NCDDG) program, initiated in 1983, partners NCI-funded academic researchers with private-sector organizations to fund cooperative agreements (U19s) in support of a multidisciplinary approach to the

Translating promising target-directed compounds into drugs for human use is an exacting task that requires very specific, interrelated activities.

discovery of new, rationally based and natural source–derived anticancer treatments and strategies. Through funding provided under a request for applications (RFA) (http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-05-001.html), which expired in May 2004, the NCDDG supports 13 multidisciplinary groups in the discovery of new anticancer drugs.

This program is one of the first examples of NCI partnering with private industry. The NCDDG program has assisted in the development of four FDA-approved anticancer agents: topotecan, NSC 609699 (Hycamtin®); Gliadel® Wafers, NSC 714372; denileukin diftitox, NSC 733971 (Ontak®); and cetuximab, NSC 714692 (Erbitux®). The Biological Resources Branch has been instrumental in the production of vaccines and other biologic agents, especially for NCDDGs that lacked a major industrial partner.



National Cancer Institute.

Gliadel® Wafers being implanted in the brain at the site of a resected tumor. DTP's NCDDG helped develop this new form of carmustine, a successful anticancer agent.

Although NCDDG projects do not support clinical trials, timely clinical evaluation of agents discovered through NCDDG is encouraged.

No new applications for this program are being accepted at this time.

Drug Development

Rapid Access to Intervention Development—for Academics

http://dtp.nci.nih.gov/docs/raid/raid_index.html

Contact:
Coordinator, RAID Program
301-496-8720, raid@dtpax2.ncifcrf.gov

Translating promising target-directed compounds into drugs for human use is an exacting task that requires very specific, interrelated activities. NCI supports this critical arm of drug development through a variety of initiatives, including DTP's Rapid Access to Intervention Development (RAID) program.

RAID provides preclinical drug and biologic development resources to academic investigators who want to conduct their own clinical trials. Once an optimal compound is selected via *R·A·N·D* or another discovery path, RAID facilitates further preclinical development.

Since its inception in 1998, the RAID program has approved 104 projects, through which 13 small molecules and 11 biologic agents later entered clinical trials.

The goal of RAID is to provide clinical proof of principle that a new molecule or approach is a viable candidate for

expanded clinical evaluation. Tasks supported by RAID include:

- Large-scale synthesis and formulation
- Pharmacology and toxicology
- *In vivo* screening
- Developmental tasks necessary to translate discoveries to the clinic
- Regulatory affairs, so that FDA requirements are likely to be satisfied by participating investigators seeking to test new molecular entities in the clinic

RAID is not a mechanism for obtaining grants. To access the services of the RAID program, academic researchers may submit applications twice yearly—February 1 and August 1. Submissions are reviewed by a panel of extramural experts who assess the strength of hypothesis, scientific novelty, and cost-benefit ratio of the project. Once a project is accepted, DTP provides drug development resources free of charge. The output of RAID activities will be both products and information made fully available to the originating investigator for support of an IND application and clinical trials.

Drug Development Group—for Academics and Industry

http://dtp.nci.nih.gov/docs/ddg/ddg_descript.html

Contact:
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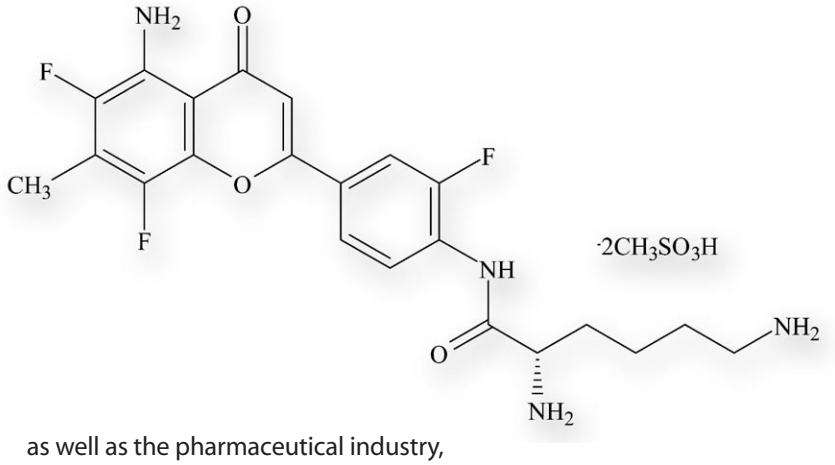
The Drug Development Group (DDG) meets monthly to consider developing drugs from discoveries in the NCI intramural and extramural academic communities, as well as the pharmaceutical industry, where the originators are certain at the outset that NCI should hold any resulting IND and manage any subsequent clinical trials. By contrast, the products of the RAID program will, in general, be returned directly to the originating investigator for clinical trials.



Molecular structure of aminoflavone prodrug (NSC 710464). An IND application was filed with the FDA in early 2006 for this DTP-produced drug.

Compounds at all stages of development are considered on an individual basis. The DDG will be responsible for oversight and for preclinical and clinical decision-making at the key "go–no go" decision points. The DDG prioritizes use of DCTD resources supporting preclinical development by DTP and clinical development by CTEP, except that the Biological Resources Branch Oversight Committee (BRB-OC) governs acquisition and production of biologics approved by DDG.

Initial presentation of an agent to the DDG requires an identified CTEP or DTP staff member to act as liaison. The NCI liaison coordinates with the originator, who supplies an application summarizing the tasks and support specifically being requested.

In 2005, aminoflavone prodrug (NSC 710464), produced by DTP, was one of the drugs that successfully made it through development under the auspices of the DDG, with an IND application filed with the FDA in early 2006. This drug may kill tumor cells without destroying bone marrow or having other toxic effects.

CURRENT FUNDING OPPORTUNITIES

The Grants and Contracts Operations Branch at DTP uses a variety of support mechanisms to increase the rate of discovery of new compounds and new approaches to speed their development as cancer therapeutics and bring them to the clinic.

Open Program Announcement for Drug Development: Small Business Innovation Research/Small Business Technology Transfer

Program Announcement:
PA-06-120: http://grants.nih.gov/grants/guide/pa-files/PA-06-120.html
(expiration date 1/3/2007)

Contact:
Ted Williams
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By funding partnerships between small pharmaceutical companies and nonprofit research institutions, the Small Business Innovation Research/Small Business Technology Transfer (SBIR/STTR) program gives drugs with potential their best commercial chance.

This grant-making program supports research that has commercialization potential. Research funded by this mechanism must be a cooperative project between small business and a research institution. Review criteria for support emphasize innovation and the potential for commercialization.

Drug Discovery

Natural Products Repository

http://dtp.nci.nih.gov/branches/npb/repository.html

DTP's Natural Products Repository is the world's largest storehouse of natural products. It houses close to 170,000 extracts from samples of more than 70,000 plants and 10,000 marine organisms collected from more than 25 countries, plus more than 30,000 extracts of diverse bacteria and fungi. The natural products stored in DTP's repository are screened against the NCI human tumor cell line assay for potential anticancer activity shortly after their collection. So far, about 4,000 natural-source extracts have shown *in vitro* activity against human cancer cells, making them worthy of further study by DTP researchers.

The Natural Products Repository, administered by the Natural Products Branch, provides extramural researchers with natural products extracts for testing against any human disease.

Synthetic Products Repository

http://dtp.nci.nih.gov/branches/dscb/repo_open.html

Since this repository began about 40 years ago, more than 500,000 proprietary and nonproprietary compounds have been submitted to the program. In addition to being a repository for NCI screens, the repository distributes compounds for research purposes both as specific vialed compounds and in plated sets for high-throughput screening.

DTP's plated sets have been instrumental in the discovery of compounds that enhance antilymphoma activity, nucleic acid antagonists with anti-HIV activity, and inhibitors of angiogenin—to name a few important advances.

The Synthetic Products Repository has recently developed a plated set to help evaluate drugs in combination. NCI's Pediatric Drug Development Group will be one of the first groups to use the new plated sets; the results of the studies will be posted on DTP's open-use Website at: http://dtp.nci.nih.gov.

DCTD Tumor/Cell Line Repository

http://dtp.nci.nih.gov/branches/btb/tumor-catalog.pdf

Since the early 1960s, DCTD has maintained this low-temperature repository, which holds transplantable *in vivo*–derived tumors and *in vitro*–established tumor cell lines from an assortment of species. The repository serves as a resource for viable, contaminant-free experimental tumor lines, many of which are not obtainable elsewhere.

