

Division of Cancer Treatment and Diagnosis

2010



Program Accomplishments | 2010



NATIONAL CANCER INSTITUTE

DIVISION OF
Cancer Treatment
and Diagnosis

Program Accomplishments

2010

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PREFACE

This edition of Program Accomplishments of the Division of Cancer Treatment and Diagnosis (DCTD) offers a multi-year review of the undertakings and achievements of this segment of the National Cancer Institute (NCI). Though not meant to be a complete inventory of the division, this report covers activities and advances from 2005 through 2010 and provides important highlights during my tenure that have helped advance the diagnosis and treatment of cancer.



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

Our greatest challenge is to increase the speed with which new treatments are brought to the millions of Americans with cancer. DCTD has implemented a number of actions to streamline the drug discovery and development process. Chief among them is the transformation of the NCI therapeutics pipeline. Working with the NCI Center for Cancer Research (CCR), we now have a unified platform, the NCI Experimental Therapeutics (NExT) program, which allows researchers to enter candidate agents into the pipeline at any of a number of key steps, such as the discovery stage or preclinical drug development. Researchers may come from academia and CCR as well as biotechnology and pharmaceutical companies. Other entry points further down the development pipeline include providing agents for testing in early- and late-stage clinical trials. In conjunction with NExT and operated similarly, DCTD has just implemented the Clinical Assay Development Program (CADP) to generate new assays that could significantly advance the ability to choose among cancer treatments for an individual patient.

In the past, clinical trial commencement was often a long and arduous process, sometimes taking years. Upon recommendations from the Operational Efficiency Working Group, we have overhauled the process of initiating clinical trials so that, as of January 1, 2011, the time allowed from submission of a concept to activation has been cut in half. For phase 1 and 2 trials, the process is targeted to take 210 days from the time that a concept is submitted to the NCI Cancer Therapy Evaluation Program (CTEP) to the time that a trial is begun. Phase 1 and 2 trials will be terminated if they are not activated in 18 months. For phase 3 studies, the target for submission to opening is 300 days, with a drop-dead date for activation of 24 months. NCI has also made administrative changes within the institute to increase the efficiency with which clinical trials are conducted. In addition, upon the 2007 recommendations of the Translational Research Working Group, a Translational Research Program was created within DCTD to move promising basic research discoveries into phase 1 clinical studies. Together, these changes should make better use of resources and increase each trial's chance of completion.

To eliminate possible redundancies and to ensure that only the most promising agents and scientifically sound proposals are approved, NCI has successfully retooled the way clinical trials are selected. Following the advice of the 2005 Clinical Trials Working Group Report, nine disease-specific steering committees for phase 3 and large phase 2 studies and one investigational drug steering committee for phase 1 and 2 trials have been established to develop, prioritize, and evaluate clinical trial proposals.

This report also underscores the contributions of the 2009 American Recovery and Reinvestment Act (ARRA), which has provided the necessary support for the division to continue critical programs that otherwise would have been extremely difficult to fund and to more rapidly advance initiatives that were already under way. These efforts span the spectrum of therapeutics development, including validation of potential targets, identification and movement of hit-to-lead molecules, conduct of preclinical activities required for an investigational new drug filing, production and formulation of critical therapeutics, and support for several key phase 0, 1, and 2 clinical trials.

Recent advances in cancer treatment and diagnosis are also highlighted in this report. Among them are a practice-changing treatment for neuroblastoma with a monoclonal antibody; the results of a landmark 8-year clinical trial of current and former smokers, conducted in partnership with our colleagues in the NCI Division of Cancer Prevention, clearly showing that screening with helical computed tomography reduces lung cancer mortality; and successful preclinical research that has led to the approval for 70% of the anticancer treatments marketed today, including the new prostate cancer therapeutic sipuleucel-T (Provenge®), the first-ever vaccine for cancer treatment.

In these pages, the reader will find summaries of recently established priorities and scientific advances made possible by the many talented and committed staff members throughout the division.



2010 Program
Accomplishments

Division of Cancer Treatment and Diagnosis

OVERVIEW

The Division of Cancer Treatment and Diagnosis (DCTD) takes prospective detection and treatment leads, facilitates their paths to clinical application, and expedites the initial and subsequent large-scale testing of new agents, biomarkers, imaging tests, and other diagnostic and therapeutic interventions (radiation, surgery, immunotherapy) in patients.

DCTD has eight major programs that work together to bring unique molecules, diagnostic tests, and therapeutic interventions from the laboratory bench to the patient bedside:

The Cancer Diagnosis Program (CDP) stimulates, coordinates, and funds specimen resources, databases related to those specimens, and research on diagnostics and improved technologies to better characterize tumors.

The Cancer Imaging Program (CIP) uses new technologies to expand the role of imaging in noninvasive diagnosis, identification of disease subsets in patients, disease staging, and treatment monitoring.

The Cancer Therapy Evaluation Program (CTEP) functions as the National Cancer Institute's (NCI's) primary clinical evaluator of new anticancer agents, radiation treatments, and surgical methods. The program administers the 11 cooperative research groups that unite researchers around the nation and the world in the pursuit of distinctive and effective new treatments for cancer.

The Developmental Therapeutics Program (DTP) serves as a vital resource in discovering potential cancer therapeutics and acquiring information pertaining to their preclinical development. The program provides research materials and manufactures new agents in bulk quantities for use in investigational new drug (IND)-directed studies.

The Radiation Research Program (RRP) provides expertise to investigators who perform novel radiotherapy research and assists in establishing future directions for radiation research.

The Translational Research Program (TRP) translates novel scientific discoveries from laboratory and/or population studies to the clinic for testing in cancer patients and determines the biological basis for clinical observations.

The Biometric Research Branch (BRB) provides state-of-the-art statistical and biomathematical analyses for DCTD and other NCI components.

The Office of Cancer Complementary and Alternative Medicine (OCCAM) aims to increase the amount of high-quality cancer research and information about the use of complementary and alternative modalities.

Additional information about NCI's Division of Cancer Treatment and Diagnosis is available at <http://dctd.cancer.gov> and <http://cancer.gov>.

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 more than 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 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 NCI's phase 1 and 2 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.

Division of Cancer Treatment and Diagnosis

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Program Director

Dr. Peter Ujhazy
Program Director

MAJOR INITIATIVES AND ACCOMPLISHMENTS

Research Emphasis for the Future

DCTD recently completed a process in which unmet research needs in cancer therapeutics and diagnostics were evaluated. Areas of research currently under-investigated in the DCTD portfolio include:

Enhancing tumor response to therapy

- Development of combination targeted therapies in clinically relevant models
- 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
- Discovery and re-discovery of drugs from natural products

Investigations of the tumor microenvironment

- Designing and testing agents that target the tumor microenvironment using new in vitro and in vivo models
- Understanding the dynamic relationship between tumors and cells in the microenvironment
- Understanding the role of the tumor microenvironment in tumor transformation and response to treatment 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
- Development of in vivo imaging–based assays of relevant biomarkers
- Integration of imaging into biomarker development strategies for new therapeutic agents and combinations
- Development of new imaging agents
- Development and application of diagnostic devices and technologies that support multi-analyte molecular assays for proof-of-mechanism clinical trials and preclinical studies
- Development of integrated diagnostic devices for real-time analysis of biospecimens
- Methods, mechanisms, and technologies to ensure the availability of appropriately collected clinical specimens for translational research

Clinical studies

- Translational and clinical studies in under-investigated diseases—pancreatic cancer, squamous cell carcinoma of the head and neck, bladder cancer, and sarcoma
- Development of pharmacodynamically based proof-of-mechanism clinical trials of investigational targeted agent combinations
- 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

Consolidating and Expediting NCI Drug Discovery and Development

The [NCI Experimental Therapeutics program \(NExT\)](#), a partnership between NCI's Division of Cancer Treatment and Diagnosis (DCTD) and the Center for Cancer Research (CCR), consolidates the institute's anticancer drug discovery and development resources in support of a goal-driven therapeutics pipeline. Combined, these resources are capable of supporting a discovery and development continuum from initial discovery through phase 2 clinical trial evaluation.

The NCI is focused on moving high-priority discovery and development projects through to proof-of-concept clinical trials.

Recognizing the importance of an integrated approach to therapeutics development, NCI senior leadership has organized a unified governance structure for the NExT program responsible for coordinating and integrating available resources.

With a goal of reaching go/no-go decisions as efficiently as possible, the purpose of the NExT program is to ensure a pragmatic approach to drug discovery and development

in support of our academic partners. In addition, NExT leverages existing scientific and development expertise across the broader NCI community.

The discovery engine of this program, the [Chemical Biology Consortium \(CBC\)](#), was launched in 2009. The NCI has established this collaborative network comprising 12 specialized and comprehensive screening and chemistry centers with world-class capabilities covering high-throughput methods, bioinformatics, medicinal chemistry, and structural biology. Additionally, DCTD's Developmental Therapeutics Program (DTP) provides the resources needed to facilitate discovery and late-stage preclinical development through the final steps of development to first-in-human studies. Integrated molecular imaging and/or pharmacodynamic assay development provided by the Cancer Imaging Program (CIP) and DTP allow early assessment of potential clinical biomarkers. These coordinated and focused research and development processes enable continued incorporation of new data and disease insights into every step of the discovery and development process, thereby increasing the potential for the successful clinical evaluation of agents. Clinical evaluation is supported by the Cancer Therapy Evaluation Program (CTEP).

NExT is envisioned to streamline the development and testing of promising new anticancer drugs and expedite their delivery to the bedside, and is specifically focused on adding value for academic investigators and on unmet needs in cancer therapeutics.

Examples of NExT Projects

During its first 10 months of existence, NExT received 128 applications, of which about 20% were approved to participate in the program. Two sanctioned projects are described here.

Discovery and Optimization Agents for the Treatment of Squamous Cell Carcinoma of the Head and Neck

In partnership with NExT, Dr. Jennifer Grandis of the University of Pittsburgh is working to identify novel inhibitors of STAT3 activation as cancer therapeutic agents. The transcription factor STAT3 is activated in more than 95% of head and neck cancers, where it regulates the expression of genes necessary for tumor survival, proliferation, and metastasis. Activation of STAT3 correlates with decreased survival of patients with head and neck cancers.

The challenge is to identify inhibitors specific for STAT3 rather than STAT1, a closely related transcription factor that functions as a tumor suppressor. It is thought that improving the selectivity and potency of STAT3 inhibitors will improve patient outcome by decreasing the risk of side effects in patients with head and neck cancer as well as other cancers in which STAT3 is activated.

To differentiate inhibitors of STAT3 from STAT1, Dr. Grandis has developed a cell-based high-content screening (HCS) imaging assay that measures the translocation of STAT3 from the cytoplasm (inactive form) to the nucleus (activated form), so that the effects of STAT3 inhibitors can be “seen” under a microscope. Optimization of the HCS assay is currently under way.

Developing Small-Molecule Candidates for Novel Treatment of Acute Lymphoblastic Leukemia

Standard chemotherapy will cure most children who develop acute lymphoblastic leukemia (ALL). Unfortunately, some rare B- and T-cell subtypes of ALL confer a poorer prognosis, and many of these patients develop resistance to chemotherapy. Finding better drugs to treat children with ALL is the objective of the NExT project from Dr. Shelton Earp of the University of North Carolina.

Dr. Earp studies Mer kinase, a protein important in macrophages for engulfing and clearing apoptotic cellular material. Mer kinase is not expressed in normal B or T lymphocytes, but Dr. Earp noticed that Mer kinase is expressed in many ALL cell lines and is highly expressed in a variety of childhood leukemias.

In target validation experiments with a mouse leukemia model, Dr. Earp used RNA interference techniques to limit the expression of Mer kinase, resulting in increased survival. A lead compound has been identified, and current NExT program efforts are focused on establishing whether this Mer kinase inhibitor is the molecule to bring forward for further testing or whether further chemical modification of its structure would improve its characteristics.

Compressing the Drug Development Timeline with Phase 0 Clinical Trials

As part of the NExT program, DCTD has developed a [new type of clinical trial \(phase 0\)](#) with the intent of compressing the drug development timeline.

The compound used in the inaugural study, ABT888, inhibits poly-(ADP ribose) polymerase, which is critical for repairing damage to DNA. The results from the first phase 0 trial showed that an approach focusing 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.

An important aspect of this trial was the development of rigorous assays to measure the molecular effects of ABT888 in tumor tissue. The study showed that the compound inhibited its target enzyme in tumor cells as well as in circulating peripheral blood mononuclear cells (PBMCs). This latter finding may allow PBMCs to be used in ongoing trials to measure whether the agent is altering its presumed target.

Phase 0 trials are useful for testing targeted therapeutic drugs with wide therapeutic indices, as well as drugs that require development of biomarkers that may be useful for future studies. There are several different types of phase 0 trials, ranging from those that examine new drugs to those that validate new imaging agents. Both of these are being evaluated in a joint effort between DCTD and the NCI's intramural program (CCR):

- First-in-human imaging studies to demonstrate agent targeting (indium-labeled trastuzumab)
- First-in-human comparisons of analogs based on target inhibition assays (indenoisoquinolines)

Phase 0 trials allow:

- Validation of targets or biomarkers in human tissue prior to the initiation of large-scale clinical trials
- Assessment of reproducibility across labs and technicians for assays used to measure the effect of the drug on the target
- Definition of standard operating procedures for handling tissues and biospecimens in the clinic

Recommendations Developed to Re-envision NCI's Clinical Trials Systems

During the last five years, three related working groups have made recommendations to NCI to improve, modernize, and streamline clinical and translational research at the institute. The end results aim to reduce by half the time it takes to open clinical trials.

These review groups were the [Clinical Trials Working Group \(CTWG\)](#), which evaluated the entire range of NCI-supported clinical trials; the [Translational Research Working Group](#), which focused on research to move basic research discoveries into phase 1 clinical studies; and the [Operational Efficiency Working Group](#), which was formed to make specific recommendations to improve the efficiency of all NCI-sponsored clinical trials.

Each of the working groups used an inclusive approach to examine ways to increase the efficiency of cancer clinical trials, decrease redundancy and administrative burdens, and better coordinate activities to enhance the development and delivery of the best therapies to cancer patients. Each of the teams assembled to advise NCI included well-respected translational and clinical research experts as well as patient advocates and practicing physicians from the cancer community, and each group solicited public comments before submitting recommendations to the institute.

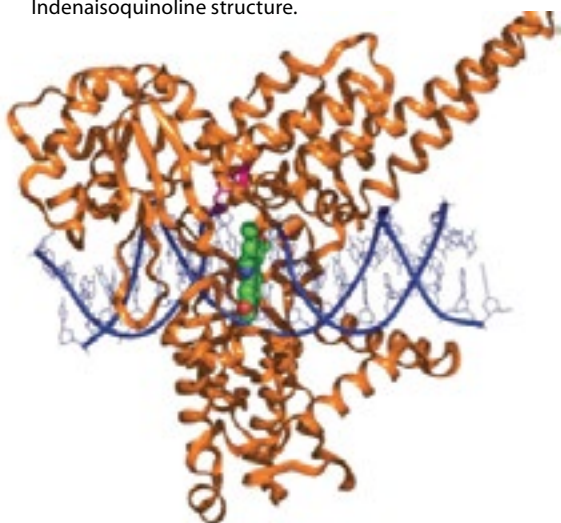
The NCI's clinical trials cooperative group program, administered by DCTD, was created in the 1950s, before the discovery of the genetic underpinnings of cancer that have led to the recent development of targeted cancer therapies and the dawning of personalized cancer treatment. Over time, the process of activating new phase 3 clinical trials conducted by NCI's cooperative groups became extraordinarily lengthy, so that on average, more than 2 years was required to open a phase 3 study and activation of most phase 1 and

2 studies required more than 500 days. A recent analysis of NCI's clinical trials activation process demonstrated that many trials, especially those that took the longest to open, never reached their accrual goals and had to be closed, wasting precious time and resources. Major changes to the NCI clinical trials system are currently being implemented on the basis of these reports.

Clinical Trials Working Group

- Recommendations made in 2005
- Chaired by Dr. James H. Doroshow
- Focused on the entire range of clinical trials supported by NCI
- Recommended 22 strategic initiatives and corresponding implementation plans for revamping the institute's cancer clinical trials system, most of which are nearing completion
- Recommendations addressed six key issues:
 1. Coordination
 2. Scientific prioritization
 3. Standardization
 4. Operational efficiency
 5. Enterprise-wide oversight
 6. Informatics
- Resulted in the creation of nine extramural disease-specific steering committees to develop, evaluate, and prioritize clinical trials at a national level
- Resulted in the creation of a new oversight structure for NCI's clinical trials program:
 - [Coordinating Center for Clinical Trials \(CCCT\)](#), which

Indenaisoquinoline structure.



- oversees implementation of the CTWG recommendations
 - **Clinical Trials and Translational Research Advisory Committee (CTAC)**, an external group, to provide strategic advice regarding NCI's clinical trials portfolio and established the Operational Efficiency Working Group
 - Clinical Trials Operating Committee (CTOC), an internal group, to coordinate and prioritize clinical research across NCI
- Resulted in a systematic review of the steps involved in opening a clinical trial and an implementation plan to decrease by 50% the time required to activate clinical trials
- Resulted in the development of support for biomarker validation clinical trials
- Resulted in changes to three existing entities to include translational research in their goals:
 1. CCCT was tasked to oversee implementation of the CTWG and TRWG recommendations.
 2. Clinical Trials Advisory Committee, an external group, became the CTAC.
 3. Clinical Trials Operating Committee, an internal group, expanded to become the **Clinical and Translational Research Operations Committee (CTROC)**.
- Resulted in the creation of the **Translational Research Program (TRP)**, the chief component of which is the Specialized Programs of Research Excellence (SPORE) program and the initiation of the first STRAP (Special Translational Acceleration Project) awards

Translational Research Working Group

- Recommendations made in 2007
- Co-chairs Dr. Ernest Hawk, Dr. Lynn Matrisian, and Dr. William Nelson
- Focused on early translational research, essential to moving basic research discoveries into phase 1 clinical studies
- Examined how NCI could best ensure that the most promising basic research concepts enter developmental pathways and are advanced rapidly and efficiently to either translational success or productive failure
- Developed 15 recommendations and implementation plans in three key categories:
 1. Coordinated management
 2. Tailored funding programs
 3. Operational effectiveness

Operational Efficiency Working Group

- Recommendations made in 2010
- Co-chaired by Dr. James H. Doroshow and Dr. Gabriel Hortobagyi
- Established under the auspices of CTAC to advise NCI on strategies to reduce the time required to activate clinical trials
- Resulted in 14 recommendations that were developed into several key initiatives:
 - Cooperative group phase 3 trial process improvements
 - Early drug development trial process improvements
 - Cancer center investigator-initiated trial process improvements
 - Process improvements applicable across trial categories

- Process improvements to enhance overall clinical trials program
- Resulted in key activation milestones to cut in half the time it takes to open clinical trials:
 - By January 2011, phase 3 trials are targeted to be activated by 300 days after submission to CTEP; trials will be terminated if not approved within 24 months.
 - By January 2011, phase 1 and 2 studies are targeted to be activated in 210 days, with trial termination if not activated in 18 months
- Resulted in the April 2010 implementation by CTEP of an action plan to improve efficiency and speed protocol development

Projects Funded by the American Recovery and Reinvestment Act of 2009

Under the umbrella of the [American Recovery and Reinvestment Act of 2009 \(ARRA\)](#), DCTD awarded funds for competitive grants and initiated and expanded several cancer diagnostics and therapeutic initiatives. These initiatives concentrate on facilitating the development of new research resources in support of clinical trials, the acceleration of early stage clinical studies, and enhancement of the NExT drug discovery and development program. Each project underwent multilevel review in NCI prior to ultimate approval from the White House. The following is a brief description of some of the DCTD ARRA projects.

Patient Characterization Center and Clinical Assay Development Program

The intent of this initiative is to improve patient outcome by translating information from the comprehensive molecular characterization of a patient's tumor and associated tissues to their clinical management. Critical to this endeavor is accelerated evaluation of molecular alterations in the tumor as well as the development and validation of clinical assays assessing these alterations. This initiative provides resources focused on the development, optimization, and validation of molecular profiling procedures and predictive assays based on profiles with clinical utility.

The initiative consists of two distinct, but technologically linked, components. The first is the Patient Characterization Center (PCC), which will molecularly characterize patient tumors using different genomic analysis platforms. Specific alterations in the genome and transcriptome of tumors are poised to become an essential parameter for stratifying patients into different clinical trials. The PCC, initially funded as a pilot program through ARRA, will continue to perform a molecular workup of patients and deposit the molecular characterization of tumor and normal tissue into a searchable database for clinicians to proactively identify potential participants for inclusion in clinical trials.

The second component of the initiative, the [Clinical Assay Development Program \(CADP\)](#), builds on data generated by the PCC to carry out the final development, optimization, and validation of clinical assays critical to individualization of

cancer therapy. In addition, it facilitates the validation of assays proposed as being integral to clinical trials. In anticipation of projects requiring a multitude of technologies, implementation of the PCC and the CADP involves active collaboration with various components of NCI with expertise in aspects critical for development of the assays. Under the ARRA timeline, initial development of the molecular characterization/diagnostic assay pipeline will be completed. To accomplish these goals, CADP comprises both the Clinical Assay Development Center (CADC) at NCI and the Clinical Assay Development Network (CADN), a group of NCI-supported service laboratories in the extramural community. Together these centers will create a process to efficiently develop diagnostic tools addressing clinical needs, including co-development of targeted agents and predictive markers.

Implementation of Operational Efficiency Working Group Recommendations at NCI's Cooperative Groups and Cancer Centers

Barriers to conducting clinical trials must be overcome to decrease the length of time necessary to evaluate the efficacy of a particular therapeutic agent, to receive approval from the U.S. Food and Drug Administration (FDA) to treat cancer patients, or to more quickly move on to the development of other potential agents. To the extent that such barriers can be overcome, the overall cost of drug development, as well as the speed with which therapeutic interventions and diagnostic capabilities become available in the clinic, are closely linked with the ability to effectively and efficiently conduct

clinical trials. The aim of this initiative is to incentivize implementation of the NCI Operational Efficiency Working Group recommendations to decrease clinical trial activation times by 50%.

Specific project-based milestones and deliverables have been established that, upon achievement, will result in funding to an individual Cancer Center or Cooperative Group. This incentive-based procedure is designed to increase the rate at which efficiency-promoting processes are implemented.

Clinical Pharmacodynamics

Validated clinical pharmacodynamic assays that reliably quantify drug effects on molecular targets in tissue specimens are critical to converting breakthroughs in molecular oncology into targeted therapeutics, and subsequently to evaluate these new drugs in patients by confirming that they work as intended in early clinical trials (phases 0, 1, and 2). DCTD's vision is to develop, clinically implement, and transfer to the oncology research community highly reproducible and informative pharmacodynamic assays. To that end, the division has made the strategic decision to use only those assay technologies that have proven clinical applicability and to apply diagnostic assay expertise and developmental principles to pharmacodynamic assays. These decisions have already yielded validated assays for several molecular targets since the program's inception in mid-2005. One of these assays accelerated the clinical development of a molecular targeted agent from phase 0 trials directly into combination phase 1 studies in five CTEP-sponsored trials,

saving over a year of development time. The molecular data from the validated assay justified bypassing any single-agent phase 1 or 2 trials, where the drug was not expected to show single-agent activity in most genetic backgrounds. DCTD expects that using multiple pharmacodynamic assays, developed by this ARRA-supported effort to simultaneously interrogate multiple molecular targets both within and across important signaling pathways in a single biopsy specimen, will allow the evaluation of rational combinations of molecularly targeted agents.

Coordination of Clinical/Translational Research Across NCI

Fostering collaboration among translational cancer researchers supported by various NCI funding mechanisms will lead to the development of a more integrated and efficient and less costly system for taking significant laboratory findings into clinical

trials. This collaboration, however, has been difficult to implement. As part of its participation in ARRA, the NCI was interested in furthering its high-priority goal of accelerating high-impact translational research by encouraging and rewarding collaborative team science. In that spirit, this initiative provided a unique incentivized opportunity for the creation of a team of investigators with the collective expertise and resources to answer, within two years, a hypothesis-driven, mechanism-of-action-oriented scientific question within the context of a clinical trial.

Adoption of New Technologies for Remote Data Capture and Protocol Authoring

To strengthen the infrastructure of its clinical trial networks, the NCI is in the process of purchasing licensing rights for a commercial clinical data management system (CDMS) software product that allows

Projects Approved for Coordination of Clinical/Translational Research across NCI	
NCI Program/Division	Project
TRP/DCTD	Predicting pancreatic cancer responses for a PARP inhibitor-based clinical trial
CTEP/DCTD	Targeted therapies for childhood acute lymphoblastic leukemia
CDP/DCTD	Translation of predictive rhabdomyosarcoma biomarkers into clinical practice
CDP/DCTD	Refining a molecular partitioning analysis model for glioblastoma
DCP	Validation of a multi-gene test for lung cancer risk
TRP/DCTD	Biomarker prediction of Gleason upgrading in prostate cancer
TRP/DCTD	Proteasome/HDAC inhibition in leukemia/MDS; phase 1 trial and correlative studies
DCP	Clinical evaluation of a bioadhesive gel for oral cancer chemoprevention
TRP/DCTD	Defining the importance of immunity to NY-ESO-1 in melanoma therapy and prognosis

CDP = Cancer Diagnosis Program; CTEP = Cancer Therapy Evaluation Program; DCP = Division of Cancer Prevention; HDAC = histone deacetylase; MDS = myelodysplastic syndrome; PARP = poly(ADP ribose) polymerase; TRP = Translational Research Program.

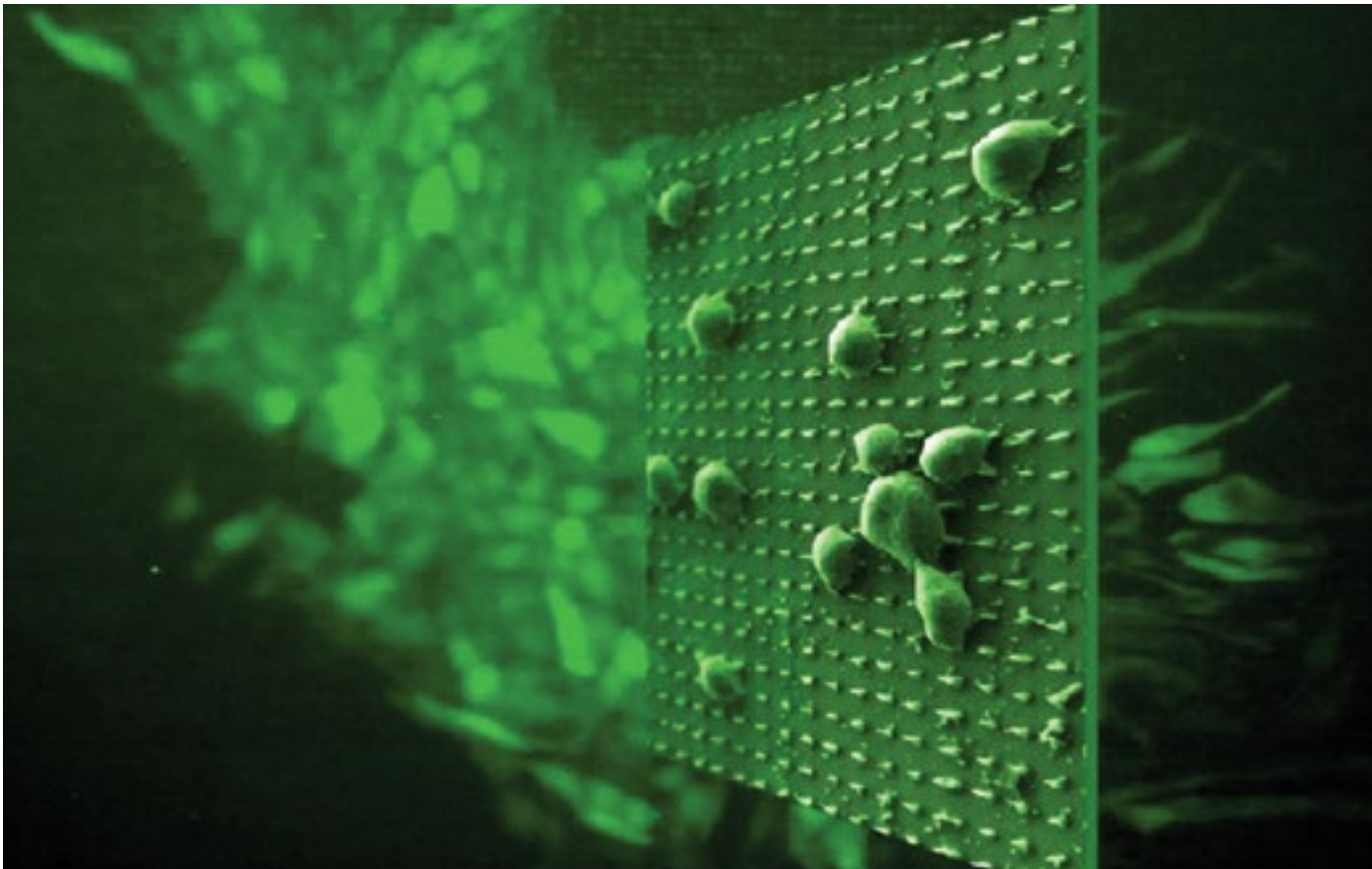
remote electronic data capture and protocol authoring, along with the related installation, support, and maintenance services, to support the conduct of cancer clinical research by all of CTEP's mechanisms. The purpose of the CDMS procurement is to:

- Deliver full-function clinical data management capability for NCI-supported studies
- Facilitate integration of clinical data with biospecimen banking, imaging, gene expression, and population databases to promote a uniform biomedical research enterprise
- Streamline the development and conduct of clinical trials

- Facilitate sharing of data and simplify collaboration

The potential benefits of using this technology include improved speed, quality, and security of clinical trial data acquisition, reduction in data discrepancies, and access to data in real time for more immediate review of adverse events as well as for interim review. The CDMS software will be integrated into existing NCI-sponsored clinical trial mechanisms.

This program, called ADOPT, focuses on accelerating the adoption and integration of this new technology for remote data capture. Importantly, ADOPT includes



Carbon nanofibers as gene delivery tool.

implementation of a core library of standardized phase 2 and 3 electronic case report forms currently being developed by NCI to improve the efficiency of data collection and to accelerate the cancer clinical trial development process used by CTEP's trial mechanisms. Careful planning, staff development, and computer resources are being provided for each clinical trial component to adopt this improved technology and build the necessary connections from their existing infrastructure to the NCI "biomedical internet." Since neither biomedical nor informational technologies are static, the trial infrastructure is being designed to allow the flexibility necessary to adapt to an evolving research environment.

Phase 1 and 2 Therapeutic and Imaging Clinical Trials

CTEP and the Cancer Imaging Program are well positioned to coordinate the rapid design and conduct of phase 1/2 and pilot trials with novel agents alone, in combination, or as part of standard therapies. Several categories of early-phase studies are currently being funded through this initiative.

Accelerating Clinical Trials of Novel Oncologic Pathways. An ARRA-funded, phase 1/2 initiative, called Accelerating Clinical Trials of Novel Oncologic Pathways (ACTNOW), is focused on accelerating progress by speeding the development of approximately 35 new clinical treatment trials. These trials test novel agents (alone, in combination, and with other standard therapies) that target new pathways by which cancer cells grow, metastasize, and develop resistance to

current treatments. A competitive review of CTEP-solicited nominees for this program from all grantees and contractors involved in this research was conducted to identify the most meritorious proposals. The selected trials have received enhanced resources to enable rapid development and approval of the treatment protocol such that 90 days from notification of the award, the trial would be either open to enrollment or in review at the local institutional review board. This timeline is significantly faster than that typically attained by industry-sponsored early clinical trials and is about nine months faster than NCI's standard approach to trial development. This accelerated timeline is being made possible through the investment of ARRA resources to:

- Allow the hiring of more staff devoted to protocol writing and statistical plans
- Increase the number of personnel available for the development of database and case report forms
- Permit the use of innovative diagnostic scans, specimen sample collection, assay development, and adequate reimbursement for the research costs associated with data management at local sites

Development of 3'-Deoxy-3'-[¹⁸F] Fluorothymidine Positron Emission Tomography as a Predictive Marker in Cancer Therapy. Promising evidence exists that mid-therapy 3'-deoxy-3'-[¹⁸F] fluorothymidine (FDG) positron emission tomography (PET) imaging may be predictive of tumor response, but interpretation is complicated by the fact that [¹⁸F]FDG PET can accumulate in inflammatory as well as malignant tissues.

Preliminary data with [¹⁸F]fluorothymidine (FLT) PET promises better prediction of response to therapy as a superior correlate to cellular proliferation without accumulation in inflammatory tissues. Establishing the utility of this radiolabeled imaging agent with PET will advance existing scientific understanding of which uptake parameters of [¹⁸F]FLT best correlate with early tumor response to chemotherapy. A direct comparison to standard-of-care [¹⁸F]FDG PET imaging parameters will be performed in this trial to determine predictive value.

Evaluation of [¹⁸F]Fluoride PET as a Pharmacodynamic Biomarker for Dasatinib, a Src Kinase Inhibitor, in Men with Castration-Resistant Prostate Cancer and Bone Metastases. It is estimated that 30–40% of patients with prostate cancer will experience a relapse after local surgery or radiation therapy. Most will develop osteoblastic bony metastasis. Prostate cancer metastases also have a strong constant osteolytic component that correlates to an elevated N-telopeptide of type I collagen excretion into the urine. Current methods of imaging bone cannot detect the therapeutic impact of existing therapies, let alone differentiate the therapeutic effects between varying therapies. Standard imaging methods such as computed tomography and magnetic resonance imaging (MRI) scans (measured with Response Evaluation Criteria in Solid Tumors [RECIST]) and bone scintigraphy fall short of enabling the determination of tumor activity and therapeutic response that would assist in treatment selection and prognostics for patients with bone metastasis.

[¹⁸F]Fluoride PET in patients undergoing treatment with dasatinib will advance scientific understanding of the effect of the drug (effect of regional bone metabolism [K_i] and fluoride delivery [K_1]) on bone metabolism and blood flow as an indirect measure of angiogenesis. Preliminary data in breast cancer patients suggest that fluoride K_1 and K_i can be independently and accurately measured for both normal bone and bone metastases. The ability to quantify the changes in fluoride kinetics in response to therapy is critical to better evaluate response to treatment. This study will explore the hypothesis that patients with significant changes, as measured by [¹⁸F]fluoride in bone metastases, resulting from dasatinib therapy may respond better and have improved progression-free survival. Further, it is anticipated that this hypothesis-generating project will potentially lead to subsequent trials of [¹⁸F] fluoride PET as a prognostic biomarker.

Application of Nanoparticle-Based MRI to Direct Brain Cancer Therapy.

Differentiation between pseudoprogression and true tumor progression is critical in decision making for treatment options in patients with brain tumors so that patients can be maintained on therapies that are effective and can be switched to other therapies if a tumor is progressing. Using standard T2-weighted and gadolinium contrast-enhanced, T1-weighted MRI sequences does not provide a reliable distinction between tumor recurrence or true progression and pseudoprogression. Dynamic susceptibility-weighted, contrast-enhanced (DSC) MRI (sometimes called perfusion-weighted imaging) measurements of relative cerebral blood volume in regions

of interest in the brain may be a useful approach to resolve this dilemma.

Ferumoxytol is an ultrasmall superparamagnetic iron oxide nanoparticle that is gaining use for brain imaging. It has been extensively tested and found to be safe, most importantly, in patients with impaired kidney function, who should not receive gadolinium-based contrast agents. Unlike gadolinium, ferumoxytol is resistant to passage through the leaky capillaries at first-pass bolus and, in the short term (minutes to hours), stays in the intravascular compartment as a blood pool marker. The funded trials (adult and pediatric) are assessing the capability of DSC MRI in combination with ferumoxytol, in comparison to the gadolinium-based contrast agent gadoteridol, to distinguish these two pathologies so that patients can receive the most efficacious therapy.

Chemical Biology Consortium and Overall Therapeutics Program

New Therapeutic Molecules. The immediate goal of CBC's New Therapeutic Molecules initiative is to prevent short-term gaps in the supply of clinical materials to treat patients on NCI-supported clinical studies. Its long-term goal is to develop sufficient efficiencies in production and evaluation of new candidate drugs to make the process more sustainable in supplying patients in clinical studies. This ARRA initiative focuses on all three cornerstones of systemic anticancer treatment: biologics, natural products, and synthetic compounds.

As a new biologic therapy begins to show promise, supply of clinical materials can be the rate-limiting step for expanding

access to larger populations. Major delays in expanding production are due to the qualification procedure of facilities and processes for production of biologics at additional sites. When the original site of production is at NCI-Frederick, NCI is in a unique position to expand capacity to treat a larger set of patients before commercial facilities can be approved by the FDA. This scenario has been fully substantiated by the recent results of the Children's Oncology Group trial demonstrating a survival advantage by adding the ch14.18 antibody to the therapy of children with neuroblastoma. This antibody, which was made by DTP without commercial support, is illustrative of NCI's commitment to finding treatments for rare cancers that generate commercial interest. Due to stimulus funding, in late 2010 NCI delivered a sufficient quantity of ch14.18 for ongoing clinical trials studying neuroblastoma. The NCI product will be used during a transition period while licensing and commercial production are established. Similarly, for the proposed Cancer Immunotherapy Network, the extramural immunotherapy community identified various molecules that are of great interest for further clinical investigation but for which there is currently no commercial source available. With stimulus funding, NCI now has the capability to move directly into the phase 1/2 arena with two agents (interleukin [IL]-15 and IL-7) and supply sufficient clinical material to support three to four peer-reviewed clinical trials with each compound.

Natural products were once the dominant source for new cancer medicines. Because of the de-emphasis of natural products by the commercial sector, there is a unique role for NCI in the investigation of therapies from



Scientists with pixon computer.

this source. The NCI collection of natural products is the largest in the world but has yet to be fully exploited. Short-term stimulus funding provides a focused opportunity to evaluate new patterns of development for natural products. NCI has been piloting a procedure for more extensive biological testing of natural-product extracts before investing scarce and expensive chemical resources to isolate the active ingredient. With stimulus resources, it is expected that investigators will be able to identify up to 100 natural-product extracts with sufficient activity to warrant further advancement of active ingredients toward the clinic.

For synthetic anticancer compounds, short-term stimulus funding is being utilized by DTP to outsource a one-year backlog of about 100 in vitro positive synthetic compounds.

Diverse Chemical Libraries for Drug Discovery. Diverse chemical libraries are critical to improving the potential hit rate from screening of new targets by CBC centers. By creating a uniform library of individual compounds, compound fragments, and fit-for-purpose libraries, NCI and the scientific community may be able to determine whether one approach is

more meritorious than another in selecting clinical candidates that may have a greater likelihood of showing activity in the clinic.

Chemical Repository for the CBC.

NCI is developing a state-of-the-art chemical repository facility to support high-throughput screening projects brought into the NEXt pipeline and then studied by CBC participants.

In Vitro/In Vivo Screening of Combination Targeted Therapeutic Drugs.

Most new anticancer agents are tested singly, but clinical cancer treatments often involve multiple agents and modalities administered in combination over time. To model clinical applications early in the drug development process, DCTD is expanding and accelerating the in vitro screening program for combinations of both approved and investigational therapeutics. Currently, DTP supports an applied drug development program that initially uses a panel of 60 human cancer cell lines for its in vitro screening of potential therapeutics. The primary endpoint of the NCI-60 cell line screen is the phenotypic reduction in cell growth and/or cell death. Subsequently, in vivo testing is performed via implantation into mice of human tumor cell line xenografts to evaluate the efficacy and toxicity of potential therapeutics. The primary endpoints of the in vivo testing are inhibition of tumor growth and toxicity. DTP has initiated an internal pilot program for combinatorial drug screening. One result of this pilot is the definition of parameters for study design, cell culture plate layout, and statistical approaches to synergy and/or additivity, throughput rates, and costs. This has formed the basis for the

establishment of a network of collaborative in vitro and in vivo screening laboratories.

The in vitro program supports the application of techniques in molecular biology (genomics, siRNA, proteomics, and more), computational and statistical modeling (such as response surface mapping for synergy), and robotics into an applied drug screening effort. Engineering principles and computational models are now being applied to describe cellular signaling pathway responses to environmental cues leading to cell growth, survival, and death. Investigators can interrogate intracellular responses to drug-induced perturbations at the molecular level in order to prospectively design combinatorial pharmacological regimens that independently modulate key signaling nodes, cooperatively block redundancy loops, and/or concurrently target epithelial, stromal, and immunologic cells. While the scientific tools to do this are available, there are relatively few published examples in applied drug development. The model developed through this program will also have applicability for scientists working with non-cancer cells and diseases.

The in vivo program expands and accelerates the ability of DTP to identify promising new combinatorial anticancer regimens and advance them to the clinic. Because the necessary bioassays are technically demanding and time consuming, the in vivo efficacy and toxicity testing of potential cancer therapeutics is a rate-limiting step in applied drug development. Currently, all xenograft testing for DTP is done at NCI-Frederick. The network collaboration supported by ARRA funds will expand access to new

tumor cell lines, animal models, and drug development expertise to help inform decision making in advancing potential new therapies to clinical trials. In addition, the in vivo study of combinations will help validate the models developed using in vitro approaches. In follow-up studies to the initial in vivo screen, tumor samples and adjacent normal tissue collected from animals receiving efficacious combinations will be assessed by genomic and proteomic technologies, and the in vitro and in vivo data from the same cell lines will be compared. Thus, the drug-targeting hypotheses generated in vitro will be corroborated in the next higher-level system, the whole organism. All of these data will be made available electronically to the entire cancer community.

Comprehensive Information Technology Program for Facilitating Drug Discovery and Development. The discovery and development of new drugs to treat cancer and other diseases increasingly relies on information technology (IT) to collect and analyze the expanding data sets derived from new technologies. The NCI-60 screen in 96-well plates was state of the art 20 years ago. Today, however, 20,800 data points are generated per week. In comparison, an ultra-high-throughput screening assay conducted in 1,536-well plates can generate 2.2 million data points

in a week. With the advent of new assays to evaluate pharmacodynamics, an experiment that did not analyze any samples from tumor or normal tissues a few years ago may now generate up to 4,000 samples to be analyzed in multiple assays at multiple sites. This creates data storage and handling issues as well as an analytical bottleneck, since correlations among as many as 10 different endpoints in one experiment is typical. The implementation and integration of new IT software for data acquisition, storage, and evaluation is imperative to drug discovery and development. A software package was selected for primary collection of all data generated by CBC projects. Implementation, however, had been slow due to the limited divisional IT resources to collect the different data streams from DCTD-funded scientists. The goal of this ARRA initiative is to integrate additional software that will facilitate the analysis of data from multiple software companies. These software packages will also be integrated to the extent possible with the current server used to manage projects for the NExT pipeline. This initiative is mission critical for DCTD to support, in an integrated manner, the various functional components of NExT, including pharmacodynamic assays; in vivo studies including toxicology, pharmacology, and efficacy; in vitro high-throughput screening assays; and microarray data capture.



2010 Program
Accomplishments

Cancer Diagnosis Program



OVERVIEW

The overarching goals of the **Cancer Diagnosis Program (CDP)** are to:

- Provide the most effective tools to optimize treatment decision making
- Bring to fruition the promise of biomarkers

CDP's initiatives over the past several years have contributed significantly to progress in the field of biomarker development and clinical application. The program is now building on lessons learned and advances in the science to launch the Clinical Assay Development Program (CADP). These programs, initially using funds from the American Recovery and Reinvestment Act of 2009 (ARRA), will facilitate the transition of assays based on new molecular insights from the research laboratory to clinical use.

The CADP will provide access to:

- NCI-sponsored service laboratories (the Clinical Assay Development Network) for evaluation of the analytical performance and clinical validity of assays
- Specimens with associated clinical data
- Reference materials and standardized reagents
- Statistical design consultation and regulatory expertise to ensure that assays evaluated in clinical trials are ready for submission to the Food and Drug Administration (FDA) or for clinical use at the conclusion of the trials

The CADP will also support an internal laboratory, the Clinical Assay Development Center (CADC), to assist with earlier phases of assay development and transition to clinical laboratory readiness.

The Patient Characterization Center (PCC), a collaborative effort among CDP, the NCI Center for Cancer Research, the NCI Community Cancer Centers Program (NCCCP), and the new cancer Human Biobank (caHUB), will provide full genomic characterization of newly diagnosed cancer patients and test the importance of results being generated by The Cancer Genome Atlas (TCGA) project and other large cancer profiling efforts. The results of these characterizations may identify patients who would benefit from trials of new interventions targeted to specific genetic alterations.

CDP's Program for the Assessment of Clinical Cancer Tests (PACCT) has provided strategic guidance to the translational cancer research community and leveraged NCI-supported programs to achieve significant research goals. These include:

- Launch of the landmark Trial Assigning Individualized Options for Treatment (TAILORx) to evaluate the ability of the OncotypeDX[®] assay to predict benefit from chemotherapy
- Publication of the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) guidelines for reporting tumor marker studies in biomedical journals
- Development of standards for analytic performance for assays incorporated into clinical trials
- Establishment of a major series of international meetings on cancer molecular markers in collaboration with the American Society of Clinical Oncology (ASCO) and the European Organisation for Research and Treatment of Cancer (EORTC)

BARBARA A. CONLEY, ASSOCIATE DIRECTOR

Barbara A. Conley, M.D., is the newly appointed Associate Director of the Cancer Diagnosis Program (CDP). She is an NCI veteran who has held previous positions at the Institute. From 1997 to 2004, she participated in several key programs within the NCI, including Senior Investigator in the Clinical

Investigations Branch of CTEP and Chief of the CDP Diagnostics Research Branch, as well as Head, Aerodigestive Diseases, in the intramural medicine branch. Immediately prior to her current appointment at DCTD, she was Chief, Division of Hematology/Oncology, at Michigan State University (MSU), as well as Scientific Director of the MSU Clinical Translational Science Institute. At MSU and the University of Maryland (1987–1997), Dr. Conley was the principal investigator on several NCI grants and an investigator with the National Surgical Adjuvant Breast and Bowel Project.



Board certified in Internal Medicine and Medical Oncology, Dr. Conley has research interests in diagnostic markers, drug development, and cancers of the aerodigestive tract. She has published extensively in many journals, including the *Journal of Clinical Oncology* and *Nature Medicine*, and is on the editorial board of several professional publications.

Dr. Conley holds an undergraduate degree from the University of Michigan and received her medical degree from MSU.



CDP has designed and implemented the [Strategic Partnerships to Evaluate Cancer Signatures \(SPECS\)](#), a cooperative agreement program that has accelerated progress in moving molecular profiles of tumor tissue from the research setting into clinical practice. New diagnostic tools developed by SPECS investigators include:

- An assay for the “intrinsic” subtypes of breast cancer (luminal A and B, HER2 and basal) that can be performed in a clinical laboratory
- A commercially available mass spectroscopic assay to predict response to epidermal growth factor receptor (EGFR) inhibitors
- An improved risk classifier for adult and pediatric patients with acute lymphoblastic leukemia, now incorporated into clinical trials
- A diagnostic signature for rhabdomyosarcoma based on genomic data that predicts outcome more reliably than standard histopathology
- A system for classification of adult non-Hodgkin lymphoma based on gene expression patterns
- A molecular signature for aggressive prostate cancer that can be applied to biopsy specimens with minimal amounts of tissue

CDP collaborates closely with the Cancer Therapy Evaluation Program (CTEP) to promote the effective integration of biomarker studies into CTEP’s cancer therapy trials and to implement recommendations of the Clinical Trials Working Group (CTWG), especially through the new Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP).

CDP also supports earlier stages of biomarker discovery research and clinical assay development through an actively managed portfolio of investigator-initiated research project grants. More than half of its grant portfolio has been developed by means of targeted initiatives designed to provide grant mechanisms, such as exploratory grants, that sustain each part of the assay development process.

Research supported by CDP extends to the development of new technologies: the instruments and analytical methods that provide the technical platforms for innovative diagnostics. These development efforts encompass:

- Genomics and next-generation sequencing
- RNA and microRNA (miRNA) expression and sequencing
- DNA methylation and epigenetic regulation
- Proteomics and immunoassays
- Metabolomics and glycomics
- Circulating tumor cells and molecules

Finally, CDP is an essential component of NCI’s program to provide cancer tissue specimens for research and to develop the tissue resources of the future. CDP provides ongoing support for two major biospecimen resources, the Cooperative Human Tissue Network and the Cooperative Group Banks, which each year provide thousands of tissue specimens with appropriate pathologic and clinical data to researchers across the country. The new Specimen Resource Locator will enable the CADP to quickly and efficiently gain access to existing tissue resources housed in pathology archives.

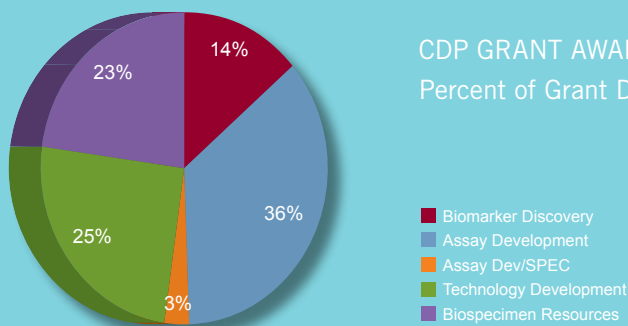
STRUCTURE AND FUNCTION

CDP strives to improve patient outcomes by effectively moving molecular diagnostics into clinical practice. The program stimulates and funds resources and research on diagnostics and improvements in technologies to better characterize cancers in order to develop information that can aid cancer patients and their physicians in clinical decision making. CDP was established as a DCTD program in 1996.

Numerous barriers have been cited to explain the slow progress in the field of biomarker and assay development. These have included, among others, the lack of appropriate specimens, the lack of a well-defined pathway for development and evaluation of clinical biomarkers, and a lack of standards that assays must meet before being incorporated into trials or clinical practice. The [Program for the Assessment of Clinical Cancer Tests \(PACCT\)](#), launched in 2000, has addressed a number of these barriers. The PACCT strategy group prepared a set of standards that assays must meet prior to incorporation into clinical trials and a set of criteria for prioritization of assays for funding through the Biomarker, Imaging and Quality of Life Supplemental Funding Program (BIQSFP). CDP staff and members of the

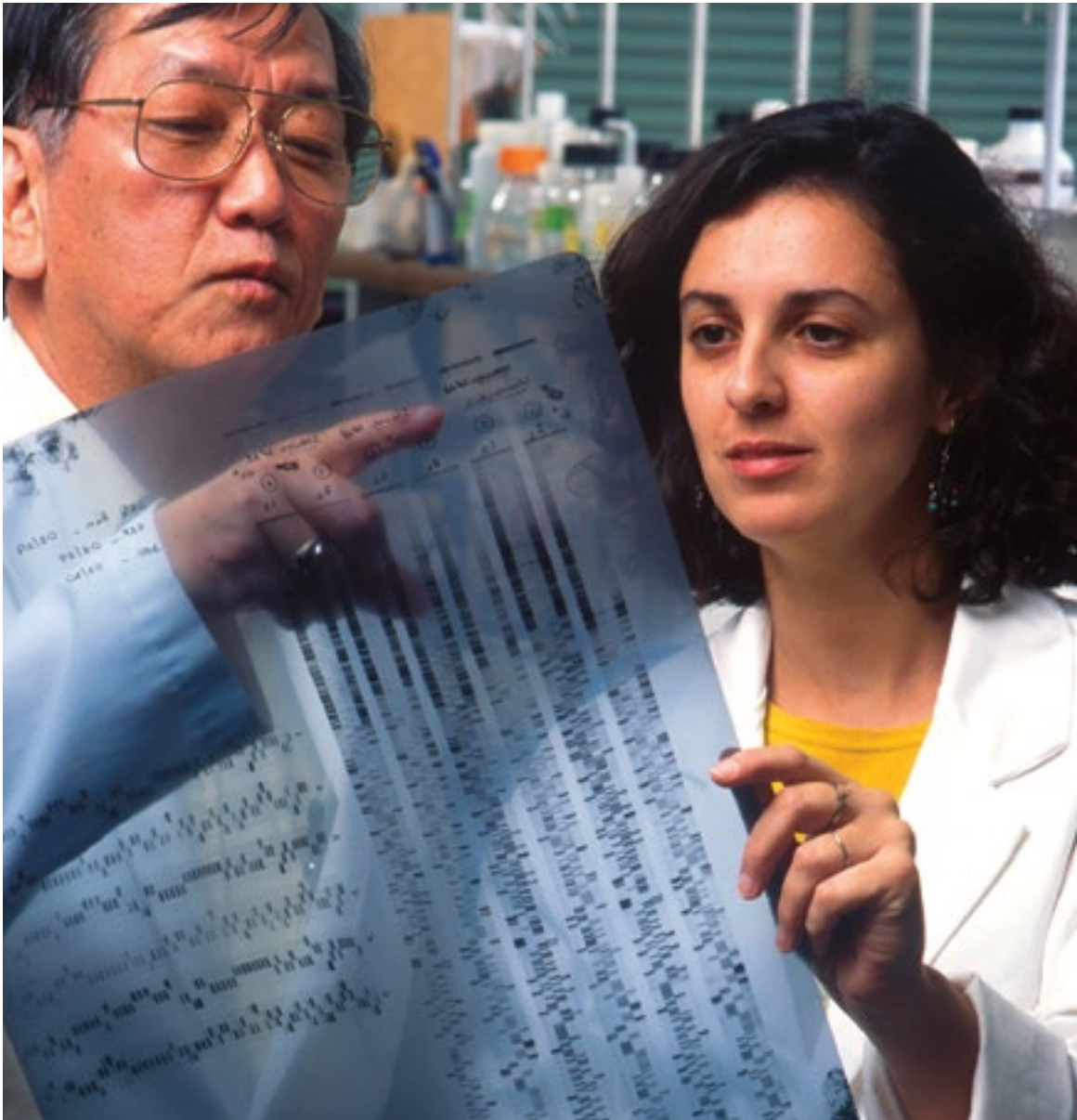
PACCT strategy group collaborated with international partners to develop guidelines for reporting studies of prognostic markers. The [Reporting Recommendations for Tumor Marker Prognostic Studies \(REMARK\)](#) guidelines were published in several major scientific journals in 2005 and 2006 and are now used by major journals as criteria for evaluation of articles submitted. A working group of PACCT led the effort to integrate biomarkers into the treatment decision-making process for patients with early-stage breast cancer; the landmark Trial Assigning Individualized Options for Treatment (TAILORx) was launched in the spring of 2006 and completed its testing and accrual of more than 11,000 patients in the summer of 2010. This trial is expected to have a major impact on the treatment of women with breast cancer. Other PACCT-directed projects have focused on ensuring that assays being evaluated in clinical trials or being used in clinical practice can be performed with sufficient reproducibility and minimal lab-to-lab variation. This is critical for dissemination of clinical laboratory tests into community practice.

These achievements, which are beginning to have an impact on medical practice, have depended on significant collaboration and coordination among basic and clinical



CDP GRANT AWARDS 2010

Percent of Grant Dollars Awarded by Areas of Scientific Investment



scientists. The “Director’s Challenge: Toward a Molecular Classification of Cancer” (1999–2004) first required the cancer research community to form multidisciplinary teams to demonstrate the power of comprehensive molecular technologies in developing profiles of molecular alterations in human tumors. Among the many noteworthy results during this time were the

discovery of mutations in the EGFR gene that are associated with response to inhibitors of EGFR signaling, as well as the identification of the “intrinsic” subtypes (luminal A, luminal B, HER2, and basal) of breast cancer. The [Strategic Partnerships to Evaluate Cancer Signatures \(SPECS\)](#) program has built on the successes of the Director’s Challenge by establishing the large interdisciplinary

teams needed to evaluate the clinical utility of molecular signatures. The SPECS program has successfully brought cancer profiles for pediatric leukemias into clinical trials. Other cancer signatures are being refined and readied for clinical testing. This initiative requires broad collaboration among clinical trials groups, translational researchers, and technology developers in industry; it has been reissued and will be adding new grants to the portfolio.

CDP directly supports research projects at all stages of the cancer biomarker development pipeline through an actively managed program of research project grants. The majority of the grants in CDP's portfolio are solicited for exploratory and developmental projects to encourage the translation of basic discovery research into diagnostic tools.

Although industry and academic researchers are actively developing novel technologies, incentives and guidance are required to encourage these researchers to focus their efforts on technologies and the application of technology that can benefit cancer patients. The NCI, with significant input from CDP staff, developed the Innovative Molecular Analysis Technologies (IMAT) program. This program supports important research to develop and apply new technologies to cancer diagnosis. CDP staff members continue to play a major role in this ongoing program. The staff also works with the technology research community to advance the development of new tools and platforms for high-throughput analysis of biomarkers and point-of-care analysis systems for clinical applications. This encompasses the development of genomic, proteomic, metabolomic, and bioinformatic technologies, and the engineering of new

devices that have the potential to be used for analysis of human tumors. CDP collaborates with programs in the NCI Office of the Director, the National Institute of Biomedical Imaging and Bioengineering (NIBIB), and bioengineering efforts across the National Institutes of Health (NIH).

CDP collaborates with CTEP to promote the effective integration of biomarker studies into DCTD's cancer therapy trials. CDP staff members review biomarker studies proposed for inclusion in concepts and protocols for CTEP trials and provide recommendations at all stages of trial design, considering both the analytic validity and the clinical utility of novel assays. This effort improves the quality of protocols while also serving CDP's planning processes by enabling staff to identify obstacles to progress in the field. Trials that include investigational biomarker assays, particularly where assays are integral to the trials, pose special challenges to the implementation of NCI's operational efficiency initiatives. Members of the CDP staff are actively engaged with CTEP and the investigators of its clinical trials consortia to improve both the efficiency and the scientific output of DCTD trials.

Research must also be supported by provision of critical resources and infrastructure. Biomarker discovery research, assay development, and evaluation of clinical utility of assays all depend on the availability of human tumor specimens with various amounts of associated demographic and clinical data. CDP has a long history of creative approaches to addressing these needs. The Cooperative Human Tissue Network (CHTN), first funded in 1987, continues to be a mainstay for the community, providing high-quality human



specimens to support biomarker discovery and early assay development. The first virtual specimen resource with significant clinical data, the Cooperative Breast Cancer Tissue Resource (CBCTR), was recently phased out, but the specimens were used to create statistically designed tissue microarrays that are still in great demand and are being provided to support prognostic marker research. The CDP also supports the specimen banking activities of the Clinical Cooperative Groups; prior to this stable support, collection of valuable specimens in the context of randomized trials was haphazard at best. Tissue collection and processing are being standardized and transparent access procedures are making the specimens more widely available for critical research.

The CADP will require large numbers of clinical specimens with associated outcome information for assessment of analytical performance of assays. Toward that end, the CDP is developing a Specimen Retrieval System (SRS) that uses natural language processing to identify cases from two health maintenance organization (HMO) members of the Cancer Research Network. Both HMOs have extensive electronic medical records systems and have agreed to provide paraffin blocks and data from cases that meet specific criteria. The system depends on open-source software developed under a previous CDP initiative. The software has been adapted to each institution's systems and has been shown to be able to remove from the records all personal information as required under the Health Insurance Portability and Accountability Act of 1996 (HIPAA), including from free-text clinical notes. Funding from ARRA will be used to collect large sets of reference specimens for the CADP.

PROGRAM ACCOMPLISHMENTS

The activities of CDP fall into three major categories:

1. Developing and evaluating assays for clinical decision making
2. Discovering biomarkers and developing enabling technologies
3. Providing the resources, particularly the human specimens, and other infrastructure to ensure that discovery and development can proceed

Development and Evaluation of Assays for Clinical Decision Making

In order for patients to benefit, biomarkers must move out of the research setting and become the basis for standardized assays that can be performed reliably in clinical laboratories as part of routine medical care. Through its Diagnostics Evaluation Branch, the CDP supports both laboratory research and clinical trials to establish both the analytic validity and the clinical utility of emerging biomarkers.

In its Diagnostics Evaluation Branch, CDP:

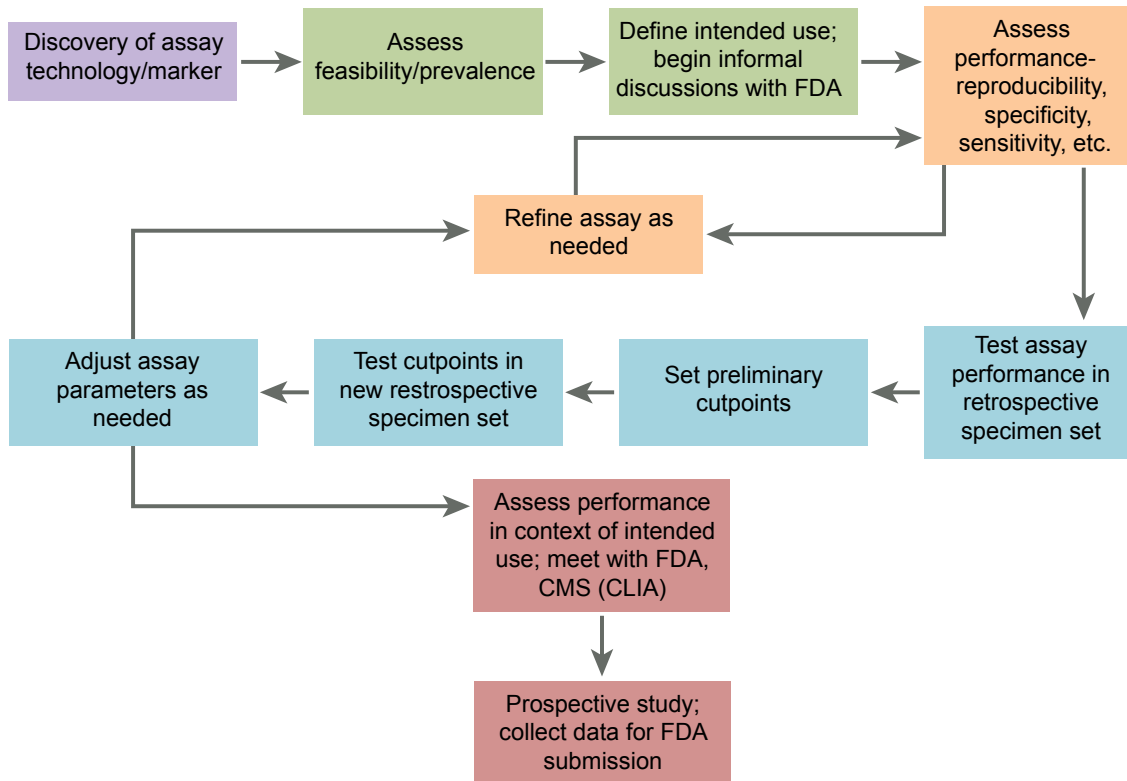
- Actively manages a portfolio of research grants to support translation of research biomarkers into clinical assays
- Pursues the effective integration of biomarker research into NCI cancer therapy trials
- Promotes the adoption of community-wide standards for assay performance in both anatomic and molecular pathology

Program for the Assessment of Clinical Cancer Tests

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 advances in new technologies and new understanding of cancer biology more efficiently and effectively into clinical practice.

PACCT is not a grants program. It leverages many NCI-supported activities to accomplish goals identified by the PACCT strategy group. The strategy group comprises scientists from academia, as well as 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 guide development of specific projects.

MARKER DEVELOPMENT PROCESS





The TAILORx Trial

The **Trial Assigning Individualized Options for Treatment (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 that have been shown to be associated with risk of recurrence in women with node-negative, hormone receptor-positive breast cancer can be used to assign patients to the most appropriate and effective treatment. The signature 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. U.S. Postal Service sales of breast cancer stamps have played a critical role in making possible a groundbreaking treatment trial by providing a portion of the funding for TAILORx. Without this support, the trial would not have been possible.

The trial is being carried out as a collaboration of CDP, CTEP, and all of the NCI clinical cooperative groups that perform breast cancer studies. Accrual was completed during 2010.

Biomarker Evaluation in NCI Cancer Therapy Trials

Members of the CDP staff review biomarker studies proposed for inclusion in CTEP clinical trials, providing critiques and recommendations for both concepts and protocols for phase 1, phase 2, and phase 3 trials. CDP staff members also serve as reviewers on Intergroup Correlative Science Committees for applications

to use specimens from the cooperative group tissue banks. Members of CDP have provided critical biomarker expertise at clinical trials planning meetings and serve on intergroup task forces. The expertise of the CDP staff has also been critical to the implementation of initiatives of the Clinical Trials Working Group (CTWG).

