



Division of Cancer Treatment and Diagnosis

Program Accomplishments **2008**

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Program Accomplishments 2008



CAM



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Foreword

The Division of Cancer Treatment and Diagnosis (DCTD) focuses its activities on developing novel diagnostics and therapies for cancer. DCTD staff members, along with colleagues throughout the National Cancer Institute (NCI), academia, and industry, are working together to generate a seamless pipeline of biomarkers and therapeutics that runs the gamut from initial efforts in discovery through late-stage clinical trials. New cancer imaging techniques play a critical role in support of this pipeline as advances in image-guided diagnosis and image-guided therapies continue to emerge.

A primary goal of NCI's DCTD is to decrease the time necessary to bring anticancer drugs and biomarkers to the clinic while enhancing our ability to predict which treatments will be most useful for each patient. At the core of this objective is the implementation of the recommendations of the Clinical Trials Working Group (CTWG) and the Translational Research Working Group (TRWG), new efforts to coordinate and enhance NCI's drug discovery and chemical-biology engines, and our continued emphasis on first-in-human clinical trials. Furthermore, DCTD has recently completed a process in which unmet research needs in cancer therapeutics and diagnostics have been evaluated. The box accompanying this message provides a summary of these areas of investigative interest for the coming year.

Under the auspices of the CTWG, which in 2005 recommended 22 strategic initiatives for revamping the institute's cancer clinical trials system, NCI has conducted a systematic review of the steps involved in opening a clinical trial. On average, it takes about 1,000 days for an NCI-supported clinical trial to move from inception within a cooperative group to activation in an NCI-designated cancer center. As a result of these findings, NCI Director John Niederhuber, M.D., has pledged to cut the time from inception to activation in half.



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

Although NCI has a robust program of clinical trials and later stage preclinical development, over the past 15 years its drug discovery efforts have received less attention. To bridge the gap between academic drug discovery and the development of anticancer agents in the clinic, NCI is in the process of reinvigorating the process of cancer drug discovery through which academia, the private sector, and government work together to enhance NCI's capability to move novel compounds through the entire pathway from synthesis and lead molecule optimization, to target qualification, pharmacology, toxicology, formulation, and first-in-human trials.

In addition to the development of small molecule anticancer agents, DCTD is working to improve the range of immunotherapeutic approaches to cancer treatment. During a DCTD workshop conducted in July 2007 (<http://web.ncifcrf.gov/research/brb/workshops/NCI%20Immunotherapy%20Workshop%2007-12-07.pdf>), the immunotherapeutic molecules in the NCI pipeline were evaluated. Workshop participants produced a prioritized list of 20 possible immunomodulatory molecules that hold particular promise for use in cancer treatment. An organized process is now in place to either produce or obtain access to these compounds for use in future NCI-supported clinical trials.

Results from NCI's first-ever phase 0 trial—showing that such studies appear to substantially compress the drug development timeline—were presented last year at the annual meeting of the American Society of Clinical Oncology. Several new therapeutic and imaging agents are being readied for additional NCI phase 0 studies in collaboration with the NCI Center for Cancer Research at the NIH Clinical Center.

DCTD is also playing an important role in the implementation of recommendations made last year by the TRWG. The TRWG report developed 15 recommendations that focus on “early translation”—work done to move basic research discoveries into phase I and phase II clinical trials. The work of the TRWG complements several CTWG-related activities, which are focused on “late translation,” that is, primarily phase III clinical trials. At the request of Dr. Niederhuber, DCTD is now overseeing the Specialized Programs of Research Excellence (SPOREs), a major NCI vehicle for translational research. The SPOREs will be the chief component of the newly formed Translational Research Program (TRP) in DCTD.

In the pages that follow, you will find a summary of recently established priorities and scientific advances made possible by the many gifted and committed staff members throughout the division.

DCTD Research Interests

Areas of research interest currently underinvestigated in the DCTD portfolio:

Enhancing Tumor Response to Therapy

- Target-based drug development
- Development of combination therapies in clinically relevant models
- Targeting molecular signaling pathways
- Reducing toxicity using image-guided interventions to target drug delivery and activation
- Studies on the beneficial or harmful effects of anticancer agents on unintended targets
- Development of approaches, including complementary medicine approaches, to improve the therapeutic index of standard and investigational anticancer therapies

Investigations of the Tumor Microenvironment

- Design and testing of agents that target the tumor microenvironment using clinically relevant models
- Exploiting the tumor microenvironment’s role in therapy
- Understanding the dynamic relationship between tumors and cells in the microenvironment
- Measuring and evaluating the role of the tumor microenvironment in tumor transformations through imaging and other noninvasive methods

Development of New Methods and Technologies

- Development of new imaging technologies, including novel hardware, new research interfaces, refinement of image processing, and further development of virtual imaging

- Validation of imaging as a biomarker, including development of methods to better determine a response to therapy
- Development of new imaging agents
- Development and application of diagnostic devices and technologies that support multi-analyte molecular assays
- Development of integrated lab-on-a-chip diagnostic devices for real-time analysis of biospecimens
- Methods, mechanisms, and technologies to ensure the availability of clinical specimens for translational research

Clinical Studies

- Translational and clinical studies in the following underinvestigated diseases: pancreatic cancer, squamous cell carcinoma of the head and neck, bladder cancer, and sarcoma
- Validation of the clinical utility of molecular profiles
- Clinical studies using imaging approaches to characterize disease anatomy, physiology, and molecular biology
- Validation of the clinical utility of novel, innovative clinical diagnostic devices
- Development of personalized medicine approaches including the discovery, development, and qualification of biomarkers to define efficacy, toxicity, dosing, and schedule of therapy

Further details concerning these areas of research can be found on the DCTD Website: <http://dctd.cancer.gov>.



Division of Cancer Treatment and Diagnosis

Program Accomplishments

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.



CAM



DCTD Overview

The multiple programs within DCTD work together toward a common goal of identifying promising research areas and translating them into improved diagnostic and therapeutic interventions for patients with cancer. 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. By determining the highest priority questions that can be examined in the laboratory, developed through translational research, and tested in clinical trials, the multidisciplinary staff members of DCTD assure that appropriate mechanisms and resources are available to increase the number of novel interventions for the wide range of cancers affecting children and adults.

Another major objective for the division is increasing the scientific vigor with which new treatments are being developed and evaluated, while helping to coordinate the administration and conduct of clinical trials with other NCI components involved in the pursuit of clinical studies.

DCTD, like all of NCI, supports many programs that could not be done without government funding. Investigators supported by the division engage in scientifically sound, high-risk research that may yield great benefits for patients with cancer, but are too difficult or risky for industry or academia to pursue. This includes a particular emphasis on the development of distinct molecular signatures for cancer, refined molecular assays, and state-of-the-art imaging techniques that will guide oncologic therapy in the future.

The eight major components of the division allow DCTD to unite a broad range of crosscutting disciplines to bring unique molecules from the laboratory bench to the patient bedside.



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 helping to select promising agents to enter human clinical trials. In addition, the program also evaluates new radiation and surgical methods; identifies biomolecular characteristics of malignant tumors that investigators may be able to exploit clinically; and administers 11 cooperative research groups that unite researchers around the nation and the world in the pursuit of distinctive and effective new treatments for cancer.

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 is responsible for integrating the activities of DCTD with NCI's other divisions and offices, as well as extramural scientists and clinicians, patient advocates, and professional cancer organizations. He leads over 800 DCTD professional staff who represent a wide array of scientific specialties in a multidisciplinary endeavor to discover and develop better diagnostic and therapeutic interventions for cancer. Since coming to the NCI, Dr. Doroshow has led the effort to modernize NCI's clinical research infrastructure through the efforts of the Clinical Trials Working Group, and has initiated several new programs to reinvigorate early therapeutics discovery and development across the institute.

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 solid tumors.

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. 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 the 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* and is a member of the editorial boards of several other journals. 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 served as a member of the U.S. Food and Drug Administration Oncologic Drugs Advisory Committee from 2004 to 2007.

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) as a clinical associate in NCI's Medicine Branch. He is board-certified in internal medicine and medical oncology.

CTEP accomplishes its goals by administering, coordinating, and funding clinical trials, as well as sponsoring other research. The program fosters collaborations within the cancer research community and works extensively with the pharmaceutical and biotechnology industries. CTEP also works closely with the NCI Coordinating Center for Clinical Trials (CCCT) and its scientific steering committees to 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, vialled 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 radiation therapy; 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.

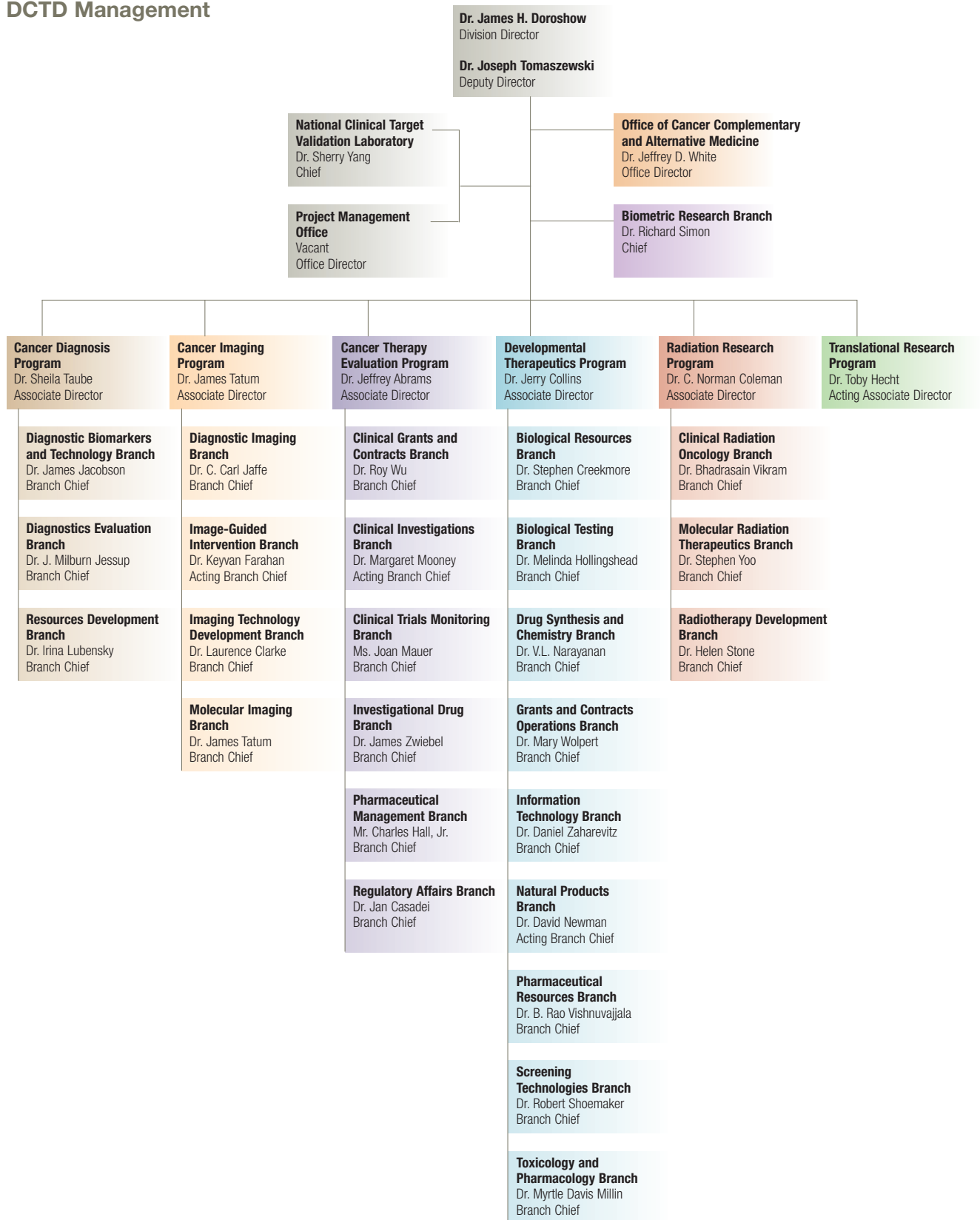
Biometrics Research Branch (BRB) provides state-of-the-art statistical and biomathematical analyses for DCTD and other NCI components and performs research in the areas of statistical, mathematical, and computational sciences that are motivated and informed by real and important problems in current cancer 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.

Office of Cancer Complementary and Alternative Medicine (OCCAM) coordinates NCI's involvement in identifying gaps in the science and creating corresponding funding opportunities in relation to complementary and alternative medicine (CAM); partners with NCI staff and other federal and nongovernmental organizations to increase the testing of CAM approaches with regard to cancer prevention, diagnosis, treatment, symptom management, and rehabilitation; develops communication products for various audiences concerning the investigation of these approaches; and helps to build bridges between CAM practitioners and the cancer research community.



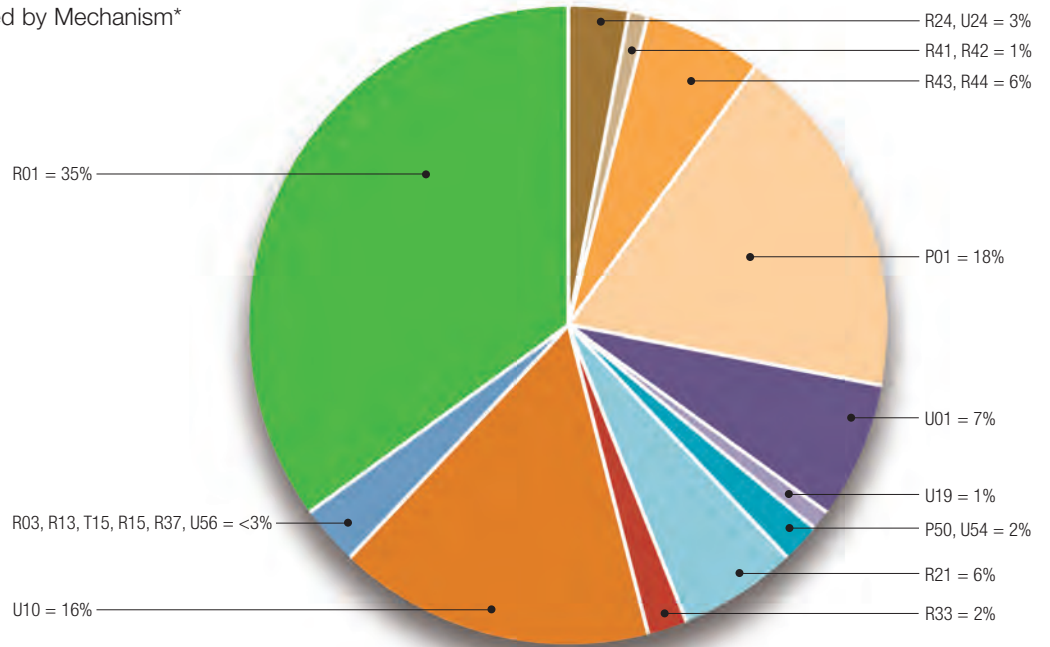
DCTD's eighth component, the **Translational Research Program** (TRP) was added to the division as this report went to press. Subsequent reports will include highlights from TRP, which houses the Specialized Programs of Research Excellence (SPOREs) grants.

DCTD Management



DCTD Research Grants

Percent of Grant Dollars Awarded by Mechanism*
Fiscal Year 2007



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
- R37 = Merit Awards
- 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 a division, DCTD staff members and their extramural colleagues are exploring various routes toward discovery, development, and delivery of cancer therapeutics. The fundamental objective is to find and develop more interventions tailored to the specific characteristics of a patient's cancer. The following summaries highlight some of the division's recent accomplishments in the areas of clinical and translational cancer research.

Changes to Early and Late Translational Research at NCI

The National Cancer Advisory Board (NCAB), within the last 4 years, has convened two broad-based panels to examine early and late translational research at NCI. The Clinical Trials Working Group (CTWG; http://integratedtrials.nci.nih.gov/ict/CTWG_report_June2005.pdf) reported its findings to the NCAB in 2005 and the Translational Research Working Group (TRWG; <http://www.cancer.gov/aboutnci/trwg/finalreport.pdf>) put forth its recommendations in 2007. The NCAB approved the findings of both groups, and important progress is being made in the implementation of these recommendations.

The CTWG focused on late translational studies, primarily phase III clinical trials, and the TRWG addressed early translational research, chiefly work done to move basic research discoveries into phase I and phase II clinical studies. The CTWG report recommended extensive changes to the NCI-supported clinical trials system that included establishing several committees that now play an important role in how NCI clinical trials are prioritized and initiated. This new infrastructure paved the way for the implementation of two of the TRWG recommendations:

- Under the auspices of CTWG, NCI established the internal Clinical Trials Operating Committee (CTOC), which the TRWG recommended be expanded to include translational research. To reflect the expansion, the committee is now known as the Clinical and Translational Research Operations Committee, or CTROC. This committee is designed to coordinate clinical trials and translational programs across the institute and to make recommendations to improve cost-effectiveness and reduce duplication and overlap among NCI components. CTROC will also evaluate new Requests for Applications and Program Announcements in these research areas prior to review by the NCI Executive Committee.
- The CTWG report recommended the formation of a Clinical Trials Advisory Committee (CTAC), an external oversight committee that oversees the implementation of CTWG initiatives, including the system to evaluate and measure the effects of the implementation. Following the recommendations of the TRWG, NCI has now expanded this committee to include oversight of translational research and the implementation of the TRWG recommendations. CTAC retains its acronym but now stands for the Clinical and Translational Advisory Committee.

The TRWG report, along with the CTWG changes, expanded the role of the recently created Coordinating Center for Clinical Trials (CCCT) (<http://ccct.nci.nih.gov/>). The center now includes a Translational Research Support Office. CCCT is managing the implementation of all CTWG and TRWG initiatives.

Progress continues in other areas affected by the recommendations of both working groups. The CTWG called for the development of disease-specific scientific steering committees.

To date, steering committees have been established in the following areas: gastrointestinal cancer; gynecologic cancer; genitourinary cancer; head and neck cancer; patient advocacy; and symptom management and health-related quality of life. The lung cancer steering committee is currently in development. These steering committees prioritize phase III concepts for therapeutic clinical trials and convene State-of-the-Science meetings to prioritize strategies for NCI-supported clinical trials.

Another major initiative recommended in the CTWG report was the development of a comprehensive database of NCI-supported clinical trials. The pilot phase of the project will begin in summer 2008. The development of this database is being spearheaded by the NCI Center for Biomedical Informatics and Information Technology, in collaboration with DCTD, CCCT, as well as NCI's Division of Cancer Prevention, Office of Communications and Education, and the Cancer Centers Program.

Evaluating the Predictive and Prognostic Value of Molecular Markers to the Epidermal Growth Factor Receptor in a Phase III Study of Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)

The DCTD's Cancer Therapy Evaluation Program (CTEP) has led a major effort by NCI, the Food and Drug Administration (FDA), and the Centers for Medicare and Medicaid (CMS) to develop a national clinical trial for non-small cell lung cancer (NSCLC) to validate a predictive marker for therapies targeted to the epidermal growth factor receptor (EGFR). The study is currently in late phase development and is expected to be activated in Fall 2008.

Both erlotinib and pemetrexed are approved second-line treatments for advanced NSCLC and are currently being tested in different first-line

and adjuvant settings. EGFR inhibition may be more effective in a selected, rather than an unselected, population. In several studies, retrospective analyses of subsets of patients have recognized molecular and/or clinical features associated with increased probability of response to EGFR inhibition. These features include EGFR gene copy number or protein expression, mutational status, proteomics profile, adenocarcinoma histology, female gender, Asian ethnicity, and smoking status. However, no prospective study has been performed to definitively address this issue. With the current available information, it is still not clear which, if any, EGFR-related marker will accurately predict a population that will benefit from EGFR inhibition.

The study, known as N0723, is an intergroup phase III study that will be led by the North Central Cancer Treatment Group and is designed to prospectively determine whether patients with advanced lung cancer and with high or low EGFR copy number have differences in outcome when treated with the tyrosine kinase inhibitor erlotinib or the chemotherapeutic agent pemetrexed, in the second-line setting. It is hypothesized that erlotinib will be superior in the patients with EGFR-positive lung cancer, whereas pemetrexed would be favored in the patients with EGFR-negative lung cancer. In addition, the study will incorporate pharmacogenetic studies for both erlotinib and pemetrexed that will be important to further identify patients with different sensitivity and toxicity profiles to these therapies.

This study will attempt to prospectively and definitively establish the value of selecting the treatment patient population based on the presence or absence of a tumor molecular marker in the patient. The study will try to answer questions regarding the predictive and prognostic value of EGFR molecular markers, as well as correlations with clinical features. Approximately 1,200 patients will be tested for the presence or absence of the marker, and the treatment populations will

be randomized based on the outcome. Both EGFR-positive or EGFR-negative patients will receive either erlotinib or pemetrexed.

Pioneering Phase 0 Study Heralds Shortened Timeline for Anticancer Drug Development

A new compound, called ABT-888, has passed the first stage of clinical examination using a new model for drug development, phase 0, that promises to shorten—by up to 1 year—the timeline for taking anticancer drugs from the laboratory to the clinic. This result was presented at the 2007 annual meeting of the American Society of Clinical Oncology (ASCO). Since the ASCO report, ABT-888 has entered more comprehensive phase I trials, and new compounds have been readied for phase 0 testing by NCI.

Instead of being assessed in a traditional phase I clinical trial, which explores drug safety and tolerance, ABT-888 was first tested in a phase 0 trial conducted as part of the NCI Experimental Therapeutics (NExT) program. This phase 0

trial showed that using an approach that focuses on mechanism of action can reduce the number of patients required for an early clinical study, and the time necessary to gather critical information for development of the drug.

ABT-888 inhibits an enzyme called poly (ADP-ribose) polymerase that is critical for repairing damage to DNA.

A critical aspect of this trial was the development of a rigorous assay to measure the molecular effect of ABT-888 in tumor tissue. The study showed that the compound inhibited its target enzyme in tumor cells as well as in circulating white blood cells. This latter finding may allow white blood cells to be used in ongoing trials to measure whether the agent is altering its presumed target.

Kummar S, Kinders R, Gutierrez M, Rubinstein L, Parchment RE, Phillips LR, Low J, Murgu AJ, Tomaszewski JE, Doroshow JH, NCI Phase 0 Working Group. Inhibition of poly (ADP-ribose) polymerase (PARP) by ABT-888 in patients with advanced malignancies: Results of a phase 0 trial. *J Clin Oncol* 2007: ASCO Annual Meeting Proceedings (Post-Meeting Edition) 25;3518.

The NCI Experimental Therapeutics Program (NExT) Program

DCTD and the Center for Cancer Research (CCR) are working in close collaboration to reinvigorate cancer drug development at NCI. Through a joint early therapeutics development program, extramural and intramural teams have prioritized a pipeline of NCI-driven targeted therapeutics for development. This program, called the NCI Experimental Therapeutics (NExT) program, combines the strengths of DCTD's extensive expertise in anticancer drug development with CCR's dynamic in-house research and its location within state-of-the-art facilities at the NIH Clinical Center.

The NExT program requires research resources that are not readily available at most medical centers engaged in

anticancer drug development. The goal of the NExT program is to shave up to 1 year off the typical 10- to 12-year drug-development cycle.

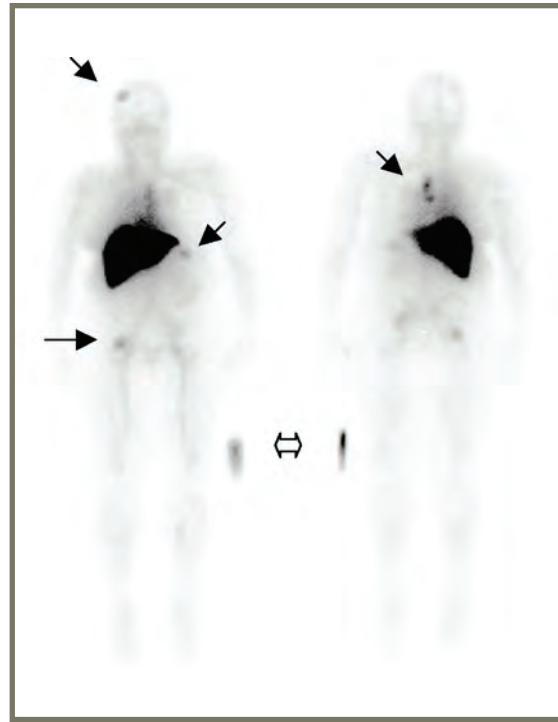
The NExT program has grown out of the reality that the number of new anticancer agents reaching human clinical trials has been modest. Even when compounds do proceed to clinical testing, they often fail because of unexpected toxicities or are not effective. NExT not only allows phase 0 trials to be conducted in humans, it brings together the teams of scientists necessary to develop and perform assays that can measure the biological effects of potential new anticancer agents. The assays provide a tool for the systematic removal of investigational agents from NCI's drug development pipeline that do not show expected biological effects and inform and expedite decisions about further clinical development.

Phase 0 Imaging Agent Study

Imaging agents are also being developed as part of the NExT program. The growing interest in these agents stems from their potential to diagnose, stage, manage, monitor, and even treat tumors. One such agent under development is ¹¹¹Indium-trastuzumab.

Trastuzumab targets the human epidermal growth factor receptor 2 (HER2), which is overexpressed in breast and other cancers. ¹¹¹Indium-trastuzumab imaging, if successful, could be used to localize HER2-positive disease in patients with metastases. It could also identify HER2-positive lymph nodes, and therefore may be useful in conjunction with sentinel node biopsy. The imaging agent may also provide a measurement of HER2 expression within tumors that are inaccessible to biopsy. Moreover, because the process in which the ¹¹¹Indium-trastuzumab is made allows other radioisotopes to be substituted for ¹¹¹Indium, a variety of radiolabeled trastuzumab agents could be made for delivering localized radioimmunotherapy to HER2-positive tumors.

A phase 0 trial using ¹¹¹Indium-trastuzumab scanned its first patient in Spring 2008.

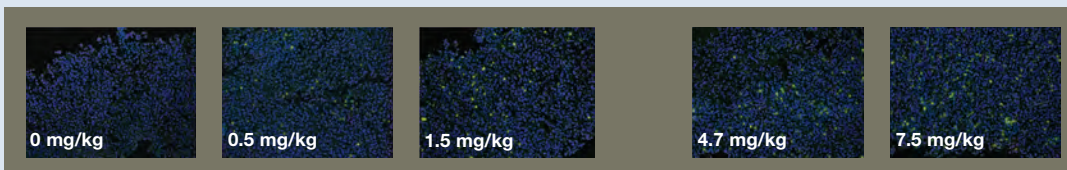


Whole body images of a patient with HER2-positive metastatic breast cancer 4 hours following injection of ¹¹¹Indium-trastuzumab. The solid arrows demonstrate uptake in bony metastases. Intense uptake in the liver is physiologic because it is the primary route of excretion. The hollow arrow indicates the location of a radiation source placed external to the patient for calibration.

More Phase 0 Activities

A new assay that has been developed for phase 0 trials measures the presence of γ -H2AX in tumor tissue. γ -H2AX is a phosphorylated version of the histone H2AX that is made when DNA is damaged in a cell. The level of γ -H2AX directly correlates with the amount of double-strand DNA breaks per cell. Thus, γ -H2AX can be used as a biomarker for DNA damage caused by chemotherapeutic drugs. The assay was validated using the DNA-damaging agent topotecan.

New drugs developed by CCR that produce double-strand DNA breaks will be monitored in phase 0/I trials using this assay. CCR developed these new agents in concert with the DCTD Developmental Therapeutics Program by searching for compounds that had characteristics of camptothecin, but were more potent and stable. In this search, the CCR team discovered a class of compounds known as idenoisoquinolines that will enter NCI clinical trials in 2008. By measuring γ -H2AX, researchers will be able to monitor how well the idenoisoquinolines hit their molecular target.



γ -H2AX response in an A375 human xenograft model 4 hours after a single dose of topotecan at the doses indicated.



Cancer Diagnosis Program

Program Accomplishments

The Cancer Diagnosis Program (CDP) strives to improve patient outcomes by effectively moving new diagnostic tools 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 Overview

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 NCI programs, offers a range of initiatives that encourage and support research in cancer diagnostics and related development of technology and specimen resources.

CDP administered approximately 250 funded grants in 2007.