Researchers can access these materials under a material transfer agreement.

DTP oversees animal-production facilities that produce inbred and hybrid strains of rats, mice, and guinea pigs. This program provides researchers nationwide with genetically defined, pathogen-free laboratory animals.

Animal Production

http://dtp.nci.nih.gov/branches/btb/services.html#AnimalProduction

DTP's Biological Testing Branch oversees animal-production facilities that produce inbred and hybrid strains of rats, mice, and guinea pigs. This program provides researchers nationwide with genetically defined, pathogen-free laboratory animals as well as animal-related services such as jugular vein cannulations, vasectomies, ovariectomies, and castrations. In 2005, the branch distributed 1,473,062 rodents to about 1700 investigators at 240 institutions.

In Vitro Screening: The Human Tumor Cell Line Assay

http://dtp.nci.nih.gov/branches/btb/ivclsp.html

In 1985, the hypothesis was put forward that a human tumor cell line screen could help investigators discover cell-type–specific agents with clinical activity against solid tumors. The emerging reality was that while correlation of *in vitro* histology to clinical activity is poor, the pattern of cellular sensitivity and resistance of the cell lines to the drug correlated with molecular target expression.

In response, DTP developed a cell-line–based screen representing the major classes of solid tumors. That allowed relatively inexpensive and rapid testing of potential therapeutic agents against broad panels of human tumors that could be adapted to the needs of natural product screening.

Since April 1990, DTP has used the human tumor cell line *in vitro* screen as its primary assay with follow-up *in vivo* evaluation in the hollow fiber assay. The screen is currently composed of 59 human tumor cell lines, representing leukemia, melanoma, and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney. These cell lines were selected partly on pragmatic terms: those selected behaved best under typical assay conditions. The screen was designed so that for each compound tested, both the absolute and the relative sensitivities of individual cell lines were reproducible to the extent that a characteristic profile or fingerprint of cellular response was generated.

Although the particular inhibitory response of a single cell line might be relatively uninformative, the pattern of response of the cell lines as a group can be used to rank a compound according to the likelihood of sharing common mechanisms. The COMPARE algorithm (a computer program) qualifies this pattern and searches an inventory of screened agents to compile a list of the compounds that have the most similar patterns of cellular sensitivity and resistance.

Extramural researchers who wish to access this service should complete an online submission form: http://dtp.nci.nih.gov/compsub/index.html. Pure compounds must be of known molecular structure, and the investigator is required to enter the molecular structure on the online submission form before sending samples of the test compound. Additional

information is available on DTP's Website: http://dtp.nci.nih.gov/docs/misc/common_files/submit_compounds.html.

In September 2005, DTP's human tumor cell line *in vitro* screening assay was reviewed by a panel of extramural experts. Because of reproducibility issues, DTP's standard operating procedures were evaluated, and a series of recommendations was made to improve quality control.

New Screening Assays

http://spheroid.ncifcrf.gov/STB/stb_index.cfm

Although NCI's human tumor cell line screen remains the benchmark, DTP's Screening Technologies Branch is developing and operating new *in vitro* screening technologies, including high-throughput molecularly targeted screens, computational tools for new approaches to data mining, dynamic data visualization tools, and cell-free biophysical assays of macromolecular interactions.

The branch's labs and offices are located on the NCI-Frederick campus and are operated under a contract with Scientific Applications International Corporation (SAIC)–Frederick.

In Vivo Testing

http://dtp.nci.nih.gov/branches/btb/hfa.html

In 1995, DTP implemented a new way to test the activity of potential anticancer compounds using cells grown inside biocompatible hollow fibers. The hollow fiber assay, developed by Dr. Melinda Hollingshead, chief of DTP's Biological Testing Branch, has the ability to provide quantitative indices of drug efficacy in heterogeneous tumors with minimal expenditures of time and materials. This system currently is being used as the initial *in vivo* experience for agents found to have reproducible activity in the *in vitro* anticancer drug screen.

The hollow fiber assay has several advantages over standard animal efficacy models. First, demonstrating that potential anticancer agents have *in vivo* efficacy in one or more animal models of neoplastic

NCI Visuals Online, Linda Bartlett, photographer.

The hollow fiber assay at full capacity allows screening of 50 or more compounds per week in a 10-day assay.

disease can require considerable investments in laboratory animals and quantity of test compound. Second, conducting studies in animal models requires substantial amounts of time and resources. Even when such studies can be conducted, it is possible that the experimental agent or series of agents will exhibit only minimal antitumor activity. Third, cancer treatments that appear promising in tissue culture are often less effective in solid tumors, in part because of the proliferative and microenvironmental heterogeneity that develops in these tumors as they grow.

The hollow fiber assay at full capacity allows screening of 50 or more compounds per week in a 10-day assay. In addition to requiring less than two weeks to complete, it requires at most only 450 mg of material, as opposed to the multigram quantities required for xenograft studies. Compounds that retard the growth of the selected tumor cell lines are recommended for the next level of testing.

Molecular Target Characterization

http://dtp.nci.nih.gov/mtargets/mt_index.html

As part of DTP's Molecular Targets Program, samples of protein, DNA, and RNA from human tumor cell lines are distributed to the intramural and extramural research community. Cell lines also are sent to various extramural researchers who measure the expression levels of various proteins or determine the status (e.g., wild type or mutant) of certain oncogenes. By using these measurements, DTP can determine whether the sensitivity of the set of human tumor cell lines is related to the expression levels of the compound that was measured.

Once the results are collected, the molecular target data are posted to the DTP Website. The program's goal is to correlate anticancer activity with molecular target measurements to identify cell lines with desired characteristics and to perform this work at a low cost. In the last 10 years, thousands of molecular targets have been measured against the human tumor cell line screen, and more than 191 projects have been initiated.

Drug Discovery and Development

DTP Website

http://dtp.nci.nih.gov

In 1994, DTP launched its Website, making its drug discovery and development services and the results from the human tumor cell line assay publicly accessible to researchers worldwide. At first, the site offered *in vitro* human cell line data for a few thousand compounds and *in vitro* anti-HIV screening data for roughly 42,000 compounds. Today, visitors who come to the site can find:

- Downloadable *in vitro* human tumor cell line data for some 43,500 compounds and 15,000 natural product extracts
- Results for 60,000 compounds evaluated in the yeast assay

- *In vivo* animal model results for 30,000 compounds
- 2-D and 3-D chemical structures for more than 200,000 compounds
- Molecular target data, including characterizations for at least 1200 targets, plus data from multiple cDNA microarray projects

In addition to browsing DTP's databases and downloading data, researchers can request individual samples or sets of compounds on 96-well plates for research, or they can submit their own compounds for consideration for screening via DTP's online submission form. Once a compound is submitted for screening, researchers can follow its progress and retrieve data using a secure Web interface.

The NCI has collected information on almost half a million chemical structures in the past 40 years. DTP has made this information accessible and useful for investigators through its 3-D database, a collection of three-dimensional structures for more than 400,000 drugs. Investigators use the 3-D database, which is maintained by DTP, to screen compounds for anticancer therapeutic activity.

Also available on DTP's Website are 127,000 connection tables for anticancer agents. A connection table is a convenient way of depicting molecular structures without relying on drawn chemical structures. As unique lists of atoms and their connections, the connection tables can be indexed and stored in computer databases where they can be used for patent searches, toxicology studies, and precursor searching, for example.

Courtesy of Essential Eye Photographics.

The Website and its databases are maintained by the Information Technology Branch.

Drug Development

Biological Resources Branch Preclinical Repository

http://web.ncifcrf.gov/research/brb/site/preclinRepo.asp

This repository, an NCI-sponsored facility, stores bulk cytokines, monoclonal antibodies, and cytokine standards under carefully controlled conditions. The repository provides a constant and uniform supply of high-quality reagents to nonprofit institutions and qualified

commercial establishments at no charge. This facility obtains new materials by donation or at reduced cost by negotiating with companies and investors. To date, the Biological Resources Branch Preclinical Repository has distributed more than 40,000 samples, and the estimated value of materials shipped to investigators is about $100,000 per year.

Radiolabeled Materials Repository

http://dtp.nci.nih.gov/docs/misc/available_samples/radiolbllist2.html

For researchers who hold a valid radioactive materials license, there are roughly 90 radiolabeled drugs available from DTP's Radiolabeled Materials Repository. Radiolabeled compounds are instrumental in noninvasive studies of biodistribution and in target pharmacokinetics of therapeutics.