The CTWG report (“Restructuring the National Cancer Clinical Trials Enterprise”) made a series of recommendations that included the need to provide support for performing assays that are essential to clinical trials. A definition was needed of standards that must be met for any assay being used to make a decision such as eligibility or assignment to a treatment arm. A PACCT working group developed a standards document and a set of criteria for prioritization for funding. These recommendations were approved (July 11, 2007) by the Clinical Trials Advisory Committee and are being implemented in the ongoing BIQSFP.

The CTWG also recommended that the problem of co-development of biomarkers and targeted agents be addressed. PACCT organized a workshop with the FDA and industry to assess the barriers and develop a white paper to address issues to be considered. The workshop, which took place in October 2007, resulted in a commentary published in the *Journal of the National Cancer Institute*.

In 2007, CDP staff issued a Request for Information (RFI), as suggested by the PACCT strategy group, to gather information about the needs of the assay development community. In addition to the anticipated responses citing the need for tissue specimens, technical and



statistical expertise, and access to the types of resources that have been incorporated into the CADP, issues related to intellectual property (IP) were cited as a major impediment. CDP presented the CADP concept to the public in a workshop with members of industry, academia, and the FDA in May 2009, and participants told CDP and the FDA that 50% of the barriers to assay development now arise from the detrimental effect of patents and licensing. The issues were discussed further at a second workshop convened later in 2009 that included representatives from diagnostic and pharmaceutical companies, a medical device trade association, academic technology transfer offices, patient advocates, the FDA, and CTEP.

Information was presented to demonstrate that as much as 40% of the cost of clinical assays is for royalty and licensing fees. These workshops contributed to the current revision of the CTEP Cooperative Research and Development Agreement (CRADA) IP options that are under review. CDP staff continue to collaborate with CTEP and NIH—industry task forces convened under the auspices of the National Center for Research Resources (NCRR) Clinical and Translational Science Awards (CTSA) program to explore additional approaches. The CADP will work to identify ways to help assay developers that are either IP neutral or that facilitate negotiations regarding licensing, royalties, or transfer of IP.



REMARK and the EORTC-NCI-ASCO Cancer Molecular Markers Collaboration

CDP has led an NCI collaboration with the European Organisation for Research and Treatment of Cancer (EORTC) to convene a series of 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 the 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. These guidelines are now being used by journals as standards for the review of manuscripts on markers.

The American Society of Clinical Oncology (ASCO) has now joined the NCI-EORTC collaboration on these meetings. With ASCO's involvement, the "Molecular Markers in Cancer" meeting, sponsored since November 2007 by EORTC, NCI, and ASCO, is being held annually. The meetings alternate between sites in the United States and Europe. A tutorial for young oncologists and scientists involved in biomarker research occurs each year in conjunction with the meeting. The 2010 meeting took place in Hollywood, Florida, in October and drew more than 450 participants. The tutorial was attended by more than 50 participants, half of whom were awarded highly competitive travel grants to cover their expenses.

Clinical Assay Standardization

Members of the CDP staff are acknowledged experts in the fields of anatomic, surgical, and molecular pathology. As members of major professional societies, they contribute to the establishment of nationwide practice guidelines for cancer pathology and tumor staging.

The CDP has also initiated proactive efforts to improve the standardization and reliability of newer assays entering into clinical practice. Pilot projects were suggested by the PACCT strategy group to assess whether assays that were either being planned for clinical trials or in commercial use met the proposed standards and were reproducible when performed in multiple labs. Loss of heterozygosity (LOH) on chromosome 18q has been shown to be associated with disease progression and poor outcome in intermediate-stage colon cancer. The use of an assay for 18q LOH to assign adjuvant therapy for patients with stage II colon cancer was approved for use in Eastern Cooperative Oncology Group trial E5202. CDP was aware that different laboratories were performing the assay with different methods. The assay for the trial was to be performed in a laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA) at MD Anderson Cancer Center, but there was concern whether other laboratories would be able to perform the assay reliably if the assay proved to be clinically important. CDP convened the clinical reference laboratories for the North Central Cancer

SPECS Projects

A number of SPECS projects are under way to refine and validate molecular signatures in a variety of cancers:

Diagnostic and Prognostic Sarcoma Signatures

Timothy J. Triche, M.D., Ph.D., Children's Hospital Los Angeles

This project is refining and validating molecular signatures that provide a more accurate diagnosis and more accurately predict the clinical behavior of common childhood sarcomas (Davicioni et al., 2009). Planning is under way with the Children's Oncology Group (COG) to incorporate a diagnostic signature for rhabdomyosarcomas into COG clinical trials.

Evaluation of Predictive Signatures of Prostate Cancer

Dan Mercola, M.D., Ph.D., University of California, Irvine

This project is refining and validating molecular signatures that predict relapse in prostate cancer patients and distinguish indolent disease from disease that will progress (Kozioł et al., 2009). A clinical version of the assay is being evaluated in collaboration with Althea Diagnostics, a small diagnostics company.

Molecular Signatures to Improve Diagnosis and Outcome Prediction in Lymphoma

Wing C. Chan, M.D., University of Nebraska Medical Center

This project is refining and validating molecular signatures for the major subclasses of non-Hodgkin lymphoma (Lenz et al., 2008a and 2008b). 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.

Leukemia Signatures for Risk of Classification & Targeting

Cheryl L. Willman, M.D., Ph.D., University of New Mexico

This project is refining and validating molecular signatures that improve risk classification and prediction of response to therapy in pediatric and adult ALL (Mullighan et al., 2009a and 2009b). A plan to incorporate a signature that predicts minimal residual disease in children with high-risk ALL into COG clinical trials is under discussion.

Molecular Signatures of Lung Cancer

David P. Carbone, M.D., Ph.D., Vanderbilt-Ingram Cancer Center

This project is refining and validating a number of types of molecular signatures in lung cancer, including serum proteomic signatures that differentiate patients with cancer from those without disease, signatures that predict risk of recurrence after surgery, and signatures that predict response to EGFR-targeted therapies (Taguchi et al., 2007). A clinical trial evaluating the signature that predicts response to anti-EGFR therapies is under way in collaboration with Genentech.

Biological Breast Cancer Classification by qRT-PCR

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

This project is refining and validating a molecular signature, PAM50, that identifies four "intrinsic" subtypes of breast tumors, using qPCR to measure gene expression in formalin-fixed, paraffin-embedded tissues (Parker et al., 2009). This signature will add useful information to the established diagnostic categories of breast cancer and help avoid under- and over-treatment. A commercial partnership has been established to pursue FDA clearance for an in vitro diagnostic assay.



Treatment Group (Mayo Clinic) and Cancer and Leukemia Group B (Brigham and Women's Hospital) cooperative groups that led other adjuvant trials in colon cancer to perform a laboratory comparability study with MD Anderson. The first phase of this study demonstrated some problems with concordance, but when the pathologists agreed on procedures for dissection and isolation of tumor and normal tissue, concordance among the laboratories improved. These results were presented at the ASCO annual meeting in 2009.

A second study was organized to address a problem with a quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR) assay. The assay in question measures BCR-ABL fusion gene transcripts in blood and is used for monitoring the molecular recurrence of chronic myelogenous leukemia (AML) after treatment. The assay has produced inconsistent results when performed in different laboratories. An international scale has been devised, but concerns have arisen in the United States and elsewhere about the lack of comparable results among clinical laboratories. CDP formed a consortium of seven major commercial reference and academic clinical laboratories to perform a comparability study. This consortium demonstrated that estimation of actual BCR-ABL gene transcripts and the international scale in a set of clinical samples varied among the laboratories by more than two orders of magnitude when each laboratory used its own test in its CLIA-certified laboratory. Introduction of a calibrator alone did not reduce this disparity in results, but the introduction of a calibrator with a common set of

primers, reagents, and standard operating procedures produced comparability among the laboratories that was within an order of magnitude. These studies will be presented in fall 2010 and have significant implications for the application of these types of sensitive assays for the measurement of gene transcripts.

Strategic Partnering to Evaluate Cancer Signatures

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

The current 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.

A formal evaluation of the SPECS program was conducted in 2008. An outside review panel concluded that “providing targeted funding for biomarker development has resulted in remarkable progress in three years” and recommended that NCI continue SPECS by inviting applications for new projects. A Funding Opportunity Announcement for SPECS II, [PAR-10-126](#), has been published, and new awards are anticipated in the spring of 2011.

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 more than 200 patients with high-risk pediatric acute lymphoblastic leukemia (ALL), generated in the leukemia SPECS project, are being combined with data being developed by investigators at St. Jude Children’s Research Hospital on genomic alterations in the same patients. The combined data are being used to identify genes that are altered in ALL and 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 has been initiated to take advantage of the gene expression data being developed on the SPECS pediatric sarcoma project. In 2009, ARRA funding permitted expansion of the TARGET program; its current portfolio of childhood cancers includes high-risk ALL, AML, osteosarcoma, neuroblastoma, and Wilms tumor.

ARRA funds have also significantly accelerated several of the SPECS projects. Antibodies to components of the proteomic signatures identified in the lung cancer SPECS project are being produced with ARRA support to the NCI Clinical Proteomics Center at Vanderbilt University. An ARRA supplement to the lymphoma SPECS project will support the translation of gene expression signatures, developed by using frozen tumor tissue, into assays that can be performed on samples of formalin-fixed, paraffin-embedded tissue. This will accelerate the application of the new assay in routine clinical practice. ARRA support will also be used to test the breast cancer gene expression signature developed at Washington University on specimens collected from several large



phase 3 clinical trials to support an application for regulatory clearance of this assay by the FDA.

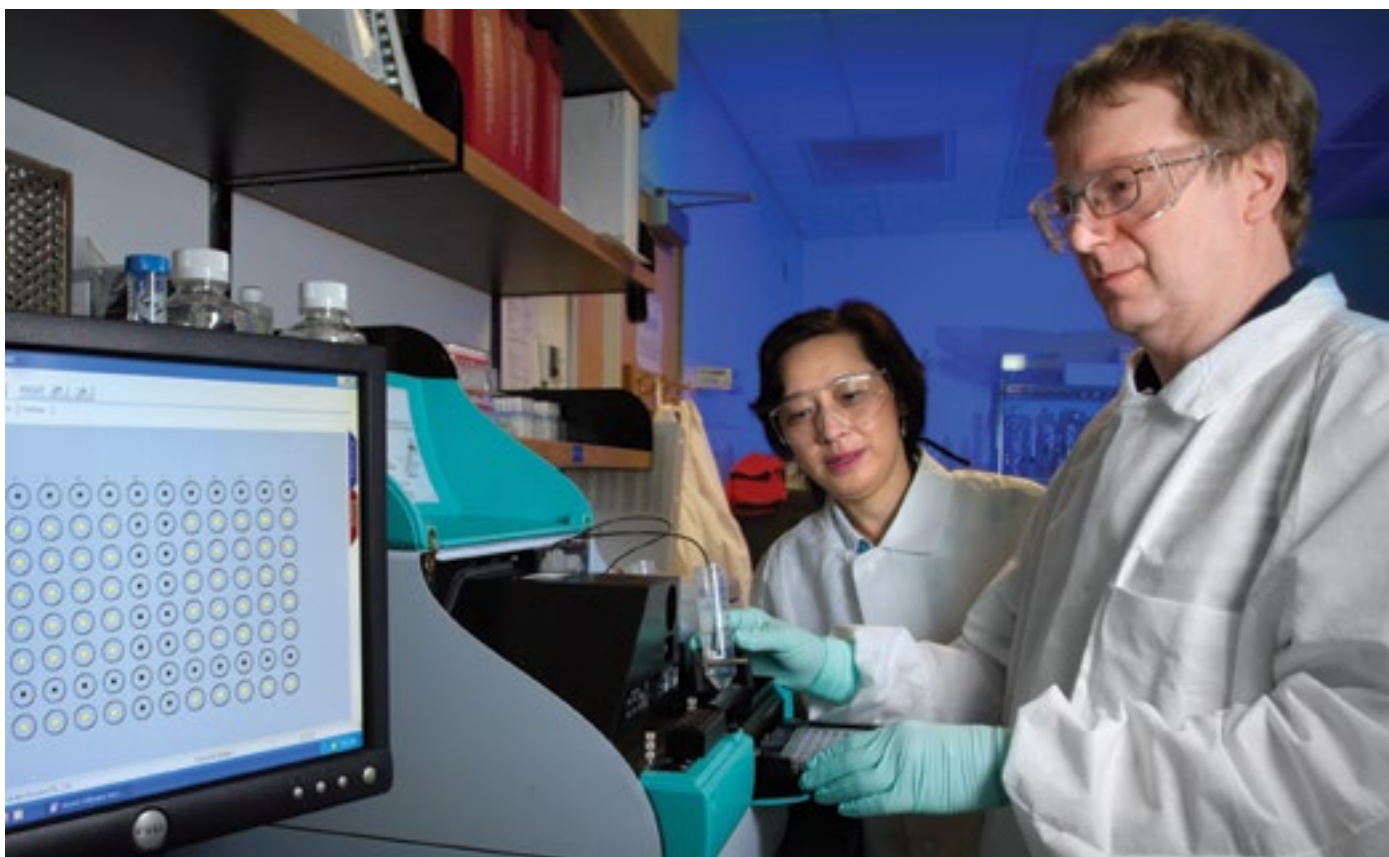
Discovery of Biomarkers and Development of Enabling Technologies

CDP promotes the discovery of diagnostic, prognostic, and predictive cancer biomarkers and advances the development of new technologies for high-throughput analysis of biomarkers and point-of-care analysis systems for clinical applications. This enterprise encompasses the development of genomic, proteomic, metabolomic, and bioinformatic technologies and the engineering of new devices that have the potential to be used

for analysis of human tumors. Through its Diagnostic Biomarkers and Technology Development Branch, CDP:

- Provides grant support for high-risk biomarker discovery projects
- Supports advances in instrumentation and IT
- Recruits specialists from outside fields into cancer research

CDP's critical role is to develop innovative grant programs supporting investigator-initiated research projects that do not fit into the typical NIH R01 award mechanism and to build collaborations that cross traditional disciplines.



CDP staff has recognized that R21 awards effectively support the initial steps to determine whether a newly identified biomarker has the potential clinical utility to justify further investment. NCI does not accept unsolicited applications for R21 (exploratory research) grants. CDP therefore maintains a program announcement for R21 applications, [Exploratory Studies in Cancer Detection, Diagnosis, and Prognosis \(PA-08-267\)](#), which is managed in collaboration with the early detection biomarkers program in the Division of Cancer Prevention. CDP R21 grants are currently supporting efforts to understand the diagnostic potential of microRNAs and to explore novel combinations of gene and protein expression.

CDP also supports a substantial proportion of the R21 and R33 awards funded through NCI's [Innovative Molecular Analysis Technologies \(IMAT\)](#) program, which provides support for investigators from fields not traditionally related to cancer biology or clinical research, such as engineers, mathematicians, informatics specialists, and physicists. Investigators supported by CDP's IMAT grants are applying increasingly sophisticated analysis technologies to the assessment of gene expression in tumor tissues and devising methods to analyze increasingly smaller amounts of sample. Until recently, CDP managed a portfolio of small business grants, and it continues to collaborate with the new NCI Small Business Innovation Research Development Center to develop contract solicitations and organize workshops.

The effective support of research in this area requires proactive effort from CDP staff to engage investigators from a multitude of disciplines and to guide them toward the most appropriate sources of both NCI grant funds and collaborators. For example, in 2009, CDP staff organized a public workshop to provide investigators developing methods to assess circulating tumor cells with an opportunity to interact not only with each other but also with clinical trialists interested in prospectively testing these new techniques.¹

Biomarker discovery is just the first in a series of steps toward the implementation of a useful clinical test. Substantial further exploratory and developmental work is required to achieve the necessary analytic performance and to establish the usefulness of a test in its intended setting. CDP has designed and promoted a comprehensive series of Funding Opportunity Announcements that provide appropriate grant mechanisms to support successive stages of developmental biomarker research:

- [Developmental Research in Cancer Prognosis and Prediction](#) (R21 and R33 awards)
- [Development, Application, and Evaluation of Prediction Models for Cancer Risk and Prognosis](#) (R21 and R01 awards, in collaboration with NCI's Division of Cancer Control and Population Sciences)
- [Correlative Studies with Specimens from Multisite Trials](#) (R21 and R01 awards, in collaboration with CTEP)

1. See "Putting Circulating Tumor Cells to the Test," *NCI Cancer Bulletin*, Vol. 6, No. 24, December 15, 2009 (<http://www.cancer.gov/aboutnci/ncicancerbulletin/archive/2009/121509/page7>).



Support from these grant programs has generated a number of assays now moving into late translation or clinical practice. Examples include:

- A seminal publication to establish a molecular classification system for melanoma
- RNA-based tests for differential diagnosis and prognosis in mesothelioma
- A clinical assay for the internal tandem duplication of the FLT3 oncogene in pediatric AML, now in use in phase 3 trials
- Biomarkers to predict response to chemotherapy for non–small-cell lung cancer

Members of the CDP staff collaborate with staff of other NCI programs and extramural investigators to monitor progress, respond to inquiries from Congress, and develop targeted initiatives in high-priority areas, such as the Community-Oriented Strategic Action Plan for Melanoma Research. CDP staff also played a pivotal role in the process to establish a chartered Cancer Biomarkers Study Section at the NIH Center for Scientific Review.

Biospecimen Resources and Biospecimen Science

Access to [high-quality tissue specimens](#) annotated with appropriate clinical and outcome data is critical to continued scientific progress. Through its Resources Development Branch, CDP:

- Develops and supports human specimen resources that provide tissue samples to translational cancer researchers

- Assists researchers in locating additional tissue resources and gaining access to the specimens needed for their research
- Supports the development of informatics tools to improve access to human specimens and associated clinical data
- Manages a portfolio of investigator-initiated research grants for development of emerging technologies in biospecimen science solicited through the IMAT program
- Serves as a source of current information on legal and ethical issues related to the use of human specimens in research for the NCI and the extramural community
- Provides expertise related to human tissue specimen resources and advises staff in NCI, NIH, and other federal and nonfederal agencies and institutions, as well as researchers and specimen resource staff throughout the world

The Resources Development Branch monitors changes in scientific needs for tissue specimen resources and acts to ensure that new requirements for specimens can be met in a timely manner.

Cooperative Human Tissue Network

The Cooperative Human Tissue Network (CHTN) provides access to human tissue for basic and translational scientists from academia and industry with the goal of accelerating discoveries in cancer diagnosis and treatment. CHTN offers prospective investigator-defined procurement of malignant, benign, diseased, and uninvolved (normal adjacent) tissues. Network institutions, organized into six divisions, coordinate the collection and distribution of tissues



across the United States and Canada. Trained personnel at member institutions perform the retrieval, preservation, and delivery of specimens obtained from surgical resections and autopsies according to protocols defined by the investigator. Since its establishment by CDP in 1987, CHTN has provided more than 800,000 high-quality specimens from a wide variety of organ sites to several thousand investigators. The CHTN also produces and distributes sections of tissue microarrays constructed from multiple tissue types with several disease-specific designs.

The CHTN consists of six divisions, one that specializes in pediatric biospecimen requests nationwide and five that serve specific geographic regions in the United States. Its Midwestern Division also serves researchers in Canada. Each division is led by an institution supported by a U01 cooperative agreement award from NCI. Six institutions currently participate in the CHTN:

1. Children's Hospital of Columbus—Pediatric Division
2. Ohio State University—Midwestern Division
3. University of Alabama, Birmingham—Southern Division Tissue
4. University of Pennsylvania—Eastern Division
5. University of Virginia—Mid-Atlantic Division
6. Vanderbilt University—Western Division

The CHTN is not a tissue bank; it primarily collects samples prospectively. Limited numbers of certain tumor types (e.g., rare pediatric tumors) are stored to ensure their availability, but specimen storage is not a significant part of CHTN's mission.

Access to the CHTN is provided to any investigator who submits a summary of the project for which the biospecimens are requested and signs the tissue and data use agreements, if appropriate. Priority is given to requests from investigators with peer-reviewed, funded research projects and to new investigators at academic or nonprofit research institutions.



Specimens from CHTN are utilized primarily in basic and early translational cancer research. Recent examples include the identification of a new polyoma virus with suggestive association to human Merkel cell carcinoma, identification of p53 isoforms that regulate cellular senescence in colon cells, and discovery of the role of SATB1, a chromatin organizer, in breast cancer progression.

The CHTN underwent an external review in 2007. The reviewers noted that approximately 850 peer-reviewed studies published between 2002 and 2006 were based on analysis of materials provided by the CHTN. During this period, more than 130 grants were obtained using CHTN biospecimens, and a large number of patents (116) were identified that cite the CHTN. The reviewers concluded: “Altogether, the CHTN has had wide-ranging and significant impact on the research community at large. The CHTN’s strength lies in the collection and distribution of a wide variety of biospecimens in response to the need of investigators.”

NCI Specimen Resource Locator and NCI Tissue Expediter

CDP provides a specimen resource locator and a tissue expediter to assist individual investigators locate specimens for their research. The NCI Specimen Resource Locator is a searchable Web database that includes resources such as tissue banks and tissue procurement systems with access to normal, benign, precancerous, and/or cancerous human tissue. Researchers can specify types of specimens, number of

cases, preservation methods, and associated data. When no match is obtained, the researcher is referred to the NCI Tissue Expediter. The NCI Specimen Locator is currently being updated and improved in collaboration with the Cancer Biomedical Informatics Grid (caBIG) and the Office of Biorepositories and Biospecimen Research.

The role of the NCI Tissue Expediter is to identify sources of human tissue specimens and to help guide researchers to appropriate resources or collaborators. The tissue expediter is a scientist with contacts in the resources community who can rapidly match investigator needs to available resources. The expediter can also help researchers identify potential collaborators when needed.

Cooperative Group Banks

The Cooperative Group Banks (CGB) collect and store high-quality, well-annotated human specimens from cancer patients enrolled in NCI-funded phase 3 and large phase 2 clinical treatment trials. These banked specimens are most useful for clinical correlative studies on uniformly treated patient populations. The Resources Development Branch has supported the CGB since 2005 through U24 awards to each of the nine Cooperative Oncology Groups, thereby ensuring that the groups implement best practices such as common data structures and standardized collection and storage practices. Currently, 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. The Group Banking Steering Committee was established with representatives from all the cooperative groups and NCI to lead and implement a harmonization of standard operating procedures and a process for fair access to specimens. A public website and a common application process are being developed to improve access to specimens by the broader research community.

Tissue Microarrays for Breast Carcinoma, Melanoma, and Colorectal Carcinoma

CDP has developed tissue microarrays (TMAs) to assist investigations in breast cancer, melanoma, and colorectal carcinoma. Application and access procedures are available at <http://cdp.nci.nih.gov/tma.html>.

Breast Cancer Progression and Prognostic

TMAs were constructed with tissue and associated pathological and clinical outcome data from the NCI Cooperative Breast Cancer Tissue Resource. The Breast Cancer Progression TMA is designed to permit comparisons of biomarker expression across three stages of disease (node negative, node positive, and metastatic). The Breast Cancer Prognostic TMA is designed for correlation of biomarkers with survival and recurrence outcomes in stage I, II, and III breast cancer. Both TMAs were designed to ensure high statistical power for the intended comparisons.

The **Melanoma Progression TMA** consists of 273 tissue specimens including nevi, primary melanomas, melanomas metastatic to the lymph node, and visceral and dermal metastatic melanomas. This TMA is designed to investigate differences in the expression of markers across various stages of melanoma progression and should be used as a screening array.

The **Colon Cancer Progression–Prognostic TMA** has more than 350 primary colon cancers and 100 control tissues and is designed for examination of associations of markers with tumor stage, clinical outcome, and other clinico-pathological variables in Stage I–IV colon cancer.



FUTURE INITIATIVES

Clinical Assay Development Program

The mission of the newly established Clinical Assay Development Program (CADP) is to increase the availability of validated and qualified diagnostic tests for patients and thereby improve access to molecularly guided therapy. This program is designed to identify promising tests, assess the need for further development, and provide services to facilitate optimization of analytical performance and to establish clinical validity so that the clinical utility of an assay can be evaluated in well-designed clinical studies. The overall goal of the CADP is to create a process to efficiently develop diagnostic tests that will address clinical needs, including co-development of targeted agents and predictive markers. Projects will meet rigorous performance standards so that they can be applied in clinical decision making. Eight external CLIA-certified laboratories have been competitively identified to assist with assay validation, and the first applications for these resources are expected in January 2011.

Specimen Retrieval System for Assay Validation

The performance characteristics of an assay must be assessed in the same types of specimens as the ones on which the assays will be performed in clinical practice. Therefore, although evidence-based, standardized preparation of specimens is an important goal, assays that are ready for use in current trials must be tested on currently available clinical material.

The CDP is establishing a Specimen Retrieval System (SRS) that will be able to provide sets of appropriate specimens to facilitate evaluation of an assay's analytical performance and initial assessment of clinical validity. These sets of specimens will come from community settings and will be associated with clinical and outcome data. The specimen sets will have to be assembled rapidly to meet assay development needs identified during clinical trial concept review.

Two member organizations of the Cancer Research Network, a subset of the HMO Research Network, are participating in a pilot study to determine whether previously developed software can identify cases that meet defined assay development needs. The software, developed by a group at Harvard as part of an earlier NCI initiative, is designed to interact with existing medical records at the participating institutions, to strip the records of protected health information, and to use natural-language processing to collect specified data related to treatment and outcomes. Sufficient progress has been made during the pilot study to allow preliminary implementation of the system. The current objective is to support the collection of specimens from 500–1,000 cases each of defined tumor types. The cases will be evaluated for their completeness, and paraffin blocks will be submitted to a repository for subsequent distribution to the Clinical Assay Development Network laboratories. Demographic and clinical data will be assembled into a database. Prior to utilization of specimens, a pathologist will review each case to ensure that it meets the requirements of the study in which it will be used.

SELECTED PUBLICATIONS

Publications by CDP Grantees

Strategic Partnerships to Evaluate Cancer Signatures (SPECS)

Molecular classification of rhabdomyosarcoma—genotypic and phenotypic determinants of diagnosis: a report from the Children’s Oncology Group, Davicioni E, Anderson MJ, Finckenstein FG, Lynch JC, Qualman SJ, Shimada H, Schofield DE, Buckley JD, Meyer WH, Sorensen PH, Triche TJ. *The American Journal of Pathology*, 2009;174:550–564.

<http://www.ncbi.nlm.nih.gov/pubmed/19147825>

- A gene expression signature determined by the Triche SPECS project to distinguish the alveolar and embryonal subtypes of rhabdomyosarcoma outperforms histology at predicting patient outcome.

The wisdom of the commons: ensemble tree classifiers for prostate cancer prognosis,

Koziol JA, Feng AC, Jia Z, Wang Y, Goodison S, McClelland M, Mercola D. *Bioinformatics*, 2009;25:54–60.

<http://www.ncbi.nlm.nih.gov/pubmed/18628288>

- The Mercola SPECS project has developed a classifier to distinguish indolent from aggressive prostate cancer.

Stromal gene signatures in large-B-cell lymphomas,

Lenz G, Wright G, Dave SS, Xiao W, Powell J, Zhao H, Xu W, Tan B, Goldschmidt N, Iqbal J, Vose J, Bast M, Fu K, Weisenburger DD, Greiner TC, Armitage JO, Kyle A, May L, Gascoyne RD, Connors JM, Troen G, Holte H, Kvaloy S, Dierickx D, Verhoef G, Delabie J, Smeland EB, Jares P, Martinez A, Lopez-Guillermo A, Montserrat E, Campo E, Braziel RM, Miller TP, Rimsza LM, Cook JR, Pohlman B, Sweetenham J, Tubbs RR, Fisher RI, Hartmann E, Rosenwald A, Ott G, Muller-Hermelink HK, Wrench D,

Lister TA, Jaffe ES, Wilson WH, Chan WC, Staudt LM. *New England Journal of Medicine*, 2008a;359:2313–2323.

<http://www.ncbi.nlm.nih.gov/pubmed/19038878>

Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways,

Lenz G, Wright GW, Emre NC, Kohlhammer H, Dave SS, Davis RE, Carty S, Lam LT, Shaffer AL, Xiao W, Powell J, Rosenwald A, Ott G, Muller-Hermelink HK, Gascoyne RD, Connors JM, Campo E, Jaffe ES, Delabie J, Smeland EB, Rimsza LM, Fisher RI, Weisenburger DD, Chan WC, Staudt LM. *Proceedings of the National Academy of Sciences of the United States of America*, 2008b;105:13520–13525.

<http://www.ncbi.nlm.nih.gov/pubmed/18765795>

- These two papers present gene expression signatures developed by the Chan SPECS project that classify therapeutically important categories of adult lymphoma.

Deletion of IKZF1 and prognosis in acute

lymphoblastic leukemia, Mullighan CG, Su X, Zhang J, Radtke I, Phillips LA, Miller CB, Ma J, Liu W, Cheng C, Schulman BA, Harvey RC, Chen IM, Clifford RJ, Carroll WL, Reaman G, Bowman WP, Devidas M, Gerhard DS, Yang W, Relling MV, Shurtleff SA, Campana D, Borowitz MJ, Pui CH, Smith M, Hunger SP, Willman CL, Downing JR. *New England Journal of Medicine*, 2009a;360:470–480.

<http://www.ncbi.nlm.nih.gov/pubmed/19129520>

JAK mutations in high-risk childhood acute

lymphoblastic leukemia, Mullighan CG, Zhang J, Harvey RC, Collins-Underwood JR, Schulman BA, Phillips LA, Tasian SK, Loh ML, Su X, Liu W, Devidas M, Atlas SR, Chen IM, Clifford RJ, Gerhard DS, Carroll WL, Reaman GH, Smith M, Downing JR, Hunger SP, Willman CL. *Proceedings of the National Academy of Sciences of the United States of America*, 2009b;106:9414–9418.

<http://www.ncbi.nlm.nih.gov/pubmed/19470474>



- These two publications from the Willman SPECS project improve the classification of infant ALL into meaningful risk categories for assignment of therapy.

Supervised risk predictor of breast cancer based on intrinsic subtypes, Parker JS, Mullins M, Cheang MC, Leung S, Voduc D, Vickery T, Davies S, Fauron C, He X, Hu Z, Quackenbush JF, Stijleman IJ, Palazzo J, Marron JS, Nobel AB, Mardis E, Nielsen TO, Ellis MJ, Perou CM, Bernard PS. *Journal of Clinical Oncology*, 2009;27:1160–1167.

<http://www.ncbi.nlm.nih.gov/pubmed/19204204>

- This paper from the Ellis SPECS project describes the PAM50 assay, which can be run in a routine clinical laboratory setting to distinguish the intrinsic subtypes of breast cancer.

Mass spectrometry to classify non-small-cell lung cancer patients for clinical outcome after treatment with epidermal growth factor receptor tyrosine kinase inhibitors: a multicohort cross-institutional study, Taguchi F, Solomon B, Gregorc V, Roder H, Gray R, Kasahara K, Nishio M, Brahmer J, Spreafico A, Ludovini V, Massion PP, Dziadziuszko R, Schiller J, Grigorieva J, Tsy-pin M, Hunsucker SW, Caprioli R, Duncan MW, Hirsch FR, Bunn PA, Jr., Carbone DP. *Journal of the National Cancer Institute*, 2007;99:838–846.

<http://www.ncbi.nlm.nih.gov/pubmed/17551144>

- This publication from the Carbone SPECS project describes a proteomic test, now commercially available as the Veristrat® assay.

Exploratory Studies in Cancer Detection, Diagnosis, and Prognosis

MicroRNA expression, survival, and response to interferon in liver cancer, Ji J, Shi J, Budhu A, Yu Z, Forgues M, Roessler S, Ambs S, Chen Y, Meltzer PS, Croce CM, Qin LX, Man K, Lo

CM, Lee J, Ng IO, Fan J, Tang ZY, Sun HC, Wang XW. *New England Journal of Medicine*, 2009;361:1437–1447.

<http://www.ncbi.nlm.nih.gov/pubmed/19812400>

- This work demonstrates the novel use of miRNA profiles for predicting survival and therapeutic response in liver cancer. The work also reveals a connection between the signaling pathways between nuclear factor kappa B and interleukin-6 and disease development that are important for disease analysis.

Development and evaluation of BioScore: a biomarker panel to enhance prognostic algorithms for clear cell renal cell carcinoma, Parker AS, Leibovich BC, Lohse CM, Sheinin Y, Kuntz SM, Eckel-Passow JE, Blute ML, Kwon ED. *Cancer*, 2009;115:2092–2103.

<http://www.ncbi.nlm.nih.gov/pubmed/19296514>

- A biomarker panel, “Bioscore,” based on tumor expression levels of B7-H1, survivin, and Ki-67 was developed for outcome prediction in RCC patients. The test promises to improve estimation of the risk of relapse and selection of appropriate forms of therapy for patients with renal cell carcinoma.

Innovative Molecular Analysis Technologies (IMAT)

Enrichment of glycoproteins using nanoscale chelating concanavalin A monolithic capillary chromatography, Feng S, Yang N, Pennathur S, Goodison S, Lubman DM. *Analytical Chemistry*, 2008;81:3776–3783.

<http://www.ncbi.nlm.nih.gov/pubmed/19366252>

- This work demonstrates how analysis of alternative pre-mRNA processing can shed additional light on differences between tumors and normal tissues as well as between different tumor types. Such studies may lead to the development of additional tools for tumor diagnosis, prognosis, and therapy.

Whole genome exon arrays identify differential expression of alternatively spliced, cancer-related genes in lung cancer, Xi L, Feber A, Gupta V, Wu M, Bergemann AD, Landreneau RJ, Litle VR, Pennathur A, Luketich JD, Godfrey TE. *Nucleic Acids Research*, 2008;36:6535–6547. <http://www.ncbi.nlm.nih.gov/pubmed/18927117>

- This modification of immobilized lectin chromatography makes this technique applicable to minimal amounts of sample material. This improves efficiency of the nanoscale monolithic capillary for analysis of glycoproteins in complex biological samples where only limited material may be available for clinical analysis.

Developmental Research in Cancer Prognosis and Prediction

Distinct sets of genetic alterations in melanoma, Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H, Cho KH, Aiba S, Brocker EB, LeBoit PE, Pinkel D, Bastian BC. *New England Journal of Medicine*, 2005;353:2135–2147. <http://www.ncbi.nlm.nih.gov/pubmed/16291983>

- These important studies generated groundbreaking discoveries for understanding the etiology of melanoma. The authors provide experimental evidence for the existence of distinct genetic pathways in the development of melanoma and propose a novel molecular classification system for melanoma based on these genetic pathways. Importantly, these newly identified molecular pathways could be targeted for treatment in various subtypes of melanoma.

Four-gene expression ratio test for survival in patients undergoing surgery for mesothelioma, Gordon GJ, Dong L, Yeap BY, Richards WG, Glickman JN, Edenfield H, Mani M, Colquitt R, Maulik G, Van Oss B, Sugarbaker DJ, Bueno

R. *Journal of the National Cancer Institute*, 2009;101:678–686.

<http://www.ncbi.nlm.nih.gov/pubmed/19401544>

- Building on prior work in which they developed and validated an algorithm for the diagnosis of mesothelioma using a series of gene ratio-based tests, these researchers describe building a molecular prognostic model for mesothelioma. These assays can be performed on the minimal amounts of tissue collected in fine-needle aspirates.

Structural and numerical variation of FLT3/ITD in pediatric AML, Meshinchi S, Stirewalt DL, Alonzo TA, Boggon TJ, Gerbing RB, Rocnik JL, Lange BJ, Gilliland DG, Radich JP. *Blood*, 2008;111:4930–4933. <http://www.ncbi.nlm.nih.gov/pubmed/18305215>

- This publication details and builds on earlier publications that define the impact of the internal tandem duplication of FLT3 oncogene in pediatric AML. These investigators have developed an assay that quantitates the amount of mutation and have used this assay as the basis for assigning therapy in two large phase 3 trials.

Randomized phase III trial of gemcitabine-based chemotherapy with in situ RRM1 and ERCC1 protein levels for response prediction in non-small-cell lung cancer, Reynolds C, Obasaju C, Schell MJ, Li X, Zheng Z, Boulware D, Caton JR, Demarco LC, O'Rourke MA, Shaw Wright G, Boehm KA, Asmar L, Bromund J, Peng G, Monberg MJ, Bepler G. *Journal of Clinical Oncology*, 2009;27:5808–5815. <http://www.ncbi.nlm.nih.gov/pubmed/19884554>

- This study shows that quantitative measurement of RRM1 and ERCC1 protein expression in routinely processed tumor specimens can be used to predict response to gemcitabine and gemcitabine plus carboplatin in lung cancer patients.



Research with Biospecimens Supplied by the CHTN

Clonal integration of a polyomavirus in human Merkel cell carcinoma, Feng H, Shuda M, Chang Y, Moore PS. *Science*, 2008;319:1096–1100. <http://www.ncbi.nlm.nih.gov/pubmed/18202256>

- Merkel cell carcinoma (MCC) is a rare but aggressive human skin cancer that typically affects elderly and immunosuppressed individuals, a feature suggestive of an infectious origin. These investigators studied MCC samples by digital transcriptome subtraction and detected a fusion transcript between the T antigen of a previously unknown polyomavirus and a human receptor tyrosine phosphatase. The prevalence and pattern of integration suggested that viral infection preceded clonal expansion of the tumor cells. Thus, this newly discovered virus may be a contributing factor in the pathogenesis of MCC.

p53 isoforms Delta133p53 and p53beta are endogenous regulators of replicative cellular senescence, Fujita K, Mondal AM, Horikawa I, Nguyen GH, Kumamoto K, Sohn JJ, Bowman ED, Mathe EA, Schetter AJ, Pine SR, Ji H, Vojtesek B, Bourdon JC, Lane DP, Harris CC. *Nature Cell Biology*, 2009;11:1135–1142. <http://www.ncbi.nlm.nih.gov/pubmed/19701195>

- The finite proliferative potential of normal human cells leads to replicative cellular senescence, which is a critical barrier to tumor progression in vivo. Fujita et al. show that the human p53 isoforms $\Delta 133p53$ and p53 β function in an endogenous regulatory mechanism for p53-mediated replicative senescence. The increased $\Delta 133p53$ and decreased p53 β isoform expression found in colon carcinoma may signal an escape from the senescence barrier during the progression from adenoma to carcinoma.

SATB1 reprogrammes gene expression to promote breast tumour growth and metastasis, Han HJ, Russo J, Kohwi Y, Kohwi-Shigematsu T. *Nature*, 2008 ;452:187–193. <http://www.ncbi.nlm.nih.gov/pubmed/18337816>

- SATB1 is a genome organizer that tethers multiple genomic loci and recruits chromatin-remodeling enzymes to regulate chromatin structure and gene expression. Han et al. show that SATB1 is expressed by aggressive breast cancer cells and its expression level has high prognostic significance, independent of lymph node status. SATB1 also directs epigenetic modifications at specific target gene loci and thereby reprograms chromatin organization and the transcription profiles of breast tumors to promote growth and metastasis; this is a new mechanism of tumor progression.

Research with Biospecimens Supplied by the Cooperative Group Banks

A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer, 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. *New England Journal of Medicine*, 2004;351:2817–2826. <http://www.ncbi.nlm.nih.gov/pubmed/15591335>

- This report is an original description of the OncoTypeDX[®] recurrence score assay.

Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer, Paik S, Tang G, Shak S, Kim C, Baker J, Kim W, Cronin M, Baehner FL, Watson D, Bryant J, Costantino JP, Geyer CE, Jr., Wickerham DL, Wolmark N. *Journal of Clinical Oncology*, 2006;24:3726–3734. <http://www.ncbi.nlm.nih.gov/pubmed/16720680>

- The authors present a retrospective demonstration that the OncoTypeDX[®]

recurrence score assay predicts benefit from chemotherapy.

Additional Publication

Medicine. Cancer's circulation problem,

Kaiser J. *Science*, 2010;327:1072–1074.

<http://www.ncbi.nlm.nih.gov/pubmed/20185704>

- This commentary was stimulated by a 2009 workshop initiated by CDP and co-sponsored by the NCI Small Business Innovation Research Development Center and the Cancer Biomarkers Research Group of the Division of Cancer Prevention. (See “Putting Circulating Tumor Cells to the Test,” *NCI Cancer Bulletin*, December 15, 2009 [<http://www.cancer.gov/ncicancerbulletin/121509/page7>]).

Publications by CDP Staff

Guidelines for the development and incorporation of biomarker studies in early clinical trials of novel agents,

Dancey JE, Dobbin KK, Groshen S, Jessup JM, Hruszkewycz AH, Koehler M, Parchment R, Ratain MJ, Shankar LK, Stadler WM, True LD, Gravell A, Grever MR. *Clinical Cancer Research*, 2010;16:1745–1755.

<http://www.ncbi.nlm.nih.gov/pubmed/20215558>

- From the Biomarkers Task Force of the NCI Investigational Drug Steering Committee, this paper presents guidelines for correlative studies and associated clinical assays to clinical investigators who participate in early-phase clinical trials.

American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer, Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, Francis G, Goldstein NS, Hayes M, Hicks DG, Lester S, Love R, Mangu PB, McShane L, Miller K, Osborne CK, Paik S, Perlmutter J, Rhodes

A, Sasano H, Schwartz JN, Sweep FC, Taube S, Torlakovic EE, Valenstein P, Viale G, Visscher D, Wheeler T, Williams RB, Wittliff JL, Wolff AC. *Journal of Clinical Oncology*, 2010;134(6):907–922. <http://www.ncbi.nlm.nih.gov/pubmed/20524868>

- This report presents practice guidelines from the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) for testing for estrogen and progesterone receptors in breast cancer.

American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer,

Harris L, Fritsche H, Mennel R, Norton L, Ravdin P, Taube S, Somerfield MR, Hayes DF, Bast RC, Jr. *Journal of Clinical Oncology*, 2007;25:5287–5312.

<http://www.ncbi.nlm.nih.gov/pubmed/17954709>

- This report presents the ASCO 2007 recommendations for the use of tumor markers in breast cancer.

Colon and Rectum, Jessup JM, Gunderson L, et al. In: Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL et al., editors. *AJCC Cancer Staging Manual, Seventh Edition*. New York, Dordrecht, Heidelberg, London: Springer Publishers. 2009:143–164.

- This chapter is the new, seventh edition of the TNM system that is used for staging all colorectal carcinoma in North America.

ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer,

Locker GY, Hamilton S, Harris J, Jessup JM, Kemeny N, Macdonald JS, Somerfield MR, Hayes DF, Bast RC, Jr. *Journal of Clinical Oncology*, 2006;24:5313–5327.

<http://www.ncbi.nlm.nih.gov/pubmed/17060676>

- This report presents the ASCO 2006 recommendations for the use of tumor markers in gastrointestinal cancers.



Reporting recommendations for tumor marker prognostic studies (REMARK), McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM. *Journal of the National Cancer Institute*, 2005;97:1180–1184.

<http://www.ncbi.nlm.nih.gov/pubmed/16932852>

- Published in six major journals in 2005–2006, the REMARK guidelines are now applied by journal editors and reviewers.

A perspective on challenges and issues in biomarker development and drug and biomarker codevelopment, Taube SE, Clark GM, Dancey JE, McShane LM, Sigman CC, Gutman SI. *Journal of the National Cancer Institute*, 2009;101:1453–1463.

<http://www.ncbi.nlm.nih.gov/pubmed/19855077>

- This is an NCI–FDA white paper developed at the request of the Clinical Trials Working Group.

American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer, Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, Dowsett M, Fitzgibbons PL, Hanna WM, Langer A, McShane LM, Paik S, Pegram MD, Perez EA, Press MF, Rhodes A, Sturgeon C, Taube SE, Tubbs R, Vance GH, van de Vijver M, Wheeler TM, Hayes DF. *Journal of Clinical Oncology*, 2007;25:118–145.

<http://www.ncbi.nlm.nih.gov/pubmed/19548375>

- This paper presents the ASCO–CAP practice guidelines for HER2 testing in breast cancer.



2010 Program
Accomplishments

Cancer Imaging Program



OVERVIEW

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

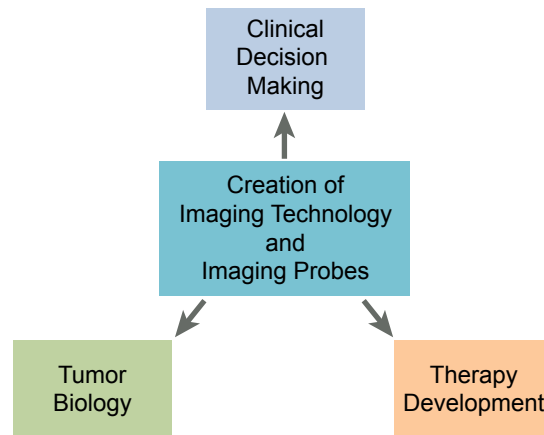
The CIP mission: visualizing the problem and directing the solution:

- Enabling discovery
- Directing development
- Personalizing care

To advance this mission, CIP supports:

- Basic biological research
- Technological innovation to provide tools
- Early-phase clinical trials
- Integration of imaging into therapeutic drug development

Imaging is an enabling scientific discipline combining advanced technology and complex computational and analytic methods to provide a unique ability to extract spatially and temporally defined information from *in vivo* systems. Imaging allows the interrogation of an intact biologic system across the spectrum from subcellular to macroscopic and from discovery to clinical decision making. In the last decade, major advances have been made in our understanding of tumor systems, in part due to advanced imaging that has not only made strides in spatial and temporal resolution but has also progressed from anatomical to functional, physiological, pharmacodynamic, and molecular domains.



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 on creating clearer and more detailed anatomic pictures of organs and tissues. Today, the primary thrust in imaging is functional or molecular imaging, which visualizes the physiological, pharmacodynamic, cellular, or molecular processes in living tissues as they take place. Advanced imaging is critical for fundamental improvements in the care of cancer patients. As NCI continues to discover new molecular signatures of cancer to develop effective therapies with lower morbidity, success can be achieved only by understanding how these targets integrate into complex biological systems. *In vivo* imaging uniquely allows noninvasive visualization of the entire organism in space and over time.

Even more sophisticated and integrated imaging will be required to provide insight into the complex, heterogeneous, and ever-changing biologic system that constitutes cancer. The challenge is to visualize the integrated genomic information needed to understand and manipulate this system through prevention and therapeutic intervention. Imaging will be critical to the

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, and in July 2008 he was named CIP Associate Director, Division of Cancer Treatment and Diagnosis. Dr. Tatum serves as an imaging expert on several NCI steering committees, including the Nanotechnology Characterization Laboratory, a joint effort of NCI, the Food and Drug Administration (FDA), and the National Institute of Standards and Technology; the Small Animal Imaging Program at NCI-Frederick; the Discovery Committee; and the Senior Advisory Committee of the NCI Experimental Therapeutics program (NExT). He frequently serves on FDA advisory panels when imaging applications are under consideration.



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.



understanding of subcellular structural and molecular interactions executed by the proteome-to-cell microenvironment and cell-cell interactions executed by complex signaling and transfer systems. Imaging currently provides information at several places across the genotype-to-phenotype axis, especially at the extremes. At one extreme, imaging is being applied increasingly to evaluate subcellular structure and biology including protein-protein interactions and compartmentalization with unique intracellular microenvironments. At the other extreme, macro-level imaging is used clinically to evaluate phenotypic changes noninvasively on a daily basis.

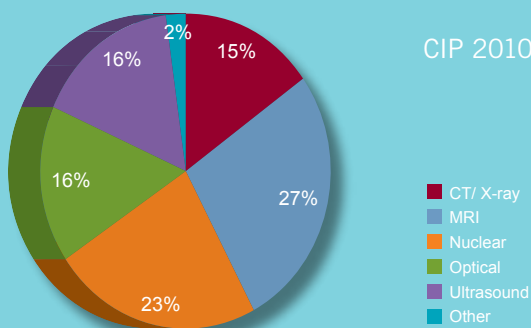
In the next decade, CIP-sponsored research will not only contribute to the basic understanding of various cancers but will also enhance the clinical role of imaging in noninvasive diagnosis, help identify disease subsets in patients, improve disease staging and treatment monitoring, and play a pivotal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

As part of its mission, CIP plays a critical role in the activities of the National Institutes of Health (NIH) and the National Cancer Institute (NCI) contributing to the integration of imaging with emerging



technologies such as nanotechnology, cancer genomics, 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.

The CIP portfolio included 352 funded grants during fiscal year 2010 (see figure, below). Of these, nearly 25% were for multiple modalities.



CIP 2010 Grants by Funding Level Across Various Imaging Modalities

Historical Note

NCI established the Diagnostic Imaging Program in October 1996. The name of the program has changed twice since that time—to “Biomedical Imaging Program” in 2001 and to “Cancer Imaging Program” in 2003—to more clearly reflect the role of the program, to both NCI and the public.

STRUCTURE AND FUNCTION

CIP encourages coordination and collaboration among experts in basic, translational, and clinical research to advance the understanding of cancer through imaging and to create better diagnosis and treatment options for patients. Its mission is to visualize problems and direct solutions by enabling discovery, directing development, and personalizing cancer care. This is done by supporting basic biological research, technological innovation to provide tools, early-phase clinical trials, and integration of imaging into therapeutic drug development.

Extracting relevant information from imaging is a major goal of CIP. More advanced imaging, as well as quantitative and directed approaches, will need to be developed through extensive collaborations to include not only biologists but also systems modelers, bioinformaticists, physicists, and chemists. An emerging example is the application of imaging as part of hypothesis testing and hardening of network models that are derived from available deductive data, including the rapidly growing “omic” space. Similar

CIP Strategic Goals

- Develop and seek approval for a new initiative to fund extramural investigators, including imagers, to design and apply imaging to better understand tumor networks and systems.
- Identify and promote the development of imaging techniques that are applicable to high-priority targets, where imaging could play a pivotal role.
- Integrate imaging biomarker development with conventional biomarker development in the therapy development pipeline as they occur in parallel, providing a more robust biomarker platform for therapy translation.
- Support the development of clinically relevant imaging techniques that do not require the intravenous injection of exogenous contrast agents.
- Expand and improve the correlation of imaging phenotype extraction data with genomic and expression data in parallel with the expansion of The Cancer Genome Atlas to map additional cancers.
- Translate imaging-derived knowledge and techniques to help realize the potential of personalized medicine.



approaches employing complex cell systems have already revealed unanticipated network connectivity when perturbed with drugs. This information has led to refined models that can be used in drug development for predicting not only target response but also toxicity. Recent work using optical imaging in a preclinical model has demonstrated that imaging allows this powerful approach to be used in a preclinical setting with the potential for clinical translation. It is anticipated that such translation will depend heavily on collaboration with ongoing research in nanotechnology.

CIP unites researchers from disciplines as diverse as radiology, nuclear medicine, bioengineering, biology, chemistry, computer science, and physics in a team approach. The program encourages extramural researchers to integrate and apply new imaging discoveries and developments to drug discovery, monitoring of therapies, and understanding cancer biology—all directly aimed at the clinical management of cancer and cancer risk.

CIP Research Areas

CIP activities and responsibilities can be divided into five broad areas:

1. Molecular imaging
2. Clinical trials
3. Image-guided intervention
4. Imaging technology development
5. Imaging informatics

Through this organization, CIP supports extramural investigators in academia and private industry as they create and apply to human disease the next generation of imaging technologies, including molecular

probes, imaging devices, new contrast agents, and image-guided therapies.

Molecular Imaging Branch

The ultimate goal of in vivo cancer molecular imaging by the Molecular Imaging Branch is to provide a definitive, minimally or noninvasive assay of the molecular status of cancer cells and their environment in preclinical models and clinical settings. The realization of that goal requires:

- In vivo molecular imaging agents that detect and report perturbations of genes, gene products, molecular pathways, pharmacodynamics, and physiological processes in cancer
- Imaging technologies capable of detecting rare events at highest resolution in vivo
- Advanced image reconstruction and processing capabilities
- Highly multidisciplinary approaches

CIP supports these approaches primarily through its extramural grant program and also by:

- Filing Investigational New Drug (IND) applications and encouraging suppliers for noncommercial positron emission tomography (PET) molecular imaging agents
- Supporting small-animal imaging to evaluate novel molecular probes and their utility to evaluate therapeutic agents
- Collaboration with the Molecular Imaging Program of the Center for Cancer Research (CCR) and the Molecular Imaging Clinic in the Clinical Center

Clinical Trials Branch

CIP supports clinical trials several ways:

- Grants and contracts to extramural investigators for exploratory trials
- Trials performed with an imaging trial-specific Cooperative Group, the American College of Radiology Imaging Network (ACRIN)
- Phase 1 and 2 Clinical Trials Contract Program
- Trial-related informatics

The Clinical Trials Branch (CTB) oversees and directs all aspects of clinical trials evaluating imaging and image-guided interventions in the phase 0 to phase 3 setting. The overarching theme for CTB is to further the evaluation of imaging in cancer management. The branch serves as the primary CIP liaison with the NCI clinical trial system and ensures that CIP and NCI goals and priorities for imaging are addressed in these activities.

Image-Guided Interventions Branch

The CIP Image-Guided Interventions Branch promotes the integration of imaging, informatics, and interventional methods to address diverse challenges, such as directed biopsy, dimensionality of scale, and targeted drug delivery. The branch is heavily involved in nanotechnology and supports the development of nano-based probes and delivery vectors where imaging plays a significant role in development or application.

Imaging Technology Development Branch

The Imaging Technology Development Branch supports the development and validation of biomedical imaging technology and methods to enable basic research and clinical investigations of cancer biology and treatment responses. Its strategy is characterized by a balanced emphasis on both current generation (commercially supported) imaging platforms and the next generation of imaging platforms. This includes an emphasis on multimodality imaging and methods of quantitative imaging on resolution scales from the molecular level to the organ level.

Imaging Informatics

CIP has been a driver of the development of imaging informatics at NCI to support preclinical, clinical, and technology development for imaging research. CIP was the initial sponsor of the Imaging Workspace of the NCI Cancer Biomedical Informatics Grid (caBIG) effort, and it continues to provide leadership in the development of critical infrastructure in support of cancer imaging research. Major developments over the past five years include establishment of the National Biomedical Imaging Archive, which provides access to more than two terabytes of curated image data in purpose-built collections driven by NCI program agendas, and the generation of standardized vocabularies and case report form templates for cancer imaging trials. CIP is also actively involved in the important area of data integration by supporting and directing a project to integrate imaging and genomic data as part of the activities of The Cancer Genome Atlas (TCGA) activities.



PROGRAM ACCOMPLISHMENTS

Major Ongoing Initiatives

CIP initiatives cover the full spectrum of research efforts from basic research to clinical trials (see figure, below). These programs serve a variety of needs in the cancer imaging community. In addition to many investigator-initiated basic research efforts, several key program announcements use the R01 and R21 grant mechanisms to foster needed research. The In Vivo Cellular and Molecular Imaging Centers (ICMIC), the Network for Translational Research (NTR): Optical Imaging in Multimodality Platforms, and ACRIN each use specialized grant mechanisms suited for their positions in the research pipeline.

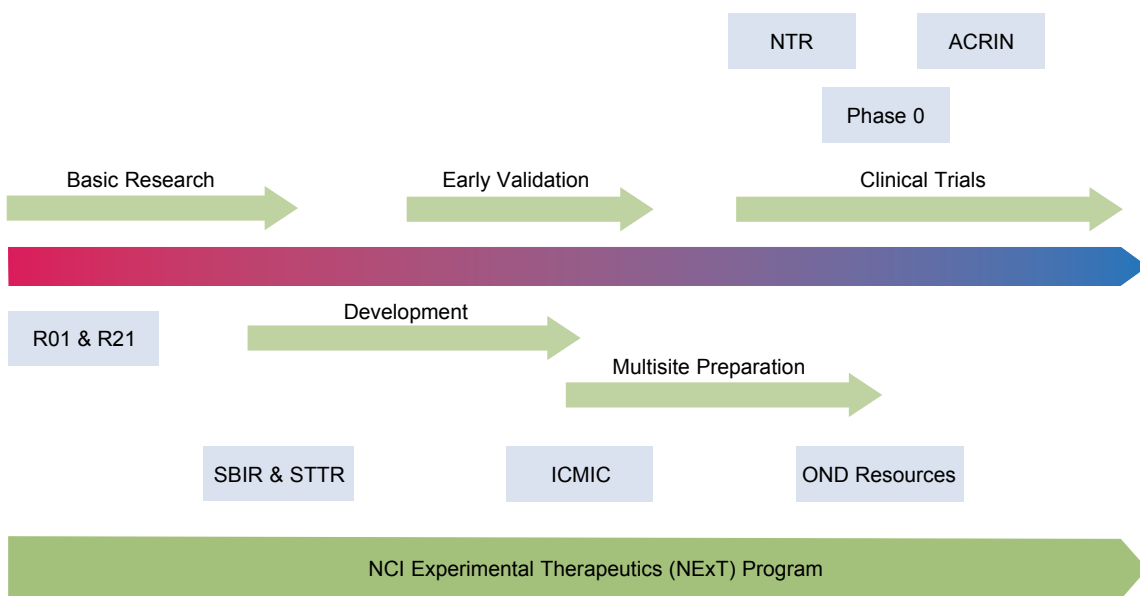
CIP also works in close collaboration with intramural NCI scientists in the development of new imaging probes. A number of these probes are PET agents for

molecular imaging directed at important targets such as angiogenesis and proliferation. This collaboration is bidirectional, forming a novel development pipeline with CCR, which is providing the infrastructure for early clinical trials of imaging probes, and DCTD, which is providing expertise in drug development.

Imaging Drug Group and NCI Experimental Therapeutics Program

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 the 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

IMAGING RESEARCH SPECTRUM AND KEY CIP PROGRAMS

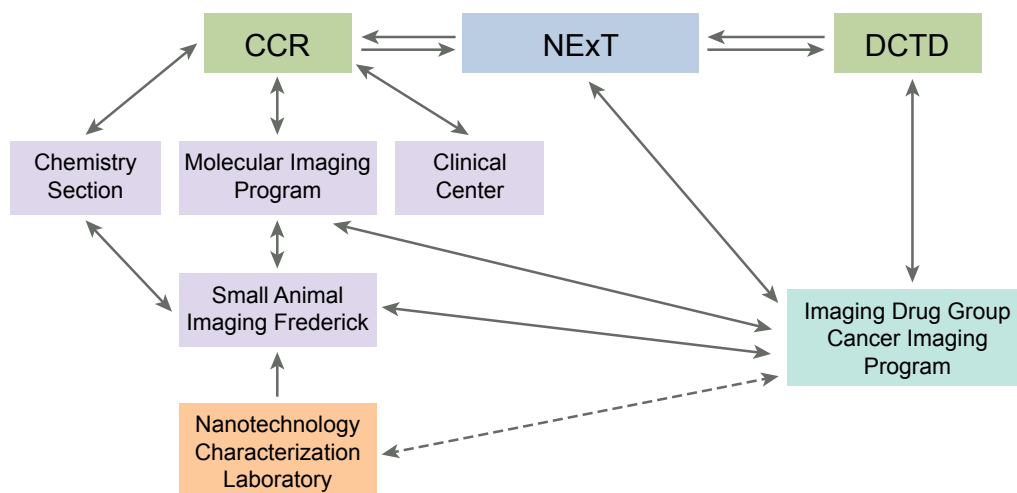


of image-guided therapeutic interventions is just beginning to be realized. However, the ability to provide this information requires significant innovations in imaging probes and systems, especially for molecular imaging agents, where the greatest opportunities and the strongest challenges lie. The 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; integrative cancer biology; strategic development of cancer interventions; and integrated clinical trials. In 2007, this imaging drug development program became the foundation for the Imaging Drug Group (IDG), which 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 in CCR and DCTD. Going forward, the [NCI Experimental Therapeutics \(NExT\)](#) initiative will take on the activities

that the DCIDE program performed. The IDG has also acted in an advisory role with the CCR Molecular Imaging Program and the Small Animal Imaging Program (SAIP-Frederick), as well as the Nanotechnology Characterization Laboratory.

The IDG was 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 the development of such discoveries as high risk (high cost, low potential revenue) that often cannot be justified in an environment of limited resources. Pre-investigational new drug application and early feasibility studies generally cannot be funded through the typical grant mechanisms because they are considered neither original nor novel research.

IMAGING DRUG DEVELOPMENT AT NCI





The NEXt program has now integrated the IDG ideas and resources and provides an excellent mechanism to bridge the gap between new discovery in imaging drugs and delivery of new agents to the cancer patient.

Clinical Trials and the IDG

Although phase 0 and imaging feasibility studies can be performed at the NIH Clinical Center, this venue is not sufficient to perform many studies due to a number of factors, including lack of PET radiochemistry capabilities and limited access to imaging time. CIP is working with academic centers and commercial vendors that have capabilities and patient populations that complement the Clinical Center's capabilities. Using this mechanism, CIP has been able to support extramural efforts to develop imaging drugs.

Later-phase clinical trials, both of imaging drugs and of imaging for the evaluation of therapy, are handled through ACRIN, a Cooperative Group managed 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, exploratory and imaging feasibility trials had been performed outside of the NCI intramural program, in part because of the NCI intramural program's limited access to the radiochemistry and imaging platform resources required to perform such studies. Over the last two years, the intramural Molecular Imaging Clinic has been developed to provide a dedicated research infrastructure for such trials. This facility is now fully

[¹⁸F]Sodium Fluoride New Drug Application

Fluoride ions accumulate in areas of increased osteogenic activity, which occur in both benign and malignant skeletal conditions.

[¹⁸F]Sodium fluoride has been used as a skeletal imaging agent to delineate areas of abnormal osteogenesis, but it is not reimbursed by the Centers for Medicare and Medicaid Services. It can be used for bone scans with PET to diagnose skeletal metastases from primary cancers elsewhere, a serious issue for many cancers, particularly breast and prostate, as well as many nonmalignant skeletal conditions. In 2007, 2.6 million bone scans were performed, the vast majority of them with a technetium agent. However, in the last three years there have been extended widespread shortages of the radiopharmaceutical because of serious problems with the few aging nuclear reactors that manufacture the precursor isotope, and these outages are expected to continue for several more years. Without bone scans, appropriate treatment for metastatic cancer may be delayed or patients may be treated with systemic therapies in the absence of definitive diagnosis, which can lead to unnecessary side effects and inappropriate expense.

In view of the public health impact of these shortages on cancer patient care, CIP filed NCI's first New Drug Application (NDA) for [¹⁸F]sodium fluoride in December 2008 so that the drug, which has a short half-life (2 hours), could be supplied by commercial firms with Drug Master Files for manufacturing the agent. FDA approval, which is expected in late 2010, will facilitate both availability to patients and reimbursement by insurance companies.



Synthesis of radiopharmaceuticals for preclinical investigations.

functional and engaged in performing multiple phase 0 and 1 imaging studies.

Synthesis of Agents

As part of the imaging drug development pipeline, the acquisition of trial-acceptable agents and precursors is a pivotal step to clinical trials. For imaging agents, the commercial interest in production is tempered by limited potential markets. Although there are a few examples of small biotechnology products, most imaging agents of interest are currently downstream markers of nucleic acid, amino acid, or lipid synthesis or 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 for both preclinical and early clinical investigations.

Molecular Imaging Radiopharmaceutical Resources

CIP has filed INDs for some [molecular imaging radiopharmaceuticals](#) to perform multicenter clinical trials and to facilitate access by the wider research community. CIP holds the following active INDs:

- [^{18}F]Fluorothymidine, targeted to areas of increased proliferation
- [^{18}F]Fluoromisonidazole, targeted to hypoxic tissues
- 16α -[^{18}F]Fluoro- 17β -estradiol, targeted to estrogen receptors
- [^{18}F]Sodium fluoride, accumulating in areas of increased osteogenic activity

An IND for [^{18}F]fluorothymidine was filed in 2004, for [^{18}F]fluoromisonidazole in



2006, for 16α - ^{18}F fluoro- 17β -estradiol in 2007, and for ^{18}F sodium fluoride in 2008; all were accepted by the Food and Drug Administration (FDA). To facilitate further clinical research on these radiopharmaceuticals by the research community, a subset of the documents filed in the IND is freely 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, including a full set of manufacturing and quality control documents and an Investigator Drug Brochure. Extramural investigators can establish the synthesis at their sites and then file their own INDs with the FDA. CIP will provide a letter to cross-reference the NCI IND file at the FDA for pharmacology, toxicology, dosimetry, and previous human experience.