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. PACCT is not a grants program and has not previously focused on building infrastructure. Instead, the program has leveraged other NCI-supported activities to accomplish goals identified by the PACCT Strategy Group. The strategy group is comprised of scientists, drawn from academia as well as the Food and Drug Administration (FDA) and NCI, 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 diagnostic issues in specific tumors as needed. The Breast Cancer Working Group's efforts led to the Trial Assigning Individualized Options for Treatment (TAILORx), which is assessing the utility of a

Major Ongoing Initiatives

Program for the Assessment of Clinical Cancer Tests

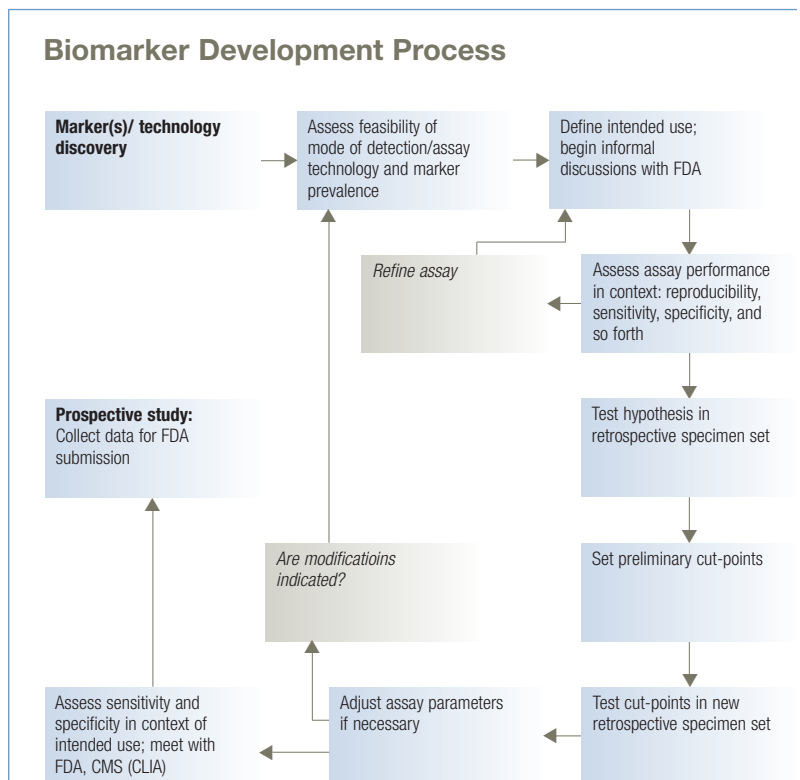
<http://www.cancerdiagnosis.nci.nih.gov/assessment/index.htm>

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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



SHEILA TAUBE, ASSOCIATE DIRECTOR

Sheila Taube, Ph.D., served as Associate Director of the Cancer Diagnosis Program (CDP) within the Division of Cancer Diagnosis and Treatment (DCTD) from 1997 until June 2008. Under Dr. Taube's leadership, CDP 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 CDP. 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 contributed to a seminal paper in the *Journal of the National Cancer Institute* on guidelines for reporting studies of 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 Organization 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 called "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.



molecular signature to identify women with early stage breast cancer who can be treated with only hormonal therapy because their risk of recurrence is so low. The signature also identifies those patients who will benefit from the addition of chemotherapy.

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. As part of these activities, PACCT initiated a study to determine the intra- and interlaboratory reproducibility of assays to determine loss of heterozygosity at chromosome 18, since this assay is being used to stratify patients in a colon cancer clinical trial being led by the Eastern Cooperative Oncology Group (ECOG). The performance of the assay is being evaluated in collaboration with the investigators running the assay for the trial and pathologists from two other cooperative groups. The pathologists also plan to evaluate the specimens from the ECOG trial and two other large adjuvant colon cancer trials to evaluate promising markers to predict response to targeted agents being used in these trials.

Another subcommittee of the PACCT Strategy Group developed criteria for prioritizing studies of essential clinical assays that will be funded through the Coordinating Center for Clinical Trials (CCCT). These criteria were reviewed and approved by NCI's Clinical Trials Advisory Committee (CTAC).

A subcommittee was also formed to develop a document specifying standards of evidence required to support the inclusion of an assay in a phase III clinical trial. The data justifying the use of the clinical assay must be included in the clinical trial protocol. The document outlining the categories of information to be required was approved by CTAC. Work is now proceeding to specify what information must be included in protocols.

A working group of PACCT organized an NCI/FDA/industry workshop to consider strategies, challenges, and barriers to the co-development of targeted therapies and predictive assays necessary to optimize the use of the therapies. Three case studies were used to illustrate the challenges and barriers: HER2/trastuzumab, epidermal growth factor receptor (EGFR)/EGFR inhibitors, and a current co-development project presented by industry. Results of the workshop discussions will be presented in a publication addressing the information needed to help make decisions about whether and how to develop the drugs and predictive assays and how best to generate that information.

Over the past several years, the PACCT Strategy Group has identified a series of barriers to the efficient development of clinically useful assays. CDP broadly advertised a Request for Information (RFI) to identify specific needs. Results from the RFI indicated the need for a variety of resources, including specimens, technical assistance, support for statistical expertise, and assay standards. There was also significant interest in having educational materials available to help inform the research community about issues related to clinical assay development. To respond to the identified needs and provide the necessary resources to the research community, CDP is developing a new program called Molecular Diagnostics Evaluation Laboratories, or MoDEL.

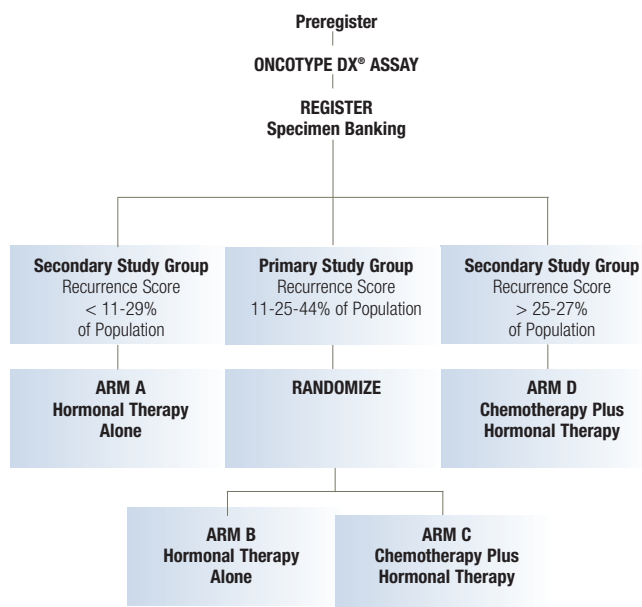
Trial Assigning Individualized Options for Treatment (TAILORx)

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Breast cancer stamp sales by the U.S. Postal Service are playing a critical role in making a groundbreaking treatment trial possible by

TAILORx Schema



providing a portion of the funding for TAILORx. Without this support, the trial would not have been possible. TAILORx, the first trial launched by PACCT, is pioneering the integration of molecular diagnostics into clinical decision making for breast cancer. The trial is testing whether a set of expressed genes 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 being tested is the 21-gene Oncotype DX[®] panel developed by Genomic Health, Inc., in collaboration with an NCI cooperative group, the National Surgical Adjuvant Breast and Bowel Project. 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. Accrual is almost two-thirds complete.

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. <http://www.ncbi.nlm.nih.gov/pubmed/15591335>.

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.

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 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



Strategic Partnering to Evaluate Cancer Signatures Projects

Childrens Hospital Los Angeles, Los Angeles, CA

<http://deais.nci.nih.gov/Query/search/details?grantID=7291522&grtSCDC=FY%202007>

PRINCIPAL INVESTIGATOR:

Timothy J. Triche, M.D., Ph.D.

This project is refining and validating molecular signatures that provide a more accurate diagnosis and that more accurately predict clinical behavior of common childhood sarcomas. Plans are under discussion with the Children's Oncology Group (COG) to incorporate a diagnostic signature for rhabdomyosarcomas into COG clinical trials.

University of California, Irvine, CA

<http://deais.nci.nih.gov/Query/search/details?grantID=7284897&grtSCDC=FY%202007>

PRINCIPAL INVESTIGATOR:

Dan Mercola, M.D., Ph.D.

This project is refining and validating molecular signatures that predict relapse in prostate cancer patients and that distinguish indolent disease from disease that will progress. A clinical version of the assay is being evaluated in collaboration with Althea Diagnostics, a small diagnostics company.

University of Nebraska Medical Center, Omaha, NE

<http://deais.nci.nih.gov/Query/search/details?grantID=7240538&grtSCDC=FY%202007>

PRINCIPAL INVESTIGATOR:

Wing C. Chan, M.D.

This project is refining and validating diagnostic and prognostic molecular signatures for the major subclasses of non-Hodgkin lymphoma. This project is a collaboration between the University of Nebraska Medical Center, NCI investigators, investigators from the clinical cooperative groups, and investigators from five international institutions.

University of New Mexico, Albuquerque, NM

<http://deais.nci.nih.gov/Query/search/details?grantID=7283610&grtSCDC=FY%202007>

PRINCIPAL INVESTIGATOR:

Cheryl L. Willman, M.D.

This project is refining and validating molecular signatures that improve risk classification and prediction of response to therapy in pediatric and adult ALL. A plan to incorporate a signature that predicts minimal residual disease in children with high-risk ALL into COG clinical trials is under discussion.

Vanderbilt-Ingram Cancer Center, Nashville, TN

<http://deais.nci.nih.gov/Query/search/details?grantID=7294922&grtSCDC=FY%202007>

PRINCIPAL INVESTIGATOR:

David P. Carbone, M.D., Ph.D.

This project is refining and validating molecular signatures in lung cancer, including serum proteomic signatures that differentiate patients with cancer from those without disease, signatures that predict risk of recurrence following surgery, and signatures that predict response to EGFR-targeted therapies. A clinical trial evaluating the signature that predicts response to anti-EGFR therapies is being initiated in collaboration with Genentech.

Washington University in St. Louis, MO

<http://deais.nci.nih.gov/Query/search/details?grantID=7273500&grtSCDC=FY%202007>

PRINCIPAL INVESTIGATOR:

Matthew J. Ellis, M.D., Ph.D.

This project is refining and validating molecular signatures that identify five subtypes of breast tumors using quantitative polymerase chain reaction to measure signatures in formalin-fixed, paraffin-embedded tissues. These signatures will add useful information to the established diagnostic categories of breast cancer and help avoid either under- or over-treatment.

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. Plans are being prepared for several of the signatures developed in SPECS to be evaluated in prospective clinical trials.

The investment in the SPECS projects is being leveraged in the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program being developed in collaboration with CTEP and the NCI Office of Cancer Genomics. Gene expression data on over 200 high-risk pediatric acute lymphoblastic leukemia (ALL) patients generated in the leukemia SPECS project are being combined with data on genomic alterations being developed on the same patients by investigators at St. Jude Children's Research Hospital. The combined data are being used to identify genes altered in ALL that are candidates for sequencing. Approximately 200 genes are being sequenced to identify mutations that may be potential targets for drug development. A second TARGET project is being initiated to take advantage of the gene expression data being developed on the SPECS pediatric sarcoma project.

Current Funding Opportunities

Phased Application Awards in Cancer Prognosis and Prediction

PROGRAM ANNOUNCEMENTS:

PA-06-434: <http://grants.nih.gov/grants/guide/pa-files/PA-06-434.html> (expiration date 05/08/2009)

PA-06-435: <http://grants.nih.gov/grants/guide/pa-files/PA-06-435.html> (expiration date 05/08/2009)

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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 5 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-06-299: <http://grants.nih.gov/grants/guide/pa-files/PA-06-299.html> (expiration date 01/08/2009)

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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 2 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.

Studies with Specimens from Multisite Trials

PROGRAM ANNOUNCEMENTS:

PA-08-134: <http://grants.nih.gov/grants/guide/pa-files/PA-08-134.html> (expiration date 05/08/2012)

PA-08-133: <http://grants.nih.gov/grants/guide/pa-files/PA-08-133.html> (expiration date 05/08/2011)

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Over the past 5 years, NCI has sponsored more than 1,500 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 in 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 2 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 honing 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.

Development, Application, and Evaluation of Prediction Models for Cancer Risk and Prognosis

PROGRAM ANNOUNCEMENTS:

PA-07-021: <http://grants.nih.gov/grants/guide/pa-files/PA-07-021.html> (expiration date 01/08/2010)

PA-07-022: <http://grants.nih.gov/grants/guide/pa-files/PA-07-021.html> (expiration date 01/08/2010)

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The purpose of these funding opportunity announcements for R01 or R21 applications is to encourage clinicians, epidemiologists, geneticists, statisticians, and translational cancer control and prevention researchers to improve existing models for cancer risk, prognosis, or response to therapy by developing innovative research projects that use existing data to develop new models for cancer risk and prognosis and/or validate new models and evaluate their utility in research and clinic settings.

These funding announcements are designed to provide a mechanism under which investigators can address two major challenges in model development: integrating diverse types of data (clinical, demographic, pathologic, environmental, epidemiologic, outcomes, and genetic data from varied data marts or warehouses), and ensuring adequate validation (using multiple separate populations to define sensitivity, specificity, and positive and negative predictive values).

Using the National Institutes of Health (NIH) Research Project Grant R01 funding mechanism, PA-07-021 focuses on well-developed projects supported by preliminary data and allows for some new data generation. Investigators proposing early phase, exploratory projects should submit applications in response to the partner funding announcement of identical scientific scope (PA-07-022), which uses the R21 mechanism and does not permit generation of new data.

Partnerships and Collaborations

European Organization for Research and Treatment of Cancer and American Society of Clinical Oncology

<http://www.eortc.be>

<http://www.asco.org>

CDP has led an NCI collaboration with the European Organization for Research and Treatment of Cancer (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. The REporting Recommendations for Tumor MARKer Prognostic Studies (REMARK) were published in several major scientific journals in 2005 and 2006. The American Society of Clinical Oncology (ASCO) has now joined the collaboration. With ASCO's involvement, the "Molecular Markers in Cancer" meeting, sponsored since November 2007 by EORTC, NCI, and ASCO, will be held annually. The meetings will alternate between sites in U.S. and Europe. A tutorial for young oncologists and scientists involved in biomarker research will occur each year in conjunction with the meeting.



Food and Drug Administration

<http://www.fda.gov>

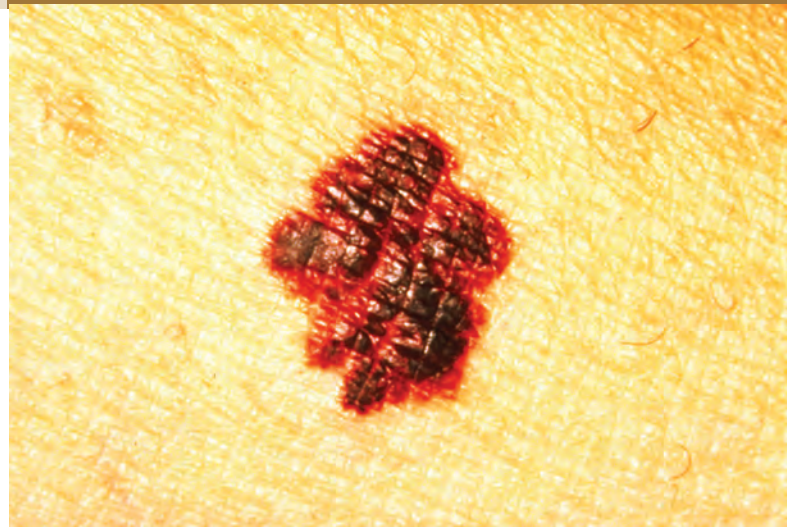
Through an interagency agreement, a CDP staff member has a joint appointment with NCI and FDA. This person has primary responsibility as a program director managing a portfolio of technology development and proteomics grants in the CDP Diagnostic Biomarkers and Technology Branch. At FDA, the staff person 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 studied by NCI grantees to detect molecular changes in cancer. The staff person also serves as a liaison between NCI and FDA on issues related to technology applications.

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 a workshop of melanoma research experts in 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 is now available to the melanoma community.



More than 50 prominent melanoma researchers met in 2005 for the Resources for Melanoma Research Workshop, which was cosponsored by CDP, the NCI skin cancer SPORE, 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 by the SPORE program. CDP will coordinate this activity to provide these valuable resources to the melanoma research community.

A new set of TMAs with matched primary lesions, lymph nodes, and metastatic lesions is currently under construction.

CDP is also involved in NCI melanoma focus groups in conjunction with the Melanoma Research Foundation and investigators from the melanoma research community. These groups are identifying and coming to consensus on the directions needed to make more progress in melanoma research.

Scientific Advances

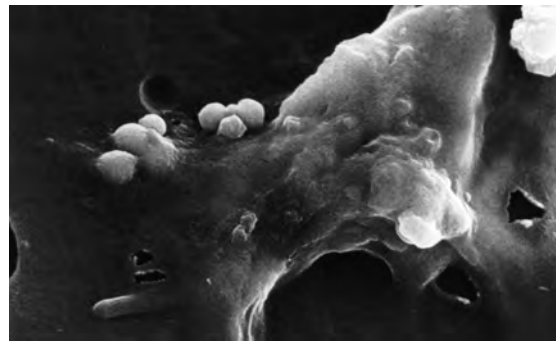
MicroRNAs in Cancer Translational Research

A workshop entitled “MicroRNA: Potential for Cancer Detection, Diagnosis, and Prognosis” was sponsored by CDP in November 2006. The importance of microRNAs (miRNAs) in regulation of gene expression and development has recently been recognized. Altered regulation of miRNA expression has been demonstrated to play a role in cancer initiation and progression. The workshop brought together leaders in the miRNA field to discuss the potential for the application of miRNAs in translational research. The workshop focused on the current understanding of miRNAs and the potential for their application in cancer diagnosis, prognosis, and as potential therapeutic targets. The workshop provided a brief overview of the basic science of miRNAs, updated approaches to the application of miRNAs in cancer diagnostics, advanced ideas regarding the potential therapeutic applications of miRNAs, discussed how lessons learned from translational cDNA array studies could inform translational miRNA studies, and discussed the next steps required to advance this field. A meeting report was published.

Tricoli JV, Jacobson JW. MicroRNA: Potential for cancer detection, diagnosis and prognosis. *Cancer Res* 2007;67:4553–55.
<http://www.ncbi.nlm.nih.gov/pubmed/17510380>

Immune Profiling Workshop Report to be Published

A meeting entitled “Profiling of Immune Response to Guide Cancer Diagnosis, Prognosis, and Prediction of Therapy” was held in Washington in November 2007 and was sponsored by CDP and the NIH Office of Rare Diseases. The meeting highlighted the importance of the role that patterns of inflammatory cells, immune modulators, and variations in the host genetic background play in influencing clinical outcome in cancer patients. Immunological criteria have been shown to be strong indicators of risk, prognosis, and response to treatment, and they could be routinely measured and



included in pathological reports. Comprehensive analysis of lymphocytic reactions (including CD8+ T lymphocytes, myeloid cells, regulatory T-cell responses, cytokines, and chemokines) and functional genetic variations in immune regulatory genes could identify groups with the best outcome in various malignancies. As these variables become useful, clinically proven metrics, they could improve current measures of staging criteria for prognosis and classification of a high-risk population of tumors influencing current strategies for effective cancer treatments. The meeting also addressed issues relevant to study design, statistical approaches, and tissue resource availability. Improvements in these areas are crucial for clinical validation to facilitate the translation of biomarkers into the clinic. A meeting report is scheduled for publication.

Ambs S, Marincola FM, Thurin M. Profiling of immune response to guide cancer diagnosis, prognosis, and prediction of therapy. *Cancer Res* 2008;68:4031-3.





Tools, Products, and Resources

Advice and Resources for Cancer Diagnostics Researchers

<http://www.cancerdiagnosis.nci.nih.gov/diagnostics/advice.htm>

The advice and resources 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 Webpage also lists literature resources for marker development methods.

Human Tissue Specimen Resources

<http://www.cancerdiagnosis.nci.nih.gov/specimens/index.htm>

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**

<http://cbctr.nci.nih.gov>

The Cooperative Breast Cancer Tissue Resource (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. CBCTR also offers TMAs that provide materials for testing associations between marker prevalence and either stage of disease or outcome.

- **Cooperative Human Tissue Network**

<http://chtn.nci.nih.gov/index.html>

The Cooperative Human Tissue Network (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 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 600,000 high-quality specimens from a wide variety of organ sites to more than 1,000 investigators. The CHTN also distributes TMAs that represent gynecologic, childhood, and other cancers. Details of these TMAs may be found on the Website.

- **NCI Clinical Trials Cooperative Groups**

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.

Disease-Specific Tissue Microarrays for Melanoma and Colorectal Carcinoma

CDP has developed TMAs to assist investigations in melanoma and colorectal carcinoma. The melanoma TMA is designed to investigate differences in prevalence of markers in various stages of melanoma progression. A TMA designed to assist investigation into disease progression is also available. CDP is now offering a colon cancer TMA that not only supports studies of marker prevalence in all stages of disease but also clinical outcome. A similar TMA for rectal carcinoma will be available in 2008, as will a TMA that permits analysis of marker expression in assorted colorectal polyps.

Tissue Expediter

<http://www.cancerdiagnosis.nci.nih.gov/specimens/finding.htm#expediter>
<http://pluto3.nci.nih.gov/tissue/default.htm>

The Tissue Expediter is a contractor who works with CDP scientists to identify sources of human tissue specimens and helps 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.

Guidelines to Help Researchers Evaluate Whether Markers or Assays Are Ready for Use in Clinical Settings: Reporting Studies of Tumor Markers

<http://www.cancerdiagnosis.nci.nih.gov/assessment/progress/remark.htm>

The REMARK guidelines resulted from a collaboration between a PACCT strategy group and an NCI-EORTC working group. REMARK includes information that should be reported in the all publications about tumor markers. These recommendations were published simultaneously in the *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 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.

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.
<http://www.ncbi.nlm.nih.gov/pubmed/16106245>

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.
<http://www.ncbi.nlm.nih.gov/pubmed/16043346>

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. *J Clin Oncol* 2005;23:9067-72.
<http://www.ncbi.nlm.nih.gov/pubmed/16172462>



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.
<http://www.ncbi.nlm.nih.gov/pubmed/16106022>

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.
<http://www.ncbi.nlm.nih.gov/pubmed/16130938>

Repository of Molecular BRAin Neoplasia DaTa

<http://rembrandt.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; <https://cabig.nci.nih.gov>), and investigators in the National Institute of Neurological Disorders and Stroke.

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 data set 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.





Cancer Imaging Program

Program Accomplishments

The Cancer Imaging Program (CIP) of the Division of Cancer Treatment and Diagnosis is an innovative program that encourages coordination and 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.





CIP Overview

The role of imaging in cancer research is changing, and CIP continues to be a catalyst for this transformation. In the past, the focus of imaging research was creating clearer and more detailed anatomic pictures of organs and tissues. Today, the primary new thrust in imaging is on functional or molecular imaging, which visualizes the physiological, cellular, or molecular processes in living tissues as they take place. Molecular imaging is critical for fundamental improvements in the care of cancer patients. While we continue to discover new molecular signatures of cancer in our crusade to develop more effective therapies with lower morbidity, these efforts can be successful only through understanding how these targets integrate into the complex systems of tumor biology. *In vivo* molecular imaging is a unique method to allow us to acquire this knowledge.

In the next decade, CIP-sponsored research will not only contribute to the basic understanding of various cancers, but it will enhance the clinical role of imaging in noninvasive diagnosis, help identify disease subsets in patients, improve disease staging and treatment monitoring, and play a pivotal role in the development of new therapies.

CIP unites researchers from disciplines as diverse as radiology, nuclear medicine, bioengineering, biology, chemistry, computer science, and physics in a team approach to problem solving. The program encourages extramural researchers to integrate and apply new imaging discoveries and developments to drug discovery, monitoring of therapies, and understanding cancer biology. This is aimed directly at the clinical management of cancer and cancer risk. CIP divides its staff and administers grants among four branches:

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

Through this organization, CIP supports and advises innovative investigators in academia and private industry as they create the next generation of imaging technologies, including molecular probes, imaging 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 and the National Cancer Institute contributing to the integration of imaging with 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 408 funded grants during fiscal year 2007.

Major Ongoing Initiatives

CIP initiatives cover the full spectrum of research efforts from basic research to clinical trials. These programs serve a variety of needs in the cancer imaging community. While many of the basic research efforts are investigator initiated, several key program announcements use the R01 and R21 grant mechanisms to foster needed research. The *In Vivo* Cellular and Molecular Imaging Centers (ICMIC), Small Animal Imaging Resource (SAIR) Program, Network for Translational Research in Optical Imaging (NTROI), and American College of Radiology Imaging Network (ACRIN) each use specialized grant mechanisms suited for their positions in the research pipeline.

CIP also works in close collaboration with intramural NCI scientists in the development of new imaging probes. A number of these probes are positron emission tomography (PET) agents for molecular imaging directed at important targets such as angiogenesis and proliferation. This collaboration is bidirectional, forming a novel development pipeline with the NCI Center for

JAMES L. TATUM, ASSOCIATE DIRECTOR

James L. Tatum, M.D., joined the Cancer Imaging Program (CIP) in 1998 as a Special Assistant to the Associate Director, lending his expertise to the areas of molecular imaging and imaging drug development. In 2006, Dr. Tatum became Chief of CIP's Molecular Imaging Branch. In July 2007, he became the Acting Associate Director of CIP, and in July 2008 was named Associate Director.



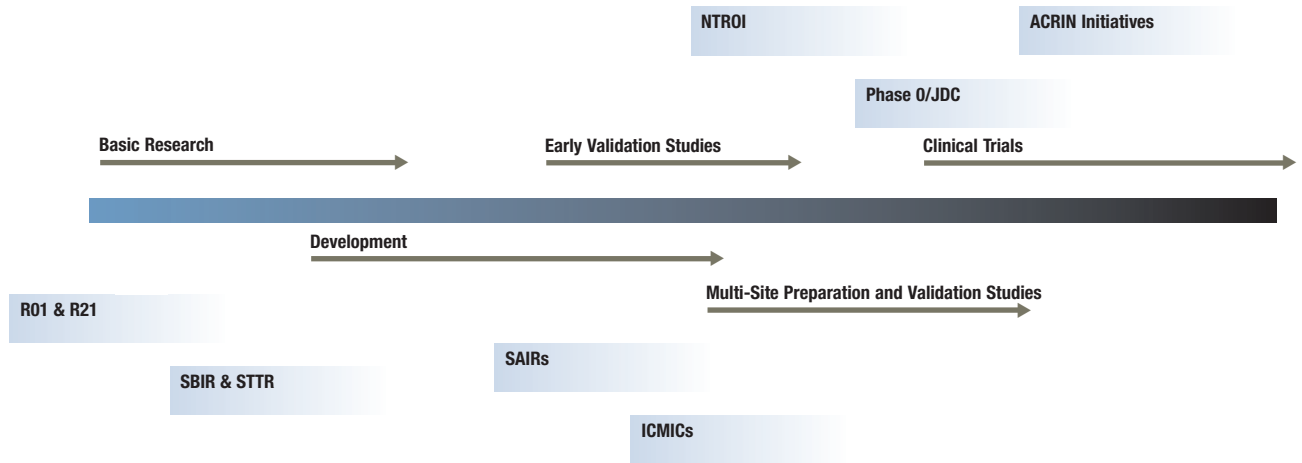
Dr. Tatum represents imaging from the NCI viewpoint on the steering committee for the Nanotechnology Characterization Laboratory (NCL), a joint effort of the National Cancer Institute, Food and Drug Administration, and National Institute of Standards and Technology. He is also a member of the NCL review panel and serves on the steering committee of the Small Animal Imaging Program at NCI-Frederick. As chair of the imaging drug group of the Joint Development Committee, he plays a key role in overseeing imaging agents in the NCI drug pipeline.

Early in his research career, Dr. Tatum focused on imaging alterations in the pulmonary capillary membrane associated with acute respiratory distress syndrome and the application of imaging techniques to evaluate drug interventions. Later, his research shifted to studies of myocardial ischemia, including acute coronary syndrome, with a focus that continues in his research today on the use of imaging in medical decision making.

Dr. Tatum received his undergraduate degree in biology from the College of William and Mary and his M.D. from the Medical College of Virginia (MCV). He completed his residency in medicine and radiology at MCV Hospitals, followed by a nuclear medicine fellowship at Duke University. He is board certified in diagnostic radiology, nuclear medicine, and nuclear cardiology. In 1978, he joined the faculty of Virginia Commonwealth University (VCU), where he was ultimately appointed Professor of both Radiology and Medicine. During his tenure at VCU, he served as the Chairman of the Division of Nuclear Medicine, Director of Nuclear Cardiology, Chairman of the Department of Radiology, Associate Vice President for Health Sciences, and Director of the Molecular Imaging Center.



The Imaging Research Spectrum and Key CIP Programs



Cancer Research (CCR), which is providing the infrastructure for early clinical trials of imaging probes while DCTD provides the expertise in drug development.