National Cancer Institute.

In early trials, 11 of 16 patients with hairy cell leukemia had complete remissions after receiving BL22.

Drug Formulation and Synthesis

DTP's Pharmaceutical Resources Branch bears the responsibility of acquiring bulk materials for formulation and synthesis, formulating drugs and testing them, clinical dosage-form production, and stability testing of clinical dosage forms. This branch provides clinical researchers, both academic and institutional, with top-quality drugs for clinical trials and formulates drug compounds that are candidates for the Drug Development Group or the RAID program.

Drug Production: Biopharmaceutical Development Program

http://wwwbdp.ncifcrf.gov/

DTP's Biological Resources Branch oversees the Biopharmaceutical Development Program (BDP), which provides biopharmaceutical development expertise and production capability to all NIH-supported investigators. The BDP produces a variety of clinical-grade biological agents from bacterial, yeast, and mammalian cells; natural products from various organisms; and DNA, RNA, and viral materials under current Good Manufacturing Practices for phase I/II human clinical trials or advanced preclinical animal testing.

Researchers have attempted to design cancer therapies to avoid toxicities associated with standard chemotherapeutic agents. BL22, one such targeted treatment, originated in an intramural NCI laboratory and was developed through DTP's biologicals production facility.

DTP produces a variety of clinical-grade biological agents from bacterial, yeast, and mammalian cells; natural products from various organisms; and DNA, RNA, and viral materials under current Good Manufacturing Practices for phase I/II human clinical trials or advanced preclinical animal testing.

The BDP was able to develop a complete, simple, and scalable clinical manufacturing process for immunotoxin production. A novel hydrophobic chromatography method was incorporated into the process to clearly separate the product, which elutes in a separate peak from the impurities. The new protocol almost tripled the yield of the final product and lowered the cost of production. This novel purification method has also been applied to other similar antibody-conjugated toxins, facilitating the manufacture of immunotoxin anticancer drugs in large scale.

BL22 showed promising results in a phase I trial: 11 of 16 patients with chemotherapy-resistant hairy cell leukemia have shown complete remission, lasting up to 18 months, mostly without major side effects. The drug is now in phase II clinical trials at NCI, involving patients with hairy cell leukemia. Commercialization efforts also are under way via a CRADA with Genecor, Inc.

The program's labs, production suites, and offices are located on the NCI-Frederick campus and are currently operated under a contract with SAIC-Frederick.

Mouse Models of Human Cancers Consortium

http://mouse.ncifcrf.gov/

Until recently, the only factors available to measure anticancer activity in any model were inhibition of cell or tumor growth and the increased lifespan of the animal. Cancer-specific molecular targets were unknown, and investigators did not have the tools to measure the therapeutic effects or targets in biologic fluid or tissue. In addition, existing models did not predict well for clinical outcome. DTP is working with the Mouse Models of Human Cancers Consortium (MMHCC) to design studies examining the predictive value of genetically engineered mouse models.

The MMHCC was established in 1998 as a collaborative program to derive and characterize mouse models, to generate resources and information, and to use innovative approaches in preclinical and drug intervention studies. The MMHCC comprises 25 principal investigators whose research groups connect more than 50 institutions in the United States and abroad. More than 80 mouse strains are now available to cancer researchers.

The MMHCC also maintains the eMICE Website (http://emice.nci.nih.gov), which provides information on mouse models by disease site; information on the applications of mouse cancer models to translational research; links to other mouse-related resources, strain repositories, and databases; access to the MMHCC Mouse Repository Website, Cancer Models Database, and Cancer Images Database; and access to the caArray Database.

Mouse models that recapitulate steps in the genesis, progression, and clinical course of human cancers provide a valuable resource to cancer researchers, particularly in the field of drug discovery and development. The availability of these models via the MMHCC repository, which makes animal strains available to all members of the scientific community, is a key to discoveries that will lead to new approaches for cancer detection, diagnosis, therapy, and prevention.

The Type 1 Diabetes Rapid Access to Intervention Development Program

http://www.niddk.nih.gov/fund/diabetesspecialfunds/T1D-RAID

Five years of success for DTP's RAID concept prompted the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to suggest a similar program for diabetes therapeutics. The Type 1 Diabetes Rapid Access to Intervention Development Program (T1D-RAID) is a cooperative program between DTP, which manages the technical resources, and NIDDK, which prioritizes and funds the projects. Like DTP's parent program, RAID, T1D-RAID makes NCI resources for the preclinical development of drugs, natural products, and biologics available on a competitive basis. DTP support includes high-throughput screening, animal studies, drug formulation, pharmacology and toxicology studies, and bulk substance acquisition.

T1D-RAID, begun in 2003, is intended to remove the most common barriers novel diabetes therapeutics face before entering clinical trials.

This program is not a grant-making mechanism. T1D-RAID is open to extramural investigators from academic institutions, non-profit research institutions, and biotechnology and pharmaceutical companies. Requests are accepted twice a year, on November 1 and April 1. Each request is reviewed by a panel of extramural experts for the strength of the scientific hypothesis and scientific novelty as well as cost-benefit considerations.

NIH RAID Pilot Program

http://nihroadmap.nih.gov/raid

Contact:
NIH-RAID Pilot Program Office
301-594-4660, NIH-RAID@niddk.nih.gov

A new pilot program announced in December 2004—NIH Rapid Access to Intervention Development (NIH RAID)—opens the door to DTP's drug-development expertise to the other Institutes and Centers. Intramural researchers outside of NCI now have access to DTP know-how in acquiring preclinical information in support of an IND application. They also will have DTP support with scale-up synthesis of the drug substance, dosage form development and manufacture, and development of analytical methods to characterize the drug substance/dosage form, assay the compound in tissues and body fluids, and carry out toxicological studies with correlative pharmacology and histopathology assessment.

Emphasis is on high-risk ideas or therapies for uncommon disorders that frequently do not attract private sector support at early stages of development. In these cases, government resources provide a means to acquire further information to assess the potential of these approaches and facilitate clinical evaluation.

The program accepts applications for these resources biannually. Two review cycles have been completed. Five Institutes are sponsoring or cosponsoring the four proposals accepted for implementation.

NIH RAID is part of NIH's Roadmap Initiatives. Projects are jointly funded by the sponsoring institute and the Roadmap

Office. The purpose of the Roadmap Initiatives is to identify major opportunities and gaps in biomedical research that no single Institute at NIH could tackle alone but that the agency as a whole must address to make the biggest impact on the progress of medical research.

NIH RAID is not a grant program. Successful projects will gain access to the government's resources as well as assistance of the NIH in establishing and implementing a product development plan.

Developmental Therapeutics Program Reference Guide for New Users

http://dtp.nci.nih.gov/guide.jsp

Where do I go if I need

- Funding
- Samples for my research

  Individual compounds, compound libraries, natural product extracts, animal and human cell lines, biologic reference reagents
- Routine screening for my compounds

  In vitro cell line screen, anti-HIV screen
- Downloadable data

  In vitro 60 cell line results, *in vitro* anti-HIV results, yeast assay, 200,000+ chemical structures, molecular targets, microarray data

I need more information about how DTP conducts

- *In vivo* testing
- Biopharmaceutical production
- Pharmacology and toxicology testing
- Formulation
- Clinical batch production

Can DTP help me if

- I need help synthesizing small quantities of compounds *(R·A·N·D)*
- I need an assay developed for high throughput *(R·A·N·D)*
- I want to file my own IND but I need formulation, pharmacology, toxicology, GMP production, etc. (RAID)
- I would like to see if NCI is interested in testing my agent in an NCI-sponsored clinical trial (DDG)

What if DTP doesn't have what I need, is there any other part of NCI that can help?

- NCI Research Resources
- Resources for NIH Intramural Researchers

I still have questions about DTP

- Call (301) 435-9160 or e-mail our Help Desk (dtpinfo@mail.nih.gov).

50th Anniversary Symposium and Timeline

http://videocast.nih.gov/ram/dtp112905a.ram

In November 2005, DTP celebrated its 50th anniversary by inviting some of the cancer research community's top names to a symposium on drug development. Speakers at this event, which can be viewed at the URL above, included Dr. Andrew von Eschenbach, then-director of NCI; Dr. James Doroshow, director, DCTD; NCI grantee Dr. Susan Band Horwitz, discoverer of paclitaxel's mechanism of action; and Dr. Bruce Chabner, former director of the NCI Division of Cancer Treatment. A key panel discussion focused on the future role of DTP in drug development. The symposium also included a keynote speech by Dr. Vincent DeVita, former director of NCI; a poster session; and a concluding talk by DTP associate director Dr. Jerry Collins on applying the lessons of the past for future success.