In addition, CIP has contracted with three commercial firms that have filed Drug Master Files for the manufacturing and distribution of ^{18}F fluorothymidine and ^{18}F sodium fluoride and one firm for ^{18}F fluoromisonidazole. This effort has made it possible for clinical investigators without radiochemistry facilities to study these agents.

Molecular Imaging

Molecular Imaging Program

The In Vivo Cellular and Molecular Imaging Centers (ICMICs), established in 1999, are five-year P50 grants that support interdisciplinary scientific teams conducting cutting-edge cancer molecular imaging research. There have been nearly 650 ICMIC-supported publications since 2005. ICMIC projects are designed to:

- Support innovative cancer molecular imaging research projects
- Support unique core facilities
- Enable awardees to initiate pilot research in promising new directions
- Provide interdisciplinary career development opportunities for investigators new to the field of molecular cancer imaging

Research supported through the ICMICs has had high impact in a number of areas:

- Enabling technologies:
 - Advances in optical imaging technology, particularly in tomographic imaging
 - Split luciferase constructs for studying protein–protein interactions
- Fundamental discoveries related to cancer biology:

Currently Funded In Vivo Cellular and Molecular Imaging Centers

Emory University: Carolyn Meltzer, PI

Massachusetts General Hospital:
Ralph Weissleder, PI

Memorial Sloan-Kettering Cancer Center:
Steven Larson, PI

Stanford University: Sanjiv Gambhir, PI

University of California, Los Angeles:
Harvey Herschman, PI

University of California, San Diego:
Robert Mattrey, PI

University of Michigan: Brian Ross, PI

Vanderbilt University: John Gore, PI

Washington University: David Piwnicka-Worms, PI

- Investigation of the relationship of hypoxia to breast tumor invasiveness and metastasis
- Direct clinical applications:
 - Combined virus and cell biotherapy
 - Use of the HSV1-sr39tk PET reporter to monitor the treatment of melanoma by genetically modified T-cells
 - Development of a PET probe for imaging T-cell activation
 - Development of magnetic nanoparticles as a clinical product

Intra/Inter-Divisional Collaborations

NCI Cancer Research Imaging Camp.

The [NCI Cancer Research Imaging Camp](#) is a collaboration between DCTD and the Division of Cancer Biology. It is an intensive six-day training course for early-career, basic cancer biologists on in vivo imaging techniques. Through lectures and hands-on laboratory sessions, participants gain experience with a wide range of imaging modalities, including advanced optical imaging, magnetic resonance imaging (MRI), PET, single-photon emission computed tomography (SPECT), computed tomography (CT), and ultrasound. On completion of this course, participants are able to select and apply the appropriate in vivo imaging technique necessary to investigate a biological hypothesis and to interpret the resulting imaging data.

Molecular Imaging and Contrast Agent Database. The [Molecular Imaging and Contrast Database \(MICAD\)](#), established

in 2004, was generated through the NIH Common Fund, which was formerly the NIH Roadmap. It is a collaboration among NCI, the National Library of Medicine, and the NIH Office of the Director. This freely accessible database catalogues, in a comprehensive and easily accessible manner, key research data on in vivo molecular imaging and contrast agents. More than 800 of approximately 4,500 molecular imaging agents have been catalogued.

Future Molecular Imaging Initiatives

Additional research is needed for molecular imaging to realize its full potential of integrating data from disparate biological sources. The discovery and development of agents and technologies to acquire high-resolution in vivo imaging data and the expansion of computational systems approaches to integrate imaging data with biological and “omic” data are necessary.

A proposed interdivisional effort between CIP and the Division of Cancer Biology will support:

- Technologies and methods to advance high-resolution intravital, in vivo microscopic imaging
- Development and validation of cancer-specific in vivo probe and reporter systems
- Integration of micro- and macroscopic data (“Google Earth” for cancer imaging)
- New approaches of modeling, integrating, and visualizing multiscale imaging data



Clinical Trials

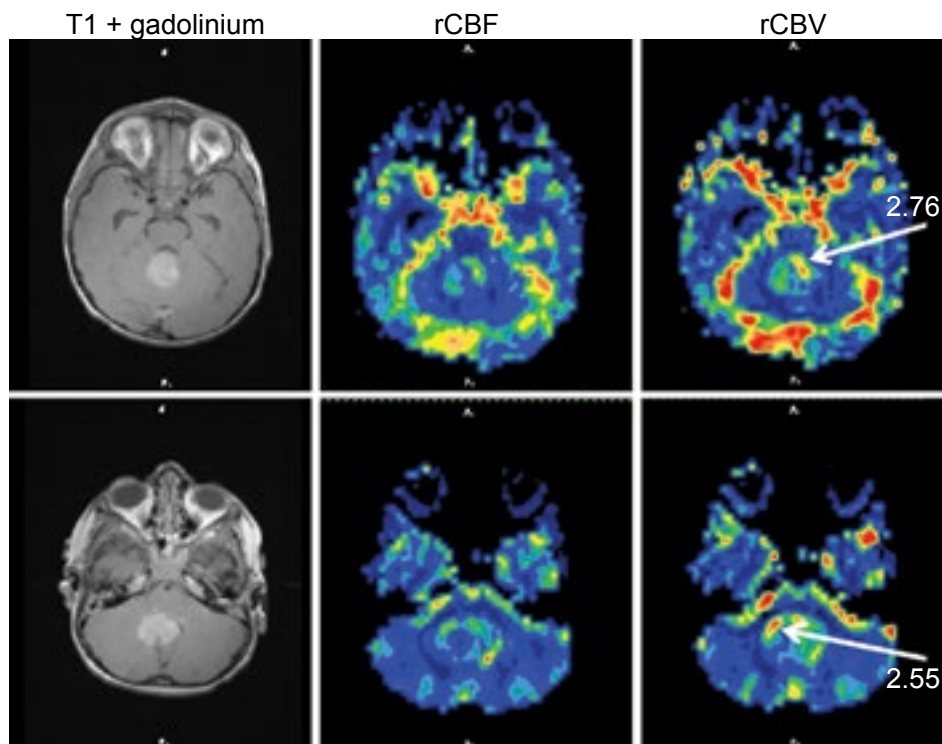
American Recovery and Reinvestment Act

As part of NCI's American Recovery and Reinvestment Act (ARRA) efforts, CIP is providing additional resources over a period of two years for the most promising early-phase trials. The studies receiving funding from this initiative are:

- Three multicenter studies evaluating [^{18}F]fluorothymidine–PET as a predictive marker in cancer therapy of solid tumors (non–small-cell lung cancer, breast cancer, and glioblastoma)
- A multicenter study evaluating [^{18}F]sodium fluoride–PET as a pharmacodynamic biomarker

- Single-center evaluations of the role of iron oxide nanoparticle (ferumoxytol) magnetic resonance to direct brain cancer therapy in both adult and pediatric populations

Images from one of the patients in the pediatric iron oxide study are shown here. The standard-of-care imaging is a T1-weighted magnetic resonance image with gadolinium-based contrast agent. Experimental imaging with ferumoxytol is a dynamic susceptibility-weighted, contrast-enhanced MRI technique that allows determination of relative cerebral blood flow and relative cerebral blood volume in selected areas of the image. Increased flow and volume indicate increased vascularity and may correlate with malignancy.



Dynamic susceptibility-weighted, contrast-enhanced MRI with ferumoxytol contrast in a five-year-old with medulloblastoma prior to surgery. The image shows heterogeneously increased vascularity and a relative cerebral blood volume (rCBV) of 2.55–2.76 in the tumor, despite homogenous gadolinium enhancement. Tumor was confirmed at resection. rCBF = relative cerebral blood flow.

American College of Radiology Imaging Network—A Cooperative Group for Multicenter Imaging Clinical Trials

NCI established the [American College of Radiology Imaging Network \(ACRIN\)](#) to provide a flexible, responsive Cooperative Group for the systematic study of novel and maturing imaging technologies in clinical trials. Funded continually for more than a decade, ACRIN has established and instituted a formal, well-integrated clinical trials infrastructure that represents an exemplary, well-leveraged resource poised to provide significant contributions in the field of research on the comparative effectiveness of advanced imaging techniques.

ACRIN is addressing the special issues of imaging clinical trials (e.g., fast-developing technologies, quality control, operator dependence) while providing multi-disciplinary, multi-institutional, inter-organizational clinical research that provides pertinence, validity, reliability, and generalizability to an extent not possible with single-institution observational studies.

In the face of several significant challenges (absence of a preexisting culture of prospective, controlled clinical trials in radiology, lack of control of patient referral, and the expectation that radiology be service-oriented centers rather than primary research units), ACRIN has established an intrinsically collaborative imaging clinical trials pipeline with ideas

emerging from key scientific committees. It conducts clinical trials that have changed or influenced clinical practice and has established an information technology infrastructure sufficient to provide core services to other NCI- and NIH-sponsored groups. ACRIN serves as a primary source for the dissemination of imaging standards, qualification of sites, core laboratories for PET and CT/MRI, as well as a National PET Registry; and National Coverage Determinations for the Centers for Medicare and Medicaid Services.

Three primary scientific objectives frame the work of ACRIN:

1. Strategies for imaging surveillance of populations at high risk for cancer
2. Imaging approaches to the characterization of disease to guide targeted therapy
3. Biomarkers of therapeutic response from implementation in clinical trials and clinical care

Currently, there are significant delays in the time required to open a clinical trial with advanced imaging as an essential component. To shorten the process, NCI and its partners, ACRIN and the American College of Radiology, plan to develop standard operating procedures and a corresponding guideline for qualifying the 58 clinically focused NCI-designated Cancer Centers as “Centers of Quantitative Imaging Excellence.”



ACRIN Lung Cancer Trial Results Show Mortality Benefit with Low-Dose CT

- Initial results from the [National Lung Screening Trial \(NLST\)](#), released in November 2010, show that current or former heavy smokers between the ages of 55 and 74 who underwent screening with low-dose helical CT at 33 participating sites experienced 20% fewer deaths from lung cancer than a group of peers who received screening with standard chest x-rays.
- NLST is a collaboration between ACRIN and the Lung Screening Study group in NCI's Division of Cancer Prevention. Over 53,000 participants were recruited, more than 3,400 over its initial goal and more than 6 months earlier than expected. The study was designed to have 90% statistical power to detect progressively smaller mortality effects. With a large number of participants in a randomized, controlled trial, NLST provides clear evidence that a screening procedure can be effective in reducing mortality from lung cancer.
- Starting in August 2002, NLST enrolled about 53,500 men and women at 33 trial sites nationwide over 20 months. Participants were required to have a smoking history of at least 30 pack-years and were either current or former smokers without signs, symptoms, or history of lung cancer. Pack-years are calculated by multiplying the average number of packs of cigarettes smoked per day by the number of years a person has smoked.
- An ancillary finding of the study, which was not the main endpoint of the trial's design, showed that all-cause mortality (deaths due to any factor, including lung cancer) was 7% lower in those screened with low-dose helical CT than in those screened with chest x-ray. Approximately 25% of deaths in the NLST were due to lung cancer; other deaths were due to factors such as cardiovascular disease.



- The ACRIN-NLST participating sites contributed to a biorepository (blood, sputum, urine), a tissue bank for future biomarker research, and the evaluation of quality-of-life issues, cost-effectiveness assessments, and the impact of screening with low-dose helical CT versus chest x-ray on smoking cessation.
- Further analysis and research will be required to fully understand the implications of these results and those of the secondary aims. Analysis of the full data set related to the primary aim is ongoing; submission of the primary manuscript is anticipated in the first quarter of 2011.



Collaboration with the Cancer Treatment Evaluation Program

As a member of the Cancer Treatment Evaluation Program (CTEP) Protocol Review Committee, CIP helps to identify opportunities for the evaluation of therapeutic response, such as demonstration projects evaluating functional imaging techniques in the assessment of response to therapy. CIP physicians are also primary reviewers and subsequent monitors for imaging-related concepts and clinical trials for molecular and functional imaging endpoints. They also ensure that NCI consensus guidelines for acquisition and interpretation of various imaging modalities are implemented.

Phase 1 and 2 Program for the Evaluation of Molecular and Functional Imaging Agents

A contract-supported infrastructure supports phase 1 (safety) and phase 2 (preliminary efficacy) clinical trials of promising imaging agents. This mechanism is evaluating the use of molecularly targeted and functional imaging agents to assess therapeutic anticancer agents. The goal of the program is to provide a mechanism to expedite the development of promising molecular probes from the laboratory to IND status as well as early clinical trials. Established because its projects are not competitive in the regular grant pool, the



program focuses on studying imaging agents in a standardized setting to evaluate reproducibility and translatability across different histologies, which is necessary for assay development. The program is evaluating nine methodologies in tumors including non–small-cell lung cancer, breast, cervical, prostate, and glioma.

Future Phase 2 Initiative

Under development by CIP and CTEP is a phase 2 consortium that includes advanced imaging support. Reflecting the need to incorporate novel imaging endpoints in the development of investigational agents, this recompleted phase 2 N01 program will include the integration of molecular imaging with investigational drug development. Participation in this program will require the inclusion of sites which have undergone qualification for advanced imaging and have identified nuclear medicine physicians and radiologists to be an integral part of the drug development team. This contract will support, in selective phase 2 treatment trials, the evaluation of molecular and functional imaging agents, in a standardized, prospective fashion to enable the evaluation of the core issues of preliminary efficacy as well as technical performance issues (reproducibility and quantitative vs. semi-quantitative analysis) that are often lacking in current trials. The imaging agents and methods that prove successful in these early clinical trials can then be validated in larger studies through clinical trials in Cancer Centers or Cooperative Groups.

Quick Trials for Imaging and Imaging-Guided Interventions

Rapid translation of promising imaging discoveries to clinical practice requires timely support that can be provided by Quick Trials. CIP sponsors a Quick Trials program announcement, [PAR-08-147](#), to provide investigators with rapid access to support through the R21 grant mechanism for pilot, phase 1, and phase 2 cancer clinical trials. In addition, the grants can be used for research on patient monitoring and laboratory studies for the preliminary evaluation of the safety and efficacy of imaging agents, as well as assessment of imaging systems, image processing, image-guided therapy, contrast kinetic modeling, three-dimensional reconstruction, and quantitative tools. The imaging and imaging-guided intervention (IGI) studies that prove successful in these early clinical trials can then be validated in larger studies through competitive R01 mechanisms or clinical trials in SPOREs, Cancer Centers, or Cooperative Groups.

National NCI Steering Committees

CIP has active representation in the national disease-specific and investigational drugs steering committees that were developed based on the recommendations of the [Clinical Trials Working Group \(CTWG\)](#). Members of CIP's Clinical Trials Branch bring perspective to the trial planning process regarding available and developing imaging tools that can help evaluate cancer patients and inform their consequent management.

In 2010, the formation of a Clinical Imaging Steering Committee (CISC) was approved. CISC is also a component of the network of committees recommended by CTWG. The CISC is a forum for the extramural imaging and oncology communities to provide strategic input to NCI regarding the significant investment in imaging activities in clinical trials. The CISC is charged with providing analyses of proposed clinical trial imaging concepts and imaging components of concepts and facilitating the sharing of ideas among a broad range of investigators, including radiologists and nuclear medicine physicians specializing in anatomic, molecular, and functional imaging; basic and translational scientists; NCI staff; community oncologists; community imagers; and patient advocates.

Biomarker Evaluation

CIP works with a variety of groups and task forces on guidelines defining the standards appropriate for adding biomarkers to therapeutic trials and for evaluating biomarkers alone. These guidelines will form the basis for funding opportunities for clinical trials in both early and late drug development. There are multiple collaborations with:

- Biomarker task force and clinical trial design task forces of the Investigational Drug Steering Committee
- Program for the Assessment of Clinical Cancer Tests (PACCT)
- Oncology Biomarker Qualification Initiative—two demonstration projects

evaluating fluorodeoxyglucose PET as a biomarker in lymphoma and lung cancer

- Interagency Oncology Task Force

Response Assessment Evaluation

In association with the European Organisation for Research and Treatment of Cancer (EORTC), NCI's Response Evaluation Criteria in Solid Tumors (RECIST) committee has developed updated guidelines for the assessment of response to therapy by anatomic imaging. These organizations are also formulating a joint guideline for the use of quantitative fluorodeoxyglucose PET in the assessment of tumor response in clinical trials. CIP is also supporting the development of a proposal for an infrastructure for the implementation of RECIST—an FDA-acknowledged imaging methodology for clinical trial endpoints where noninvasive imaging is required to track tumor change over time.

For the Agency for Healthcare Research and Quality (AHRQ), CIP staff members have served as reviewers for CMS-related evaluation of the application for Medicare reimbursement for fluorodeoxyglucose PET in glioma, pancreatic, ovarian, cervical, testicular, and small-cell lung cancer.

An NCI-CMS task force has successfully implemented strategies to extend CMS reimbursement for fluorodeoxyglucose PET studies in all NCI-sponsored phase 2 and 3 therapeutic clinical trials.

As part of the trans-NCI International Trials Collaboration Group, CIP has been working on identifying both barriers and opportunities for enhanced participation in international trials.



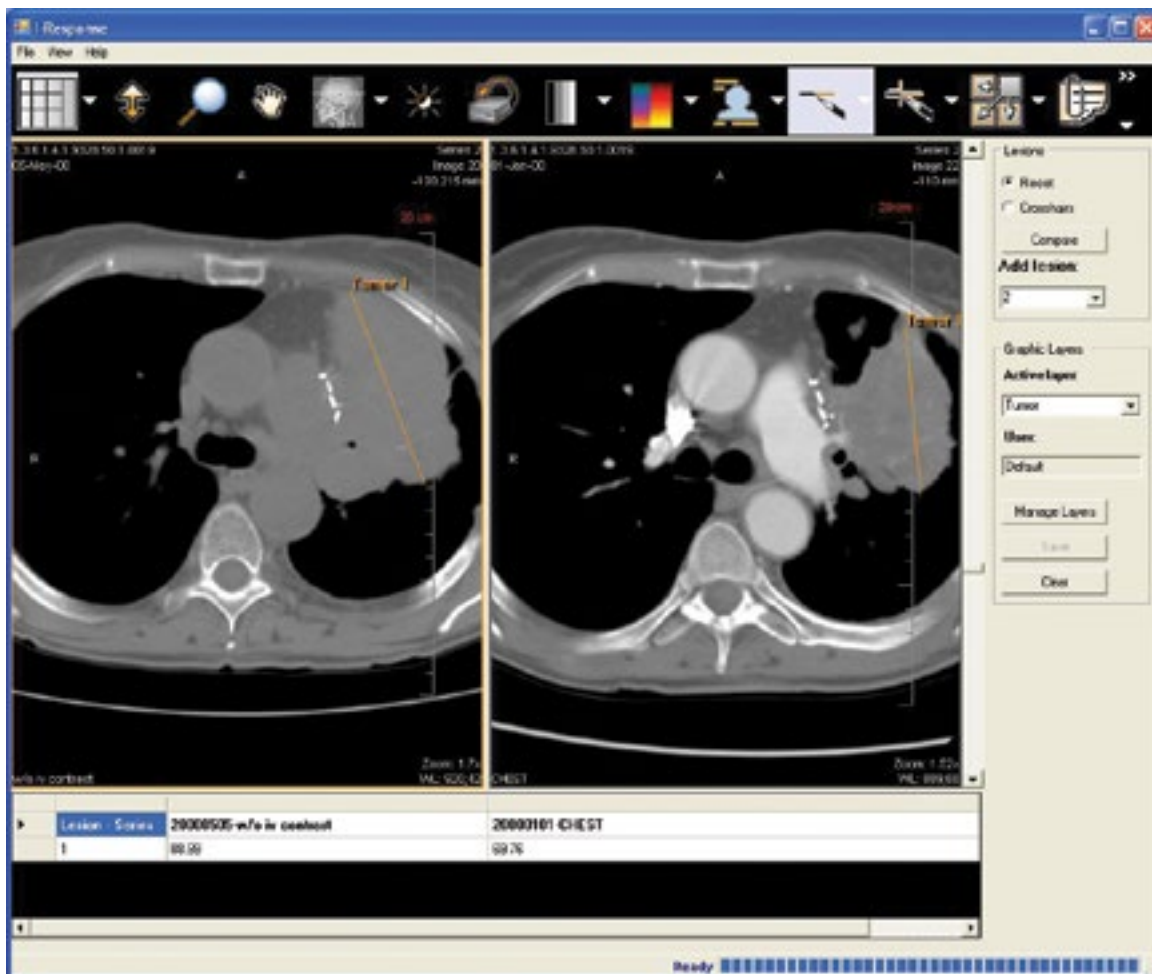
Clinical Trial Information Technology Infrastructure

Because of the efforts of CIP's Clinical Trials Branch, NCI has successfully launched the revised Adverse Event Expedited Reporting System (AdeERS), an electronic mechanism that will for the first time capture severe adverse events in imaging and image-guided interventions studies. In addition, a customizable clinical metadata system—C3D—has been successfully adopted in six imaging protocols at phase 1/2 contract sites and is being piloted in an ACRIN trial.

Simultaneously, the common data element directory for imaging trials has been growing and is being shared across ACRIN and other Cooperative Groups trials.

Image-Guided Intervention

Extramural funding of IGI-related research at NCI includes traditional P01, R01, R21, R33, Small Business Technology Transfer (STTR) (R41/R42), and Small Business Innovation Research (SBIR) (R43/R44) grants, as well as a one-time issuance of four two-year administrative supplements



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

for SPOREs in 2005. Since 2002, there have been several IGI-related Program Announcements at NCI. These programs continue and include SBIR/ STTR, exploratory R21, and R01 initiatives:

- **Image-Guided Interventions (SBIR) PA-10-079 and (STTR) PA-10-080:** The overall goals of the IGI initiative are to provide support for the development and optimization of fully integrated cancer imaging, monitoring, and therapy systems and the validation of integrated IGI systems through clinical evaluations. These initiatives were adopted by the NCI SBIR Development Center and were recently reissued.
- **Quick Trials for Imaging and Image-Guided Interventions:** Exploratory Grants (R21), [PAR-08-147](#), was summarized previously (see “Quick Trials for Imaging and Imaging-Guided Interventions”).
- **Image-Guided Drug Delivery in Cancer (R01), PA-09-253:** The Imaging-Guided Drug Delivery (IGDD) initiative encourages innovative translational research in the development of quantitative in vivo imaging characterization of IGDD in cancer, including characterizations of the target, delivery validation, and therapy response. This initiative will support research in the development of integrated imaging-based platforms for multifunctional and multiplexed drug delivery systems in cancer. Validation studies in nonhuman primates or large animal models and first-in-human studies directed toward translation of IGDD technology into the clinic are appropriate for this initiative. A goal of this research is the development of minimally invasive or noninvasive “theranostic” (combined diagnostic and

therapeutic) approaches to cancer in order to optimize the therapeutic ratio and to provide quantitative imaging evaluation of therapy. These grants will also support the development of techniques to identify and modulate features of the tumor micro-environment for selective drug targeting and release. Imaging will not only play a major role in the development of such techniques but may well guide their delivery and release. The first application receipt date for this initiative was February 5, 2010, resulting in 12 pending applications. This initiative was developed in collaboration with the NCI Alliance for Nanotechnology in Cancer.

Previous IGI Program Announcements include the Academic–Industrial Partnerships for the Development and Validation of In Vivo Imaging Systems and Methods for Cancer Investigators (R01) and Quantitative Imaging for Evaluation of Response to Cancer Therapies (U01).

For the future, the challenge for IGI is to apply image-guided techniques in unique applications to address tumor complexity and heterogeneity. Major emphasis will be placed on improved methods for rational and directed biospecimen identification and collection. It is critical to address the issue of co-correlation at vastly different physical scales and the integration of such disparate data to allow valid alignment of imaging-defined phenotypes with biologic characteristics. Developing techniques that minimize the intrinsic errors of random sampling and alignment are not trivial but essential to advancing the understanding of human cancer.



Imaging Technology

Image Database Consortia

The creation of image database consortia has stimulated the development of more standardized methods for quantitative imaging by not only the academic research community, but also professional imaging societies such as the Radiological Society of North America (RSNA), the Society of Nuclear Medicine (SNM), the American Association of Physicists in Medicine (AAPM) and the International Society of Magnetic Resonance in Medicine (ISMRM). In addition, the FDA is reviewing how to incorporate these resources in the process of accelerating FDA approval of clinical decision tools.

Network for Translational Research for Optical and Multimodal Imaging Platforms

The [Network for Translational Research \(NTR\): Optical Imaging in Multimodality Platforms](#) is an outgrowth of an earlier network, the Network for Translational Research in Optical Imaging (NTROI), which addressed the logistical and research issues of translating imaging methods to the clinical setting. The research scope was expanded to include the integration of multimodal and molecular imaging methods with optical imaging methods, including nanocarriers and nanoproboscopes.

This new network, consisting of four centers, has developed several leading-edge multimodal platforms, such as opto-acoustic tomography, optical-nuclear tomography, and catheter-based combined optical–US miniaturized detectors targeted at relevant cancer problems. NTR members are engaged in the development of consensus-based

strategies to validate these new technologies in partnership with more than 20 industry partners. An important organizational feature of the NTR is the structure of working groups, called research support cores. These cores do not reside within the individual centers but work across all centers to solve common problems that arise in imaging research, such as initiation of Good Laboratory Practices (GLP) and establishment of standard operating procedures. The network's success is partly attributable to the fact that it is highly leveraged with other NCI funding initiatives, such as NCI's P50 molecular imaging centers and the Nanotechnology Alliance. Scientists from FDA and the National Institute of Standards and Technology are active participants in this network.

Quantitative Imaging Network for the Measurement of Therapy Response

Quantitative Imaging Network (QIN) teams have created multidisciplinary teams of oncologists, radiologists, medical physicists, and computer informatics scientists. During the first steering committee meeting, in March 2009, members agreed to populate an NCI public resource with prospective data from several clinical trial networks and compare the performances of academic software tools and modeling methods against this database.

Future Imaging Technology Initiatives

In 2010, the Cancer Research UK agreed to have its four molecular imaging centers collaborate with NCI's QIN and NTR to develop international resources for quantitative imaging.

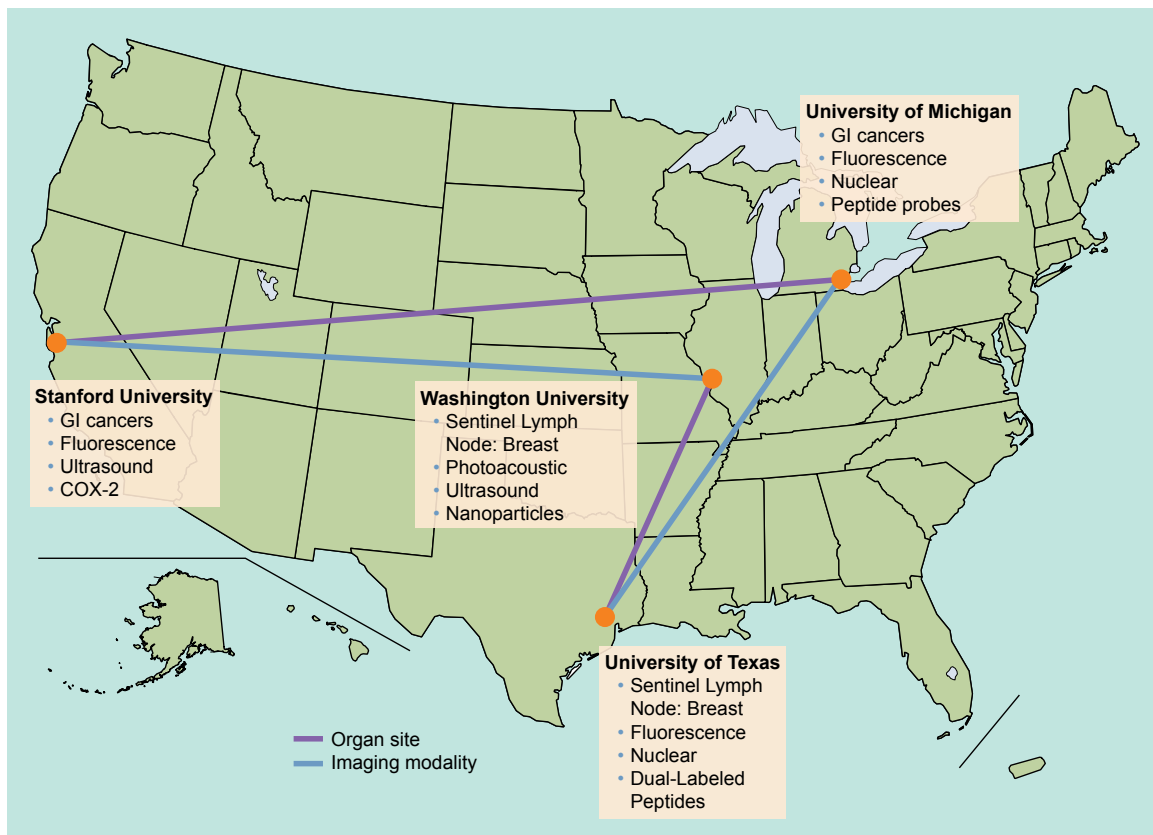
As progress is made in the development of novel therapies directed at several molecular targets, it is important to ensure that the performance of current and next-generation imaging platforms is maintained for basic and clinical research investigations for several years. To meet these increasing performance requirements, it is important to leverage research resources and maintain consensus on imaging standards across NIH and international funding agencies. Specific foci include:

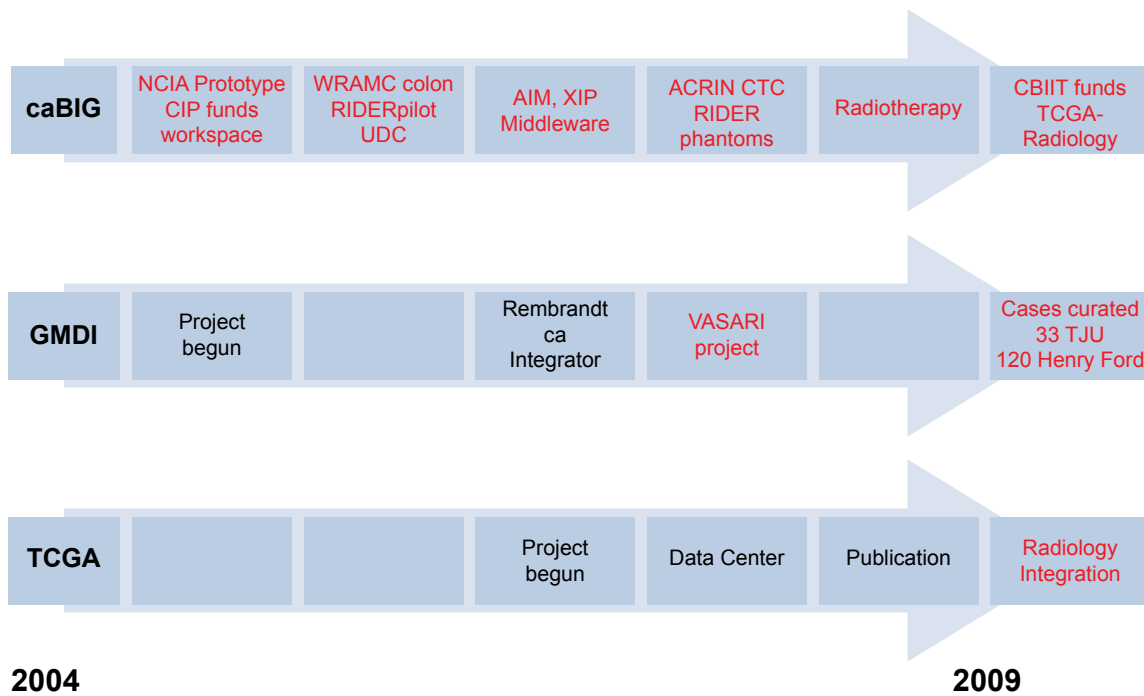
- QIN: Informatics and imaging archiving to host the anticipated exponential growth of shared images and metadata while meeting caBIG interoperability

standards required for data integration—clinical decision making

- NTR: Expand the range of the imaging platforms to be developed and validated to provide the imaging tools necessary to support CIP interest in the role addressing “systems biology” in vivo, such as multiparametric imaging of stem cell pathways. An example initiative is the emerging role of microMRI for imaging at resolution scales close to the cellular level with the potential for enhanced investigations of metastatic cancer with several orders of magnitude of improvement in sensitivity, particularly for preclinical investigations.

NETWORK FOR TRANSLATIONAL RESEARCH CENTERS AND METHODS OF INTERCONNECTIVITY





Imaging informatics (CIP activities in red).

Imaging Informatics

National Biomedical Imaging Archive

The [National Biomedical Imaging Archive \(NBIA\)](#) provides a multiplicity of research image data collections that encourage the development of reliable, quantitative measurement of change over time by supplying temporally longitudinal clinical response imaging studies to a wide research community. The archive sets the stage for real-time, multi-institutional image accessibility that could support protocol stratification strategies in adaptive trials and enables cross-disciplinary research on

response measurement fundamentals and analysis reproducibility studies.

NBIA, developed in concert with caBIG, of the NCI Center for Biomedical Informatics and Information Technology, is a scalable, Web-accessible image repository. The archive was developed to support the image processing community's goals of advancing computer-aided diagnosis and hybrid human-machine detection of disease. As of 2009, the image repository contained more than 2.5 terabytes of curated image data and more than 4 million images from a range of clinical

THE NATIONAL BIOMEDICAL IMAGING ARCHIVE WEBSITE



imaging instruments, including CT, MRI, PET/CT, and radiation therapy.

Currently, 11 public and nine restricted-access collections are available to researchers. Included in the archive are images associated with multiple high-profile scientific initiatives in the imaging community.

Complementary to the archive has been the development of advanced, standards-based tools to enable de-identification of medical image data for public consumption. In collaboration with the Radiological Society of North America, a Clinical Trial Processor tool has been modified to operationalize current de-identification guidelines from Digital Imaging and Communications in Medicine (DICOM).



Future Informatics Initiatives

CIP continues to host curated image collections in support of ongoing clinical trials and active research activities. An important focus of ongoing and future informatics activities is to collect, curate, and characterize image data for cases populating TCGA data sets. So far, considerable progress has been made with the glioblastoma collection.

CIP is pursuing informatics projects that link imaging characteristics with molecular data from brain tumors in the REMBRANDT (Repository of Molecular Brain Neoplasia Data)/VASARI (Visually Accessible REMBRANDT Images) and TCGA/Data Portal initiatives. REMBRANDT, a joint initiative of the NCI and the National Institute of Neurological Disorders and Stroke, was launched in 2005. The repository hosts publicly accessible data from molecular research and clinical trials related to brain cancers, including gliomas

and astrocytomas, along with a wide variety of Web-based analysis tools to facilitate understanding of critical correlations among the different brain tumors.

Already, REMBRANDT information has been used to mount MRI images from more than 150 cases to give network accessibility to cross-disciplinary researchers wishing to study phenome-to-genome connectivity. By using these cases, a set of imaging features were developed to explore phenome-to-genome correlations.

CIP has also provided resources for the development and curation of case report forms for five phase 2 imaging clinical trials. CIP leveraged the NCI caBIG Cancer Central Clinical Database (C3D) clinical trial management system so that the resulting terminologies and form templates have been registered for reuse in the NCI Cancer Data Standards Repository.

SELECTED PUBLICATIONS

From 2005 to 2010, nearly 3,000 papers were published by CIP grantees:

- 1.5% in journals with impact factor greater than 20
- 3.5% in journals with impact factor 10–20
- 21% in journals with impact factor 5–10

Image-guided, noninvasive, spatiotemporal control of gene expression, Deckers R, Quesson B, Arsaut J, Eimer S, Couillaud F, Moonen CT. Proceedings of the National Academy of Sciences of the United States of America, 2009;106:1175–1180.

<http://www.ncbi.nlm.nih.gov/pubmed/19164593>

- A direct, noninvasive, and non-ionizing method, using magnetic resonance–guided focused ultrasound in combination with a heat-inducible promoter (HSP70), was used for the in vivo spatiotemporal control of transgene activation.

Diagnostic parameters to differentiate benign from malignant ovarian masses with contrast-enhanced transvaginal sonography, Fleischer AC, Lyshchik A, Jones HW III, Crispens MA, Andreotti RF, Williams PK, Fishman DA. Journal of the Institute of Ultrasound in Medicine, 2009;28:1273–1280.

<http://www.ncbi.nlm.nih.gov/pubmed/19778872>

- Data from this successful R21 study with potential high public health impact suggest that prospective analysis of the AUC, peak enhancement, and the half wash-out time provide the greatest diagnostic accuracy for contrast-enhanced transvaginal sonography in the differentiation between benign and malignant ovarian masses. If validated in a multicenter setting, this widely available, low-cost tool has the potential to optimize global patient care.

In vivo magnetic enrichment and multiplex photoacoustic detection of circulating tumour cells, Galanzha EI, Shashkov EV, Kelly T, Kim JW, Yang L, Zharov VP. Nature Nanotechnology, 2009;4:855–860.

<http://www.ncbi.nlm.nih.gov/pubmed/19915570>

- Circulating tumor cells in the bloodstream of mice can be detected by rapid photoacoustic methods, then receptor bound and magnetically captured. Gold-plated carbon nanotubes conjugated with folic acid were used as a second contrast agent for photoacoustic imaging to improve detection sensitivity and specificity. This approach allows circulating tumor cells to be concentrated from a large volume of blood, with potential for the early diagnosis of cancer and the prevention of metastasis in humans.

Role of imaging in pretreatment evaluation of early invasive cervical cancer: results of the intergroup study American College of Radiology Imaging Network 6651–Gynecologic Oncology Group 183, Hricak H, Gatsonis C, Chi DS, Amendola MA, Brandt K, Schwartz LH, Koelliker S, Siegelman ES, Brown JJ, McGhee RB, Jr, Iyer R, Vitellas KM, Snyder B, Long HJ III, Fiorica JV, Mitchell DG. Journal of Clinical Oncology, 2005;23:9329–9337.

<http://www.ncbi.nlm.nih.gov/pubmed/16361632>

- This study is the first and largest intergroup, multicenter study to compare cervical cancer staging by International Federation of Gynecology and Obstetrics (FIGO) clinical staging, CT, and MRI in women with early-stage cervical carcinoma using surgicopathologic findings as the reference standard. Results of this study suggest that the inclusion of CT and/or MRI may result in significantly improved clinical staging.



Regulation of transgenes in three-dimensional cultures of primary mouse mammary cells demonstrates oncogene dependence and identifies cells that survive deinduction, Jechlinger M, Podsypanina K, Varmus H. *Genes & Development*, 2009;23:1677–1688.

<http://www.ncbi.nlm.nih.gov/pubmed/19605689>

- The development of a three-dimensional culture system that allows the study of oncogene dependence in primary mouse mammary epithelial cells provides a more rapid and less costly system than transgenic mice in which to analyze responses to induction and deinduction of oncogenes.

Diffusion-weighted magnetic resonance imaging for predicting and detecting early response to chemoradiation therapy of squamous cell carcinomas of the head and neck, Kim S, Loevner L, Quon H, Sherman E, Weinstein G, Kilger A, Poptani H. *Clinical Cancer Research*, 2009;15:986–994.

<http://www.ncbi.nlm.nih.gov/pubmed/19188170>

- This study evaluated the utility of apparent diffusion coefficient (ADC) in the prediction and early detection of the response to therapy in head and neck squamous cell carcinomas and concluded that ADC is an accurate marker for both the prediction and early detection of response to chemoradiation therapy in these cancers.

Noninvasive localized delivery of Herceptin to the mouse brain by MRI-guided focused ultrasound-induced blood-brain barrier disruption, Kinoshita M, McDannold N, Jolesz FA, Hynynen K. *Proceedings of the National Academy of Sciences of the United States of America*, 2006;103:11719–11723.

<http://www.ncbi.nlm.nih.gov/pubmed/16868082>

- The first report on noninvasive local delivery of Herceptin through the blood–brain barrier under MRI guidance in a mouse model shows

that this method has potential for noninvasive treatment of brain metastasis.

MRI evaluation of the contralateral breast in women with recently diagnosed breast cancer, 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. *New England Journal of Medicine*, 2007;356:1295–1303.

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

- This study, an excellent example of how imaging clinical trials can inform clinical practice, demonstrated the benefit of adding an MRI study of the contralateral breast to the standard diagnostic work-up following a new diagnosis of breast cancer. Finding cancer in the opposite breast at the time of initial diagnosis will affect the need for, and stress induced by, multiple or delayed treatments, cost, and potentially, morbidity.

Combined transductional untargeting/retargeting and transcriptional restriction enhances adenovirus gene targeting and therapy for hepatic colorectal cancer tumors, Li HJ, Everts M, Yamamoto M, Curiel DT, Herschman HR. *Cancer Research*, 2009;69:554–564.

<http://www.ncbi.nlm.nih.gov/pubmed/19147569>

- This report presents an example of integrating advanced imaging approaches in the design and targeting of clinically relevant gene therapy vehicles.

LRP6 overexpression defines a class of breast cancer subtype and is a target for therapy, Liu CC, Prior J, Piwnicka-Worms D, Bu G. *Journal of the National Academy of Sciences of the United States of America*, 2010;107:5136–5141.

<http://www.ncbi.nlm.nih.gov/pubmed/20194742>

- This study is an excellent example of a multidisciplinary approach to the identification and validation of LRP6 as a therapeutic target using in vivo imaging technologies.

[¹⁸F]Fluorodeoxyglucose positron emission tomography correlates with Akt pathway activity but is not predictive of clinical outcome during mTOR inhibitor therapy, Ma WW, Jacene H, Song D, Vilardell F, Messersmith WA, Laheru D, Wahl R, Endres C, Jimeno A, Pomper MG, Hidalgo M. *Journal of Clinical Oncology*, 2009;27:2697–2704.

<http://www.ncbi.nlm.nih.gov/pubmed/19380450>

- A clinical trial and preclinical studies in murine models demonstrated that [¹⁸F]fluorodeoxyglucose (FDG)–PET is not predictive of proliferative response to mTOR inhibitor therapy. The findings suggest that mTOR inhibitors suppress the formation of mTORC2 complex, resulting in the inhibition of Akt and glycolysis independent of proliferation in a subset of tumors. Changes in FDG-PET may be a pharmacodynamic marker for Akt activation during mTOR inhibitor therapy. FDG-PET may be used to identify patients with persistent Akt activation following mTOR inhibitor therapy.

The functional interplay between EGFR over-expression, hTERT activation, and p53 mutation in esophageal epithelial cells with activation of stromal fibroblasts induces tumor development, invasion, and differentiation, Okawa T, Michaylira CZ, Kalabis J, Stairs DB, Nakagawa H, Andl CD, Johnstone CN, Klein-Szanto AJ, El-Deiry WS, Cukierman E, Herlyn M, Rustgi AK. *Genes & Development*, 2007;21:2788–2803. <http://www.ncbi.nlm.nih.gov/pubmed/17974918>

- Using pharmacological and genetic approaches to decrease MMP-9, invasion into the underlying extracellular matrix could be partially suppressed. Tumor differentiation was influenced by the type of fibroblasts within the stromal extracellular matrix. Methods from Western blots through whole mouse imaging of tumor cells with fluorescence were used in the research. Taken together, alterations in key oncogenes

and tumor suppressor genes in esophageal epithelial cells, the composition and activation of fibroblasts, and the components of the extracellular matrix conspire to regulate the physical and biological properties of the stroma.

Visualizing fewer than 10 mouse T cells with an enhanced firefly luciferase in immunocompetent mouse models of cancer, Rabinovich BA, Ye Y, Etto T, Chen JQ, Levitsky HI, Overwijk WW, Cooper LJ, Gelovani J, Hwu P. *Proceedings of the National Academy of Sciences of the United States of America*, 2008;105:14342–14346. <http://www.ncbi.nlm.nih.gov/pubmed/18794521>

- This report addresses the long-standing problem of how to express firefly luciferase in mouse T cells at sufficient magnitude to achieve signal intensity suitable to detect fewer than 10,000 T cells at a given location in a mouse. The study demonstrates enumeration of infiltrating mouse lymphocytes consisting of less than 0.3% of total cellularity, representing a significant improvement over standard quantitative methods, including flow cytometry.

Reduction of TRAIL-induced Mcl-1 and cIAP2 by c-Myc or sorafenib sensitizes resistant human cancer cells to TRAIL-induced death, Ricci MS, Kim SH, Ogi K, Plataras JP, Ling J, Wang W, Jin Z, Liu YY, Dicker DT, Chiao PJ, Flaherty KT, Smith CD, El-Deiry WS. *Cancer Cell*, 2007;12:66–80. <http://www.ncbi.nlm.nih.gov/pubmed/17613437>

- The team investigated whether c-Myc action on the mitochondria is required for TRAIL sensitivity and found that Myc sensitized cells with defective intrinsic signaling to TRAIL. TRAIL induced expression of antiapoptotic Mcl-1 and cIAP2 through activation of NF-κB. Both Myc and the multi-kinase inhibitor sorafenib block NF-κB. Combining sorafenib with TRAIL in vivo



showed dramatic efficacy in TRAIL-resistant tumor xenografts, so the combination of TRAIL with sorafenib holds promise for further development.

Association between rectal optical signatures and colonic neoplasia: potential applications for screening,

Roy HK, Turzhitsky V, Kim Y, Goldberg MJ, Watson P, Rogers JD, Gomes AJ, Kromine A, Brand RE, Jameel M, Bogovejic A, Pradhan P, Backman V. *Cancer Research*, 2009;69:4476–4483.

<http://www.ncbi.nlm.nih.gov/pubmed/19417131>

- This study determined that the micro-architecture of uninvolved rectal mucosa is altered in subjects harboring neoplasia elsewhere in their colon and may allow cancer risk stratification for colon cancer using biomedical optics. The potential impact on clinical practice would be that primary care practitioners would be able to determine either the need or timing for optical colonoscopy, saving both lives and dollars.

Imaging biomarkers predict response to anti-HER2 (ErbB2) therapy in preclinical models of breast cancer,

Shah C, Miller TW, Wyatt SK, McKinley ET, Olivares MG, Sanchez V, Nolting DD, Buck JR, Zhao P, Ansari MS, Baldwin RM, Gore JC, Schiff R, Arteaga CL, Manning HC. *Clinical Center Research*, 2009;15:4712–4721.

<http://www.ncbi.nlm.nih.gov/pubmed/19584166>

- This study evaluated noninvasive methods of imaging as predictive biomarkers (apoptosis, glucose metabolism, and cell proliferation) of response to trastuzumab in mouse models of breast cancer with HER2 overexpression compared to nonresponding tumor-bearing cohorts. Results indicate the value of further clinical evaluation of both apoptosis and [¹⁸F]fluorothymidine PET as a biomarker of response to trastuzumab in HER2-positive breast cancer.

Imaging the pharmacodynamics of HER2 degradation in response to Hsp90 inhibitors,

Smith-Jones PM, Solit DB, Akhurst T, Afroze F, Rosen N, Larson SM. *Nature Biotechnology*, 2004;22:701–706.

<http://www.ncbi.nlm.nih.gov/pubmed/15133471>

- This report describes the use of ⁶⁸Ga-labeled anti-HER2 F(ab')₂ fragment to quantify the loss and recovery of HER2 induced by 17-AGG in animal tumors.

The FLARE intraoperative near-infrared fluorescence imaging system: a first-in-human clinical trial in breast cancer sentinel lymph node mapping,

Troyan SL, Kianzad V, Gibbs-Strauss SL, Gioux S, Matsui A, Oketokoun R, Ngo L, Khamene A, Azar F, Frangioni JV. *Annals of Surgical Oncology*, 2009;16:2943–2952.

<http://www.ncbi.nlm.nih.gov/pubmed/19582506>

- This study demonstrates the clinical translation of an innovative optical imaging system that provides high sensitivity, high resolution, and real-time image guidance in oncologic surgery.

Noninvasive imaging of pancreatic inflammation and its reversal in type 1 diabetes,

Turvey SE, Swart E, Denis MC, Mahmood U, Benoist C, Weissleder R, Mathis D. *Journal of Clinical Investigation*, 2005;115:2454–2461.

<http://www.ncbi.nlm.nih.gov/pubmed/16110329>

- Magnetic nanoparticle–MRI detected vascular leakage in association with insulinitis in murine models of type 1 diabetes, permitting noninvasive visualization of the inflammatory lesions in vivo in real time. This strategy allowed prediction, within 3 days of completing treatment with an anti-CD3 monoclonal antibody, which NOD mice with recent-onset diabetes are responding to therapy and may eventually be cured.

Trafficking mesenchymal stem cell engraftment and differentiation in tumor-bearing mice by bioluminescence imaging, Wang H, Cao F, De A, Cao Y, Contag C, Gambhir SS, Wu JC, Chen X. *Stem Cells*, 2009;27:1548–1558.

<http://www.ncbi.nlm.nih.gov/pubmed/19544460>

- This study describes the application of in vivo imaging methodologies to demonstrate that mesenchymal stem cells can selectively migrate to, survive, and proliferate within both subcutaneous breast cancer and lung metastasis, in both premature and mature tumors.

Small-molecule modulators of p53 family signaling and antitumor effects in p53-deficient human colon tumor xenografts, Wang W, Kim SH, El-Deiry WS. *Proceedings of the National Academy of Sciences of the United States of America*, 2006;103:11003–11008.

<http://www.ncbi.nlm.nih.gov/pubmed/16835297>

- This study describes the application of bioluminescence imaging in a high-throughput cell-based screen of small molecules (the DTP diversity set) for those that activate p53 responses.

Volumetric tomography of fluorescent proteins through small animals in vivo, Zacharakis G, Kambara H, Shih H, Ripoll J, Grimm J, Saeki Y, Weissleder R, Ntziachristos V. *Proceedings of the National Academy of Sciences of the United States of America*, 2005;102:18252–18257.

<http://www.ncbi.nlm.nih.gov/pubmed/16344470>

- Quantitative tomographic fluorescence imaging was used in whole animals for both superficial and deep-seated (2–3-mm) fluorescent protein activity in vivo.

Molecular imaging of Akt kinase activity, Zhang L, Lee KC, Bhojani MS, Khan AP, Shilman A, Holland EC, Ross BD, Rehemtulla A. *Nature Medicine*, 2007;13:1114–1119.

<http://www.ncbi.nlm.nih.gov/pubmed/17694068>

- This study describes a new reporter molecule whose bioluminescence activity within live cells and in mice can be used to measure Akt activity. Akt activity in cultured cells and tumor xenografts was monitored quantitatively and dynamically in response to activation or inhibition of receptor tyrosine kinase, inhibition of phosphoinositide 3-kinase, or direct inhibition of Akt.





2010 Program
Accomplishments

Cancer Therapy Evaluation Program

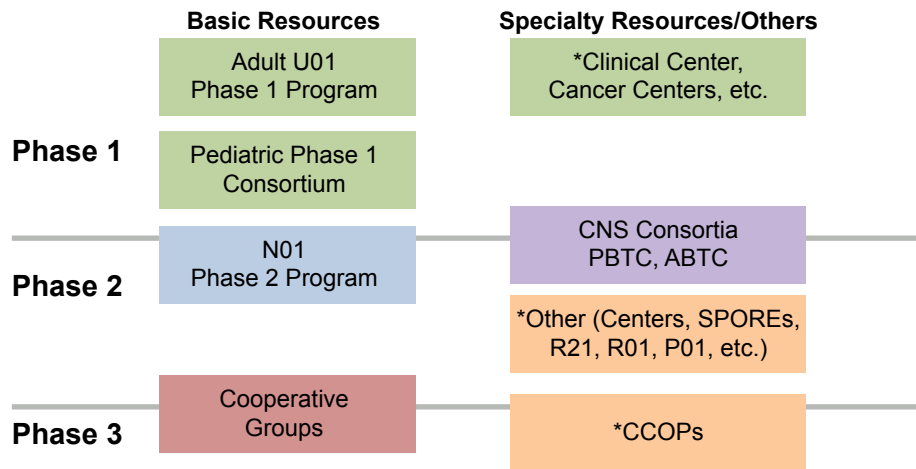


OVERVIEW

The Cancer Therapy Evaluation Program (CTEP) coordinates the clinical treatment development program of the Division of Cancer Treatment and Diagnosis (DCTD). CTEP manages a broad range of clinical trials that are closely integrated with preclinical discovery and development fostered by other DCTD programs. Once an approach (drug, surgery, radiation, immunotherapy) has obtained promising efficacy and adequate safety in preclinical testing, CTEP is resourced to move the therapy from first-in-human safety trials through definitive, randomized, controlled trials that meet U.S. Food and Drug Administration (FDA) requirements for approval.

CTEP staff directs the monitoring of 800 treatment clinical trials that are located throughout the nation, funded by more than 40 cooperative agreements and contracts, and involve about 30,000 patients annually. This level of activity makes CTEP the largest publicly funded clinical trials organization in the world. The program is responsible for many of the major studies that have altered cancer treatment over the last three decades. The trials are conducted by clinical trials networks of U.S. and international members and have been conceived to offer both scientific expertise and accrual capability. The trial networks, supported in whole or part by CTEP, are aligned as shown in the accompanying diagram.

NCI/CTEP THERAPEUTICS DEVELOPMENT PROGRAM



* Non-CTEP-funded resources. CNS = central nervous system; PBTC = Pediatric Brain Tumor Consortium; ABTC = Adult Brain Tumor Consortium; SPORE = Specialized Program of Research Excellence.

JEFFREY S. ABRAMS, ASSOCIATE DIRECTOR

In June 2007, Jeffrey S. Abrams, M.D., was selected after a nationwide search to lead the Cancer Therapy Evaluation Program (CTEP) as Associate Director. 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. 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 the phase 3 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 3 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 3 treatment trials, and has overseen implementation of NCI's Central Institutional Review Board.



Dr. Abrams, whose NCI achievements have been recognized by five NIH Merit Awards and several Performance Awards, is the author of more than 80 publications in the field of breast cancer and clinical trials, eight book chapters, and nine monographs.

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.



CTEP staff members comprise physicians, scientists, nurses, pharmacists, and other specialists. Transitioning from phase 0 to phase 3 studies requires a full complement of clinical trials services that reside in CTEP's seven branches:

1. The **Investigational Drug Branch (IDB)** is responsible for trials of new chemotherapeutic and biological antitumor investigational agents and for evaluating their pharmacokinetics and pharmacodynamic efficacy.
2. The **Clinical Investigations Branch (CIB)** develops and implements disease-oriented treatment strategies across the spectrum of human malignancies through strategy and consensus meetings and treatment program development.
3. The **Clinical Grants and Contracts Branch (CGCB)** manages two investigator-initiated grant programs—Clinical Oncology and Surgical Oncology—that encompass clinical agent development at the molecular, cellular, and whole-body levels as well as the development of treatment regimens and methodologies.
4. The **Regulatory Affairs Branch (RAB)** ensures that CTEP meets its regulatory responsibilities as the sponsor of Investigational New Drug Applications (INDs) and fosters partnerships with industry by implementing collaborative agreements.
5. The **Pharmaceutical Management Branch (PMB)** authorizes and distributes CTEP-sponsored new agents to registered physicians and for annual investigator registration.
6. The **Clinical Trials Monitoring Branch (CTMB)** manages quality assurance and quality control of clinical therapeutic trials sponsored by DCTD and prevention trials sponsored by the Division of Cancer Prevention.
7. The **Clinical Trials Operations and Informatics Branch (CTOIB)** manages the Protocol and Information Office and is responsible for the CTEP Enterprise System (the relational database that allows all CTEP branches to conduct their operations) and development of all new software and hardware needs.

By offering extramural investigators support and expertise, CTEP branches enable the academic community to overcome many of the regulatory, pharmaceutical, and scientific barriers that can hinder the implementation of clinical trials. CTEP holds more than 100 INDs for new agents, primarily through Cooperative Research and Development Agreements (CRADAs) with pharmaceutical partners, thereby providing extramural investigators latitude in early-phase trials to explore new schedules, doses, and proof-of-concept and mechanism-of-action studies. By expanding the number of diseases in which agents developed by pharmaceutical companies are studied, CTEP's early clinical trials program adds value to the industry drug development plan, which is focused primarily on FDA registration. Depending on the scope and expertise of the pharmaceutical partner, CTEP-sponsored researchers can either perform trials in common cancers or can focus on areas that are less market driven, such as pediatric and hematologic tumors; complex tumors requiring multidisciplinary approaches,

such as head-and-neck cancers and brain tumors; and multiple uncommon tumors. In addition, a particular niche filled by CTEP in recent years involves early combination trials with experimental agents from two or more companies. CTEP has been able to forge multi-company partnerships through the creation of a novel intellectual property (IP) agreement that enables collaborators to share IP when they co-develop drug combinations. The BeST phase 2 trial in renal cell cancer¹ is but one recent example in which multiple experimental combinations of novel agents (sunitinib and bevacizumab, sunitinib and temsirolimus, sorafenib and bevacizumab) are compared with the best single agent (sunitinib) in advanced disease, using drugs from different sponsors.

When promising signals are seen in phase 2 trials performed by CTEP's early trials networks, the Cooperative Group Program is prepared to move these ideas into controlled, randomized, phase 3 trials. Some recent examples include:

- An international intergroup partnership between the North Central Cancer Treatment Group (NCCTG) and the European Organisation for Research and Treatment of Cancer (EORTC) for two trials that will be carried out in Grade 3 glioma, 1p/19q co-deleted and non-deleted patients testing the role of temozolomide as an addition to radiation therapy
- Chimeric 14.18 monoclonal antibody, a study in neuroblastoma as a complement to the Children's Oncology Group (COG)

¹Bevacizumab, Sorafenib, and Temsirolimus in Treating Patients with Metastatic Kidney Cancer. Information available at <http://clinicaltrials.gov/ct2/show/NCT00378703>.

phase 3 study to allow for FDA approval of this novel treatment regimen

- The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-47, a test of trastuzumab in low HER-2 expressors as adjuvant therapy in more than 4,000 patients with breast cancer

CTEP's trial systems have been under intense evaluation by NCI scientific advisory boards, by Congress, and by the public. This is understandable and appropriate, as clinical trials represent for the public their most tangible contact with the promise offered by cancer research. Consecutive reviews of CTEP and NCI clinical trials in general have called for greater efficiency in developing trials and enrolling patients, enhanced use of technology to improve methodology and reduce costs, and more transparent and prioritized review systems to ensure that the most important trials are performed. The NCI has responded to these challenges with sweeping changes in how it conducts trials and reviews science. The most important changes include:

- **Disease-Specific Steering Committees:** Committees focused on specific diseases refine, evaluate, and prioritize new agents and trial concepts. The committees include leadership from all of NCI's major clinical trials mechanisms (Cooperative Groups, Specialized Programs of Research Excellence [SPOREs], early clinical trials networks) but also involve community physicians, patient advocates, ad-hoc experts, and



NCI staff. They sponsor Clinical Trials Planning Meetings to evaluate ideas with the relevant investigator community and provide evaluations that form the basis for prioritizing the most important trial questions for each cancer type. Each committee member has one vote (NCI staff represent less than 25% of the committee), and the reviews are publicly available.

- **Central Institutional Review Board:** Numerous surveys of investigators have indicated that institutional review boards (IRBs) pose a significant

barrier to the speedy development of clinical trials and enrolling patients in trials. NCI responded by creating the first government-sponsored central institution review board (CIRB) in 1999. The CIRB has expanded to review all phase 3 adult Cooperative Group trials (>200 trials reviewed) and all trials performed by COG. There are 300 IRBs nationwide that have joined the CIRB, representing more than 700 sites.

- **Cancer Trials Support Unit:** CTEP supports 10 Cooperative Groups, some of which overlap in their research interests.



Although competition for new trial ideas is desirable because it promotes innovative approaches, sponsorship by NCI of competing trials tended to slow overall accrual and risked duplicating resources for marginal gains. The Cancer Trials Support Unit (CTSU) offers the Cooperative Groups a contract mechanism through which all group trials are made available via a single online menu. This approach enables investigators in any group to enter patients on relevant trials, regardless of whether they belong to the group leading the trial. The CTSU has matured and is now a one-stop shop for online regulatory filing, patient registration, and data management. The “group-first” view of the Cooperative Group system has slowly given way to a new approach whereby Disease-Specific Steering Committees select the best trial ideas, which are then offered to the entire investigator

community to promote rapid enrollment, irrespective of group membership.

- **CTEP Enterprise and Clinical Trials Systems:** CTEP has embraced standards and consistency in clinical trials design, monitoring, and reporting. Among the many products that CTEP currently requires in its trials, some of the most used are:
 - Common Case Report Forms and Common Data Elements
 - Adverse Event Expedited Reporting System (AdEERS)
 - Common Data Update System
 - Common Clinical Data Management System (in development)
- **Operational Efficiency:** On the basis of recommendations from an NCI advisory board, CTEP and its investigator community have agreed to partner on new timelines to promote rapid protocol implementation. Phase 1 and 2 studies

will now be targeted to go from letter of intent (LOI)/concept to protocol activation within 7 months, and phase 3 studies will target a 10-month timeline. Once achieved, this would represent a 75% improvement over past timelines. This improvement will be achieved by employing new personnel to assist clinical trialists, leveraging technology to track timelines and monitor performance, and incentivizing investigators by rewarding compliance.





PROGRAM ACCOMPLISHMENTS

Following is a brief discussion of CTEP's seven branches, their recent accomplishments, and future projects. The advances enumerated here are selected examples resulting from efforts carried out by CTEP in cooperation with the extramural clinical trials community.

Investigational Drug Branch

Background

The Investigational Drug Branch (IDB) oversees the portfolios of approximately 100 IND agents, nearly all of which are being developed under agreements with biotechnology and pharmaceutical companies. IDB staff members evaluate agents for potential clinical development by NCI, initiate drug development plans, review study proposals, and oversee the conduct and analyze the data of trials under CTEP INDs. IDB focuses entirely on acquiring and developing novel agents. Staff members meet regularly with pharmaceutical companies, serve on multiple NCI drug development committees, and interact with academic, industry, and FDA investigators. A major focus of CTEP drug development is exploration of investigational drug combinations based upon strong rationale and preclinical data. CTEP is well positioned to be a leader in testing novel combinations because of its large IND portfolio and long tradition as a safe harbor for IP.

NCI Investigational Drug Steering Committee.

The NCI Investigational Drug Steering Committee (IDSC) was established in November 2005 on the recommendation of the Clinical Trials Working Group, which reviewed the national clinical research enterprise. The IDSC is composed of a

Steering Committee, 10 task forces, and three working groups. Members of the IDSC include the principal investigators of NCI's early drug development grants and contracts, representatives from the Cooperative Groups, a patient advocate, biostatisticians, and NCI staff.

IDSC goals are to:

- Provide external strategic input into the prioritization of phase 1 and 2 trials for new agents
- Increase transparency of the prioritization process
- Optimize clinical trial designs to improve effectiveness of early-phase therapeutics

CTEP DRUG DEVELOPMENT PLANS REVIEWED BY THE IDSC

Date	Agent	Class
November 2006	IMC-A12	IGF-1R Inhibitor
February 2008	SCH 727965	CDK Inhibitor
October 2008	IL-12	Immunomodulator
November 2008	GDC-0449	Hedgehog Inhibitor
January 2009	RO4929097	Notch Inhibitor
March 2009	OSI-906	IGF-1R Inhibitor
March 2009	MK-2206	AKT Inhibitor
April 2009	ABT-263	bcl-2 Inhibitor
May 2009	AZD-8055	mTOR Inhibitor

The phase 1 Clinical Trials Program uses the U01 grant mechanism to achieve its goals. In this program, there are 14 Cooperative Agreements with 17 NCI-designated Cancer Centers distributed across the United States and Canada. The Phase 2 N01 Clinical Trials Program comprises nine contracts and includes 29 NCI-designated Cancer Centers

distributed across the United States and Canada. These contracts are undergoing recompetition in 2010. Funds from the American Recovery and Reinvestment Act of 2009 (ARRA) allowed creation of the Accelerating Clinical Trials of Novel Oncologic Pathways (ACTNOW) program. The allotted funds, \$36 million, created 37 clinical trials and NCI support contracts.

Accomplishments

Solicitations for Trials. Thirteen solicitations for trials have been issued since 2006, and eight more are planned for 2010 (see table).