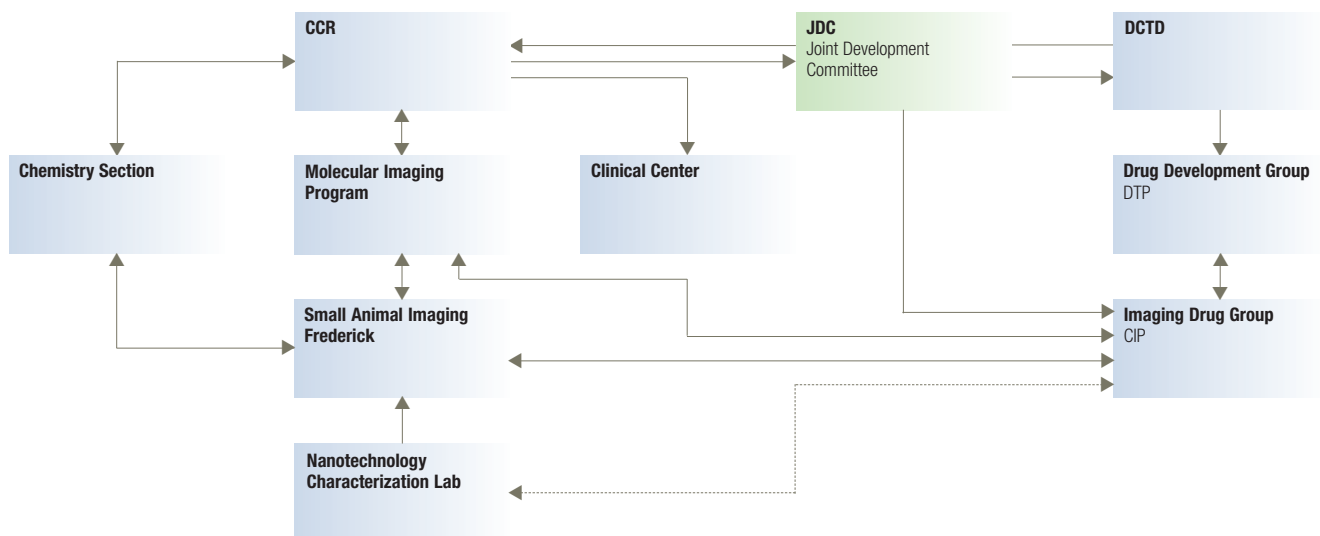
Imaging Drug Group

Molecular imaging has an enormous impact on the entire spectrum of clinical cancer management and cancer research. Almost every NCI Strategic Priority will depend on information and knowledge gained from imaging, whether it is from the use of molecular imaging as a surrogate marker, assay, or therapeutic effectiveness metric or from a greater understanding of tumor biology and molecularly targeted therapeutic interventions. The great promise of image-guided therapeutic interventions is just beginning to be realized. However, the ability to provide this information requires significant innovations in imaging systems, especially for molecular imaging agents, where the greatest opportunities and the strongest challenges lie. The Development of Clinical Imaging Drugs and Enhancers (DCIDE) program was an important contributor of molecular imaging drugs for the strategic priorities in early detection, prevention, and prediction; inte-

grative cancer biology; strategic development of cancer interventions; and integrated clinical trials. In the last year this imaging drug development program became the foundation for the Imaging Drug Group (IDG) that integrated the activities of several cross-institute imaging drug activities into one decision-making committee. In doing so, the IDG subsumed the DCIDE program and formed bridges to other important programs, such as the DCTD-CCR Joint Development Committee (JDC) program, and with the DCTD Drug Development Group (DDG) program. The IDG also acts in an advisory role with the CCR Molecular Imaging Program (MIP) and Small Animal Imaging Program (SAIP-Frederick) as well as the Nanotechnology Characterization Laboratory (NCL).

The IDG, developed during the past year, is essential for facilitating the development of novel imaging agents because very few alternative sources of funds exist for such studies. For most academic investigators who discover interesting new lead compounds for imaging agents, the regulatory process is unfamiliar and daunting terrain. Most commercial entities and universities correctly view development of such discoveries as high risk (high cost, low potential

Imaging Drug Development at NCI



revenue) that often cannot be justified in an environment of limited resources. Pre-investigational new drug (pre-IND) application and early feasibility studies cannot generally be funded through the typical grant mechanisms because they are considered neither original research nor novel. The IDG provides an excellent mechanism to bridge the gap between new discovery in imaging drugs and delivery of new agents to the cancer patient.

The Broader IDG Mandate

The IDG also:

- Centralizes imaging drug development under one group; although it is administratively in CIP, it has broad representation and thus the capability to steer multiple resources to overcome barriers.
- With the active partnership between DTP (DDG) and CIP (IDG), synthesis and scale-up of imaging drug precursors and/or drugs for preclinical studies is leading to IND and good manufacturing practices (GMP) preparation for first-in-human studies.
- Through collaboration with the CCR's MIP and the implementation of the SAIP-Frederick, IDG has the resources for pre-clinical imaging studies. IDG also serves as the imaging subcommittee for the JDC and thus plays a role in phase 0/1 imaging drug studies conducted in the intramural program at the NIH Clinical Center (CC).
- IDG, acting in accord with JDC, allows for collaboration between DCTD and CCR. CCR has expertise and resources that are of mutual interest to DCTD and vice versa, paramount of which are access to a clinical platform and clinical populations for DCTD and access to imaging drug expertise and resources for CCR.



Clinical Trials and the IDG

While the JDC offers a mechanism to perform phase 0 and imaging feasibility studies at the CC, this venue is not sufficient to perform many studies due to a number of factors, including lack of PET radiochemistry capabilities, limited access to imaging time, and lack of access to appropriate patient populations. CIP is working with academic centers and commercial vendors that have capabilities and patient populations that complement the CC capabilities. Using this mechanism, CIP has been able to support DDG and JDC imaging drug development needs. This mechanism comprises a significant portion of the IDG portfolio.

Later phase clinical trials both of imaging drugs and of imaging in the evaluation of therapy are funded through the ACRIN cooperative group, which is funded by CIP. Another mechanism for inclusion of imaging in therapy trials is by supplements to trials being funded through other cooperative groups.

NCI Imaging Clinic

As noted above, exploratory and imaging feasibility trials are primarily performed outside of the NCI intramural program. This is partly related to the limited access of the NCI intramural program to either radiochemistry or imaging platform resources required to perform such studies. Over the last few years with the creation of an intramural MIP, the concept of an NCI Imaging Clinic has been developed to provide a dedicated research infrastructure for such trials. During the last year the planning and implementation of this facility have been initiated.

Synthesis of GMP Agents

As part of the imaging drug development pipeline, the acquisition of GMP-produced agents and precursors is a pivotal step to clinical trials. For imaging agents, the commercial interest in production is tempered by limited potential markets. While there are a few examples of small biotech products, most imaging agents of interest at the current time are labeled species of existing drugs, through a process of chelation or by synthesis of labeled species from precursor compounds. CIP has developed mechanisms to secure these materials.



Clinical Trials

American College of Radiology Imaging Network Clinical Trials

CIP continues to fund ACRIN under a cooperative agreement mechanism. ACRIN, funded since 1999, has the mission to develop a consortium that generates, executes, and reports on multicenter clinical trials in cancer imaging. ACRIN has gained a position of leadership in imaging clinical trials through their primary scientific role and imaging expertise in the conduct of clinical trials. A well-developed infrastructure (including a statistical headquarters at Brown University and a collection of active scientific committees) supports complex medical imaging multicenter trials accruing to date over 76,000 participants across

more than 100 institutions. Through its sophisticated technological infrastructure and extensive engagement with the imaging and oncology research communities, ACRIN is in a unique position to perform the rigorous trials that validate emerging imaging approaches to clinical care and clinical research and to establish standards for their implementation.

ACRIN underwent a comprehensive external review in June 2007 to evaluate its progress, and it received a high rating, making continued funding possible. At their annual meeting in September 2007, ACRIN presented recent scientific achievements, and the original principal investigator (PI), Bruce Hillman, M.D., introduced his successor, Mitchell Schnall, M.D., Ph.D., who will act as PI for the coming funding cycle.

Current CIP Trials

Recruiting	Accrual Goal
CIP Lead (All Early/Exploratory)	
OHSU, Response to Therapy, Recurrent Glioblastoma, MR with Ferumoxytol	12
Wayne State, Response to Therapy, Breast, ¹⁸ FAU/FMAU PET	15
Wayne State, Feasibility, Lung, ¹¹ C-AMT PET	10
OHSU, Response to Combination Therapy, Glioblastoma, MR with Ferumoxytol	12
Trials for Validation of Imaging-Based Biomarkers from the Oncology Biomarker Qualification Initiative (OBQI)	
CALGB 50303, FDG-PET Imaging in Non-Hodgkin Lymphoma to Predict Tumor Response to Treatment	478
ACRIN 6678, ¹⁸ FDG-PET/CT as a Predictive Marker of Tumor Response and Patient Outcome: Prospective Validation in Non-Small Cell Lung Cancer	228
ACRIN Lead	
ACRIN 6660, Pediatric Malignancy Staging with Whole-body MRI	226
ACRIN 6673, Hepatocellular carcinoma, Image-guided Therapy, Radiofrequency Ablation	120
ACRIN 6677, Brain Tumors, Staging with MR Perfusion Imaging and MR Spectroscopy	121
ACRIN Collaborative	
ACRIN 6671 (GOG), Cervix, ¹⁸ FDG-PET/CT and MRI Using Ultrasmall Superparamagnetic Iron Oxide (USPIO) Particles (CIP IND)	325
ACRIN 6668, Lung Cancer, Predicting Therapy Response with ¹⁸ FDG-PET	250
ACRIN 6675 (SWOG), Melanoma, Therapy monitoring with ¹⁸ FDG-PET	110
NCI 7529 Cancer Inst NJ, Breast, Dynamic Contrast-enhanced (DCE) MRI	40
RTOG 0522, Brain, Predicting Response to RT, ¹⁸ FDG-PET/CT	720



In Follow Up Actual Accrual

ACRIN Lead

ACRIN 6654, National Lung Screening Trial (NLST), CT screening for Lung Cancer	18,893
ACRIN 6666, Breast Screening with Ultrasound (US)	2,809

ACRIN Collaborative

ACRIN 6651(GOG), Staging with CT and MRI (Analysis)	208
ACRIN 6657 (CALGB), I-SPY Breast Trial with Imaging End Point	237
ACRIN 6662 (NABBT), Malignant Glioma, Retrospective Trial Volume Measurement Reliability with MRI	48
ACRIN 6665 (RTOG), Gastrointestinal Stromal Tumor (GIST), Therapy Monitoring with ¹⁸ F-FDG-PET	63

In Analysis and Publication Actual Accrual

ACRIN Lead

ACRIN 6658, Supraglottic Cancer, Volume Measurement Reliability with CT	24
ACRIN 6659, Staging Prostate Cancer with MRI and MRS	134
ACRIN 6652, Digital Mammographic Imaging Screening Trial (DMIST), Digital Versus Film-Screen Mammography	49,520
ACRIN 6656, Diagnostic Accuracy of CT Colonography	117
ACRIN 6661, Bone Metastases, Therapy with Radiofrequency Ablation	66
ACRIN 6664, National CT Colonography Trial	2,617
ACRIN 6667, Screening of Contralateral Breast with MRI	1,007

In Development

CIP Lead (All Early/Exploratory)

UW, Predict Response to Therapy, Cervix, ¹⁸ F-MISO-PET
UW, Predict Response to Therapy, Breast, ¹⁸ F-FES-PET
VCU, Response to Therapy, Breast, ¹⁸ F-FLT-PET
VCU & JHU, Response to Therapy, Lung, ¹⁸ F-FLT-PET
Cornell, ¹³ N Gemcitabine-PET, Response to Therapy
Arkansas, ¹¹ C-SN-38-PET, Response to Irinotecan Therapy

ACRIN Lead

ACRIN 6674, Breast, Focused Ultrasound Ablation under MRI Guidance
ACRIN 6672 (CALGB), Bladder, Therapy Planning with USPIO-enhanced MRI
ACRIN 6676 (ECOG), Renal Cell Carcinoma, Staging with CT and MRI
Wash U, Predict Response to Therapy, Cervix, ⁶⁴ Cu-ATSM

ACRIN Collaborative

SWOG 0518, Carcinoid Tumors, Response to Therapy, CT Using Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines
SWOG 0502, GIST, Response to Therapy, ¹⁸ F-FDG PET/CT
RTOG 0625, Brain, response to Therapy, DCE-MRI
ACOSOG Z4033, Lung, Response to RFA ¹⁸ F-FDG PET

Clinical Trial Support

Image Response Assessment Teams

CIP continues to manage the Image Response Assessment Team (IRAT) program with the Association of American Cancer Institutes (AACI) as the coordinating center. In 2007, the IRATs completed their third and last year of funding. The primary goal of IRATs has been to promote functional and molecular imaging endpoints in therapy trials. IRATs are members of cancer center programs or those who participate in Specialized Programs of Research Excellence (SPOREs) grants. Once imaging protocols are approved, the IRATs have taken responsibility for analysis, interpretation, and integration of data. Over the course of the first 2 years of support, IRATs have facilitated standardization and adoption of specific protocols.

The IRATs have made progress in advancing solutions to qualitative and quantitative imaging analysis in the context of physiologic and anatomic properties inherent in images. They have also coordinated acquisition and use of phantoms to advance image instrument calibration and quality assurance of images useful as biomarkers in therapy trials.

Virtual Imaging Evaluation Workspace

Started in 2007 as a joint effort between CIP and the Cancer Therapy Evaluation Program (CTEP), the Virtual Imaging Evaluation Workspace (VIEW) establishes a technical infrastructure to permit timely collection of images and relevant patient information from cancer therapy clinical trials. This 3-year program will broadly enable expert independent review of these images for large clinical trials upon request. Central image collection and analysis may be necessary when clinical images play a key role in trial result validity—such as protocol-defined primary or secondary endpoints of progression-free survival or time to progression or when imaging data are utilized for decision making in trials that include therapeutic crossover or Bayesian designs. The expert independent reads will generate quantitative, semi-quantitative, or qualitative data as prespecified by an image charter agreed to by the Food and Drug Administration (FDA) and included in the trial protocol document.

This infrastructure provides image collection processes that may also be requested for phase I and phase II trials, non-therapeutic trials, or non-FDA relevant trials, where sponsors—NCI/CTEP or otherwise—deem it necessary or desirable.

IRAT Institutions and Their IRAT Principal Investigators

Arizona Cancer Center

Robert Gillies, Ph.D.

Holden Comprehensive Cancer Center, University of Iowa

Michael Graham, M.D., Ph.D.

Memorial Sloan-Kettering Cancer Center

Lawrence Schwartz, M.D.

Ohio State University Comprehensive Cancer Center, James Cancer Hospital & Solove Research Institute

Michael Knopp, M.D., Ph.D.

Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University

Richard Wahl, M.D.

Siteman Cancer Center of Barnes Jewish Hospital Washington University School of Medicine

Barry Siegel, M.D.

UC Davis Cancer Center, the University of California

John Boone, Ph.D.

University of Pittsburgh Cancer Institute

James Mountz, M.D., Ph.D.



Translational Research

In Vivo Cellular and Molecular Imaging Centers

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

CONTACT:

Anne E. Menkens, Ph.D.
301-435-9024, am187k@nih.gov

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 5 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.

Network for Translational Research: Optical Imaging

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

CONTACT:

Houston Baker, Ph.D.
301-594-9117, bakerhou@mail.nih.gov

The Network for Translational Research in Optical Imaging (NTROI) is a cooperative group of four research centers, each of which is itself a multi-institutional specialized research resource team organized to develop, integrate, and validate specific optical imaging technologies for faster translation to clinical applications in cancer early detection, diagnosis, guided therapy delivery, and therapeutic response. A broad range of technologies is represented, such as single and multimodal devices, software, targeted and non-targeted imaging agents, and therapeutic agents. CIP's objective for networking these centers is to focus a wide range of expertise on all aspects of the technology translation process—from invention through validation to clinical studies aimed at securing FDA approval. The network approach facilitates the sharing of methods and strategies for translating optical imaging to the clinical environment. NTROI investigators have used its structure to establish collaborations more effectively and leverage more work out of existing and new research funding from both within and outside the network. They have leveraged funds derived from a wide range of NIH funding mechanisms, such as SBIR, STTR, R21, R33, R01, P30, and P50 grants.

In Vivo Cellular and Molecular Imaging Center Institutions and Principal Investigators

Johns Hopkins University

Zaver Bhujwala, Ph.D.

Massachusetts General Hospital

Ralph Weissleder, M.D., Ph.D.

Memorial Sloan-Kettering Cancer Center

Ron Blasberg, M.D.

Stanford University

Sanjiv (Sam) Gambhir, M.D.

University of California, Los Angeles

Harvey Herschman, Ph.D.

University of Michigan

Brian Ross, Ph.D.

University of Missouri-Columbia

Wynn Volkert, Ph.D.

Washington University in St. Louis

David Piwnica-Worms, M.D., Ph.D.

PARADIGM SHIFT

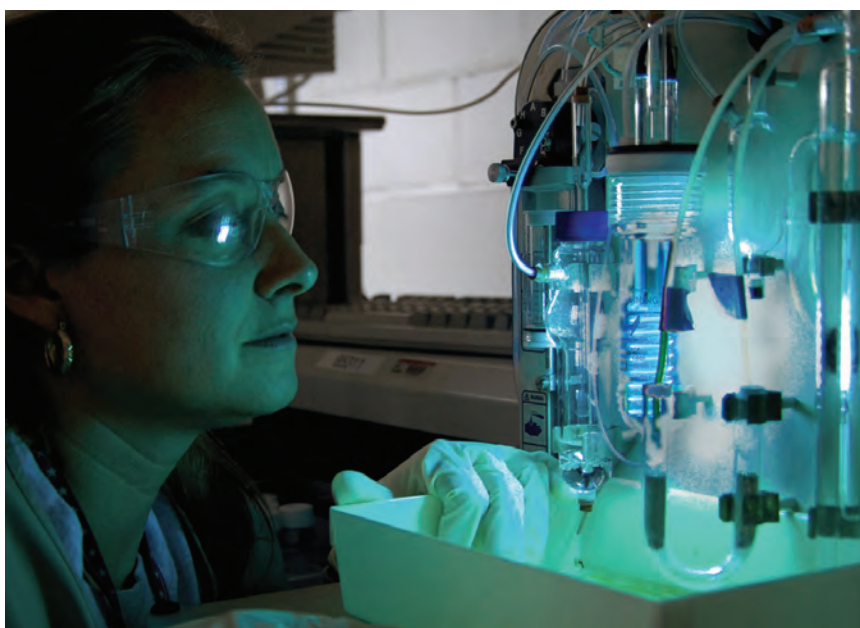
The recent emergence and rapid growth of new optical imaging methods for cancer imaging stems from newly established technologies to directly measure, for example, endogenous molecular and functional features, and even perform high-resolution microscopy *in vivo* using fiber optics, well beyond the capabilities of long-established lens-based compound optical microscopy. From inception, the NTROI concept was to engineer a paradigm shift toward faster, more effective translation of leading prototype medical optical systems to clinical use.

By 2007, NTROI investigators achieved multiple successes, among them spectrometry for breast screening and real-time *in vivo* differentiation of adenocarcinoma from high- and low-grade dysplasia in Barrett's esophagus. The breast spectrometer has been licensed to FirstScan, Inc., and a commercializable prototype recently started clinical studies for diagnosis of X-ray dense breasts. The optical spectrometer, which was developed for biopsy site selection during Barrett's surveillance, has been licensed to two companies, with Optimum Technologies, Inc., commercializing the spectrometer platform and

another undisclosed company developing an integrated fiber-optic front end into biopsy forceps and snares for applications in the esophagus and colon. NTROI investigators have strong associations with multiple industrial partners, mostly high-technology small businesses, who are actively accelerating the translation of the technologies toward clinical practicality. The industrial partners provide experience and expertise in quality control and analysis, performance validation, and development under GMP standards—all important for successful translational research.

PROGRAM RENEWAL

The NCI Board of Scientific Advisors recently approved renewal of NTROI for 2008. The reissued RFA (<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-002.html>) has been modified to place more emphasis on combining new optical modes with established medical imaging and spectroscopic modalities to create multimodality platforms capable of delivering improved diagnostic sensitivity and specificity.





Small Animal Imaging

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.

To make imaging tools available to a greater pool of researchers, CIP created the Small Animal Imaging Resource (SAIR) Program. 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

Small Animal Imaging Resource Program Institutions and Principal Investigators

University of Michigan

Brian Ross, Ph.D.

University of Texas M.D. Anderson Cancer Center

John Hazle, Ph.D., and Juri Gelovani, M.D., Ph.D.

University of Pennsylvania

Jerry Glickson, Ph.D.

Memorial Sloan-Kettering Cancer Center

Jason Koutcher, Ph.D.

Washington University

Joseph Ackerman, Ph.D.

Duke University

G. Allan Johnson, Ph.D.

Johns Hopkins University

Martin Pomper, M.D.

Massachusetts General Hospital

Ralph Weissleder, M.D., and Umar Mahmood, M.D., Ph.D.

Vanderbilt University

John C. Gore, Ph.D.

University of California, Los Angeles

Michael E. Phelps, Ph.D.

Case Western Reserve University

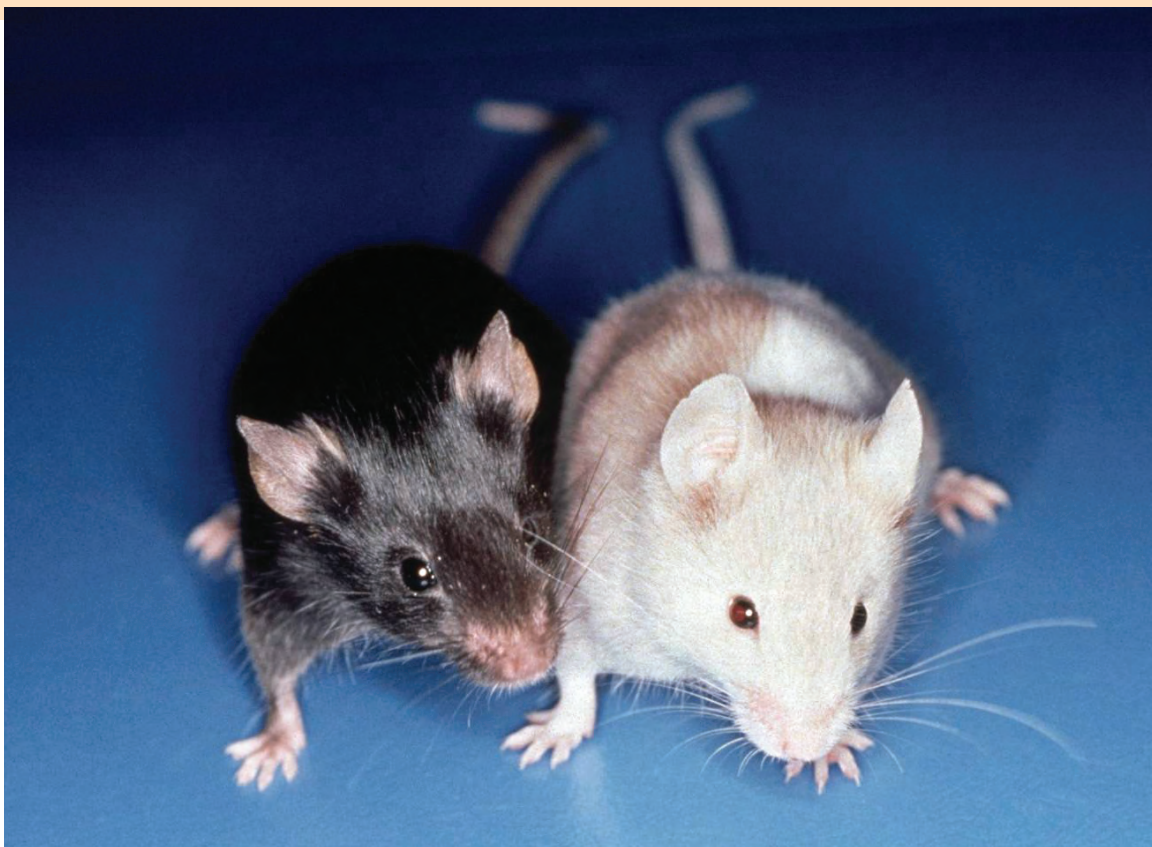
Jeffrey Duerk, Ph.D.

University of California, Davis

Simon Cherry, Ph.D.

University of Texas SW Medical Center at Dallas

Ralph P. Mason, Ph.D., and A. Dean Sherry, Ph.D.



CIP is funding 13 SAIRs 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, and the previous initiative, which was released in 2003. These small animal resources focus on different topics. For example, the SAIR at Case Western Reserve University established a shared resource for the Northern Ohio region, with six participating institutions. During 2007, there were 35 independent projects with 22 different

researchers. They are implementing a training program for their region based on the imaging camp that the NCI sponsored in 2007. At the Memorial Sloan-Kettering Cancer Center, SAIR funding was used to add an ultra-high-resolution ultrasound imaging system to be used with and without microbubble contrast agents. The options available provide true 3-D ultrasound images, allowing assessment of tumor size and blood flow without the use of ionizing radiation.



Intramural Program Support: Small Animal Imaging Program at NCI-Frederick

<http://web.ncifcrf.gov/rtp/lasp/intra/saip/default.asp>

The NCI-Frederick Small Animal Imaging Program (SAIP) was established under the Laboratory Animal Sciences Program (LASP) through collaboration among DCTD and several other NCI components to provide NCI investigators with a state-of-the-art *in vivo* imaging facility. The SAIP became operational in October 2006 with the installation of a 3.0 Tesla MRI unit. Additional equipment added since then includes a Xenogen IVIS SPECTRUM for bioluminescence and fluorescence imaging, a CRi Maestro for fluorescence imaging, a VisualSonics Vevo 770 40Mhz ultrasound unit for real-time sonography, and a Siemens Inveon MicroPET scanner. A Siemens Inveon

microSPECT/CT imaging platform that will dock to the microPET device and a Fuji FLA-5100 autoradiography/fluorescence/chemiluminescence unit have been ordered.

Although SAIP is not fully staffed at this point, there are 16 active imaging protocols with over 600 imaging studies completed and 11 proposed additional protocols under review at this time. In addition, while SAIP continues to collaborate and support the partnership that led to the formation of the program, it has developed an extensive set of collaborations with other programs at Frederick and with industry. Collaborations within LASP have provided unparalleled expertise in animal sciences. Collaborations with CIP-funded SAIRs are oriented toward improved animal handling, standardized imaging, bioinformatics, and assay systems.

NCI-Frederick SAIP Imaging Capabilities



Informatics

National Cancer Image Archive

The National Cancer Image Archive (NCIA), developed in concert with the NCI Center for Bioinformatics (NCICB) cancer Biomedical Informatics Grid (caBIG), is a scalable, network-accessible image repository tool to address the broadest possible image processing community (medical and non-medical) that can advance computer-aided diagnosis and hybrid man-machine detection of disease. It also can provide network distributable images for measuring response to therapy in clinical trials. As of 2007, the image repository contains more than 3 terabytes of data and more than one million images from a range of clinical imaging instruments, including CT, MRI, and PET/CT.

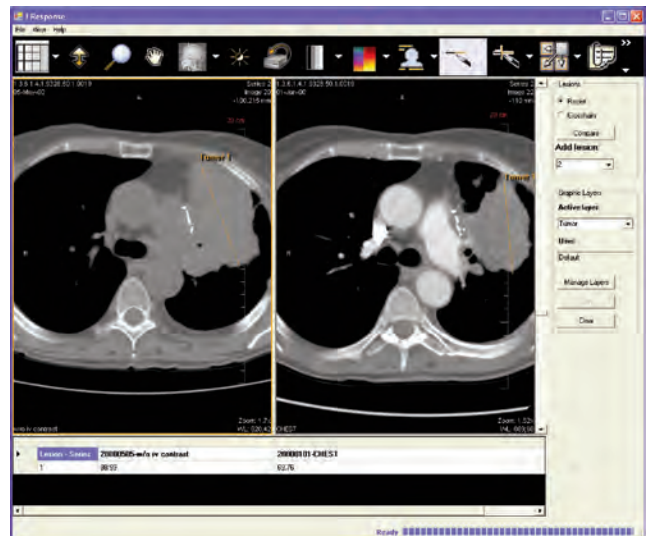


Network access is created in an open-source, open-software environment devised on a confederated model that encourages diverse cross-disciplinary research entities to share images, using free downloadable software from the caBIG Website. The network connects images stored at ACRIN and the Pediatric Brain Tumor Consortium to caBIG.

Currently, eight specific collections are available to researchers. The content and objectives of the Lung Image Database Consortium (LIDC) was defined by a public-private partnership to advance computer-aided diagnosis of lung disease. The Reference Image Database for

Evaluation of Response (RIDER) serves a research community that is developing computer methods for assessing tumor change over time during therapy as a function of anatomic size, dynamics, and molecular imaging methods. Of special note are Web-searchable image collections such as PET/CT phantom data from a variety of clinical instrument manufacturers provided by the American Association of Physicists in Medicine, which will aid in exploring and characterizing machine image artifacts, accuracy, and reliability.

The archive thus provides sophisticated tools for transferring, searching, and downloading large or small portions of the collections in their originally acquired format. In addition, the NCI server offers a variety of downloadable viewing and analytic software tools. One of those meriting special attention is the Cedara I-Response viewer, which is tightly linked operationally to the NCI image server. Exploiting the advantage of the linkage between the archive and the viewer tool, CIP brought together clinical researchers at the Roswell Park Cancer Institute and the University of Rochester to conduct, across the internet, an experiment for jointly assessing lung tumor response to therapy. The images are transmitted from the central server to the investigators, who can assemble independent measures to evaluate agreement and reproducibility.



RECIST measurements taken on a lung tumor at two different times.



The Image Workspace

An important component of the NCI Image Archive effort is the closely associated, CIP-coordinated “Imaging Workspace.” The Workspace consists of more than 60 extramural imaging informatics experts from across the country representing multiple subspecialty areas, unified by a common objective to develop online software to:

- Facilitate the sharing of image display, processing, and analysis algorithms
- Develop computing tools that exploit caBIG’s potential to promote interoperability, improve security, and support more efficient sharing of image data and software algorithms
- Create a “standard” means of adding information/knowledge to an image in a clinical environment to create a future in which image content and observer-placed overlays can be easily and automatically searched
- Create a means of describing image acquisition devices and protocols in a unified fashion that is not proprietary to a vendor
- Provide a set of tools that users can apply to a collection of images to generate measurements that reflect “truth” and allow determination of the consistency of any measurement method for detecting change

Current Funding Opportunities

CIP supports high-quality extramural research in a number of ways. Investigator-initiated research ideas remain central to the strong portfolio. Here, individual investigators or teams of collaborators generate research ideas based on their perception of the progress of science and the current needs in the field of biomedical imaging. That is, those who are close to the problems are researching solutions. Funding mechanisms include R01, R21, and small business grants.

In addition to investigator-initiated research projects, CIP creates direction in imaging research through specific program announcements. For example, these announcements direct the attention of clinical researchers to the generation of clinical trials or to support academic and industrial researchers to meet translational research goals that might otherwise go unfulfilled. Several of the current program announcements supported by CIP are listed here.