DTP also marked the anniversary by launching an interactive timeline recounting the organization's involvement in drug development over the last 50 years. DTP's timeline can be accessed at: http://dtp.nci.nih.gov/timeline/flash/index.htm.

Toward a Fully Synthetic Carbohydrate-Based Anticancer Vaccine

Vaccines are a new and potentially powerful approach to the treatment and prevention of cancer. The possibility is that a vaccine will elicit an immunological response to cancer. Some types of cancer cells, including those of the breast, colon, and prostate, exhibit cell-surface carbohydrates not found on normal cells. Efforts are being made to develop a vaccine that will induce antibodies against these tumor-associated carbohydrates.

To be effective, a vaccine will need to induce predominantly powerful IgG type antibodies, produced after activation of helper T cells, rather than the relatively weak IgM type antibodies initially produced by B cells. Success to date has been quite limited because the traditional approach of synthesizing two-component vaccines employing a tumor-associated carbohydrate and a carrier protein had resulted in a predominately IgM response with insufficient IgG response.

However, DTP-supported research has led to development of a carbohydrate anticancer vaccine that elicits a strong IgG antibody response. This vaccine consists of three synthetic components: a carbohydrate known as Tn antigen found only on cancer cells, a small peptide known to activate T cells, and a fatty acid substituted peptide adjuvant (immune booster). This three-part construct was used to immunize mice, which subsequently exhibited high ratios of IgG to IgM antibodies against the Tn tumor-specific carbohydrate. Innovative aspects of this work include the specific three-component design employed and the successful strategies used to synthesize and link the three components.

Buskas T, Li Y, Boons GJ. Synthesis of a dimeric Lewis antigen and the evaluation of the epitope specificity of antibodies elicited in mice. *Chem Eur J* 2005;11:5457–67.

Borman S. Cancer vaccine is best in class. *Chem Eng News* 2005;83:10.

Exploiting Angiogenesis for Induction of Tumor Dormancy

Research funded by DTP and conducted by Dr. Robert Kerbel, Sunnybrook Health Science Centre in Toronto, Ontario, produced a new approach to cancer treatment called metronomic therapy, which uses small, daily doses of chemotherapeutic agents given with antiangiogenic agents to keep tumors dormant.

With this approach, patients are not cured, but tumors are controlled by starving them and inhibiting growth.

Metronomic therapy remains a controversial area; however, these pioneering experiments have improved treatment outcomes. The goal is to identify biomarkers to monitor the status of tumor progression in patients and to try successive combinations of anticancer agents that will keep tumors dormant until a cure can be achieved.

This approach has many benefits: treatments are not expensive because they usually involve existing anticancer agents, existing agents can be quickly translated to the clinic, and treatments are often given at doses that are well tolerated.

In animal studies, researchers have shown that the circulating bone marrow–derived endothelial progenitor cells (circulating endothelial progenitors, or CEPs) are the source of tumor blood vessels and the target of certain drugs. By combining a 5-fluorouracil (5-FU) prodrug called tegafur-uracil (UFT), which targets CEPs, and antitumor agents such as cyclophosphamide, a standard alkylating agent, there was an enhanced survival of tumor-bearing mice. CEP levels can also be used as a biomarker to establish optimal doses of the drugs. A number of combinations are now in clinical testing.

Shaked Y, Emmengger U, Man S, Cervi D, Bertolini F, Ben-David Y, Kerbel RS. The optimal biological dose of metronomic chemotherapy regimens is associated with maximum antiangiogenic activity. *Blood* 2005;106:3058–61.

Munoz R, Man S, Shaked Y, Lee C, Wong J, Francia G, Kerbel RS. Highly efficacious nontoxic treatment for advanced metastatic breast cancer using combination UFT-cyclophosphamide metronomic chemotherapy. *Cancer Res* (In press).

Mancuso P, Colleoni M, Calleri A, Orlando L, Maisonneuve P, Pruneri G, Agliano A, Goldhirsch A, Shaked Y, Kerbel RS, Bertolini F. Circulating endothelial cell kinetics and viability predict survival in breast cancer patients receiving metronomic chemotherapy. *Blood* [Epub Mar 16 2006].

Ferrara N, Kerbel RS. Angiogenesis as a therapeutic target. *Nature* 2005;438:967–74.

Kerbel RS. Antiangiogenic therapy: a universal chemosensitization strategy for cancer? *Science* (In press).

Targeting Hypoxic Cell Signaling for Drug Discovery

DTP researchers collaborated with investigators in CCR to establish the activity of DNA topoisomerase I inhibitors as selective inhibitors of HIF-1α, a key regulator of hypoxic cell signaling. Because of this research, a clinical trial of topotecan as an HIF-1α inhibitor was designed and approved in 2005. This trial opened in early 2006 and is currently recruiting patients. Additional information on the clinical trial can be found at: http://bethesdatrials.cancer.gov/clinical-research/search_detail.asp?ProtocolID=NCI-05-C-0186.

Recent efforts have defined additional mechanistic categories of HIF-1α inhibitory compounds identified in high-throughput drug screening as exemplified by the sequence-specific DNA binder echinomycin. The primary drug candidate (NSC 644221) was identified as a screening lead with yet a different mechanism of action. Preliminary xenograft studies support the potential of this compound for *in vivo* modulation of

HIF-1α. Studies of endothelial cells have defined an HIF-1α–dependent autocrine signaling loop important for angiogenesis. The hope is that by increasing understanding of the role of HIF-1α in tumor and normal cells and identifying and characterizing novel inhibitors, targeted therapy can be optimized.

Kong D, Park EJ, Stephen AG, Calvani M, Cardellina JH, Monks A, Fisher RJ, Shoemaker RH, Melillo G. Echinomycin, a small-molecule inhibitor of hypoxia-inducible factor-1 DNA-binding activity. *Cancer Res* 2005;65:9047–55.

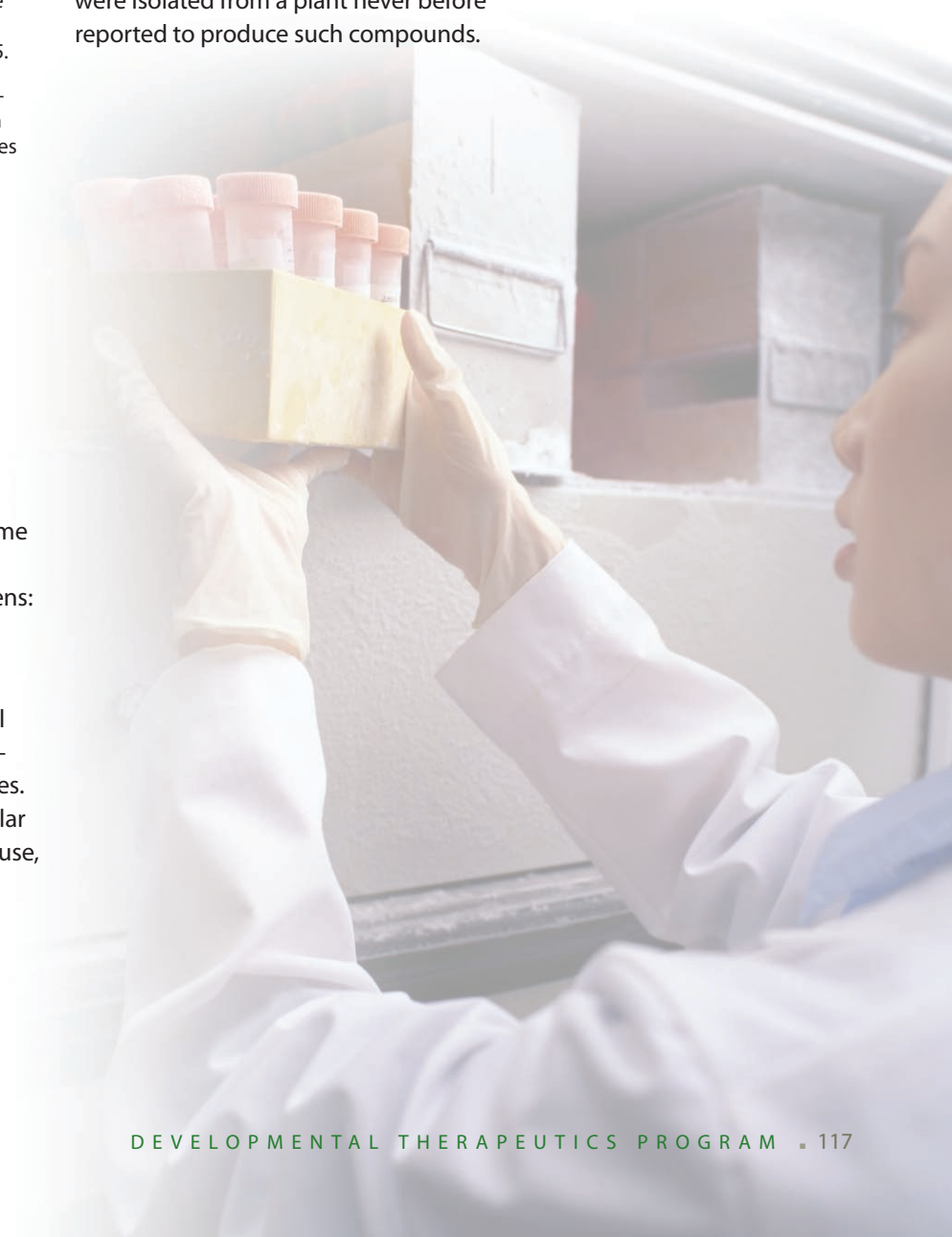
Calvani M, Rapisarda A, Uranchimeg B, Shoemaker RH, Melillo G. Hypoxic induction of an HIF-1α-dependent bFGF autocrine loop drives angiogenesis in human endothelial cells. *Blood* 2006;107:2705–12.