OI Summary (Includes Phase 1 and Phase 2 Proposals). Seventeen new-agent solicitations were issued (2005–2009), and 102 of 519 (20%) of LOIs were approved. A total of 226 of 458 (49%) unsolicited LOIs were approved.

Phase 1 U01 Program. The Phase 1 U01 Program executes early-drug development plans for novel agents in the NCI CTEP IND portfolio and includes phase 1 single-agent clinical trials, phase 1 agent combination trials, limited phase 2 trials, and pilot clinical trials of novel agents that target relevant cancer cell signaling pathways and

AGENT SOLICITATIONS

Year Released	Agent	Mechanism of Action
2006	Dasatinib	Tyrosine kinase inhibitor
	Reolysin	Wild-type reovirus
	Pertuzumab	Her1/2 antibody
	AZD6244	MEK inhibitor
	GX15-070	Bcl-2 inhibitor
	ABT-888	PARP inhibitor
	AT-101	Bcl-2 inhibitor
2007	IMC-A12	IGF-1R antibody
2008	SCH 727965A	CDK inhibitor
	GDC-0449	Hedgehog inhibitor
	Interleukin-12	Cytokine
2009	RO4929097	Notch inhibitor
	ABT-263	Bcl-2 inhibitor
Planned for 2010	OSI906	Small-molecule IGF-1R inhibitor
	AMG 386	Angiopoietin-2 peptibody antagonist
	AT-13387	HSP90 inhibitor
	SCH-90077	CHK1 inhibitor
	MK-1775	wee-1 inhibitor
	Arq 197	cMet inhibitor

CDK = cyclin-dependent kinase; CHK = checkpoint kinase; IGF = insulin-like growth factor; MAPK/ERK kinase; PARP = poly-(ADP ribose) polymerase.



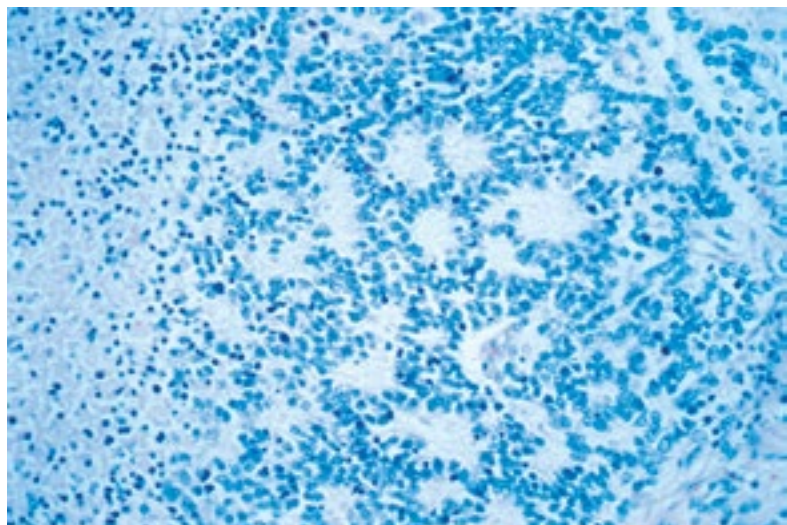
essential cellular machinery involved in the regulation of angiogenesis, cell survival and apoptosis, proliferation, and differentiation. From 2005 through May 2010, results from this program generated 218 publications, including abstracts.

Scientific progress:

- More than 100 investigational combinations studied
- A total of 40 investigational combinations have moved forward to phase 2 disease-specific testing
- Monographs on management of toxicities associated with antiangiogenic agents have been published
- Comprehensive reviews of molecularly targeted agents and their development status have been published
- Population pharmacokinetic analyses for a number of novel agents have been published
- Hepatic and renal dysfunction studies of 10 investigational agents have been completed, published, and in five cases, used in licenses to provide dosing recommendations for patients with organ dysfunction
- Novel clinical trials have begun to investigate drug interactions in patients receiving anti-retroviral therapy, and a new consortium has been formed to work with the AIDS Malignancy Consortium

In addition, new areas of molecularly targeted agent research have been established:

- Cancer stem cell and embryonic signaling pathway inhibitors
- DNA repair and programmed cell death

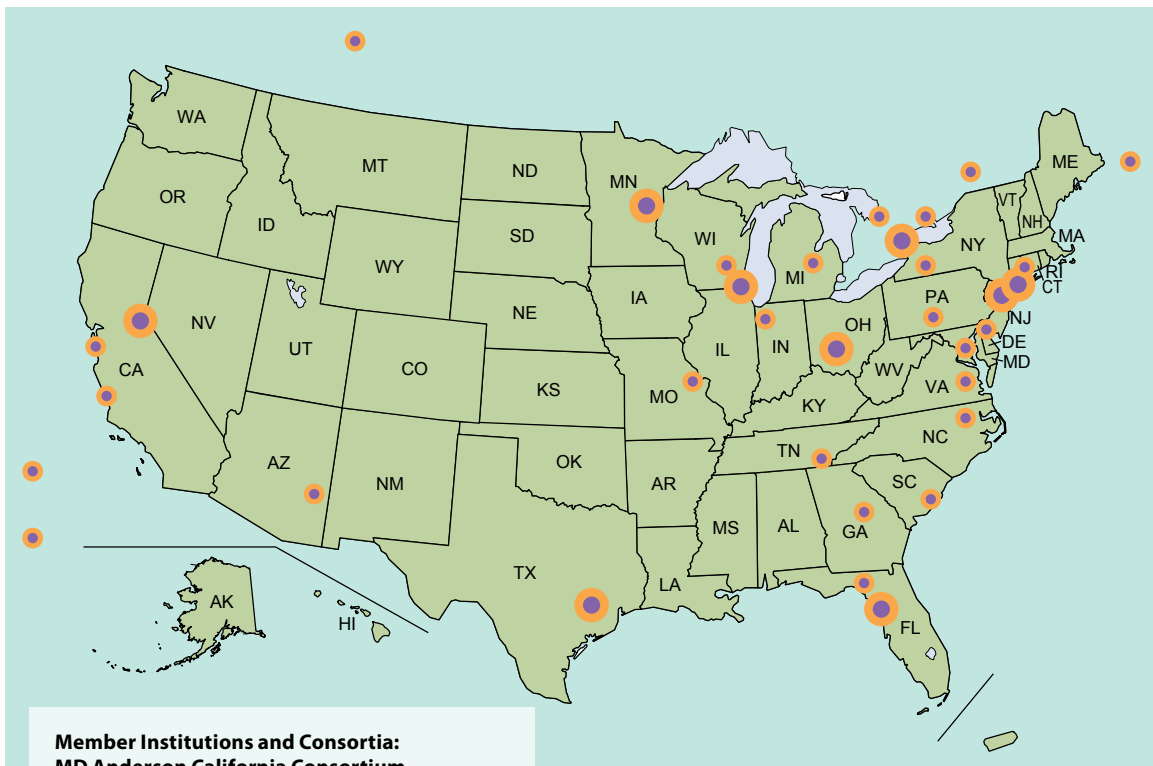


- PI3'K, Akt, and mTOR pathway inhibitors
- C-Met and HGF inhibitors
- Novel antimetabolic agents
- Novel agents to interrogate the microenvironment
- Heat-shock protein inhibitors
- Insulin growth factor receptor inhibitors

Phase 2 N01 Program. The Early Therapeutics Development with Phase 2 Emphasis has created a flexible platform so that early clinical trials consortia are prepared to rapidly evaluate the biologic effects of NCI-sponsored anticancer agents on their molecular targets and to determine clinically relevant correlates. The current program includes nine contracts that involve consortia comprising 29 NCI Cancer Centers distributed across the United States and Canada.

The network currently has about 4,300 patients enrolled in approximately 140 clinical trials. Approximately 40 investigational combination trials were initiated, including 10 involving more than

THE PHASE 2 N01 NETWORK



Member Institutions and Consortia:

MD Anderson California Consortium

UC Davis, City of Hope, USC, U of Pittsburgh

University of Chicago

U of C network, U of Michigan, U of Maryland, College of Wisconsin

NY Phase 2 Consortium

Montefiore, Weill Cornell, Mt. Sinai, Columbia, North Shore, U Conn, Sydney

Mayo Phase 2 Consortium

U of Wisconsin, Johns Hopkins, Wayne State, Washington U, UCSF, CTRG Pacific Rim), Mayo Arizona and Jacksonville, U of Colorado, U of Iowa

Memorial Sloan-Kettering

Princess Margaret Phase 2 Consortium

Hamilton, Kingston, London, Edmonton, McGill, Halifax, Sunnybrook, Vancouver, Roswell Park, Fox Chase

Ohio State University

Southeast Phase 2 Consortium

Moffitt, UNC, Vanderbilt, Emory, Virginia Commonwealth, Medical University of South Carolina

one unapproved agent, i.e., “novel/novel.”

Examples include:

- Protocol 8121:** A Phase 2 Study of Temsirolimus (CC-779, NSC 683864) and IGF-1 Receptor Antibody IMC-A12 (NSC 742460) in Patients with Metastatic Sarcomas. Rationale: Activation of Akt due to mTOR blockade is mediated by IGF signaling and can be inhibited in vitro by IGF-1R antibody.
- Protocol 8233:** A Phase 2 Trial of Temsirolimus and Bevacizumab in Patients with Endometrial, Ovarian, Hepatocellular Carcinoma, Carcinoid, and Islet Cell Cancer. Based on single-agent data in patients and preclinical data for the combination, 250 patients will be enrolled in five separate tumor cohorts. All nine N01 contractors are participating. This trial is rapidly



enrolling via CTSU, which is managing registration and data, and electronic remote data capture and blood and tumor specimen collection is being done on all patients for future analysis.

The trials are for 18 cancer indications, including rare diseases not likely to be evaluated in company-sponsored trials, such as hepatobiliary cancer and adenoid cystic carcinoma. Promising response rates and/or survival outcomes have opened new areas for further exploration, e.g., AZD6244 (MEK) in biliary cancers, bevacizumab in hepatocellular carcinoma, and sorafenib for imatinib- and sunitinib-resistant gastrointestinal stromal tumor. Correlative studies have shed light on molecular characteristics of tumors; e.g., imatinib for patients with stage III/IV melanoma with c-kit mutations: three out of nine patients harboring somatic alteration of exon 11 of the c-kit gene had major responses to imatinib.

ACTNOW Program, Supported by ARRA Funds.

The goal is to accelerate the initiation and completion of 37 early-phase clinical trials of new treatment regimens. A total of \$31 million has been dedicated for phase 1 and 2 trials, plus \$5 million for support contracts, including those to assist the investigators with data monitoring and statistical analysis. Support for the clinical trials included hiring of staff, acquisition of technologies for diagnostic scans, specimen sample collection, assay development, and the reimbursement of research costs associated with data management at the participating sites. Examples of ACTNOW trials include studies of the Hedgehog inhibitor, GDC-0449, in adults and children with medulloblastoma; and the poly-(ADP ribose) polymerase (PARP) inhibitor

ABT-888 in patients with BRCA 1/2-mutated breast and ovarian cancer.

CTEP-Sponsored Phase 2 Trials Leading to Pivotal Trials. A number of phase 2 studies sponsored by CTEP have led to pivotal clinical trials. Examples include the following:

- The 40% overall response rate in cutaneous T-cell lymphoma seen in the NCI Clinical Center multicenter, phase 2 trial of single-agent romidepsin led to a company-sponsored pivotal, single-arm, phase 2 international trial of romidepsin in cutaneous T-cell lymphoma that confirmed the NCI trial results. The FDA approved romidepsin for cutaneous T-cell lymphoma in November 2009.
- Patients treated with bortezomib for mantle cell lymphoma in a CTEP-sponsored early clinical trial exhibited a high response rate, leading to a company-sponsored pivotal trial that resulted in approval of the agent for this indication in December 2006.
- Chimeric 14.18 antibody for neuroblastoma

IDB Staff Fostering Career Development of Junior Clinical Investigators. The Career Development LOI (CrDL) program is intended to increase the LOI success rate and facilitate the career development of junior investigators. The CrDL process is designed to promote junior faculty by providing a competitive advantage for LOIs submitted by junior investigators and mentoring in the LOI development and review process, including providing expert commentary for clinical trial proposals. A total of 126 CrDLs have been submitted since the program's inception in November



2007, of which 36% have been approved and 13% were in review in May 2010. Fellows and junior faculty rotate at CTEP, which includes participation in:

- Review of LOIs and protocols
- Scientific presentations by biotechnology and pharmaceutical companies seeking CTEP collaboration
- Opportunity to present data from CTEP-sponsored trials at the

semi-annual CTEP Early Drug Development Meeting

Future Initiatives

A number of intra- and inter-divisional collaborations are planned for the future:

- Increased integration of imaging and correlative sciences into CTEP clinical trials
 - With the DCTD Cancer Imaging Program: incorporation of molecular imaging in CTEP IND agent trials carried out in the Phase 2 N01 Program
 - With caHUB: collection, processing, and storage of high-quality patient samples from CTEP IND trials. This initiative will leverage the efforts of CTEP in its drug development program with the sample processing and storage capabilities of the Cancer Human Biobank (caHUB). These samples will be made available to investigators with validated laboratory assays of exploratory biomarkers
- Phase 1/2 trials of irradiation combined with targeted agents with the DCTD Radiation Research Program
- Evaluation of drug/drug Interactions and pharmacology using human hepatic microsomes with the University of Pittsburgh, the AIDS Malignancy Consortium, and the CTEP Organ-Dysfunction Working Group



Clinical Investigations Branch

Background

The Clinical Investigations Branch (CIB) is responsible for the scientific coordination and oversight of definitive, practice-changing clinical trials of innovative oncology treatments, including single- or multiple-agent or combined modality interventions and targeted therapies for adult, adolescent, and pediatric populations conducted nationally by the extramural scientific community:

- NCI Clinical Trials Cooperative Group Program
- Pediatric and adult brain tumor clinical trials consortia
- Pediatric phase 1 Consortium, New Approaches to Neuroblastoma Consortium, Pediatric Preclinical Testing Program, and the Childhood Cancer Therapeutically Applicable Research to

Generate Effective Treatments (TARGET) Initiative

CIB physicians, nurses, and allied health professionals provide oversight of essential services and collaborations associated with these national clinical trial networks, including:

- Cancer Trials Support Unit (CTSU), which provides centralized patient enrollment as well as administrative and regulatory support for the conduct of clinical trials
- NCI Central Institutional Review Board (CIRB) for adult and pediatric Cooperative Group trials
- Coordination with other NCI programs regarding collection, banking, and use of clinical biospecimens in conjunction with validated data from multi-institutional clinical trials
- Collaborations with international clinical trials organizations on treatment trials



Clinical Trials Program and Recent Accomplishments

The NCI Clinical Trials Cooperative Group Program is distinctive among randomized, large-scale NIH-supported clinical trials programs because it provides a standing infrastructure for clinical trials continuously available to test new therapeutic interventions. There are a total of 2,097 sites, including NCI Comprehensive Cancer Centers, other academic and community institutions, 50 Community Clinical Oncology Programs (CCOPs), and 13 minority-based CCOPs, as well as over 18,000 registered investigators from the extramural scientific community participating in the NCI Clinical Trials Cooperative Group Program.

The CTEP 10 Cooperative Groups

- American College of Surgeons Oncology Group
- Cancer and Acute Leukemia Group B
- Children's Oncology Group
- Eastern Cooperative Oncology Group
- Gynecologic Oncology Group
- National Cancer Institute of Canada Clinical Trials Group (limited to intergroup participation)
- National Surgical Adjuvant Breast and Bowel Project
- Radiation Therapy Oncology Group
- North Central Cancer Treatment Group
- Southwest Oncology Group

ch14.18 Boosts Survival in Neuroblastoma by 20%

In 2010, researchers from a randomized phase 3 clinical trial coordinated by the Children's Oncology Group reported that administering a new form of immunotherapy, which included the ch14.18 antibody, to children with neuroblastoma increased the percentage of those who were alive and free of disease progression after 2 years. The percentage rose from 46% for children receiving a standard therapy to 66% for children receiving ch14.18 plus standard therapy.

These trial results establish ch14.18 immunotherapy as a new standard of treatment for children with high-risk neuroblastoma.

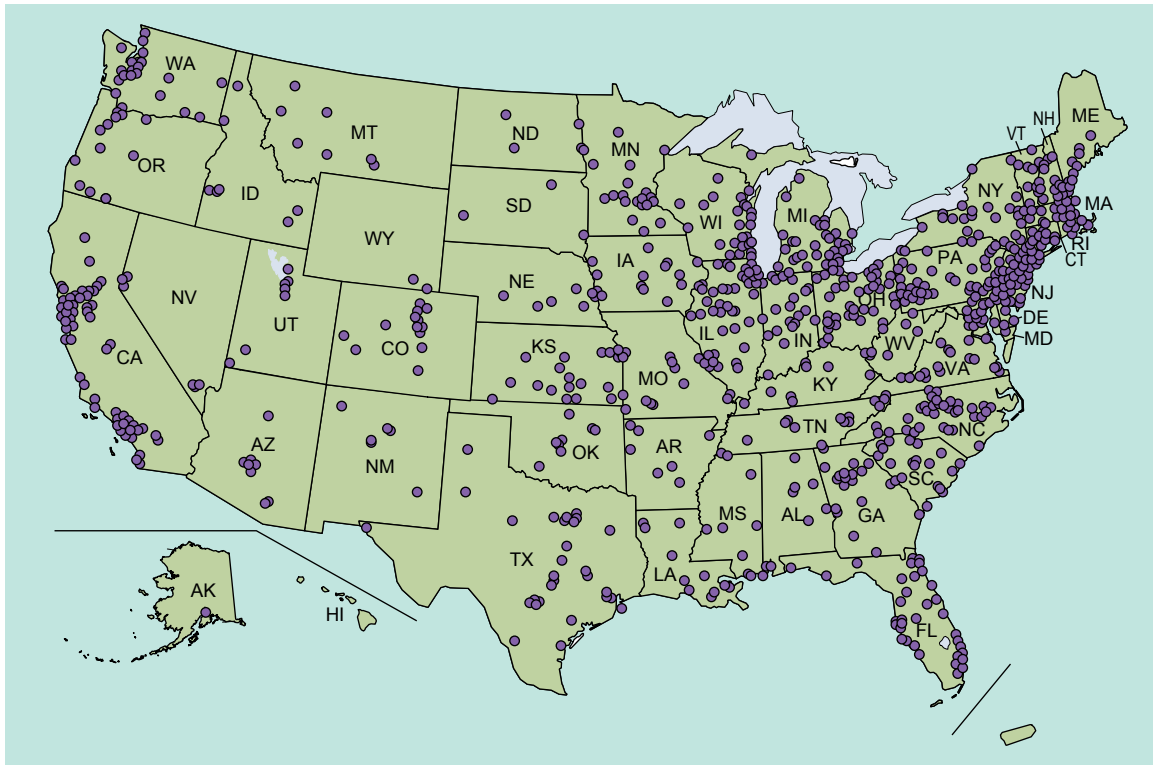
The ch14.18 used in this trial was manufactured in the DCTD Developmental Therapeutics Program (DTP). Until the antibody is ready for marketing by a commercial entity, DTP will continue to supply the agent for clinical trials.

In addition, CTEP also supports quality assessment and support services for the groups through:

- **Quality Assurance Review Center:** Provides radiotherapy quality assurance and diagnostic imaging management for large trials conducted via the NCI group program
- **Radiological Physics Center:** Assures groups that sites participating in group clinical trials deliver prescribed radiation doses and develop quality assurance procedures



U.S. COOPERATIVE GROUP CLINICAL TRIALS SITES (NO. OF SITES BY STATE WITH PATIENTS CURRENTLY ENROLLED IN AN OPEN TRIAL)



ACCRAAL AND TRIAL NUMBERS FOR OPEN COOPERATIVE GROUP TREATMENT TRIALS: 2005–2009, WITH 2010 ESTIMATES

Phase	2005 Studies/Patients	2006 Studies/Patients	2007 Studies/Patients	2008 Studies/Patients	2009 Studies/Patients	2010 Studies/Patients
Phase 1	36/590	35/547	30/285	27/320	35/376	25/350
Phase 2	258/4,773	239/4,446	200/3,758	175/3,165	147/2,920	175/3,000
Phase 3	117/21,732	111/20,983	117/20,163	119/22,595	129/24,604	110/24,500
Other (pilot)	17/600	16/275	15/175	14/203	13/319	15/300
Total	428/27,695	401/26,251	362/24,281	355/26,283	324/28,209	325/28,150

Approximately 370 Cooperative Group treatment trials are open to accrual in any given year (see table). An additional 90 trials are closed to accrual but still have patients on active study therapy each year. These numbers represent an average over the last five years.

A new process for evaluating prospective large-scale trials has been put into place to promote utilization of the broadest expertise for selecting these trials and to ensure an open, transparent process. Disease-Specific Steering Committees were established in 2006. Each committee includes expertise from across the oncology



community in the particular disease or organ system, including representatives from the Cooperative Groups, Cancer Centers, SPOREs, community oncologists, basic and translational scientists, biostatisticians, patient advocates, and NCI oncologists. The committees break out into task forces to serve as think tanks for new ideas and develop Clinical Trials Planning Meetings as appropriate to engage the community in seeking the most important questions to pose in new trials. Over 50 phase 2 and 3 trials had been reviewed by the committees as of May 2010.

CTSU and FLEX Programs. The CTSU was established in 2002 to increase physician and patient access to NCI-sponsored clinical trials, reduce the regulatory burden on investigators participating in clinical trials, and streamline and standardize trial data collection and reporting. Since its inception, CTSU has:

- Increased phase 3 trial cross-group accrual from 20% to 40%, resulting in wider access of trials to the extramural community and enrollment of more than 8,000 patients annually in collaborative trials
- Diminished the regulatory and administrative burden for trial enrollment handling over 8,000 primary trial and amendment approvals each month
- Provided standardized data management services for multiple phase 3 clinical trials
- In 2009, initiated the Oncology Patient Enrollment Network (OPEN), a Web-based registration system for patient enrollments into group trials that is integrated with CTSU regulatory/roster data and each groups' registration/randomization systems and provides the ability to enroll patients on a 24/7 basis via one centralized system

A pilot program, the CTSU-Flex program, was instituted in 2008 to extend the infrastructure support of the CTSU to other NCI-supported clinical trial networks, including Cancer Center Phase 2 Consortia trials supported by the IDB and cancer control and symptom management trials sponsored by the Division of Cancer Prevention. The CTSU-Flex program supported approximately 15 non-group clinical trials in 2009 and extended participation to other NCI-supported programs, including the SPOREs, in 2010.

Novel Cooperative Group Phase 3 Clinical Trials and International Collaborations. Following are examples of major phase 3 trials incorporating novel treatment strategies and molecularly targeted therapies. These trials



are also examples of studies that would not have been conducted by industry alone, several requiring international collaboration:

- Program for the Assessment of Clinical Cancer Tests (PACCT-1):** The NSABP repository of biospecimens from previously conducted phase 3 trials helped lead to the development and validation of the Oncotype Dx[®] test, a 21-gene assay that provides an individual, quantitative assessment of the likelihood of disease recurrence in the form of a recurrence score. The Oncotype Dx[®] test is being used in the intergroup Trial Assigning Individualized Options for Treatment (TAILORx) study, led by the Eastern Cooperative Oncology Group (ECOG) and involving international participation, to determine the value of chemotherapy in hormone receptor–positive and lymph node–negative women. This trial will enroll approximately 11,000 patients and complete accrual in 2010.
- Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma (ASSURE):** This intergroup trial, led by ECOG, is evaluating two different tyrosine kinase inhibitors (sunitinib and sorafenib) from different pharmaceutical companies as adjuvant therapy in renal cancer against the current standard of care, which is observation after complete surgical resection. This trial may define new therapy in a potentially curable patient population. Approximately 2,000 patients will be enrolled in the study, which completed accrual in 2010.
- Phase 3 Double-Blind Study of Induction and Consolidation Chemotherapy plus Midostaurin or Placebo in Newly Diagnosed Patients Less Than 60 Years of Age with FLT-3 Mutated Acute Myeloid Leukemia:** This international intergroup

trial, led by Cancer and Acute Leukemia Group B (CALBG), is evaluating therapy in a molecularly defined subset of a rare disease. Central molecular FLT-3 analysis is being conducted in specified labs in the United States, Europe, Russia, South America, and Australia. This trial may define molecular therapy for patients with poor-risk acute myelogenous leukemia (AML), where advances have not been previously realized. The trial completed its target accrual goal of 500 patients in 2010.

- Phase 3 Randomized Study of Concurrent Chemoradiotherapy and Adjuvant Temozolomide with versus Without Bevacizumab in Patients with Newly Diagnosed Glioblastoma or Gliosarcoma:** This intergroup trial, led by the Radiation Therapy Oncology Group, is evaluating the benefit of adding the monoclonal antibody bevacizumab to the standard treatment of temozolomide and radiation for



patients with glioblastoma after maximal surgical resection. This trial is rapidly following up on a scientific advance showing that bevacizumab was active in the treatment of recurrent glioblastoma to determine whether it can extend survival in an earlier stage of disease. The study involves central pathologic confirmation of glioblastoma as well as stratification based on molecular risk profiling and methylation status, which are prognostic indicators in this disease. The trial is accruing quickly and is on target to complete its total accrual goal of 720 patients in 2011.

- **Phase 3 Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2-Overexpressing Esophageal Adenocarcinoma:** This phase 3 study was recently approved to evaluate a new molecularly targeted therapy for a specific subset of patients with a rare disease in a potentially curative clinical setting. This trial follows a 2009 scientific advance that demonstrated a survival advantage for patients who have

advanced gastric and gastroesophageal junction adenocarcinoma that overexpresses HER2 and who received trastuzumab in combination with chemotherapy. This trial will screen 600–700 patients to identify the estimated 25–32% of patients with disease that overexpresses HER2 in order to evaluate the benefit of adding trastuzumab to trimodality adjuvant therapy in esophageal adenocarcinoma.

Accomplishments

Extramural investigators of the CTEP-supported clinical trial programs present primary trial results as well as other outcomes from research associated with the clinical trials in 300–400 publications and abstracts each year from the extramural scientific community. Group trials have also been responsible for FDA approval of multiple new agents for several indications, resulting in widespread access of these agents to the patients in the United States.

SELECTED NCI-SUPPORTED COOPERATIVE GROUP TRIALS SUPPORTING FDA-APPROVED INDICATIONS

Year	Drug	Sponsoring Organization	Cancer Site
2004	Letrozole	National Cancer Institute of Canada, Intergroup	Breast
	Oxaliplatin	North Central Cancer Treatment Group, Intergroup	Colon
	Taxotere	Southwest Oncology Group	Breast
	Nelarabine	Children's Oncology Group	Leukemia
2006	Bevacizumab	Eastern Cooperative Oncology Group, Intergroup	Colon, lung
	Trastuzumab	National Surgical Adjuvant Breast and Bowel Project, North Central Cancer Treatment Group, Intergroup	Breast
2008	Bevacizumab	Eastern Cooperative Oncology Group, Intergroup	Breast
	Imatinib mesylate	American College of Surgeons Oncology Group	Gastrointestinal stromal tumor



Future Initiatives

CTEP Initiatives to Expand Cancer Clinical

Trials Access to HIV-Infected Persons. Cancer has emerged as the leading cause of death in HIV-infected persons in the United States and other countries where effective combination antiretroviral therapy (cART) is widely available. Most cancer clinical trials, however, have traditionally excluded persons with HIV infection because, prior to cART, HIV-associated morbidity and mortality made these patients vulnerable to excess risk. Three new CTEP initiatives, funded by the NCI Office of the Director, will provide the evidence required to address barriers that prevent wide inclusion of HIV-infected persons in cancer clinical trials:

1. HIV-infected patients are being included as separate cohorts in selected randomized phase 3 and large phase 2 oncology treatment trials to provide preliminary information on feasibility and safety.
2. Two transplant trials are being conducted through the National Heart, Lung, and Blood Institute and the NCI-co-sponsored Blood and Marrow Transplant Clinical Trials Network in collaboration with the NCI AIDS Malignancy Consortium to assess the safety and feasibility of autologous or allogeneic stem cell transplantation in HIV-infected persons with hematologic cancers. An attempt will be made to identify human leukocyte antigen-matched donors who are homozygous for the CCR5D32 mutation, which renders individuals not infectable by the most common HIV strains. These

recipients may be removed from cART and assessed using ultrasensitive single-copy HIV mRNA assays to investigate the possibility that HIV eradication can be achieved in this manner.

3. Several studies are being funded to define agent doses that can be safely used in various cART combinations. As these interactions are defined and found to be safe, NCI-sponsored trials that currently exclude those with HIV infection because of concerns regarding pharmacokinetic interactions will be amended to include those with HIV infection, thus expanding access of HIV-infected persons to a large number of trials.

ADOPTION of New Technologies for Remote Data Capture and Protocol Authoring for Clinical Trials.

ADOPT is a multipronged approach to integrate standardized information technology (IT) tools and processes into the infrastructure of the NCI national clinical trial networks. Standardization and a common infrastructure will improve the efficiency and effectiveness of the networks while also providing an opportunity to reduce clinical trial costs and timelines. Total ARRA funding of \$19.2 million over 2 years was given to fund Cooperative Groups, Consortia, and 48 Cancer Centers to adopt these new technologies, including:

- Clinical data management system: a common remote data capture system for all networks
- Electronic protocol authoring for rapid development of protocol documents
- Electronic case report forms for rapid, standardized collection of clinical data

Pediatric Translational and Clinical Research Programs

CTEP staff members also support a comprehensive research program for children with cancer that ranges from the discovery of new therapeutic targets, to the definitive clinical evaluation of new therapeutic strategies in phase 3 trials, to studying the late effects of successful cancer treatment in long-term survivors of childhood

cancers. This pediatric research program is critical because pharmaceutical companies lack the market incentives to justify the systematic study of novel treatments in the pediatric oncology setting. CTEP sponsors pediatric clinical trials, primarily COG, its phase 1 consortium, the New Approaches to Neuroblastoma Therapy (NANT) Consortium, and the Pediatric Brain Tumor Consortium.





- **Children's Oncology Group (COG)**
COG 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 clinical trials are the primary source of data used to define the standard of care for childhood cancers. Examples of recent advances identified in COG phase 3 clinical trials include:
 - Addition of imatinib to standard chemotherapy improves outcomes for children with Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL).
 - Compressing the interval between treatment courses improves outcomes for children with Ewing sarcoma.
 - The disialoganglioside-targeted monoclonal antibody ch14.18 improves outcomes for children with high-risk neuroblastoma when given with granulocyte macrophage-colony-stimulating factor and interleukin-2 after autologous bone marrow transplantation.
- **COG Phase 1/Pilot Consortium:** The COG Phase 1/Pilot Consortium efficiently and expeditiously develops and implements pediatric phase 1 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 competitively selected from among COG member institutions. Recent examples of important phase 1 studies include:
 - The anaplastic lymphoma kinase (ALK) inhibitor PF-2341066, with a specific focus on patients with ALK-mutant neuroblastoma and ALK-positive anaplastic large cell lymphoma
 - The anti-IGF-1R monoclonal antibody IMC-A12, studied both as a single agent and also in combination with the mTOR inhibitor temsirolimus
 - The oncolytic virus NTX-010, which appears to be uniquely active against neuroendocrine tumors such as neuroblastoma
- **Pediatric Brain Tumor Consortium**
The primary objective of the Pediatric Brain Tumor Consortium (PBTC) is to rapidly conduct phase 1 and 2 clinical evaluations of new therapeutic drugs, intrathecal agents, delivery technologies, biological therapies, and radiation treatment strategies for children with brain tumors. A focus of the PBTC is conducting the initial studies in children of targeted agents that directly address recurring genomic lesions in pediatric brain tumors, as illustrated by the following:
 - The PBTC is conducting the initial pediatric study of the hedgehog pathway inhibitor GDC-0449. The agent is highly relevant to medulloblastoma cases with sonic hedgehog pathway activation.
 - The PBTC is evaluating the MEK inhibitor AZD6244 in children with recurrent or progressive pilocytic astrocytoma. BRAF activation through its fusion to a nearby gene is observed in most cases of pilocytic astrocytoma.

- **Childhood Cancer TARGET**
The childhood cancer TARGET Initiative, a collaborative effort with the NCI Office of Cancer Genomics and COG, systematically applies genomic characterization methods to identify genes that are recurrently altered in specific childhood cancers under the hypothesis that these altered genes provide therapeutically relevant insights into the pathways on which cancers depend for growth and survival. The TARGET Initiative first studied ALL and neuroblastoma. Important discoveries through the ALL TARGET Initiative include identifying the poor outcome associated with IKZF1 (Ikaros) alterations, identifying activating JAK family mutations in high-risk B precursor ALL, and identifying novel gene fusions involving the CRLF2 gene in a subset of patients with high-risk B-precursor ALL. The TARGET Initiative has expanded to include a total of five different childhood cancers: ALL, AML, neuroblastoma, high-risk Wilms tumor, and osteosarcoma.

- **The Pediatric Preclinical Testing Program**

The pediatric Preclinical Testing Program (PPTP) systematically tests novel anticancer agents against pediatric preclinical models to develop datasets to assist clinical researchers in selecting the agents and combination therapies that are most likely to be effective for childhood solid tumors and leukemias. Since 2005, more than 30 agents or combinations of agents have been tested against the PPTP's molecularly characterized

panel of childhood cancers. PPTP results have driven development of the following agents:

- The Bcl-2 family inhibitor ABT-263 in children with ALL
- The Aurora A kinase inhibitor MLN8237 for children with ALL and neuroblastoma
- The MEK inhibitor AZD6244 for children with recurrent pilocytic astrocytoma

Clinical Grants and Contracts Branch

Background

The Clinical Grants and Contracts Branch (CGCB) manages grant programs in clinical and surgical oncology. The branch supports investigator-initiated therapeutic research projects by coordinating multiple activities that include:

- Annual review of grant progress, financial accounting, and approval and oversight of amended aims and plans for recompetition
- Identification of potential areas of scientific investigation that overlap among investigators to promote collaborations and support for grantee projects by facilitating the procurement of agents, resources, or trials support from other CTEP and NCI branches
- Promotion of broad national programs of clinical consortia, including the Chronic Lymphocytic Leukemia Research Consortium, the Blood and Marrow Transplant Clinical Trials Network, and the Adult Brain Consortium



- Advice to extramural investigators on funding opportunities, mechanisms, and the grant application process

Team science is the hallmark of CGCB's research portfolio; the research carried out in the CGCB portfolio usually requires collaboration among different investigators in different disciplines. As it moves from the R series grant mechanism to the program project grants (P01s) and the U01 cooperative agreements, team science becomes more complex and requires more coordination on the part of CGCB staff.

FY 2009 CGCB PORTFOLIO*

Mechanism	Number
P01	48
R01	127
R03	3
R13	11
R21	58
R37	2
U01 CGCB	4
U24 CGCB	2
RC1	0
RC2	0
TOTAL	253

*Exclusive of cooperative agreements (U10, U01, U24s) assigned to CIB and IDB.

Accomplishments

Major accomplishments of the team science projects supported under investigator-initiated R01 and R37 grants include the following:

- A microfluidic device was developed to isolate highly purified circulating tumor cells from the blood of patients. This led to confirmation of the expected epidermal growth factor receptor (EGFR)-activating mutation, the T790M mutation, in circulating tumor cells in 92% of blood samples from patients with advanced non-small-cell lung cancer who were resistant to gefitinib in a multi-center clinical trial.
- Intensification of systemic and intrathecal chemotherapy led to omission of the prophylactic cranial irradiation in childhood ALL without compromising overall survival.
- It was found that genetic polymorphism of the inosine triphosphate pyrophosphatase gene determines mercaptopurine metabolism and severe febrile neutropenia after combination chemotherapy for ALL patients in which mercaptopurine doses are individualized on the basis of thiopurine methyltransferase genotype.

The P01 grants in particular serve as an important bridge between the preclinical and the clinical sciences. Through the P01 mechanism, many basic scientific advances are developed, refined, and then developed into testable clinical hypotheses. The U01 cooperative agreements continue the progress made in P01 grants by performing

multicentered phase 2 and 3 clinical trials. Finally, the U24 cooperative agreements, a resource-related mechanism, provide important infrastructure for investigator-initiated research activities.

Major NCI-Supported Multisite Initiatives

Chronic Lymphocytic Leukemia Research Consortium. The Chronic Lymphocytic Leukemia Research Consortium is a premier example of translational science activity. For example, research findings from this P01 unveiled the potential role of oncogenes and microRNAs in the pathogenesis of chronic lymphocytic leukemia (CLL) and the skewed expression of ultra-conserved noncoding RNAs in human CLL relative to normal lymphocytes. MicroRNA34a, which is induced by activation of TP53, is involved in post-transcriptional silencing of the gene encoding the zeta-associated protein of 70 kilodaltons (ZAP-70). A mouse model of CLL developed in this P01 has permitted the evaluation of the capacity of lenalidomide to reverse the defective immunologic synapse observed in CLL patients. During the performance of this clinical study, laboratory work on patient samples revealed the role of an oncofetal protein, ROR1, and its defined ligand, Wnt5f, in the pathogenesis of CLL. Of particular interest, AD-ISF35 gene therapy induces anti-ROR1 autoantibodies in patients. Several promising drugs, including flavopiridol, 9-(2-phosphonylmethoxyethyl) guanine, GS-9219, beta-phenylethyl isothiocyanate, and XIAP antagonists, are also in development in this highly interactive P01.

Phase 3 Melanoma Trials (P01). The Principal Investigator at the John Wayne Cancer Institute has been awarded two P01 grants supporting international, multisite, randomized phase 3 trials in melanoma. Three trials from these grants are currently funded by NIH Comparative Effectiveness Research ARRA funds. The results of these trials will change the clinical practice of medicine for treatment of cutaneous melanoma:

1. Multicenter Selective Lymphadenectomy Trial (MSLT)-I examines the accuracy and clinical efficacy of sentinel node biopsy as a staging alternative to complete lymphadenectomy in patients with clinical stage I melanoma.
2. MSLT-II asks the provocative clinical question of whether melanoma patients with a positive sentinel node biopsy need additional immediate complete lymphadenectomy.
3. A Phase 3 Randomized Trial of Surgical Resection With or Without BCG versus Best Medical Therapy as Initial Treatment in Stage IV Melanoma

Brain Tumor Consortium. The Adult Brain Tumor Consortium, supported under the U01 mechanism, is a multi-institutional consortium. More than 50 clinical trials have been initiated in the last 5 years, involving over 2,000 patients studied in more than 18 new chemotherapy agents and strategies. This work has resulted in more than 80 publications and has initiated several original procedures:

- In the field of neuro-oncology, giving experimental drugs pre-operatively to assess tumor PK and pharmacodynamic endpoints



- Conducting gene transfer using adenoviral p53 in a novel design of biopsy, gene transfer, rapid resection of gene transfer, and further assessment of gene transfer
- Systematically describing the interaction of anticonvulsant enzyme-inducing agents with numerous chemotherapy agents

Cancer Childhood Survivor Study. The U24 Childhood Cancer Survivor Study (CCSS) is composed of two retrospectively ascertained cohorts of pediatric cancer survivors. The first cohort comprises approximately 20,000 survivors of pediatric cancers diagnosed between 1970 and 1986 at 27 contributing clinical centers and approximately 4,000 of their siblings. The second group is an equally large cohort of survivors diagnosed between 1987 and 1999. Major accomplishments of the CCSS are:

- Assembling a cohort of pediatric cancer survivors of this scale—the largest in the world
- Initiating, between 1998 and 2008, a total of 134 distinct studies. Of studies for which analysis is complete, 64 have so far resulted in at least one peer-reviewed publication.

Major Co-Funded Networks

Pharmacogenomics Research Network (U01).

The Pharmacogenomics Research Network (PGRN), supported by the U01 mechanism, has been funded since 2000 under a trans-NIH initiative led by the National Institute of General Medical Sciences. The goal of PGRN is to fund the highest-quality pharmacogenomics research for understanding the genomic basis of variable drug



responses, both therapeutic and adverse, with the potential for significance and/or impact leading to eventual translation into clinical application. The PGRN has deposited data and information for sharing into the Pharmacogenomics Knowledge Base (PharmGKB). CGCB has co-funded three PGRN sites. Their major accomplishments include:

- Providing FDA with information on the association of UGT1A1 polymorphisms with toxicity and the pharmacokinetics of irinotecan for a label change
- Reporting a preliminary clinical observation on a significant effect of polymorphisms in ABC and SLC transporter genes on the pharmacokinetics and pharmacodynamics of irinotecan
- First demonstration of the relationship between tamoxifen metabolism and its clinical effects that led the NCI to adopt endoxifen as a drug for intramural development and clinical use
- Reporting a significant association between potent wild-type CYP2D6 (inherited gene) activity and low HOXB13/IL17BR (tumor genes) expression ratio with increased disease-free survival and overall survival in tamoxifen-treated, estrogen receptor-positive breast cancer patients

Blood and Marrow Transplant Clinical Trials Network (U01).

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) was created through the U01 mechanism to address important issues in hematopoietic stem cell transplantation and to evaluate promising therapies for the treatment of both hematopoietic malignancies and nonmalignant disease. The network has a particularly effective, flexible structure composed of 16 core clinical centers and a data coordinating center, as well as the ability to add affiliate clinical centers on an as-needed basis to help with accrual. The network is supported at the NIH by a partnership between NCI and the National Heart, Lung, and Blood Institute, which is the lead institute. The network collaborates with other consortia, such as NCI Clinical Trials Cooperative Groups, to perform multisite clinical trials.

- The BMT CTN performs multicentered phase 2 and 3 clinical trials. There are 10 active open clinical trials, seven trials that are closed to accrual and are either in follow-up or data analysis, and four new protocols in development. More than 3,000 patients have been accrued to BMT CTN trials since 2003.
- The BMT CTN completed enrollment in 2007 on a study comparing tandem autologous transplantation with autologous transplantation followed by matched sibling allogeneic transplantation with a nonmyeloablative conditioning regimen in patients with multiple myeloma. Autologous transplantation is widely accepted as a standard of care for these patients. Allogeneic transplantation offers a potential graft-versus-myeloma effect, and this study addresses whether it offers additional benefit compared with

tandem autologous transplantation. In addition, the study evaluates the role of 1-year maintenance therapy with thalidomide plus dexamethasone after tandem autologous transplantation.

- An example of the benefits of collaboration with other consortia, the BMT CTN has helped the Cooperative Groups finish three trials that were lagging in accrual before the network joined, and recently joined a fourth trial. The multiple myeloma trial, known as CALGB 100104, closed early after reaching a positive outcome on the treatment arm. Prior to the participation of the BMT CTN, the trial was in danger of closing due to lack of accrual. Similarly, the Cooperative Groups have joined the majority of BMT CTN-led studies for treatment of hematopoietic malignancies.

New Initiative: The Cancer Immunotherapy Network

Immunotherapeutic approaches to treat cancers have demonstrated limited success despite considerable progress in understanding the biology of antitumor immune responses. A number of key immune modulators have shown a great deal of promise in preclinical studies, but these immune-modifying agents have yet to find a way to the clinic. To address this deficiency, a Request for Applications (RFA) has been developed that aims to fund a new Cancer Immunotherapy Trials Network (CITN) with FY 2010 funding. The RFA seeks to create a single consortium of leading investigators in immunotherapy to jointly develop and conduct phase 1 and early phase 2 multi-institutional clinical trials that could not be conducted efficiently by a single institution.



Regulatory Affairs Branch

Background

The Regulatory Affairs Branch (RAB) develops partnerships with industry and academics that allow for co-development of novel therapeutics and ensures that CTEP meets all its regulatory responsibilities with FDA regarding INDs.

Accomplishments

Standard non-negotiable agreement clauses have been developed, including multiparty data-sharing language, which is critical to CTEP's success in running combination studies of agents proprietary to different companies. A nonexclusive royalty-free licensing option incentivizes multiple companies to collaborate on a single trial. RAB's standard "IP Option to Collaborator"/"Combination IP Option" language addresses collaborator IP rights with respect to inventions generated under a CTEP funding agreement.

Most recently, a proposed revision to the IP Option was developed and published in the Federal Register for public comment. There has been a lack of clarity regarding ownership interest in inventions generated from data and agent-treated samples. With more and more clinical studies of targeted therapies incorporating biomarkers, which potentially could lead to a new diagnostic, the proposed language addresses the disposition of such IP.

Examples of studies moving forward due to CTEP-sponsored CRADAs using IP agreement terms include:

- Combination of a PARP inhibitor (AZD2281) with an anti-angiogenic agent (cedirinib) in ovarian cancer, based on the single-agent activity of each agent and the potential for synergy based on the additional anti-angiogenic effects of PARP inhibition
- Study to test the combination of PDGRFA and mTOR inhibition utilizing the tyrosine kinase inhibitor imatinib and the rapamycin analogue everolimus in the treatment of synovial sarcomas
- A proposed phase 2 trial in ovarian cancer testing a combination of the vascular targeted agents bevacizumab and fosbretabulin

RAB actively manages a portfolio of approximately 100 INDs, representing a wide variety of agents.

The following INDs were filed in 2009:

- Recombinant *Saccharomyces cerevisiae*-CEA(610D): GI-62076 from GlobeImmune; immunotherapeutic
- SCH727965: Schering-Plough Research Institute; cyclin-dependent kinase inhibitor
- Fostamatanib disodium: R935788 from Rigel Pharmaceuticals; syk kinase inhibitor
- 5-Fluoro-2'-deoxycytidine and tetrahydrouridine: NCI, fluoropyrimidine antimetabolite prodrug; biomodulator
- LMP400 and LMP776: NCI; topoisomerase 1 inhibitor
- RO4929097: Hoffmann-LaRoche; selective gamma-secretase inhibitor

RAB is CTEP's primary interface with the FDA on an assortment of activities. To facilitate interactions among the FDA, NCI, and industry, RAB coordinates an FDA-NCI monthly meeting with the FDA Oncology Director and staff. This standing meeting is used to discuss issues of common interest related to oncology drugs and their approval, with the ultimate goal of streamlining drug development.

Examples of Targeted/Novel Agents Under CTEP IND

EGFR/HER pathway:
 Erlotinib (OSI Pharm)
 Gefitinib (AstraZeneca)
 Cetuximab (ImClone)
 Trastuzumab (Genentech)
 Pertuzumab (Genentech)
 Lapatinib (GSK)

IGF-1R: IMC-A12 (ImClone)
 MEK: AZD6244 (AstraZeneca)
 mTOR: CCI-779 (Wyeth)
 AKT: MK2206 (Merck)

Signal transduction/cell cycle:
 Flavopiridol (Sanofi)
 SCH 727965 (Merck)

Stem cell-targeted agents:
 DC-0449 (Genentech)
 O4929097 (Roche)

Other:
 Dasatinib (BMS)
 FTI (R115777) (J&J)
 Imatinib (Novartis)

Anti-angiogenesis:
 Sunitinib (Pfizer)
 Bevacizumab (Genentech)
 VEGF Trap (Aventis)
 Sorafenib (Bayer)
 Cediranib (AstraZeneca)
 Cilengitide (EMD)

BCL-2 family:
 AT-101 (Ascenta)
 GX15-070 (Gemin X)
 ABT-263 (Abbott)

HDAC inhibitors:
 Vorinostat (Merck)
 Belinostat (TopoTarget)
 Depsipeptide (Gloucester)

Protease/chaperone:
 PS-341 (Millennium)
 17-AAG (NCI)

Immune modulators:
 Anti-CTLA-4 (Medarex)
 1-Methyltryptophan (New Link Genetics)

Pharmaceutical Management Branch

Background

The Pharmaceutical Management Branch (PMB) provides pharmaceutical services for clinical trials sponsored by CTEP. Because CTEP manages clinical trials of more than 100 investigational agents, research pharmacists in PMB must be focused on the latest advances in oncology practice and provide guidance for the thousands of sites around the country performing research with these novel agents. In brief, this branch provides a unique national resource for experimental oncology products and supports CTEP's clinical research effort by providing the extramural community with specific pharmaceutical services, regulatory oversight, and administrative support.

Accomplishments

Active Investigator Registration. More than 18,000 investigators are registered with PMB to receive shipments. Of these, 16,000 are domestic investigators and 2,000 are international investigators. Nearly 44,000 investigational agent shipments supported CTEP-sponsored trials in 2009:

- Foreign shipments: 1,600 (15 countries)
- "Blinded-order" shipments: 29,000 (for 30 blinded protocols accruing patients)
- Standard order shipments: 13,000
- Shipment accuracy rate: 99.991% (less than 1 error in 10,000 shipments)

Specialized Resources Available to Support Randomized, Placebo-Controlled Studies. The development, implementation, support, and monitoring of blinded trials require



the development of specialized computer programming for each trial to ensure that the correct medication or placebo reaches the appropriate patient in a timely manner. There are 30 blinded trials eligible to accrue patients and six more in development.

Investigator Community Service and Support Projects. PMB provides a number of support services to the research community. The PMB website provides investigators and the associated community valuable and time-saving online tools to meet regulatory requirements. The website receives about 1,200 hits per month. The *Inside PMB* newsletter is an innovative and creative publication that has been distributed quarterly for seven years to investigators and associates. The newsletter is now distributed 100% electronically and all editions are posted on the website for reference. PMB also has an after-hours e-mail address where investigators and support staff can send questions 24 hours a day, 7 days a week, 365 days per year. The address is particularly helpful for sites outside the continental United States and international sites. The routine response time is within one business day, and there are more than 350 inquiries per month. Finally, PMB distributes Investigator Brochures, which contain confidential and important information required by the investigator to develop and conduct clinical trials. PMB has implemented a responsive and cost-effective method of distributing the brochures to investigators via the Internet. For institutions that cannot receive the documents electronically, PMB provides a CD by mail; 84% are sent via e-mail and 16% via CD. Nearly 13,000 Investigator Brochures are distributed annually.

Clinical Trials Monitoring Branch

Background

The Clinical Trials Monitoring Branch (CTMB) supports the phase 1, phase 2, and Cooperative Group Programs by providing a quality assurance system for CTEP-sponsored trials. This system ensures that data are reliable and compliant with protocols and that they meet regulatory and Good Clinical Practice requirements.

Accomplishments

The Quality Assurance Program includes:

- Establishing standards for evaluating the conduct of research and the reporting of audit findings
- Ensuring the protection of research patients
- Monitoring the conduct of clinical trials by conducting onsite audits to ensure data quality, compliance with the protocol, and adherence to regulatory requirements, NCI policies, and Good Clinical Practice requirements
- Continuing education of investigators and research institutional sites through onsite audits to share information on data quality, data management, and other aspects of quality assurance

Scope of program:

- The Quality Assurance Program includes institutions conducting phase 1 and phase 2 trials (including N01 sites), Cooperative Groups, CCOPs, Cancer Centers, and all other institutions conducting clinical research trials sponsored by CTEP/ and NCI

- Oversight and coordination of audit procedures for international sites participating in CTEP or DCTD clinical trials

**AUDIT STATISTICS, JANUARY 2005 TO
JANUARY 2010**

Organization/Type Study	Audits	Protocols	Patient Cases
Phase 1/2 studies	364	195	288
Cooperative Groups	10,292	3,732	74,692
Cancer Centers and single institutions	114	495	543

New initiatives:

- To strive for 100% of clinical research data to be submitted electronically
- Utilization of informatics infrastructure to perform robust remote data monitoring to identify trends in data elements suggestive of data irregularities
 - Explore the feasibility of utilizing the informatics infrastructure to support remote data auditing of source documents contained in electronic medical records, thereby reducing costs associated with logistical issues such as travel and site preparation. An end-user's group composed of representatives from several of the Cooperative Groups has been established to investigate and test the feasibility of this approach and to identify and address barriers such as HIPAA, ensuring security, firewalls, etc.

Clinical Trials Operations and Informatics Branch

Background

The Clinical Trials Operations and Informatics Branch (CTOIB) supports the development and management of CTEP-sponsored clinical trials through the use of IT tools and systems and the business activities of the Protocol Information Office. CTOIB oversees these two functional areas, which serve as the backbone for the CTEP trial review and management process.

Protocol and Information Office

In 2009, the Protocol Information Office processed:

- 160 unsolicited LOIs
- 258 protocols
- 312 mass-solicited LOIs
- 364 revisions
- 41 concepts
- 1,326 amendments

CTEP Enterprise System

The CTEP Enterprise System (CTEP ESYS) is the central IT system used to manage the development and conduct of CTEP-sponsored clinical trials. The CTEP ESYS also supports the Division of Cancer Prevention CCOP and CIP-sponsored trials. The CTEP ESYS comprises 22 applications that are both internal and external facing. CTOIB has been involved in the development of NCI-centralized protocol databases (i.e., the Clinical Trials Registration Program) and as a result has been in the process of modernizing the CTEP ESYS to facilitate



the complete integration of all required NCI internal databases. CTOIB integration activities include:

- Clinical trials reporting program
- Electronic case report forms
- Electronic protocol authoring, review, and commenting tools (ePA)
- Remote data capture systems (a clinical data monitoring system project)

The CTEP ESYS has been utilized since 1997 and allows CTEP to report data on adverse events, accrual, demographics, and response to interested parties to reliably assess the performance of clinical trials.

The CTEP ESYS contains data on:

- 10,097 LOIs
- 892,014 patient records
- 1,061 concepts
- 396,078 expedited adverse-event reports
- 21,847 protocols
- 901,826 expedited and routine adverse-event reports

The CTEP ESYS contains three critical components used for submitting information to CTEP:

1. Adverse event expedited reporting system (AdeERS)—Used by members of the external community to inform IND sponsors and the FDA of serious adverse events occurring during trials
2. Clinical data update system (CDUS)—Used by the external community to submit patient accrual information,

demographic makeup of accrued patients, response data, and routine adverse events to CTEP to facilitate stronger oversight of trial conduct.

3. Identity and access management (IAM)—Used by members of the external community and CTEP to securely manage access to applications. IAM allows for single-source sign-on to all CTEP-managed applications and reduces the need for multiple usernames and passwords. The CTEP ESYS also stores all of the data related to the Clinical Toxicity Criteria for Adverse Event (CTCAE), which allows for usage of current terminology when submitting adverse-event data.

Operational Efficiency Working Group Involvement

To support the Operational Efficiency Working Group (OEWG) recommendations to improve protocol development timelines, CTOIB is opening its services for use by extramural investigators. The timeline reports website will provide a centralized protocol tracking service so that all investigators will have 24/7 online access to information about the status of their protocols in the development and approval process. This will help CTEP and its investigators to reduce protocol development timelines by more than 75%.

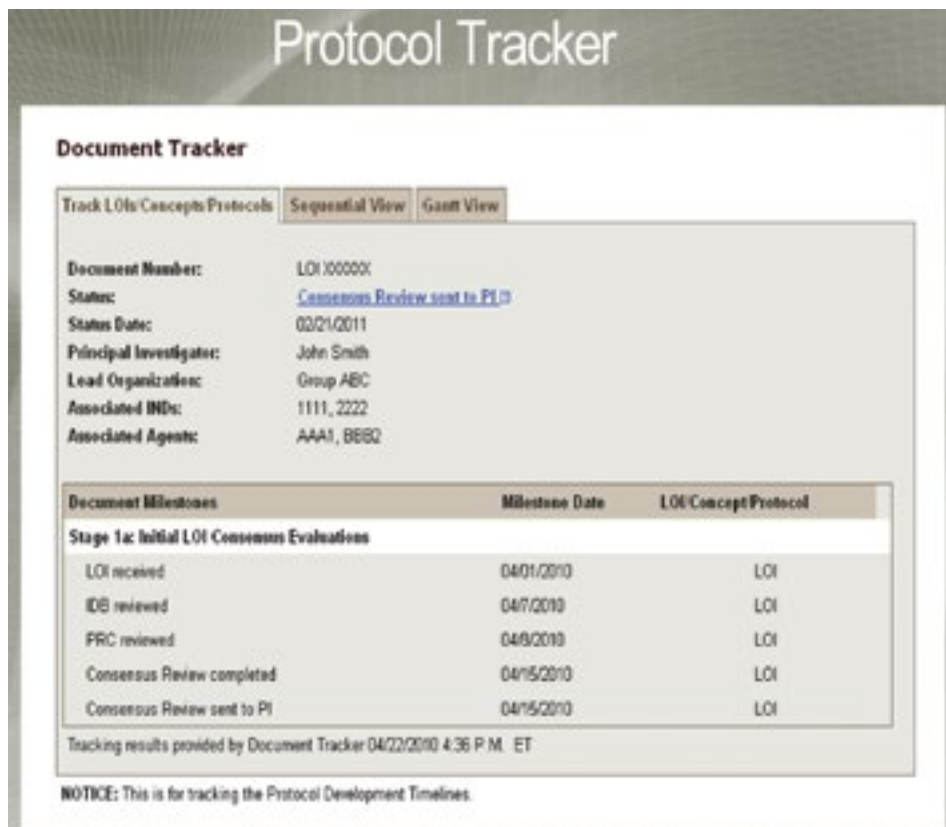
FUTURE DIRECTIONS

There are three key areas of focus for CTEP over the next 5 years: (1) expanded efforts in targeted therapeutics in early-phase trials, (2) improvement in development and accrual timelines for large phase 2 and 3 trials, and (3) increased contributions to the mentoring of the next generation of clinical investigators.

Expand Targeted Therapeutics in Phase 1/2

Trials. To remain at the forefront of cancer treatment, CTEP must increasingly focus its efforts and resources on clinical trials that have the greatest likelihood of disrupting the most important mechanisms of cancer cell growth, differentiation, and metastases. Translating scientific discoveries into clinically effective and safe interventions will require CTEP to:

- Serve as the key clinical facilitator for the newly created NCI Experimental Therapeutics (NExT) program, designed to reinvigorate the ability of academic investigators to bring novel agents into the clinic
- Improve and expand relationships with pharmaceutical and biotechnology companies to leverage their investments in drug discovery as agents increasingly target smaller, molecularly defined populations
- Design trials enriched with biomarkers, using improved technology, especially in solid tumors, to enable pre- and post-therapy assessments of tissue, blood, and functional imaging
- Integrate and align drug development efforts with other major NCI biomarker





and pathway discovery programs, such as the Cancer Human Biobank, the Clinical Assay Development Program, Patient Characterization Centers, and The Cancer Genome Atlas Project

Improve Timelines for Developing and Accruing to Large Phase 2 and 3 Trials:

- Monitor and track the target timelines for every CTEP-sponsored protocol
- Develop metrics that allow realistic expectations of the workload (number of trials) that can be supported with the resources provided to investigators by CTEP
- Coordinate with patient advocates, community physicians, and other allies to educate cancer patients about clinical trials and the benefits of participation
- Leverage technology to promote consistent standards, templates, tools, and reports so that clinical trial methods become more uniform throughout the NCI system

Expand CTEP Contributions to Mentoring the Next Generation of Clinical Investigators:

- Expand the CTEP fellowship program, whereby U.S. oncology fellows spend 1–3 months at CTEP participating in protocol review
- Increase attendance from U.S. fellows at CTEP's Early Drug Development Meetings
- Continue the CrDL LOI program for new fellows
- Continue annual meetings of the American Society of Clinical Oncology with young investigators hosted by CTEP

SELECTED PUBLICATIONS

Investigational Drug Branch

Patients with chemotherapy-refractory mantle cell lymphoma experience high response rates and identical progression-free survivals compared with patients with relapsed disease following with single agent bortezomib: results of a multicentre phase 2 clinical trial, O'Connor OA, Moskowitz C, Portlock C, Hamlin P, Straus D, Dumitrescu O, Sarasohn D, Gonen M, Butos J, Neylon E, Hamelers R, Mac-Gregor Cortelli B, Blumel S, Zelenetz AD, Gordon L, Wright JJ, Vose J, Cooper B, Winter J. *British Journal of Haematology*, 2009;145:34–39.

<http://www.ncbi.nlm.nih.gov/pubmed/19220284>

Lack of therapeutic effect of the histone deacetylase inhibitor vorinostat in patients with metastatic radioiodine-refractory thyroid carcinoma, Woyach JA, Kloos RT, Ringel M, Arbogast D, Collamore M, Zwiebel J, Grever M, Villalona-Calero M, Shah MH. *Journal of Clinical Endocrinology and Metabolism*, 2009;94:164–170.

<http://www.ncbi.nlm.nih.gov/pubmed/18854394>

Phase 2 multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma, Piekarcz RL, Frye R, Turner M, Wright JJ, Allen SL, Kirschbaum MH, Zain J, Prince HM, Leonard JP, Geskin LJ, Reeder C, Joske D, Figg WD, Gardner ER, Steinberg SM, Jaffe ES, Stetler-Stevenson M, Lade S, Fojo AT, Bates SE. *Journal of Clinical Oncology*, 2009;27:5410–5417.

<http://www.ncbi.nlm.nih.gov/pubmed/19826128>

A phase 2 study of vorinostat in acute myeloid leukemia, Schaefer EW, Loaiza-Bonilla A, Juckett M, DiPersio JF, Roy V, Slack J, Wu W, Laumann K, Espinoza-Delgado I, Gore SD; Mayo P2C Phase II Consortium. *Haematologica*, 2009;94:1375–1382.

<http://www.ncbi.nlm.nih.gov/pubmed/19794082>

Carboplatin and paclitaxel in combination with either vorinostat or placebo for first-line therapy of advanced non-small-cell lung cancer, Ramalingam SS, Maitland ML, Frankel P, Argiris AE, Koczywas M, Gitlitz B, Thomas S, Espinoza-Delgado I, Vokes EE, Gandara DR, Belani CP. *Journal of Clinical Oncology*, 2010;28:56–62.

<http://www.ncbi.nlm.nih.gov/pubmed/19933908>

Guidelines for the development and incorporation of biomarker studies in early clinical trials of novel agents, Dancey JE, Dobbin KK, Groshen S, Jessup JM, Hruszkewycz AH, Koehler M, Parchment R, Ratain MJ, Shankar LK, Stadler WM, True LD, Gravell A, Grever MR; Biomarkers Task Force of the NCI Investigational Drug Steering Committee. *Clinical Cancer Research*, 2010;16:1745–1755.

<http://www.ncbi.nlm.nih.gov/pubmed/20215558>

Approaches to phase 1 clinical trial design focused on safety, efficiency, and selected patient populations: a report from the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee, Ivy SP, Siu LL, Garrett-Mayer E, Rubinstein L. *Clinical Cancer Research*, 2010;16:1726–1736.

<http://www.ncbi.nlm.nih.gov/pubmed/20215542>

The design of phase 2 clinical trials testing cancer therapeutics: consensus recommendations from the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee, Seymour L, Ivy SP, Sargent D, Spriggs D, Baker L, Rubinstein L, Ratain MJ, Le Blanc M, Stewart D, Crowley J, Groshen S, Humphrey JS, West P, Berry D. *Clinical Cancer Research*, 2010;16:1764–1769.

<http://www.ncbi.nlm.nih.gov/pubmed/20215557>

Clinical Investigations Branch

Selected Practice-Changing NCI-CTEP-Supported Group Phase 3 Trials (2004–2009)

Brain Cancer—RTOG-9402. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Oncology Group Trial 9402, Cairncross G, Berkey B, Shaw E, Jenkins R, Scheithauer B, Brachman D, Buckner J, Fink K, Souhami L, Laperriere N, Mehta M, Curran W. *Journal of Clinical Oncology*, 2006;27:2707–2714.

<http://www.ncbi.nlm.nih.gov/pubmed/16782910>

Breast Cancer—NSABP B-31 and NCCTG-N9831. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer, Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N. *New England Journal of Medicine*, 2005;353:1673–1684.

<http://www.ncbi.nlm.nih.gov/pubmed/16236738>

Childhood/Pediatric Cancers:

COG-ANBL0032: Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma, Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, Smith M, Anderson B, Villablanca JG, Matthay KK, Shimada H, Grupp SA, Seeger R, Reynolds CP, Buxton A, Reisfeld RA, Gillies SD, Cohn SL, Maris JM, Sondel PM; Children's Oncology Group. *New England Journal of Medicine*, 2010;363:1324–34.