Clinical Trials and Related Research

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

PROGRAM ANNOUNCEMENT:

PAR08-147: <http://grants.nih.gov/grants/guide/pa-files/PA-08-147.html> (expiration date 04/12/2011)

CONTACT:

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301-496-9531, shankarl@mail.nih.gov

Keyvan Farahani, Ph.D.

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

The goal of this funding opportunity announcement is to fund applications focused on the following areas of research:

- Phase I or II clinical trials of novel imaging agents to ensure their safety and efficacy so that further evaluations of their clinical potential can proceed
- Feasibility studies in image-guided intervention, to establish treatment parameters and early therapeutic efficacy for these methods
- Clinical feasibility (“proof-of-principle”) studies or clinical trials to demonstrate potential efficacy of promising discoveries in imaging or image-guided therapy methodologies or technologies

Clinical Cancer Therapy and Prevention Research (R01)

PROGRAM ANNOUNCEMENT:

PA-07-356: <http://grants.nih.gov/grants/guide/pa-files/PA-07-356.html> (expiration date: 05/08/2010)

CONTACT:

Keyvan Farahani, Ph.D.
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The goals of this announcement are to fund applications to conduct translational, clinical, therapeutic, and prevention studies and trials for neoplastic diseases in humans and to encourage clinical researchers to collaborate with basic scientists to translate insights in cancer genetics, cancer epigenetics, and cancer biology into innovative cancer intervention studies and trials. Clinical trials may be done with or without laboratory correlative studies. However, studies to support innovative correlative laboratory studies retrospectively and prospectively linked to therapeutic/preventive clinical trials are also encouraged.

In Vivo Cancer Imaging Exploratory/Developmental Grants (R21)

PROGRAM ANNOUNCEMENT:

PA-06-371: <http://grants1.nih.gov/grants/guide/pa-files/PA-06-371.html> (expiration date 05/08/2009)

CONTACT:

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This announcement aims to fund exploratory/developmental research focused on *in vivo* cancer imaging. The R21 mechanism will provide investigators at all career levels with a defined level of funding adequate for the initial development and/or feasibility testing of high-impact concepts. Research topics may cover the entire spectrum of *in vivo* cancer imaging research, from basic discovery of new cancer imaging agents and technologies, through preclinical testing and validation, to the early feasibility testing of those novel agents and technologies in small clinical trials.

Technology Development

Academic-Industrial Partnerships for Development and Validation of In Vivo Imaging Systems and Methods for Cancer Investigation

PROGRAM ANNOUNCEMENT:

PAR-07-214: <http://grants.nih.gov/grants/guide/pa-files/PAR-07-214.html> (expiration date 03/06/2010)

CONTACT:

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Under an earlier program announcement (PA), teams from both academia and industry were supported to develop and deliver at the end of the funding period a validated biomedical imaging system and/or methods specifically designed to support large-scale preclinical investigations or clinical trials. The imaging systems could be designed for drug discovery, early cancer detection, image-guided intervention, or measurement of drug response. The initial PA (a 2-year R21 mechanism) was successful and was replaced during 2007 by a 5-year R01 mechanism, providing an improved timeline and level of support required to develop and validate, for example, multimodality imaging platforms that have improved sensitivity and specificity for targeted cancer investigations.

PAs generated over the last decade by CIP have proved to be successful not only at increasing the grant portfolio, but also enhancing it with the inclusion of technology development and its translation to clinical investigations. A series of PAs that ran from FY 2000 to FY 2007, “Novel Technologies for *In Vivo* Imaging,” used the R21/R33, R41, R42, R43, and R44 funding mechanisms. The announcement has not been renewed, but in 8 years attracted large numbers of grant applications and experienced above-average funding success rates. A good fraction of those grants have already produced commercial products. For example, at the 2006 meeting of the Radiological Society of North America (RSNA), the Koning, Inc., booth displayed the commercial prototype and clinical results of its CIP-funded project to develop high-resolution cone beam volume CT for breast imaging. Eighty feet down the same aisle, Creatv MicroTech, Inc., displayed antiscatter grids, commercial products that improve clarity, resolution, and contrast for X-ray and nuclear medicine imaging that were developed under several grants supported by CIP.

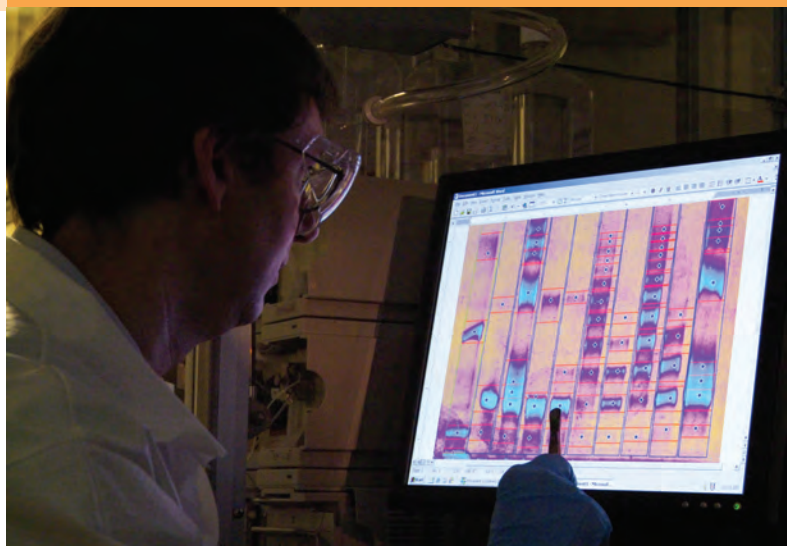


Image-Guided Cancer Interventions

PROGRAM ANNOUNCEMENTS:

STTR PA-07-041: <http://grants.nih.gov/grants/guide/pa-files/PA-07-041.html>

SBIR PA-07-042: <http://grants.nih.gov/grants/guide/pa-files/PA-07-042.html> (expiration dates 09/08/2009)

CONTACT:

Keyvan Farahani, Ph.D.

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

These funding announcements support the development and clinical validation of systems for image-guided interventions (IGIs) for cancer. Specifically, the goals of this program are to provide support for:

- Development and optimization of fully integrated cancer imaging, monitoring, and therapy systems
- Validation of integrated IGI systems through clinical evaluations
- Development of multiple prototype integrated IGI systems as required for multisite clinical evaluations
- Partnerships among small business, large business, and academic clinical centers, as well as small business joint ventures

Partnerships and Collaborations

Professional Societies

American Association for Cancer Research

<http://www.aacr.org>

The American Association for Cancer Research (AACR) is the oldest and largest scientific organization in the world focused on every aspect of high-quality, innovative cancer research. Its reputation for scientific breadth and excellence attract the premier researchers in the field. The programs and services of the AACR foster the exchange of knowledge and new ideas among scientists dedicated to cancer research, provide training opportunities for the next generation of cancer researchers, and increase public understanding of cancer. The AACR cooperated with CIP on the first Cancer Imaging Camp and may be able to add this activity to its training programs in the future.

American Cancer Society

<http://www.cancer.org>

The American Cancer Society (ACS), a nationwide, community-based voluntary health organization with more than 3,400 local offices throughout the United States, has worked in partnership with CIP on several initiatives. For example, ACS helped with the National Lung Screening Trial (NLST), a study supported by CIP and the NCI Division of Cancer Prevention, by recruiting nearly 50,000 current or former smokers in just 18 months. ACS recently assisted CIP with recruitment of patients for the National CT Colonography Trial, which needs the participation of more than 2,300 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 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 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 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 3 years. Once they have participated in their first round of trials, they will disseminate their methods and successes with IRATs at other institutions.



Industrial Partners

AMAG Pharmaceuticals, Inc.

<http://www.amagpharma.com>

NCI, through CIP, holds clinical trials agreements with AMAG Pharmaceuticals, Inc., to study two novel nanoparticle magnetic resonance contrast agents, ferumoxytol and ferumoxtran-10, which were developed by the company. An exploratory clinical trial with ferumoxytol in patients with glioblastoma multiforme was completed in 2005, and another exploratory clinical trial has been completed in patients with prostate or breast cancer. A multicenter trial with ferumoxtran-10 for staging patients with cervical cancer commenced in 2007. Two exploratory trials of ferumoxytol to evaluate response to chemoradiation in patients with newly diagnosed and recurrent glioblastoma multiforme are under way.

Federal Agencies

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 the Centers for Medicare & Medicaid Services (CMS). The seventh NFBIO took place in February 2007 and focused on image-guided oncology interventions and opportunities for collaborations in conducting related clinical trials. The meeting was attended by members of academia, industry, NCI, FDA, and CMS.

The Interagency Council on Biomedical Imaging in Oncology (ICBIO) 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 1 hour for an informal and confidential discussion. More information is available on the council's Webpage: <http://imaging.cancer.gov/programsandresources/specializedinitiatives/ICBIO>.

National Institute of Standards and Technology

CIP and FDA, in collaboration with National Institute of Standards and Technology (NIST), have an interagency agreement to develop databases for evaluating image-processing methods for cancer screening, diagnosis, and treatment.

The cancer imaging program, in collaboration with the National Institute of Biomedical Imaging and Bioengineering (NIBIB) and other NIH components, has encouraged NIST to explore the development of reference standards for biomedical imaging and the role of imaging as a biomarker in particular. This collaboration has resulted in the organization of an inter-federal agency workshop to address imaging standards that has included all imaging stakeholders, with representatives from different imaging societies, imaging industries, and pharmaceutical companies. A comprehensive report (<http://usms.nist.gov/workshops/bioimaging.htm>) has been generated and has led to the collective involvement of imaging societies to address physical standards for quantitative imaging as a biomarker.

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 to encourage the rapid development of more advanced medical imaging methods for imaging as a biomarker (Biomarker Consortium) and as a resource for the Imaging Database Resources Initiative (IDRI).

Biomarker Consortium

The Oncology Biomarker Qualification Initiative (OBQI) is an agreement among FDA, NCI, and CMS to collaborate on improving the development of cancer therapies and the outcomes for cancer patients through biomarker development and evaluation.

Biomarkers are biologic indicators of disease or therapeutic effects that can be measured through dynamic imaging tests, as well as tests on blood, tissue, and other biologic samples. This initiative is the first time these three Department of Health and Human Services (DHHS) agencies have focused together on biomarkers as a way of speeding the development and evaluation of cancer therapies.

The collaboration is developing scientific understanding of how biomarkers can be used to assess the impact of therapies and better match therapies to patients. For instance, OBQI will address questions such as how particular biomarkers can be used to:



- Assess after one or two treatments if a patient's tumor is responding to treatment
- Determine more definitively if a tumor is dying, even if it is not shrinking
- Identify which cancer patients are at high risk of their tumor coming back after therapy
- Determine if a patient's tumor is likely to respond at all to a specific treatment
- Efficiently evaluate whether an investigational therapy is effective for tumor treatment

The goal of OBQI is to validate particular biomarkers so that they can be used to evaluate new, promising technologies in a manner that will shorten clinical trials, reduce the time and resources spent during the drug development process, improve the linkage between drug approval and drug coverage, and increase the safety and appropriateness of drug choices for cancer patients. By working with academic and industry scientists, as well as professional organizations, the OBQI teams can foster the development of key information on biomarkers through clinical trials.

The first two OBQI projects to be implemented will serve to validate and standardize the use of fluorodeoxyglucose positron emission tomography (FDG-PET) scanning, which can characterize biochemical changes in a cancer. Under the collaboration, researchers will conduct a trial in patients being treated for non-Hodgkin lymphoma to determine if FDG-PET is a predictor of tumor response to therapy. Another trial in patients with non-small cell lung cancer will examine the correlation between changes in tumor FDG uptake during chemotherapy and patient survival, and it will determine the reproducibility of quantitative measurements of tumor FDG uptake. Data resulting from this evidence-based study will help both FDA and CMS work with drug developers based on a common understanding of these types of assessments.



Imaging Database Resources Initiative

http://www.fnih.org/index.php?option=com_content&task=view&id=575&Itemid=701

Directed by CIP, 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 LIDC and draws on resources from the CIP-cosponsored NLST.

Eight medical imaging companies are participating in the 2-year initiative: Agfa HealthCare, Eastman Kodak, Fujifilm Photo Film Company, General Electric, iCAD, Inc., Philips Medical Systems, Riverain Medical, and Siemens Medical Solutions. The IDRI database is expected to be completed by March 2008, and will be the first public-private partnership database resource to be completed by the FNIH.

CIP is expanding its efforts to speed the development and dissemination of quantitative informatics tools for imaging and integration of other patient data for clinical decision making, with a particular emphasis on imaging as a biomarker for drug and therapy response, and plans to explore further collaboration with the FNIH.

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 RSNA, the NCI Center for Bioinformatics, and NIBIB on a pilot project called the Reference Image Database to Evaluate Response to therapy in lung cancer.

RIDER, which is part of the larger LIDC initiative (<http://imaging.cancer.gov/programsandresources/InformationSystems/LIDC>), 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 imaging lung cancer.

The RIDER pilot project thus far has resulted in an initial Web-accessible resource of serial CT data compatible with caBIG.

Image Archive: <http://ncia.nci.nih.gov/collections/>

Documentation: <http://gforge.nci.nih.gov/projects/rider/>

The RIDER project has rapidly expanded to include images 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 CMS reimbursement of software tools.

RIDER is striving to accomplish all its goals using open-source software tools for validation of clinical decision tools so that researchers and industry can tailor applications to meet their individual specifications for the measurement of drug response using quantitative imaging as a biomarker.

National Center for Image-Guided Therapy

<http://www.ncigt.org/>

CIP is collaborating with the National Center for Research Resources and NIBIB to co-fund the National Center for Image-Guided Therapy (NCIGT) at the Brigham and Women's Hospital at Harvard School of Medicine. NCIGT, funded as a Biomedical Technology Resource Center through a U41 mechanism, serves as a national resource for all aspects of medical therapy enhanced by computation and imaging, with the common goal of providing more effective patient care.



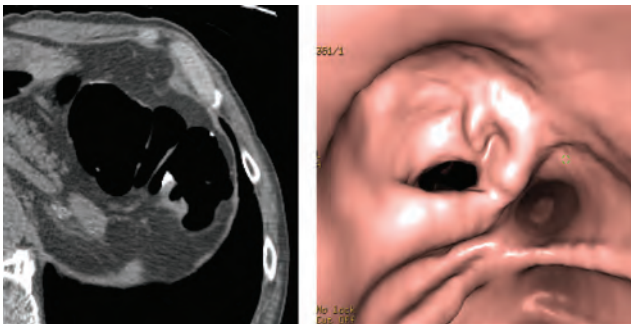


Scientific Advances

Results of Six ACRIN Clinical Trials

Findings from six medical imaging clinical trials coordinated by ACRIN were presented during the network's 2007 Fall Meeting in Arlington, Virginia. Key results presented include:

- **ACRIN 6664:** The primary results of the National CT Colonography Trial, led by C. Daniel Johnson, M.D., from the Mayo Clinic, demonstrated that CT colonography (CTC) is highly accurate for the detection of intermediate and large polyps and that the accuracy of CTC is comparable to colonoscopy. This clinical trial evaluating CTC as a primary colorectal cancer screening modality is the largest to date, with 2,600 participants.



An early stage colon carcinoma is depicted on axial-slice CTC on the left and in a 3-D CTC reconstruction on the right.

- **ACRIN 6666:** Wendie Berg, M.D., Ph.D., from American Radiology Services, Johns Hopkins University, and the lead investigator of the Screening Breast Ultrasound in High-Risk Women trial, reported that ultrasound combined with mammography found statistically significant more cancers than mammography alone in the trial's first-year screening results. However, investigators also found that the risk of false-positive results was higher with screening ultrasound and could remain a barrier to its increased use.
- **ACRIN 6659:** A study led by Jeffrey Weinreb, M.D., Yale University School of Medicine, on the use of MRI combined with MR spectroscopy (MRS) for staging of prostate cancer at 1.5 T magnet strength found no overall improvement in accuracy for combined MRI/MRS over MRI alone.
- **ACRIN 6661:** A study led by Damian Dupuy, M.D., Rhode Island Hospital, of radiofrequency ablation (RFA) for treating painful bone metastasis demonstrated that RFA can be safely performed and offers an effective symptomatic treatment option for select patients whose cancer has metastasized to the bone.
- **ACRIN 6652:** A cost-effectiveness analysis of digital mammography was presented by the study's lead author, Anna Tosteson, Sc.D., from Dartmouth-Hitchcock Medical Center. She reported that age-targeted digital mammography breast cancer screening appears cost effective. In contrast, universal digital mammography screening is not, at the present time, cost effective based on current reimbursement rates. The analysis data arose from the Digital Mammographic Imaging Screening Trial first reported in 2005.

- **ACRIN 6667:** A study led by Constance Lehman, M.D., Ph.D., that found that MRI detects cancers in the opposite breast of women newly diagnosed with breast cancer was reported in the March 29, 2007, issue of the *New England Journal of Medicine*. MRI of women diagnosed with cancer in one breast detected over 90 percent of cancers in the opposite breast that had been missed by mammography and clinical breast exam at initial diagnosis. Given the established rates of mammography and clinical breast exams for detecting cancer in the contralateral breast, adding an MRI scan to the diagnostic evaluation effectively doubled the number of cancers immediately found in these women. The study recruited 1,007 women from 25 institutions who had a recent diagnosis of cancer in one breast. Of these, 969 women completed the study, which began in April 2003. All of the women enrolled had a negative mammogram and negative clinical breast exam of the opposite breast within

90 days prior to the MRI. After receiving an MRI, 33 contralateral breast cancers were diagnosed in the study. Thirty of these tumors, or 91 percent, were diagnosed as a result of MRI. The other three cancers were detected on subsequent mastectomies.

Lehman CD, Gatsonis C, Kuhl CK, Hendrick RE, Pisano ED, Hanna L, Peacock S, Smazal SF, Maki DD, Julian TB, DePeri ER, Bluemke DA, Schnall MD; ACRIN Trial 6667 Investigators Group. MRI evaluation of the contralateral breast in women with recently diagnosed breast cancer. *NEJM* 2007;356:1295–303.

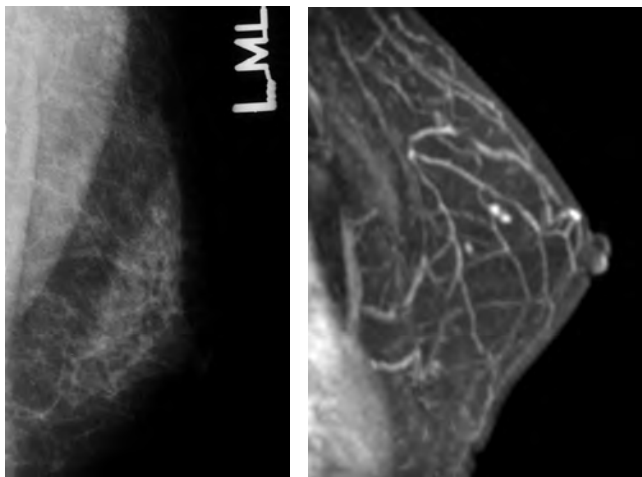
<http://www.ncbi.nlm.nih.gov/pubmed/17392300>

Cancer Prevention and Preemption

A *Cancer Biomarkers* paper reported the results of a workshop held on the potential of imaging for cancer prevention and preemption. The concept of intraepithelial neoplasm as a precursor of cancer has generated opportunities to examine drug or device intervention strategies that may reverse or retard the sometimes lengthy process of carcinogenesis. Chemopreventive agents with high therapeutic indices, well monitored for efficacy and safety, are greatly needed. Also needed are less invasive or minimally disruptive visualization and assessment methods to safely screen nominally healthy, but at-risk patients, often for extended periods and at repeated intervals. Imaging devices, alone or in combination with anticancer drugs, may also provide novel interventions to treat or prevent precancer.

Kelloff GJ, Sullivan DC, Baker H, Clarke LP, Nordstrom R, Tatum JL, Dorfman GS, Jacobs P, Berg CD, Pomper MG, Birrer MJ, Tempero M, Higley HR, Petty BG, Sigman CC, Maley C, Sharma P, Wax A, Ginsberg GG, Dannenberg AJ, Hawk ET, Messing EM, Grossman HB, Harisinghani M, Bigio IJ, Griebel D, Henson DE, Fabian CJ, Ferrara K, Fantini S, Schnall MD, Zujewski JA, Hayes W, Klein EA, DeMarzo A, Ocak I, Ketterling JA, Tempany C, Shtern F, Parnes HL, Gomez J, Srivastava S, Szabo E, Lam S, Seibel EJ, Massion P, McLennan G, Cleary K, Suh R, Burt RW, Pfeiffer RM, Hoffman JM, Roy HK, Wang T, Limburg PJ, El-Deiry WS, Papadimitrakopoulou V, Hittelman WN, MacAulay C, Veltri RW, Solomon D, Jeronimo J, Richards-Kortum R, Johnson KA, Viner JL, Stratton SP, Rajadhyaksha M, Dhawan A; Workshop Program Committee. Workshop on imaging science development for cancer prevention and preemption. *Cancer Biomarkers* 2007;3:1–33.

<http://www.ncbi.nlm.nih.gov/pubmed/17655039>



A patient already diagnosed with breast cancer in the right breast had a negative mammogram of the left breast, but MRI detected that the left breast actually harbored an early stage cancer (bright nodules visible in the MRI image to the right).



Pilot Study: Ferumoxytol in Magnetic Resonance Studies of Brain Tumors

A CIP-funded pilot study at Oregon Health and Science University is investigating the potential role of ferumoxytol in MRI of malignant brain tumors. Ferumoxytol is an iron oxide nanoparticle that targets phagocytic cells and can be used for pathology that has a significant phagocytic component. The investigators compared ferumoxytol imaging, perfusion, and magnetic resonance angiography 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. 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. The potential of ferumoxytol nanoparticle magnetic resonance imaging, perfusion, and angiography in central nervous system malignancy: A pilot study. *Neurosurgery* 2007;60:601–12.
<http://www.ncbi.nlm.nih.gov/pubmed/17415196>

Tools, Products, and Resources

Cancer Research Imaging Camp: An Educational Opportunity for Basic Cancer Researchers

<http://imaging.cancer.gov/NewsAndMeetings/workshops/CRIC>

One result of NCI investment in imaging technology has been the creation of sophisticated imaging technology dedicated to small animal imaging especially suitable to the mouse models of cancer that now permeate basic and translational research. Optimal use of these new methods requires a highly specialized research team; however, opportunities to receive hands-on training from skilled experts across a range of platforms are extremely limited. CIP funded the first NCI Cancer Research Imaging Camp in 2007 to provide a unique training experience to 16 young investigators interested in using *in vivo* imaging in their research.

Postdoctoral fellows and early career-level faculty in fields related to basic cancer biology attended this special intensive course on *in vivo* and live-cell imaging techniques. Through lectures and hands-on laboratory sessions, participants were given experience with a wide range of imaging modalities, including advanced optical imaging, MRI, PET, SPECT, CT, and ultrasound. CIP will repeat the camp in 2008, expanding the number of student slots to 24. The AACR cooperated in this activity and may be able to add this camp to its training portfolio in the future.

Lung Imaging Database Consortium

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

The LIDC, funded by CIP, comprises five institutions that are developing consensus guidelines and metrics for the use of spiral CT lung images. It is expected to be completed in 2008.

Virtual Colonoscopy Training Collection

<http://ncia.nci.nih.gov/ncia/collections>

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.

This database currently provides 52 complete cases (26 with polyps) consisting of 3-D CT data, several 2-D images, pathology reports, virtual and optical colonoscopy reports, and an optical colonoscopy video.

National Forum on Biomedical Imaging in Oncology

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

The 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 2-day meeting concentrates on a different topic each time it is held. Planning is under way for the next meeting.

Interagency Council on Biomedical Imaging in Oncology

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

In informal, confidential meetings, the ICBIO brings representatives of NCI, FDA, and CMS together with technology developers. Developers receive advice from a multi-agency perspective on the spectrum of scientific, regulatory, and reimbursement issues related to commercializing new imaging devices or technologies.





Development of Clinical Imaging Drugs and Enhancers

<http://imaging.cancer.gov/programsandresources/specializedinitiatives/dcide>

The DCIDE program is a competitive program to expedite and facilitate the development of promising investigational imaging enhancers (contrast agents) or molecular probes from the laboratory to IND status. Through the DCIDE program, the developer of a promising diagnostic agent or probe will be given access to the preclinical development resources of NCI in a manner that is intended to remove the most common barriers between laboratory discoveries and IND status.

NCI-Frederick Small Animal Imaging Program

<http://web.ncifcrf.gov/rtp/lasp/intra/saip/>

The NCI-Frederick SAIP was established in October 2006 to provide NCI Investigators with a state-of-the-art *in vivo* imaging facility. Capabilities include optical imaging, ultrasound, magnetic resonance imaging, positron emission tomography, and access to a range of appropriate contrast agents.

Tracer Resources

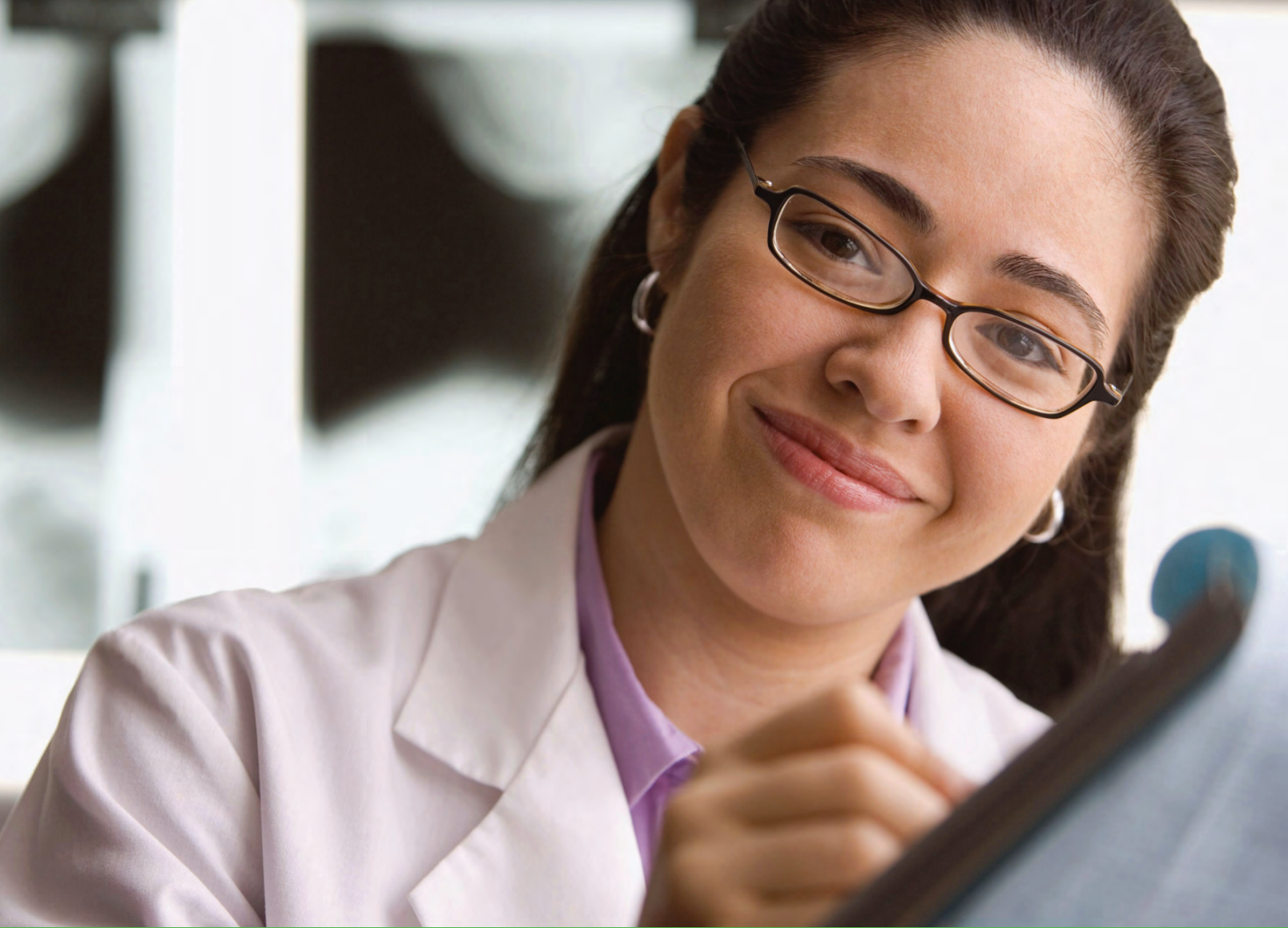
<http://imaging.cancer.gov/programsandresources/Cancer-Tracer-Synthesis-Resources>

CIP has been creating INDs for imaging agents so that multicenter clinical trials can be performed. CIP holds active INDs for [^{18}F] fluorothymidine ([^{18}F]FLT); [^{18}F] fluoromisonidazole; 1H-1-(3-[^{18}F]-fluoro-2-hydroxy-propyl)-2-nitro-Imidazole (FMISO); and 16-[^{18}F]fluoro-17,-estradiol ([^{18}F]FES).