Natural Products–Based Drug Discovery

Progress has been made in coupling cell-based, molecular-targeted high-throughput screens and crude natural product extracts for anticancer drug discovery. Screening campaigns of the DTP Natural Products Repository of some 70,000 extracts were carried out using three distinct molecular-targeted screens: the HIF-1α, CEBPα, and IkB kinase (IKK) signaling pathways.

HIF-1α is a key regulator of hypoxic cell signaling. CEBPα is a regulator of differentiation of myeloid and other cell types. The IKK signaling pathway is of particular importance in the pathogenesis of diffuse, large B-cell lymphomas.

High-throughput screening data were analyzed to identify active extracts to prioritize potential compounds for bioassay-directed isolation of active constituents. Selected extracts were then fractionated by high-pressure liquid chromatography in conjunction with spectroscopic monitoring to generate samples for testing in the molecular-targeted screen of interest. It has been possible to track activity through successive chemical separation steps and isolate chemical entities responsible for the activity. Camptothecin derivatives were isolated from a plant never before reported to produce such compounds.



This included a camptothecin derivative never before found in nature. Structure elucidation work is in progress for compounds isolated from all three screens.

Two novel antifungal compound series were reported in 2005. These represented the conclusion of work under a CRADA with SAIC for antimicrobial drug discovery. DTP Screening Technologies Branch (STB) investigators developed a novel fermentation process to produce the antitumor lead pleurotin and supported a large-scale plant recollection effort to isolate novel tropane alkaloids.

Meragelman TL, Tucker KD, McCloud TG, Cardellina JH 2nd, Shoemaker RH. Antifungal flavonoids from Hildegardia barteri. *J Nat Prod* 2005;68:1790–2.

Klausmeyer P, McCloud TG, Tucker KD, Cardellina JH 2nd, Shoemaker RH. Aspirochlorine class compounds from Aspergillus flavus inhibit azole-resistant Candida albicans. *J Nat Prod* 2005;68:1300–2.

Chin YW, Jones WP, Waybright TJ, McCloud TG, Rasoanaivo P, Cragg GM, Cassady JM, Kinghorn AD. Tropane aromatic ester alkaloids from a large-scale re-collection of *Erythroxylum pervillei* stem bark obtained in Madagascar. *J Nat Prod* 2006;69:414–7.

Shipley SM, Barr AL, Graf SJ, Collins RP, McCloud TG, Newman DJ. Development of a process for the production of the anticancer lead compound pleurotin by fermentation of Hohenbuehelia atrocaerulea. *J Ind Microbiol Biotechnol* 2006;33:463–8.

Development of Novel High-Throughput Screening Technology for Identification of Inhibitors of Transcription Factor-DNA Binding

STB investigators worked with Dr. Charles Vinson, CCR Laboratory of Metabolism, to develop, optimize, and characterize a screen for four of the B-Zip family of transcription factors that are known to have oncogenic effects. A high-throughput screen of the NCI diversity set identified a single chemotype effective in disrupting B-Zip–DNA interactions. Further work is in progress to define the activity of this chemotype in cell-based reporters for B-Zip activity and to evaluate additional leads identified in high-throughput screening of chemical libraries. STB investigators have generalized this technology to develop a screen for inhibitors of ASPL-TFE3 chimeric transcription factor-DNA interaction. This chimeric transcription factor results from a chromosomal translocation characteristic of alveolar soft-part sarcoma. In sarcoma and in other pediatric tumors, such as alveolar rhabdomyosarcoma, the chromosomal translocation and associated chimeric transcription factor present a potentially exploitable therapeutic target.

Rishi V, Potter T, Laudeman J, Reinhart R, Silvers T, Selby M, Stevenson T, Krosky P, Stephen AG, Acharya A, Moll J, Oh WJ, Scudiero D, Shoemaker RH, Vinson C. A high-throughput fluorescence-anisotropy screen that identifies small molecule inhibitors of the DNA binding of B-ZIP transcription factors. *Anal Biochem* 2005;340:259–71.

RADIATION RESEARCH PROGRAM

The Radiation Research Program supports research to find new ways of using radiation therapy more effectively and with fewer side effects, which is paramount for maintaining patients' quality of life.

OVERVIEW

Killing cancer cells while minimizing damage to healthy cells is the goal of radiation therapy. About half of all patients with cancer undergo radiation therapy, the majority of these with curative intent. Finding new ways of using radiation therapy more effectively and with fewer side effects is paramount for maintaining patients' quality of life. This entails innovative uses of technology and biology and integration in multimodality cancer care and research.

As part of an ongoing effort to stimulate research in radiotherapy and radiation biology, the Radiation Research Program (RRP) supports clinical, translational, and basic research at the Division of Cancer Treatment and Diagnosis (DCTD) by:

- Providing expertise to investigators who perform cutting-edge research using radiation and other forms of energy
- Assisting the radiotherapy research community in establishing priorities for the future direction of radiation research
- Providing medically underserved communities with access to radiation therapy
- Evaluating the effectiveness of radiation research being conducted by National Cancer Institute (NCI) grantees

RRP also coordinates its activities with other radiation research programs at NCI, the National Institutes of Health (NIH), other federal agencies, and national and international research organizations. Additionally, RRP serves as a focal point for extramural investigators concerned with clinically related radiation oncology and biology research.

Dr. C. Norman Coleman, Associate Director

C. Norman Coleman, M.D., holds an undergraduate degree in mathematics from the University of Vermont and received his medical training at Yale University School of Medicine. Dr. Coleman completed his internship and residency in internal medicine at the University of California, San Francisco, and a fellowship in medical oncology at NCI.

Board-certified in internal medicine, medical oncology, and radiation oncology, Dr. Coleman was a tenured faculty member at the Stanford University School of Medicine before joining Harvard Medical School in 1985 as the Viola D. Fuller American Cancer Society Professor and Chairman of the Joint Center for Radiation Therapy. In 1999, he became Director of NCI's Radiation Oncology Sciences Program. Dr. Coleman created this program to coordinate all radiation oncology activities across all NCI components. He then served as Chief of the Center for Cancer Research's Radiation Oncology Branch from 1999 until 2004.

Dr. Coleman currently is Associate Director of the DCTD Radiation Research Program, a Special Advisor to the Director of NCI's Center for Cancer Research, and a Special Advisor to the NCI Director. Since 2004, he has been the Senior Medical Advisor at the Office of Public Health Emergency Preparedness for the U.S. Department of Health and Human Services. He also has written extensively in his field and has won numerous awards, including the 2005 Gold Medal Award from ASTRO (American Society for Therapeutic Radiation Oncology) for his many scientific and professional contributions to the fields of radiation oncology and radiation biology.