<http://www.ncbi.nlm.nih.gov/pubmed/20879881>

COG-AALL0031: Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia:



a children's oncology group study, Schultz KR, Bowman WP, Aledo A, Slayton WB, Sather H, Devidas M, Wang C, Davies SM, Gaynon PS, Trigg M, Rutledge R, Burden L, Jorstad D, Carroll A, Heerema NA, Winick N, Borowitz MJ, Hunger SP, Carroll WL, Camitta B. *Journal of Clinical Oncology*, 2009;27:5175–5181.
<http://www.ncbi.nlm.nih.gov/pubmed/19805687>

COG-AEWS0031: Randomized comparison of every-two-week v. every-three-week chemotherapy in Ewing sarcoma family tumors (ESFT), Womer RB, West DC, Krailo MD, Dickman PS, Pawel B; Children's Oncology Group AEWS0031 Committee. *Journal of Clinical Oncology*, 2008;26(May 20 suppl; abstr 10504).
http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/10504

COG-CCG-1961: Early postinduction intensification therapy improves survival for children and adolescents with high-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group, Seibel NL, Steinherz PG, Sather HN, Nachman JB, Delaat C, Ettinger LJ, Freyer DR, Mattano LA Jr, Hastings CA, Rubin CM, Bertolone K, Franklin JL, Heerema NA, Mitchell TL, Pyesmany AF, La MK, Edens C, Gaynon PS. *Blood*, 2008;111:2548–2555.
<http://www.ncbi.nlm.nih.gov/pubmed/18039957>

Colorectal Cancer. NCCTG-N9741: A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer, Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts SR. *Journal of Clinical Oncology*, 2004;22:23–30.
<http://www.ncbi.nlm.nih.gov/pubmed/14665611>

GI Stromal Tumors/Sarcoma. ACOSOG-Z9001: Adjuvant imatinib mesylate after resection of localized, primary gastrointestinal stromal tumour: a randomized, double-blind, placebo-controlled trial, DeMatteo RP, Ballman KV,

Antonescu CR, Maki RG, Pisters PW, Demetri GD, Blackstein ME, Blanke CD, von Mehren M, Brennan MF, Patel S, McCarter MD, Polikoff JA, Tan BR, Owzar K; American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team. *Lancet*, 2009;373:1097–1104.
<http://www.ncbi.nlm.nih.gov/pubmed/19303137>

Gynecologic Cancers. GOG-0172: Intraperitoneal cisplatin and paclitaxel in ovarian cancer, Armstrong D, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, Copeland LJ, Walker JL, Burger RA; Gynecologic Oncology Group. *New England Journal of Medicine*, 2006;354:34–43.
<http://www.ncbi.nlm.nih.gov/pubmed/16394300>

Leukemia (AML). E1900: Anthracycline dose intensification in acute myeloid leukemia, Fernandez HF, Sun Z, Yao X, Litzow MR, Luger SM, Paietta EM, Racevskis J, Dewald GW, Ketterling RP, Bennett JM, Rowe JM, Lazarus HM, Tallman MS. *New England Journal of Medicine*, 2009;361:1249–1259.
<http://www.ncbi.nlm.nih.gov/pubmed/19776406>

Lung Cancer. NCIC-CTG BR.10: Vinorelbine plus cisplatin vs. observation in resected non-small cell lung cancer, Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, Cormier Y, Goss G, Inculet R, Vallieres E, Fry W, Bethune D, Ayoub J, Ding K, Seymour L, Graham B, Tsao MS, Gandara D, Kesler K, Demmy T, Shepherd F; National Cancer Institute of Canada Clinical Trials Group; National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators. *New England Journal of Medicine*, 2005;353:2589–2597.
<http://www.ncbi.nlm.nih.gov/pubmed/15972865>

Prostate Cancer. SWOG 99-16: Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer, Petrylak DP, Tangen CM, Hussain MHA, Lara PN Jr, Jones JA, Taplin ME, Burch PA, Berry D, Moinpour C, Kohli M, Benson MC, Small EJ, Raghavan D, Crawford ED. *New England Journal*

of Medicine, 2004;351:1513–1520.
<http://www.ncbi.nlm.nih.gov/pubmed/15470214>

Surgery. *NCCTG and Clinical Outcomes of Surgical Therapy Study Group: A Comparison of laparoscopically assisted and open colectomy for colon cancer*, Nelson H, Sargent DJ, Wieand SJ; Clinical Outcomes of Surgical Therapy Study Group. *New England Journal of Medicine*, 2004;350:2050–2059.
<http://www.ncbi.nlm.nih.gov/pubmed/15141043>

Clinical Grants and Contracts Branch

Detection of mutations in EGFR in circulating lung-cancer cells, Maheswaran S, Sequist LV, Nagrath S, Ulkus L, Brannigan B, Collura CV, Inserra E, Diederichs S, Iafraite AJ, Bell DW, Digumarthy S, Muzikansky A, Irimia D, Settleman J, Tompkins RG, Lynch TJ, Toner M, Haber DA. *New England Journal of Medicine*, 2008;359:366–377.
<http://www.ncbi.nlm.nih.gov/pubmed/18596266>

Treating childhood acute lymphoblastic leukemia without cranial irradiation, Pui CH, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC, Ribeiro RC, Rubnitz JE, Raimondi SC, Onciu M, Coustan-Smith E, Kun LE, Jeha S, Cheng C, Howard SC, Simmons V, Bayles A, Metzger ML, Boyett JM, Leung W, Handgretinger R, Downing JR, Evans WE, Relling MV. *New England Journal of Medicine*, 2009;360:2730–2741.
<http://www.ncbi.nlm.nih.gov/pubmed/19553647>

Genetic polymorphism of inosine triphosphate pyrophosphatase is a determinant of mercaptopurine metabolism and toxicity during treatment for acute lymphoblastic leukemia, Stocco G, Cheok MH, Crews KR, Dervieux T, French D, Pei D, Yang W, Cheng C, Pui CH, Relling MV, Evans WE. *Clinical Pharmacology and Therapeutics*, 2009;85:164–172.
<http://www.ncbi.nlm.nih.gov/pubmed/18685564>

Germline genomic variants associated with childhood acute lymphoblastic leukemia, Treviño LR, Yang W, French D, Hunger SP, Carroll WL, Devidas M, Willman C, Neale G, Downing J, Raimondi SC, Pui CH, Evans WE, Relling MV. *Nature Genetics*, 2009;41:1001–1007.
<http://www.ncbi.nlm.nih.gov/pubmed/19684603>

Karyotypic abnormalities create discordance of germline genotype and cancer cell phenotypes, Cheng Q, Yang W, Raimondi SC, Pui CH, Relling MV, Evans WE. *Nature Genetics*, 2005;37:878–882.
<http://www.ncbi.nlm.nih.gov/pubmed/16041371>

Sentinel-node biopsy or nodal observation in melanoma, Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Elashoff R, Essner R, Nieweg OE, Roses DF, Hoekstra HJ, Karakousis CP, Reintgen DS, Coventry BJ, Glass EC, Wang HJ; MSLT Group. *New England Journal of Medicine*, 2006;355:1307–1317.
<http://www.ncbi.nlm.nih.gov/pubmed/17005948>

Tcl1 expression in chronic lymphocytic leukemia is regulated by miR-29 and miR-181, Pekarsky Y, Santanam U, Cimmino A, Palamarchuk A, Efanov A, Maximov V, Volinia S, Alder H, Liu CG, Rassenti L, Calin GA, Hagan JP, Kipps T, Croce CM. *Cancer Research*, 2006;66:11590–11593.
<http://www.ncbi.nlm.nih.gov/pubmed/17178851>

Tcl1 functions as a transcriptional regulator and is directly involved in the pathogenesis of CLL, Pekarsky Y, Palamarchuk A, Maximov V, Efanov A, Nazaryan N, Santanam U, Rassenti L, Kipps T, Croce CM. *Proceedings of the National Academy of Sciences of the United States of America*, 2008;105:19643–19648.
<http://www.ncbi.nlm.nih.gov/pubmed/19064921>

ZAP-70 enhances IgM signaling independent of its kinase activity in chronic lymphocytic leukemia, Chen L, Huynh L, Apgar J, Tang



L, Rassenti L, Weiss A, Kipps TJ. *Blood*, 2008;111:2685–2692.
<http://www.ncbi.nlm.nih.gov/pubmed/18048647>

ZAP-70 directly enhances IgM signaling in chronic lymphocytic leukemia, Chen L, Apgar J, Huynh L, Dicker F, Giago-McGahan T, Rassenti L, Weiss A, Kipps TJ. *Blood*, 2005;105:2036–2041.
<http://www.ncbi.nlm.nih.gov/pubmed/15514014>

ZAP-70 compared with immunoglobulin heavy-chain gene mutation status as a predictor of disease progression in chronic lymphocytic leukemia, Rassenti LZ, Huynh L, Toy TL, Chen L, Keating MJ, Gribben JG, Neuberg DS, Flinn IW, Rai KR, Byrd JC, Kay NE, Greaves A, Weiss A, Kipps TJ. *New England Journal of Medicine*, 2004;26:351:893–901.
<http://www.ncbi.nlm.nih.gov/pubmed/15329427>

Blood and Marrow Transplant Clinical Trials Network State of the Science Symposium 2007, Ferrara JL, Anasetti C, Stadtmauer E, Antin J, Wingard J, Lee S, Levine J, Schultz K, Appelbaum F, Negrin R, Giralt S, Bredeson C, Heslop H, Horowitz M. *Blood Marrow Transplantation*, 2007;13:1268–1285.
<http://www.ncbi.nlm.nih.gov/pubmed/17950914>

Phase 1 study of temozolomide and irinotecan for recurrent malignant gliomas in patients receiving enzyme-inducing antiepileptic drugs: a North American Brain Tumor Consortium study, Lohin ME, Prados M, Wen P, Junck L, Lieberman F, Fine H, Fink KL, Mehta M, Kuhn J, Lamborn K, Cloughesy T, DeAngelis LM, Robins IH, Yung WKA. *Clinical Cancer Research*, 2007;13:7133–7138.
<http://www.ncbi.nlm.nih.gov/pubmed/18056194>

A phase 1 trial of erlotinib in patients with nonprogressive glioblastoma multiforme postradiation therapy, and recurrent malignant gliomas and meningiomas, Raizer JJ, Abrey LE, Lassman AB, Chang SM, Lamborn KR, Kuhn JG, Yung WKA, Gilbert MR, Aldape KA, Wen P, Fine HA, Mehta M, DeAngelis LM, Lieberman F, Cloughesy TF, Robins IH, Dancey J, Prados MD; North American Brain Tumor Consortium. *Neuro-Oncology*, 2010;12:87–94.
<http://www.ncbi.nlm.nih.gov/pubmed/20150371>



2010 Program
Accomplishments

Developmental Therapeutics Program



OVERVIEW

The [Developmental Therapeutics Program \(DTP\)](#) provides services, resources, and leadership to the academic and private-sector research communities worldwide to facilitate the discovery and development of new cancer therapeutic and imaging agents. Historically, DTP has been involved in the discovery or development of more than 70% of the anticancer therapeutics on the market today. Two of the five new drugs approved by the U.S. Food and Drug Administration (FDA) in 2009 were developed by DTP—pralatrexate, for peripheral T-cell lymphoma; and romidepsin, a depsipeptide, for cutaneous T-cell lymphoma. DTP also contributed to the preclinical development of sipuleucel-T (Provenge), a new treatment for prostate cancer approved by FDA in 2010 as the first therapeutic vaccine.

DTP provides unique services to the cancer research community:

- Materials:
 - Samples of individual compounds for research
 - Large plated sets of compounds for high-throughput screening
 - Biopharmaceuticals, such as monoclonal antibodies and cytokines
 - Tumor cell lines and cell line extracts (DNA, RNA)
 - Laboratory animals
- Data sets and data mining tools:
 - Data from in vitro screening of compounds submitted by investigators
 - Web-based databases of historical screening records

- Data-mining tools, such as the COMPARE, and the molecular targets program
- Grants:
 - In 2010, 901 active grants were managed by DTP.

DTP maintains resources for a robust discovery and development infrastructure:

- Natural product collection, extraction, and characterization
- Chemical libraries, chemical synthesis, and structure–activity modeling
- In vitro and in vivo preclinical efficacy testing
- Lead compound synthesis, pharmaceutical optimization, formulation, and manufacturing under current Good Manufacturing Practice (cGMP)
- Pharmacology and toxicology testing, under current Good Laboratory Practice (cGLP)
- Technical document preparation and review for Investigational New Drug (IND) applications to the FDA
- Academic investigator access to research and development resources through the [National Cancer Institute \(NCI\) Experimental Therapeutics \(NExT\)](#) program

DTP provides leadership to the cancer research community:

- Overcoming financial and technical barriers to high-risk projects
- Addressing unmet medical needs

JERRY M. COLLINS, ASSOCIATE DIRECTOR

Jerry M. Collins, Ph.D., is an internationally recognized pharmacologist who 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 NCI's Pharmacokinetics Section. From 1988 until 2005, Dr.

Collins served as the Director of the FDA 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's areas of expertise are clinical pharmacology, the application of pharmacokinetic and pharmacodynamic principles to cancer research, and increasing biomarker efficacy with positron emission tomography (PET).

Dr. Collins received his bachelor degree from Drexel University and his master and doctoral degrees from the University of Pennsylvania. He has authored or co-authored over 180 papers in the field of clinical pharmacology, primarily emphasizing the applications of pharmacokinetic and pharmacodynamic principles in the field of cancer. His current work also includes extending these principles with PET imaging.



Recent Leadership Example:

Chimeric Monoclonal Antibody 14.18 for the Treatment of High-Risk Neuroblastoma

- Monoclonal antibody ch14.18 targets a specific glycolipid, GD2, on the surface of neuroblastoma cells
- Approximately 500 new high-risk neuroblastoma patients diagnosed per year in the United States
- ch14.18 manufacturing processes developed by the DTP Biological Resources Branch
- In 2010, ch14.18 plus granulocyte macrophage–colony-stimulating factor (GM-CSF), interleukin 2 (IL-2), and isotretinoin in combination becomes new standard treatment for pediatric neuroblastoma; the combination increased overall survival to 66%, compared with 46% for the previous standard of care
- DTP, the sole ch14.18 manufacturer, will supply all eligible clinical trial patients until a marketing partner receives FDA approval of the antibody

Innovative scientific and administrative initiatives implemented by the Division of Cancer Diagnosis and Treatment (DCTD) and DTP senior leadership to support the research community and increase the pipeline of anticancer agents in development:

- In 2009, the [Chemical Biology Consortium \(CBC\)](#) was established
 - 12 member institutions, mostly extramural, but also including the NCI

intramural chemical biology groups and the NIH Chemical Genomics Center

- Will bring medicinal chemistry, molecular target assay development, and high-throughput library screening to bear on cancer-related pathways and drug discovery for academic investigators
- The CBC is the early discovery engine for the NExT initiative
- NExT initiative established in 2009
 - Brought together the Rapid Access to Intervention Development (RAID) program, the Drug Discovery Group, the Joint Development Committee, and other pipelines under a single, well-documented system of peer review and governance
- DTP staff and resources are integral to the implementation of the CBC and NExT drug discovery and development initiatives

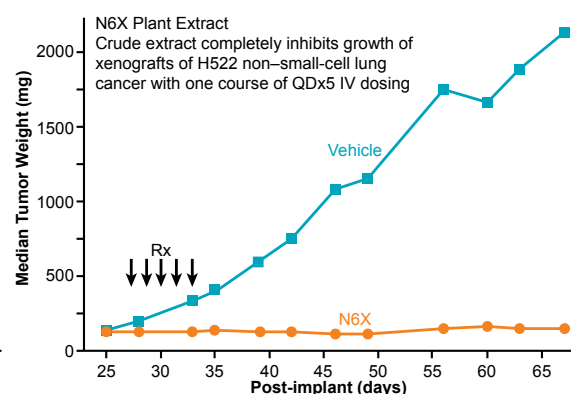
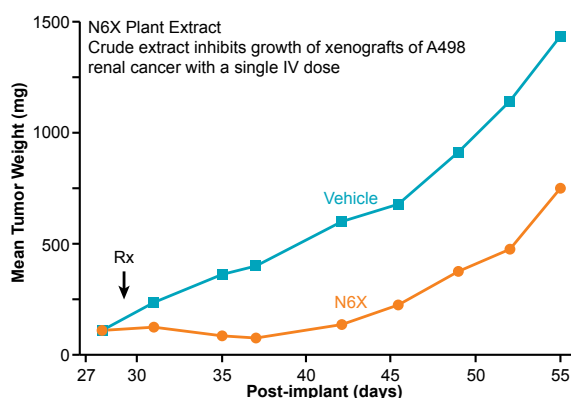
A re-invigorated natural products initiative to enhance the NCI drug discovery pipeline:

- Pharmaceutical companies have largely abandoned development of molecules derived from natural products
- Evaluation of the sources of new drugs from January 1981 to June 2006 reveals that approximately 78% of drugs in the cancer treatment arena were naturally derived directly or inspired, i.e., competitively inhibiting a natural product substrate
- DTP has the world's largest natural product repository
- DTP has returned to testing natural product extracts after a six-year hiatus

- Evaluating potential new opportunities related to fungi, the conditions under which they are grown, and the modulation of the products they produce
- Recent discovery from the crude extract of a plant from Papua, New Guinea,

that inhibits growth of A498 renal cell cancers in mice with a single intravenous (IV) dose and H522 non-small-cell lung cancer with a single course (daily for five days, IV), with minimal toxicity; the active ingredient is being identified in ongoing research

N6X PAPUA, NEW GUINEA, PLANT EXTRACT—PRELIMINARY ACTIVITY

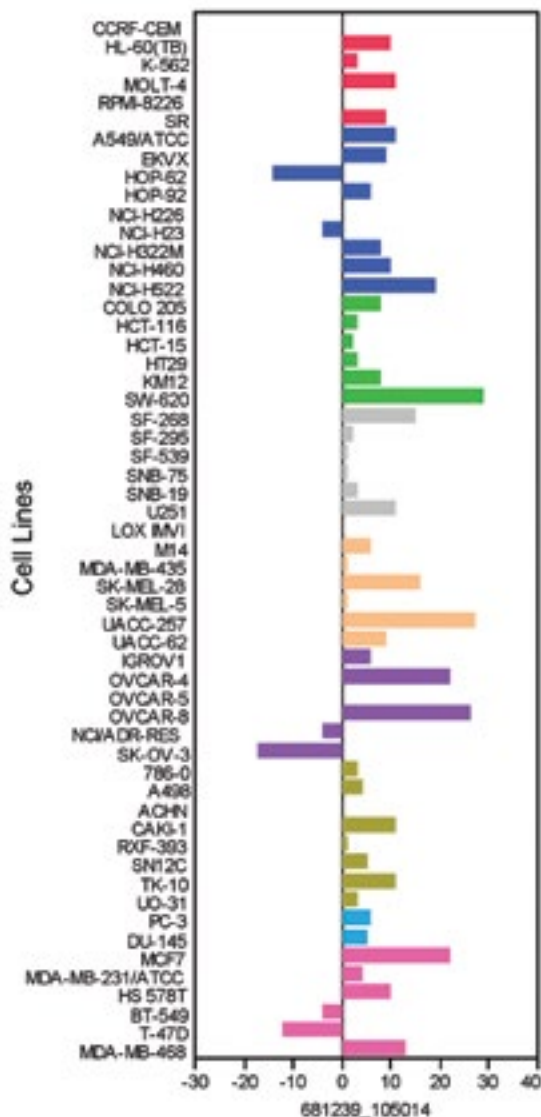


Most chemotherapy regimens involve combinations of agents:

- DTP has initiated projects to evaluate combinations of agents in the NCI-60 cell line screening assay and the in vivo hollow-fiber and xenograft models. An example of a striking combination: bortezomib, a proteasome inhibitor, and cladribine, a purine analog
- The datasets from the combinatorial screening of FDA-approved anticancer drugs in the NCI-60 cell lines will be placed in the public domain on the DTP website

To complement empirical approaches to drug-combination discovery:

- DTP is characterizing the genetic signatures of the NCI-60 cell line panel after exposure to critical FDA-approved drugs, using a systems biology model to characterize the gene responses of these lines as a function of time and drug-induced perturbations; data will guide selection of the most appropriate cell lines to use in the testing of new molecularly targeted agents, in elucidating pathway crosstalk, redundancy, and feedback loops, etc., to interrogate targets
- Data will be posted on the DTP website for extramural data mining



Evaluation of the combination of bortezomib and cladribine in the NCI-60 cell line panel. Bars to the right demonstrate degree of synergy/additivity.

To enhance the rapid evaluation of agents entering the clinic, DTP expertise is being applied to pharmacodynamic assay development:

- Platforms such as enzyme-linked immunosorbent assay (ELISA) and quantitative immunofluorescence are being used to develop validated clinical assays
 - Assays were developed to measure poly(ADP ribose) levels in patient tumor samples to monitor clinical response to the poly(ADP ribose) polymerase (PARP) inhibitor ABT-888
 - Because these assays were the best available on a national level, technicians from other institutions have been trained at the NCI and the assay technology was thus transferred to the scientific community to facilitate clinical studies of PARP inhibitors
- Assays for several other markers in tumor biopsy specimens, such as γ -H2AX and Met, are in development

In summary, DTP provides services, resources, and leadership to the academic and private sector worldwide to facilitate the discovery and development of new cancer therapeutic and imaging agents.

Approved Cancer Treatment Drugs Developed with DTP Involvement

2010	Sipuleucel-T
2009	Romidepsin (NSC 630176) Pralatrexate (NSC 713204)
2004	Cetuximab (NSC 632307)
2003	Bortezomib (NSC 681239)
1998	Denileukin diftitox (NSC 697979)
1996	Polifeprosan 20 with carmustine implant (NSC 714372) Topotecan (NSC 609699)
1995	All-trans retinoic acid (NSC 122758)
1992	2-Chlorodeoxyadenosine (NSC 105014) Paclitaxel (NSC 125973) Teniposide (NSC 122819)
1991	Fludarabine phosphate (NSC 312887) Pentostatin (NSC 218321)
1990	Hexamethylmelamine (NSC 13875) Levamisole (NSC 177023)
1989	Carboplatin (NSC 241240)
1988	Ifosfamide (NSC 109724)
1987	Mitoxantrone (NSC 301739)
1983	Etoposide (NSC 141540)
1982	Streptozotocin (NSC 85998)
1979	D Daunorubicin (NSC 82151)
1978	Cisplatin (cis-platinum) (NSC 119875)
1977	Carmustine (BCNU) (NSC 409962)
1976	CCNU (NSC 9037)
1975	Dacarbazine (NSC 45388)
1974	Doxorubicin (NSC 123127) Mitomycin C (NSC 26980)
1973	Bleomycin (NSC 125066)
1970	Floxuridine (FUDR) (NSC 27640) Mithramycin (NSC 24559) Mitotane (o-p'-DDD) (NSC 38721)
1969	Cytarabine (ARA-C) (NSC 63878) Procarbazine (NSC 77213)
1967	Hydroxyurea (NSC 32065)
1966	Pipobroman (NSC 25154) Thioguanine (NSC 752)
1964	Melphalan (NSC 8806) Actinomycin D (NSC 3053)
1963	Vincristine (NSC 67574)
1962	Fluorouracil (NSC 19893)
1961	Vinblastine (NSC 49842)
1959	Cyclophosphamide (NSC 26271) Thiotepa (NSC 6396)
1957	Chlorambucil (NSC 3088)

STRUCTURE AND FUNCTION

DTP's mission is to facilitate the discovery and preclinical development of novel therapeutic agents and imaging tools. Created by Congress in 1955 as the Cancer Chemotherapy National Service Center, DTP serves as a vital resource for the acquisition of preclinical information and the distribution of research materials, including Internet-accessible data and tools, vial and plated compounds, tumor cells, cell extracts, and animals, as well as bulk and formulated drugs for IND-directed studies.

Through its uniquely governmental role in providing resources and support to academic investigators and the private sector, DTP has facilitated the discovery and development of more than 70% of the anticancer therapeutics on the market today. Although many academic and private-industry laboratories are also focused on drug discovery, barriers are presented by financial and technical burdens, as well as lack of funding and infrastructure, that may keep promising therapeutic agents from being developed and reaching patients. DTP helps to overcome barriers to the development of therapeutic agents by providing the resources and leadership necessary to pursue high-risk projects aimed at unmet medical needs. The management and oversight of a large research grant portfolio, worldwide distribution services for data and research materials, and a robust in-house and contract-based drug discovery and development infrastructure are organized under nine highly interactive



branches. These activities are presented here under the scientific themes of service, discovery, and development.

In 2006, an extramural advisory group was convened to review the RAID program, leading to the restructuring of that program. More recently, beginning in 2009, the inputs to DTP's drug discovery and development pipeline were reorganized under the NExT and CBC initiatives. The Joint Development Committee of the Center for Cancer Research (CCR) and DCTD, the Drug Development Group of DCTD, the RAID program, the Rapid Access to NCI Discovery Resources (RAND) program, and the National Cooperative Drug Discovery Groups (NCDDG) were then phased out and merged into the unified NExT program.

Out of Business

The formation of the NCI Experimental Therapeutics (NExT) program terminated the following individual programs:

- Joint Development Committee
- Drug Development Group
- Rapid Access to Intervention Development (RAID)
- Rapid Access to NCI Discovery Resources (RAND)
- National Cooperative Drug Discovery Groups

PROGRAM ACCOMPLISHMENTS

Grants and Contract Operations Branch

Under the theme of "Service," the Grants and Contracts Operations Branch (GCOB) manages approximately 600 extramural investigator-initiated grants and 42 contracts. GCOB grants focus on preclinical research that accelerates the discovery, development, and evaluation of agents to treat cancer. Drugs discovered and developed by GCOB grantees continue to come to market; the current portfolio promises conceptual insights and novel drugs addressing a range of targets and mechanisms.

GCOB History

GCOB was created in 1986 to manage the biochemistry and pharmacology grants portfolio, provide administrative assistance for DTP drug discovery and development contracts, and serve as government partner for the NCDDGs. These grants bridge the gap between basic cancer research and the clinic in the field of drug discovery and development. Branch staff members participate in both NIH-wide grant initiatives, such as the Enhancing Peer Review initiative under the American Recovery and Reinvestment Act of 2009 (ARRA), as well as in drug discovery efforts sponsored by NCI (e.g., NExT, CBC) and by NIH. Examples of the latter are the Molecular Libraries Program and the International Cooperative Biodiversity Groups Program, which is located at the NIH Fogarty International Center but is co-funded and managed by several NIH Institutes, Centers, and other agencies.

These grants support research with therapeutic intent, including those studying chemistry, natural products, and mechanism of action. Areas of emphasis are drug discovery, biosynthesis of natural products, targeted drug delivery, nanotechnology, high-throughput screening, cancer stem cells, and drug studies covering diverse targets, mechanisms, and processes, such as angiogenesis, metastasis, extracellular matrix, apoptosis and autophagy, cell signaling, DNA repair, and cancer cell metabolism.

In fiscal year (FY) 2010, program directors in GCOB and the Biological Resources Branch managed 901 active grants. R01 grants historically funded by DTP have led to marketed agents since 2005. Examples include pralatrexate, which was the first drug specifically for treating peripheral T-cell lymphoma (2009) and was the first marketed drug from the former RAID program; and pemetrexed, for malignant pleural mesothelioma (2004), with a later indication (2008) combined with cisplatin for locally advanced and metastatic non-small-cell lung cancer.

GCOB manages the DTP contract process from concept to award, serving as the liaison for project officers with other offices, coordinating the development of concepts and Requests for Proposals (RFPs), and arranging award selection meetings. During FY 2009, GCOB coordinated the administration of \$197,000 in ARRA funds for DTP synthesis contracts. Branch staff also organized meetings such as the 2007 workshop with the National Institute of General Medical Sciences on translational science and drug repositioning for other diseases; cosponsored Program Announcements with the National Institute of Diabetes and Digestive and

Kidney Diseases on high-throughput screens and with the NCI Division of Cancer Biology on cancer stem cells; informed investigators about the new NExT program at national meetings; reviewed manuscripts; chaired reviews for the Veterans Administration; participated in training sessions for young and minority scientists; served as Science Officers for the NIH Molecular Libraries Program; participated in the creation of the NIH Translational Research Interest Group; and served on the NIH Leadership Committee.

GCOB Accomplishments

Cetuximab: FDA approved cetuximab under the trade name Erbitux in 2006 as part of combination therapy with radiation for the treatment of squamous cell carcinoma of the head and neck. In May 2008, cetuximab was approved for the treatment of KRAS wild-type metastatic colorectal cancer expressing the epidermal growth factor receptor (EGFR).

ch14.18: Positive results of a phase 3 trial of the chimeric anti-GD2 monoclonal antibody ch14.18 were published in 2010. ch14.18 in combination with GM-CSF, IL-2, and isotretinoin became the standard of care for children with high-risk neuroblastoma. Clinical lots of antibody were made by DTP, and marketing approval is pending.

Sipuleucel-T: FDA approved sipuleucel-T (as Provenge) in May 2010 for castration-resistant prostate cancer. Sipuleucel-T is considered the first approved therapeutic cancer vaccine.



GCOB Future Plans

DTP plans to continue to support the best translational research based on peer review and clinical need, conduct portfolio analysis to identify gaps for new initiatives, catalyze interactions among scientists, educate the scientific community on peer review and grant policy changes and DCTD drug development services, and organize workshops.

Information Technology Branch

Under the theme of “Service,” the Information Technology Branch (ITB) provides scientific computing support and development for DTP. ITB staff work to understand DTP’s needs with regard to data capture, storage, searching, and analysis and to translate them into specific programming tasks. ITB efforts fall into two broad categories, internal and external. Internal efforts focus on infrastructure for DTP screening activities, including compound scheduling and shipping, experiment setup, data capture, report generation, and decision support and recording. External efforts focus on the DTP public Web pages and involve not only making DTP data available to the research community, but also making available DTP data analysis tools, such as COMPARE.

ITB Accomplishments and Ongoing Activities

Support for Continued Development of Screening Program. Although the basic experimental protocol for the NCI-60 cell line screen is established, continuous changes in the details are implemented. A recent change instituted a 60–cell line, one-dose

ITB History

ITB was formed in 1989 to guide the implementation of computer resources to make the Human Tumor Cell Line Screen (NCI-60) operational. The initial work of the branch primarily focused on the details of the NCI-60 cell line screen, but two developments led to an increased scope for its activities:

- The COMPARE algorithm proved valuable for taking full advantage of screening data. In addition to capturing, recording, and reporting the data, ITB is actively involved in looking for ways to make better use of data.
- DTP Web pages were developed to provide the research community with easy access to a large amount of chemical and biological data from DTP. Thus ITB’s “customers” expanded from just DTP staff to the greater research community.

prescreen. ITB managed the needed changes in the shipping, data capture, reporting, and workflow systems.

Support for In Vivo Screening. Computer systems for assignment, data capture, and reporting for both the hollow-fiber and xenograft in vivo screens have been implemented to better integrate the data from these screens into the larger DTP dataset.

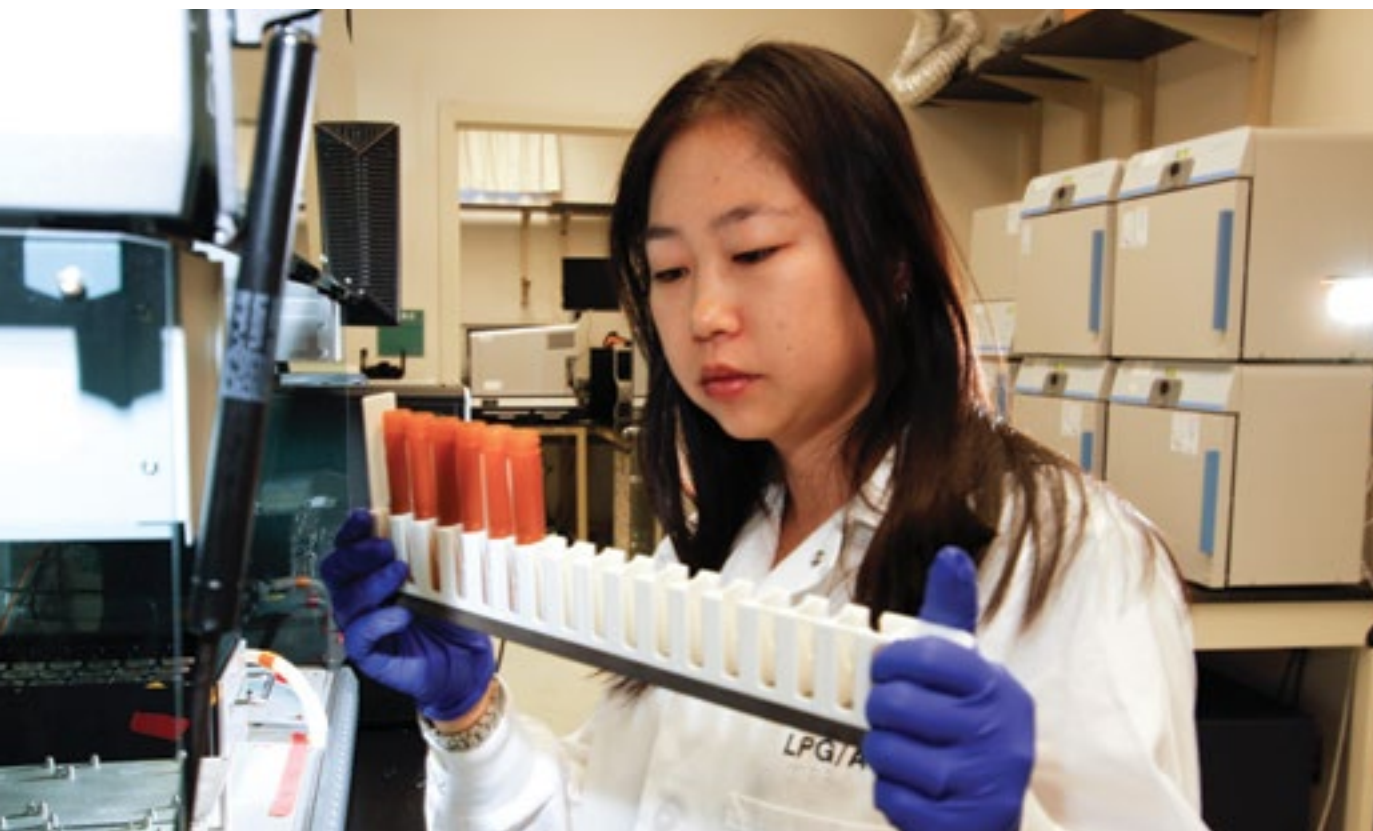
Support for Combination Studies. DTP has committed to a significant effort in looking at combinations of agents in the NCI-60 cell line screen, and ITB has created the

computer systems to capture, store, and report the data generated. The screen design allows for testing of “rational” combinations of pathway-specific agents but also casts a wider net, allowing for the discovery of synergistic combinations that would not otherwise be predicted. The screen utilizes three cell lines, chosen from the NCI-60 cell lines, for the diversity of their molecular characteristics. Each new agent is tested in these three cell lines, in combination with a panel of approximately 65 of FDA-approved oncology drugs. Promising combinations are then tested against the entire NCI-60 panel. To date, 28 test agents have been through the three-cell combination screen (a total of 1,820 drug combinations in each of three cell lines). Then, 32 combinations with promising

results were selected for combination testing in the NCI-60 cell line screen. Some of the active combinations are expected (e.g., mTOR inhibitor plus PI3 kinase inhibitor), whereas others are unexpected (e.g., vincristine plus EGFR inhibitors).

Compound Submission. A Web-based submission form for researchers to submit their compounds to NCI for screening collects the information necessary to process these submissions, as well as allowing the submitters to follow the progress of their compounds through screening and access data as the assays are completed.

Molecular Targets. The NCI-60 cell line panel, utilized to screen for novel anticancer agents, has an ongoing program





to molecularly characterize the cell lines. More than 300 laboratories worldwide have contributed to this effort, and the results are available for data mining through the DTP website. These projects have consisted of small-scale projects focusing on targets of interest to a particular laboratory as well as large-scale, genome-wide studies. These larger studies include the characterization of messenger RNA (mRNA) by microarrays (six platforms, five independent groups), high-density arrays of single-nucleotide polymorphisms (two platforms, three groups), characterization of microRNA (three independent laboratories), metabolomic data, and genome-wide DNA methylation. In addition, a project is in progress to sequence the exome of these cell lines.

Compound Order System. DTP's large repository of collected compounds is accessed via a Web interface that lets researchers request samples of individual compounds or request plated sets of compounds with an electronic Material Transfer Agreement automatically generated and routed, minimizing paperwork and processing time.

Website Development. ITB continues to maintain and develop the DTP Web pages. This effort is to provide data generated from DTP's screening programs to the research community, and to provide current information on accessing DTP resources and Web front ends to analysis tools such as COMPARE. The Website is popular with the research community, with Web page hits now running at more than 10,000 per day. Of the more 10,000 unique visitors per month, about 5% return at least ten times a month.

PubChem. ITB was closely involved with the initial creation of the [PubChem](#) database;

approximately one-third of the initial structures and 100% of the initial bioassay data originated from DTP. ITB continues to update the DTP data in PubChem to provide an additional resource for the research community.

Interagency Agreement. An agreement between DTP and the U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID) has supported a molecular modeling team that is stronger than either institution could have developed independently, allowing collaborations on projects that are of interest to both (e.g., phosphatase inhibition).

ITB Future Plans

The ITB chief has served on the Molecular Libraries Project Team since its inception. DTP has sent more than 4,000 compounds to the Molecular Library repository, and the first batch of these compounds has now been tested in nearly 200 assays. These compounds have also been through the NCI-60 screen, so there is an unprecedented opportunity to examine the detailed relationship of molecular activity to screening pattern of activity. In addition, the number of probe compounds created by the Molecular Library effort has risen to nearly 100. Efforts are under way to test these probe compounds in the NCI-60 cell line screen. Because many of the targets of these probes are cancer related, there should be a number of compounds that show interesting activity. It also will enrich the set of patterns known to be associated with a particular mechanism.

Drug Synthesis and Chemistry Branch

Under the theme of “Service,” the Drug Synthesis and Chemistry Branch (DSCB) supports the discovery and development of novel anticancer agents by:

- Worldwide scientific liaison activities with academic and industrial colleagues to stimulate the acquisition of a diverse

set of synthetic compounds, natural products, and combinatorial libraries for in vitro cancer screening

- Management of the storage, inventory, documentation, and distribution of samples for research purposes
- Synthesis of cold and radiolabeled compounds for in vitro and in vivo studies

DSCB Accomplishments and Ongoing Activities

DSCB STRUCTURE

External Synthesis Contracts	<ul style="list-style-type: none"> • Supports Biological Evaluation Committee and NExT initiatives • Synthesis of benchmark clinical and preclinical candidates
Chemical Repository	<ul style="list-style-type: none"> • Procurement of new compounds for NCI-60 testing • Distribution of compounds for external research activities
Laboratory of Synthetic Chemistry	<ul style="list-style-type: none"> • Supports CBC discovery initiative • Synthesis of benchmark compounds • Internal supplier of new compounds through vigorous medicinal chemistry program

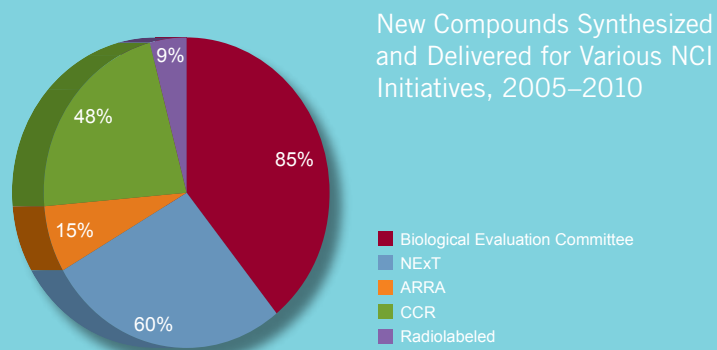
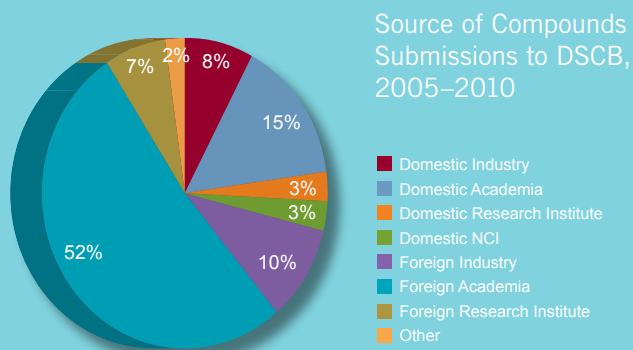
DISTRIBUTION AND PROCUREMENT

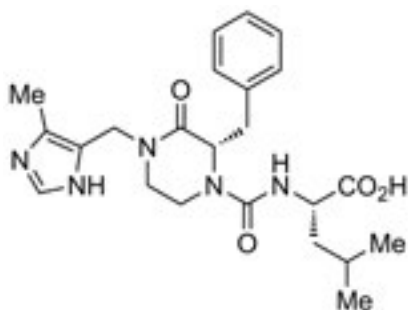
SUMMARIES, 2005–2010

Year	Compounds Shipped	Plates Shipped*	New Compounds (NSCs)
2005	11,753	3,470	2,972
2006	12,418	7,329	2,391
2007	19,964	4,742	3,194
2008	25,842	3,223	2,716
2009	28,830	5,649	2,469
2010†	37,638	2,284	2,671

*Plates include: Structural diversity set, mechanistic diversity set, natural products set, combination set, approved oncology drugs set, random plates of open compounds.

†Through October 31, 2010.





GGTI - NSC 732082

New compound synthesized by DSCB. GGTI-NSC 732082 is a geranylgeranyltransferase type I (GGTase I) inhibitor. An IND for this compound was recently submitted.

DSCB Future Plans

- Design and execute strategy to increase the quality, quantity, and diversity of compound submissions to the NCI compound collection, with the goal of improving the overall quality of the collection (with regard to molecular properties and pathway diversity)
 - Design and implement strategy for extraction, visualization, and analysis of data (experimental and virtual) for NSC compounds that allows for the identification of trends and formation of hypotheses necessary for rapid and efficient project progression
 - Develop and execute a strategy for the implementation of a vigorous DSCB medicinal chemistry program aimed at the design and synthesis of targeted anticancer agents
- Support the CBC initiative by management and oversight of CBC discovery projects as they proceed through program [Stage Gates](#) and provide input and guidance with regard to the selection of projects
 - Support DTP combination study initiative through the acquisition and synthesis of marketed clinical and preclinical anticancer benchmark agents and candidates

Natural Products Branch

Under the themes of “Service” and “Discovery,” the [Natural Products Branch \(NPB\)](#) comprises the Natural Products Repository and the Natural Products Support Group.

The Natural Products Repository is the largest storehouse of natural products in the world, housing nearly 170,000 extracts from more than 70,000 plants, more than 10,000 marine organisms collected from more than 25 countries, and more than 30,000 extracts of diverse bacteria and fungi.

The Natural Products Support Group extracts natural product samples for testing in the NCI-60 cell line, provides compound plating support service for all drugs and natural products entering the NCI-60 queue, and conducts discovery research to characterize and purify extracts showing promising screening results.

NPB Accomplishments

NPB originated the Natural Products Repository program in 1991 to maximize the potential of plant, microbial, and marine invertebrate extracts derived from the raw materials that were collected by NPB collection contractors. Since 1996, extracts have been made available to any organization or investigator to investigate their potential in any disease related to NIH interests. Extracts are provided for the costs of shipment. Since 1998, 96-well plates of dried extracts of all sources and types have been provided to NPR recipients, followed by provision of more material for cancer-related screens.

SAMPLES SHIPPED TO NON-DCTD INVESTIGATORS AND COLLABORATORS BY NPB*, 2005–2010

Year	Vials	Plates	Extracts†	Cultures
2005	604	998	88,428	
2006	3,670	1,634	147,462	
2007	4,682	440	43,402	10
2008	5,252	752	73,717	9
2009	7,540	7,000	623,540	1

*In conjunction with the Natural Products Repository.

†Extract total is calculated from [(plates x 88) + vials].

In addition, 1,000 bottles reserved for studies related to in vivo activity are currently in the Natural Products Support Group (NPSG) laboratories, and a significant number of plates (over 500 per year) are shipped to the CCR Molecular Targets Laboratory for their assays. In recent years, NPSG upgraded its analytical and robotic liquid handling capabilities to

state-of-the-art systems and assumed the production of test samples from all sources for the revised NCI-60 cell line in vitro screen, now modeled after the one-dose prescreen system in use for extracts. It also revised its dilution methodology to aid in the production of enough materials to cover the increased capability of the NCI-60 cell line screen and adapted a piece of standard equipment to deliver submicroliter volumes of dimethylsulfoxide (DMSO)-dissolved materials when necessary. The group is currently responsible for the production of all weighed samples for the expanded in vivo hollow-fiber and xenograft assay materials and, with the filling of the current slot, for the production of all solubilized materials for all in vivo assays performed for the Biological Testing Branch.

NPSG has been essential in the reinvestigation of an old technique for antitumor drug discovery, the use of crude active extracts in two in vivo assays. As a result of NPSG's close cooperation with the in vivo testing laboratories of the Biological Testing Branch, crude extracts from plant and marine sources that demonstrated activity against xenografts have been identified and, in a number of cases, deconvoluted and the "active principles" purified and identified. In one case, two known agents—a tubulin-interactive agent and an actin inhibitor—have shown what appears to be in vivo synergy that has been confirmed in in vitro follow-up studies at levels well below those reported for the individual agents. In other cases, both known and previously unidentified natural products have been identified. All are undergoing further evaluation, and other extracts are in the testing process.



Activities in Support of NExT

Two major achievements are related to the former RAID program project—withacnistin A and a project on silvestrol. Both of these materials are plant-derived agents obtained from tropical countries, Costa Rica and the Island of Borneo, respectively:

- Withacnistin A as a STAT3 inhibitor was the subject of a successful RAID application from the University of South Florida. In conjunction with NPSG, DTP identified the material supplied as a mixture of withacnistin A and two simple derivatives. The active material was withacnistin A. NPB then developed a source in Costa Rica, negotiated the necessary collaboration agreements with Costa Rica, and obtained one gram of pure material for evaluation. A suitable water-miscible formulation was devised and is undergoing evaluation with the aim of further development.
- Silvestrol entered the DTP system from Sarawak (a Malaysian State on the Northwest coast of Borneo) via a routine pure compound submission. NPB-sponsored investigators have developed the compound, which has a very interesting activity against chronic lymphocytic leukemia (CLL), being a “T-cell sparing” cytotoxin. The NPSG successfully aided in purifying the compound from the Indonesian source. Currently, it has demonstrated *in vivo* activity in the hollow-fiber assay (at DTP) and in a model of CLL, as well as *in vitro* efficacy against hepatoma cells (at Ohio State University). NPB is in the middle of negotiations with Sarawak for the provision of plant raw material to evaluate methods of purification that are not currently available. As in the case of withacnistin, DTP was able to develop a water-miscible formulation that gave extremely good bioavailability on intravenous administration.

NPB Future Plans

- Activation of “Cryptic Biosynthetic Clusters”: NPSG has had a microbiology component as part of a collaboration with the U.S. Department of Agriculture’s Noxious Weeds Research Group at Fort Detrick in Frederick, Maryland, and from this and other sources, has amassed more than 30,000 cultures, mainly fungi, but also some actinomycetes. It has become obvious from genomic analyses of microbial genomes that there are between 10 and 40 or more potential biosynthetic clusters per microbe that are not normally expressed under the culture conditions used:
 - In conjunction with NPSG chemists, some initial “cluster activation” experiments were performed that demonstrated new metabolite peaks on subsequent analyses. These experiments have increased in number with preliminary indications of novel metabolites (as yet of unknown activity) being expressed.
 - The ultimate aim is to initially induce and/or produce previously unknown metabolites, identify and screen them as potential lead structures, and then

elaborate such clusters from a production aspect when a suitable lead structure is identified, thus using the current relatively large microbial collection as a source of novel anti-tumor agents and/or leads for chemical modification.

- Continuation of the marine collection program that has been running for more than 23 years

Biological Resources Branch

Under the themes of “Service” and “Development,” the Biological Resources Branch (BRB) supports research in biological therapies and provides resources to explore potential leads for the treatment of cancer and related conditions. Classes include recombinant proteins, monoclonal antibodies, genetically modified viruses, bacteria or mammalian cells, peptides, and oligonucleotides. These entities may function as cytokines, growth factors, vaccines, adjuvants, or other immunomodifying agents. BRB has a coordinated portfolio of research grants and contracts that represent the flexible utilization of all three legs of the discovery and development process:

- Peer-reviewed, grant-supported, investigator-initiated discovery
- Access to consistent and high-quality supplies of reliable reagents for detailed preclinical studies
- Pilot-scale production capability for clinical-grade material for early-phase proof-of-concept safety studies



Preparation of the cGMP fill station. This small-scale automated filling machine is useful for the lots typically manufactured by BDP for products like rhIL-15 or ch14.18. Between 100 and 10,000 vials are filled and sealed in a single run. Validation studies for each vial and stopper size are typically performed at the 5,000-vial scale and must be repeated before vialing a clinical product if more than 1 year has elapsed since the last validation.

BRB Accomplishments and Ongoing Activities

Funded Grants in the Biologicals Portfolio

The BRB biologicals portfolio contains approximately 170 grants that support concept discovery and development in nonclinical models and laboratory studies conducted in parallel with ongoing clinical trials.

Preclinical Repository and the Biopharmaceutical Development Program

The Preclinical Repository was established in 1988 to acquire, usually by donation, and distribute qualified biological reagents to peer-reviewed academic investigators to enable more reliable model studies. The Biopharmaceutical Development Program (BDP) was established at NCI-Frederick in 1993 to manufacture biologicals at pilot

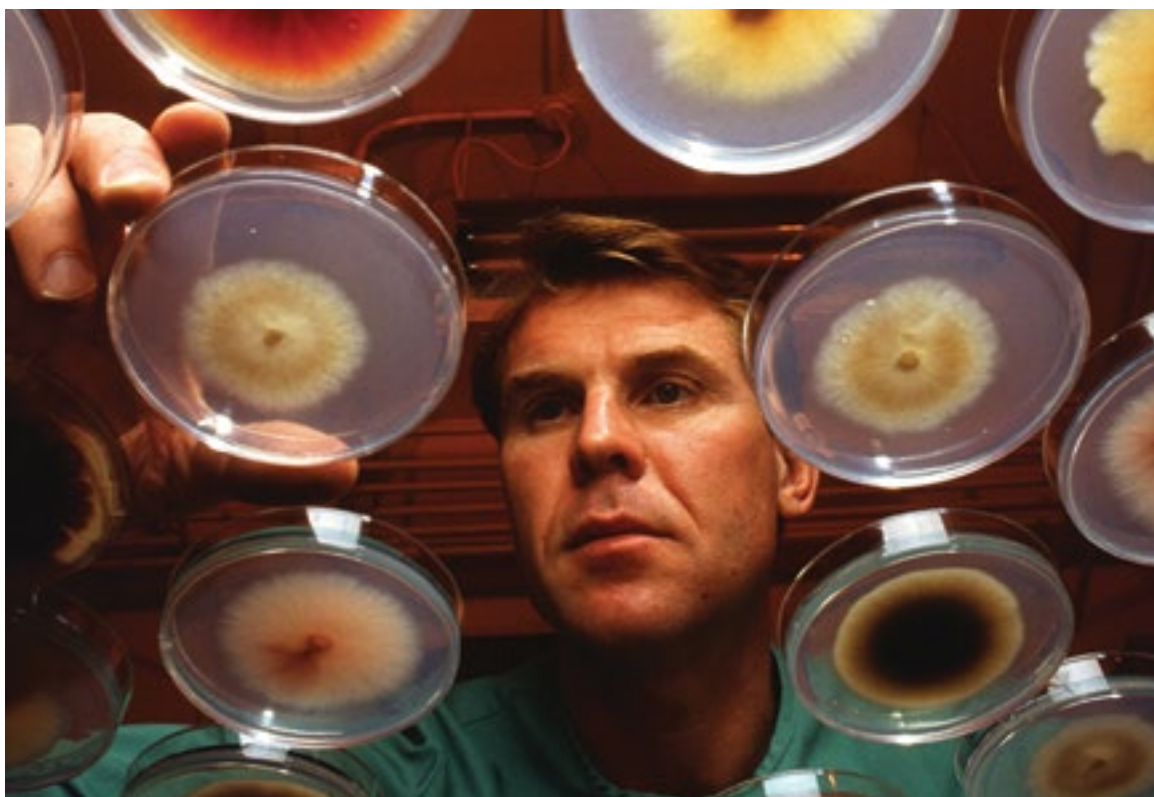


scale for first-in-human, proof-of-concept studies. BDP products are used in preclinical development, phase 1 and 2 clinical studies, or selected phase 3 trials. Approved outside projects are funded by interagency transfers to NCI if they are from a government source, or by NCI Cooperative Research and Development Agreements (CRADAs) if they come from a commercial partner.

Technical expertise and specialized capabilities available to BRB and BDP support applications beyond cancer treatment for collaborations with other government programs, such as the National Institute of Allergy and Infectious Diseases (NIAID) and USAMRIID for vaccine development in infectious diseases, and the National Institute of Diabetes and Digestive

and Kidney Diseases for approaches to abort the autoimmune course of early type 1 diabetes. In addition, staff expertise is frequently tapped for advice or training by a range of programs outside DCTD that are involved in drug development:

- Service on grant and contract Source Evaluation Groups or Special Emphasis Panels for non-NCI initiatives
- Participation in steering committees for new NIH programs in infectious disease or nanotechnology applications
- In-plant training experience for senior staff of new biopharmaceutical programs and academic institutions in developing countries
- Technical expertise for site visits of new foreign production plants in NIH collaborations



BRB Preclinical Repository

- Bulk cytokines, monoclonal antibodies, cytokine standards, and other highly sought research reagents, maintained under carefully controlled storage conditions
- Consistent supply of high-quality reagents for scientists with peer-reviewed support at nonprofit institutions. Reagents may also be shipped to qualified commercial establishments when the donating institution agrees
- Initial repository inventory significantly augmented with thousands of vials of cytokine standards from the United Kingdom's National Institute of Biological Standards and Control (NIBSC) for distribution to U.S. investigators, and 80,000 vials of rHu-IL2 from industry
- In five years, inventory has increased from 140 to more than 200 bulk cytokines, monoclonal antibodies, cytokine reference standards, and other research reagents. Over 16,000 vials of the different reagents were shipped domestically and internationally to nearly 3,000 scientists
- The BRB negotiates with companies and investigators to obtain, by donation or at reduced cost, new materials to enrich the repository supply of reagents. Many donated lots are expired commercial clinical

materials that are retested or revealed by the BDP to generate high-quality reagents for research and development. Some highlights of those negotiations during the past five years include:

- Over \$20,000,000 of annexin protein reagents, useful for apoptosis imaging, were donated in 2005. This shipment included 120 clinical-grade kits that are stored under GMP-suitable conditions for possible clinical studies.
- Two hundred fifty vials of rHu-IL4 were donated in 2005.
- A total of 1,900 vials of rHu14.18-IL2 fusion protein were provided in 2006. rHu14.18-IL2 is in clinical trials, and the donated reagent is provided as a research-grade resource for preclinical studies by noncommercial researchers.
- An entire -80°C freezer of rabbit antisera to dozens of proteins involved in NF- κ B signal transduction, developed at NCI-Frederick (2006)
- Over 4,000 vials of rhIL-6 (2006)
- 11,000 vials of recombinering reagents (bacterial strains and plasmid vectors) donated (2007) from the NCI laboratory of origin at NCI-Frederick. The demand for these reagents is so large that the total number of shipments sent and requests received per month have doubled.



The Biopharmaceutical Development Program

In the past 5 years, BDP released 76 clinical or toxicology lots in addition to numerous other GMP entities, such as master cell banks, control lots, diluents, and other associated products. BDP provides quality control and quality assurance/regulatory support for its products, including technical packages for pre-IND meetings with FDA; Chemistry, Manufacturing, and Control documents for IND applications; and post-filing technical and regulatory assistance. Besides projects that have been discussed under the BDP Grant Portfolio section, following are some of the most prominent products produced during this interval:

ch14.18 Monoclonal Antibody

Currently, this is the highest priority project for BDP. ch14.18 is an anti-GD2+ antibody. Disialoganglioside (GD2) is a surface antigen on neuroblastoma, osteosarcoma, glioblastoma, melanoma, and small-cell lung cancer. It is also found on peripheral pain fibers. A family of antibodies against GD2+ was generated in the 1980s at the Scripps Institute. Chimerization was performed in collaboration with the Damon/Abbott/Repligen Corp. Phase 1 and 2 studies explored the use of these agents singly and in combination, demonstrating modest activity in neuroblastoma as a single agent or in combination with IL-2 or GM-CSF.

At the 2009 meeting of the American Society of Clinical Oncology, the Children's Oncology Group reported an interim analysis of a randomized,

controlled, phase 3 trial showing a 20% increase in progression-free survival at 2 years. After discussions with FDA, the control arm was closed and the phase 3 study continued to provide treatment access pending transfer of the product to a commercial entity. The [final results of this trial](#) were published in September 2010, marking a new standard of care for pediatric neuroblastoma.

NCI advertised a CRADA and selected a collaborator, and work is under way on process development for commercial-scale production. Meanwhile, for at least the next two years, BDP will continue to manufacture a supply of antibody until the collaborator has satisfactorily established and qualified its commercial process. Extramural investigators are exploring additional indications.



cGMP downstream column purification. Chromatography at this scale is used to support multi-gram cGMP lots for projects like the ch14.18 monoclonal antibody. Columns and resins at this scale are expensive, but the resin can be sterilized, recharged, and reused to purify the same product for a limited number of cycles, depending on validated process data. Three or four sequential columns with different separation methods (e.g., size, charge, affinity/hydrophobicity) are typically used for purification of a cGMP product at BDP. A column of this size can purify about 25 grams of ch14.18 in a single pass.

Hu14.18–IL-2 Fusion Protein

Hu14.18–IL-2 fusion protein is another agent in the same anti-GD2 family as ch14.18. In studies coordinated at the University of Wisconsin, this fusion protein is in phase 1/2 clinical trials in neuroblastoma and melanoma. The product has been in commercial development by EMD, although most of the clinical lots were actually manufactured at BDP. Under a CRADA, BDP is currently transferring its process and testing information to support validation of EMD's new commercial-scale process.



cGMP 80L Fermentation of rhIL-15. Production of rhIL-15 involves refolding, purification, and pooling of product derived from fermentation paste. Several fermentations in this 80-L fermentor at 50-L working volume are run for one 1-gram lot of rhIL-15.

Recombinant Human IL-15

BDP has developed a process for clinical-grade manufacture of IL-15 in an *Escherichia coli* production system. FDA approved the initial IND in April 2010, and the first clinical trials are under way in CCR for renal cell cancer and melanoma, using daily long-bolus infusions over five days. A second trial planned by NIAID will be conducted with HIV-positive patients using continuous IV infusion. The corresponding toxicology studies are ongoing, and the IND is planned for filing later in 2010. Supported by ARRA funds, additional manufacture is planned for 2010–2011. Extramural investigators ranked IL-15 as the highest priority in immunotherapy agent polls in 2007–2009. The current extramural supply will be made available to initial studies under the new STRAP (Special Translational Research Acceleration Project) and CTIN (Clinical Immunotherapy Network) mechanisms as the first priority, followed by studies supported under more conventional mechanisms.



Cetuximab Development

Cetuximab illustrates utilization of all three legs of the BRB discovery and development process. In the late 1980s, investigators in a BRB/DTP-supported collaborative agreement developed anti-EGF receptor monoclonal antibodies. BRB contracted production to manufacture high-quality murine antibodies in gram quantities to support the preclinical evaluation of several candidate antibodies, alone and in combination with chemotherapy or radiotherapy. Combination studies explored use of the antibody to improve results over chemotherapy or radiotherapy alone. Two murine antibodies advanced to small pilot imaging studies in cancer patients. BRB resources were used to chimerize one murine antibody.

Cetuximab was approved by the FDA in 2004, and a small biotechnology company acquired the rights to the antibody from the originating academic institution.

BRB Grant Programs

Significant events in the BRB grants portfolio during the past 5 years have included the following:

- Amy Heimberger, University of Texas, MD Anderson, received the prestigious Presidential Early Career Award for Scientists and Engineers (PECASE). Her research focused on the modulation of microglia and T-cell interactions in malignant glioma and suggested potential immunomodulating approaches to treat malignant glioma.
- A BRB-sponsored investigator, while researching the role of STAT3 signaling in head and neck cancer, discovered that a decoy oligonucleotide (STAT3 decoy) could inhibit activation of the STAT3 pathway in tumor cells and result in tumor cell death. The former RAID program, by providing translational support, including GMP, IND-directed toxicology and regulatory affairs, was able to translate the STAT3 decoy oligonucleotide from bench to clinic in only 18 months. The researcher is now pursuing a DTP project for a small-molecule drug to target the same pathway.
- Other researchers funded by BRB have developed anti-PD1, anti-CD137, and anti-B7-H4 antibodies for cancer therapy. These agents received high priority in a 2007 workshop to identify immune modifier agents for NCI development.
- Another investigator originated an adult leukemia project in the former RAID program that developed a selective depletion reagent in memory T cells for AlloSCT Immune Reconstitution. The material, produced with RAID support, is now in clinical trials at Yale

University and the Fred Hutchinson Cancer Research Center at the University of Washington.

Biological Testing Branch

Under the themes of “Discovery” and “Development,” the Biological Testing Branch (BTB) provides oversight and technical direction to support preclinical development of new chemotherapeutic agents. To accomplish this, BTB is responsible for:

- Planning, directing, and managing a program to screen compounds for evidence of preclinical efficacy in rodent models
- Developing new in vitro and in vivo screening models
- Conducting in vitro combination screening assays to identify potentially beneficial drug combinations
- Providing preclinical support to the pharmacodynamic assay development and validation effort
- Defining the mechanisms of action for new experimental agents under development by DTP
- Providing preclinical and clinical pharmacokinetic support to the DCTD drug development effort
- Producing, providing quality control, and distributing genetically and biologically defined rodents to NCI, NIH, and the grantee community
- Maintaining a repository of experimental animal and human tumor cell lines for use in research performed by the program and other qualified investigators

BTB Accomplishments and Ongoing Activities

- Assessed over 570 synthetic molecules, 375 natural product extracts, and 40 unique vehicle formulations for determination of maximum tolerated dose in preparation for in vivo efficacy studies
- Conducted over 250 hollow-fiber assays with more than 700 unique new molecules or natural product extracts for in vivo activity; 96 met the standard criteria for activity and were referred for subcutaneous xenograft testing
- Conducted 1,190 xenograft studies assessing antitumor activity of small-molecule and natural product extracts. These represent 120 unique tumor models, including human and canine xenografts, classical mouse tumors, and transgenic mouse breast tumor models.
- Pharmacologic assessments of over 30 compounds, including assay development and validation and pharmacokinetic assessment in rodents after IV, intraperitoneal, and oral administration
- Provided animal model support for pharmacodynamic assay development and validation for the PARP inhibition assay for ABT-888, the methylation-inhibition assay for FydC + THU, and the γ -H2AX assay for the indenoisoquinolines
- Successfully generated hybridoma ascites stocks to allow purification and validation of adequate antibody to support the PARP assay for a range of NCI-supported clinical trials of ABT-888
- Provided pharmacology assay support for the phase 0 clinical trial of ABT-888 (NSC 737664) and provided real-time



pharmacology results to the Clinical Center staff so appropriate dose escalation and tumor biopsy collections could be coordinated

- Developed the methodology for collecting and preserving needle biopsy samples for evaluation in the PARP-inhibition assays that support the PARP inhibitor ABT-888 clinical trials; methods successfully transferred to the γ -H2AX studies
- Prepared and shipped 300–350 orders annually, representing an annual distribution of more than 2,000 vials of cells and tumor fragments
- Prepared mRNA array samples from over 80 unique human tumor xenografts with samples collected at passages 1, 4, and 10 from serially passaged tumor material
- Animal Production Program:
 - Distributed 5,727,888 mice and rats to various grantees
 - Transitioned from the use of skin grafting and biochemical testing to molecular testing to ascertain the integrity of its inbred strains. This has resulted in more rapid recognition of genetic drift and the ability to remove undesired breeding stock early in the production process.
 - Moved into a new state-of-the-art facility in early 2009
 - Successfully cryogenically preserved 30 strains and stocks of mice and rats; nine remain for completion. Through this effort, the Animal Production Program has eliminated 11 low-demand strains and stocks, as they can now be supplied on an as-needed basis via embryo recovery.