An IND for FLT was filed in 2004 and one for FMISO was filed in 2006 and accepted by the FDA. To facilitate further research on these radiopharmaceuticals by the community, a subset of the documents filed in the IND is being made available to the research community to implement routine synthesis of tracers at their own facilities and to assist investigators with the filing of their own INDs. These documents include a full set of manufacturing and quality control documents and an Investigator Drug Brochure, all of which have been accepted by the FDA as part of the NCI INDs. Investigators at each site can implement the synthesis and testing in their radiochemistry laboratory, modifying the documentation as necessary to suit local conditions. Investigators can then write and file their own IND with the FDA by modifying it to fit local conditions and adding the investigator's proposed clinical protocol. CIP will provide a letter to cross-reference the NCI IND file at the FDA for pharmacology, toxicology, dosimetry, and previous human experience.

Additionally, CIP has contracted with a commercial firm to file a drug master file for the manufacturing and distribution of one of these tracers and is collaborating with two other firms on both FLT and FMISO. This effort will make it possible for clinical investigators without radiochemistry facilities to study these agents.

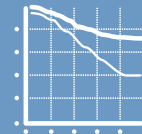




Cancer Therapy Evaluation Program

Program Accomplishments

The Cancer Therapy Evaluation Program (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.





CTEP 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.

The milestone of a declining death rate 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 800 treatment trials are sponsored by the Cancer Therapy Evaluation Program (CTEP) within the Division of Cancer Treatment and Diagnosis (DCTD).

CTEP is organized into eight 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

During fiscal year 2007, CTEP:

- Managed 828 active clinical trials
- Supervised 100 active Investigational New Drugs (INDs)
- Oversaw the recruitment of about 28,700 patients to CTEP-sponsored clinical trials

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. CTEP accomplishes its goals by 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 also administered over 350 grants in 2007.

Major Ongoing Initiatives

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 members 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 allow drugs from two different companies to be combined in a clinical trial in a way that preserves the interests of each company while allowing this critical research to move forward. Intellectual property and liability concerns can slow

JEFFREY S. ABRAMS, ASSOCIATE DIRECTOR

In June 2007, Jeffrey S. Abrams, M.D., a long-time DCTD staff member, was selected to lead the Cancer Therapy Evaluation Program (CTEP) as Acting Associate Director, following the retirement of Dr. Michael Christian who had directed the program for 10 years. After a nationwide search, Dr. Abrams was named Associate Director in July 2008. Dr. Abrams has been a member of CTEP since 1993, when he joined as a clinical research scientist to oversee the breast cancer treatment trials portfolio and participate in clinical trials at the NIH Clinical Center and the National Naval Medical Center.



In 2004, Dr. Abrams was appointed Chief of the Clinical Investigations Branch. In this position, he was responsible for the direction of the NCI Clinical Trials Cooperative Group program, which performs nearly all the phase III cancer treatment trials sponsored by NCI and is the institute's primary vehicle for conducting definitive, practice-changing clinical trials. As branch chief, Dr. Abrams supervised a staff that collectively oversees, reviews, and coordinates more than 150 active phase III trials in all varieties of cancer. He pioneered the Cancer Trials Support Unit, which has established a national network of physicians to participate in NCI-sponsored phase III treatment trials.

Dr. Abrams, whose NCI achievements have been recognized by five NIH Merit Awards and several Performance Awards, is the author of over 70 original publications in the field of breast cancer and clinical trials, eight book chapters, and nine monographs. He is often called upon to speak at national and international meetings on breast cancer diagnosis and treatment as well as methods to enhance the performance of large clinical trials.

Dr. Abrams graduated from the medical school of Catholic University of Louvain, Belgium, in 1979. In 1982, he completed an internal medicine residency at St. Agnes Hospital in Baltimore, MD, and an oncology fellowship at the University of Maryland in 1984. A Fulbright scholarship took him to the Jules Bordet Institute in Belgium for a clinical research fellowship in oncology from 1984 to 1985. In 1985, Dr. Abrams returned to the University of Maryland where he directed the Breast Cancer Evaluation Program until 1992 and served as Associate Professor of Medicine and Oncology.



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 that is 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.

Early Clinical Trials (Phase I-II Program)

CTEP implements and monitors a comprehensive cancer therapy clinical contract/grant program that sponsors clinical trials of novel anticancer agents that have demonstrated high activity in animals in the preclinical phase of the cancer therapy development program.

To complete its agent development plans and to respond to new scientific opportunities, CTEP must be able to place phase I and II trials quickly. The CTEP Phase I-II Early Clinical Trials Program is the main mechanism for completing early clinical trials for NCI's extensive therapeutics development program. It also provides the foundation for identifying the clinical activity that leads to definitive phase III clinical trials. The early clinical trials program has been restructured over the past six years. Phase I investigators are funded via cooperative agreements and participate in first-in-human and organ dysfunction trials in addition to dose-finding studies of combination therapies. Regarding the disease-focused phase II trials, over 20 NCI-

designated Cancer Centers are involved in the program and generally serve as the nexus for the various clinical trials consortia. The phase II program has been very successful in increasing patient accrual, which has grown by an average of 15 percent each year. In the first five years of the phase II program, 216 protocols studying 41 agents were activated, with about half that number completed or closed. About 5,000 patients were enrolled at 170 institutions. This resource is critical for accelerating therapeutics development because it provides a quick and efficient way to obtain phase II results.

A specific brain tumor consortium has been developed to perform phase I-II clinical trials in adults with glioblastoma multiforme and other brain tumors. A similar effort exists in childhood central nervous system (CNS) malignancies (see page 63).

Clinical Trials Cooperative Group Program

<http://ctep.cancer.gov/industryCollaborations/default.htm#collaborations>

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. The program's mission encompasses a wide variety of investigational efforts.

Cooperative groups consist of networks of researchers who develop and conduct cancer treatment clinical trials. The Clinical Trials Cooperative Group Program reaches scientists and patients throughout the nation.

- In 2007, of all the new patients accrued to CTEP-sponsored trials, about 23,000 entered into cooperative group studies
- About 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, funding for NCI cooperative groups is not linked to a specific clinical trial.

Clinical Trials Cooperative Groups

CTEP uses the U10 mechanism to fund the following groups via cooperative agreements:

- American College of Surgeons Oncology Group (ACOSOG)
- Cancer and Leukemia Group B (CALGB)
- Children’s Oncology Group (COG)
- Eastern Cooperative Oncology Group (ECOG)
- European Organization 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

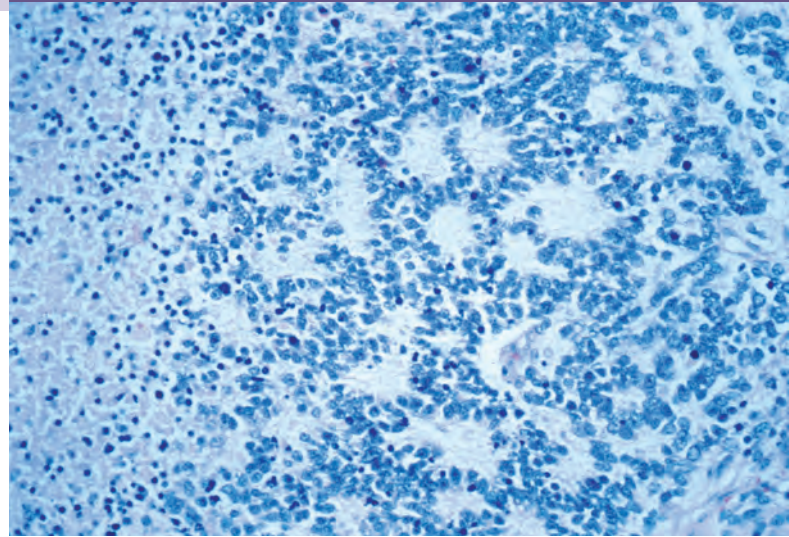
<http://www.pbtc.org/>

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 mechanisms, 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. It 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 5,000 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 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 (PPTP):** This 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 of these same agents. Although these examples support the potential predictive value of preclinical models, validation of the models across a broader range of pediatric cancers and therapeutic agents is needed. Since 2005, more than 25 agents or combinations of agents have been tested against PPTP's molecularly characterized panel of childhood cancers.

CTEP-Supported Grants

CTEP sponsors more narrowly focused, disease-specific research in which clinical trials with a heavy translational focus are funded via RO1 and PO1 grants or U01 and U19 cooperative agreements.

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 implementation of a remote data capture system for the collection of clinical trial data



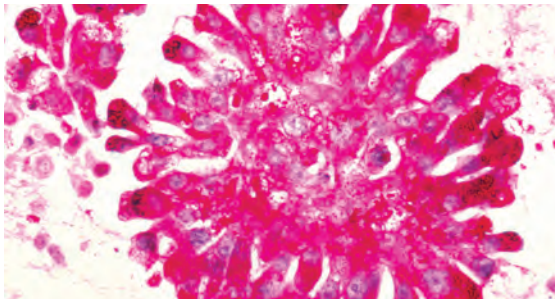
Significant Ongoing Clinical Trials

Prioritizing Targeted Agents for Pediatric Clinical Evaluation

Testing whether new targeted agents are effective in pediatrics has become critical for CTEP. Substantial efforts have been devoted to finding an effective mechanism for such testing.

The Pediatric Preclinical Testing Program (PPTP) presented testing results for seven molecularly targeted agents at national meetings in 2007, including results for the following:

- the antiangiogenic agent sunitinib
- the mTOR inhibitor rapamycin
- the Hsp90 inhibitor 17-DMAG
- the Bcl-2 family inhibitor ABT-263
- the ErbB2 inhibitor lapatinib
- the HDAC inhibitor vorinostat
- the anti-IGF-1 receptor monoclonal antibody 19D12



Particularly promising results were observed for ABT-263 against the PPTP's acute lymphoblastic leukemia (ALL) panel. Three of six ALL xenografts achieved complete remissions to ABT-263, with two of these remissions being maintained for 3 weeks following treatment cessation. In contrast to the high activity for ABT-263 in the ALL panel, little activity was observed for ABT-263 as a single agent against the PPTP's solid tumor xenografts. The xenografts of the ALL panel had higher levels of Bcl-2 expression than the solid tumor xenografts.

Promising results were also noted for the anti-IGF-1 receptor monoclonal antibody 19D12 against the PPTP's osteosarcoma and Ewing sarcoma panels. Complete remissions were observed for one of five Ewing sarcoma xenografts and for two of six osteosarcoma xenografts.

Descriptions of high-priority clinical trials sponsored by CTEP appear below.

Early Phase Trial 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. Promising preliminary results from the phase I studies of sorafenib plus bevacizumab and temsirolimus plus bevacizumab were reported at the 2007 annual meeting of the American Society of Clinical Oncology. Novel multi-arm phase II studies in renal cell cancer, glioblastoma, and melanoma are currently under way.

Definitive, Late Phase Trials

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

<http://clinicaltrials.gov/ct2/show/NCT00326898>

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 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 cell 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. This intergroup trial, E2805, is being led by the Eastern Cooperative Oncology Group (ECOG) and opened in June 2006, within a few months of the drugs' approvals by FDA for treatment of advanced renal cancer. 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. E2805 is accruing ahead of schedule with more than a third of the total accrual of 1,332 patients enrolled as of October 2007.

Phase III Study of R-CHOP versus R-Dose-Adjusted-EPOCH with Molecular Profiling in Untreated De Novo Diffuse Large B-Cell Lymphomas

<http://www.clinicaltrials.gov/ct2/show/NCT00118209>

This randomized trial is studying rituximab when given together with two different combination chemotherapy regimens to compare how well they work in treating patients with diffuse large B-cell non-Hodgkin lymphoma (DLBCL).

Specifically, this phase III trial, being led by the Cancer and Leukemia Group B (CALGB) and known as CALGB-50303, is testing R-CHOP (bolus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) versus R-DA-EPOCH (rituximab, dose-adjusted continuous infusion doxorubicin, vincristine, and etoposide with bolus cyclophosphamide and oral prednisone). R-CHOP is the standard of care in DLBCL but results in cure of 40 to 60 percent of patients. Evidence suggests that R-EPOCH overcomes some of the biologically determined features of tumor resistance that limit R-CHOP effectiveness. This study has rigorous scientific endpoints that include acquisition of fresh tumor samples to conduct DNA microarray studies that have proven useful in determining lymphoma histogenetic origins associated with prognosis. In this manner, it may be possible to determine the subset of patients for whom R-EPOCH confers superior treatment outcome so that patients at risk can be offered optimal therapy based on individual molecular diagnostic criteria. Additionally, this study is examining the use of positron emission tomography scanning with fluorodeoxyglucose (FDG-PET) as a biomarker of prognostic significance. Early FDG-PET normalization may indicate favorable outcome, whereas persistent FDG-PET abnormalities may indicate poor outcome. If confirmed, the advantage of a biomarker determination such as this would enable early treatment modifications for patients with suboptimal therapeutic effects. This study has important implications for further informing DLBCL biology, treatment, and biomarker technology.

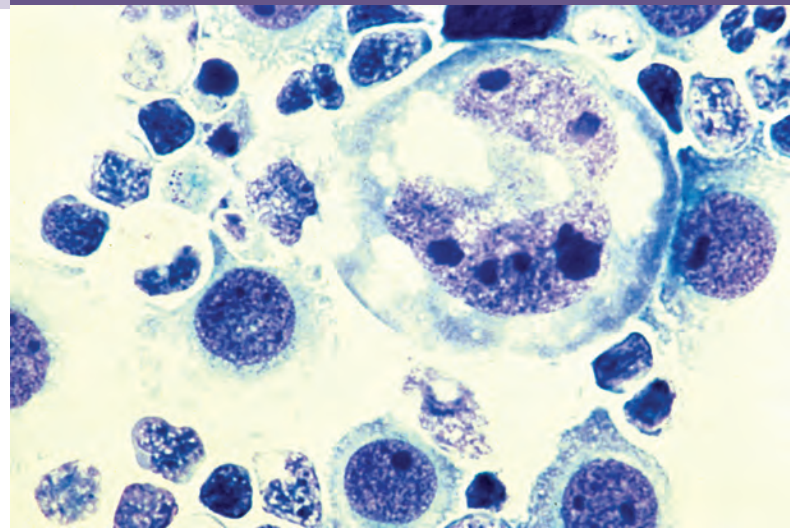


Trial Assessing Individualized Options for Treatment (TAILORx) in the Adjuvant Setting for Women with Breast Cancer

<http://clinicaltrials.gov/ct2/show/NCT00310180>

The Trial Assessing Individualized Options for Treatment (TAILORx), an ongoing randomized clinical trial, is testing the benefit of adjuvant chemotherapy in women with early stage breast cancer selected using a molecular profiling assay.

Prior studies have validated that Oncotype DX®, a molecular profiling test that analyzes the expression of a 21-gene panel in biopsy samples from women with estrogen-dependent, lymph-node negative breast cancer, can predict the risk of breast cancer recurrence. The studies also appear to identify which of those patients will benefit most from chemotherapy. Currently, chemotherapy is recommended for most women with this type of breast cancer, many of whom may be adequately treated with hormone therapy alone. The NCI-sponsored cooperative groups are conducting TAILORx to determine whether hormonal therapy alone is inferior to the standard of chemotherapy plus hormonal therapy in women with estrogen-dependent, lymph-node negative breast cancer. To date, over 2,300 women have been enrolled in this study with an additional 2,300 registered. The results of this study could potentially show that many women can be spared the short- and long-term toxic effects and costs of chemotherapy each year.



Randomized Trials Evaluate the Addition of Bevacizumab or Cetuximab in Combination with Chemotherapy in Patients with Resected 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. The current standard for adjuvant therapy in patients with stage III colon cancer that has been surgically resected is FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin).

Recent phase III trials that evaluated newer, targeted agents in patients with metastatic colorectal cancer demonstrated the clinical benefit of two combinations: bevacizumab, a recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF) that prevents the growth and maintenance of tumor blood vessels, with chemotherapy; and cetuximab, a recombinant, chimeric monoclonal antibody directed against the epidermal growth factor receptor (EGFR) with antineoplastic activity, with chemotherapy. These combinations are now being evaluated in three large, phase III randomized trials in patients who have undergone complete surgical resection of their colon cancer.

- **National Surgical Adjuvant Breast and Bowel Project Study**

<http://clinicaltrials.gov/ct2/show/NCT00096278>

The National Surgical Adjuvant Breast and Bowel Project conducted a large, randomized phase III trial, NSABP C-08, in patients with stage II or III colon cancer to evaluate the clinical benefit of adding bevacizumab to FOLFOX adjuvant chemotherapy along with an additional 6 months of bevacizumab alone. This study opened approximately 6 months after FDA approval of bevacizumab in combination with 5-fluorouracil-based chemotherapy for the treatment of metastatic colorectal cancer. The study enrolled over 2,700 patients between September 2004 and October 2006 and results are pending.

- **North Central Cancer Treatment Group Study**

<http://clinicaltrials.gov/ct2/show/NCT00079274>

The North Central Cancer Treatment Group is leading a large, randomized, intergroup phase III trial, N0147, in patients with stage III colon cancer to evaluate the clinical benefit of adding cetuximab to FOLFOX adjuvant chemotherapy. This study on the clinical benefit of cetuximab was also activated within approximately 6 months of the FDA approval of cetuximab as single-agent therapy to treat patients with advanced colorectal cancer that has spread to other parts of the body. Since September 2004, the N0147 study has enrolled more than 1,800 patients out of a total accrual target of approximately 2,300 patients. The study is projected to close to accrual soon.

- **Eastern Cooperative Oncology Group**

<http://clinicaltrials.gov/ct2/show/NCT00217737>

The role of adjuvant therapy in patients with stage II colon cancer (cancer that extends through the wall of the colon but not to the lymph nodes or other organs) is controversial. ECOG is leading a large, intergroup phase III trial, E5202, for patients with stage II colon cancer in which specific biological features (tumor markers) believed to predict tumor recurrence will be used to define a “high-risk” group of patients with stage II colon cancer. Tumors from patients will be assessed for microsatellite stability (MSS) and loss of heterozygosity (LOH) at chromosome 18q. Patients with disease that is at “high-risk” for recurrence based on MSS status and LOH at chromosome 18q are randomized to standard chemotherapy (FOLFOX) or to standard chemotherapy in combination with bevacizumab. Patients with disease that is considered at “low-risk” of recurrence are assigned to observation only.

Incorporating Novel Agents into the Treatment of Pediatric Acute Lymphoblastic Leukemia

COG has initiated three protocols that introduce novel agents into treatment regimens for children with newly diagnosed ALL:

- The ALL0434 protocol is evaluating whether the addition of nelarabine to a standard ALL regimen can improve outcome for children with T-cell ALL. COG previously demonstrated that nelarabine can induce complete remissions as a single agent in children with recurrent T-cell ALL.
- The ALL0622 protocol is studying whether the Src/Abl inhibitor dasatinib can improve outcome for children with Philadelphia chromosome positive (Ph⁺) ALL when it is



administered concurrently with standard agents used to treat ALL. Dasatinib is approved for the treatment of imatinib-refractory chronic myeloid leukemia (CML), and it has shown single-agent activity in children and adults with Ph⁺ ALL.

- The ALL0631 study is evaluating the FLT3 inhibitor lestaurtinib (CEP-701) in infants with ALL whose leukemia cells have translocations involving the myeloid/lymphoid or mixed-lineage leukemia (MLL) gene. The FLT3 kinase is consistently highly expressed and activated in ALL with the MLL gene rearrangement. FLT3 inhibitors selectively kill ALL cells with the MLL gene rearrangement *in vitro* and *in vivo*, and they synergize with chemotherapy.

COG is also studying molecularly targeted agents in children with relapsed ALL and has protocols evaluating the mTOR inhibitor rapamycin and the CD22-targeted monoclonal antibody epratuzumab.

Phase III Treatment Trials in Early Stage Non-Small Cell Lung Cancer Will Assess the Clinical Benefit of Bevacizumab as Part of Adjuvant Therapy and Surgical Resection Techniques

Two definitive phase III studies involving early stage non-small cell lung cancer (NSCLC) were activated in June 2007. ECOG is leading an intergroup trial, E1505, for patients with early stage NSCLC to test if the addition of bevacizumab (angiogenesis inhibition) to standard chemotherapy will improve survival in patients undergoing surgery with curative intent. This study is based on the results of another CTEP-sponsored phase III study in patients with advanced non-squamous NSCLC (E4599) that showed that adding bevacizumab to standard chemotherapy for patients with NSCLC provides a statistically and clinically significant survival advantage with tolerable toxicity.

<http://www.clinicaltrials.gov/ct2/show/NCT00324805>



The CALGB is conducting a phase III study, CALGB-140503, that will compare two types of surgical resection (standard lobectomy versus sublobar resection) for small (≤ 2 cm) peripheral tumors.

<http://www.clinicaltrials.gov/ct2/show/NCT00499330>

The results of these two phase III trials may have profound impacts on the management and quality of life of patients with early stage lung cancer.

Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006; 355:2542–50.
<http://www.ncbi.nlm.nih.gov/pubmed/17167137>

Phase III Trial in Advanced Non-Small Cell Lung Cancer Will Assess FDG-PET/CT as Predictive Marker of Response and Patient Outcome

<http://clinicaltrials.gov/ct/show/NCT00424138>

The American College of Radiology Imaging Network is conducting a study, ACRIN 6678, to prospectively validate FDG-PET in conjunction with computed tomography (CT) as a predictive marker of response and patient outcome in patients with advanced NSCLC. This study was activated in March 2007 and is the result of a joint effort between CTEP, DCTD's Cancer Imaging Program, the FDA, and the Centers for Medicare and Medicaid under the Oncology Biomarker Qualification Initiative. This study may have an impact on how new targeted therapies are applied to patients with lung cancer.

Phase III Trial Evaluating Radiotherapy to the Pelvic Lymph Nodes with Short-Term Androgen Deprivation in Prostate Cancer Patients with a Rising Prostate-Specific Antigen after Radical Prostatectomy

<http://clinicaltrials.gov/ct/show/NCT00567580>

Men with a rising prostate-specific antigen (PSA) after prostatectomy constitute an increasing patient population in the U.S. Radiotherapy to the prostate bed is the standard salvage treatment in the absence of systemic metastases. Such treatment can provide durable PSA responses in approximately 30 to 40 percent of a heterogeneous patient population.

The Radiation Therapy Oncology Group is conducting a phase III trial, RTOG 0534, which opened in early 2008, that will accrue the most favorable population of men in order to ask whether radiotherapy can not only decrease PSA but provide long-term freedom from progressive disease and whether this is impacted by concurrent androgen deprivation or pelvic lymph node irradiation.

International Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Study—The ALTTO Study

<http://clinicaltrials.gov/show/NCT00490139>

Two targeted medications designed to treat an aggressive form of breast cancer are being tested in a new study involving 8,000 participants in 50 countries across six continents—a clinical trial that investigators hope will provide a new model for global cancer research. This trial, dubbed ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization study), will be one of the first global initiatives in which two large, academic breast cancer research networks covering different parts of the world have jointly developed a study in which all care and data collection are standardized, regardless of where patients are treated. The networks are The Breast Cancer Intergroup of North America (TBCI), based in the United States, and the Breast International Group (BIG) in Brussels, Belgium. TBCI consists of six NCI-funded clinical trials cooperative groups.

ALTTO is designed to answer the most pressing questions regarding use of two widely used cancer agents: whether one agent is more effective, which agent is safer for patients, and what benefit will be derived by taking the drugs separately, in tandem order, or together. The trial, also known as BIG 2-06/N063D, is a randomized, phase III study, which is considered the gold standard method for proving drug effectiveness.



The two agents tested in ALTTO are drugs designed to treat HER2-positive tumors, which is a particularly aggressive form of cancer that affects approximately 20 to 25 percent of breast cancer patients. Both agents, trastuzumab and lapatinib, have already been approved by the FDA for use for treatment of HER2-positive breast cancer. ALTTO will provide the first head-to-head comparison of trastuzumab and lapatinib in the earliest, most treatable stages of cancer. It is also one of the first large-scale studies to evaluate lapatinib's effectiveness in treating early breast cancer.

ALTTO is one of the first trials of its scope in which translational research—taking science from bench to bedside—plays a critical role. In ALTTO, biological material will be collected from thousands of patients to determine a tumor profile that responds best to the drugs—information that could lead to individualized patient care and, possibly, to development of next generation agents.

Current Funding Opportunities

Therapy and Prevention Research

PROGRAM ANNOUNCEMENT:

PA-07-356: <http://grants.nih.gov/grants/guide/pa-files/PA-07-356.html> (expiration date 05/08/2010)

CONTACT:

Heng Xie, M.D., Ph.D.

301-496-8866, xiehe@mail.nih.gov

This CTEP announcement will provide selected investigators with up to 5 years of support for new intervention studies and trials. At present, the traditional R01 research grant mechanism is underused 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-Site Trials

PROGRAM ANNOUNCEMENT:

PA-08-134: <http://grants.nih.gov/grants/guide/pa-files/PA-08-134.html> (expiration date 05/08/2012)

CONTACT:

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301-496-8866, xiehe@mail.nih.gov

CTEP, along with DCTD's Cancer Diagnosis Program and the Cancer Biomarkers Research Group within NCI's Division of Cancer Prevention, 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.

Quick-Trials for Novel Cancer Therapies and Prevention: Exploratory Grants

PROGRAM ANNOUNCEMENT:

PAR-08-025: <http://grants.nih.gov/grants/guide/pa-files/PAR-08-025.html> (expiration date 11/10/2010)

CONTACT:

Heng Xie, M.D., Ph.D.

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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.



Partnerships and Collaborations

Exploratory Investigational New Drug Studies

Exploratory investigational new drug (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 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 100 active INDs, and almost half of these are being co-developed with members of industry.

CTEP Collaborators and Agents

Collaborators	Agent Names
Abbott Laboratories	ABT-888 (NSC 737664)
Ascenta Therapeutics	(R)-(-)-Gossypol acetic acid (AT-101) (NSC 726456)
AstraZeneca International	AZD0530 (NSC 735464) AZD2171 (cediranib) (NSC 732208) AZD6244 (NSC 741078) ZD1839 (gefitinib) (NSC 715055)
Bayer Group	BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate) (NSC 724772)
Berlex Laboratories	Alemtuzumab (NSC 715969) GM-CSF (sargramostim) (NSC 613795)
Biogen Idec	In2B8/Y2B8 Radiolabeling Kit (ibritumomab tiuxetan) (NSC 710085) Rituximab (MoAb C2B8 anti CD20, chimeric) (NSC 687451)
Bristol-Myers Squibb	BMS-247550 (ixabepilone) (NSC 710428) BMS-214662 (farnesyl transferase inhibitor) (NSC 710086) BMS-354825 (dasatinib) (NSC 732517)
Celgene Corporation	CC-5013 (lenalidomide) (NSC 703813) Thalidomide (NSC 66847)
Cephalon, Inc.	Arsenic trioxide (As ₂ O ₃) (NSC 706363)
CuraGen Corporation, TopoTarget	Belinostat (PXD 101) (NSC 726630)
Cytokinetics, Inc.	SB-715992 (ispinesib) (NSC 727990)
Eisai, Inc.	E7389 (halichondrin B analog) (NSC 707389)
Gemin X Pharmaceuticals	Obatoclox mesylate (GX15-070MS) (NSC 729280)

Collaborators	Agent Names
Genentech, Inc.	Bevacizumab (rhuMAb VEGF) (NSC 704865) Pertuzumab (NSC 740102) Trastuzumab (NSC 688097)
Genta, Inc.	G3139 (oblimersen) (NSC 683428)
GlaxoSmithKline	506U78 (nelarabine) (NSC 686673) GW572016 (lapatinib) (NSC 727989) GW786034 (pazopanib) (NSC 737754)
Gloucester Pharmaceuticals	Romidepsin (depsipeptide; FK228) (NSC 630176)
Helsinn Group	XL119 (becatecarin, rebeccamycin analog) (NSC 655649)
ImClone Systems	IMC-A12 (NSC 742460) Cetuximab (C225) (NSC 714692)
Ipsen	SJG-136 (NSC 694501)
Johnson & Johnson	R115777 (tipifarnib) (NSC 702818)
Keryx Biopharmaceuticals	O(6)-Benzylguanine (NSC 637037) Perifosine (NSC 639966) UCN-01 (7-hydroxystaurosporine) (NSC 638850)
Lorus Therapeutics, Inc.	GTI-2040 (NSC 722929)
Medarex, Inc.	MDX-010 (MDX-CTLA4; ipilimumab) (NSC 720801)
MedImmune, Inc.	MEDI-522 (monoclonal antibody anti-alpha V beta 3 integrin) (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) Irofulven (MGI-114) (NSC 683863)
Millennium Pharmaceuticals	MLN-518 (tandutinib) (NSC 726292) PS-341 (bortezomib) (NSC 681239)
Mitos Pharmaceuticals	Tempol (NSC 142784)
NewLink Genetics	1-Methyl-[D]-tryptophan (NSC 721782)
Novartis Pharmaceuticals	STI-571 (imatinib) (NSC 716051)
Oncolytics Biotech, Inc.	Oncolytic Reovirus (Dearing Type 3) (NSC 729968)
OSI Pharmaceuticals	OSI-774 (erlotinib) (NSC 718781)
Pfizer, Inc.	Sunitinib malate (SU011248 L-malate) (NSC 736511)
Pharmacyclics, Inc.	Motexafin gadolinium (NSC 695238)
Pharmion Corporation	Azacitidine (NSC 102816)
Reata Pharmaceuticals	CDDO (NSC 711193)
Sanofi-aventis	Flavopiridol (alvocidib) (NSC 649890) Oxaliplatin (NSC 266046) Docetaxel (NSC 628563) Tirapazamine (NSC 130181) VEGF Trap (aflibercept) (NSC 724770)
Seattle Genetics, Inc.	SGN-30 (NSC 731636)
Syndax Pharmaceuticals	MS-275 (NSC 706995)
Tigris Pharmaceuticals, Inc.	AFP464 (aminoflavone prodrug) (NSC 710464)
The Vaccine Company	Proteinase 3 PR1 peptide (NSC 698102)
Vion Pharmaceuticals	Triapine (NSC 663249)
Wellstat Biologics Corporation	PV701 (NSC 700553)
Wyeth Pharmaceuticals	CCI-779 (temsirolimus) (NSC 683864)
Total: 46	Total: 67

As of November 2007



Scientific Advances

In 2007, several clinical trial results were reported that will likely change the way patients with multiple myeloma, acute promyelocytic leukemia, childhood B-cell lymphoma, and gastrointestinal stromal tumors are treated.