RRP supports research involving a variety of radiation therapeutic modalities:

- Radiation therapy using high-energy photons and new technology for the physical delivery of radiation therapy, including intensity-modulated radiation therapy (IMRT) with novel applications of linear accelerator technology, brachytherapy using temporary and permanent implantation of radioactive sources, and particle therapy, in particular the most widely used form, proton therapy
- Other sources of energy to treat cancer, including photodynamic therapy using lasers or other light sources combined with a light-sensitive drug (sometimes called a photosensitizing agent) and hyperthermia (heat), alone or in combination with radiation and/or chemotherapeutic drugs

The RRP encompasses three branches:

- The Radiotherapy Development Branch
- The Clinical Radiation Oncology Branch
- The Molecular Radiation Therapeutics Branch

Working with NCI and NIH Grant and Contract Awardees

The primary responsibility of RRP is to the grantees and contractors of NCI and NIH awards. In 2005, RRP administered 207 grants, primarily through the Radiotherapy Development Branch.

The research portfolio of RRP encompasses a broad range of topics, including basic radiation physics track structure; DNA damage and repair; radiation-inducible molecular changes, including signaling and apoptosis; tumor biology; radiation sensitizers and protectors; image-guided radiation therapy; systemic targeted radionuclide therapy (STaRT); and others. The field of radiation therapy is unique in the breadth of expertise and knowledge required for optimal clinical use.

RRP helps stimulate new areas of investigation by bringing together experts in workshops.

Among the unique initiatives of RRP is the annual Young Investigators Workshop, in which emerging leaders come together to discuss research and to build new collegial relationships as well as learn about the ins and outs of the NCI grant process.

Cancer Disparities Research Partnership Program

http://www3.cancer.gov/rrp/CDRP

Contact:
Frank Govern, Ph.D.
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Cancer health disparities are exemplified by differences in cancer morbidity and mortality as a function of gender, ethnicity, and socioeconomic status. Health care institutions that provide cancer services to medically underserved, low-income, minority populations often are not linked effectively to the national cancer research enterprise and struggle to maintain state-of-the-art cancer care.

RRP's Cancer Disparities Research Partnership (CDRP) program aims to reduce the negative consequences associated with cancer health disparities. This goal will be reached by building clinical trials research in radiation oncology in institutions that care for a disproportionate number of medically underserved segments of the U.S. population. These groups traditionally have not been involved in NCI-sponsored research.

The CDRP program has four components:

- Planning, developing, and conducting radiation oncology clinical trials
- Planning, developing, and implementing nurturing partnerships between grantee institutions in underserved areas and experienced academic research institutions actively involved in NCI-sponsored cancer research
- Establishing a compatible telemedicine system (TELESYNERGY®) at each CDRP grantee institution and its primary partner to augment the partnerships
- Supporting a Patient Navigator to facilitate access to radiation oncology services, including clinical trials, by addressing barriers—financial, geographic, and cultural—that impact timely cancer care delivery to patients from target populations

Under a request for applications CA-03-018 (http://grants1.nih.gov/grants/guide/rfa-files/RFA-CA-03-018.html), which expired in 2002, RRP awarded six

NCI Visuals Online, Diane A. Reid, photographer.

TELESYNERGY® systems are growing in utilization and being used in unique ways in solid support of the awardee-mentor relationships to ensure the safe and effective conduct of clinical research in community hospitals serving minority populations.

Cancer Disparities Research Partnerships

Laredo Medical Center, Laredo, TX
http://www3.cancer.gov/rrp/CDRP/laredo.html

- Principal investigator: Dr. Yadvindera Bains
- Primary partner: University of Texas Health Science Center at Houston

Rapid City Regional Hospital, Rapid City, SD
http://www3.cancer.gov/rrp/CDRP/rapidcity.html

- Principal investigator: Dr. Daniel Petereit
- Primary partner: University of Wisconsin Comprehensive Cancer Center

Centinela Freeman Regional Medical Center, Memorial Campus, Inglewood, CA
http://www3.cancer.gov/rrp/CDRP/dfmh.html

- Principal investigator: Dr. Michael L. Steinberg
- Primary partner: University of Southern California Health Sciences Campus

New Hanover Regional Medical Center, Wilmington, NC
http://www3.cancer.gov/rrp/CDRP/nhrmc.html

- Principal investigator: Dr. Patrick D. Maguire
- Primary partner: University of North Carolina School of Medicine

Singing River Hospital, Pascagoula, MS
http://www3.cancer.gov/rrp/CDRP/srhs.html

- Principal investigator: Dr. W. Sam Dennis
- Primary partner: University of Alabama at Birmingham Comprehensive Cancer Center

UPMC McKeesport, McKeesport, PA
http://www3.cancer.gov/rrp/CDRP/upmc.html

- Principal investigator: Dr. Dwight E. Heron
- Primary partners: Washington University in St. Louis School of Medicine and Roswell Park Cancer Institute

Cooperative Planning Grants for CDRPs using the U56 mechanism. The unique aspect of this innovative program is that the health disparity region is the primary grantee, with the academic affiliations (cancer centers, universities, cooperative groups) being chosen by the grantees. While the program is still in its early years, the six grantee institutions, which are new to clinical trials research, are partnering with major academic radiation oncology departments that are actively involved in RRP-sponsored cancer research. Indeed, the Radiation Therapy Oncology Group (RTOG) now has a robust Cancer Disparities Committee. These stable, long-term

partnerships between the institutions stimulate increasing minority and underserved patients' participation in clinical trials of new cancer therapies and improve patient access to quality cancer treatments. The CDRP program also will increase the likelihood of detecting population differences in response to treatments.

The results achieved under this RRP program have been impressive. Less than halfway through the six-year program, there are 58 research protocols active and accruing 125 patients at the sites. Many additional patients have been provided navigation services by Patient Navigators at the awardees' sites. TELESYNERGY® systems are growing in utilization and being used in unique ways in solid support of the awardee-mentor relationships to ensure the safe and effective conduct of clinical research in community hospitals serving minority populations.

The CDRP program runs until 2008. A thorough outcome and process evaluation will be conducted over the next two years to ensure appropriate implementation, to facilitate midcourse corrections, and to help RRP determine whether to re-fund and reissue the CDRP program. It is the intention of RRP to request renewal and possible expansion of this innovative program.

TELESYNERGY®

http://www3.cancer.gov/rrp/CDRP/telesynergy_info.html

For patients located in medically underserved areas such as rural or economically disadvantaged locales, access to cutting-edge medical care and physician

The "Walking Forward" program is an example of the CDRP approach in action. It is a scientific collaborative program between a CDRP grant recipient—the Rapid City Regional Hospital—and its primary partner, the University of Wisconsin Comprehensive Cancer Center. The Rapid City Regional Hospital serves approximately 100,000 Native Americans from surrounding communities and reservations. The Pine Ridge Reservation is currently the poorest in the United States and suffers from some of the highest cancer mortality rates. Because conventional courses of cancer treatment lasting six to eight weeks may be a barrier to care, RRP-sponsored investigators are conducting innovative clinical trials with a shortened course of treatment. A molecular predisposition to treatment side effects is also being explored.

Kevin Molloy, RN, Patient Navigator, Rapid City Regional Hospital, photographer.

Native American blessing ceremony for the new radiation therapy system installed at Rapid City Regional Hospital in 2004. This cutting-edge technology is being used by the CDRP program to enhance Native American participation in clinical trials.

With TELESYNERGY® as a link, health care institutions that attend to underserved areas can now develop and sustain clinical trials and become part of the national cancer research effort. TELESYNERGY® also makes distance learning possible for health care providers.

specialists is often unobtainable and participation in clinical trials unlikely.

The leadership at RRP sought to bridge this gap by developing a telemedicine system called TELESYNERGY®. RRP investigators worked together with researchers from the NIH Center for Information Technology (CIT).

TELESYNERGY® is a combination of computer hardware, telecommunications software, medical equipment, and human expertise that allows clinicians to collaborate as if they were in the same room. With the system, cancer center specialists can consult on cases all over the nation and abroad and mentor investigators who work with patients in underserved areas to promote participation in clinical trials. Currently, 22 institutions in the United States and five international organizations are linked via the system.