BTB Collaborations with Intramural CCR Staff

- Studies to assess the presence of purported tumor stem cells in the NCI-60 cell line tumor panel, with the goal of generating a renewable population for drug testing. BTB provided the in vivo tumorigenicity support for several collaborative efforts.

- Development of an in vitro and in vivo model of alveolar soft-part sarcoma (ASPS), the first successful establishment of an ASPS tumor in mice after implantation of fresh human tumor tissues. This tumor can be serially passaged in mice while maintaining its genotypic and phenotypic characteristics and provided cellular material for in vitro studies, including establishing an ASPS human tumor cell line. A therapeutic trial demonstrated that antiangiogenic therapies (bevacizumab and topotecan) can suppress growth of the xenografted tumors
- Development of a method to label rodent tumors with a stable luciferase–green fluorescent protein probe without

requiring the tumor cells to be cultivated in vitro, providing a method for labeling transgenic as well as classic rodent tumors without the loss of heterogeneity that can occur when tumor cells are forced to establish and grow on plastic

BTB Collaborations with Extramural Staff

- Experimental studies by DTP identified a series of 21 artemisinin dimers with prominent in vitro anticancer activity. The mechanism of action for the molecule was assessed, and one of the structures was selected as a lead candidate (NSC 724910) for preclinical drug development by NCI

Collaborative Efforts between BTB and the Phase 0 Program

- A PARP inhibition assay was developed to support the [phase 0 clinical trial](#) of ABT-888 (NSC 737664). BTB provided the preclinical animal model support for development and validation of the clinical assay, including establishing the methods used to collect and stabilize tumor biopsies for subsequent analysis. As the clinical trial progressed, additional studies were requested to support changes to the clinical protocol.
- ABT-888 plasma and urine quantification in human samples from the phase 0 clinical trial. The assay developed at Abbott and transferred to the FDA was successfully imported and validated at the NCI-Frederick laboratories in less than one month so that local, real-time pharmacokinetic analyses could be conducted to support clinical decisions in the phase 0 trial.

- In vivo studies assessed the maximum tolerated dose of three indenoisoquinolines (NSC 724998, 725776, 704644) selected for clinical development. This provided starting doses for in vivo efficacy and pharmacodynamic assays of these agents against a series of xenograft models. The early data strongly supported dropping one of the three agents and focusing efforts on NSCs 725776 and 724998, based on an immunohistochemical stain for γ -H2AX. Studies of athymic nude mouse skin biopsies demonstrated that the mouse was a poor donor for surrogate skin modeling, so rat models of human tumor xenografts were established, requiring one-hour IV infusions of the test agents with subsequent harvest of tumor and skin biopsy samples for analysis. NSCs 743400 (salt of 724998) and 725776 are currently undergoing phase 1 clinical trials with biopsy collections.



- A series of indenoisoquinoline molecules were developed at Purdue University and CCR and submitted to DTP for evaluation in the NCI-60 cell line screen. A series of molecules were selected for in vivo assessment in the hollow-fiber assay, subsequent xenograft analyses were conducted in a subset of the selected agents, and a set of lead molecules (NSC 725776, 724998, 704644) was selected for clinical development.

Screening Technologies Branch

Under the themes of “Discovery” and “Development,” the Screening Technologies Branch (STB) is the organizational component of DTP that is responsible for the development and operation of in vitro drug screening tools that are relevant to the discovery of novel therapeutic agents for the treatment of cancer. This is accomplished through projects conducted by SAIC at NCI-Frederick and the efforts of government staff scientists.

Molecularly Targeted High-Throughput Screening

A variety of molecularly targeted screening campaigns were conducted, using both cell-based and cell-free technologies. Eleven different targets were tested against 17,280 compounds in a four-dose format. Several targets were screened against much larger libraries, including CHK2 kinase, which was tested in more than 200,000 compounds, resulting in the identification

of a novel chemotype with specificity for in vitro CHK2 inhibition. STB staff developed computational tools for data mining and informational analysis of high-throughput screening data.

Human tumor stem cells

- Development of the infrastructure and instrumentation for a new flow cytometry laboratory
 - Development of methodologies necessary to characterize cellular markers associated with human tumor stem cells (labeled with different fluorescent probes) to measure the simultaneous expression of putative stem cell markers CD 24, CD 44, CD 133, CD 166, CD 243, and CD 326
 - Testing of all 60 cell lines in the DTP 60 cell line tumor panel three to four times for these markers
- Demonstration of the utility of producing human colon tumor colonospheres from colon tumor cell lines grown under serum-free conditions
- Evaluation of laminin coating of plates to generate more homogenous cell populations
- Development of a high-throughput assay methodology to generate drug sensitivity phenotypes of putative tumor cells grown under various culture conditions
- Evaluation of an in vitro model of cancer stem cells based on induction with a small molecule (SC-1) in the colon tumor subpanel of the NCI-60

Modulators of autophagy

- In collaboration with the Cancer Institute of New Jersey, a new DTP initiative was begun to develop a high-content screen for modulators of autophagy
- Utilizing BD Pathway 435 high-content cell imaging instrumentation and engineered cell lines, autophagy induction by a library of test compounds was assessed and technology is being developed to extend studies to detect inhibitors of autophagy

Migration/invasion of human tumor cells

- Laboratory work was initiated to characterize the in vitro migration/invasion phenotype of the NCI-60 tumor cell line panel using real-time cellular impedance technology
- Variables were examined that can potentially affect this assay; numerous panel cell lines were tested and methods developed to quantify the basic phenotypes and the effects of experimental compounds on cellular migration/invasion

Hypoxic cell signaling

- Discovery and development of small molecule inhibitors of the transcription factor hypoxia-inducible factor-1 (HIF-1) with emphasis on novel mechanisms of action (e.g., DNA binding and protein-protein interaction) and natural products, areas in which DTP is unique compared with academia and industry
- Translation of findings from preclinical models to early clinical trials, emphasizing biomarker-based studies and combination studies including investigational agents; examples are:
 - A Pilot Trial of Oral Topotecan for the Treatment of Refractory Advanced Solid Neoplasms Expressing HIF-1 α (NCI-05-C-0186)
 - A Pilot Study of Weekly EZN-2208 (Pegylated SN-38) in Combination With Bevacizumab in Refractory Solid Tumors (LOI 8610)





Alveolar soft part sarcoma

- Characterization of patient samples of this rare sarcoma (NCT00340353) to elucidate biology and potential therapeutic targets. Expression array studies revealed common patterns of altered gene expression and noteworthy changes in genes related to angiogenesis
- In collaboration with BTB, generation of the first xenograft model of the disease and use in exploring potential therapeutic vulnerabilities
- Isolation and characterization of the first alveolar soft part sarcoma cell line (ASPS-1)
- Initial validation of some novel therapeutic targets, including small interfering RNA (siRNA) directed against the characteristic fusion protein
- Development and pilot-scale screening for novel small-molecule inhibitors of targets unique to the tumor

Genomics

- Genomic profiling of the NCI-60 cell lines in response to treatment with anticancer drugs to provide a genomic taxonomy of selected clinical agents. The data will be made public through caArray
- Genomics support for intramural collaborators and small companies to develop possible biomarkers or novel mechanism for small molecules
 - PXD101 (NSC 726630), an inhibitor of histone deacetylases (NCI CRADA 01940), depletes expression of aurora kinases A and B and allowed

identification of a gene-response profile that may provide a pharmacodynamic fingerprint of PXD101 activity

- Expression of CHK2 and activated CHK2 proteins in the NCI-60 cell lines was profiled to provide relevant cell line models for evaluation of novel NCI-discovered, specific CHK2 inhibitors

Anti-tubulin drugs—mechanism of action

- Characterization of mechanisms of action of all classes of anti-tubulin and anti-actin compounds
- Evaluation of intracellular effects of agents, including intracellular metabolism
- Locating binding sites by photoaffinity labeling and protein sequencing
- Current major projects with three custom radiolabeled compounds (halichondrin B, peloruside A, and spongistatin)

Toxicology and Pharmacology Branch

Under the theme of “Development,” the Toxicology and Pharmacology Branch (TPB) provides essential toxicology and pharmacology data and expertise for drugs, biologicals, and imaging agents in development for clinical trials. Most of the data are submitted to FDA.

TPB Accomplishments and Ongoing Activities

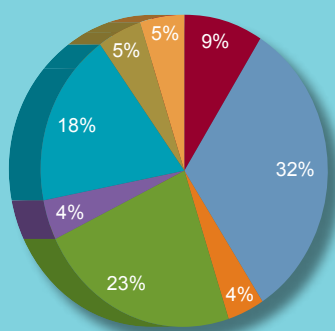
- Provide expertise to extramural community
- Create tailored preclinical strategies and study designs for safety assessment

- Guide studies by pharmacokinetics and pharmacodynamics, enabling correlation with toxicity
- Establish relationships between pharmacokinetics and pharmacodynamics, toxicity, and safety across species
- Incorporate in vitro toxicity data and studies as appropriate
- Compare toxicity with accepted clinical agents as necessary
- Demonstrate the sequence and extent of adverse effects as they relate to dose and exposure; minimize toxicity by change in route and/or schedule
- Establish safe operating parameters for initial clinical administration of promising new anticancer drug candidates
- Identify potential toxicology and pharmacology hurdles for targets and chemical scaffolds during the earliest stages of project development
- Contribute a unique body of knowledge to enhance mechanistic understanding of toxicities associated with anticancer agents
 - A unique role for NCI is to provide access to key preclinical findings to encourage and catalyze mechanistic investigation

TPB Future Plans

Investigative Toxicology and Absorption, Distribution, Metabolism, and Excretion (ADME) Program: A New Initiative with Expanded Impact

- Investigative toxicology resources deliverable to extramural scientists
- Functional toxicogenomics data resource: mRNA assessments for the characterization of molecular changes in vital organs (heart, lung, liver, kidney, nervous system, etc.) induced by



Development Status of Compounds with Filed INDs Supported by TPB, 2004–2009

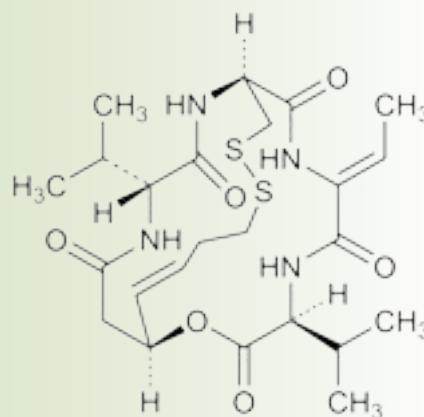
- Unknown Status of Trial
- Phase 1 Clinical Trials Under Way
- Phase 2 Clinical Trials Under Way
- Licensed
- In Negotiations to License
- Trial Approved
- Clinical Hold
- Approved for Use



Case Study for Tailored Preclinical Safety Assessment: Depsipeptide (Romidepsin)

- Background
 - Isolated from *Chromobacterium violaceum*
 - Induced morphological reversion of H-ras-transformed NIH3T3 cells
 - Inhibits proliferation; causes G1 and G2/M arrest
 - Histone deacetylase (HDAC) inhibitor (HDAC1 and HDAC2)
 - Dropped by Fujisawa due to cardiotoxicity in dogs
- TPB separated efficacy from cardiotoxicity so that the drug could move forward in the clinic
- Relationship between depsipeptide efficacy and cardiac toxicity revealed a new schedule permitting clinical testing
 - Intermittent schedule more active, less toxic in mice and less cardiotoxic in dogs

- Permitted FDA approval of NCI-sponsored trials
- FDA Advisory Committee recommends Gloucester Pharmaceuticals' romidepsin (depsipeptide) for approval for cutaneous T-cell lymphoma
- A New Drug Application (NDA) for romidepsin in cutaneous T-cell lymphoma approved November 2009



marketed anticancer agents, investigational agents, and combinations

- In vivo specimens, in vitro cell culture, three-dimensional spheroid and organ tissue slice systems
- Assessment of novel toxicity biomarkers

Most preclinical toxicology and pharmacokinetic data generated on investigative agents are unpublished and not available as a public data resource. This new initiative will make critical new molecular toxicology data for targeted therapeutic agents available to extramural investigators.

Mechanistic Toxicology
Molecular Strategies
Uptake and Metabolism

- Cell-based assays
- Computerbased pathway modeling
- Protein-based toxicity biomarkers
- In vivo studies
- mRNA-based assays
- In silico models and predictive tools

Cellular Systems
Compound Characterization

- Tissue slice systems
- Cell culture systems
- Bone marrow assay

Pharmaceutical Resources Branch

Under the theme of “Development,” the Pharmaceutical Resources Branch (PRB) provides comprehensive pharmaceutical services to various programs of the DCTD and other parts of NCI and NIH. The primary objective of PRB is to supply high-quality chemical substances and formulated products in support of preclinical studies and human clinical trials. Most of the data generated are submitted to the FDA. This objective is accomplished essentially through contract management activities.

The major contract areas managed by PRB staff include:

- Chemical synthesis and large-scale GMP production
- Analytical services and quality control
- Pharmaceutical research and development for identifying dosage forms and novel formulations
- Clinical dosage form manufacturing and shelf life surveillance

PRB Ongoing Activities

- Chemical resources
 - Small-scale synthesis including probe runs, process optimization, and large-scale GMP synthesis, ranging from relatively short synthesis of one to two steps to complicated and challenging multistep synthesis involving 20 or more steps supported by three chemical synthesis contracts
- Analytical
 - Develop validated assays to certify purity, identity, and quality of test agents per FDA guidelines and industry standards
 - Prepare specifications for bulk chemical substances of all lots and release for IND-directed current Good Laboratory Practice toxicology studies and for use in manufacturing clinical supplies
- Pharmaceutical research and development
 - Develop dosage forms suitable for use in human clinical trials



- Evaluate salts, non-aqueous solvents, and surfactants; emphasis given to newer techniques to improve solubility or stability (emulsions, prodrugs, and complexation)
- Evaluate dosage form for chemical content, activity in rodent models whenever possible, and feasibility for manufacture on production scale, supported by three pharmaceutical research and development contracts
- Pharmaceutical production
 - Pharmaceutical production contract for parenteral drug products, including freeze-dried, emulsion, and liquid-filled dosage forms
 - Production of capsules and tablets for oral use, with capability to produce creams/gels for topical use
 - Adherence to strict cGMP guidelines and regular inspection by the U.S. FDA, U.K., and other European regulatory authorities
- Shelf-life surveillance
 - Stability program for each clinical batch of drug to certify potency, degradation products, and other aspects as required
 - Testing schedules per FDA and other guidelines

PRB Accomplishments

- Produced clinical supplies and chemistry, manufacturing, and control data to support 10 INDs sponsored by DCTD and 6 INDs sponsored under the former NCI RAID mechanism; several new clinical candidates in advanced IND development stages
- Synthesized 96 distinct compounds ranging in batch sizes of grams to

multi-kilograms, often manufacturing additional batches

- Validated high-pressure liquid chromatographic methods developed for 45 distinct compounds in advanced development; 185 individual lots underwent complete analytical assessment and released for advanced preclinical studies (IND directed) and/or for use in preparing clinical dosage forms
- Prepared approximately 50 batches of parenteral dosage forms, including freeze-dried products, liquid-filled products, nanosuspensions, and emulsions



- Prepared oral dosage forms (mostly capsules) of 13 distinct compounds in multiple batches and multiple strengths to accommodate dosing needs in ongoing clinical trials
- Conducted shelf-life studies at multiple points each year on an average of 80 distinct batches of drug products
- Conducted preformulation and formulation work to identify conditions for preparing suitable and stable formulations; results transferred to the clinical dosage form manufacturers for preparation of actual clinical supplies
- A nanosuspension clinical formulation of water-insoluble 17-allylamino-17-demethoxygeldanamycin (17-AAG) was developed as a two-component system to overcome solubility as well as chemical and physical instabilities of the drug and the formulation, respectively. This formulation is currently in advanced phase 2 studies sponsored by NCI
- Microfluidized formulations of early preclinical candidates are developed and delivered routinely to aid in mouse efficacy and early animal toxicology studies of water-insoluble compounds

PRB Future Plans

- Include newer approaches to enhancing oral bioavailability of drug candidates, including self-emulsifying drug delivery systems, and prodrug approach
- Develop targeted delivery of established drugs using various techniques including conjugation, nanosuspensions, and coated liposomes

SELECTED PUBLICATIONS

Grants and Contracts Operations Branch: Grantee Publications

Novel mutant-selective EGFR kinase inhibitors against EGFR T790M, Zhou W, Ercan D, Chen L, Yun CH, Li D, Capelletti M, Cortot AB, Chirieac L, Iacob RE, Padera R, Engen JR, Wong KK, Eck MJ, Gray NS, Jänne PA. *Nature*, 2009;462:1070–1074. <http://www.ncbi.nlm.nih.gov/pubmed/20033049>

- Wong and Gray are co-winners of the 2010 American Association for Cancer Research's Team Science Award for work partially supported by these grants, along with six other GCOB grantees.

Identification of an intestinal folate transporter and the molecular basis for hereditary folate malabsorption, Qiu A, Jansen M, Sakaris A, Min SH, Chattopadhyay S, Tsai E, Sandoval C, Zhao R, Akabas MH, Goldman ID. *Cell*, 2006;127:917–928. <http://www.ncbi.nlm.nih.gov/pubmed/17129779>

- The PI's long-standing interest in anti-folate metabolism led to the discovery of proton-coupled folate transporter (PCFT), a low-pH intestinal folate transporter. The finding has high impact on understanding of folate metabolism; more recently, the PI identified PCFT as a primary transporter of the new-generation anti-folate pemetrexed (R01CA082621).

A chromatin-mediated reversible drug-tolerant state in cancer cell subpopulations, Sharma SV, Lee DY, Li B, Quinlan MP, Takahashi F, Maheswaran S, McDermott U, Azizian N, Zou L, Fischbach MA, Wong KK, Brandstetter K, Wittner B, Ramaswamy S, Classon M, Settleman J. *Cell*, 2010;141:69–80.

<http://www.ncbi.nlm.nih.gov/pubmed/20371346>

- Highlighted in *Nature*, this study presents the groundbreaking finding that subpopulations of “drug-tolerant persisters” employ transient epigenetic changes to protect the drug-treated population. (R01CA115830; basis for newly funded R01CA142825)



Migrastatin analogues target fascin to block tumour metastasis, Chen L, Yang S, Jakoncic J, Zhang JJ, Huang XY. *Nature*, 2010;464:1062–1066. <http://www.ncbi.nlm.nih.gov/pubmed/20393565>

- The actin-bundling protein fascin was identified as the target of migrastatin, a natural product known to inhibit tumor cell migration and metastasis. Thus, fascin may be a future target for drug discovery. (R01CA136837)

Discovery and development of the anticancer agent salinosporamide A (NPI-0052), Fenical W, Jensen PR, Palladino MA, Lam KS, Lloyd GK, Potts BC. *Bioorganic & Medicinal Chemistry*, 2009;17:2175–2180. (See also *Developing a new resource for drug discovery: marine actinomycete bacteria*, Fenical W, Jensen PR, *Nature Chemical Biology*, 2006;2:666–673.)

<http://www.ncbi.nlm.nih.gov/pubmed/19022674>

- Novel potent anticancer leads were discovered from newly discovered genus of deep-sea microbes, including NPI-0052 (salinosporamide A), a potent and highly selective inhibitor of 20S proteasome now in phase 2 development. A synthetic analog of halimide, NPI-2358, a potent vascular disrupting agent, is currently in phase 2 clinical trials. (R37CA44848-24)

Information Technology Branch

Analysis of FDA-approved anti-cancer agents in the NCI-60 panel of human tumor cell lines, Holbeck SL, Collins JM, Doroshow JH. *Molecular Cancer Therapeutics*, 2010;9:1451–1460.

<http://www.ncbi.nlm.nih.gov/pubmed/20442306>

- Describes the testing of current oncology drugs in the NCI-60 panel. Data now publicly available at <http://dtp.cancer.gov>; compounds available as a plated set.

Characterization of microRNA expression levels and their biological correlates in human cancer cell lines, Gaur A, Jewell DA, Liang Y, Ridzon D, Moore JH, Chen C, Ambros VR, Israel MA. *Cancer Research*, 2007;67:2456–2468.

<http://www.ncbi.nlm.nih.gov/pubmed/17363563>

- The investigators measured the expression profiles of 241 human microRNAs and developed evidence for the identification of specific microRNAs as candidate oncogenes and tumor suppressor genes in different tumor types.

MicroRNA expression profiles for the NCI-60 cancer cell panel, Blower PE, Verducci JS, Lin S, Zhou J, Chung JH, Dai Z, Liu CG, Reinhold W, Lorenzi PL, Kaldjian EP, Croce CM, Weinstein JN, Sadee W. *Molecular Cancer Therapeutics*, 2007;6:1483–1491.

<http://www.ncbi.nlm.nih.gov/pubmed/17483436>

- Comparison of microRNA expression patterns and compound potency patterns showed significant correlations, suggesting that microRNAs may play a role in chemoresistance.

Drug Synthesis and Chemistry Branch

Synthesis and evaluation of Apogossypol atropisomers as potential Bcl-xL antagonists, Wei J, Rega MF, Kitada S, Yuan H, Zhai D, Risbood P, Seltzman HH, Twine CE, Reed JC, Pellecchia M. *Cancer Letters*, 2009;273:107–113.

<http://www.ncbi.nlm.nih.gov/pubmed/18782651>

Synthesis of gemcitabine triphosphate (dFdCTP) as a tris(triethylammonium) salt, Risbood PA, Kane CT Jr, Hossain T, Vadapalli S, Chadda SK. *Bioorganic and Medicinal Chemistry Letters*, 2008;18:2957–2958.

<http://www.ncbi.nlm.nih.gov/pubmed/18396042>

NIH translational programs for assisting pre-clinical drug discovery and development, Misra RN. In: *Annual Reports in Medicinal Chemistry*, Vol. 45. Bethesda, MD: National Institutes of Health, National Cancer Institute, Developmental Therapeutics Program. 2010:361–377.

Natural Products Branch

Anticancer agents from natural products, Cragg, GM, Kingston, DGI, Newman DJ (eds). Boca Raton, FL: Taylor and Francis, 2005.

Recent progress of marine products as anticancer drugs, Newman DJ, Cragg GM. In: Chabner B (ed), *Marine Anticancer Compounds in the Era of Targeted Therapies*. Barcelona: Permanyer Publications, 2008:51–84.

Impact of natural products on developing new anti-cancer agents, Cragg GM, Grothaus PG, Newman DJ. *Chemical Reviews*, 2009;109:3012–3043.
<http://www.ncbi.nlm.nih.gov/pubmed/19422222>

Microbial antitumor drugs: natural products of microbial origin as anticancer agents, Newman DJ, Cragg GM. *Current Opinion in Investigational Drugs*, 2009;10:1280–1286.
<http://www.ncbi.nlm.nih.gov/pubmed/19943200>

Biological Testing Branch

Complex display of putative tumor stem cell markers in the NCI-60 tumor cell line panel, Stuelten CH, Mertins SD, Busch JI, Gowens M, Scudiero DA, Burkett MW, Hite KM, Alley M, Hollingshead M, Shoemaker RH, Niederhuber JE. *Stem Cells*, 2010;28:649–660.

Molecular analysis reveals heterogeneity of mouse mammary tumors conditionally mutant for Brca1, Wright MH, Robles AI, Herschkowitz JI, Hollingshead MG, Anver MR, Perou CM, Varticovski L. *Molecular Cancer*, 2008;7:29.
<http://www.ncbi.nlm.nih.gov/pubmed/18394172>

Preclinical modeling of a phase 0 clinical trial: qualification of a pharmacodynamic assay of poly(ADP-ribose) polymerase in tumor biopsies of mouse xenografts, Kinders RJ, Hollingshead M, Khin S, Rubinstein L, Tomaszewski JE, Doroshow JH, Parchment RE; NCI Phase 0 Clinical Trials Team. *Clinical Cancer Research*, 2008;14:6877–6885.
<http://www.ncbi.nlm.nih.gov/pubmed/18980982>

Designing phase 0 cancer clinical trials, Murgu AJ, Kummur S, Rubinstein L, Gutierrez M, Collins J, Kinders R, Parchment RE, Ji J, Steinberg SM, Yang S, Hollingshead M, Chen A, Helman L, Wiltrott R, Tomaszewski JE, Doroshow JH.

Clinical Cancer Research, 2008;14:3675–3682.
<http://www.ncbi.nlm.nih.gov/pubmed/18559582>

Phase 0 clinical trial of the poly(ADP-ribose) polymerase (PARP) inhibitor ABT-888 in patients with advanced malignancies, Kummur S, Kinders R, Gutierrez ME, Rubenstein L, Parchment RE, Phillips LR, Ji J, Monks A, Low J, Chen A, Murgu AJ, Collins J, Steinberg SM, Eliopoulos H, Giranda VL, Gordon G, Helman L, Wiltrott R, Tomaszewski JE, Doroshow JH. *Journal of Clinical Oncology*, 2009;27:2705–2711.
<http://www.ncbi.nlm.nih.gov/pubmed/19364967>

Proteomic analysis identifies oxidative stress induction by adaphostin (NSC 680410), Stockwin LH, Bumke MA, Yu SX, Webb SP, Collins JR, Hollingshead MG, Newton DL. *Clinical Cancer Research*, 2007;13:3667–3681.
<http://www.ncbi.nlm.nih.gov/pubmed/17575232>

ARC (NSC 188491) has identical activity to sangivamycin (NSC 65346), including inhibition of both P-TEFb and PKC, Stockwin LH, Yu SX, Stotler H, Hollingshead MG, Newton DL. *BMC Cancer*, 2009;9:63.
<http://www.ncbi.nlm.nih.gov/pubmed/19232100>

Screening Technologies Branch

Echinomycin, a small-molecule inhibitor of HIF-1 DNA binding activity, Kong D, Park EJ, Stephen AG, Calvani M, Cardellina JH, Monks A, Fisher RJ, Shoemaker RH, Melillo G. *Cancer Research*, 2005;65:9047–9055.
<http://www.ncbi.nlm.nih.gov/pubmed/16204079>

- This report is the first demonstration of a novel mechanism of HIF-1 inhibition by blocking HIF DNA binding.

Increased antitumor activity of bevacizumab in combination with hypoxia inducible factor-1 inhibition, Rapisarda A, Hollingshead M, Uranchimeg B, Bonomi CA, Borgel SD, Carter JP, Gehrs B, Raffeld M, Kinders RJ, Parchment R, Anver MR, Shoemaker RH, Melillo G. *Molecular Cancer Therapeutics*, 2009;8:1867–1877.
<http://www.ncbi.nlm.nih.gov/pubmed/19584228>



- This is the first demonstration that HIF-1 inhibition may synergize with antiangiogenic agents by blocking therapy-induced HIF-1-mediated survival pathways.

Gene expression signature of belinostat in cell lines is specific for histone deacetylase inhibitor treatment, with a corresponding signature in xenografts, Monks A, Hose CD, Pezzoli P, Kondapaka S, Vansant G, Petersen KD, Sehested M, Monforte J, Shoemaker RH. *Anticancer Drugs*, 2009;20:682–692.

<http://www.ncbi.nlm.nih.gov/pubmed/19606018>

- This report describes the unique profile of response in both cell lines and corresponding xenografts.

Cellular inhibition of checkpoint kinase 2 (Chk2) and potentiation of camptothecins and radiation by the novel Chk2 inhibitor PV1019 [7-nitro-1H-indole-2-carboxylic acid {4-[1-(guanidinohydrazono)-ethyl]-phenyl}-amide], Jobson AG, Lountos GT, Lorenzi PL, Llamas J, Connelly J, Cerna D, Tropea JE, Onda A, Zoppoli G, Kondapaka S, Zhang G, Caplen NJ, Cardellina JH 2nd, Yoo SS, Monks A, Self C, Waugh DS, Shoemaker RH, Pommier YJ. *Journal of Pharmacology and Experimental Therapeutics*, 2009;331:816–826.

<http://www.ncbi.nlm.nih.gov/pubmed/19741151>

- The investigators identified unique cell line models with activated Chk2 kinase and introduced methods to measure Chk2 inhibition.

Intracellular activation and deactivation of tasidotin, an analog of dolastatin 15: correlation with cytotoxicity, Bai R, Edler MC, Bonate PL, Copeland TD, Pettit GR, Ludueña RF, Hamel E. *Molecular Pharmacology*, 2009;75:218–226.

<http://www.ncbi.nlm.nih.gov/pubmed/18927208>

- Tasidotin, a dolastatin 15 analogue, was intracellularly degraded successively to an active

pentapeptide and an inactive tetrapeptide, and cytotoxicity in leukemic cell lines best correlated with the second reaction (slow degradation leading to greater cytotoxicity).

Gene expression profiling of alveolar soft part sarcoma, Stockwin LH, Vistica DT, Kenney S, Schrupp DS, Butcher DO, Raffeld M, Shoemaker RH. *BMC Cancer*, 2009;9:22.

<http://www.ncbi.nlm.nih.gov/pubmed/19146682>

- This paper presents the first comprehensive gene analysis on alveolar soft-part sarcoma tumors.

Toxicology and Pharmacology Branch

Identifying the safety profile of Ad5.SSTR/TK.RGD, a novel infectivity-enhanced bicistronic adenovirus, in anticipation of a phase I clinical trial in patients with recurrent ovarian cancer, Matthews K, Noker PE, Tian B, Grimes SD, Fulton R, Schweikart K, Harris R, Aurigemma R, Wang M, Barnes MN, Siegal GP, Hemminki A, Zinn K, Curiel DT, Alvarez RD. *Clinical Cancer Research*, 2009;15:4131–4137.

<http://www.ncbi.nlm.nih.gov/pubmed/19509153>

Modulation of gemcitabine (2',2'-difluoro-2'-deoxycytidine) pharmacokinetics, metabolism, and bioavailability in mice by 3,4,5,6-tetrahydrouridine, Beumer JH, Eiseman JL, Parise RA, Joseph E, Covey JM, Egorin MJ. *Clinical Cancer Research*, 2008;14:3529–3535.

<http://www.ncbi.nlm.nih.gov/pubmed/18519786>

Pharmacokinetics, metabolism, and oral bioavailability of the DNA methyltransferase inhibitor 5-fluoro-2'-deoxycytidine in mice, Beumer JH, Eiseman JL, Parise RA, Joseph E, Holleran JL, Covey JM, Egorin MJ. *Clinical Cancer Research*, 2006;12:7483–7491.

<http://www.ncbi.nlm.nih.gov/pubmed/17138702>



2010 Program
Accomplishments

Radiation Research Program



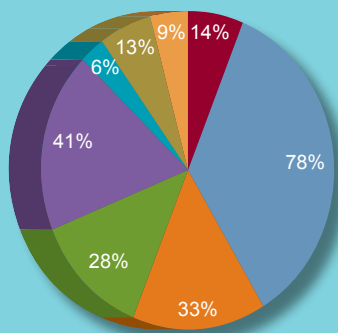
OVERVIEW

The field of radiation oncology has a unique scientific and clinical breadth that includes radiation and stress biology, complex tumor and normal tissue systems, innovative technology, electronic data acquisition and analysis, image-guided therapy, multimodality cancer treatment, outreach to the underserved, and medical and societal response to the threats from nuclear and radiological terrorism. With its research base in basic biology and physics and with clinical care that encompasses the entire spectrum of oncology, radiation oncology has a unique role in multidisciplinary translational science collaboration. Radiation therapy is used in more than half of patients during the course of their cancer treatment and is effective both as a curative modality and for palliation. The Radiation Research Program (RRP) is the sole program focused on therapeutic radiation sciences within the extramural programs of the National Cancer Institute (NCI).

As part of ongoing efforts to stimulate research in radiotherapy and radiation biology, the RRP supports basic,

translational, and clinical research in the Division of Cancer Treatment and Diagnosis (DCTD) by:

- Providing expertise to investigators and potential grantees who perform cutting-edge research using radiation and other forms of energy
- Helping to lead the radiotherapy research community in establishing priorities for the future direction of radiation research
- Developing unique models and capabilities to help and mentor medically underserved communities in the United States and worldwide to access cancer clinical trials
- Evaluating the effectiveness of radiation research being conducted by NCI grantees
- Advising the NCI-funded clinical trials groups and Cancer Therapy Evaluation Program (CTEP) regarding scientific priorities and quality assurance in clinical studies with radiotherapy
- Providing laboratory support for preclinical evaluation of systemic agents that can be used with radiation (through the Molecular Radiation Therapeutics Program on the Frederick campus)



Distribution of 2009 Grants in Percentages by RRP Research Areas



C. NORMAN COLEMAN, ASSOCIATE DIRECTOR

C. Norman Coleman, M.D., Associate Director for the Radiation Research Program (RRP), received his medical training at the 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. He is

board certified in internal medicine, medical oncology, and radiation oncology. Dr.

Coleman was a tenured faculty member in Radiology and Medicine at the Stanford

University School of Medicine before joining Harvard Medical School in 1985 as the

Alvan T. and 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 heading RRP, he served as Chief of

the Center for Cancer Research's Radiation Oncology Branch from 1999 until 2004.

He has written extensively in his field and has won numerous awards, including

the 2005 Gold Medal Award from the American Society for Therapeutic Radiation

Oncology, for his many scientific and professional contributions to the fields of radiation oncology and radiation biology.



Dr. Coleman is currently Associate Director of the DCTD Radiation Research Program, Senior Investigator in the Radiation Oncology Branch, 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 the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services.



- Serving as the NCI's liaison and advisor on mitigation of radiation injury to normal tissue in programs addressing radiological and nuclear terrorism in the National Institute for Allergies and Infectious Diseases (NIAID) and the Office of the Assistant Secretary for Preparedness and Response (ASPR) in the Department of Health and Human Services

RRP coordinates its activities with other radiation research efforts at NCI, in particular the Divisions of Cancer Biology, the Center for Cancer Research's Radiation Oncology and Radiation Biology Branches, and the Division of Cancer Epidemiology and Genetics, as well as at the National Institutes of Health (NIH), other federal agencies, and national and international research organizations. RRP serves as a focal point for extramural investigators who are concerned with clinically related radiation oncology and biology research.

The RRP research portfolio comprises approximately 200 grants. The grant award mechanisms used by RRP and their distribution in terms of research support in

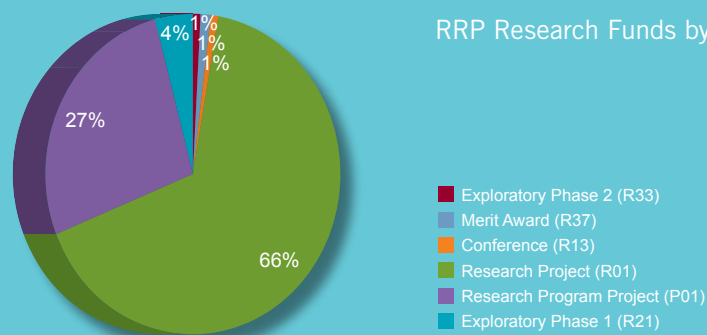
2009 are shown in the accompanying chart (see below). The predominant mechanism is the individual research project grant (R01), followed by research program project grants (P01).

STRUCTURE AND FUNCTION

The [Radiation Research Program \(RRP\)](#) is divided into three branches:

1. Radiotherapy Development Branch
2. Clinical Radiation Oncology Branch
3. Molecular Radiation Therapeutics Branch

The primary responsibility of RRP is to the grantees and contractors of NCI and NIH. In 2009, RRP administered 212 awarded grants, primarily through the Radiotherapy Development Branch. In addition to grants management and related duties, RRP program staff members advise on and act as reviewers for grants and contracts submitted to the Department of Defense



(DoD) and consult on radiation issues with program staff in NIAID.

Radiotherapy Development Branch

The field of radiation oncology is unique in the breadth of expertise and knowledge required for both preclinical development and optimal clinical use. The research portfolio of the Radiotherapy Development Branch (RDB) encompasses a broad range of topics, such as radiation-inducible molecular changes in both tumor and normal tissues, including signaling and apoptosis; tumor biology and microenvironmental changes relating to radiation response; radiation sensitizers and protectors; normal tissue injury and treatment; systemic targeted radionuclide therapy, including radioimmunotherapy; and nonionizing radiation-based therapies such as photodynamic therapy. RDB and the Clinical Radiation Oncology Branch collaboratively manage grants that deal with image-guided radiotherapy and particle therapies, as well as basic radiation physics track structure and radiation chemistry. RDB also collaborates with NCI's Center to Reduce Cancer Health Disparities, especially on issues relating to minority accrual to cancer clinical trials.

Clinical Radiation Oncology Branch

The Clinical Radiation Oncology Branch (CROB) manages a grant portfolio dealing with clinical and translational research in radiation oncology as well as the technical and physical aspects of radiation research and development. In addition to managing the RRP grant portfolio, CROB devotes a substantial effort to supporting NCI, NIH, the U.S. Department of Health and Human Services, and government-wide activities

such as technology development and assessment and comparative effectiveness research. The branch works extensively with:

- DCTD partners, such as CTEP and the Cancer Imaging Program (CIP), assisting with their cooperative clinical trial groups and early-phase trials consortia
- The Coordinating Center for Clinical Trials with several of its steering committees and their task forces (e.g., head and neck, thoracic malignancies, breast, gastrointestinal, genitourinary, gynecological, investigational drugs, and symptom management and quality of life subcommittees)
- The cancer Biomedical Informatics Grid (caBIG) in developing demonstration projects using radiation oncology as a platform
- NIAID in identifying opportunities for radiation countermeasure investigators to decrease toxicity of treatment in cancer patients
- The Food and Drug Administration (FDA) in identifying needs and opportunities for post-marketing surveillance of devices cleared for use in radiation oncology
- The Agency for Healthcare Research and Quality and the National Academy of Sciences in identifying priorities and opportunities for comparative effectiveness research in cancer in general and in prostate cancer in particular
- DoD (Armed Forces Radiobiology and Research Institute [AFRRI]) in exploring ways in which clinical trials in cancer patients may help in licensing of countermeasures



- The Department of Veterans Affairs in facilitating quality improvement in radiation oncology at Veterans Health Administration (VHA) facilities as well as in improving connectivity among various components of the VHA electronic health record and with other radiation oncology networks, such as the Radiation Therapy Oncology Group (RTOG)

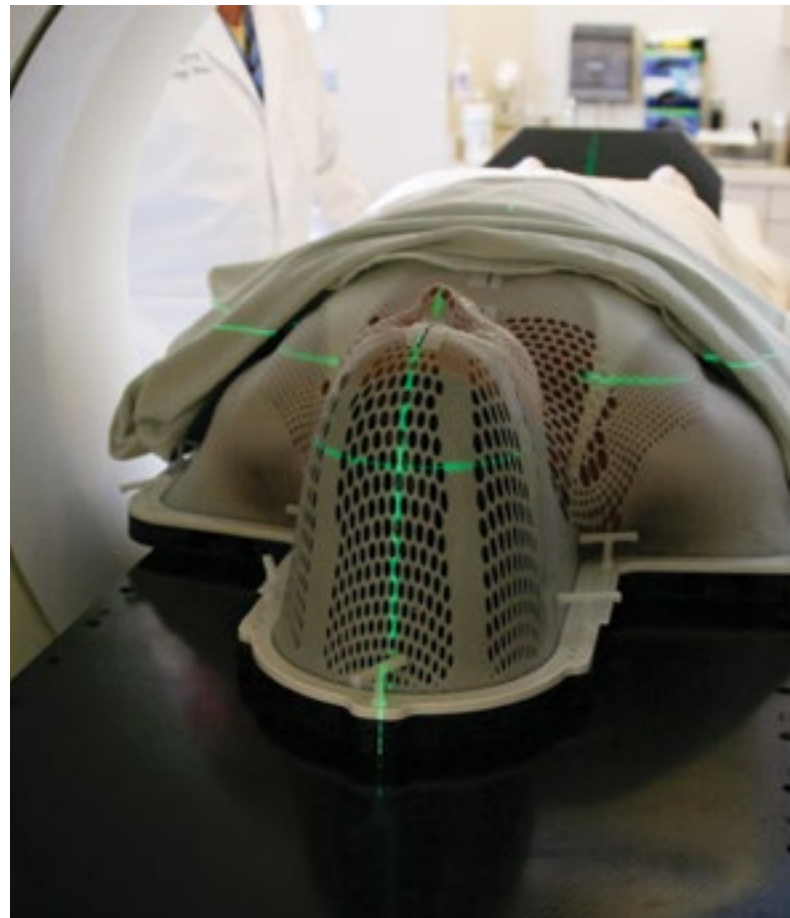
Molecular Radiation Therapeutics Branch

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) and CTEP in DCTD, investigators in the Radiation Biology and Radiation Oncology Branches in the Center for Cancer Research (CCR), and university and industry collaborators specifically addressing research and development needs in combined modality therapy using radiation. It stimulates the development of radiation modifiers for tumor sensitization and normal tissue protection for radiotherapy improvement, optimizes radiomodifiers and assays to better guide clinical trial designs, identifies putative radioresponsive targets, and studies mechanisms of action of radiomodifiers. On the NCI-Frederick campus, MRTB works in coordination with DTP and with drug development activities and molecular imaging in DCTD and CCR. The MRTB also plays a major role in developing radiosensitizers as part of the recently initiated NCI Experimental Therapeutics program (NEXt).

Capabilities

The current capabilities of the MRTB laboratory at NCI-Frederick include:

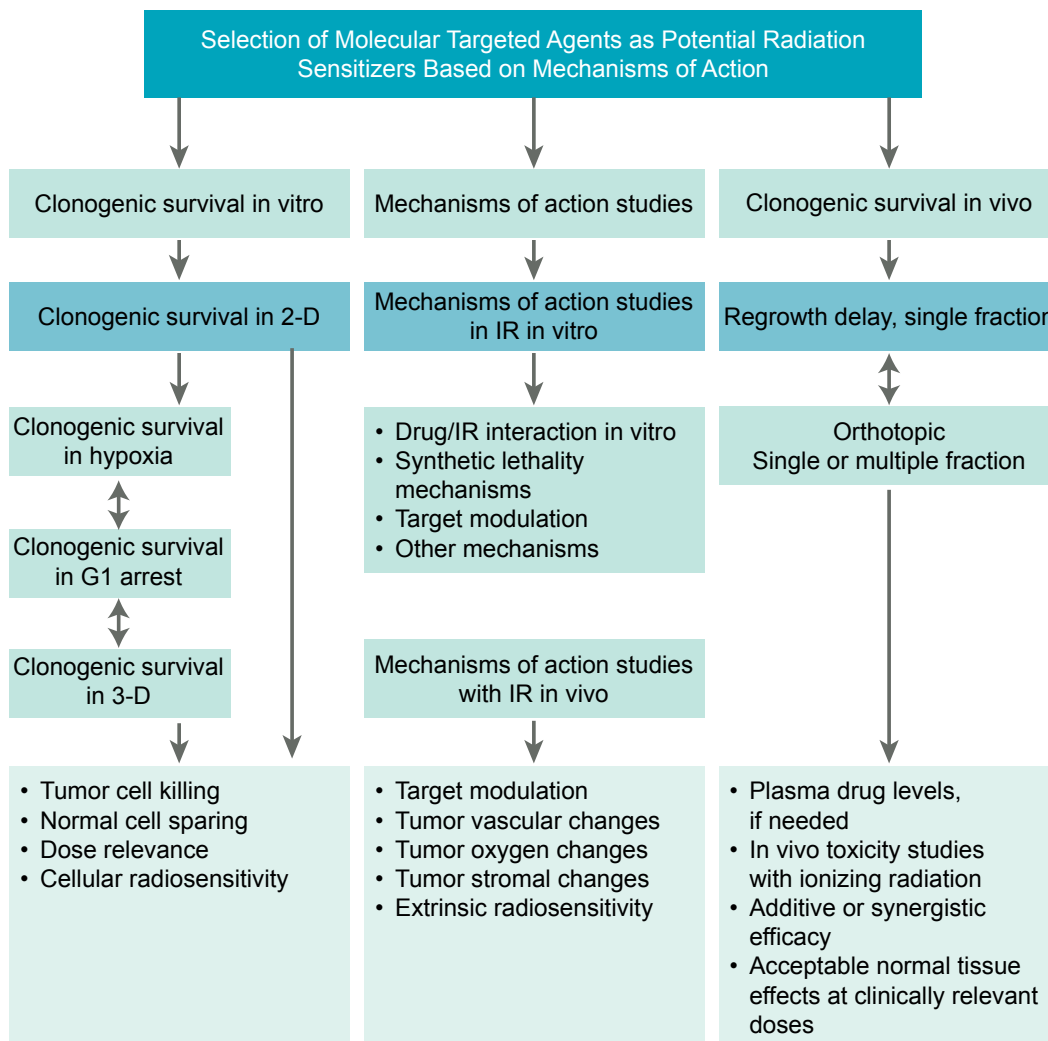
- Testing of anticancer agents with ionizing radiation, using an in vitro clonogenic assay in various human cancer and normal cell lines
- Evaluating potential radiation modifiers, using in vivo xenografts or orthotopic mouse models
- Determining mechanisms of action of potential radiation modifiers, using a variety of molecular and biochemical approaches



MRTB also collaborates actively with the CIP Small Animal Imaging Program to utilize various noninvasive imaging modalities to assess tumors' response to investigational agents plus ionizing radiation. In addition, MRTB partners with DTP's Biological Testing Branch and Screening Technologies Branch to further develop animal models that can be used in the fields of radiation biology and radiation oncology, and to identify potential radiation modifiers from the initial screening phase. MRTB has also been collaborating actively with CTEP to proactively evaluate potential radiosensitizers.

Plans for Drug Development and Serving as a National Resource

The experimental paths for drug evaluation are shown below. These are designed to be efficient in throughput yet stringent enough to have good predictive accuracy of an agent's eventual clinical utility. MRTB serves the radiation biology and radiation oncology research communities by developing and disseminating optimized in vitro and in vivo assays (such as in vitro clonogenic assays and animal studies).





PROGRAM ACCOMPLISHMENTS

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



The [Advanced Technology Consortium \(ATC\)](#) (U24CA081647) capitalizes on the infrastructure and strengths of the nation's existing quality assurance (QA) programs—including the Image-Guided Therapy Center, the RTOG, the Radiological Physics Center, and the Quality Assurance Review Center—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, and verification digital data. Specifically, the ATC:

- Maintains, manages, and improves electronic data submission of advanced technology (three-dimensional conformal radiotherapy, intensity-modulated radiation therapy, stereotactic body radiotherapy, and brachytherapy), protocol credentialing and case data, archival storage, and remote QA review process
- Develops novel, Web-based, remote-review tools to enhance the efficient and

effective review of protocols by utilizing advanced modular-design technologies to promote the development of efficient tools and subsystems to achieve compatibility with existing software standards, including caBIG

- Assists cooperative groups to develop and manage advanced-technology clinical trial protocols, including:
 - Tumor/target volume and organ-at-risk definitions
 - Credentialing requirements and evaluation criteria
 - Electronic data submission requirements and instructions
 - QA review procedures
- Serves as an educational resource to the nation's clinical trial cooperative groups and participating institutions for support of clinical trials on advanced-technology radiation therapy

This activity also successfully competed for supplemental funding from the American Recovery and Reinvestment Act of 2009 and was awarded funding that will enhance and expand its efforts to create more robust electronic review and additional clinical trial groups.

Radiobiology Bioterrorism Research and Training Group

The Radiobiology Bioterrorism Research and Training Group (RABRAT) is an informal working group of representatives of government agencies that are involved in radiation research, including the low-dose program of the Department of Energy (DoE), the normal tissue medical countermeasures program of NIAID, radiation biology and biodosimetry of AFRRRI (DoD),

space radiation (National Aeronautics and Space Administration [NASA]), and others interested in radiation sciences and preparedness for radiation accidents and terrorism events. Its purpose is to keep the agencies informed of ongoing activities and to avoid both gaps and duplication of effort. Members include, in addition to those from RRP, representatives of the U.S. Department of Health and Human Services, other NCI divisions (Division of Cancer Epidemiology and Genetics, Division of Cancer Biology, and Division of Cancer Prevention), other Institutes (NIAID), and other government agencies (FDA, DoD, DoE, Environmental Protection Agency, NASA, and Department of Homeland Security [DHS], and Emergency Assistance Center/Training Site). RABRAT meets three to four times per year.

Cancer Disparities Research Partnership

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 intends to reduce the negative consequences associated with cancer health disparities.

During the pilot U56 CDRP planning phase (2002–2008), six grantee institutions succeeded in establishing:

- Clinical trial research infrastructures at community-based institutions to



facilitate the participation of targeted ethnic and minority, medically underserved, or low-income populations in the latest NCI-sponsored radiation oncology or combined modality treatment trials

- Mentoring partnerships with cancer centers and institutions with clinical trials expertise, and particularly, cancer centers experienced in clinical trials; these partnerships were facilitated by the provided telemedicine system (**TELESYNERGY**)
- Community education and outreach activities and patient navigation program to facilitate patient recruitment and accrual into clinical trials

From these accomplishments, RRP succeeded in 2008 to reissue the CDRP program as a limited competition RFA ([RFA-CA-09-502](#)). In September 2009, three grantees (Rapid City Regional Hospital in Rapid City, South Dakota; Singing River Health System in Pascagoula, Mississippi; and New Hanover Regional Medical Center in Wilmington, North Carolina) received five-year funding, while the University of Pittsburgh Medical Center's McKeesport Hospital in McKeesport, Pennsylvania, received a two-year award. A final U54 implementation phase of the CDRP program was begun to allow time for the grantees to stabilize their existing clinical research infrastructure and modify or adopt new strategies to maximize the access, accrual, and participation of their minority and underserved populations onto all types of NCI-sponsored cancer clinical trials, i.e., cancer prevention, symptom management and cancer control, surgical, medical, and radiation oncology.

FUTURE INITIATIVES

As cells and tissues use complex systems to perform their functions, and as optimal clinical cancer care requires a coordinated system of expertise and functions, the RRP approaches its entire portfolio and that of its potential collaborators as a complex system. Advances in almost any one area can potentially impact another, and it is the program's strategic vision not only to be aware of advances in radiation and related fields but also to strengthen existing links and develop new links that can accelerate advances. Further, through its own in-house research and development (including the CCR) as well as through workshops, program staff endeavor to lead the field into new areas of opportunity. The broad but highly interrelated fields are

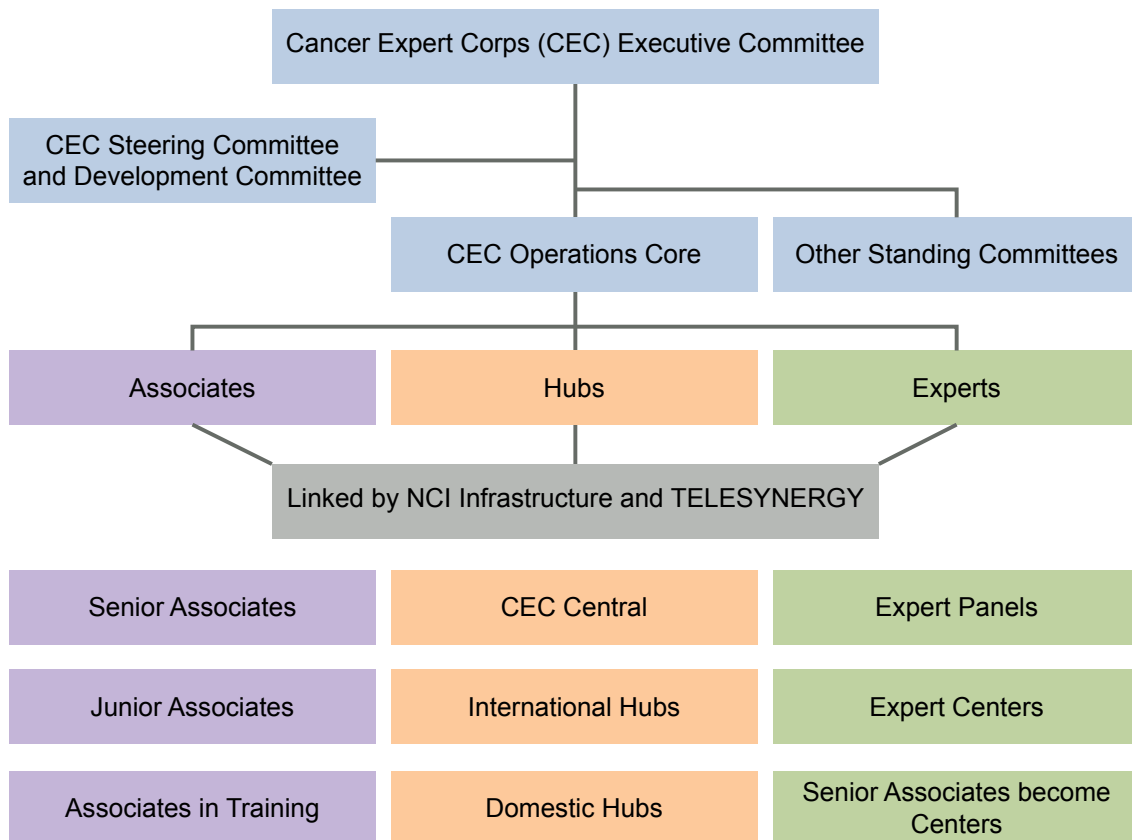
- Basic molecular and cell biology
- Complex tumor biology
- Normal tissue injury
- Molecular imaging and image-guided therapy
- Stress biology
- Molecularly targeted therapeutics with radiation
- Quality assurance for prospective clinical trials
- Electronic databases to facilitate comparative effectiveness research and international collaboration
- Outreach to the underserved through technology and mentoring
- International collaboration for nuclear safety and terrorism response
- International oncology-based diplomacy

With a staff actively engaged in research planning and conduct through its MRTB, collaboration with CCR, NIAID, and ASPR's Biomedical Advanced Research and Development Authority, RRP generates a strong level of enthusiasm, collaboration, and innovation among agencies, investigators, and partners. This leadership has helped to sustain a critical mass of talent and enthusiasm within government (RABRAT), the new Radiation Education Initiative described later, and a new means of bringing cancer advances to underserved populations worldwide (Cancer Expert Corps).

Cancer Expert Corps: The "Peace Corps" for Cancer

The **Cancer Expert Corps (CEC)** concept is being developed under NCI with RRP as the lead. CEC will be 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 United States and worldwide. It is a "Peace Corps" for cancer.

CANCER EXPERT CORPS





The CEC will have three components:

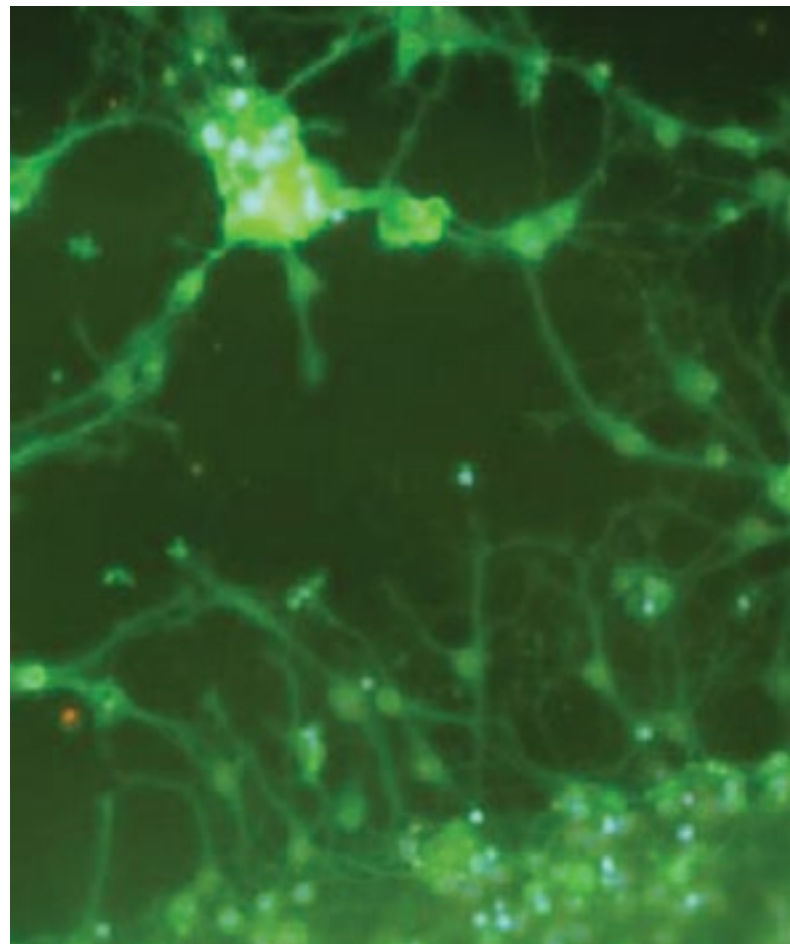
1. **Associates:** Members of medical facilities and locations that serve underserved populations and are interested in participating and investing in improving the quality of care and life for their affected citizens
2. **Experts:** CEC expert panels comprising international experts from a broad range of oncology disciplines and health care delivery services that provide mentoring for associates based on long-term, person-to-person connectivity
3. **Infrastructure:** Hubs (i.e., infrastructure) located worldwide to coordinate the associate–expert linkage so that their time is spent on mentoring and education

While seeking a stable source of support, CEC is working with a number of agencies and groups to develop mentor–mentee relationships so that the program will start off with vigorous activity. Among the groups being approached for partnership are the International Network for Cancer Treatment and Research, the American Society of Clinical Oncology, RTOG, the World Health Organization’s International Agency for Research on Cancer, the Union for International Cancer Control, and the International Atomic Energy Agency. A number of international partners have already made commitments to participate.

Radiobiology Education Initiative

Future progress in radiation sciences depends upon a cadre of scientists who are both knowledgeable about radiation effects on cells and tissues and technologically trained to a high standard. Classically

trained radiobiologists are approaching retirement age, and newer-generation scientists from more focused specialties (such as molecular biology), in many cases, have not received the broad training that ensures success in radiation-related research. To this end, an effort is being made to enhance current training in the radiation sciences through the development of a supplemental training course that will incorporate radiobiology, radiation physics, and experimental methodology. The aim is to provide, at a national level, enhanced radiation training and to coordinate this



effort among a number of existing training programs, national societies (e.g., the American Society for Therapeutic Radiation Oncology and the Radiation Research Society), and international groups (e.g., the European Society for Therapeutic Radiology and Oncology). Current plans call for a one-week intensive course and the development, through this course, of Internet-based teaching tools that would be available globally.

Translating Normal Tissue Medical Countermeasures Developed for Terrorism to the Oncology Clinic

Another initiative that is under way aims to translate the findings obtained by research on radiation terrorism countermeasures for use in clinical radiotherapy in order to decrease the adverse effects of cancer treatment. To this end, a workshop was held in 2010 bringing investigators studying radiation injury to normal tissues for developing radiation protectors and mitigators to meet with cancer clinical trialists, industry representatives, and program officials from the Small Business Innovation Research (SBIR)/Small Business Technology Transfer division at NIH. RRP has proposed an SBIR Request for Proposals for developing radioprotectors for clinical use in cancer patients. A second SBIR proposal for genomic screening for radiosensitivity was also proposed, and both have been accepted for publication.

SELECTED PUBLICATIONS

Grantee Publications

Stereotactic body radiation therapy for inoperable early stage lung cancer, Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, Fakiris A, Bezjak A, Videtic G, Johnstone D, Fowler J, Gore E, Choy H. *JAMA*, 2010;17:1070–1076.

<http://www.ncbi.nlm.nih.gov/pubmed/20233825>

- This cooperative group trial established a new standard of care for patients with inoperable early-stage lung cancer.

Induction and concurrent taxanes enhance both the pulmonary metabolic radiation response and the radiation pneumonitis response in patients with esophagus cancer, McCurdy M, McAleer MF, Wei W, Ezhil M, Johnson V, Khan M, Baker J, Luo D, Ajani J, Guerrero T. *International Journal of Radiation Oncology, Biology, Physics*, 2010;76:816–823.

<http://www.ncbi.nlm.nih.gov/pubmed/19525073>

- Radiation pneumonitis developing weeks or months after radiation therapy is a serious complication that often limits effective therapy of thoracic cancers. These investigators have discovered the pulmonary metabolic radiation response, which may enable clinicians to identify patients at risk of radiation pneumonitis at a time when alternative treatments can be considered; it offers mechanistic insights that may lead to interventions for preventing pneumonitis.

Inhibition of vasculogenesis, but not angiogenesis, prevents the recurrence of glioblastoma after irradiation in mice, Kioi M, Vogel H, Schultz G, Hoffman RM, Harsh GR, Brown JM. *Journal of Clinical Investigation*, 2010;120:694–705.

<http://www.ncbi.nlm.nih.gov/pubmed/20179352>



- In this report, the authors show, in an intracranial xenograft model of glioblastoma multiforme, that irradiation of the tumor induces recruitment of bone marrow-derived cells, restoring the radiation-damaged vasculature by vasculogenesis, thereby allowing the growth of surviving tumor cells.

Proton vs carbon ion beams in the definitive radiation treatment of cancer patients, Suit H, Delaney T, Goldberg S, Paganetti H, Clasie B, Gerweck L, Niemierko A, Hall E, Flanz J, Hallman J, Trofimov A. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology*, 2010;95:3–22.

<http://www.ncbi.nlm.nih.gov/pubmed/20185186>

- This study established charged-particle radiation therapy at the forefront of modern radiation therapy techniques, and in this review the investigators explore opportunities for further gains.

Apoptotic cells activate the “phoenix rising” pathway to promote wound healing and tissue regeneration, Li F, Huang Q, Chen J, Peng Y, Roop DR, Bedford JS, Li C-Y. *Science Signaling*, 2010;3(110):ra13.

<http://www.ncbi.nlm.nih.gov/pubmed/20179271>

- Dying cells in wounded tissues send signals to stimulate the proliferation of stem or progenitor cells, which in turn start the process of tissue regeneration and wound healing. Caspases 3 and 7 are key players involved in this process.

Involving American Indians and medically underserved rural populations in cancer clinical trials, Guadagnolo BA, Petereit DG, Helbig P, Koop D, Kussman P, Fox Dunn E, Patnaik A. *Clinical Trials*, 2009;6:610–617.

<http://www.ncbi.nlm.nih.gov/pubmed/19933720>

- Clinical trial participation in this medically underserved population was low overall but approximately threefold higher than reported national accrual rates. Lack of availability of protocols for common cancer sites, as well as stringent protocol inclusion criteria, were the primary obstacles to clinical trial enrollment. Targeted interventions with a patient navigation program were used to engage American Indian patients and may have resulted in higher clinical trial enrollment among this racial/ethnic group.

Radioimmunotherapy of breast cancer metastases with alpha-particle emitter ²²⁵Ac: comparing efficacy with ²¹³Bi and ⁹⁰Y, Song H, Hobbs RF, Vajravelu R, Huso DL, Esaias C, Apostolidis C, Morgenstern A, Sgouros G. *Cancer Research*, 2009;69:8941–8948.

<http://www.ncbi.nlm.nih.gov/pubmed/19920193>

- Preclinical comparative evaluation of alpha particle emitter dosimetry, biodistribution, and efficacy for radio-immunotherapy. The data suggest that ²²⁵Ac-labeled anti-HER-2/neu monoclonal antibody could significantly prolong survival in patients with HER-2/neu-positive metastatic breast cancer.

Self-assembling chimeric polypeptide-doxorubicin conjugate nanoparticles that abolish tumours after a single injection, MacKay JA, Chen M, McDaniel JR, Liu W, Simnick AJ, Chilkoti A. *Nature Materials*, 2009;8:993–999.

<http://www.ncbi.nlm.nih.gov/pubmed/19898461>

- This report describes the development of artificial recombinant chimeric polypeptides that spontaneously self-assemble into sub-100-nm-sized, near-monodisperse nanoparticles on conjugation of diverse hydrophobic molecules, including chemotherapeutics. When used to deliver chemotherapeutics

to a murine cancer model, chimeric polypeptide nanoparticles had a fourfold higher maximum tolerated dose than free drug and induced nearly complete tumor regression after a single dose.

A modeling analysis of the effects of molecular size and binding affinity on tumor targeting,

Schmidt MM, Wittrup KD. *Molecular Cancer Therapeutics*, 2009;8:2861–2871.
<http://www.ncbi.nlm.nih.gov/pubmed/19825804>

- The authors present a simple, mechanistic model that can be used to understand and predict the complex interplay between molecular size, affinity, and tumor uptake for molecules across a broad size spectrum.