Low-dose Steroid Combined with Lenalidomide Prolongs Survival Compared with High-dose Steroid for Multiple Myeloma Treatment

High-dose steroids have been a standard component of multiple myeloma therapy for decades. Although the use of high-dose steroids was recognized as toxic, the assumption was that the high doses of steroids were required for clinical efficacy. However, a recent phase III trial conducted by ECOG, E4A03, in patients with newly diagnosed multiple myeloma compared standard high-dose steroids to low-dose steroids in patients receiving lenalidomide. A total of 445 patients were enrolled in this study between 2004 and 2006. Patients were randomized to one of two treatment arms. One patient group received lenalidomide and dexamethasone given at standard doses. The second group received standard-dose lenalidomide and low-dose dexamethasone. Patients in the study who received low-dose dexamethasone and lenalidomide had a one-year survival of 96 percent compared to 86 percent for patients treated with the standard doses of dexamethasone and lenalidomide. In addition, there were fewer side effects associated with the low-dose dexamethasone and lenalidomide. The shorter survival in those receiving the standard high-dose steroid therapy was due both to more myeloma deaths and adverse events. This study has defined a new standard of care in multiple myeloma.

Rajkumar SV, Jacobus S, Callander N, Fonseca R, Vesole D, Williams M, Abonour R, Siegel D, Greipp P. Phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): A trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol* 2007; ASCO Annual Meeting Proceedings (Post-Meeting Edition) 25;LBA8025.

Arsenic Compound Improves Survival of Adults with Uncommon Form of Leukemia

A phase III intergroup led by the CALGB trial demonstrated a positive benefit from consolidation therapy with arsenic trioxide (As_2O_3) on event-free survival and overall survival among patients with newly diagnosed acute promyelocytic leukemia (APL). Between June 1999 and March 2005, 582 patients were enrolled in this study. Patients were randomized to receive two courses of As_2O_3 for 5 days each week for 5 weeks as a first consolidation regimen if they achieved remission after induction therapy with oral tretinoin (ATRA), daunorubicin, and cytarabine. Subsequent consolidation included two courses of ATRA and daunorubicin. Patients in complete remission were then randomized to 1 year of ATRA maintenance (7 days repeated every other week) with or without 6-mercaptopurine (daily) plus methotrexate (weekly). Event-free survival, the primary endpoint, was 77 percent at 3 years on the As_2O_3 arm (median, not reached) compared to 59 percent at 3 years on the standard arm (median, 63 months). Overall survival was 86 percent on the As_2O_3 arm compared to 77 percent on the standard arm at 3 years. This study demonstrates that the addition of two courses of As_2O_3 consolidation therapy following remission induction significantly improves event-free survival and overall survival in adults with APL.

Stock W, Moser B, Powell BL, Appelbaum FR, Tallman MS, Larson RA, Feusner JH, Bloomfield CD, Willman C, Gallagher RE. Prognostic significance of initial clinical and molecular genetic features of acute promyelocytic leukemia (APL): Results from the North American Intergroup Trial, C9710. *J Clin Oncol* 2007; ASCO Annual Meeting Proceedings (Post-Meeting Edition) 25;7016.

Highly Effective, Less Toxic Therapy for Mature B-cell non-Hodgkin Lymphoma (NHL) in Children

The FAB/LMB96 trial for children with mature B-cell NHL, such as Burkitt lymphoma, was an

international collaboration that included COG researchers as well as investigators from France and the United Kingdom. One objective of the study was to assess the possibility of reducing treatment in children with intermediate-risk mature B-cell NHL without jeopardizing survival. Patients in this risk group were randomized to receive the previous standard therapy or to receive an experimental treatment in which the cyclophosphamide dose and/or the duration of treatment was reduced. Children receiving the reduced treatment had 4-year event-free survival rates exceeding 90 percent, demonstrating that this group of patients can be cured with a four-course treatment with a total dose of only 3.3 g/m² cyclophosphamide and only 120 mg/m² doxorubicin.

The FAB/LMB96 study additionally attempted to reduce treatment without lowering outcome in patients with high-risk characteristics who had either CNS involvement, extensive bone marrow involvement, or both. For high-risk patients, those receiving the standard treatment had superior outcome compared to those receiving reduced treatment. Patients with bone marrow involvement and no CNS disease receiving the standard treatment had 4-year event-free survival of 91 percent, while those with CNS disease had 4-year event-free survival of 75 percent.

The FAB/LMB96 study optimized treatment for children with mature B-cell NHL and demonstrated the feasibility of large international trials for children with cancer.

Cairo MS, Gerrard M, Sposto R, Auperin A, Pinkerton CR, Michon J, Weston C, Perkins SL, Raphael M, McCarthy K, Patte C; FAB LMB96 International Study Committee. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. *Blood* 2007;109:2736–43. <http://www.ncbi.nlm.nih.gov/pubmed/17138821>

Patte C, Auperin A, Gerrard M, Michon J, Pinkerton R, Sposto R, Weston C, Raphael M, Perkins SL, McCarthy K, Cairo MS; FAB/LMB96 International Study Committee. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: It is possible to reduce treatment for the early responding patients. *Blood* 2007;109:2773–80. <http://www.ncbi.nlm.nih.gov/pubmed/17132719>

Imatinib Mesylate Decreases Cancer Recurrence for Patients with Primary Gastrointestinal Stromal Tumor

Preliminary results from a large, randomized, placebo-controlled clinical trial for patients with primary gastrointestinal stromal tumor (GIST) demonstrated that patients who received imatinib mesylate after complete removal of their tumor were significantly less likely to have a recurrence of their cancer compared to those who did not receive imatinib. This intergroup clinical trial, Z9001, was led by the American College of Surgeons Oncology Group.

Over 600 patients with primary tumors 3 cm or larger that had been completely removed with surgery were enrolled in the trial between June 2002 and April 2007. Patients were randomized to one of two treatment arms. One patient group received imatinib at a dose of 400 milligrams per day for 1 year. The second group received placebo for 1 year. Neither the patients nor their physicians knew which treatment the patients were receiving. Patients who developed a recurrence of their cancer while on study therapy were unblinded to their treatment assignment. Those patients who had been on placebo subsequently received imatinib and those who had been on imatinib continued their imatinib therapy, but at a higher dose. Researchers found that approximately 97 percent of patients in the study who received one year of imatinib after surgery did not have a recurrence of their cancer compared to 83 percent of patients who received one year of placebo. In addition, imatinib therapy was well tolerated by most patients enrolled in the study. The difference in recurrence-free survival was most pronounced in patients with tumors between 6 and 10 cm and tumors greater than 10 cm. There was no difference in overall survival for patients on the two treatment arms.

DeMatteo R, Owzar K, Maki R, Pisters P, Blackstein M, Antonescu C, Blanke C, Demetri G, von Mehren M, Ballman K; American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team. Adjuvant imatinib mesylate increases recurrence free survival (RFS) in patients with completely resected localized primary gastrointestinal stromal tumor (GIST): North American Intergroup Phase III trial ACOSOG Z9001. Presented at: 43rd American Society of Clinical Oncology (ASCO) Annual Meeting, June 2–5, 2007. Chicago, IL. Abstract #10079.



Tools, Products, and Resources

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.

Community Clinical Oncology Program

<http://prevention.cancer.gov/programs-resources/programs/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 at the community level. One-third of patients accrued to 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 2007, 49 CCOPs and 14 minority-based CCOPs across the country received funding for participation in NCI-approved trials. Altogether, the program comprises 3,600 participating physicians, 400 participating hospitals working on more than 230 active treatment trials, and more than 60 active prevention and control trials.



CTEP's Online Resources for Investigators

<http://ctep.cancer.gov/investigatorResources/default.htm>

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

- *Investigators' Handbook:* (http://ctep.cancer.gov/investigatorResources/investigators_handbook.htm) 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:* (http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers) Standards used to grade, assign attribution, and report adverse effects experienced by patients in clinical trials
- *Adverse Event Expedited Reporting System (AdEERS):* (http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_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:* (http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers) A dictionary of terms that are used when collecting patient information for clinical trials or cancer care
- *Clinical Data Update System (CDUS):* (http://ctep.cancer.gov/protocolDevelopment/default.htm#cde_data_pol_cdus) The mechanism used when submitting specified data for CTEP-approved clinical trials
- *Clinical Trials Monitoring Branch—Auditing Information System (CTMB-AIS):* (<http://ctep.cancer.gov/branches/ctmb/default.htm>) 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/industryCollaborations2/default.htm>

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:* (<http://ctep.cancer.gov/industryCollaborations2/default.htm>) 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:* (<http://ctep.cancer.gov/industryCollaborations2/default.htm>) 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:* (http://ctep.cancer.gov/industryCollaborations2/model_agreements.htm) A collection of 14 model documents in Microsoft Word for use by industry collaborators
- *NCI/Cooperative Group/Industry Relationship Guidelines:* (http://ctep.cancer.gov/industryCollaborations2/default.htm#guidelines_for_collaborations) 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:* (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) A description of the policy governing intellectual property rights and proprietary data protections under government-industry collaborations
- *CTEP Pharmacogenomics Guidelines:* (<http://ctep.cancer.gov/industry/>) CTEP's guidelines for investigators and pharmaceutical/biotechnology companies concerning the conduct of pharmacogenetics protocols linked to CTEP-sponsored clinical trials

Patient Information about NCI Clinical Trials

Finding Clinical Trials

<http://www.cancer.gov/clinicaltrials/finding/treatment-trial-guide>

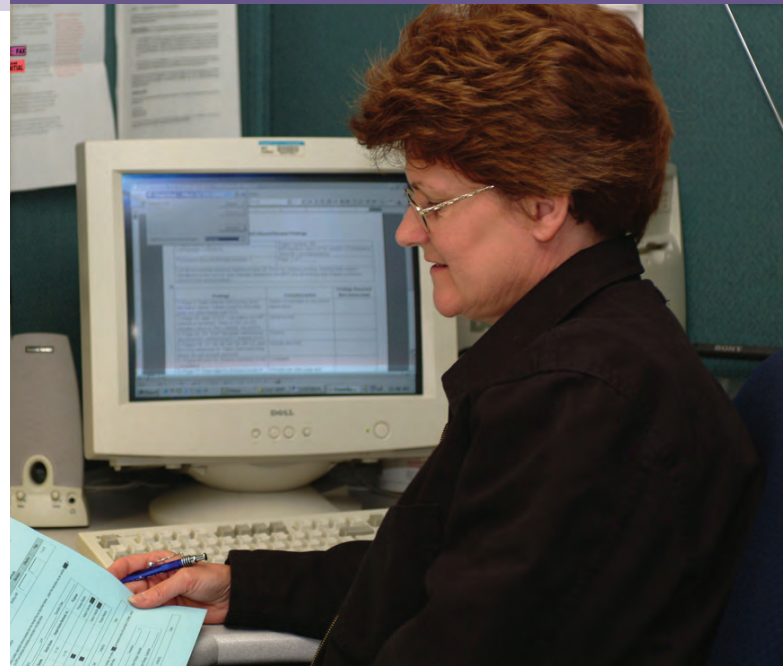
A detailed, yet simple guide called “How to Find a Cancer Treatment Trial” helps patients to:

- 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 Cancer Clinical Trials

<http://www.cancer.gov/clinicaltrials/search>

The NCI's database of cancer clinical trials provides protocol summaries in lay language for patients and in a more detailed format for health professionals. 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.



Developmental Therapeutics Program

Program Accomplishments

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





DTP Overview

DTP's roster of drug success stories is impressive. On that list is paclitaxel, 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 grant. It was a DTP contractor who formulated the drug for use in clinical trials. Bortezomib is another DTP success story. In cooperation with its commercial sponsor, bortezomib was screened and formulated by DTP. Approved by the Food and Drug Administration (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 therapeutic agents 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, vialled and plated compounds, tumor cells, and animals; and providing bulk drugs for investigational new drug (IND)-directed studies.

Approved Cancer Treatment Drugs Developed with DTP Involvement

2004 Cetuximab (NSC 632307)	1977 Carmustine (BCNU) (NSC 409962)
2003 Bortezomib (NSC 681239)	1976 CCNU (NSC 9037)
1998 Denileukin diftitox (NSC 697979)	1975 Dacarbazine (NSC 45388)
1996 Polifeprosan 20 with carmustine implant (NSC 714372)	1974 Doxorubicin (NSC 123127)
Topotecan (NSC 609699)	Mitomycin C (NSC 26980)
1995 All-trans retinoic acid (NSC 122758)	1973 Bleomycin (NSC 125066)
1992 2-chlorodeoxyadenosine (NSC 105014)	1970 Floxuridine (FUDR) (NSC 27640)
Paclitaxel (NSC 125973)	Mithramycin (NSC 24559)
Teniposide (NSC 122819)	Mitotane (o-p'-DDD) (NSC 38721)
1991 Fludarabine Phosphate (NSC 312887)	1969 Cytarabine (ARA-C) (NSC 63878)
Pentostatin (NSC 218321)	Procarbazine (NSC 77213)
1990 Hexamethylmelamine (NSC 13875)	1967 Hydroxyurea (NSC 32065)
Levamisole (NSC 177023)	1966 Pipobroman (NSC 25154)
1989 Carboplatin (NSC 241240)	Thioguanine (NSC 752)
1988 Ifosfamide (NSC 109724)	1964 Melphalan (NSC 8806)
1987 Mitoxantrone (NSC 301739)	Actinomycin D (NSC 3053)
1983 Etoposide (NSC 141540)	1963 Vincristine (NSC 67574)
1982 Streptozotocin (NSC 85998)	1962 Fluorouracil (NSC 19893)
1979 Daunorubicin (NSC 82151)	1961 Vinblastine (NSC 49842)
1978 Cisplatin (cis-platinum) (NSC 119875)	1959 Cyclophosphamide (NSC 26271)
	Thiotepa (NSC 6396)
	1957 Chlorambucil (NSC 3088)

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 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

Major Ongoing Initiatives

Drug Discovery Initiatives

International Cooperative Biodiversity Groups

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

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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 (ICBGs) 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. Additionally, this research 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 5,000 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 plant species new to science and many novel compounds have been discovered.

The program has been re-competed under the updated RFA-08-007 (<http://grants.nih.gov/grants/guide/rfa-files/RFA-TW-08-003.html>), and awards are expected during 2008. Four governmental agencies are cosponsoring RFA-08-007: National Institutes of Health (NIH), National Science Foundation (NSF), Department of Energy (DOE), and Department of Agriculture (USDA). The participating components of the governmental organizations are: Fogarty International Center (FIC/NIH); National Cancer Institute (NCI/NIH); National Institute of Mental Health (NIMH/NIH); National Institute of General Medical Sciences (NIGMS/NIH); National Center for Complementary and Alternative Medicine (NCCAM/NIH); Office of Dietary Supplements (ODS/NIH); Directorate for Biological Sciences (NSF); Office of Biological and Environmental Research (DOE); and Cooperative State Research, Education, and Extension Service (USDA).

Rapid Access to NCI Discovery Resources

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

CONTACT:

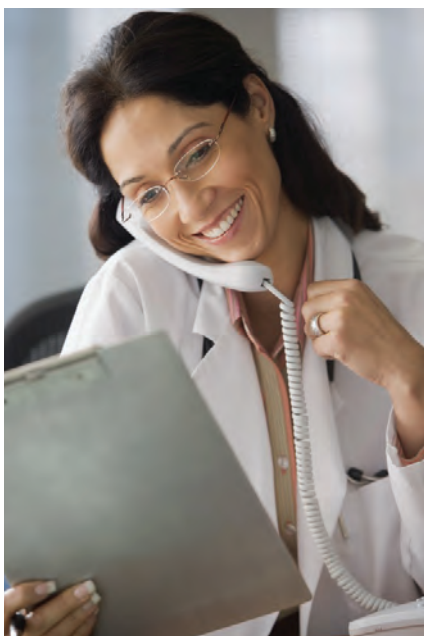
R·A·N·D

Office of the DTP Associate Director

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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.

In 2001, NCI began Rapid Access to NCI Discovery Resources, or R·A·N·D, a program to provide DTP resources to academics and nonprofit organizations 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 they 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 analog generation, structure-activity studies, and lead optimization
- Bioassay-directed natural product isolation and characterization
- *In vivo* testing

R·A·N·D is not a mechanism for obtaining grants. To access the contract-based services of the R·A·N·D program, academic and nonprofit 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 contracts. All output from the project is returned to the originator for further investigation.

Among the recipients of R·A·N·D services is Dr. Deborah Lannigan, University of Virginia, whose research group is studying the ribosomal S6 kinase (RSK) family, which are downstream effectors of mitogen-activated protein kinase. RSK is overexpressed in about 50 percent of breast and prostate cancers compared to normal tissue. DTP is supporting this research with a high-throughput screening campaign combined with molecular modeling of the active site of the protein.



Drug Discovery and Development Initiative

National Cooperative Drug Discovery Groups Program—for Academics and Industry

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

CONTACT:

Mary K. Wolpert, Ph.D.

301-496-8783, wolpermtm@exchange.nih.gov

DTP's National Cooperative Drug Discovery Groups (NCDDG) program, initiated in 1983, partners NCI-funded academic researchers with private-sector organizations to fund cooperative agreements (U19s) in support of a multi-disciplinary approach to the discovery of new, rationally based and natural source-derived anticancer treatments and strategies.

This program is one of the first in which NCI began partnering with private industry. The NCDDG program has assisted in the development of four FDA-approved anticancer agents: topotecan (NSC 609699); polifeprosan 20 with carmustine implant (NSC 714372); denileukin difitox (NSC 733971); and cetuximab (NSC 714692). 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.

Although NCDDG projects do not support clinical trials, timely clinical evaluation of agents discovered through NCDDG is encouraged. Currently, NCI funds nine groups. Of the current awardees, the NCDDG headed by Dr. Garth Powis of the University of Texas M.D. Anderson Cancer Center has been successful in developing PX-478, a HIF-1 alpha inhibitor, and bringing it to clinical testing. Additionally, a PI3 kinase inhibitor, which was derived from the natural product wortmannin, is in late stage preclinical development and will likely enter clinical testing in 2008.

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

Drug Development Initiatives

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 126 projects, through which 15 small molecules and 17 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:

Office of the DTP Associate Director
301-496-8720, ddg@dtpax2.ncifcrf.gov

The Drug Development Group (DDG) meets monthly to consider developing drugs from discoveries in the NCI intramural and extramural academic communities, as well as with the pharmaceutical industry, where successful development leads to an NCI-sponsored clinical trial. By contrast, the products of the RAID program will, in general, be returned directly to the originating investigator for clinical trials.

Compounds at all stages of development are considered on an individual basis. The DDG is 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 (one exception is that the Biological Resources Branch Oversight Committee 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.





Tools, Products, and Resources

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 50 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 vialled 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 of nucleic acid antagonists with anti-HIV activity, and of 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 a low-temperature repository that 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.

Animal Production

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

DTP's Biological Testing Branch oversees animal-production facilities that produce inbred, outbred, and hybrid strains of rats and mice. 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 2007, the branch distributed 951,566 rodents to about 1,750 investigators at 250 institutions.

In Vitro Screening: The Human Tumor Cell Line Assay (NCI60)

<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 a drug may correlate with molecular target expression.

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 mouse models. The screen is currently composed of 60 human tumor cell lines (NCI60), 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 the online submission form at <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 at 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 recommendations were made to improve quality control.

DTP has also instituted, as the first step in the screening process, a one-dose NCI60 screen. This screen has a higher throughput and thus more rapid turn-around time for suppliers. Compounds that pass criteria are screened against the NCI60 at five doses.



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 macro-molecular interactions.

The branch's labs and offices are located on the NCI-Frederick campus and are operated under a contract with Science 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 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 microenvironment heterogeneity that develops in these tumors as they grow.

The hollow fiber assay at full capacity allows screening of 50 or more compounds per 10-day assay. In addition to requiring less than two weeks to complete, the assay requires at most only 450 mg of material, as opposed to the multigram quantities required for many 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 communities. Cell lines also are sent to 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. Since the early 1990s, nearly 300 research groups have contributed to the molecular characterization of the NCI60 panel of human tumor cell lines, which the DTP uses to screen potential new agents for anticancer activity. To date, over 300,000 measurements have been completed, with 132,000 available to the public.

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 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 1,200 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 50 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 200,000 drugs. Investigators use the 3-D database 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.

The Website and its databases are maintained by DTP's Information Technology Branch.

Drug Development

Biological Resources Branch Preclinical Repository

<http://web.ncifcrf.gov/research/brb/PreClinRepo-Home.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/radiobl1ist2.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.

Drug Formulation and Synthesis

http://dtp.nci.nih.gov/branches/prb/prb_operations.html

DTP's Pharmaceutical Resources Branch bears the responsibility of acquiring bulk materials for formulation and synthesis, formulating drugs and testing them, producing clinical dosage forms, 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 under development by the DDG or the RAID program.

Drug Production

Biopharmaceutical Development Program

<http://www.bdp.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 targeted 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.

The BDP was able to develop a complete, simple, and scalable clinical manufacturing process for BL22 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. An improved version, HA-22, has subsequently been developed that has higher affinity targeting to the CD-22 antigen. This drug is has been licensed to MedImmune, a subsidiary of AstraZeneca. Using material made by the BDP at NCI-Frederick, HA-22 is in clinical trials at NCI and elsewhere in the U.S. and Europe in patients with hairy cell leukemia, chronic lymphocytic leukemia, and non-Hodgkin lymphoma. 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.

The Type 1 Diabetes Rapid Access to Intervention Development Program

<http://t1diabetes.nih.gov/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 available NCI resources for the preclinical development of drugs, natural products, and biologics 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, nonprofit 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 Rapid Access to Intervention Development Pilot Program

<http://nihroadmap.nih.gov/raid>

CONTACT:

NIH-RAID Pilot Program Office
301-594-4660, NIH-RAID@nidk.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 NIH 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.



Scientific Advances

Grants and Contracts Operations Branch 2007 Highlight

Samuel J. Danishefsky was awarded the First Annual American Association for Cancer Research (AACR) Award for Outstanding Achievement in Chemistry in Cancer Research. Professor Danishefsky has continuously been an NCI grantee for at least 30 years, and he currently holds two grants in the Grants and Contracts Operations Branch research portfolio, including a Merit Award. He is both Professor of Chemistry at Columbia University and Director of the Bioorganic Chemistry Laboratory at Memorial Sloan-Kettering Cancer Center. Professor Danishefsky studies the chemistry of both natural product-inspired small molecules and of complex oligosaccharides and glycopeptides with the intent of developing anticancer therapeutics, and this AACR award recognized his many leading contri-

butions in these fields. His lab's important recent accomplishments include the development of epothilone-based small molecule drugs and synthetic carbohydrate-based anticancer vaccines; agents of both types are in clinical development.

From the Sea to Clinical Trials

Dr. William Fenical at the Scripps Institution of Oceanography (SIO), University of California at San Diego (UCSD), is an internationally recognized leader in the field of marine natural products. His research has received sustained NCI support and he currently holds a MERIT award for his pioneering work in marine microbe-based drug discovery.

Despite historical successes with antitumor antibiotics, over the past several decades the efficacy of antibiotics and anticancer drugs derived from microbial sources has diminished due in

Developmental Therapeutics Program Reference Guide for New Users

<http://dtp.nci.nih.gov/guide.html>

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 data, 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 a high-throughput assay developed (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)



large part to development of drug resistance. Traditional terrestrial microbial sources for new drug leads are yielding reduced returns after years of intensive research. Exploring the world's vast unexplored oceans for marine microbes as a source for new microbes and novel drug leads was thought to be a rewarding endeavor. Dr. Fenical and his team combined marine microbiology techniques with modern drug discovery tools, explored deep ocean sediments, and made the seminal discovery of a new genus of obligate marine actinomycetes, named *salinospora*, from deep ocean sediments.

Dr. Fenical's work has continued to focus on genetically unique marine microbes, and he and his team have found new strains of obligate marine microbes that require seawater to grow in culture. Through morphology and 16S rRNA phylogenetic analyses, these new bacteria represent the first major actinomycete taxon reported exclusively from the sea. This finding is significant as it provides further evidence of the important roles actinomycetes play in marine ecology and biocomplexity. He and his team have found a number of novel biologically active compounds, two of which are currently in phase I development. One is salinosporamide A, which has an unusual fused γ -lactam- β -lactone bicyclic structure and is a potent 20S proteasome inhibitor (IC_{50} 1.3 nM). The compound has been licensed to Nereus Pharmaceuticals and is in phase I clinical development for the treatment of multiple myeloma, lymphomas, and solid tumors. Due to the success of bortezomib, which has received marketing approval for the treatment of multiple myeloma, the proteasome is a high interest drug target. In preclinical studies, this drug appears superior to bortezomib and shows: 1) a broader and longer lasting proteasome inhibition profile; 2) efficacy against bortezomib-, lenalidomide-, thalidomide-, and dexamethasone-resistant tumor cells from multiple myeloma patients; 3) efficacy against a wider range of tumors, including many solid tumor models; 4) less cytotoxicity to normal

cells; 5) a 7- to 10-fold higher *in vivo* potency; 6) potential for administration both orally and by intravenous injection on a once-a-week schedule; 7) marked enhancement of efficacy when used in combination with chemotherapeutics and biologics such as bevacizumab, cetuximab, irinotecan, FOLFOX, FOLFIRI, and oxaliplatin. Recently, Dr. Bradley Moore, also of SIO at UCSD, and collaborators have completed the genome sequence of the producing strain, and his team discovered and subsequently characterized a novel chlorination pathway by which salinosporamide incorporates the chlorine atom, which is key to the drug's ability to bind to the proteasome. Genetic engineering of the pathway can lead to analogs not available in nature. These exciting developments clearly demonstrate the potential of finding new chemical entities as cancer drugs from natural sources.

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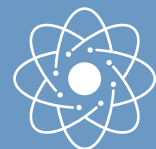
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Radiation Research Program

Program Accomplishments

The Radiation Research Program (RRP) 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.





RRP 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 and cancer care
- Evaluating the effectiveness of radiation research being conducted by National Cancer Institute (NCI) grantees

RRP also coordinates its activities with other radiation research efforts 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.

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) and image-guided radiotherapy, brachytherapy using temporary and permanent implantation of radioactive sources, and particle therapy, in particular the most widely used form, proton therapy. Carbon ion therapy is also under development worldwide.
- 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.

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 2007, RRP administered 202 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; normal tissue injury

and treatment; 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 are the Young Investigators Workshops, in which emerging leaders come together to discuss research and to build new collegial relationships as well as learn about the NCI grant process.

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, a fellowship in medical oncology at NCI, and a fellowship in radiation oncology at Stanford University.



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, and in addition to RRP, he 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, and a Special Advisor to the NCI Director. Since 2004, he has been the Senior Medical Advisor and Team Leader of the Chemical, Biological, Radiological, and Nuclear Team in the Office of Preparedness and Operations in the Office of the Assistant Secretary for Preparedness and Response in the Department of Health and Human Services. He 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.



The RRP encompasses three branches:

- Radiotherapy Development Branch
- Clinical Radiation Oncology Branch
- Molecular Radiation Therapeutics Branch

Partnerships and Collaborations

Cancer Disparities Research Partnership Program

<http://www3.cancer.gov/rrp/CDRP>

CONTACT:

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Cancer health disparities are exemplified by differences in cancer morbidity and mortality as a function of gender, ethnicity, or 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 mentoring 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 Patient Navigators to facilitate access to radiation oncology services, including clinical trials, by addressing financial, geographic, and cultural barriers 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 2003, RRP awarded six Cooperative Planning Grants for CDRPs using the U56 mechanism. The unique aspect of this innovative program is that the health disparity institution is the primary grantee. The mentoring academic institution (cancer center, university, or cooperative group) is chosen by the grantee. NOVA Research is conducting an ongoing evaluation and review to help guide program enhancements. With the success evident in the first 5-year grant period, the program is moving toward renewal, with the challenge being how to sustain the success of grantees. Indeed, the Radiation Therapy Oncology Group (RTOG) now has a robust Cancer Disparities Committee and the American Society of Therapeutic Radiology and Oncology (ASTRO) has a health disparities symposium as part of the annual meeting so that addressing health disparities is a strong focus of radiation oncology. Lessons learned from the CDRP program are shared with other health disparities programs at NCI and NIH, such as the Center to Reduce Cancer Health Disparities.