TELESYNERGY® Functionalities

- **Videoconferencing**
  - Simultaneous video and audio streams
  - Compatible with all videoconference systems on the open market, including PolyCom® and PictureTel®
- **Data Exchange**
  - DICOM image transfer (store and forward)
  - Data transfer, any type
- **Image Manipulation and Analysis**
  - X-rays, CT, MRI, ultrasound, etc.
- **Clinical and Research Microscopy**
- **Interactive Discussions and Teaching Sessions**
- **Imaging Add-ons as Needed**
  - Retinal camera, ultrasound machine, video colposcope, video laryngoscope, and others
- **Health Insurance Portability and Accountability Act of 1996 (HIPAA)–Compliant**

TELESYNERGY® units also link researchers globally. Currently, there are international systems situated in places such as Dublin, Belfast, Belgium, and Amman.

RRP continues to deploy TELESYNERGY® systems throughout the country and Europe. It also provides installation, training, and ongoing technical troubleshooting support and coordinates multisite TELESYNERGY® conferences.

Civilian Medical Response to Radiation-Related Events

http://www.hhs.gov/ophep/

RRP faculty are working with the Office of Public Health Emergency Preparedness (OPHEP) in the Department of Health and Human Services (DHHS) to develop the civilian medical response plan for radiological/nuclear terrorism. This involves efforts with a number of federal agencies, including the Department of Homeland Security (DHS), the Department of Energy (DOE), the Department of Defense (DoD), and the Homeland Security Council of the White House.

Medical Countermeasures against Radiological and Nuclear Threats Program

http://www3.niaid.nih.gov/research/topics/radnuc

Contact:
Carl Newman
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Weaponized radiation has become an uncomfortable reality in the post-9/11 world. Potential threats include radiological "dirty bombs" and nuclear explosives, but very few medical products exist to counter the variety of acute and long-term injuries that could result from nuclear or radiological attacks. To respond, DHHS, OPHEP, and NIH have issued a $47 million new NIH research program called Medical Countermeasures against Radiological and Nuclear Threats. The program is developing diagnostics, preventatives, and treatments for radiation sickness following a radiological event. RRP is the predominant NCI presence in this program because of its active radiation oncology program and extensive clinical expertise in radiobiology. In addition, several RRP senior members participated in the program's design.

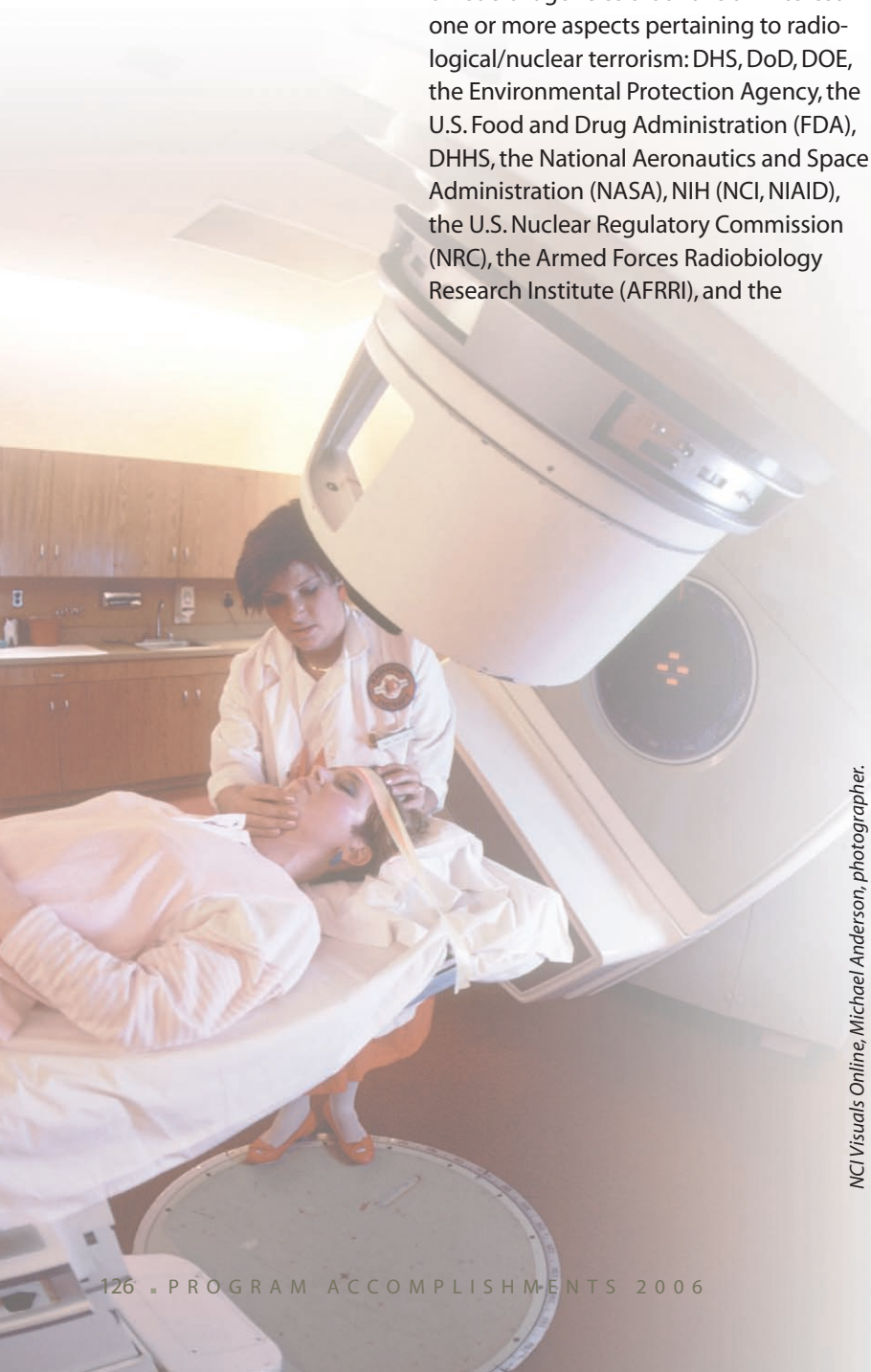
Under this initiative, RRP is collaborating with the National Institute of Allergy and Infectious Diseases (NIAID), the lead institute at NIH for the development of biodefense countermeasures. NIAID's research portfolio includes many in-depth studies of the immune system, which is especially vulnerable to radiation.

Twelve grants, four contracts, and two interagency agreements have recently been formalized through this new NIH research program. Central to this effort is the establishment of a network of multidisciplinary extramural Centers for Medical Countermeasures against Radiation (CMCRs) charged with developing new technologies to counter a radiological event and facilitate interactions with regulatory and public health organizations. This is the first federal-civilian research program dedicated to the development of medical countermeasures to be used by civilians in the event of exposure to radiation. The spin-off for normal tissue injury from cancer treatment is obvious and makes this investment an excellent use of the new federal dollars. Additional information is available on the NIAID Website at: http://www3.niaid.nih.gov/research/biodefense/biod_related.htm.

The relatively small size of the radiation research programs in NCI makes collaborative programs such as ROSP and RABRAT terrific vehicles for building a critical mass of ideas, talent, and enthusiasm.

Radiation Bioterrorism Research and Training

RRP has organized an informal group, Radiation Bioterrorism Research and Training (RABRAT), comprising representatives of federal agencies that have an interest in one or more aspects pertaining to radiological/nuclear terrorism: DHS, DoD, DOE, the Environmental Protection Agency, the U.S. Food and Drug Administration (FDA), DHHS, the National Aeronautics and Space Administration (NASA), NIH (NCI, NIAID), the U.S. Nuclear Regulatory Commission (NRC), the Armed Forces Radiobiology Research Institute (AFRRI), and the Radiation Emergency Assistance Center/Training Site (REAC/TS). The purpose is to inform each other and coordinate activities among agencies. This effort has been helpful in developing a strong collaborative climate for radiation experts working in government and for the extramural research and development communities.



NCI Visuals Online, Michael Anderson, photographer.

Radiation Oncology Sciences Program

http://ccr.cancer.gov/labs/lab.asp?labid=147

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The Radiation Oncology Sciences Program (ROSP) is a virtual NCI umbrella organization designed to enhance radiation oncology and biology activities across NCI's divisions, including those involved in intramural and extramural research. In addition to RRP, ROSP includes the Center for Cancer Research (CCR) Radiation Oncology Branch and Radiation Biology Branch. ROSP activities are domestic and international and contain patient outreach components.