Systems biology modeling of the radiation sensitivity network: a biomarker discovery platform,

Eschrich S, Zhang H, Zhao H, Boulware D, Lee JH, Bloom G, Torres-Roca JF. *International Journal of Radiation Oncology, Biology, Physics*, 2009;75:497–505.
<http://www.ncbi.nlm.nih.gov/pubmed/19735874>

- The authors developed a novel radiation-biomarker discovery platform, using a systems biology modeling approach. The platform may have a significant impact on the integration of biology into the practice of clinical radiation oncology.

Pretargeting CD45 enhances the selective delivery of radiation to hematolymphoid tissues in nonhuman primates,

Green DJ, Pagel JM, Nemecek ER, Lin Y, Kenoyer A, Pantelias A, Hamlin DK, Wilbur DS, Fisher DR, Rajendran JG, Gopal AK, Park SI, Press OW. *Blood*, 2009;114:1226–1235.
<http://www.ncbi.nlm.nih.gov/pubmed/19515724>

- Pretargeted radioimmunotherapy testing in nonhuman primates demonstrated a significant improvement in target-to-normal organ ratios of absorbed radiation compared with directly radiolabeled bivalent antibody 1.

Tumor vascular changes mediated by inhibition of oncogenic signaling, Qayum N, Muschel RJ, Im JH, Balathasan L, Koch CJ, Patel S, McKenna WG, Bernhard EJ. *Cancer Research*, 2009;69:6347–6354.
<http://www.ncbi.nlm.nih.gov/pubmed/19622766>

- The authors demonstrate that inhibition of tumor signaling can alter tumor vascularization and hypoxia with potential therapeutic benefit in a dose-dependent manner.

Tumor vasculature is regulated by PHD2-mediated angiogenesis and bone marrow-derived cell recruitment,

Chan DA, Kawahara TL, Sutphin PD, Chang HY, Chi JT, Giaccia AJ. *Cancer Cell*, 2009;15:527–538.
<http://www.ncbi.nlm.nih.gov/pubmed/19477431>

- How bone marrow-derived cells are recruited to the tumor and their contribution to the tumor vasculature is poorly understood. The authors show that two factors regulated by PHD2 in an HIF-independent but NF- κ B-dependent manner contribute to tumor angiogenesis and growth. The results support a critical role for PHD2 in regulating tumor angiogenesis.

Hypoxia-induced lysyl oxidase is a critical mediator of bone marrow cell recruitment to form the premetastatic niche,

Erler JT, Bennewith KL, Cox TR, Lang G, Bird D, Koong A, Le QT, Giaccia AJ. *Cancer Cell*, 2009;15:35–44.
<http://www.ncbi.nlm.nih.gov/pubmed/19111879>

- This report demonstrates a critical role for lysyl oxidase (LOX) in premetastatic niche formation. The results support targeting LOX for the treatment and prevention of metastatic disease.

An interferon-related gene signature for DNA damage resistance is a predictive marker for chemotherapy and radiation for breast cancer,

Weichselbaum RR, Ishwaran H, Yoon T, Nuyten DSA, Baker SW, Khodarev N, Su AW, Shaikh AY, Roach P, Kreike B, Roizman B, Bergh J, Pawitan Y, van de Vijver MJ, Minn AJ. *Proceedings of*



the National Academy of Sciences of the United States of America, 2008;105:18490–18495.

<http://www.ncbi.nlm.nih.gov/pubmed/19001271>

- An experimentally derived interferon-related DNA damage resistance signature (IRDS) is associated with resistance to chemotherapy and/or radiation across different cancer cell lines. The IRDS improves outcome prediction when combined with standard markers, risk groups, or other genomic classifiers.

An imaging-based tumour growth and treatment response model: investigating the effect of tumour oxygenation on radiation therapy response, Titz B, Jeraj R. *Physics in Medicine and Biology*, 2008;53:4471–4488.

<http://www.ncbi.nlm.nih.gov/pubmed/18677042>

- The authors describe the development of tumor response assessment modeling based on quantitative positron emission tomography scans as a measure of hypoxia. This model could be used to transform patient-specific data into voxel-based biological objectives for treatment planning and to investigate biologically optimized dose prescriptions.

The combination of epidermal growth factor receptor inhibitors with gemcitabine and radiation in pancreatic cancer, Morgan MA, Parsels LA, Kollar LE, Normolle DP, Maybaum J, Lawrence TS. *Clinical Cancer Research*, 2008;14:5142–5149.

<http://www.ncbi.nlm.nih.gov/pubmed/18698032>

- This report shows that the epidermal growth factor receptor (EGFR) inhibitors cetuximab and erlotinib increase the efficacy of gemcitabine-radiation and supports the integration of EGFR inhibitors with gemcitabine-radiation in clinical trials for pancreatic cancer.

Establishing trusting partnerships for successful recruitment of American Indians to clinical trials, Petereit DG, Burhansstipanov L. *Cancer*

Control, 2008;15:260–268.

<http://www.ncbi.nlm.nih.gov/pubmed/18596679>

- Cancer mortality rates among American Indians in the Northern Plains are among the highest in the nation. American Indians appear to experience more intense side effects from therapeutic radiation than do other populations. This differential response to treatment, a disparity in itself, might be overcome if the molecular reasons were better understood. The authors discuss how implementation of a genetic study relied on achieving a trusting partnership with American Indians because a lack of trust has historically been a barrier to performing research with this population.

Noninvasive assessment of cancer response to therapy, Han Z, Fu A, Wang H, Diaz R, Geng L, Onishko H, Hallahan DE. *Nature Medicine*, 2008;14:343–349.

<http://www.ncbi.nlm.nih.gov/pubmed/18297085>

- The authors report the results of preclinical testing of peptide ligands selected for their ability to discern responding from nonresponding cancers within days of initiating therapy.

Matrix metalloproteinase-9 is required for tumor vasculogenesis but not for angiogenesis: role of bone marrow-derived myelomonocytic cells, Ahn GO, Brown JM. *Cancer Cell*, 2008;13:193–205.

<http://www.ncbi.nlm.nih.gov/pubmed/18328424>

- These researchers found that tumors unable to grow in irradiated tissue of matrix metalloproteinase-9 (MMP-9) knockout mice could be restored to grow by transplantation of wild-type bone marrow. CD11b-positive myelomonocytic cells from transplanted bone marrow were responsible for tumor growth and the development of immature blood vessels. The results suggest targets for adjunct therapy to enhance tumor response to radiotherapy.

Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck, Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, Jones CU, Sur R, Raben D, Jassem J, Ove R, Kies MS, Baselga J, Youssoufian H, Amellal N, Rowinsky EK, Ang KK. *New England Journal of Medicine*, 2006;354:567–578.

<http://www.ncbi.nlm.nih.gov/pubmed/16467544>

- This article presents the first clinical use of a molecularly targeted agent combined with radiation as a cytotoxic treatment. The demonstration that modulating tumor signaling provides an advantage in both local control and overall survival is a seminal finding.

RRP Staff Publications

Establishment of a radiogenomics consortium, West C, Rosenstein BS, Alsner J, Azria D, Barnett G, Begg A, Bentzen S, Burnet N, Chang-Claude J, Chuang E, Coles C, De Ruyck K, De Ruysscher D, Dunning A, Elliott R, Fachal L, Hall J, Haustermans K, Herskind C, Hoelscher T, Imai T, Iwakawa M, Jones D, Kulich C; EQUAL-ESTRO, Langendijk JH, O’Neils P, Ozsahin M, Parliament M, Polanski A, Rosenstein B, Seminara D, Symonds P, Talbot C, Thierens H, Vega A, West C, Yarnold J. *International Journal of Radiation Oncology, Biology, Physics*, 2010;76:1295–1296.

<http://www.ncbi.nlm.nih.gov/pubmed/20338472>

- This report describes the formation of a Radiogenomics Consortium established to aid in the identification of genetic variants, primarily single-nucleotide polymorphisms, associated with the development of normal tissue toxicities resulting from radiation therapy.

A small interfering RNA screen of genes involved in DNA repair identifies tumor-specific radiosensitization by POLQ knock-down, Higgins GS, Prevo R, Lee YF, Helleday T, Muschel RJ, Taylor S, Yoshimura M, Hickson ID, Bernhard EJ, McKenna WG. *Cancer Research*,

2010;70:2984–2993.

<http://www.ncbi.nlm.nih.gov/pubmed/20233878>

- This publication describes a novel method for high-throughput screening for synthetic lethality of molecular targeting combined with radiation. The DNA repair enzyme PolQ is newly identified as a contributor to tumor cell survival after irradiation.

Modulating tumor vasculature through signaling inhibition to improve cytotoxic therapy,

Maity A, Bernhard EJ. *Cancer Research*, 2010;70:2141–2145.

<http://www.ncbi.nlm.nih.gov/pubmed/20179191>

- This review describes new findings that inhibition of tumor cell signaling can enhance tumor response to radiation and cytotoxic drugs by enhancing vascular function and tumor oxygenation.

Triage dose assessment for partial-body exposure: dicentric analysis, Prasanna PG, Moroni M, Pellmar TC. *Health Physics*, 2010;98:244–251.
<http://www.ncbi.nlm.nih.gov/pubmed/20065689>

Distinct signaling pathways after higher or lower doses of radiation in three closely related human lymphoblast cell lines, Lu TP, Lai LC, Lin BI, Chen LH, Hsiao TH, Liber HL, Cook JA, Mitchell JB, Tsai MH, Chuang EY. *International Journal of Radiation Oncology, Biology, Physics*, 2010;76:212–219.

<http://www.ncbi.nlm.nih.gov/pubmed/20005454>

Current status and future potential of advanced technologies in radiation oncology. Part 1.

Challenges and resources, Vikram B, Coleman CN, Deye JA. *Oncology*, 2009;23:279–283.

<http://www.ncbi.nlm.nih.gov/pubmed/19418829>

Current status and future potential of advanced technologies in radiation oncology. Part 2. State of the science by anatomic site, Vikram B, Coleman CN, Deye JA. *Oncology*, 2009;23:380–385.

<http://www.ncbi.nlm.nih.gov/pubmed/19476269>



Medical response to a radiologic/nuclear event: integrated plan from the Office of the Assistant Secretary for Preparedness and Response, Department of Health and Human Services, Coleman CN, Hrdina C, Bader JL, Norwood A, Hayhurst R, Forsha J, Yeskey K, Knebel A. *Annals of Emergency Medicine*, 2009;53:213–222.

<http://www.ncbi.nlm.nih.gov/pubmed/18387707>

- This report outlines a scientifically based comprehensive planning framework and Web-based “just-in-time” medical response information called Radiation Event Medical Management describing a medical response plan in the event of a nuclear event.

Re: Intensity-modulated radiation therapy dose prescription, recording, and delivery: patterns of variability among institutions and treatment planning systems, Deye J, Purdy J, Vikram B. *Journal of the National Cancer Institute*, 2008;100:1263–1264.

<http://www.ncbi.nlm.nih.gov/pubmed/18728288>

Published Reports and Program Descriptions

Synopsis of partial-body radiation diagnostic biomarkers and medical management of radiation injury workshop, Prasanna PG, Blakely WF, Bertho JM, Chute JP, Cohen EP, Goans RE, Grace MB, Lillis-Hearne PK, Lloyd DC, Lutgens LC, Meineke V, Ossetrova NI, Romanyukha A, Saba JD, Weisdorf DJ, Wojcik A, Yukihiro EG, Pellmar TC. *Radiation Research*, 2010;173:245–253.

<http://www.ncbi.nlm.nih.gov/pubmed/20095857>

Report from the Radiation Therapy Committee of the Southwest Oncology Group (SWOG):

Research Objectives Workshop 2008, Okunieff P, Kachnic LA, Constine LS, Fuller CD, Gaspar LE, Hayes DF, Hooks J, Ling C, Meyskens FL Jr, Philip PA, Raben D, Smalley SR, Swanson GP, Teicher BA, Thomas CR Jr, Vikram B, Zelefsky MJ, Baker LH. *Clinical Cancer Research*, 2009;15:5663–5670.

<http://www.ncbi.nlm.nih.gov/pubmed/19723641>

Quality assurance needs for modern image-based radiotherapy: recommendations from 2007 interorganizational symposium on

“quality assurance of radiation therapy: challenges of advanced technology,” Williamson JF, Dunscombe PB, Sharpe MB, Thomadsen BR, Purdy JA, Deye JA. *International Journal of Radiation Oncology, Biology, Physics*, 2008;71(1 suppl):S2–S12.

<http://www.ncbi.nlm.nih.gov/pubmed/18406928>

Hypoxia: importance in tumor biology, noninvasive measurement by imaging, and value of its measurement in the management of cancer therapy, Tatum JL, Kelloff GJ, Gillies RJ, Arbeit JM, Brown JM, Chao KS, Chapman JD, Eckelman WC, Fyles AW, Giaccia AJ, Hill RP, Koch CJ, Krishna MC, Krohn KA, Lewis JS, Mason RP, Melillo G, Padhani AR, Powis G, Rajendran JG, Reba R, Robinson SP, Semenza GL, Swartz HM, Vaupel P, Yang D, Croft B, Hoffman J, Liu G, Stone H, Sullivan D. *International Journal of Radiation Biology*, 2006;82:699–757.

<http://www.ncbi.nlm.nih.gov/pubmed/17118889>



2010 Program
Accomplishments

Translational Research Program

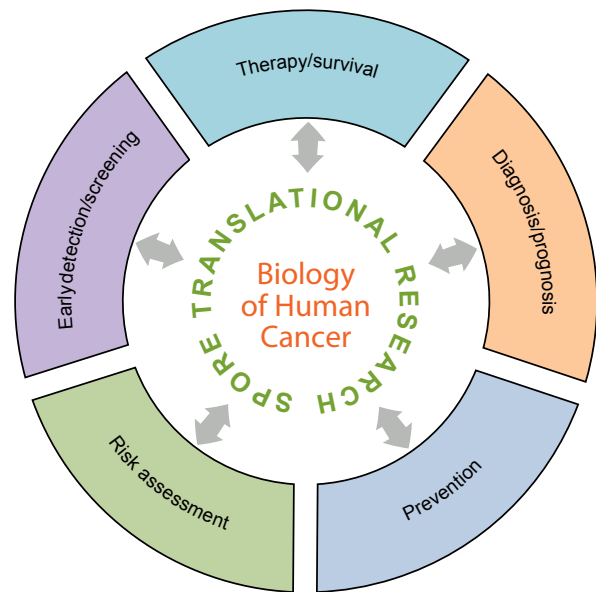


OVERVIEW

The **Translational Research Program (TRP)** of the Division of Cancer Treatment and Diagnosis (DCTD) is committed to reducing cancer incidence and mortality and improving survival and quality of life for cancer patients. The TRP uses advances in basic sciences to develop new approaches for the prevention, diagnosis, and treatment of cancer by fostering interdisciplinary investigations and coordinating the resources of the National Cancer Institute (NCI) with those of academia, industry, and nonprofit organizations and foundations.

These objectives are accomplished by:

- Supporting the **Specialized Programs of Research Excellence (SPOREs)** to translate novel scientific discoveries into clinical testing, including early-phase clinical trials
- Encouraging a multidirectional approach to translational research (as shown in the diagram)
- Promoting research in high-incidence as well as rare cancers
- Facilitating the cross-fertilization of ideas, leveraging resources, and ensuring access of resources to projects and investigators to bring discoveries from the laboratory to the clinic in the most efficient manner
- Supporting additional grant mechanisms for translational research



There are currently 65 SPOREs located at academic centers in 23 states across the United States, representing 16 organ sites and systems:

- | | |
|--------------------|-----------------|
| • Bladder | • Lung |
| • Brain | • Lymphoma |
| • Breast | • Myeloma |
| • Endometrium | • Ovarian |
| • Gastrointestinal | • Pancreatic |
| • Head and neck | • Prostate |
| • Kidney | • Sarcoma |
| • Leukemia | • Skin/melanoma |

The SPOREs are a cornerstone of the NCI's efforts to promote collaborative, interdisciplinary translational research. In each individual SPORE, this goal is achieved by:

- Focusing on a specific organ site or a group of highly related cancers
- Supporting research projects that will result in new and diverse approaches to

TOBY T. HECHT, ACTING ASSOCIATE DIRECTOR

Toby T. Hecht earned a Ph.D. in microbiology and immunology from the Albert Einstein College of Medicine, studying the effect of virus infections on the expression of cell surface antigens. She did her postdoctoral research at Yale University in genetics and lymphocyte development before coming to the NIH, where among other accomplishments, she and her collaborators created a unique T-cell hybridoma to study the fine specificity of antigenic control of both proliferation and gamma-interferon production, as well as a Hodgkin lymphoma-specific monoclonal antibody that has been used in both human imaging and therapy trials. Dr. Hecht has worked for over 30 years at the NIH, 23 of which were spent at the NCI in programmatic activities and biological agent development. She has also guided many projects (from conception to testing in the clinic) through the former NCI Rapid Access to Intervention Development (RAID) program and the Drug Development Group. Some of the agents have been licensed by pharmaceutical companies and have reached the marketplace. Cetuximab is currently used in a subset of patients with colorectal cancer, head and neck cancers, and other epidermal growth factor receptor-positive malignancies, either alone or in combination with other therapeutics. Chimeric 14.18, an anti-disialoganglioside monoclonal antibody, has recently completed evaluation in a successful phase 3 trial and will become part of the standard of care for patients with neuroblastoma. In 2008, Dr. Hecht was chosen to oversee the transition of the Organ Systems Branch, the program that administered the SPOREs, from the Office of the NCI Director to the Division of Cancer Treatment and Diagnosis, in order to fully integrate this program into the translational science activities of NCI. She is now working to bring the SPORE guidelines up to date and to explore new ways to promote collaborations among translational researchers.





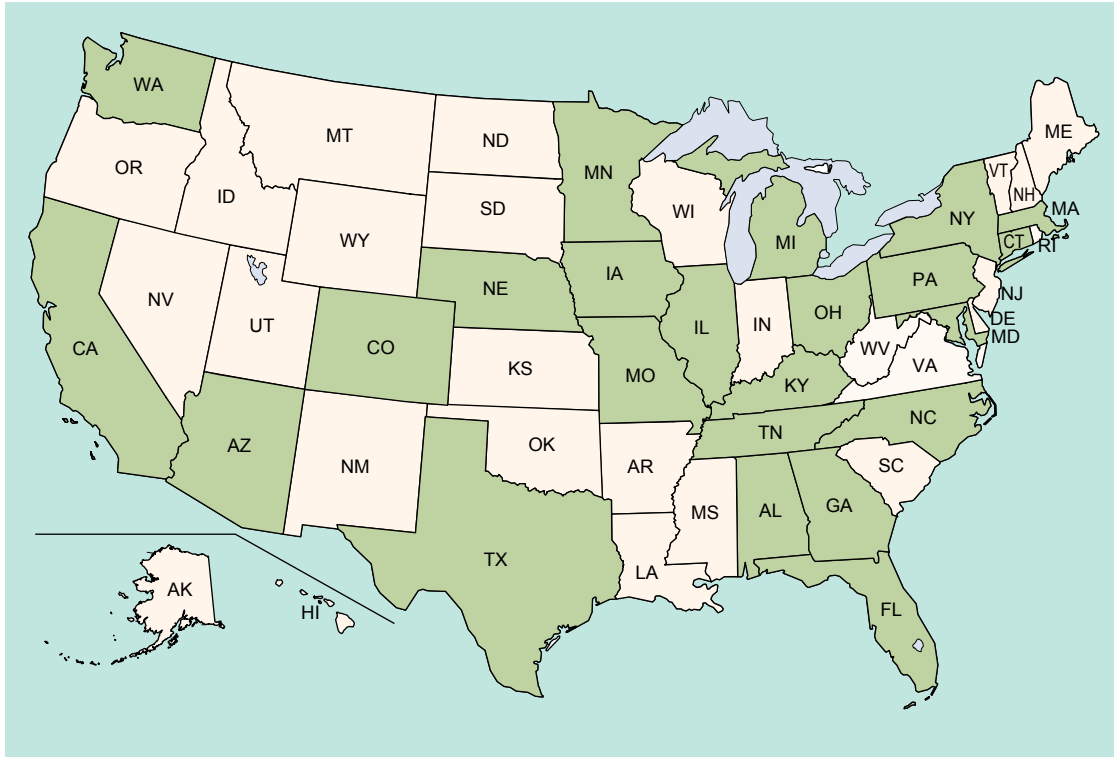
- the prevention, early detection, diagnosis, and treatment of human cancers
- Encouraging cross-fertilization between various biomedical disciplines by requiring a minimum of four diverse translational research projects per program and involving both basic and clinical or applied scientists in each research project
- Requiring a dedicated pathology or biospecimen specialized resource core to ensure access to clinical materials
- Supporting a development research program to promote pilot projects of cutting-edge research (basic, clinical, or translational)
- Supporting a career development program to promote the transition of both young and established investigators to translational cancer research in the proposed organ site
- Requiring collaboration among other SPOREs and across NCI-funded networks to promote translational advancement

SPORE ORGAN SITE DISTRIBUTION, 1992–2010*

Site	RFA					PAR									
	1992–1995	1996–1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	
Breast	4	6	6	9	9	9	9	10	8	10	11	10	10	8	
Prostate	2	3	3	4	8	11	11	11	11	8	7	7	9	9	
Lung	2	3	3	3	6	6	7	7	7	5	6	6	7	7	
Gastrointestinal	1	2	2	2	2	4	4	5	4	4	5	5	5	6	
Ovary			4	4	4	4	4	5	4	4	4	4	4	4	
Bladder					1	1	1	1	1	1	1	1	1	1	
Skin					1	2	2	3	3	3	3	5	3	4	
Brain						2	2	4	4	4	3	4	2	2	
Head & neck						3	3	4	4	4	3	5	4	5	
Lymphoma						2	2	3	3	3	3	4	4	4	
Endometrial							1	1	1	1	1	0	1	2	
Cervical							1	1	1	1	1	0	1	1	
Kidney							1	1	1	1	1	0	1	1	
Leukemia							1	1	1	1	1	1	2	2	
Myeloma							1	1	1	1	1	1	1	2	
Pancreas							3	3	3	3	3	2	2	3	
Sarcoma														1	
Total SPOREs	9	14	18	22	31	44	53	61	57	54	54	55	57	62	

*Excluding grants receiving interim funding. Several grants are co-funded.

STATES WITH ACTIVE SPORE GRANTS IN FISCAL YEAR 2010



- Providing flexibility to SPORE investigators to realign resources and substitute research projects if translational objectives are not being met during the course of the funding period
- Encouraging the advice of patient advocates

In addition to SPOREs, the TRP funded the following mechanisms from 2005 to 2010:

- Coordination of clinical and translational research across the NCI (2009 to present), part of the larger Grand Opportunities program, funded by the 2009 American Recovery and Reinvestment Act of 2009 (ARRA), to support the collaborative efforts of translational scientists across different NCI programs and funding mechanisms
- Progress for Patients award program (2002–2009), a public–private partnership between the Avon



Foundation and the NCI in conjunction with the Foundation for the National Institutes of Health, to fund innovative translational research in breast cancer

- Administrative supplements to support inter-SPORE collaborations to advance translational science (2000–2007)

BACKGROUND

Mission

The mission of TRP is to integrate scientific advancements in the understanding of the biology of human cancer with the development of new interventions for the prevention, diagnosis, and treatment of cancer patients, and populations at risk for cancer, by fostering broad interdisciplinary investigations that focus on bringing discoveries from the laboratory to the clinic, and coordinating the resources of NCI with those of academia, industry, and nonprofit organizations and foundations to reduce cancer incidence, morbidity and mortality, to extend survival, and to increase the quality of life of cancer patients. This is accomplished by:

- Planning, advising, coordinating, evaluating, and supporting the SPOREs, which use the P50 grant funding mechanism, to translate novel scientific discoveries from the laboratory and/or population studies to the clinic for testing in humans with cancer, to determine the biological basis for clinical observations, and to use specimens from clinical studies

to determine correlations between biomarkers and outcomes in patients

- Encouraging and facilitating collaborations among the SPOREs, Cancer Centers, other NCI- and NIH-funded mechanisms and programs, and outside organizations, to increase cross-fertilization of ideas, leverage resources, reduce duplication, and ensure access of resources to projects and investigators
- Establishing high-quality organ-specific tumor specimen banks to provide research resources for the cancer research community
- Maintaining the Developmental Research Program and Career Development Program of the SPOREs to promote high-risk and/or high-payoff projects and to ensure the development of promising researchers who are new to translational research
- Supporting research in high-incidence cancers as well as in rare cancers
- Collaborating with patient advocates who support translational science in cancer

History Through 2008

The organ-specific research programs at NCI trace their origins to the Breast Cancer Task Force of the 1960s. With the passage of the National Cancer Act of 1971, NCI established additional task forces for cancers of the bladder, prostate, and large bowel, and in 1976 for pancreatic cancer, through the National Organ Site Program, which was later reorganized into the Organ Systems Program—Organ Systems Branch.

1991: Congress appropriates funds for the NCI to establish the SPOREs through the P50 grant mechanism that links laboratory studies with clinical research to rapidly translate basic research discoveries into clinical medicine.

1992: NCI issues the first solicitation for applications and makes the first SPORE awards in three organ sites (breast, prostate, lung), followed by one gastrointestinal (GI) award in 1993. The Organ Systems Branch in the Office of Centers, Training and Resources, in the Office of the NCI Director, is given the task of providing programmatic oversight of the SPORE program.

1995: NCI expands the number of SPORE awards per organ site.

1999: The Board of Scientific Advisors approves the expansion of the SPORE Program from 4 to 16 organ sites. The Executive Committee approves a supplemental program to support clinical trials.

2000: The funding opportunity for SPOREs becomes a Program Announcement (PAR) rather than a Request for Applications (RFA).

2002: Progress for Patients, an Avon–NCI Award Program, is launched to fund innovative translational research in breast cancer.

2003: The SPORE program undergoes a major expansion, to 61 grants, due to doubling of the NIH budget.

2007: The Executive Committee approves the expansion of the SPORE Program to all organ sites in addition to the currently funded 16 sites.

2008: The Organ Systems Branch is transferred to DCTD and reorganized into TRP.

Recent History (2009–2010)

On October 2, 2009, TRP reissued for an additional three years a Funding Opportunity Announcement that uses the P50 (Specialized Centers) SPORE grant mechanism and is open to translational cancer research in any organ site or group of highly related cancers. As a result of ARRA, the NCI participated in the [Grand Opportunities \(GO\) Program \(RFA-OD-09-004\)](#), using the RC2 grant mechanism, to support research on high-impact translational research by encouraging and rewarding collaborative team science. The particular opportunity, Coordination of Clinical/Translational Research Across the NCI, was an initiative issued by TRP for the benefit of the entire NCI for groups of extramural scientists with diverse expertise and original, creative ideas to work together on translational cancer research projects of significant scope and consequence that, nonetheless, could be completed within two years.

The requirements for applying were strict: applicants had to form a team with a coordinating investigator(s) and other non-coordinating investigators; two or more institutions had to be involved; members of the team had to be currently funded by different NCI funding mechanisms, which could include Cancer Centers, SPOREs, P01s, R01s, phase 1 U01s, phase 2 N01s, the Early Detection Research Network, Cooperative Groups, the Clinical Trials Support Unit, Clinical Consortia, or other NCI-supported translational research mechanisms; and the team had to perform intensive, high-impact, and if possible, paradigm-shifting studies associated with an ongoing or a new (ready to proceed) clinical trial.



Nine RC2 GO grants were funded covering a broad range of organ site cancers, both common and rare, including blood malignancies, pancreatic, lung, prostate,

and oral epithelial cancers, as well as melanoma, glioblastoma, and childhood rhabdomyosarcoma.

COORDINATION OF CLINICAL/TRANSLATIONAL RESEARCH (GO GRANTS) ACROSS NCI

NCI Program/Division	Grant
TRP/DCTD	Predicting pancreatic cancer responses for a PARP inhibitor-based clinical trial A randomized clinical trial to treat pancreatic cancer patients with standard chemotherapy drugs (irinotecan, cisplatin, bleomycin, and mitomycin C) with and without olaparib, a new poly(ADP ribose) polymerase (PARP) inhibitor
CTEP/DCTD	Targeted therapies for childhood acute lymphoblastic leukemia A clinical study designed to identify high-risk patients who would benefit from Janus kinase (JAK) inhibitor therapy. JAK mutations are associated with high risk of relapse in children with acute lymphoblastic leukemia (ALL).
CDP/DCTD	Translation of predictive rhabdomyosarcoma biomarkers into clinical practice Development of a new assay to stratify patients with low, intermediate, and high risk of childhood rhabdomyosarcoma to provide risk-tailored treatments
CDP/DCTD	Refining a molecular recursive partitioning analysis model for glioblastoma Refinement of the existing glioblastoma classification models using new molecular, genetic, and epigenetic biomarkers to establish distinct prognostic groups of patients treated with radiation and temozolomide
Cancer Biomarkers Research Group/DCP	Validation of a multi-gene test for lung cancer risk Establishment of a prospective cohort to test the validity of a new lung cancer risk assay that measures the activity of 14 key antioxidant, DNA repair, and transcription factor genes
TRP/DCTD	Biomarker prediction of Gleason upgrading in prostate cancer Development of new biomarkers that can discriminate prostate cancer patients with pure Gleason grade (GG) 3 from those who have a mix of GG3 and GG4, with GG4 not being readily detectable in prostate biopsy samples
TRP/DCTD	Proteasome/HDAC inhibition in leukemia/MDS; phase 1 trial and correlative studies A clinical trial of the histone deacetylase inhibitor (HDAC) belinostat (PXD-101) and the proteasome inhibitor bortezomib in patients with refractory acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML)–blast crisis, and high-risk myelodysplastic syndromes (MDS)
Lung and Upper Aerodigestive Cancer Research Group/DCP	Clinical evaluation of a bioadhesive gel for oral cancer chemoprevention An assessment of chemopreventive efficacy of dried black raspberries on microscopical oral epithelial dysplastic lesions
TRP/DCTD	Defining the importance of immunity to NY-ESO-1 in melanoma therapy and prognosis Validation of clinical benefits of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)–blocking antibodies for melanoma patients with preexisting or induced immunity to cancer- and testis-specific antigen NY-ESO-1

CTEP = Cancer Therapy Evaluation Program (DCTD); CDP = Cancer Diagnosis Program (DCTD); DCP = Division of Cancer Prevention (NCI).

PROGRAM ACCOMPLISHMENTS

Brain Tumors

- **Nanoliposomal irinotecan containing gadoteridol, a paramagnetic contrast agent, was successfully delivered into precise brain locations in preclinical experiments.** This protocol was developed by the University of California San Francisco (UCSF) Brain SPORE. Infusion into spontaneously occurring gliomas in dogs was controlled by real-time magnetic resonance imaging. A phase 1 clinical trial based on convection-enhanced delivery of liposomes is planned.
- **GWAS identified novel risk loci for glioblastoma.** The UCSF Brain SPORE, in collaboration with the Duke University Brain SPORE, performed a genome-wide association study (GWAS) of 275,895 autosomal variants among 692 glioma

cases and 3,992 controls. The study revealed that variants in CDKN2B (9p21) and RTEL1 (20q13.3) regions are associated with high-grade glioma susceptibility. This association was consistent in both the discovery and the replication phase. (Nature Genetics, 2009;41:905)

Bladder Cancer

- **Specific “forerunner genes” associated with early intraurothelial preneoplasia may contribute to the development of bladder cancer.** Forerunner genes are clonal genetic alterations discovered by the MD Anderson Cancer Center Bladder SPORE through a whole-organ histologic and genetic mapping strategy of human bladder cancer. Forerunner genes are located next to or within well-known tumor suppressors (including Rb) and appear to contribute to the earliest clonal expansion stages of urothelial neoplasia.

CHROMOSOMAL REGIONS INVOLVED IN THE DEVELOPMENT OF BLADDER CANCER





This provides new insight into the concept of “field defect,” which explains the high frequency of recurrence that characterizes the natural history of bladder cancer. (Proceedings of the National Academy of Sciences [PNAS], 2007;104:13732)

- **Risk assessment model predicts bladder cancer susceptibility.** Epidemiologic study of bladder cancer by the MD Anderson Bladder SPORE has resulted in the first robust risk-assessment model of epithelial cancer based on clinical, epidemiologic, and genetic information to predict bladder cancer susceptibility (J Clin Oncol, 2007;31:4974). This model is presently being refined by incorporating emerging new data, including newly discovered bladder cancer-associated genetic polymorphisms. This risk assessment model is the basis for the development of a Web-based tool for cancer risk assessment and has the potential to direct surveillance and the decision to deliver adjuvant therapy.
- **Aurora kinase A-based approach holds promise for detection of high-risk cancer.** MD Anderson Bladder SPORE investigators measured aurora kinase A (AURKA) gene copy number in urine sediments in hope of developing new approaches for bladder cancer detection and for surveillance of bladder cancer (Journal of the National Cancer Institute [JNCI], 2008;100:1401). This method may identify tumors with aggressive natural history and offers potential utility as a prognostic marker. A licensing agreement has been negotiated with a major diagnostic company to develop this marker for clinical use.

Breast Cancer

- **Abrogated response to cellular stress identifies ductal carcinoma in situ tumors associated with future tumor events.** As demonstrated by the UCSF Bay Area Breast SPORE, overexpression of p16 or COX-2, coupled with proliferation increase, measured by high level of Ki67 in DCIS samples, significantly increases the risk of subsequent tumor events within the first decade after lumpectomy. The clinical significance of these biological phenotypes is currently being validated in a large, independent cohort of women previously diagnosed with ductal carcinoma in situ. (Cancer Cell, 2007;12:479)



- **Protein kinase D1 regulates coufilin-mediated migratory competence of tumor cells.** Dynamic actin remodeling processes at the leading edge of migrating tumor cells depend on a complex temporal and spatial interplay of Rho GTPases, kinases, and phosphatases. The Mayo Breast

SPORE demonstrated that expression of constitutively active protein kinase D1 (PKD1) in invasive tumor cells enhances the phosphorylation of cofilin and therefore effectively blocks the formation of free actin–filament barbed ends and cell migration. (Nature Cell Biology, 2009;11:545)

- **Residual breast cancers after conventional therapy display mesenchymal as well as tumor-initiating features.** The Breast SPORE at Baylor University defined a gene expression signature common for both CD44⁺/CD24^{-/low} and mammosphere (MS)-forming cells and examined whether tumor cells surviving after initial treatment were enriched for cells bearing this CD44⁺/CD24^{-/low}/MS signature. This signature was found in the recently discovered “claudin-low” aggressive molecular subtype of breast cancer, as well as in tumor cells remaining after either endocrine therapy (letrozole) or chemotherapy (docetaxel), consistent with the selective survival of tumor-initiating cells post-treatment. (PNAS, 2009;106:13820)

Gastrointestinal Cancers

- **Targeting of polyamine synthesis reduces recurrence of colon adenomas.** A prospective, randomized, placebo-controlled trial combining difluoromethylornithine, a selective inhibitor of polyamine, and sulindac, a COX-2 inhibitor, was completed by the Arizona GI SPORE and other NCI grantees. A 70% reduction of all adenomas and a 90% reduction of advanced and/or multiple adenomas, as compared with placebo, were reported without evidence of serious toxicities.

This proof-of-principle trial indicates that targeting polyamine synthesis and inflammation can be an effective strategy to prevent the recurrence of colon adenomas. (Cancer Prevention Research, 2008;1:32)

- **A gene expression profile predicting colon cancer progression was developed.** Through an exploratory biomarker study using a murine colon cancer metastasis model and colon cancer patient gene expression datasets, the GI SPORE at Vanderbilt developed a gene expression profile for identifying patients with recurrent colon cancer. Recurrence score was significantly associated with increased risk of metastasis and death from colon cancer across all pathologic stages and specifically in stage II and stage III patients. This unique profile, which predicts cancer recurrence and death independently of other conventional methods, is currently being validated on larger cohorts. (Gastroenterology, 2010;138:958)
- **Progression markers of Barrett’s esophagus (BE) was established and validated.** In collaboration with NCI and the Early Detection Research Network, investigators from seven GI/Pancreatic Cancer SPORE sites performed a retrospective, multicenter, double-blind validation study of eight BE methylation biomarkers for progression prediction in 145 non-progressors and 50 progressors. Using coefficients from a multivariate logistic regression analysis and a linear combination of the eight markers with age, this methylation-based panel can predict neoplastic progression in BE and has potential clinical value in improving both the efficiency of surveillance



endoscopy and the early detection of esophageal adenocarcinoma. (Cancer Research, 2009;69:4112)

Gynecologic Cancers

- **Concatenated multi-type L2 proteins in adjuvant have potential as pan-oncogenic human papillomavirus vaccines.** The Cervical SPORE at Johns Hopkins University found that, unlike the human papillomavirus (HPV) type 16 L2 polypeptide, multitype L2 fusion proteins 11-200X3 and 11-88X5 induced high neutralizing antibody titers against all heterologous HPV types tested. Specifically, 11-20X3 formulated in GPI-0100 adjuvant or alum with 1018 ISS provided equally effective protection of mice against HPV-16 challenge as compared with the standard HPV-16 L1 virus-like particles. (JNCI, 2009;101:782)

Head and Neck Cancer

- **A STAT3 decoy decreases expression of STAT3 in squamous cell head and neck tumors.** With additional support from the former NCI Rapid Access to Intervention Development (RAID) program to manufacture clinical-grade material, the Head and Neck Cancer SPORE at the University of Pittsburgh has completed a phase 0 pharmacodynamic study of the transcription factor STAT3. A primary endpoint in this trial is to test whether STAT3 is modulating its target in head and neck tumors by directly injecting STAT3 decoy immediately prior to tumor resection, when the patient is under anesthesia. A biopsy was obtained prior to decoy administration, and the resected tumor specimen was studied

after treatment to determine STAT3 target gene expression. The expression levels of the STAT3-activated target genes encoding Bcl-X_L and cyclin D1 were generally decreased in the resected tumor compared with levels in the biopsies obtained prior to STAT3 decoy administration.

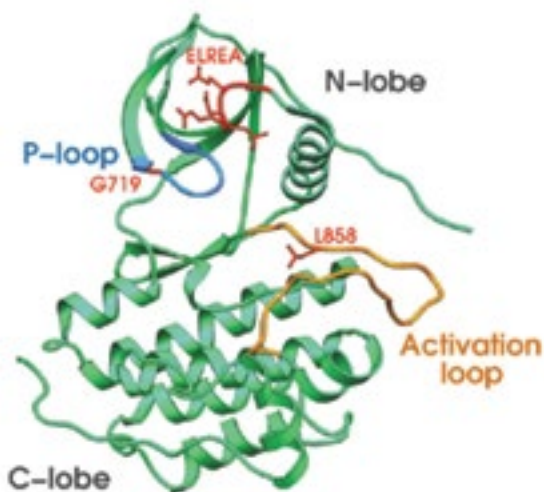
Leukemia

- **Development and optimization of the hypomethylating agent decitabine leads to FDA approval for treatment of myeloid malignancies.** Preclinical studies with decitabine showed that the drug is active at doses much lower than the maximal tolerated dose. The MD Anderson Cancer Center Leukemia SPORE has developed a methylation test to monitor patients on trial. This assay was used in successful phase 3 studies, which led to FDA approval of the drug by the U.S. Food and Drug Administration (FDA) for the treatment of myeloid leukemia and myelodysplastic syndrome. (Blood, 2006;108:3271; Cancer Research, 2006;66:5495; Cancer, 2006;106:1794 and 2007;109:1133)
- **FLT3 is a druggable target in acute myeloid leukemia.** The MD Anderson Leukemia SPORE developed an assay to measure the activity of lestaurtinib, the FLT3 inhibitor that was used in the conduct of phase 1 and 2 clinical trials of this agent with considerable responses to therapy. These trials served as a proof of principle that FLT3 inhibition leads to clinical effects in patients with AML. Currently, combination studies with FLT3 inhibitors are under way. (Blood, 2006;108:3477 and 2006;108:3262)

Lung Cancers

- **EGFR mutations and amplification are established as predictive markers in lung cancer therapy.** The earlier discovery by SPORE investigators that EGFR mutations in non-small cell lung carcinomas may predict response to tyrosine kinase inhibitors changed the paradigm of targeted therapy and allowed Lung Cancer SPOREs at Dana Farber/Harvard Cancer Center, University of Colorado, Vanderbilt University, and University of Texas South Western to investigate mechanisms of drug resistance. The studies generated a number of benchmark papers that were used for new designs of phase 2 and 3 clinical trials. (Science, 2004;304:1497; New England Journal of Medicine, 2005;352:786; JNCI, 2005;97:643; Cancer Research, 2005;65:226; Nature, 2009;462:1070)

A PART OF THE EGFR ECTODOMAIN



- **Randomized phase 2 chemoprevention study of iloprost versus placebo in subjects at high risk for lung cancer yields positive results.** In a collaborative effort, Lung Cancer SPOREs, organized in the Lung Cancer Biomarkers and Chemoprevention Consortium, provided preclinical data and executed a phase 2 chemoprevention study with the prostacyclin analogue iloprost that showed significant improvement in all three histological measures in former smokers. Currently, a phase 3 study is planned in collaboration with the cooperative groups. (American Journal of Respiratory and Critical Care Medicine, 2010;181:A6834)
- **Pilot study of gefitinib and fulvestrant in the treatment of postmenopausal women with advanced non-small-cell lung cancer shows increased overall survival.** The Pittsburgh Lung Cancer SPORE spearheaded the first study that has demonstrated safety and feasibility of utilizing an anti-estrogenic drug along with an anti-EGFR agent in women with advanced lung cancer. The combination showed activity with 41% overall survival at 1 year, a major improvement, compared with an overall survival rate of 25–30% with standard care. Women whose tumors had high levels of nuclear estrogen receptor-beta (ER- β) showed the best response to this combination, supporting a role for ER- β in lung cancer. A follow-up phase 2 study is now open. (Lung Cancer, 2009;64:51)
- **Serum-based marker predicts responses in lung cancer treatment.** Vanderbilt Lung Cancer SPORE investigators developed a mass spectrometry-based proteomic test that was commercialized by Biodesix and is used in clinical



trials. The test showed predictive value in identifying patients who were likely to benefit from treatment with EGFR inhibitors. An overall survival benefit was observed in patients identified by the test in all three EGFR inhibitor-containing treatment regimens evaluated in the study, including gefitinib, erlotinib-bevacizumab, and cetuximab. (JNCI, 2007;99:846)

- **miR-93, miR-98, and miR-197 regulate expression of tumor suppressor gene FUS1.** The University of Texas South Western/MD Anderson Lung Cancer SPORE discovered that loss of expression of tumor suppressor gene FUS1 is an early event in lung cancer pathogenesis, and FUS1 replacement therapy is currently in clinical trials for the treatment of non-small-cell lung cancer. This study has demonstrated that FUS1 is translationally repressed by several microRNAs and that microRNA expression and FUS1 expression are inversely correlated in tumor specimens. These miRNAs are potential therapeutic targets that could be inhibited in conjunction with FUS1 replacement therapy to improve its efficacy. (Molecular Cancer Research, 2009;7:1234)

Lymphoma

- **Bortezomib induces viral gene expression and thus enables enzyme-targeted radiation therapy in herpesvirus-associated tumors.** A study conducted by the Johns Hopkins University Lymphoma SPORE investigates the possibility of using a pharmacologic agent to modulate viral gene expression to target radiotherapy of tumor tissue. In a mouse model, targeting

of a therapeutic radiopharmaceutical required activation of viral gene expression by pretreatment with bortezomib to slow or stop tumor growth or to achieve tumor regression. Bortezomib-induced enzyme-targeted radiation therapy illustrates the possibility of pharmacologically modulating tumor gene expression to design targeted radiotherapy interventions. (Nature Medicine, 2008;14:1118)

- **Serum B-lymphocyte stimulator levels are elevated in patients with familial lymphoproliferative disorders.** Serum B-lymphocyte stimulator (BLyS) levels are elevated in patients with a family history of B-cell chronic lymphocytic leukemia and correlate with the presence of a thymidine at position 871 of the BLyS promoter. Studies published by the Iowa-Mayo Lymphoma SPORE also discovered the mechanism of elevated BLyS levels, which may be helpful for development of BLyS-measuring assays and identification of patients who may benefit from BLyS-lowering therapy. In clinical trials, it may be possible to identify patients who have a higher chance of responding to these therapies on the basis of on their BLyS promoter sequence or serum BLyS levels. (Blood, 2004;104:2247; Journal of Clinical Oncology, 2006;24:983)

Myeloma

- **Novel targeted therapies for multiple myeloma prove active against the disease.** Clinical trials led by the Dana Farber-Harvard Myeloma SPORE confirmed remarkable activity of the proteasome inhibitor bortezomib in patients with advanced multiple

myeloma, leading to FDA approval of this agent for the treatment of recurrent multiple myeloma in 2005. (Molecular Cancer Therapeutics, 2005;4:686)

- **Preclinical studies have validated that lenalidomide targets the tumor cell and demonstrated molecular mechanisms of drug resistance.** Studies conducted by the Dana Farber–Harvard Myeloma SPORE were rapidly translated to phase 1 trials led by the SPORE and to a multicenter phase 2 trial that confirmed both activity against multiple myeloma and a favorable side effect profile. On the basis of these results, two phase 3 trials confirmed the superiority of lenalidomide plus dexamethasone over dexamethasone alone for the treatment of recurrent multiple myeloma, culminating in FDA approval of lenalidomide for relapsed multiple myeloma in 2006. (Blood, 2006;108:3458)
- **Novel combination studies for refractory multiple myeloma.** Numerous compounds that synergize with bortezomib and lenalidomide in the treatment of relapsed and refractory multiple myeloma have been conducted by the Dana Farber–Harvard Myeloma SPORE. (Journal of Clinical Oncology, 2009;27:5713)
- **Genomics defines distinct myeloma subgroups.** Studies by the Dana Farber–Harvard Myeloma SPORE provided the first DNA-based prognostic classification of multiple myeloma and identified previously unrecognized genes to be targeted in novel myeloma therapies. Highly expressed genes in multiple myeloma cells include cell survival pathway genes such as *mcl-1*, *dad-1*, *caspase 8*, and Fas-associated death domain (FADD)–like apoptosis regulator

(FLIP); oncogene and transcriptional factors such as *Jun-D*, *Xbp-1*, *calmodulin*, *Calnexin*, and *FGFR-3*; stress response and ubiquitin/proteasome pathway–related genes; and various ribosomal genes reflecting increased metabolic and translational activity. (Blood, 2004;103:1799; Cancer Cell, 2006;9:313)



Ovarian Cancer

- **Fibroblast growth factor-1 was identified as a prognostic marker for ovarian cancer.** The Dana Farber–Harvard Ovarian SPORE, in collaboration with the MD Anderson Ovarian SPORE, performed oligonucleotide-based comparative genomic hybridization on 42 microdissected high-grade serous ovarian carcinomas. Two chromosomal regions, 4p16.3 and 5q31-5q35.3, exhibited the highest correlation with overall survival ($P < 0.01$). Further



validation and correlation analyses suggested that fibroblast growth factor-1 (FGF-1) and 5q31 overexpression may lead to increased angiogenesis and autocrine stimulation of cancer cells, resulting in poorer overall survival for patients with high-grade advanced serous ovarian carcinoma. (Journal of Clinical Oncology, 2007;25:2281)

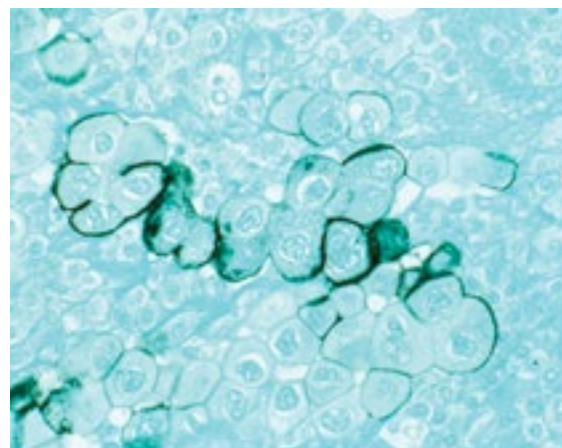
- **Targeting endothelin B receptor could enhance the efficacy of tumor immunotherapy.** The Fox Chase Ovarian SPORE identified genes associated with the presence or absence of tumor-infiltrating lymphocytes (TILs). Overexpression of endothelin B receptor (ET_BR) correlates with the absence of TILs and short patient survival, while the blockade of ET_BR showed increased endothelial adhesion of T cells that enhances antitumor immune mechanism. (Nature Medicine, 2008;14:28)
- **B7-H4, human epididymis protein 4, mesothelin, DcR3, and spondin-2 have been identified as potential biomarkers for early detection of ovarian cancer.** Samples from the Carotene and Retinol Efficacy Trial were used by the Fred Hutchinson Cancer Center Ovarian SPORE for new biomarker identification. CA125, human epididymis protein 4 (HE4), and mesothelin showed only slight elevation approximately three years before the onset of the disease but substantially increased within one year before the diagnosis. (JNCI, 2010;102:26)

Pancreatic Cancer

- **Early detection of pancreatic cancer was reported in groups of high-risk cancer patients.** The GI SPORE at Johns Hopkins, which leads a working

consortia including all NCI-funded GI and Pancreatic SPORE sites and 15 other groups, developed a systemic and standardized screening procedure for detecting pancreatic cancer in the early stage, using endoscopic ultrasound with computerized tomography combined with endoscopic ultrasonography–fine-needle aspiration and endoscopic retrograde cholangiopancreatography. An 8–10% detection rate was reported in subjects with inherited genetic syndromes and familial pancreatic cancer. (Clinical Gastroenterology and Hepatology, 2006;4:766)

- **High-risk loci of pancreatic cancer are identified by GWAS.** The Mayo Pancreatic SPORE led and coordinated a collaborative effort that identified eight high-risk single-nucleotide polymorphisms that map to three loci on chromosomes 13q22.1, 1q32.1, and 5p15.33. This research study performed a GWAS of pancreatic cancer in 3,851 cancer patients and 3,934 normal control subjects drawn from 12 prospective cohorts and eight case–control studies supported by other NIH funding mechanisms. (Nature Genetics, 2010;42:224)



- **A hereditary pancreatic cancer–related gene was discovered.** Through sequencing of the protein-coding genes in a patient with familial pancreatic cancer, the John Hopkins GI SPORE identified a new truncating germline mutation in *PALB2* that appeared to be responsible for the patient’s predisposition to the disease. Analysis of 96 additional patients with familial pancreatic cancer revealed and validated the role of *PALB2* as a susceptibility gene for pancreatic cancer. These results illustrate that unbiased sequencing of protein-coding regions can lead to the identification of genes responsible for a hereditary diseases. (Science, 2009;324:217)
- **Genetic abnormalities were revealed by deep sequencing of pancreatic cancer.** The Johns Hopkins University GI SPORE performed a comprehensive genetic analysis of 24 pancreatic cancers (23,219 transcripts, representing 20,661 protein-coding genes) and found that pancreatic cancers contain an average of 63 genetic alterations. This defined a core set of 12 cellular signaling pathways, and it was found that each pathway is genetically altered in 67–100% of the tumors. Dysregulation of these core pathways and processes through genetic mutations can explain the major features of pancreatic tumorigenesis. (Science, 2008;321:1801)

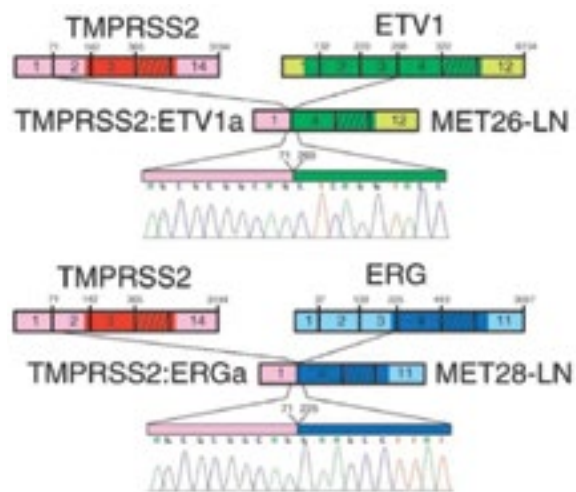
Prostate Cancer

- **The fusion of two ETS transcription factors, ERG and ETV1, to the 5’ untranslated region of TMPRSS2 were identified as common gene rearrangements in prostate cancer.** Fluorescent in situ hybridization showed that most human prostate cancers harbor this gene rearrangement. University of Michigan Prostate SPORE investigators conducted in vitro functional

analysis, which indicated that the androgen-responsive promoter elements of TMPRSS2 mediate the overexpression of the ETS genes. Given the high prevalence of prostate cancer, this TMPRSS2 fusion with ETS family members is likely to be the most common causal gene translocation to be identified in human carcinomas. (Science, 2005;310:644)

While this seminal discovery has important implications for understanding prostate carcinogenesis and for targeted therapeutics, the first clinical applications are likely to be in aiding the interpretation of histopathology for prostate cancer and for noninvasive detection of prostate cancer (Cancer Research, 2008;689:645). Investigations with TMPRSS2:ERG-negative prostate cancer have led to the discovery of SPINK1 as a marker for aggressive tumors. (Cancer Cell, 2008;13:519)

FUSIONS OF TMPRS TO THE ETS FAMILY OF TRANSCRIPTION FACTORS



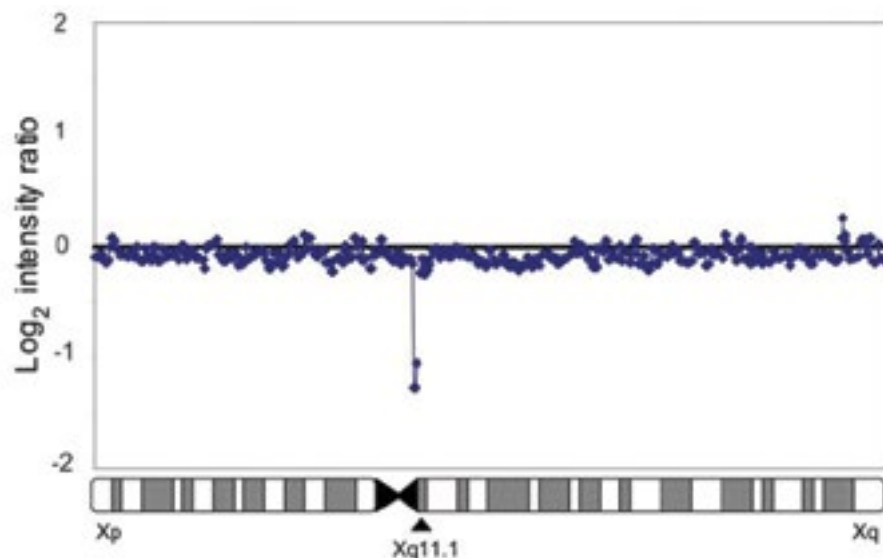


Renal Cancer

- **X-chromosome gene, WTX, is commonly inactivated in Wilms Tumor.** The Dana Farber–Harvard SPORE in Renal Cancer identified WTX, an X chromosome gene, whose inactivation accounts for approximately one-third of Wilms tumors (Science, 2007;315:642). Similar to WT1, WTX shares a restricted temporal and expression pattern that leads to normal

renal development. In contrast to WT1, carcinogenesis with WTX occurs by a monoallelic “single-hit” event targeting the single X chromosome in males or the active X chromosome in females. The Renal SPORE is developing a WTX antibody and in situ hybridization probes to enable assessment of WTX expression in tissue sections.

REPRESENTATIVE ARRAY CGH PROFILE FOR A WTX DELETION IN XQ11.1 IN A MALE PATIENT WITH WILMS TUMOR



Skin Cancer

- **N-RAS and B-RAF mutation frequencies increase with progression of primary melanomas.** This study was conducted to test whether mutation acquisition coincides with conversion from in situ to invasive melanomas. The MD Anderson Melanoma SPORE found that N-RAS and/or B-RAF mutations were present in 40% (6 of 15) of in situ melanomas,

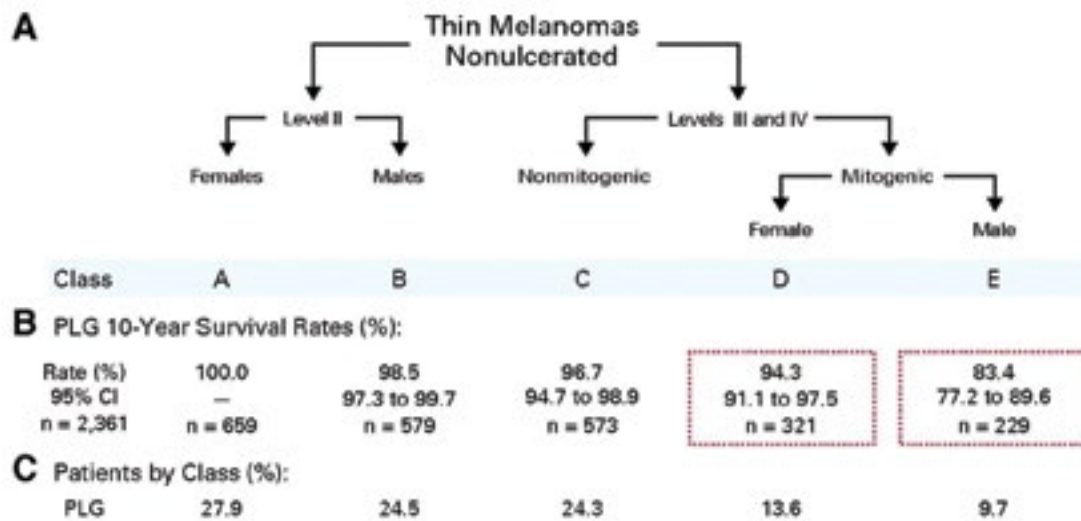
55% (17 of 29) of radial invasive tumors, and 75% (22 of 29) of vertical invasive tumors. (J Invest Dermatol, 2009;129:1483)

- **A BRAF kinase inhibitor promotes aggressiveness of melanoma cells that do not have BRAF mutations.** The Yale Skin SPORE reported that plaxxikon (PLX4032), a BRAF^{V600K} mutant kinase

inhibitor currently used in clinical trials, had an opposite effect on BRAF wild-type melanoma cells, enhancing proliferation, reducing cell adherence, and increasing mobility, via activation of RAF1 and the MAPK pathway. The authors concluded that only patients with mutant BRAF^{V600K/E} should be selected for treatment and that patients should be monitored for any secondary tumors that may not carry the BRAF mutation, or for recurrences of tumor cells that have lost the mutant BRAF allele. (Pigment Cell & Melanoma Research, 2010;23:190)

- **Identification of high-risk tumors among thin cutaneous melanomas.** Most melanoma patients have microscopically thin (≤ 1 -mm) primary lesions and are treated with excision, but metastatic recurrences present serious problems. The Wistar Skin SPORE identified additional criteria to explain survival heterogeneity. The new prognostic tree will better discriminate patients with significant risk of metastasis. (Journal of Clinical Oncology, 2007;25:1129)

NEW PROGNOSTIC TREE AND PROFILES FOR MELANOMA



(A) The prognostic tree. (B) Class-specific 10-year survival rates and 95% confidence intervals for pigmented lesion group (PLG) patients with non-ulcerated thin melanomas (N = 2,361). (C) The percentage of patients in each class. Classes with the lower survival rates are outlined with a red dotted line.



PROGRAM COLLABORATIONS

Collaborations and partnerships are essential for success in translational research. Over the years, TRP program staff and SPORE teams have reached beyond their programs and grants to partner with other government programs, foundations, and industry to move discoveries into early-phase clinical testing. Highlighted

here are more recent projects to illustrate the range of collaborations and partnerships driven by SPOREs.

RAID—A Former Program in the DCTD Developmental Therapeutics Program

Biological agents in the former RAID program have been distributed to SPORE researchers.

BIOLOGICAL AGENTS PROVIDED TO SPORE INVESTIGATORS

SPORE PI	Agent	Type	Organ Site
Bigner	MR1-1	Immunotoxin	Brain
Ambinder	EBV supernatant	Virus	Lymphoma
Dubinett	AD-CCL21	Adenovirus-encoding chemokine	Lung
Wu	CRT-E7	E7 vaccine	Cervical
Thompson	TRVP-1 protein	Apoptotic activity	Prostate
Yung	Ad Δ 24 RGD	Conditionally replicating adenovirus	Brain
Vickers	AdCox2RGD	Cox-2 promoter enhanced infectivity	Pancreatic
Grandis	STAT3 decoy ODN	Antisense oligodeoxynucleotide	Head and neck
Russell	MV-NIS	Oncolytic virus with a sodium iodide symporter transgene	Brain, ovary

Office of HIV and AIDS Malignancy

The extended survival of HIV-positive patients as a result of advanced therapies leads to an increased incidence of disease-related malignancies. In collaboration with the NCI's Office of HIV and AIDS Malignancy, projects were launched to explore the character of HIV-related lymphoma, lung, and head and neck cancers.

One project is conducting a retrospective study followed by a prospective collection of tumor and blood samples at all five Head and Neck Cancer SPORE Centers to

obtain fresh specimens necessary for the assessment of changes in the functional immune markers in HIV-positive and HIV-negative patients with head and neck cancers undergoing current therapies.

Lymphoma SPOREs focus on the characterization of the AIDS lymphoma genome, identification of environmental factors and autoantigens in the pathogenesis of HIV-positive and -negative lymphomas, plasma markers in AIDS lymphoma, and treatment of HIV Hodgkin disease.

Lung Cancer SPOREs are exploring molecular differences between tumors of HIV-positive lung cancer patients and matched HIV-negative lung cancer control subjects by performing high-throughput genome analyses. They are investigating new genetic epidemiology markers associated with the development of lung cancer in HIV-positive patients, and they study the role of viral cofactors that characterize the increased risk of developing lung cancer in these patients.

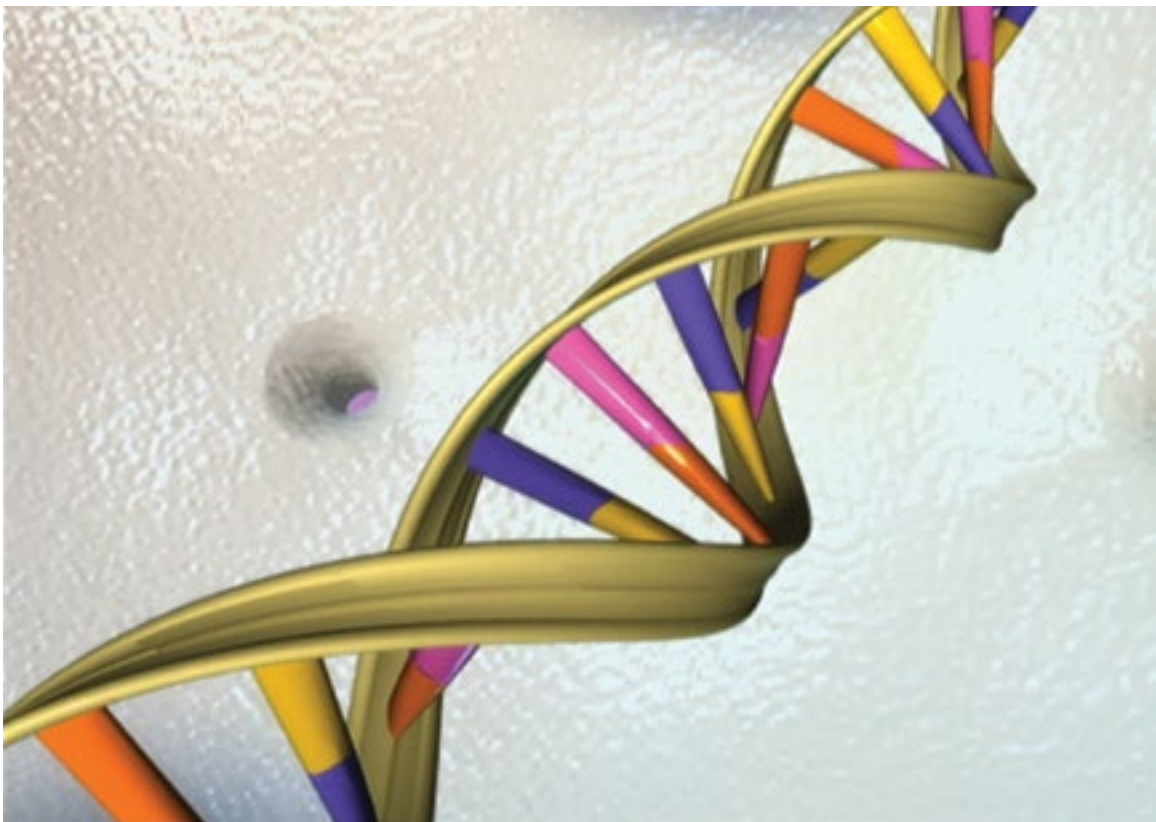
The Cancer Genome Atlas

The Cancer Genome Atlas (TCGA) is a comprehensive and coordinated effort to accelerate understanding of the molecular basis of cancer through genome analysis.