Cancer Disparities Research Partnerships

Rapid City Regional Hospital, Rapid City, SD

<http://www3.cancer.gov/rp/CDRP/rapidcity.html>

Principal investigator: Daniel Petereit, M.D.
Primary partner: University of Wisconsin Comprehensive Cancer Center

New Hanover Regional Medical Center, Wilmington, NC

<http://www3.cancer.gov/rp/CDRP/nhrmc.html>

Principal investigator: Patrick D. Maguire, M.D.
Primary partner: University of North Carolina School of Medicine

Centinel Freeman Regional Medical Center, Memorial Campus, Inglewood, CA

<http://www3.cancer.gov/rp/CDRP/dfmh.html>

Principal investigator: Michael L. Steinberg, M.D.
Primary partner: University of Southern California Health Sciences Campus

Singing River Hospital, Pascagoula, MS

<http://www3.cancer.gov/rp/CDRP/srhs.html>

Principal investigator: W. Sam Dennis, M.D., Ph.D.
Primary partner: University of Alabama at Birmingham

UPMC McKeesport, McKeesport, PA

<http://www3.cancer.gov/rp/CDRP/upmc.html>

Principal investigator: Dwight E. Heron, M.D.
Primary partners: Washington University in St. Louis School of Medicine and Roswell Park Cancer Institute





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 6 to 8 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.

When we look into the eyes of our relatives, we know how precious life is.

WALKING Forward
To'kaktiya zanniyān omani pi ye/yo.

Walking Forward, a program of Rapid City Regional Hospital (in partnership with the National Cancer Institute), seeks ways to help families and communities protect life and health. By working together, doctors, other health care workers, and people in the community can address cancer prevention, detection, and early treatment. We are committed to walking forward toward a healthier life for all the people we serve.

Mitakuye oyasin!

Hear more about the Walking Forward program on KILI Radio every other Wednesday from 10-11 a.m.

For more information call 800-232-0115 ext. 2305 | E-mail: walkingforward@rcri.org

RAPID CITY REGIONAL HOSPITAL
353 Fairmont Blvd., Rapid City, SD

Cancer Disparities Research Partnership

TELESYNERGY®

http://www3.cancer.gov/rrp/CDRP/telesynergy_info.html

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For patients located in medically underserved areas such as rural or economically disadvantaged locales in the U.S. and worldwide, access to cutting-edge medical care and physician 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 to develop the system.

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, 23 institutions in the U.S. and seven 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, examination camera, and others
- **Health Insurance Portability and Accountability Act of 1996 (HIPAA)–Compliant**
- **Moving toward Web-based approach to reduce operating costs and increase accessibility**

TELESYNERGY units also link researchers globally. Currently, there are systems in Dublin, Ireland; Belfast, Northern Ireland; Brussels, Belgium; and Amman, Jordan.

RRP continues to deploy TELESYNERGY systems throughout the U.S. and Europe. It also provides installation, training, and ongoing technical support and coordinates multisite TELESYNERGY conferences.

Civilian Medical Response to Radiation-Related Events

<http://www.hhs.gov/aspr/>

CONTACT:

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RRP staff are working with the Office of Preparedness and Emergency Operations 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:

Richard Hatchett, M.D.

301-496-1886, hatchettr@niaid.nih.gov

Weaponized radiation has become an uncomfortable reality in the post-9/11 world. Potential threats include radiological “dirty bombs” and nuclear explosives. 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, the U.S. Government, through the National Institute of Allergy and Infectious Diseases (NIAID), has established a 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.

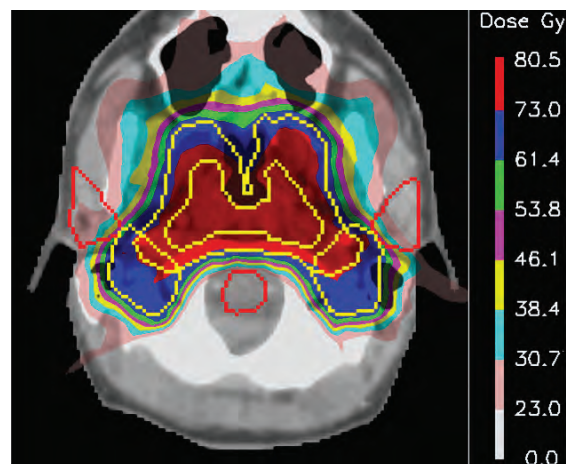
Under this initiative, RRP is collaborating with NIAID, the lead institute at NIH for the development of biodefense countermeasures. NIAID’s research portfolio includes many in-depth studies of the immune system, which is especially vulnerable to radiation.

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 the injuries from 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.

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 (EPA), the Food and Drug Administration (FDA), DHHS, National Aeronautics and Space Administration, NIH (NCI, NIAID), the Nuclear Regulatory Commission, the Armed Forces Radiobiology Research Institute, and the Radiation Emergency Assistance Center/Training Site. The purpose of RABRAT 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.



Cancer Expert Corps

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The Cancer Expert Corps (CEC) is a concept under development with a planned launch in 2008. It is a global initiative that will improve the quality of life of cancer patients (with direct applicability to other diseases) by bringing protocol-based treatment (and ultimately the possibility for participation in cancer clinical trials), education, and mentoring to underserved populations in the U.S. and world wide. It is a “Peace Corps for Cancer.”

The three components of the CEC are:

- Medical facilities/locations serving underserved populations (called “Recipients”) who are interested in participating and investing in improving the quality of care/life for their affected citizens
- CEC Expert Panels comprised of international experts from a broad range of oncology disciplines and healthcare delivery services that provide the mentoring for the Recipients based on long-term, person-to-person connectivity
- Hubs, or infrastructure, located worldwide to coordinate the Recipient-Expert linkage so that their time is spent on mentoring and education

CEC will be launched with the Foundation for the NIH as a public-private partnership.

Scientific Advances

Of the many successful programs within the RRP grant and contract portfolio, three scientific advances are presented below, one each for technology development, molecular radiation therapy, and quality assurance for high-technology radiation therapy and international networking.

Enhancing Treatment Accuracy and Precision

A goal in modern radiotherapy is to shape the radiation field closely to the tumor in 3 dimensions to minimize the risk of radiation damage to the normal tissues surrounding the tumor. In some tumor sites, this is complicated by motion of both the tumor and normal tissue, such as the movement of both normal lung and lung tumors during breathing. Special imaging and computer programs are being developed to accommodate this motion. Paul Keall, Ph.D., and his colleagues at Stanford University have developed a method to obtain 4-dimensional images of the lungs from a spiral computed tomography (CT) imaging scan. It involves assigning each CT “slice” to one of eight phases of the breathing cycle. The distortion of the image is greatly reduced by this process. Most commercial CT machines now incorporate this technique.

Weiss K, Wijesooriya K, Dill SV, Keall PJ. Tumor and normal tissue motion in the thorax during respiration: Analysis of volumetric and positional variations using 4D CT. *Int J Radiat Oncol Biol Phys* 2007;67:296–307. <http://www.ncbi.nlm.nih.gov/pubmed/17189078>

Vedam SS, Keall PJ, Kini VR, Mostafavi H, Shukla MP, Mohan R. Acquiring a four-dimensional computed tomography dataset using an external respiratory signal. *Phys Med Biol* 2003;48:45–62. <http://www.ncbi.nlm.nih.gov/pubmed/12564500>



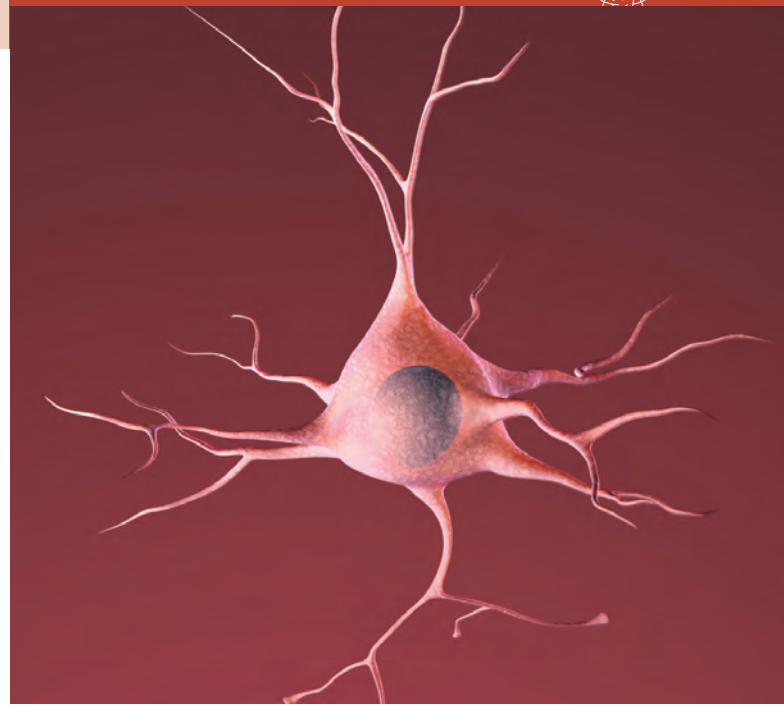
Improving Outcome for Patients with Brain Tumors

Patients with brain tumors are often treated with radiotherapy to the brain. Unfortunately, 20 to 50 percent of these patients experience a progressive dementia because of the effects of the radiation on normal brain tissue. Pioglitazone, a drug used in the treatment of diabetes, prevented the cognitive decline in rats that were given whole-brain irradiation. Pioglitazone was administered in the animals' food from 3 days before irradiation to 4 or 54 weeks after irradiation. Treatment for 4 weeks after irradiation was as effective as treatment for 54 weeks. If pioglitazone treatment was not started until after irradiation, it was less effective. If similar results can be shown in brain cancer patients, it will greatly improve the quality of life of cancer survivors.

Zhao W, Payne V, Tommasi E, Diz DI, Hsu FC, Robbins ME. Administration of the peroxisomal proliferator-activated receptor gamma agonist pioglitazone during fractionated brain irradiation prevents radiation-induced cognitive impairment. *Int J Radiat Oncol Biol Phys* 2007;67:6–9. <http://www.ncbi.nlm.nih.gov/pubmed/17189061>

Radiation Quality Assurance for High-Technology Treatment—Advanced Technology Consortium

The Advanced Technology Quality Assurance Consortium (ATC) capitalizes on the infrastructure and strengths of the nation's existing quality assurance (QA) programs—including the Image-Guided Therapy Center (ITC), RTOG, Radiological Physics Center (RPC), and the Quality Assurance Review Center (QARC)—to develop and maintain an advanced medical informatics infrastructure that provides an environment in which institutions can submit and QA Centers can receive, share, and analyze volumetric multimodality imaging/treatment planning/verification (ITPV) digital data. Specifically, the ATC:



- Maintains, manages, and improves the current electronic data submission of advanced technology (3-dimensional CRT, IMRT, stereotactic body radiotherapy [SBRT], and brachytherapy), protocol credentialing and case data, archival storage, and remote QA review process.
- Develops novel Web-based remote-review tools that will enhance the efficient and effective review of protocols utilizing advanced technologies. The system is modular in design to promote efficient tools and subsystems development that achieve compatibility with existing software standards, including the cancer Bioinformatics Grid (caBIG).
- Assists cooperative groups in the development and management of advanced technology clinical trials protocols, including:
 - Tumor/target volume and organ-at-risk definitions
 - Credentialing requirements and evaluation criteria
 - Electronic data submission requirements/instructions
 - QA review procedures
- Serves as an educational resource to the nation's clinical trial cooperative groups and participating institutions for support of advanced technology radiation therapy clinical trials.

Molecular Radiation Therapeutics Branch

The Molecular Radiation Therapeutics Branch (MRTB) is an RRP in-house laboratory program that serves as a focal point for collaborations with the Developmental Therapeutics Program (DTP) in DCTD, investigators in the Radiation Biology and Radiation Oncology branches in the Center for Cancer Research (CCR), and university and industry collaborators interested in combined modality therapy using radiation. In 2008, MRTB will undergo a major expansion on the NCI-Frederick campus, in proximity with DTP drug development and molecular imaging in DCTD and CCR. A new chief for the branch is being recruited.

Tools, Products, and Resources

National Institute of Biomedical Imaging and Bioengineering

<http://www.nibib.nih.gov/>

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) is an institute 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 3-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 image-guided therapy technology development.

RRP's collaboration with NIBIB accelerates the pace of discovery and speeds the development of biomedical technologies that prevent or treat illnesses.

National Electrical Manufacturers Association and the American College of Radiology Digital Imaging and Communications in Medicine Standard

<http://dicom.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), 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 standard. DICOM 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.



Meetings and Workshops

Quality Assurance of Radiation Therapy: The Challenges of Advanced Technology

This 3-day meeting, held in February 2007, was sponsored jointly by ASTRO, the American Association of Physicists in Medicine (AAPM), and NCI. It included more than 40 invited speakers from the radiation oncology and industrial engineering/human factors communities and attracted nearly 350 attendees.

The conference was a follow-up to an NCI quality assurance (QA) workshop held in September 2005. Its broad goal was to address the widespread concern that current QA practices and protocols do not cost-effectively or adequately safeguard advanced technology radiation therapy patients against treatment delivery errors that have the potential to degrade the expected therapeutic ratio or, in extreme cases, to cause acute injury. Conference speakers were asked to systematically assess their area of practice expertise for strengths, weaknesses, and gaps in the associated safety and quality infrastructure. With some exceptions, available QA guidelines, which were mainly formulated in the 2-dimensional radiotherapy era, were found to not adequately address quality for the more complex and variable image-based or image-guided conformal radiotherapy procedures. While updating or expanding prescriptive QA protocols would address some of these deficiencies, the conference organizers concluded that new approaches are needed in the areas of image-based planning and image-guided and computer-controlled therapies. A more flexible and process-centered approach that better balances catastrophic error mitigation and quality erosion and with greater physician and vendor involvement was recommended. Industrial engineering approaches to risk analysis and mitigation, which have dramati-

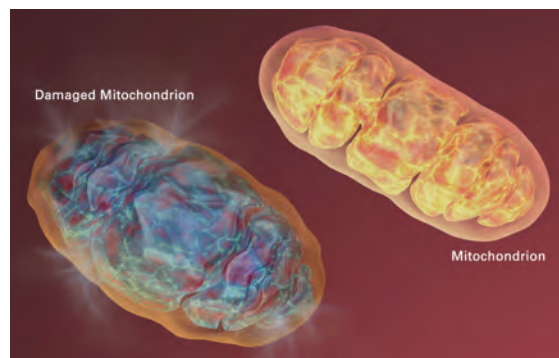
cally lowered mortality in anesthesia and the airline industry, were thought to be promising approaches for developing a more cost-effective, risk-based, and effective QA infrastructure for radiation therapy. The proceedings of this workshop are being published as a special section in the *International Journal of Radiation Oncology* Biology* Physics*.

Radiation Carcinogenesis and Post-Exposure Mitigation

RRP conducted a workshop in September 2006 addressing a key issue related to radiological/nuclear terrorism, that of radiation-induced cancers. The unpredictable nature of a terrorism event is such that a classical radioprotectant, which must be given before exposure, cannot be used. Rather, countermeasures are required that are effective even when given after radiation exposure. RRP brought together experts in radiation carcinogenesis to focus on post-exposure interventions. This topic is relevant to clinical radiation oncology, as well as to countering radiation terrorism.

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.





Biometric Research Branch

Program Accomplishments

The Biometric Research Branch (BRB) is DCTD's statistical and biomathematical component. BRB members provide statistical leadership for DCTD national research programs in clinical trials, developmental therapeutics, developmental diagnostics, diagnostic imaging, and statistical and computational genomics.

BRB Overview

During 2007, 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) collaborate and consult with DCTD scientific administrators and NCI intramural investigators, and (2) conduct 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>.

Partnerships and Collaborations

Cancer Therapy Evaluation Program

<http://ctep.cancer.gov/>

BRB investigators Drs. Edward Korn, Larry Rubinstein, Boris Freidlin, and Sally Hunsberger collaborate extensively with the Cancer Therapy Evaluation Program (CTEP). These activities include statistical review of all CTEP-sponsored clinical trials, service on Data Safety Monitoring Committees of the cooperative oncology

groups, participation on the investigational drug and disease area steering committees and task forces, 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.

BRB statisticians, in collaboration with CTEP staff, recently published 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.

Dancey J, Freidlin B, Rubinstein LV. Accelerated titration designs. In: *Statistical Methods for Dose-Finding Experiments*. Chevret S, ed. New York: John Wiley & Sons; 2006.

Kummar S, Kinders R, Rubinstein L, Parchment RE, Murgo AJ, Collins J, Piceral O, Low J, Steinberg SM, Gutierrez M, Yang S, Helman L, Wilttrout R, Tomaszewski JE, Doroshow JH. Compressing drug development timelines in oncology using phase '0' trials. *Nat Rev Cancer* 2007;7:131-9. <http://www.ncbi.nlm.nih.gov/pubmed/17251919>

Hudis CA, Barlow WE, Costantino JP, Gray RJ, Pritchard KI, Chapman JA, Sparano JA, Hunsberger S, Enos RA, Gelber RD, Zujewski JA. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: The STEEP system. *J Clin Oncol* 2007;25:2127-32. <http://www.ncbi.nlm.nih.gov/pubmed/17513820>

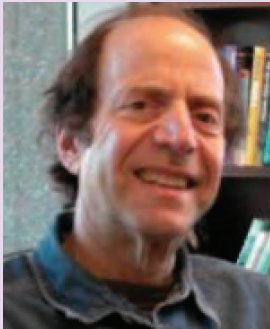
Cancer Diagnosis Program

<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

RICHARD SIMON, BRANCH CHIEF

Richard Simon, Ph.D., is Chief of the Biometric Research Branch in the Division of Cancer Treatment and Diagnosis. Dr. Simon holds a doctoral degree in applied mathematics and computer science from Washington University in St. Louis, MO. He has been at the National Institutes of Health (NIH) 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 (FDA). 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 7,000 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.

proposals, R21/R33 grants, cooperative group correlative science protocols, and requests for specimens from NCI-funded tissue resources. They also provide statistical expertise in the monitoring and development of important NCI initiatives, such as tissue resources, the Program for the Assessment of Clinical Cancer Tests (PACCT), and the Strategic Partnering to Evaluate Cancer Signatures (SPECs) Program. They provide statistical leadership for the establishment, maintenance, and utilization of CDP-funded tissue resources, conduct pathologist concordance studies, design tissue microarrays, review applications for tissue, and oversee data management. Dr. McShane is a member of the Strategy Group for PACCT (<http://cancerdiagnosis.nci.nih.gov/assessment/index.htm>). She and Dr. Korn provided statistical leadership in developing a national clinical trial to evaluate epidermal growth factor receptor (EGFR) biomarkers to predict benefit of erlotinib in patients with non-small cell lung cancer.

Director's Challenge Groups

<http://cancerdiagnosis.nci.nih.gov/challenge/index.htm>

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.

Microarrays are a 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 laboratories. BRB's Dr. Dobbin headed 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.

This consortium of four Director's Challenge groups, working in collaboration with CDP staff and Dr. Dobbin, went on to complete the largest study to date of the potential of gene expression signatures for prognosis in lung cancer. Expression signatures of over 400 patients were measured, and predictors of outcome were developed by each academic group. The signatures were then evaluated on two independent validation sets, with Dr. Dobbin ensuring integrity of the study. The validation sets were blinded and also provided so-called external validation, that is, they were generated at different institutions. The findings of the study present a far more realistic and detailed assessment of the potential clinical utility of gene expression-based prognostic predictors in this disease setting than any previous study.

Childhood Cancer Therapeutically Applicable Research to Generate Effective Treatments Initiative

The Therapeutically Applicable Research to Generate Effective Treatments (TARGET) Initiative is a public-private partnership to identify and validate therapeutic targets so that new, more effective treatments can be developed for children with cancer. Its immediate goal is to make major advances in identifying and validating therapeutic targets for two or more childhood cancers.

Working on the acute lymphocytic leukemia (ALL) TARGET pilot project, Drs. Dobbin and James Jacobson of CDP, and Malcolm Smith of CTEP, analyzed a set of paired gene expression microarray data and copy number abnormality data from single nucleotide polymorphism arrays on a set of patients from a clinical trial of the Children's Oncology Group. These data were first used as a proof-of-principle to show that known translocation subgroups in ALL could be identified and then extended to identify potential new subgroups. Their results are being pooled together with results from academic collaborators at the University of New Mexico and St. Jude Children's Research Hospital to identify potential therapeutic targets that will be further validated in another phase of the project.

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. Additionally they have engaged in a public-private partnership with Roche diagnostics to develop a custom microarray chip that can assist in the diagnosis and prognostic evaluation of patients with lymphoma. Dr. George Wright, BRB, serves as primary statistician for the many publications of this group. This collaboration has produced many major publications, which have appeared in leading medical journals.

Dave SS, Fu K, Wright GW, Lam LT, Kluin P, Boerma EJ, Greiner TC, Weisenburger DD, Rosenwald A, Ott G, Müller-Hermelink HK, Gascoyne RD, Delabie J, Rimsza LM, Braziel RM, Grogan TM, Campo E, Jaffe ES, Dave BJ, Sanger W, Bast M, Vose JM, Armitage JO, Connors JM, Smeland EB, Kvaloy S, Holte H, Fisher RI, Miller TP, Montserrat E, Wilson WH, Bahl M, Zhao H, Yang L, Powell J, Simon R, Chan WC, Staudt LM; Lymphoma/Leukemia Molecular Profiling Project. Molecular diagnosis of Burkitt's lymphoma. *N Eng J Med* 2006;354:2431–42. <http://www.ncbi.nlm.nih.gov/pubmed/16760443>

Shaffer AL, Wright G, Yang L, Powell J, Ngo V, Lamy L, Lam LT, Davis RE, Staudt LM. A library of gene expression signatures to illuminate normal and pathological lymphoid biology. *Immunol Rev* 2006;210:67–85. <http://www.ncbi.nlm.nih.gov/pubmed/16623765>

Iqbal J, Neppalli VT, Wright G, Dave BJ, Horsman DE, Rosenwald A, Lynch J, Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Campo E, Ott G, Muller-Hermelink HK, Delabie J, Jaffe ES, Grogan TM, Connors JM, Vose JM, Armitage JO, Staudt LM, Chan WC. BCL2 expression is a prognostic marker for the activated B-cell-like type of diffuse large B-cell lymphoma. *J Clin Oncol* 2006;24:961–8. <http://www.ncbi.nlm.nih.gov/pubmed/16418494>

Roberts RA, Wright G, Rosenwald AR, Jaramillo MA, Grogan TM, Miller TP, Frutiger Y, Chan WC, Gascoyne RD, Ott G, Muller-Hermelink HK, Staudt LM, Rimsza LM. Loss of major histocompatibility class II gene and protein expression in primary mediastinal large B-cell lymphoma is highly coordinated and related to poor patient survival. *Blood* 2006;108:311–18. <http://www.ncbi.nlm.nih.gov/pubmed/16543468>

Davies AJ, Rosenwald A, Wright G, Lee A, Last KW, Weisenburger DD, Chan WC, Delabie J, Braziel RM, Campo E, Gascoyne RD, Jaffe ES, Muller-Hermelink K, Ott G, Calaminici M, Norton AJ, Goff LK, Fitzgibbon J, Staudt LM, Lister A. Transformation of follicular lymphoma to diffuse large B-cell lymphoma proceeds by distinct oncogenic mechanisms. *Br J Haematol* 2007;136:286–93. <http://www.ncbi.nlm.nih.gov/pubmed/17278262>

NCI Center for Cancer Research (CCR)

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

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 members collaborate with CCR investigators in the areas of statistical genomics and biostatistics.

Dr. Paul Albert, BRB, serves as principal statistician for CCR clinical studies in the areas of neuro-oncology, urologic oncology, radiation oncology, pathology, metabolism, molecular imaging, 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 recent past included analysis of the Polyp Prevention Trial, which resulted in four publications in 2006 and 2007. In the area of radiation oncology, Dr. Albert and CCR researchers published seven papers in 2006 and 2007, and collaborations with the Urologic Oncology Branch led to two publications.

Dr. Larry Rubinstein, BRB, has provided statistical leadership to the NCI Phase 0 Clinical Trials Working Group, made up of DCTD and CCR staff. He served as statistician and developed an innovative design to assess pharmacodynamic endpoints for the NCI phase 0 PARP inhibitor trial, which resulted in a *Nature Reviews Cancer* publication.

BRB staff members also collaborate extensively with CCR investigators on the design and analysis of laboratory and clinical studies utilizing DNA microarrays. Dr. Joanna Shih, BRB, serves as principal statistician for numerous collaborations with CCR investigators. Dr. Simon actively interacts with CCR investigators and leads a semi-monthly DNA microarray data analysis workshop for intramural investigators. Drs. Shih, McShane, Dobbin, and Yingdong Zhao are also active in teaching and collaborating with intramural investigators on genomic studies.

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. Rubinstein.

Dr. Rubinstein helped to develop and implement a method for determining the statistical significance of *in vitro* treatment effects associated with adding a new agent to an established agent or combination.

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

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

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

Garcia-Pineros A, Hildesheim A, Dodd L, Kemp TJ, Williams M, Harro C, Lowy DR, Schiller JT, Pinto LA. Cytokine and chemokine profiles following vaccination with human papillomavirus type 16L1 virus-like particles. *Clin Vaccine Immunol* 2007;14:984–89.

<http://www.ncbi.nlm.nih.gov/pubmed/17596432>

Dodd LE, Sengupta S, Chen IH, den Boon JA, Cheng YJ, Westra W, Newton MA, Mittl BF, McShane L, Chen CJ, Ahlquist P, Hildesheim A. Genes involved in DNA repair and nitrosamine metabolism and those located on chromosome 14q32 are dysregulated in nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev* 2007;15:2216–25.

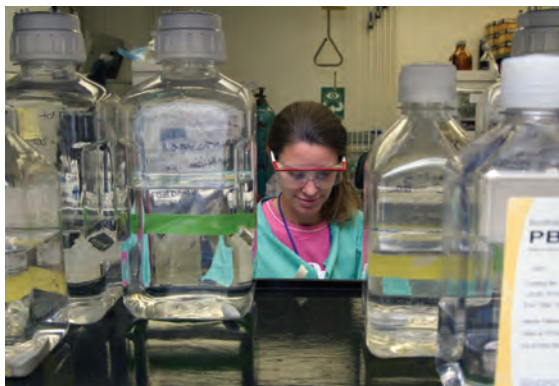
<http://www.ncbi.nlm.nih.gov/pubmed/17119049>

Scientific Advances

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

Many molecularly targeted anticancer agents entering the definitive stage of clinical development benefit only a subset of treated patients. This may lead to missing effective agents by the traditional broad-eligibility randomized trials due to the dilution of the overall treatment effect. This has changed the paradigm for the design of phase III clinical trials for evaluation of new drugs and the requirements for the early clinical trials that enable the design of effective phase III trials. Dr. Simon is recognized as an international leader in developing this new approach to predictive medicine.

Dr. Simon previously published 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. Dr. Simon also developed a design in which the primary analysis of a randomized clinical trial comparing a new treatment to control is performed for all randomized patients but using a reduced threshold of significance of 0.04. If the overall analysis is not significant, then a comparison of new treatment to control for a single prospectively defined subset of biomarker positive patients is performed



using a significance threshold of 0.01. This enables sponsors to develop and measure predictive biomarkers in settings where they do not have strong *a priori* confidence in the importance of the classifier. This design is proving popular with pharmaceutical sponsors.

Drs. Simon and Freidlin have developed adaptive designs for settings where either the predictive biomarker is not defined at the start of the phase III trial or where a decision threshold is not defined in advance. With these adaptive designs, patient eligibility for the phase III trial is not restricted based on a biomarker, but the designs do require that tumor specimens be collected at the time of entry.

Dr. Simon has interacted with scientists from industry and the 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. To facilitate the application of this approach, Dr. Simon has given invited talks and interacted with numerous pharmaceutical, biotech, and diagnostics companies.

Simon R. Validation of pharmacogenomic biomarker classifiers for treatment selection. *Cancer Biomark* 2006;2;89–96.
<http://www.ncbi.nlm.nih.gov/pubmed/17192063>

Simon R. Development and validation of biomarker classifiers for treatment selection. *J Stat Plan Inference* (In press).

Jiang W, Freidlin B, Simon R. Biomarker-adaptive threshold design: A procedure for evaluating treatment with possible biomarker-defined subset effect. *J Natl Cancer Inst* 2007;99;1036–43.
<http://www.ncbi.nlm.nih.gov/pubmed/17596577>

Simon R. New challenges for 21st century clinical trials. *Clin Trials* 2007;4;167–69.
<http://www.ncbi.nlm.nih.gov/pubmed/17456517>

Simon R, Wang SJ. Use of genomic signatures in therapeutics development. *Pharmacogenomics J* 2006;6;166–73.
<http://www.ncbi.nlm.nih.gov/pubmed/16415922>

Simon R. Validation of pharmacogenomic biomarker classifiers for treatment selection. *Cancer Biomark* 2006;2;89–96.
<http://www.ncbi.nlm.nih.gov/pubmed/17192063>

Simon R. A checklist for evaluating reports of expression profiling for treatment selection. *Clin Adv Hematol Oncol* 2006;4;219–24.
<http://www.ncbi.nlm.nih.gov/pubmed/16728933>

Methodology Development in Computational Cancer Biology and Statistical Genomics

Drs. Alain Dupuy, a guest researcher from France, and Simon have reviewed all publications on whole-genome expression profiling of cancers that used patient outcomes. They wrote a critical review of these publications and developed guidelines for use by authors, journal reviewers, and readers. This publication is the third most downloaded paper published by the *Journal of the National Cancer Institute* for the past 12 months.

Dupuy A, Simon RM. Critical review of published microarray studies for cancer outcome and guidelines on statistical analysis and reporting. *J Natl Cancer Inst* 2007;99:147–57.
<http://www.ncbi.nlm.nih.gov/pubmed/17227998>

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 the 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 cases.