While having no resources specifically allocated to it, ROSP facilitates translational research and supports collaborative approaches within NCI and between NCI and the extramural community. It also gives intramural investigators an opportunity to learn about the workings of the extramural community. The relatively small size of the radiation research programs in NCI makes collaborative programs such as ROSP and RABRAT terrific vehicles for building a critical mass of ideas, talent, and enthusiasm.

Of the many successful programs within the RRP grant and contract portfolio, three scientific advances are presented, one each for physics, tumor biology, and drug-radiation interaction.

New Image Detector May Enable Researchers to Determine Tumor Volume

Acquiring high-quality megavoltage images at extremely low radiation doses will enable more frequent and useful imaging. This is becoming a reality, thanks to a new image detector being developed through RRP-sponsored research at the University of Michigan and the Palo Alto Research Center. The new detection technology may make megavoltage computed tomography (MVCT) possible at clinically practical doses, enabling visualization of tumor volume with the patient in the treatment position, thereby minimizing errors due to patient or organ motion. Moreover, MVCT is subject to less X-ray scatter and is less sensitive to the presence of metal objects (dental fillings or hip implants) in the imaged volume than diagnostic (kilovoltage) CT, where such factors result in severe artifacts. Such benefits will enable the radiotherapy community to better achieve the central goal of radiotherapy—delivering maximum dose to the tumor while sparing normal, healthy tissue and critical organs.

Sawant A, Antonuk LE, El-Mohri Y, Li Y, Su Z, Wang Y, Yamamoto J, Zhao Q, Du H, Daniel J, Street R. Segmented phosphors: MEMS-based high quantum efficiency detectors for megavoltage X-ray imaging. *Med Phys* 2005:32;553–65.

Normalization of Tumor Vasculature

Because cancer cells in solid tumors require access to blood vessels for growth and metastasis, inhibiting vessel formation through a process called antiangiogenesis offers hope for reducing the mortality and morbidity from these tumors. However, when administered as single agents, antiangiogenic drugs have produced only modest objective responses in clinical trials, and overall, they have not yielded significant long-term survival benefits. In contrast, when given in combination with chemotherapy, bevacizumab, an antibody targeted against the potent angiogenic molecule vascular endothelial growth factor (VEGF), has produced an unprecedented five-month increase in survival in colorectal cancer patients.

Work by Dr. Rakesh Jain of Massachusetts General Hospital, supported with NCI funding managed by RRP, has led to a better understanding of the molecular and cellular underpinnings of vascular normalization. This research suggests that certain antiangiogenic agents improve delivery of drugs and oxygen to the targeted cancer cells by transiently improving blood flow to tumors. The increased drug penetration to the tumor can enhance the outcome of chemotherapy, and increased levels of oxygen can enhance the efficacy of radiation therapy and many chemotherapeutic agents. This work may ultimately lead to more effective therapies, not only for cancer but also for other diseases with abnormal vasculature, as well as regenerative medicine, in which the goal is to create and maintain a functionally normal vasculature.

Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science* 2005:307;58–62.

Enhanced Radiosensitivity

The Molecular Radiation Therapeutics Branch of DCTD has as one of its goals the development of new molecular therapeutics for radiation oncology. Publications this year by Dr. Phil Tofilon include:

- The first report showing that inhibitors of histone deacetylase, or HDAC, a modulator of chromatin structure and gene expression that affects radiation response, enhance radiosensitivity
- The first study to show that gamma-H2AX, a marker of DNA damage, can serve as an indicator of drug-induced radiosensitization
- The first demonstration that inhibition of DNA methylation results in enhanced tumor cell radiosensitivity
- The identification of ErbB3 (an epidermal growth factor receptor) expression as a predictor of the susceptibility to radiosensitization induced by Hsp90 (a protein that appears in heat-shocked cells) inhibition

Dote H, Cerna D, Burgan WE, Carter DJ, Cerra MA, Hollingshead MG, Camphausen K, Tofilon PJ. Enhancement of *in vitro* and *in vivo* tumor cell radiosensitivity by the DNA methylation inhibitor zebularine. *Clin Cancer Res* 2005:15;4571–9.

This RRP in-house laboratory program serves as a focal point for collaboration with the Developmental Therapeutics Program in DCTD, investigators in the Radiation Biology Branch and Radiation Oncology Branch in the Center for Cancer Research, and university and industry collaborators interested in combined modality therapy using radiation.

NCI Visuals Online, Linda Bartlett, photographer.

National Institute of Biomedical Imaging and Bioengineering

http://www.nibib.nih.gov/publicPage.cfm?pageID=639

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) is a component within NIH devoted to merging the physical and biological sciences to develop new technologies that improve health. Through an alliance with RRP, NIBIB engages in multidisciplinary medical physics and bioengineering research and aims to aid in the integration of technologies. RRP collaborative efforts include three-dimensional imaging for radiation oncology treatment planning, molecular diagnostic imaging, and numerous bioinformatics applications. RRP and NIBIB work together to explore new funding mechanisms tailored for imaging technology development.

RRP's collaboration with NIBIB accelerates the pace of discovery and speeds the development of biomedical technologies that prevent or treat illnesses. Sophisticated imaging techniques allow scientists to peer into the human body as never before. Recent developments in bioengineering promise to enhance the body's natural ability to recover from injury and disease.

National Electrical Manufacturers Association and the American College of Radiology Digital Imaging and Communications in Medicine Standard

http://www.nema.org

RRP promotes collaboration between imaging sciences and radiation oncology to develop objective determinations of tumor volumes. To facilitate this collaborative research, the American College of Radiology and the National Electrical Manufacturers Association (NEMA) have developed Digital Imaging and Communications in Medicine (DICOM 3), a standard that allows communication between medical image devices. Published by NEMA, the standard is entirely based on freely available software. NEMA recently released a 16-part update of the DICOM 3 standard.

DICOM 3 is used by virtually all medical professionals who use images, including specialists in cardiology, endoscopy, mammography, ophthalmology, orthopedics, pathology, pediatrics, radiation therapy, radiology, and surgery. RRP has participated in the extension of DICOM to DICOM–RT, which includes objects that are unique to radiotherapy such as dose distributions and the treatment delivery parameters.

Quality Assurance in Radiation Therapy Workshop

In September 2005, an RRP-led roundtable meeting addressed quality assurance (QA) issues for advanced technology radiation therapy. In this roundtable discussion, called "Quality Assurance in Radiation Therapy," researchers began to develop more robust QA for radiation therapy treatment planning and delivery. Attendees included physicists and physician experts using advanced radiation therapy technologies. The result was the creation of a white paper report on QA that lists recommendations for future NCI funding initiatives.

Image-Guided Therapy Retreat

RRP participated in an Image-Guided Therapy interagency retreat in 2006. It brought together leaders of federal government agencies, including the Centers for Medicare & Medicaid Services, DoD, DOE, FDA, NASA, NIH, the National Institute of Standards and Technology, and the National Science Foundation, who are interested in advancing image-guided technologies for human health interventions.

Young Investigators Workshop

ROSP/RRP held its fourth Young Investigators (YI) Workshop on the NIH campus in September 2005. This workshop was specifically targeting Radiation Oncology residents (PGY-4/PGY-5) and junior faculty within one year of completion of their residency who were interested in pursuing academic physician-scientist careers.

Co-chaired by Dr. Dennis Hallahan, chair of Radiation Oncology at Vanderbilt University Medical School, and Dr. Mark Dewhirst, professor, Department of Radiation Oncology, Duke University Medical Center, the workshop provided the attendees with: (1) scientific information on the most promising translational radiation oncology research areas; (2) information about grant funding opportunities, grant tips, and the grant review process; and (3) the opportunity to ask questions of the clinician/scientist speakers about the obstacles, barriers, and insights encountered in the pursuit of their academic careers as physician-scientists. Thirty-two residents and eight junior faculty representing 23 different academic institutions attended this highly successful workshop. During the various discussions, the speakers' and attendees' active input helped to identify the problems and challenges likely to be encountered by young physician-scientists in radiation oncology that RRP and NCI can start to help address by hosting a YI workshop like this.

Normal Tissue Injury and Countermeasures

Scientists from RRP participate actively in workshops organized by NIAID, as well as seminars and presentations related to normal tissue countermeasures.

RRP is planning a workshop related to the potential for post-exposure intervention to mitigate radiation-induced carcinogenesis, a topic relevant to clinical radiation oncology as well as radiation terrorism.

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