Lusa L, Cappelletti V, Gariboldi M, Ferrario C, DeCecco L, Reid JF, Toffanin S, Gallus G, McShane LM, Diadone MG, Pierotti MA. Questioning the utility of pooling samples in microarray experiments with cell lines. *Int J Biol Markers* 2006;21:67–73.
<http://www.ncbi.nlm.nih.gov/pubmed/16847808>

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. To facilitate implementation of this method, an online interactive tool for sample size determination is provided on the BRB Website.

Dobbin KK, Simon RM. Sample size planning for developing classifiers using high dimensional DNA Microarray data. *Biostatistics* 2007;8:101–17.
<http://www.ncbi.nlm.nih.gov/pubmed/16613833>

Dobbin KK, Zhao Y, Simon RM. How large a training set is needed to develop a classifier? *Clin Cancer Res* 2008;14:108–14.
<http://www.ncbi.nlm.nih.gov/pubmed/18172259>

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 biological specimens 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 prediction outcomes. Several BRB statisticians, including Dr. Laura Lusa, a visiting scientist from Milan, 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. *Stat Med* 2007;26:1102–13. <http://www.ncbi.nlm.nih.gov/pubmed/16755534>

Lusa L, McShane LM, Reid JF, DeCecco L, Ambroggi E, Biganzoli M, Gariboldi M, Pierotti MA. Challenges in projecting clustering results across gene expression profiling data sets. *J Natl Cancer Inst* 2007;21:1715–23. <http://www.ncbi.nlm.nih.gov/pubmed/18000217>

Identifying genes whose expression is correlated with a categorical phenotype is the key objective of many expression profiling studies. BRB statisticians performed an evaluation of a commonly used method, “SAM,” and compared it to a more straightforward multivariate permutation method. In a second project, a proposal to modify a Bonferroni adjustment to account for false positives was critically reviewed.

Korn EL, Li MC, McShane LM, Simon R. An investigation of two multivariate permutation methods for controlling the false discovery proportion. *Stat Med* 2007;26:4428–40. <http://www.ncbi.nlm.nih.gov/pubmed/17357994>

Korn EL, Freidlin B. A note on controlling the number of false positives. *Biometrics* (In press).

Meta-Analysis of Phase II Melanoma Clinical Trials

In collaboration with several cancer cooperative groups, Dr. Korn performed a meta-analysis of metastatic melanoma phase II trials using individual patient data. All clinical trials with available data closed to accrual from 1975 to 2005 were included. It was found that the inter-study variability in 12-month survival rate could be dramatically reduced if one controlled for the prognostic mix of patients. This study will enable phase II studies of new therapeutics to utilize a historical control predictor of 12-month survival adjusted for the prognostic mix of patients included in the new study.

Korn EL, Liu PY, Lee SJ, Chapman JA, Niedzwiecki D, Suman VJ, Moon J, Sondak VK, Atkins MB, Eisenhauer EA, Parulekar W, Markovic SN, Saxman S, Kirkwood JM. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. *J Clin Oncol* 2008;26:527–34. <http://www.ncbi.nlm.nih.gov/pubmed/18235113>

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, in collaboration with CTEP staff, discussed and evaluated several new design approaches, including innovative dual-endpoint designs to enable evaluation of new agents for which both tumor response rate and progression-free survival are important, in a recent book on novel anticancer agents.

Korn EL, Rubinstein LV, Hunsberger SA, Pluda JM, Eisenhauer E, Arbuck SG. Clinical trial designs for cytostatic agents and agents directed at novel molecular targets. In: *Novel Anticancer Agents: Strategies for Discovery and Clinical Testing*. Adjei AA, Buolamwini JK, eds. Burlington, MA: Academic Press; 2006.

Rubinstein LV, Dancy JE, Korn EL, Smith MA, Wright, JJ. Early average change in tumor size in a phase 2 trial: Efficient endpoint or false promise? *J Natl Cancer Inst* 2007;99:1422–3. <http://www.ncbi.nlm.nih.gov/pubmed/17895470>

Randomized Clinical Trial Design for Assessing Non-Inferiority When Superiority is Expected

The randomized clinical trial is the gold standard for definitive evaluation of new therapies. Randomized clinical trials designed to show that the therapeutic efficacy of a new therapy is not unacceptably inferior to that of standard therapy are called noninferiority trials. Traditionally, noninferiority trials have required very large sample sizes. Sometimes, a new treatment regimen with a favorable toxicity and/or tolerability profile is also expected to have some modest improvement in efficacy. In such specialized settings BRB researchers have described a “hybrid” trial design approach that requires a dramatically smaller sample size than a standard noninferiority design. This hybrid design can naturally incorporate a formal test of superiority as well as noninferiority.

Freidlin B, Korn EL, George SL, Gray R. Randomized clinical trial design for assessing noninferiority when superiority is expected. *J Clin Oncol* 2007;25;5019–23.

<http://www.ncbi.nlm.nih.gov/pubmed/17971602>

Proposal for the Use of Progression-Free Survival in Unblinded Randomized Trials

Progression-free survival is an attractive endpoint for clinical trials when an overall survival endpoint may be confounded by additional treatments given after progression. When a trial is performed in an unblinded manner, however, there is the potential for bias between the treatment arms because of the subjective aspects of the progression endpoint. The magnitude of this potential bias is discussed and methods for lessening it are suggested in a recent article by BRB staff and other NCI researchers in the *Journal of Clinical Oncology*. They proposed carrying forward any progression information to two designated time points for the statistical analysis for trials that are not blinded. This proposal, possibly combined with central review of progression scans for these two time points, essentially eliminates any bias with little risk of major efficiency loss as compared to using the reported progression times.

Freidlin B, Korn EL, Hunsberger S, Gray R, Saxman S, Zujewski JA. Proposal for the use of progression-free survival in unblinded randomized trials. *J Clin Oncol* 2007;25;2122–6.

<http://www.ncbi.nlm.nih.gov/pubmed/17513819>



Release of Data from an Ongoing Randomized Clinical Trial for Sample Size Adjustment or Planning

The determination of an appropriate sample size is a key issue in planning and designing randomized clinical trials. In settings with time-to-event or binary outcomes, the required sample size depends on the control-arm event (response) rate. An accurate estimate of this rate often is not available at the planning stage. Therefore, noncomparative control-arm or pooled-arm event rates from an ongoing trial are sometimes released for sample size adjustment or planning purposes. Drs. Freidlin and Korn have shown that such noncomparative data release may still contain information on the relative treatment benefit and may thus adversely affect the ongoing trial. A simple approach to minimizing the effect of the data release is suggested in their recent article in *Statistics in Medicine*.

Freidlin B, Korn EL. Release of data from an ongoing randomized clinical trial for sample size adjustment or planning. *Stat Med* 2007;26:4074–82. <http://www.ncbi.nlm.nih.gov/pubmed/17328095>

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 non-standard type of analysis of clinical trial data (“likelihood-based methods”) can eliminate the problems with multiple comparisons. Drs. Korn and Freidlin examined this proposition in detail and found it to be lacking.

Korn EL, Freidlin B. The likelihood as statistical evidence in multiple comparisons in clinical trials: No free lunch. *Biom J* 2006;48:346–55. <http://www.ncbi.nlm.nih.gov/pubmed/16845900>

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 can be improved upon.

Korn EL, Freidlin B. Conditional power calculations for clinical trials with historical controls. *Stat Med* 2006;25:2922–31. <http://www.ncbi.nlm.nih.gov/pubmed/16479548>

Longitudinal Data Analysis

Dr. Albert has 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 method for analyzing longitudinal biomarker data subject to lower limits of detection has been developed. The work was motivated by collaborative research with the Vaccine Branch of CCR. Dr. Albert was invited to write a chapter on shared random parameter models in a seminal book on longitudinal data analysis. He was also invited to write a paper on random effects modeling approaches for modeling longitudinal data subject to missingness for a special issue of *Statistical Issues in Medical Research*.

Albert PS. Modeling longitudinal biomarker data with multiple assays that have different known detection limits. *Biometrics*, 2008;64:527–37. <http://www.ncbi.nlm.nih.gov/pubmed/17764483>

Albert PS, Follmann DA. Random effects and latent processes approaches for analyzing binary longitudinal data with missingness: A comparison of approaches using opiate clinical trial data. *Stat Methods Med Res* 2007;16:417–39. <http://www.ncbi.nlm.nih.gov/pubmed/17656452>



Evaluating Diagnostics

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. Dr. Albert developed new methodology for estimating receiver operating characteristic (ROC) curves from repeated tests without a gold standard. Drs. Dodd and Korn studied the evaluation of diagnostic tests in randomized treatment trials.

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

Albert PS. Imputation approaches for estimating diagnostic accuracy for multiple tests from partially verified designs. *Biometrics* 2007;63:947–57. <http://www.ncbi.nlm.nih.gov/pubmed/17825024>

Dodd LE, Korn EL. Lack of generalizability of sensitivity and specificity with treatment effects. *Stat Med* (In press).



Mathematical Modeling of Cancer Oncogenesis

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.

Simon R, Zhang X. On the dynamics of breast tumor development in women carrying germline *BRCA1* and *BRCA2* mutations. *Int J Cancer* 2008;122:1916–7. <http://www.ncbi.nlm.nih.gov/pubmed/18098285>

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, Giulianotti M, Simon R, Mariuzza R, Pinilla C, Martin R. Redundancy in antigen-presenting function of the HLA-DR and -DQ molecules in the multiple sclerosis-associated HLA-DR2 haplotype. *J Immunol* 2006;176:1951–61. <http://www.ncbi.nlm.nih.gov/pubmed/16424227>

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. <http://www.ncbi.nlm.nih.gov/pubmed/16323241>

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; 2007.

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. They performed a meta-analysis of comparative genomic hybridization studies of nasopharyngeal carcinoma. In a separate project they studied the genomic basis of melanoma progression in patients undergoing immunotherapy.

Nambiar A, Duquesnoy R, Adams S, Zhao Y, Oblitas J, Leitman S, Stroncek D, Marincola F. HLA matchmaker-driven analysis of responses to HLA-typed platelet transfusions in alloimmunized thrombocytopenic patients. *Blood* 2006;107:1680–7. <http://www.ncbi.nlm.nih.gov/pubmed/16269623>

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. *Cancer Res* 2006;66:2953–61. <http://www.ncbi.nlm.nih.gov/pubmed/16540643>

Li X, Wang E, Zhao YD, Ren JQ, Jin P, Yao KT, Marincola FM. Chromosomal imbalances in nasopharyngeal carcinoma: A meta-analysis of comparative genomic hybridization results. *J Transl Med* 2006;4:4. <http://www.ncbi.nlm.nih.gov/pubmed/16423296>

Sabatino M, Zhao YD, Voiculescu S, Nickoloff BJ, Karai L, Monaco A, Marincola FM, Wang E. Conservation of a core of genetic alterations over a decade of recurrent melanoma supports the melanoma stem cell hypothesis. *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 methods for analysis of their data. The existing suite of tools is continually updated as new methods of analysis and elucidation of pathway annotation are developed.

BRB-ArrayTools software may be downloaded from BRB's Website and may be used for noncommercial purposes free of charge. BRB-ArrayTools has over 7,000 registered users in 70 countries. It is a successful experiment in using software to empower biomedical scientists to take advantage of DNA microarray software. The software is programmed and maintained under a contract with SRA International and the EMMES Corporation.

The BRB Website contains a message board where users of BRB-Array Tools share information and ask questions. This message board is international and quite active.

Simon R, Lam AP, Li MC, Ngan M, Menezes S, Zhao Y. Analysis of gene expression data using BRB-Array Tools. *Cancer Informatics* 2007;2:11–17. http://la-press.com/article.php?article_id=43

Xu X, Zhao Y, Simon R. Gene set expression comparison kit for BRB-ArrayTools. *Bioinformatics* 2008;24(1):137–9. <http://www.ncbi.nlm.nih.gov/pubmed/18006549>

Gene Expression Datasets

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

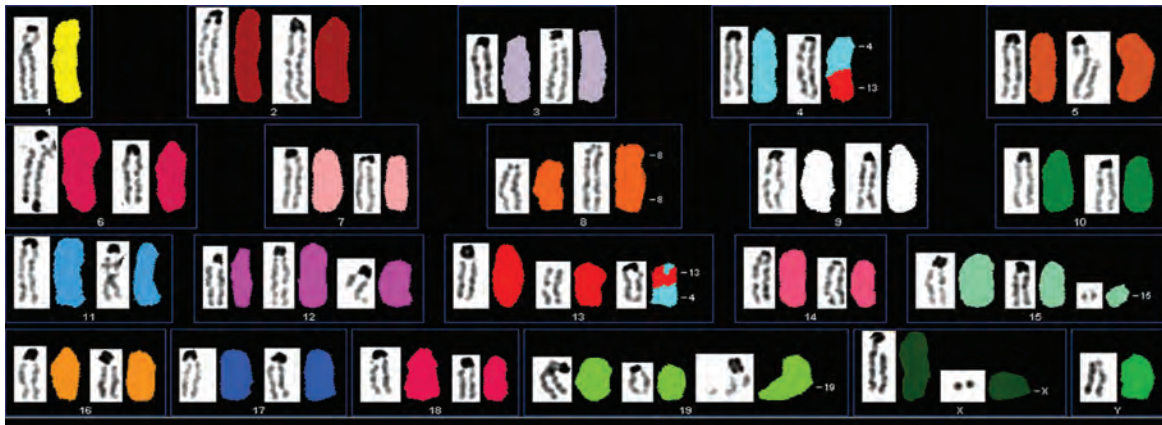
Dr. Zhao has developed a data archive of publicly available gene expression datasets and corresponding clinical data for published human cancer gene expression profiling studies. The data are stored as BRB-ArrayTools project folders. This makes it easy for BRB-ArrayTools users to make their data publicly 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 over 100 major studies of human cancer. Dr. Zhao has also developed with SRA/Emmes contractors a module in BRB-ArrayTools for automatically importing microarray gene expression datasets and associated clinical patient information from the Gene Expression Omnibus archive of the National Center for Biotechnology Information (NLM/NIH).

Software and Technical Report Archive

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

The BRB Website contains other software, such as that for the generation of optimal and mini-max two-stage phase II clinical trial designs and 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.

Drs. Simon and Zhao have developed interactive Web-based software for the planning of randomized clinical trials for the co-development of new drugs and evaluation of predictive biomarkers. These programs facilitate the use of enrichment designs developed by Drs. Simon and Maitourna, the stratified biomarker designs of Drs. Simon and Wang, and the adaptive designs developed by Drs. Simon and Freidlin for converting retrospective correlative science to prospective personalized medicine. The interactive tools also include a program for planning the number of cases needed for the development of a predictive classifier based on gene expression profiles, implementing a method developed by Drs. Dobbin and Simon.





Office of Cancer Complementary and Alternative Medicine

Program Accomplishments

The Office of Cancer Complementary and Alternative Medicine (OCCAM), established in October 1998, coordinates and enhances the activities of the National Cancer Institute with regard to complementary and alternative medicine (CAM).

CAM

CAM Overview

OCCAM's goal is to increase the amount of high-quality cancer research and information about the use of complementary and alternative modalities by:

- Promoting and supporting research of CAM disciplines and modalities as they relate to the prevention, diagnosis, and treatment of cancer, cancer-related symptoms, and side effects of conventional treatment
- Coordinating NCI's CAM research and information activities
- Coordinating NCI's collaboration with other governmental and nongovernmental organizations on CAM cancer issues
- Providing an interface with health practitioners and researchers regarding CAM cancer issues

Selected Funded Projects

Colorectal Chemoprevention with Calcium and Vitamin D

(5R01CA098286-05)

John Baron, M.D.

Dartmouth Medical School

<http://clinicaltrials.gov/ct2/show/NCT00153816>

OCCAM provides supplemental funding for this grant to augment the accrual of under-represented minority patients. The Vitamin D/Calcium Polyp Prevention Study is a double-blind, placebo-controlled trial of vitamin D (1000 IU daily) and/or calcium supplementation (1200 mg) for the prevention of large bowel adenomas. Each subject is treated and followed for either 3 or 5 years depending on the colonoscopic follow-up schedule adopted by his or her gastroenterologist.

The main specific hypotheses are:

- Supplementation with vitamin D3 (1,000 IU/day) reduces the risk of new adenomas in patients with a recent history of these tumors
- Supplementation with both vitamin D3 and calcium carbonate (1,200 mg calcium/day) reduces the risk of new adenomas more than supplementation with calcium carbonate alone

A supplement to this grant provided by OCCAM is funding additional recruitment of minority subjects and women.

Nucleoside Analogs as Anticancer Compounds

(3R01CA063477-11A1S1)

Yung-Chi Cheng, Ph.D.

Yale University

OCCAM provides a supplement to this grant to support the establishment of preclinical *in vivo* animal models and methodologies to systematically investigate the effect of botanicals (specifically the herbal mixture PHY906) and conventional cancer chemotherapeutics on a set of biological markers, including an RNA expression panel and chemokine proteomics. The investigators will initially use the Colon-38 mouse model system and irinotecan, a standard anticancer agent used to treat colorectal cancer, and an agent that these investigators have already studied in combination with PHY906. The investigators will evaluate in a systematic fashion the biological effects of PHY906 alone, irinotecan alone, and the combination of PHY906 and irinotecan on *in vivo* gene expression profiles and chemokine levels.

JEFFREY D. WHITE, DIRECTOR

Jeffrey D. White, M.D., holds a bachelors of science in applied and engineering physics from Cornell University, and an M.D. from Howard University. His internal medicine, hematology, and medical oncology training was done at the Washington Hospital Center. He is board certified in internal medicine and medical oncology.



In 1990, Dr. White came to NCI as a Medical Staff Fellow in the Metabolism Branch, where he performed preclinical and clinical immunology research with a focus on monoclonal antibody therapies for leukemias and lymphomas, predominantly adult T-cell leukemia/lymphoma. In 1997, he became the Director of the Branch's Clinical Trials and Clinical Care Program. Dr. White is a member of the Ernest E. Just Biomedical Society.

In 1995, Dr. White became an oncology consultant to the National Institutes of Health (NIH) Office of Alternative Medicine. In October 1998, he was named the Director of the newly formed OCCAM at NCI. OCCAM joined the Division of Cancer Treatment and Diagnosis (DCTD) in 2007.

Dr. White has been involved in mentoring students on many levels, including those in the Student Research Training Program and various minority high school programs. He has served as an attending physician at the Washington Hospital Center and as a visiting professor at the Institute of Biomedical Sciences, Academia Sinica in Taipei, Taiwan.

A Phase II/III Study Comparing Acupuncture-Like Transcutaneous Electrical Nerve Stimulation (ALTENS) versus Pilocarpine in Treating Early Radiation-Induced Xerostomia

(RTOG 0537)

Raimond Wong, M.D.

Margaret and Charles Juravinski Cancer Centre

<http://clinicaltrials.gov/ct/show/NCT00656513>

OCCAM provides partial funding support for this clinical trial through a supplement to the Radiation Therapy Oncology Group Community Clinical Oncology Program. The study investigators hypothesize that ALTENS stimulation of relevant acupuncture points using traditional Chinese medicine (TCM) principles may be effective treatment of radiation-induced xerostomia. The investigators propose to study ALTENS treatment (given with the Codetron unit) versus pilocarpine in treating radiation-induced xerostomia. Eligible study subjects will be randomized into two groups: 1) ALTENS treatment, three 20-minute treatments weekly for 6 weeks, and 2) pilocarpine, 5 mg three times daily for 6 weeks.

The primary objectives are:

- Phase II component: To assess the rate of successful delivery of ALTENS treatment (given with the Codetron unit), defined as a patient completing 12 of 18 protocol prescribed sessions
- Phase III component: To assess the change in overall xerostomia score as measured by the 15-item University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS) from baseline to 1, 3, and 6 months post treatment

Oldenlandia diffusa for Prostate Cancer Treatment

(1R21CA133865-01A2)

Jin-Rong Zhou, Ph.D.

Beth Israel Deaconess Medical Center

The principal investigator plans to conduct preclinical studies to preliminarily assess the efficacy of the Chinese herb *Oldenlandia diffusa* (OD) for prostate cancer treatment. OD has been used in Chinese folk medicine as an anti-cancer agent. However, there have been limited preclinical studies to investigate its efficacy and to identify its active anticancer components. Preliminary data showed that OD inhibited the growth of prostate cancer cells in part via induction of apoptosis and inhibited cancer cell invasion and angiogenesis *in vitro*. The investigators hypothesize that OD contains bioactive components that interact in a synergistic or additive manner to target prostate cancer growth, metastasis, and angiogenesis.

Choline Metabolism in Prostate Cancers: Response to Dietary Soy Phytochemicals

(R21CA130013-01A1)

Sandra Gaston, Ph.D.

Beth Israel Deaconess Medical Center

This study will use magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) of choline to monitor the effects of dietary soy on prostate cancer in the LNCaP-SCID mouse model. The hypothesis to be tested is that changes in prostate cancer growth in response to a soy phytochemical dietary supplement can be monitored by changes in tumor choline metabolism, both at the level of gene expression (choline kinase, phospholipase D, and lysophosphocholine) and MRS spectra of choline metabolites (phosphocholine and glycerophosphocholine). The goals are to monitor changes in tumor size, mass, and volume in androgen-sensitive and androgen-independent

tumors in response to a soy-based diet and correlate this findings with choline levels via gene expression and MRS. Another goal is to explore the gene catalog for genes that show a positive or negative response with the expression of choline kinase that might be linked to choline-altering activities in other cancers.

Wine for Cancer-Associated Anorexia

(1R01CA124614-01A1)

Aminah Jatoi, M.D.

Mayo Clinic Rochester

Cancer-associated anorexia or loss of appetite occurs in more than 80 percent of patients with advanced incurable cancer. It is one of the top three symptoms of concern for cancer patients, and it is a strong predictor of early demise. A plethora of epidemiological and nutritional studies point to a direct relationship between wine consumption and increased weight and/or caloric intake. The aims of the study are:

- To determine whether the combination of wine plus megestrol acetate improves appetite better than megestrol acetate alone in patients with cancer-associated anorexia
- To summarize and compare the adverse events associated with wine plus megestrol acetate versus megestrol acetate alone
- To explore whether wine in combination with megestrol acetate alters the hormonal milieu that modulates appetite

Current Funding Opportunity

Developmental Projects in Complementary Approaches to Cancer Care

PROGRAM ANNOUNCEMENT:

PA-06-400: <http://grants.nih.gov/grants/guide/pa-files/PA-06-400.html> (expiration date 05/08/2009)

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In an ongoing effort to help promote dialogue and collaboration between CAM practitioners and conventional cancer researchers, as well as promote research focusing on complementary approaches in cancer, this program announcement has been re-issued for a second time.

Originally released in December 2001, this program announcement soliciting grant applications was generated by OCCAM and the National Center for Complementary and Alternative Medicine to encourage and support the development of basic and clinical complementary cancer research. The support for exploratory/developmental projects through these R21 grants is intended to provide the basis for more extended research projects by establishing methodological feasibility, strengthening the scientific rationale, and allowing the collection of data for these projects. This announcement is also intended to attract the entry of promising investigators into research of these topics.

Examples of applicable complementary approaches include, but are not limited to, nutritional approaches, natural products, mind-body approaches, energy therapies, herbal medicines, and interventions based on medical systems such as TCM or Ayurvedic medicine.

Partnerships and Collaborations

Guang An Men Hospital, Chinese Academy of Chinese Medicine, Beijing, China

http://www.cintcm.ac.cn/gam/e_index2.html

As a result of the 2006 OCCAM-sponsored conference *Traditional Chinese Medicine and Cancer Research: Fostering Collaborations; Advancing the Science*, NCI gained a new fellow, Dr. Jie Li, from Beijing, China.



Dr. Li of the Research Center of Oncology at Guang An Men hospital in Beijing attended the conference as a participant, along with the director of his department, Dr. Hongsheng Lin, a guest speaker who presented her clinical study of improving median survival

time of lung cancer with a TCM intervention. Dr. Li's specialty is utilizing the TCM mixture Sheng Qi formula, a Chinese medicine compound, to decrease the side effects of chemotherapy.

During the conference, Drs. Lin and Li met with Dr. O.M. Zack Howard, a staff scientist with the Laboratory of Molecular Immunoregulation (LMI), Cancer and Inflammation Program, Center for Cancer Research at NCI-Frederick. LMI, OCCAM, and Guang An Men hospital agreed that a co-funded postdoctoral training at NCI, sponsored by the Office of International Affairs, was a good way to begin collaborating on this specific area of cancer CAM research.

Dr. Li has been working with Dr. Howard to explore the anticancer effect and immune-stimulating effects of the Sheng Qi formula. A novel aspect of their project is the use of a murine model of inflammatory breast cancer to assess the impact of the herbal formula on the function of myeloid immunosuppressive cells.

The Chinese government's Ministry of Science and Technology has agreed to provide funds to extend Dr. Li's fellowship.

Tools, Products, and Resources

NCI's Annual Report on Complementary and Alternative Medicine: Fiscal Year 2006

www.cancer.gov/cam/attachments/CAMAnnualReportFY2006.pdf

OCCAM released the publication *NCI's Annual Report on Complementary and Alternative Medicine: Fiscal Year 2006* in 2008. This report was created to share with its many stakeholders the various contributions and activities related to cancer CAM research and information dissemination that NCI supports.

The report featured an analysis of NCI's CAM research portfolio and highlighted examples of cancer CAM communications, training, conference, and research activities.

Cancer CAM Research Funding Directory

http://www.cancer.gov/cam/research_funding_directory.html

One of the biggest obstacles associated with the field of cancer CAM research is in finding funding. Although there exists a recognized process for applying for federal funds, there is a plethora of nonfederal funding sources that are not as easy to locate or identify. The difficulty in finding nonfederal funding can then, in turn, be a barrier to obtaining federal funding for foundational or exploratory research. Nonfederal funding is often needed to back preliminary research that aids in providing proof of concept required to acquire larger-scale grants from NIH.

To assist cancer CAM researchers in identifying potential funding sources for their proposed projects, OCCAM developed a directory of non-federal funding sources titled the Cancer CAM Research Funding Directory. The directory contains contact information, organizational characteristics, an overview of the organizations funding programs/processes, and the particular CAM funding interests of a growing number of foundations, advocacy groups, nonfederal government organizations, and private sector organizations.

To be included in this new funding resource, organizations must meet two criteria:

- Open Grant Application Process—accepts investigator submitted grant applications
- Interest in cancer and/or CAM research—accepts grant applications for cancer CAM research

When researchers are asked what OCCAM can do to help them, grant funding always tops the list. Often, even fairly small amounts of funds can allow a researcher to get critical data that can improve the quality and competitiveness of an application to NIH. Investigators of large, research-intense institutions may have access to information about a range of funding

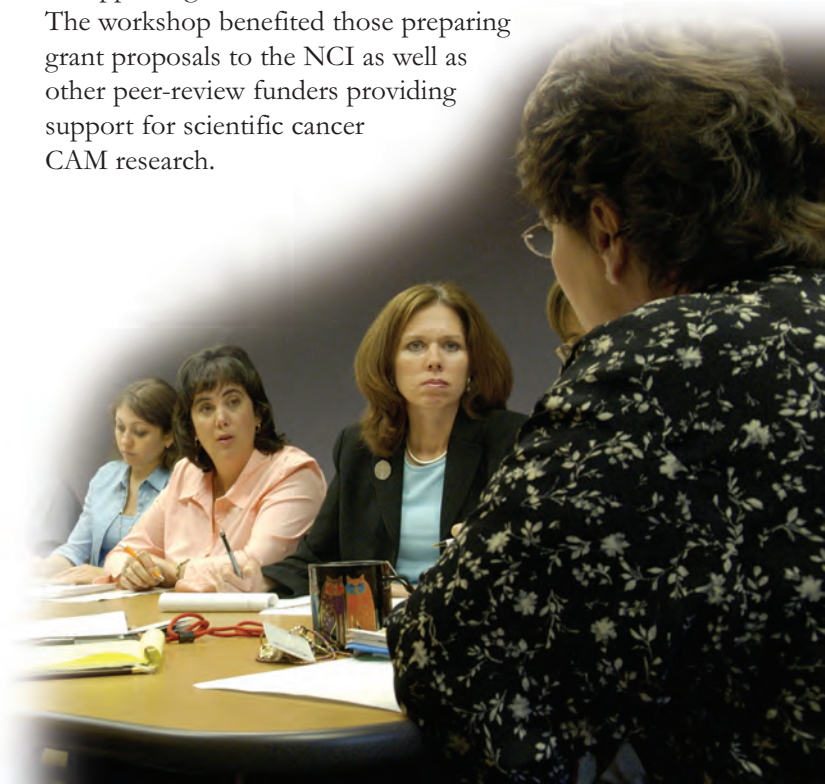
sources, but for smaller centers, this information may not be as easy to come by. This database provides unique information for researchers looking to have their cancer CAM research financially supported.

Cancer CAM Grant Writing Workshop

<http://www.cancer.gov/cam/attachments/howtowrite.pdf>

In November 2006, OCCAM led the workshop *Strategies for Success: How to Write a Grant in Cancer CAM*. This technical assistance workshop was offered as a preconference activity during the 3rd International Conference of the Society for Integrative Oncology (SIO; <http://www.integrativeonc.org/index.php>). Held in Boston, MA, the 1-day workshop was intended for researchers with an interest in cancer CAM and addressed many of the issues commonly raised by review committees.

Specifically, the workshop focused on the challenges unique to preparing applications in cancer CAM topics and presented some of the potential solutions for applicants. In addition to a mock review session, the agenda included presentations from NIH program staff interested in supporting research in cancer CAM. The workshop benefited those preparing grant proposals to the NCI as well as other peer-review funders providing support for scientific cancer CAM research.





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