- A number of glioblastoma multiforme samples were submitted through the Brain SPOREs. Analysis shows the disruption of major tumorigenic pathways, including Rb (78%), p53 (87%), and RTK/TAS/PI3K (88%), in most of the tumor samples. (Nature, 2008;455:1061)
- A number of Ovarian SPOREs submitted ovarian serous cystadenocarcinoma biospecimens to TCGA. The study, which is ongoing, reveals the presence of p53 mutations in all analyzed tumors.

Early Detection Research Network

In an effort to improve early detection and diagnosis of cancer, SPOREs created a multifaceted partnership with investigators in the Early Detection Research Network (EDRN) of





the NCI Division of Cancer Prevention. The Lung Cancer Biomarkers Working Group, created by SPORE and EDRN investigators with support from NCI staff, established a collection of well-characterized plasma and serum reference sets from patients with early lesions. These sets are available nationwide to scientists for independent qualification of their assays.

Ovarian SPORE investigators are collaborating with EDRN to identify a panel of biomarkers to detect preclinical disease, using biospecimens from the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial. The study identified CA125, HE4, CA72.4, and CA15.3 as the top-performing early-detection biomarkers. The study is approved for phase 4 (prospective screening).

NCI Cancer Biomedical Informatics Grid

Over the past five years, informatics experts, together with translational researchers at the 11 institutions with Prostate SPOREs, have been successfully engaged with the NCI Center for Biomedical Informatics and Information Technology to develop and implement a scalable bioinformatics system to enable multi-institutional specimen location and data sharing for biomarker-related studies. The work was initiated to enable the conduct of the multicenter Inter-SPORE Prostate Biomarkers Study (IPBS), which served as a “real-world” test for the informatics system. The developers of NCI’s caTissue Suite (the Cancer Biomedical Informatics Grid’s [caBIG’s] biorepository tool for biospecimen inventory management) accepted many of the IPBS data elements for general use, particularly for the pre-analytical parameters of collection,

processing, and storage of specimens, as well as clinical annotation of specimens, that are potential confounding factors in the downstream biomarker analysis.



This effort has served to pilot the development of a virtual data repository for a network of specimen biorepositories across the nation, as recommended by the National Biospecimen Network Blueprint. Currently, this strong collaboration with highly dedicated informatics specialists at 11 institutions is working to achieve a sustainable infrastructure of interoperable biorepositories that can support any number of queries and widespread data sharing across the Prostate SPOREs. As part of their participation in NCI’s caBIG, the Prostate SPOREs have accomplished a robust implementation of a federated model of interoperable biorepositories that enhance the availability of tissues and other biomaterials to support translational cancer research.

Department of Defense

Prostate Cancer SPOREs have a partnership with the Prostate Cancer and the Prostate Cancer Clinical Trials Consortium (PCCTC), which is sponsored by the Department of Defense. The PCCTC endeavors to design,

implement, and complete hypothesis-driven phase 1 and 2 trials of novel agents and combination treatments that could prolong the lives of patients with prostate cancer. A majority of PCCTC principal investigators are also leaders of clinical research projects in one of the SPOREs in Prostate Cancer, and nearly all the Prostate SPORE institutions are members of the consortium. Many of the Prostate SPORE clinical trials are now being conducted inter-institutionally through the PCCTC infrastructure.

Office of Cancer Centers

The Avon–NCI Progress for Patients Award Program, a partnership among NCI, the Avon Foundation, and the Foundation for the National Institutes of Health, had been funded in part by the TRP (formerly the Organ Systems Branch) and the Office of Cancer Centers (formerly the Cancer Centers Branch). It supports projects focused on innovative, early-phase clinical interventions aimed at the prevention, detection, diagnosis, or treatment of breast cancer. From 2002 to 2009, the Avon Foundation provided more than \$30 million to fund breast cancer research through a limited competition involving the NCI-designated Cancer Centers and the SPORE grantees. The awards were intended to minimize delays in conducting novel and promising phase 1 and 2 clinical trials and studies focusing on risk assessment or validation of biomarkers in human subjects.

NCI Translational Research Interactive Network

The TRP, together with the NCI Office of Communications and Education, has created the NCI Translational Research

Interactive Network (NTRIN; pronounced “enter in”), a social media site that allows researchers and administrators interested in cancer translational research to find one another online. Similar to other social media sites, such as Facebook, the site includes an opportunity for this community to discuss issues, exchange information, and establish collaborations.

NTRIN includes groups, forums, a chat feature, and announcements that are directed to the community at large. The groups include organ-specific cancers, such as skin, prostate, and lung cancers, as well as groups that span organ sites, such as biomarkers and immune response modifiers. A group has been established for each of the six Translational Research Working Group pathways to the clinic. In addition, there is a group for SPORE administrators to discuss current and relevant information about managing their grants.

There are currently more than 250 members of NTRIN. To retain the focus on translational cancer research and the sharing of ideas that could lead to collaboration, entrance to the network is by invitation only. (Researchers interested in joining should e-mail the site at: ncintrin@mail.nih.gov).

NIH Office of Research on Women’s Health

The Research Enhancement Award Program in the Office of Research on Women’s Health (ORWH), National Institutes of Health (NIH), provides transitional funding awards for highly meritorious grant submissions on women’s health research that have just missed the funding paylines established by NIH institutions and centers. Qualified applications are selected by



ORWH on a competitive basis. In fiscal year 2009, the ORWH and TRP co-funded the Washington University SPORE in Endometrial Cancer.

National Institute of Neurological Disorders and Stroke and the National Institute of Dental and Craniofacial Research

Other NIH institutes consistently express interest in supporting SPORE applications that match institutional research priorities and hold promise in reducing the burden of disease in their respective organ sites. In particular, the National Institute of Dental and Craniofacial Research contributed one-third of the total cost for three Head and Neck Cancer SPOREs from 2002 to 2010. The National Institute of Neurological Disorders and Stroke co-funded the Duke Brain Cancer SPORE from 2004 to 2009.

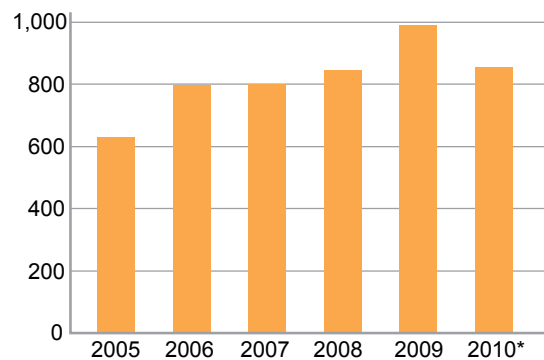
FUTURE INITIATIVES

- Increase translational cancer research in organ sites that are underrepresented in the NCI portfolio: pancreas, bladder, sarcoma, and head and neck
- Increase research in organ sites that represent the deadliest cancers (not represented above) where additional translational research is warranted: liver, esophagus, stomach, brain, ovary, lung, and myeloma
- Change cancer patient care, based on validated scientific studies, toward a more personalized approach to risk assessment, early detection, prognosis of outcome, and prediction of treatment options, including efficacy and toxicity

- Advance studies on dynamic relationship between tumors and cells/mediators in the microenvironment to translational science to make a difference in diagnosis and treatment of cancer
- Advance the goals of translational research by facilitating collaborations between SPOREs and other NCI-funded mechanisms such that discoveries can move quickly and seamlessly along pathways from the laboratory to phase 1 and phase 2 trials and beyond, with strong correlative study support

SELECTED PUBLICATIONS

SPORE PUBLICATIONS



*2010 has been annualized.

EGFR mutation and resistance of non-small-cell lung cancer to gefitinib, Kobayashi S, Boggon TJ, Dayaram T, Jänne PA, Kocher O, Meyerson M, Johnson BE, Eck MJ, Tenen DG, Halmos B. *New England Journal of Medicine*, 2005;352:786–792. <http://www.ncbi.nlm.nih.gov/pubmed/15728811>

- This work builds on a seminal discovery of EGFR mutations as predictors of response to tyrosine kinase inhibitors made earlier by the Dana Farber–Harvard Lung Cancer SPORE. Despite the dramatic responses to

anilinoquinazoline inhibitors, most patients ultimately relapse. The paper reports a case of a patient with EGFR-mutant, gefitinib-responsive advanced non-small-cell lung cancer who had a relapse after two years of complete remission during treatment with gefitinib due to a second EGFR mutation.

MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling,

Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, Lindeman N, Gale CM, Zhao X, Christensen J, Kosaka T, Holmes AJ, Rogers AM, Cappuzzo F, Mok T, Lee C, Johnson BE, Cantley LC, Jänne PA. *Science*, 2007;316:1039–1043.

<http://www.ncbi.nlm.nih.gov/pubmed/17463250>

- Gefitinib-sensitive lung cancer cells developed resistance to gefitinib as a result of focal amplification of the MET proto-oncogene. Inhibition of MET signaling in these cells restored their sensitivity to gefitinib. MET amplification was detected in 4 of 18 (22%) lung cancer specimens that had developed resistance to gefitinib or erlotinib. The resistance occurs by driving ERBB3 (HER3)-dependent activation of PI3K, a pathway thought to be specific to EGFR/ERBB family receptors. MET amplification may promote drug resistance in other ERBB-driven cancers as well.

Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer,

Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM, Mehra R, Sun XW, Varambally S, Cao X, Tchinda J, Kuefer R, Lee C, Montie JE, Shah RB, Pienta KJ, Rubin MA, Chinnaiyan AM. *Science*, 2005;310:644–648.

<http://www.ncbi.nlm.nih.gov/pubmed/16254181>

- Recurrent gene fusions of the 5' untranslated region of TMPRSS2 to ERG or ETV1 have been identified in prostate cancer tissues with outlier expression. Of 29 prostate cancer samples studied, 23 harbored rearrangements in ERG or ETV1. Cell line experiments

suggest that the androgen-responsive promoter elements of TMPRSS2 mediate the overexpression of ETS family members in prostate cancer. These results have profound implications for the molecular diagnosis and treatment of prostate cancer.

Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study,

Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, Deming SL, Geradts J, Cheang MC, Nielsen TO, Moorman PG, Earp HS, Millikan RC. *JAMA*, 2006;295:2492–2502.

<http://www.ncbi.nlm.nih.gov/pubmed/16757721>

- Immunochemical surrogates for each breast cancer subtype were applied to 496 cases of invasive breast cancer from the North Carolina Breast Cancer Study that oversampled premenopausal and African American women. The basal-like cancer subtype was more prevalent among premenopausal African American women (39%) than among postmenopausal African American women (14%) or non-African American women of any age (16%), probably contributing to the poor prognosis of young African American women with breast cancer.

An X chromosome gene, WTX, is commonly inactivated in Wilms tumor,

Rivera MN, Kim WJ, Wells J, Driscoll DR, Brannigan BW, Han M, Kim JC, Feinberg AP, Gerald WL, Vargas SO, Chin L, Iafrate AJ, Bell DW, Haber DA. *Science*, 2007;315:642–645.

<http://www.ncbi.nlm.nih.gov/pubmed/17204608>

- Wilms tumor is a pediatric kidney cancer associated with inactivation of the WT1 tumor-suppressor gene in 5–10% of cases. Here somatic deletions have been identified in a previously uncharacterized gene on the X chromosome. This gene, WTX, was inactivated in one-third (15 of 51) of Wilms tumors tested. Tumors with mutations in WTX lack WT1 mutations. In contrast to biallelic



inactivation of autosomal tumor-suppressor genes, WTX is inactivated by a monoallelic “single-hit” event targeting the single X chromosome in tumors from males and the active X chromosome in tumors from females.

Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers,

Sakai W, Swisher EM, Karlan BY, Agarwal MK, Higgins J, Friedman C, Villegas E, Jacquemont C, Farrugia DJ, Couch FJ, Urban N, Taniguchi T. *Nature*, 2008;451:1116–1120.

<http://www.ncbi.nlm.nih.gov/pubmed/18264087>

- Acquired resistance to cisplatin in ovarian tumors with BRCA2 mutations can be mediated by secondary intragenic mutations in BRCA2 that restore the wild-type BRCA2 reading frame. This mechanism was highlighted by the analysis of cell lines and tissue samples of recurrent ovarian cancer.

Intrinsic resistance of tumorigenic breast cancer cells to chemotherapy,

Li X, Lewis MT, Huang J, Gutierrez C, Osborne CK, Wu MF, Hilsenbeck SG, Pavlick A, Zhang X, Chamness GC, Wong H, Rosen J, Chang JC. *Journal of the National Cancer Institute*, 2008;100:672–679.

<http://www.ncbi.nlm.nih.gov/pubmed/18445819>

- Paired breast cancer core biopsies were obtained from patients with primary breast cancer before and after treatment with neoadjuvant chemotherapy or lapatinib (for HER2-positive patients). The mammosphere-forming capacity and CD44⁺/CD24^{-/low} status of the residual cancer cells was analyzed in both groups before and after treatment. The percentage of CD44⁺/CD24^{-/low} mammosphere-forming cells increased in the chemotherapy treatment group, whereas lapatinib treatment did not lead to statistically significant increase in the proportion of breast cancer-initiating cells,

suggesting a possible strategy for eliminating these cells to improve long-term survival.

Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth,

Montgomery RB, Mostaghel EA, Vessella R, Hess DL, Kalthorn TF, Higano CS, True LD, Nelson PS. *Cancer Research*, 2008;68:4447–4454.

<http://www.ncbi.nlm.nih.gov/sites/pubmed/18519708>

- The levels of androgens and the transcripts encoding steroidogenic enzymes was evaluated in benign prostate tissues, untreated primary prostate cancers, metastases from patients with castration-resistant prostate cancer, and xenografts derived from castration-resistant metastases. Metastatic samples displayed significantly higher levels of testosterone and steroidogenic enzyme transcripts than did those in primary prostate cancers from untreated eugonadal men, suggesting that ongoing steroidogenesis and maintenance of intra-tumoral androgens may contribute to castration-resistant disease.

Core signaling pathways in human pancreatic cancers revealed by global genomic analyses,

Jones S, Zhang X, Parsons DW, et al. *Science*, 2008;321:1801–1806.

<http://www.ncbi.nlm.nih.gov/pubmed/18772397>

- Comprehensive genetic analysis of 24 pancreatic tumors included sequencing of 23,219 transcripts representing 20,661 protein-coding genes and a number of microarray-based screenings for homozygous deletions and amplifications. On average, 63 genetic alterations defining a core set of 12 cellular signaling pathways were identified for each of the 24 tumors. Dysregulation of these core pathways and processes can explain the major features of pancreatic tumorigenesis.

The background features a blue grid pattern transitioning into an orange grid pattern. Overlaid on this are several 3D, semi-transparent geometric shapes in shades of green, blue, red, and grey. In the lower portion, a network diagram with circular nodes and connecting lines is visible on the orange background.

2010 Program
Accomplishments

Biometric Research Branch



OVERVIEW

The **Biometric Research Branch (BRB)** is the statistical and biomathematical component of the National Cancer Institute's (NCI's) Division of Cancer Treatment and Diagnosis (DCTD). It provides statistical leadership for DCTD programs and conducts research in clinical trials methodology, statistical genomics, and bioinformatics.

BRB investigators combine collaboration and consultation with DCTD and the Center for Cancer Research (CCR) investigators and conduct self-initiated research in biostatistics, statistical genomics, and bioinformatics. This has enabled BRB to recruit and retain a world-class research staff, provide high-quality collaboration and consultation to DCTD and NCI scientists, and make major research contributions motivated by important problems of cancer research.

BRB does not have a grant, cooperative agreement, or contract portfolio and does not sponsor or fund extramural research.

The major areas of BRB research include:

- Efficient clinical trial designs
- Integrating genomics in clinical trials
- Biomarkers in clinical trials
- Statistical genomics of cancer
- Bioinformatics resources for the research community

BACKGROUND

Extramural Clinical Studies

Specific BRB staff members are designated to collaborate with the DCTD programs covering clinical trials, drug discovery,

molecular diagnostics, and biomedical imaging. It is the philosophy of BRB that a statistician must be deeply involved in a research area to make important contributions in that area. For extramural clinical trials, statisticians are assigned responsibilities by cancer type so that they develop in-depth knowledge about their areas of responsibility. BRB statisticians:

- Review protocols for all DCTD-sponsored clinical trials
- Participate with NCI and extramural scientists in strategy development, concept review, and protocol review meetings
- Serve on all Cooperative Group data monitoring committees and were instrumental in the establishment of the data monitoring committee system
- Serve as liaison to Cooperative Group statistical centers

BRB statisticians work closely with the staffs of the Cancer Diagnosis Program and the Cancer Imaging Program on a wide variety of projects:

- Reviewing correlative science and cancer imaging protocols submitted by the Cooperative Groups
- Participating in the development of treatment-related molecular and imaging biomarkers
- Collaborating on the planning and conduct of extramural programs for the development and application of molecular and imaging diagnostics technology

From these collaborations, BRB staff conducts research on new biostatistical methodology for clinical trials, preclinical drug development, and evaluation of molecular diagnostics and cancer imaging.

RICHARD SIMON, CHIEF

Richard Simon, Ph.D., is Chief of the DCTD Biometric Research Branch. Dr. Simon holds a doctoral degree in applied mathematics and computer science from Washington University in St. Louis, Missouri. He has been at the National Institutes of Health since 1969 and has developed many of



the statistical methods used today in cancer clinical trials. He has published more than 450 papers on the application of biostatistical methodology to cancer research and biomedicine. His publications have had a major impact on the conduct of cancer clinical trials and statistical genomics. Dr. Simon became involved with DNA microarrays in 1997 based on his interactions with Dr. Jeff Trent of the National Human Genome Research Institute. After completing numerous courses in biotechnology, genomics, and computational biology, he established the Molecular Statistics and Bioinformatics Section, 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 and new methods for the planning and analysis of DNA microarray studies and has integrated software (BRB-ArrayTools) for the analysis of microarray data that has more than 11,000 registered users in 65 countries. In recent years, Dr. Simon has established himself as an international leader in statistical genomics, evaluation of prognostic signatures, and innovative clinical trial designs for the development of new drugs with genomic companion diagnostics. His group is increasing focus on methods of analysis of tumor sequencing data and systems biology modeling of oncogenesis.



Genomic Analysis

The objective of the Molecular Statistics and Bioinformatics Section (MSB) is to develop and apply mathematical, statistical, and computational methods for the utilization of genomic, gene expression, and other molecular biology data to cancer research and to train scientists in statistical genomics and bioinformatics. The MSB has established itself as an international center of expertise for the analysis of DNA microarray gene expression profile data, particularly in the development and validation of gene expression-based prognostic or predictive signatures. MSB microarray research has included four dimensions:

1. Collaboration in major microarray expression profiling projects
2. Development of new statistical methodology for the design and analysis of microarray studies
3. Development of freely distributed software for the analysis of microarray-based studies
4. Training of postdoctoral research fellows for careers in statistical genomics

Intramural Collaboration

BRB staff collaborates with numerous intramural laboratories on the analysis of gene expression, copy number variation, and genomic sequencing data. Staff members have developed innovative statistical methods for planning and analyzing gene expression studies. In addition to numerous publications describing new methodology, BRB staff members have published the book *Design and Analysis of DNA Microarray*

Investigations as well as influential review articles in major medical journals that identify major problems in the use of array technology. BRB staff members have developed an integrated software platform for microarray gene expression and copy number analysis. The software, BRB-ArrayTools, is targeted to biologists and has been distributed on request to more than 11,000 users in over 65 countries. The software is used in all major cancer centers and pharmaceutical and biotechnology companies. BRB-ArrayTools incorporates the best statistical analysis methods and serves as a vehicle for education in the proper analysis of DNA microarray data. Staff of the MSB teaches semimonthly classes on the analysis of DNA microarray data for users of the NCI microarray facility. The training program includes training of postdoctoral research fellows in statistical genomics. BRB has hosted visitors from several countries for multi-month visits for training and research in the use of genomics in cancer research.

BRB collaborates actively with laboratories and branches of the CCR and provides statistical collaboration support to the following CCR units:

- Cancer Studies Prevention Branch
- Neuro-oncology Branch
- Urologic Oncology Branch
- Metabolism Branch
- Radiation Oncology Branch

BRB provides extensive collaboration and consultation in high-dimensional genomic data analysis to Dr. Lou Staudt's laboratory and to numerous other laboratories in CCR.

PROGRAM ACCOMPLISHMENTS

Of the hundreds of publications of which a staff member of the BRB is either senior author or one of the first three authors, only a selected number are shown and discussed here. The citations refer to the references in the “Selected Publications” at the end of this chapter.



Clinical Trial Design

Early Trials

DCTD and CCR have pioneered small, first-in-human, proof-of-principle, phase 0 studies. These studies, permitted by a 2006 guidance from the U.S. Food and Drug Administration (FDA), will be extremely helpful in expediting early drug development and to determine at a very early point in development whether an agent is effectively addressing its intended molecular target. Dr. Rubinstein of BRB provided statistical leadership to the NCI phase 0 Clinical Trials Working Group, which is made up of DCTD and CCR staff, and developed an innovative statistical design to assess pharmacodynamic endpoints for the NCI phase 0 poly-(ADP ribose) polymerase (PARP) inhibitor trial (Kummar et al. 2007; Murgu et al. 2008). Dr. Hunsberger and other BRB staff also published phase 1 designs for optimizing a biologic endpoint (Hunsberger et al. 2005).

In collaboration with DCTD’s Cancer Therapy Evaluation Program (CTEP) and the NIH Clinical Bioethics Department, BRB staff conducted analyses to ensure the acceptable toxicity of phase 1 drug trials over the prior decade. Their published reviews indicated that the efficiency of accelerated titration designs was greater than that of the standard phase 1 design. BRB statisticians, in collaboration with CTEP staff, recently published a review of the use of accelerated titration designs in practice (Heath et al. 2009). The accelerated titration design is a novel design for phase 1 trials and permits more rapid dose escalation as well as dose titration within individual patients.



BRB statisticians developed designs for randomized phase 2 trials limiting sample size by relaxing the constraints on type 1 and type 2 error (Rubinstein et al. 2005, 2009). The designs are especially useful in testing the addition of molecularly targeted agents to cytotoxic therapy, where the endpoint is progression-free survival rather than tumor response. They developed innovative dual-endpoint designs to enable evaluation in phase 2 trials of new agents for which both tumor response rate and progression-free survival are important.

Many new anticancer agents are not cytotoxic and therefore may not cause tumors to shrink appreciably. However, these agents may still offer significant clinical benefits to patients by delaying the progression of disease. Because the development of standard phase 1, 2, and 3 clinical trials of agents depends on the ability of the agents to show activity in phase 2 trials by tumor shrinkage, new approaches are needed. BRB statisticians Drs. Hunsberger, Korn, and Rubinstein evaluated several new design approaches, including innovative dual-endpoint designs to enable the evaluation of new agents for which both tumor response rate and progression-free survival are important. Dr. Freidlin and colleagues (2005) evaluated a randomized discontinuation design. Initially, all patients are given the new drug. After some fixed period (e.g., 4 months), patients are evaluated; responders continue on the drug, progressors are taken off the study, and patients with stable disease are randomized between continued administration of the drug or observation and/or placebo. This design uses an enrichment strategy to focus on those patients who are more likely to

benefit from the drug. Drs. Hunsberger, Zhao, and Simon (2009) examined the efficiency of seamless phase 2 and 3 designs. Randomized phase 2 studies are needed because the traditional paradigm for the development of oncology drugs—that is, a single-arm, phase 2 study—does not provide adequate information to determine whether a phase 3 study is needed. They introduced seamless, integrated phase 2 and 3 designs and provided a Web-based sample size program.

It would be extremely valuable if there were a reliable way to use historical data for comparison for future single-arm, phase 2 trials (Korn and Freidlin 2006). One approach BRB took to this investigation was to examine the inter-trial variability of meaningful clinical endpoints across previously conducted negative phase 2 trials; if this variability is small enough, then one could safely use a historical rate based on pooled results from the previous trials. Even if the inter-trial variability were too large, a historical rate could safely be used if the variability could be made small enough by controlling for prognostic variables. BRB staff collaborated with investigators from five NCI Cooperative Groups to use this methodology to examine setting benchmarks for phase 2 trials for metastatic melanoma (Korn et al. 2008). BRB obtained individual-level data on 2,100 patients enrolled into 42 phase 2 metastatic melanoma trials (70 trial arms) conducted from 1975 to 2005. The six-month progression-free survival rates were too variable for use as a historical benchmark, even when the important prognostic variables for progression-free survival (derived by analyzing the individual-level data) were controlled

for. However, the inter-trial variability in overall survival rates was driven down to zero by controlling for the covariates sex, performance status, and presence or absence of visceral metastases. The paper included all the information required for a future phase 2 investigator to generate a reliable historical benchmark for overall survival in a trial based on the prognostic characteristics of the patients in the trial. The methodology used by Dr. Korn et al. (2008) to develop the melanoma benchmarks is being used in pancreatic, lung, and brain cancer to determine whether benchmarks for future phase 2 trials in these diseases can be developed.

Randomized Phase 3 Trials

Non-inferiority trials have traditionally required very large sample sizes. BRB statisticians have been developing more efficient methods for planning and monitoring non-inferiority trials (Freidlin et al. 2007, 2009, 2010). For example, sometimes a new treatment regimen with a favorable toxicity and/or tolerability profile is also expected to have some modest improvement in efficacy. BRB staff developed a new “hybrid” phase 3 clinical trial design for this setting (Freidlin et al. 2007), which requires a dramatically smaller sample size than a standard non-inferiority design. This hybrid design can naturally incorporate a formal test of superiority as well as non-inferiority.

Needed are more efficient randomized, controlled designs that accelerate development, minimize costs, and make trials more appealing to patients. BRB has developed methodological and logistical frameworks for conducting rigorous

multi-arm designs that compare several experimental treatments with a common control arm (Freidlin et al. 2008). Relative to conducting separate randomized, controlled trials for each experimental agent, this multi-arm design requires considerably less total sample size than multiple two-arm trials.

Interim Monitoring

An interim monitoring plan specifies when the accruing outcome data should be analyzed and what positive results would be needed to stop the trial early for efficacy, or what null or negative results would be needed to stop the trial for futility. Recent concerns have been raised in the literature that interim monitoring will lead to too many false-positive results and that results released early because of interim monitoring will be biased in a positive direction. BRB addressed these concerns in two ways. Staff members conducted a comprehensive review of all NCI Cooperative Group randomized trials that stopped early for positive results and showed that, with further follow-up, the results of these trials remained strongly positive for practically all of the trials (Korn et al. 2009). Staff also examined, from a statistical perspective, the positive bias expected because of early stopping, showing that when this bias is examined properly, it is relatively small except for trials that are stopped very early (Freidlin and Korn 2009a).

Reviewing the complex nature of stopping a trial for futility, BRB argued that many cancer trials could be improved by a more aggressive approach to futility monitoring and that some commonly used monitoring guidelines may result in stopping for lack of benefit even when a nontrivial,



beneficial treatment effect is observed (Freidlin and Korn 2009b). BRB researchers have a proposal for a formal futility rule that is easy to understand and implement, has good statistical properties in terms of stopping early when the null hypothesis is true, and loses very little power as compared with a trial design without futility monitoring (Freidlin et al. 2010).

Some trials—for example, non-inferiority trials—often require a long follow-up period to reach the maturity needed for a definitive analysis. However, before that point is reached, the immature trial data may be more complete than any other publicly available data that patients are using to make treatment decisions. This suggests that early release of outcome data from an ongoing trial could be very useful to current patients. BRB presented a proposal that allows for early release of outcome data from a carefully specified subset of non-inferiority trials (Korn et al. 2005).

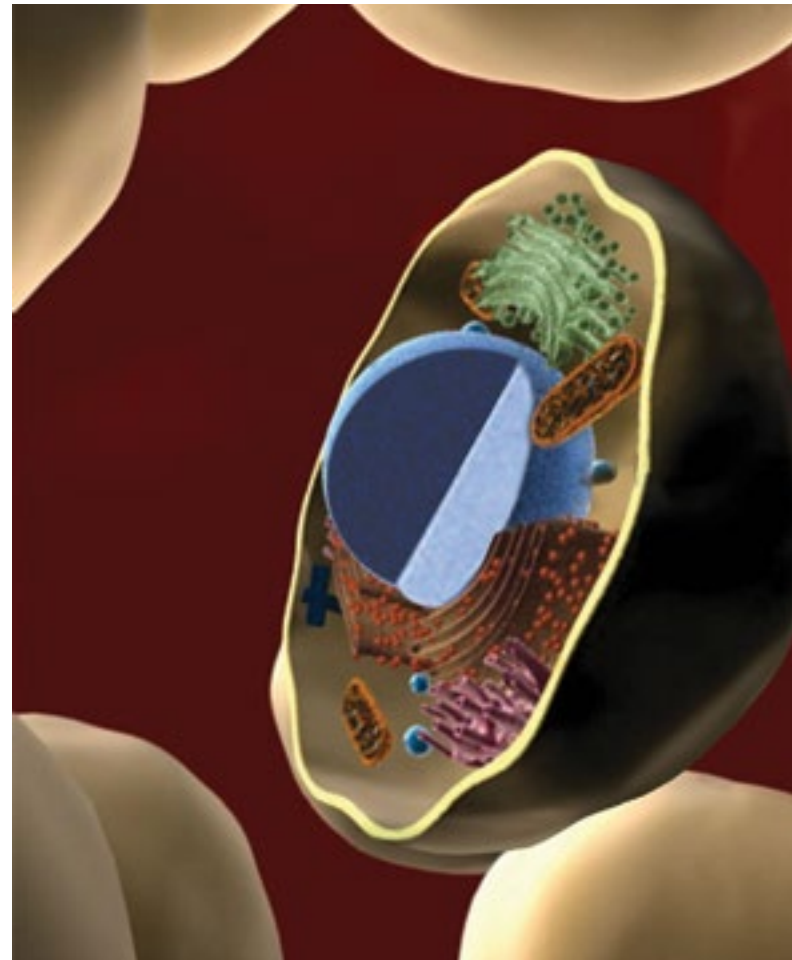
BRB statisticians, in collaboration with CTEP staff, developed Early Stopping Guidelines for Slow Accruing Trials, which are used to monitor accrual to Cooperative Group phase 3 trials. This allows early identification of the trials that are likely to fail to reach their objectives. The guidelines were developed and validated by using the CTEP database containing 239 phase 3 Cooperative Group trials (Freidlin and Korn 2007).

Progression-Free Survival Endpoint

Progression-free survival—the time from randomization to tumor progression or death—has been increasingly used in randomized trials in oncology. The

endpoint is observed sooner than overall survival, has direct clinical relevance in some settings, and most important, is not confounded by effective salvage treatments that are given after progression. However, in an unblinded trial, there can be multiple sources of bias in using a progression-free survival endpoint.

One source of bias is that patients on one arm may be more likely to get an unscheduled progression evaluation (scans, etc.) than those on the other arm; this is referred to as “evaluation-time bias.” To eliminate this potential bias, BRB proposed



and evaluated a design in which formal progression evaluations occur at two scheduled time points (Freidlin et al. 2007).

Another potential bias results from having an unblinded local investigator evaluate a patient's scans for progression. To lessen this potential source of bias, there has been much interest in using a blinded independent central review of patient scans to be used in a separate analysis of progression-free survival. In fact, in some cases, FDA has required such a review and analysis. BRB researchers showed, however, that central review adds its own source of bias to the analysis (Dodd et al. 2008). Together with FDA and industry colleagues, BRB organized a joint NCI–FDA–Industry Progression-Free Survival Workshop in 2009. At the workshop, BRB staff presented an audit approach that

allows a rigorous, independent confirmation of the progression-free-survival treatment benefit observed by local evaluation while optimizing the use of resources. BRB statisticians have also developed guidelines for the validation of novel imaging technologies for use as cancer trial endpoints (Sargent et al. 2009) and evaluated whether stable disease is a valid endpoint in single-arm phase 2 trials of molecularly targeted agents (Vidaurre et al. 2009).

Genomics in Clinical Trial Design

Standard approaches to clinical trials have in some cases led to overtreatment of many patients with drugs from which only a minority benefit. The hallmark of cancer is heterogeneity, and molecularly targeted drugs are likely to benefit only a subset of treated patients. Hence, the effectiveness





of targeted agents may be missed when the traditional broad approach to eligibility is used in randomized clinical trials. Dr. Simon and a postdoctoral fellow (2005) demonstrated that the number of patients needed for randomized clinical trials can be enormously reduced if a genomic biomarker is used to select those patients who are most likely to benefit or to exclude those who are least likely to benefit. Dr. Simon has subsequently introduced a roadmap for the development and analytical validation of genomic predictive biomarkers in early-phase clinical trials (Simon 2005) and their use as candidate predictive biomarkers in randomized trials where the credentials of the biomarkers are not sufficiently well established for use as eligibility exclusion criteria (Simon 2006, 2007, 2008, 2010).

These designs have been of substantial interest to investigators in academia, as well as those in industry and regulatory agencies. The designs provide a basis for a reliable predictive oncology, as they separate the data used for biomarker development from those used for prospective evaluation of whether treatment benefit, as assessed in randomized clinical trials, is enhanced in “test-positive” patients. The designs provide for “prospective subset analysis” in a statistically valid manner that provides level I evidence for the effectiveness of a new treatment in a prospectively selected subset of patients. The designs permit a “fallback” analysis plan in circumstances where there is uncertainty about the credentials of the marker.

Multiple publications introduce increasingly flexible and adaptive designs that, for example, permit the prospective use of multiple candidate predictive biomarkers and unspecified thresholds of positivity

(Jiang et al. 2007). For settings where an assay or signature that identifies sensitive patients is not available at the time the definitive study is designed, BRB developed an adaptive signature design. The design combines the prospective development of a gene expression–based classifier to select sensitive patients with a properly powered test for overall effect (Freidlin and Simon 2005) to demonstrate that a candidate predictive biomarker test can be prospectively incorporated into a randomized phase 3 design without compromising the ability to detect an overall effect. Recently, BRB researchers published a cross-validated extension of the adaptive signature design (Freidlin et al. 2010) that considerably improves the ability both to identify a predictive biomarker and to establish its validity for identifying patients who do and do not benefit from the new treatment. These new designs have been of major interest to the pharmaceutical and biotechnology industries as well as FDA. Dr. Simon has been invited to speak with most large pharmaceutical companies developing cancer drugs, at internal FDA meetings, and at meetings of the American Association for Cancer Research and the American Society of Clinical Oncology (ASCO). Dr. Simon has recently generalized the approach of the cross-validated, adaptive-signature design to provide a general framework for the adaptive development and evaluation of predictive classifiers of which patients benefit or do not benefit from the new treatment in the context of a single randomized clinical trial (Simon, 2010). This provides a strong statistical framework for predictive oncology and is

not limited to the use of gene expression profiling as the candidate biomarkers.

Recognizing that it is not always feasible to conduct prospective clinical trials for evaluating the value of predictive biomarkers, Dr. Simon, in collaboration with Drs. Hayes and Paik (2010), published an influential paper concerning the use of archived tissues from randomized clinical trials for the focused evaluation of a candidate marker. Their “prospective–retrospective design” approach was used for establishing that patients with K-RAS mutated advanced colorectal cancer do not benefit from anti–epidermal growth factor receptor antibodies and led to the restriction of the labeling indication for cetuximab and panitumumab. Dr. Simon served on the FDA advisory committee for that review. The publication by Drs. Simon, Hayes, and Paik revised a previously published “Levels of Evidence Scale for Biomarkers” that had been developed by Dr. Hayes and that has been used by ASCO in its standards-of-care recommendations.

Definitive evaluation of the clinical utility of predictive biomarkers requires conducting large randomized controlled trials. Efficient design of such trials is therefore crucial for the timely introduction of these medical advances into clinical practice. A variety of designs have been proposed for this purpose, including the enrichment design (i.e., randomize only those patients who are biomarker positive), the biomarker-strategy design (i.e., randomize between a control arm and a strategy arm where the treatment is determined by the biomarker), and the biomarker-stratified design (i.e., randomize all patients between the two treatment

arms and record the biomarker status on all to allow for separate evaluations of the treatment effect in the different biomarker status subgroups). To guide the design and interpretation of these types of randomized trials evaluating predictive biomarkers, Dr. Freidlin and colleagues (2010) presented an in-depth comparison of the advantages and disadvantages of commonly used trial designs.

Biomarkers

In a recent paper, BRB researchers discussed how biomarkers can be used most effectively in phase 2 trials and the substantial technical, logistical, statistical, and ethical challenges that can be encountered (McShane et al. 2009). The use of a biomarker surrogate in place of a definitive endpoint in a clinical trial can sometimes be advantageous when it is impractical, invasive, or very time consuming to obtain the definitive endpoint. The appropriate way to evaluate trial-level surrogacy is from a series of phase 3 trials in which both the surrogate endpoint and the definitive endpoint are available. This is in contrast to evaluating whether a surrogate is associated with an outcome for individuals given a certain treatment (individual-level surrogacy), for which data from patients receiving that treatment can be used without requiring a series of phase 3 trials. BRB staffers discussed statistical methods for assessing whether the surrogate-endpoint results of a trial can be used in place of definitive-endpoint results (Korn et al. 2005).

For a biomarker to be used clinically, it must be demonstrated that the biomarker assay meets acceptable standards of



analytical performance. In addition, if the biomarker assay will be performed in more than one laboratory, the results must be comparable across laboratories. BRB statisticians have been involved in several studies evaluating biomarker assays. One example is a study to evaluate the reproducibility of gene expression microarray assays conducted in four laboratories (Dobbin et al. 2005). Even after biomarker tests are in widespread use in clinical settings, a lack of standardization between laboratories can become problematic, for example, in the case of HER2 testing for breast cancer. Dr. McShane was a member of the ASCO–College of American Pathologists panels that developed testing guidelines for HER2 and estrogen/progesterone receptors in breast cancer.

Despite years of research and hundreds of reports on tumor markers in oncology, relatively few tumor markers have emerged as clinically useful. A variety of methodological problems have been cited to explain the frequent failure of tumor markers to advance to the clinic. Many tumor marker studies have not been reported in a rigorous fashion, and published articles often lack sufficient information to allow adequate assessment of the quality of the study or the generalizability of study results (McShane et al. 2005). The development of guidelines for the reporting of tumor marker studies was a major recommendation of the NCI–European Organisation for Research and Treatment of Cancer’s First International Meeting on Cancer Diagnostics in 2000. Dr. McShane co-chaired an effort to produce the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK), which recommend specific

information that should be reported about the study design, preplanned hypotheses, patient and specimen characteristics, assay methods, and statistical analysis methods. In addition, the guidelines suggest helpful presentations of data and important elements to include in discussions. The goal of these guidelines is to encourage transparent and complete reporting so that the relevant information will be available to others to help them to judge the usefulness of the data and understand the context in which the conclusions apply. The REMARK guidelines were simultaneously published in five major oncology journals in 2005 (McShane et al. 2005a–e) and have been widely referenced. Several journals now require that submitted articles about tumor markers adhere to the REMARK guidelines. Dr. McShane and co-authors have recently completed a follow-up paper that provides further explanation and elaboration on the REMARK guidelines and presents examples from the published literature of good reporting for each of the REMARK items.

Dr. Simon, his postdoctoral fellows, and other collaborators have developed a widely used methodology for the development and validation of prognostic and predictive classifiers based on pretreatment gene expression profiling (Simon 2005, 2006). Dr. Alain Dupuy, a guest researcher from France, and Dr. Simon reviewed all publications on whole-genome expression profiling of cancers that used patient outcome. They wrote a critical review of these publications and developed guidelines for use by authors, journal reviewers, and readers. This publication has been heavily cited.

Drs. Subramanian and Simon (2010) reviewed studies that developed prognostic

gene expression signatures for early-stage non-small-cell lung cancer. They found that none of the signatures had demonstrated patient utility and found serious methodological problems in the studies. Their review was published in the *Journal of the National Cancer Institute*. A follow-up article on the evaluation of prognostic signature studies was published in *Nature Reviews: Clinical Oncology* (Subramanian and Govinda 2010).

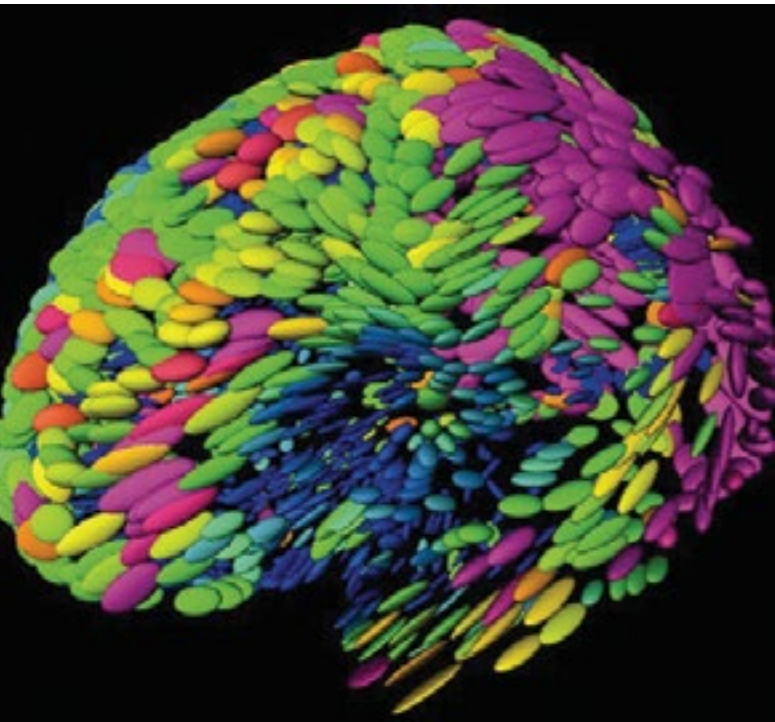
Statistical Genomics

BRB investigators have developed an important methodology for studying the genomics of cancer and particularly for utilizing abundance data on genome-wide transcripts for understanding biological mechanisms and clinical applications. Drs. Dobbin and Simon (2007, 2008) developed methods for planning sample

sizes in studies whose objective is to identify genes that are differentially expressed among phenotypic or genotypic classes of tissue. They considered how sample size depends on the microarray hybridization design that is utilized with dual-label arrays and considered a wide range of designs, including the common reference design, the balanced block design, and the loop design. They also developed a method for sample size planning in clinical studies whose objective is to develop a predictor of outcome or of phenotypic and/or genotypic class based on whole-genome expression profiling. Making the planning tools available interactively on the BRB website has facilitated the broad use of this methodology.

The goal of many clinical studies in which gene expression microarray profiling is used is to develop a multivariate classifier to predict the outcome of disease from a gene expression profile measured in a biological specimen from the patient. Techniques such as cross-validation or “bootstrapping” can be used in this setting to assess predictive power and, if applied correctly, can result in a less biased estimate of the predictive accuracy of a classifier. However, re-sampling methods are frequently misused in the analysis of microarray data, as noted by Dr. Simon (2005) and in the surveys of Drs. Dupuy and Simon (2007). Dr. Simon and his postdoctoral fellows have conducted fundamental studies of how to most effectively utilize re-sampling with high-dimensional data when the number of variables greatly exceeds the number of samples.

The publications by Drs. Molinaro, Simon, and Pfeiffer (2005) and by Drs. Varma and





Simon (2008) are highly cited. Drs. Jiang, Varma, and Simon (2008) developed a methodology for calculating valid confidence intervals for prediction error, using bootstrap re-sampling. 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 performance of prognostic classifiers that have been reported in prominent biomedical journals in the past few years should be interpreted with great caution (Lusa et al. 2007). Drs. Lusa and McShane (2007) have demonstrated serious problems in using gene clustering as a substitute for supervised classification for developing disease classifications, and Drs. Lusa, Korn, and McShane (2008) introduced a new approach to integrating the gene filtering process into the search for genes that are differentially expressed among conditions. Identifying genes whose expression is correlated with a categorical phenotype is the key objective of many expression profiling studies. Drs. Korn and colleagues (2007, 2008) performed an evaluation of a commonly used method—statistical analysis of microarrays (SAM)—and compared it with a multivariate permutation method that they developed.

Bioinformatics and Systems Biology

BRB-ArrayTools, designed by Dr. Simon et al. (2007), is a comprehensive software program that is widely recognized as the most statistically sound package available for the analysis of DNA microarray data. The package supports the use of data from all

current expression platforms. The computations are performed by sophisticated and powerful analytics, using state-of-the-art statistical and computational methods. 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. The software has over 11,000 registered users in 66 countries and has been cited in more than 1,100 publications. It is a successful experiment in using software to empower biomedical scientists to take advantage of DNA microarray software. BRB actively adds features to the power of BRB-ArrayTools, including new analysis and visualization tools, new types of genomic data that can be analyzed, and new ways of integrating pathway information and other biological data into the genomic analyses.

The [BRB website](#) contains other software, such as that for the generation of optimal and minimax two-stage phase 2 clinical trial designs and for managing dose administration for patients on accelerated titration phase 1 designs, and designing clinical trials for the co-development of targeted therapies and companion diagnostics. The website also contains technical reports and PowerPoint presentations of talks given by BRB staff. The BRB website averages approximately 50,000 page hits per month by external users. The interactive sample size tools themselves are accessed several thousand times each month.

Drs. Zhao and Simon have collaborated with Dr. Martin of the National Institute of Neurological Disorders and Stroke 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 et al. 2010). Drs. Zhang and Simon used age–incidence data to try to determine the number of rate-limiting events in breast cancer oncogenesis (Zhang and Simon 2005; Simon and Zhang 2008). 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 that is characteristic of point mutations in normal mammalian cells. The initial set of three mutational events appears to destabilize the genome and puts in place a process that almost inevitably leads to an invasive tumor. Age–incidence data for breast cancer in BRCA1 and BRCA2 mutation carriers were most consistent with loss of the wild-type BRCA allele and one additional mutational event leading to oncogenesis.

International Leukemia/Lymphoma Molecular Profiling Project

One BRB statistician has been focused on the analysis of high-dimensional genetic data, in particular with respect to the molecular characterization of lymphoma. In this enterprise, BRB has been involved in an extensive collaboration with the laboratory of Dr. Lou Staudt of CCR and with the Lymphoma/Leukemia Molecular Profiling Project (LLMPP). LLMPP is an international consortium of institutes that have pooled resources, expertise, and patient samples in an effort to understand

the molecular underpinnings of lymphoid malignancies, redefining their classification in molecular terms. In addition, they hope to define molecular correlates of clinical parameters that can be used in prognosis and in the selection of appropriate therapy. For this project, the BRB staff member has been acting as the primary statistician, analyzing the vast array of data that this group has compiled and generating models that are statistically rigorous and accurate while also biologically meaningful. The collaboration has produced dozens of publications identifying molecular subtypes of lymphoma and suggesting molecular pathways to oncogenesis. Most of these studies involved gene expression and copy number or methylation profiling. CCR recently purchased a Solexa high-throughput gene sequencer that can be used to investigate a large number of interesting questions, including the identification of protein binding sites, regions of histone methylation and modification, and novel mutations arising in lymphoma subtypes, as well as the analysis of gene interaction. Each of these investigations produces different styles of data that require different analysis techniques. Analysis of the data provided by the sequencer has begun, and statistical methodology will be developed as necessary.

FUTURE INITIATIVES

In upcoming years, BRB plans to focus on:

- Development and application of statistical methods to facilitate and accelerate the development and clinical evaluation of effective molecularly targeted therapeutics for individual patients and companion diagnostics



- Development and application of statistical and mathematical methods for enhancing the understanding of oncogenesis with next-generation sequencing, whole-genome characterization technology, and systems biology approaches
- Development and application of statistical, mathematical, and computational methods for using genomic data to elucidate tumor pathogenesis and identify key molecular targets for cancer prevention, early detection, and therapy
- Development of statistical and mathematical methods for enhancing the effectiveness of cancer investigations and for expediting the development of technology of potential importance for biomedical investigation
- Further development of BRB-ArrayTools software to extend its capabilities to next-generation sequencing data

SELECTED PUBLICATIONS

BRB staff members have been first, second, third, or senior authors on hundreds of publications during 2005–2010. Following is a list of highly selected publications to illustrate the quality, relevance, and breadth of this research.

Clinical Trial Methodology

Blinded independent central review of progression free survival in phase III clinical trials: important design element or unnecessary expense? Dodd LE, Korn EL, Freidlin B, Jaffe CC, Rubinstein LV, Dancey J, Mooney MM. *Journal of Clinical Oncology*, 2008;22:3791–3796.
<http://www.ncbi.nlm.nih.gov/pubmed/18669467>

Evaluation of randomized discontinuation design, Freidlin B, Simon R. *Journal of Clinical*

Oncology, 2005;23:5094–5098.
<http://www.ncbi.nlm.nih.gov/pubmed/15983399>

Release of data from an ongoing randomized clinical trial for sample size adjustment or planning, Freidlin B, Korn EL. *Statistics in Medicine*, 2007;26:4074–4082.
<http://www.ncbi.nlm.nih.gov/pubmed/17328095>

Proposal for the use of progression-free survival in unblinded randomized trials, Freidlin B, Korn EL, Hunsberger S, Gray R, Saxman S, Zujewski JA. *Journal of Clinical Oncology*, 2007;25:2122–2126.
<http://www.ncbi.nlm.nih.gov/pubmed/17513819>

Randomized clinical trial design for assessing non-inferiority when superiority is expected, Freidlin B, Korn EL, George SL, Gray R. *Journal of Clinical Oncology*, 2007;25:5019–5023.
<http://www.ncbi.nlm.nih.gov/pubmed/17971602>

Multi-arm clinical trials of new agents: some design considerations, Freidlin B, Korn EL, Gray R, Martin A. *Clinical Cancer Research*, 2008;14:4368–4371.
<http://www.ncbi.nlm.nih.gov/pubmed/18628449>

Monitoring for lack of benefit: a critical component of a randomized clinical trial, Freidlin B, Korn EL. *Journal of Clinical Oncology*, 2009a;27:629–633.
<http://www.ncbi.nlm.nih.gov/pubmed/19064977>

Stopping clinical trials early for benefit: impact on estimation, Freidlin B, Korn EL. *Clinical Trials*, 2009b;6:119–125.
<http://www.ncbi.nlm.nih.gov/pubmed/19342463>

A general inefficacy interim monitoring rule for randomized clinical trials, Freidlin B, Korn EL, Gray R. *Clinical Trials*, 2010;7:197–208.
<http://www.ncbi.nlm.nih.gov/pubmed/20423925>

Theoretical and practical application of traditional and accelerated titration phase I clinical

trial designs: the Wayne State University experience, Heath E, LoRusso P, Ivy S, Rubinstein L, Christian M, Heilbrun L. *Journal of Biopharmaceutical Statistics*, 2009;19:414–423.
<http://www.ncbi.nlm.nih.gov/pubmed/19384685>

Dose escalation trial designs based on a molecularly targeted endpoint, Hunsberger S, Rubinstein LV, Dancey J, Korn EL. *Statistics in Medicine*, 2005;24:2171–2181.
<http://www.ncbi.nlm.nih.gov/pubmed/15909289>

A comparison of phase II study strategies, Hunsberger S, Zhao Y, Simon R. *Clinical Cancer Research*, 2009;15:5950–5955.
<http://www.ncbi.nlm.nih.gov/pubmed/19789306>

Assessing surrogates as trial endpoints using mixed models (with discussion), Korn EL, Albert PS, McShane LM. *Statistics in Medicine*, 2005;24:163–190.
<http://www.ncbi.nlm.nih.gov/pubmed/15515150>

Preliminary data release for randomized clinical trials of non-inferiority: a new proposal, Korn EL, Hunsberger S, Freidlin B, Smith MA, Abrams JS. *Journal of Clinical Oncology*, 2005;23:5831–5836.
<http://www.ncbi.nlm.nih.gov/pubmed/16027441>

Conditional power calculations with historical controls, Korn EL, Freidlin B. *Statistics in Medicine*, 2006;25:2922–2931.
<http://www.ncbi.nlm.nih.gov/pubmed/16479548>

Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma: determining progression-free and overall survival benchmarks for future phase II Trials, 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. *Journal of Clinical Oncology*, 2008;26:527–534.
<http://www.ncbi.nlm.nih.gov/pubmed/18235113>

Stopping or reporting early for positive results in randomized clinical trials: the NCI cooperative group experience, 1990–2005, Korn EL, Freidlin B, Mooney M. *Journal of Clinical Oncology*, 2009;10:1712–1721.
<http://www.ncbi.nlm.nih.gov/pubmed/19237631>

Compressing drug development timelines in oncology using phase ‘0’ trials, Kummar S, Kinders R, Rubinstein L, Parchment R, Murgu A, Collins J, Pickeral O, Low J, Steinberg S, Gutierrez M, Yang S, Helman L, Wiltrott R, Tomaszewski J, Doroshow J. *Nature Reviews Cancer*, 2007;7:131–139.
<http://www.ncbi.nlm.nih.gov/pubmed/17251919>

Designing phase 0 cancer clinical trials, Murgu A, Kummar S, Rubinstein L, Gutierrez M, Collins J, Kinders R, Parchment R, Ji J, Steinberg S, Yang S, Hollingshead M, Chen A, Helman L, Wiltrott R, Tomaszewski J, Doroshow J. *Clinical Cancer Research*, 2008;14:3675–3682.
<http://www.ncbi.nlm.nih.gov/pubmed/18559582>

Design issues of randomized phase II trials and a proposal for phase II screening trials, Rubinstein LV, Korn EL, Freidlin B, Hunsberger S, Ivy SP, Smith MA. *Journal of Clinical Oncology*, 2005;23:7199–7206.
<http://www.ncbi.nlm.nih.gov/pubmed/16192604>

Randomized phase II designs, Rubinstein L, Crowley J, Ivy P, LeBlanc M, Sargent D. *Clinical Cancer Research*, 2009;15:1883–1890.
<http://www.ncbi.nlm.nih.gov/pubmed/19276275>

Validation of novel imaging methodologies for use as cancer clinical trial endpoints, Sargent D, Rubinstein L, Schwartz L, Dancey J, Gatsonis C, Dodd L, Shankar L. *European Journal of Cancer*, 2009;45:290–299.
<http://www.ncbi.nlm.nih.gov/pubmed/19091547>

Stable disease is not preferentially observed with targeted therapies and as currently defined has limited value in drug development,



Vidaurre T, Wilkerson J, Simon R, Bates SE, Fojo T. *The Cancer Journal*, 2009;15:366–373.
<http://www.ncbi.nlm.nih.gov/pubmed/19826355>

Methodology for Genomic Clinical Trials

Adaptive signature design: an adaptive clinical trial design for generating and prospectively testing a gene expression signature for sensitive patients, Freidlin B, Simon R. *Clinical Cancer Research*, 2005;11:7872–7878.
<http://www.ncbi.nlm.nih.gov/pubmed/16278411>

The cross-validated adaptive signature design, Freidlin B, Jiang W, Simon R. *Clinical Cancer Research*, 2010;16:691–698.
<http://www.ncbi.nlm.nih.gov/pubmed/20068112>

Randomized clinical trials with biomarkers: design issues, Freidlin B, McShane LM, Korn EL. *Journal of the National Cancer Institute*, 2010;102:152–160.
<http://www.ncbi.nlm.nih.gov/pubmed/20075367>

Biomarker-adaptive threshold design: a procedure for evaluating treatment with possible biomarker-defined subset effect, Jiang W, Freidlin B, Simon R. *Journal of the National Cancer Institute*, 2007;99:1036–1043.
<http://www.ncbi.nlm.nih.gov/pubmed/17596577>

Effective incorporation of biomarkers into phase II trials, McShane LM, Hunsberger S, Adjei AA. *Clinical Cancer Research*, 2009;15:1898–1905.
<http://www.ncbi.nlm.nih.gov/pubmed/19276274>

Evaluating the efficiency of targeted designs for randomized clinical trials, Simon R, Maitnourim A. *Clinical Cancer Research*, 2005;10:6759–6763.
<http://www.ncbi.nlm.nih.gov/pubmed/15501951>

Roadmap for developing and validating therapeutically relevant genomic classi-

fiers, Simon R. *Journal of Clinical Oncology*, 2005;23:7332–7341.
<http://www.ncbi.nlm.nih.gov/pubmed/16145063>

Use of genomic signatures in therapeutics development, Simon R, Wang SJ. *The Pharmacogenomics Journal*, 2006;6:166–173.
<http://www.ncbi.nlm.nih.gov/pubmed/16415922>

New challenges for 21st century clinical trials, Simon R. *Clinical Trials*, 2007;4:167–169.
<http://www.ncbi.nlm.nih.gov/pubmed/17456517>

The use of genomics in clinical trial design, Simon R. *Clinical Cancer Research*, 2008;14:5984–5993.
<http://www.ncbi.nlm.nih.gov/pubmed/18829477>

Lost in translation: problems and pitfalls in translating laboratory observations to clinical utility, Simon R. *European Journal of Cancer*, 2008;44:2707–2713.
<http://www.ncbi.nlm.nih.gov/pubmed/18977655>

Use of archived specimens in evaluation of prognostic and predictive biomarkers, Simon R, Paik S, Hayes DH. *Journal of the National Cancer Institute*, 2009;101:1–7.
<http://www.ncbi.nlm.nih.gov/pubmed/19815849>

Clinical trial designs for evaluating the medical utility of prognostic and predictive biomarkers in oncology, Simon R. *Personalized Medicine*, 2010;7:33–47.
<http://www.ncbi.nlm.nih.gov/pubmed/20383292>

Clinical trials for predictive medicine: new challenges and paradigms, Simon R. *Clinical Trials*, 2010;7:516–524.
<http://www.ncbi.nlm.nih.gov/pubmed/20338899>

Cancer Biomarkers

Interlaboratory comparability study of cancer gene expression analysis using oligonucleotide

microarrays, Dobbin KK, Beer DG, Meyerson M, Yeatman TJ, Gerald WJ, Jacobson JW, Conley B, Buetow KH, Heiskanen M, Simon RM, Minna JD, Girard L, Misek DE, Taylor JMG, Hanash S, Naoki K, Hayes DN, Ladd-Acosta C, Enkemann SA, Viale A, Giordano TJ. *Clinical Cancer Research*, 2005;11:565–572.

<http://www.ncbi.nlm.nih.gov/pubmed/15701842>

Sample size planning for developing classifiers using high dimensional DNA microarray data, Dobbin K, Simon R. *Biostatistics*, 2007;8:101–117. <http://www.ncbi.nlm.nih.gov/pubmed/16613833>

How large a training set is needed to develop a classifier for microarray data? Dobbin K, Zhao Y, Simon R. *Clinical Cancer Research*, 2008;14:108–114. <http://www.ncbi.nlm.nih.gov/pubmed/18172259>

Critical review of published microarray studies for cancer outcome and guidelines on statistical analysis and reporting, Dupuy A, Simon RM. *Journal of the National Cancer Institute*, 2007;99:147–157. <http://www.ncbi.nlm.nih.gov/pubmed/17227998>

Identification of clinically useful cancer prognostic markers: what are we missing? McShane LM, Altman DG, Sauerbrei W. *Journal of the National Cancer Institute*, 2005;97:1023–1025. <http://www.ncbi.nlm.nih.gov/pubmed/16030294>

REporting Recommendations for Tumor MARKer Prognostic Studies (REMARK), McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM for the Statistics Subcommittee of the NCI-EORTC Working Group on Cancer Diagnostics. *British Journal of Cancer*, 2005;93:387–391; *European Journal of Cancer*, 2005;41:1690–1696; *Journal of Clinical Oncology*, 2005;23:9067–9072; *Journal of the National Cancer Institute*, 2005;97:1180–1184; *Nature Clinical Practice Oncology*, 2005;2:416–422. <http://www.ncbi.nlm.nih.gov/pubmed/16932852>

Development and validation of therapeutically relevant multi-gene biomarker classifiers, Simon R. *Journal of the National Cancer Institute*, 2005;97:866–867. <http://www.ncbi.nlm.nih.gov/pubmed/15956642>

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

A checklist for evaluating reports of expression profiling for treatment selection, Simon R. *Clinical Advances in Hematology and Oncology*, 2006;4:219–224. <http://www.ncbi.nlm.nih.gov/pubmed/16728933>

Development and evaluation of therapeutically relevant predictive classifiers using gene expression profiling, Simon R. *Journal of the National Cancer Institute*, 2006;98:1169–1171. <http://www.ncbi.nlm.nih.gov/pubmed/16954463>

Gene expression-based prognostic signatures in lung cancer: ready for clinical use? Subramanian J, Simon R. *Journal of the National Cancer Institute*, 2010;102:464–474. <http://www.ncbi.nlm.nih.gov/pubmed/20233996>

What should physicians look for in evaluating reports of prognostic gene-expression signatures? Subramanian J, Simon R. *Nature Reviews Clinical Oncology*, 2010;7:327–334. <http://www.ncbi.nlm.nih.gov/pubmed/20421890>

Statistical Genomics

A comparison of bootstrap methods and an adjusted bootstrap approach for estimating prediction error in microarray classification, Jiang W, Simon R. *Statistics in Medicine*, 2007;26:5320–5334. <http://www.ncbi.nlm.nih.gov/pubmed/17624926>



Calculating confidence intervals for prediction error in microarray classification using resampling, Jiang W, Varma S, Simon R. *Statistical Applications in Genetics and Molecular Biology*, 2008;7(1):Article 8. <http://www.ncbi.nlm.nih.gov/pubmed/18312213>

An investigation of two multivariate permutation methods for controlling the false discovery proportion, Korn EL, Li M-C, McShane LM, Simon R. *Statistics in Medicine*, 2007;26:4428–4440. <http://www.ncbi.nlm.nih.gov/pubmed/17357994>

A note on controlling the number of false positives, Korn EL, Freidlin B. *Biometrics*, 2008;64:227-231. <http://www.ncbi.nlm.nih.gov/pubmed/17900315>

Appropriateness of some resampling-based inference procedures for assessing performance of prognostic classifiers derived from microarray data, Lusa L, McShane LM, Radmacher MD, Shih JH, Wright GW, Simon R. *Statistics in Medicine*, 2007;26:1102–1113. <http://www.ncbi.nlm.nih.gov/pubmed/16755534>

Challenges in projecting clustering results across gene expression profiling data sets, Lusa L, McShane LM, Reid JF, De Cecco L, Ambrogio F, Biganzoli E, Gariboldi M, Pierotti MA. *Journal of the National Cancer Institute*, 2007;99:1715–1723. <http://www.ncbi.nlm.nih.gov/pubmed/18000217>

A class comparison method with filtering enhanced variables selection for high dimensional data sets, Lusa L, Korn EL, McShane LM. *Statistics in Medicine*, 2008;27:5834–5849. <http://www.ncbi.nlm.nih.gov/pubmed/18781559>

Prediction error estimation: a comparison of resampling methods, Molinaro A, Simon R, Pfeiffer R. *Bioinformatics*, 2005;21:3301–3307. <http://www.ncbi.nlm.nih.gov/pubmed/15905277>

Bias in error estimation when using cross-validation for model selection, Varma S, Simon R. *BMC Bioinformatics*, 2006;7:91. <http://www.ncbi.nlm.nih.gov/pubmed/16504092>

Bioinformatics, Immunoinformatics, and Systems Biology

Estimating the number of rate-limiting genomic changes for human breast cancer, Zhang X, Simon R. *Breast Cancer Research and Treatment*, 2005;91:121–124. <http://www.ncbi.nlm.nih.gov/pubmed/15868439>

On the dynamics of breast tumor development in women carrying germline BRCA1 and BRCA2 mutations, Simon R, Zhang X. *International Journal of Cancer*, 2008;122:1916–1917. <http://www.ncbi.nlm.nih.gov/pubmed/18098285>

The Norton-Simon hypothesis: designing more effective and less toxic chemotherapeutic regimens, Simon R, Norton L. *Nature Clinical Practice Oncology*, 2006;3:406. <http://www.ncbi.nlm.nih.gov/pubmed/16894366>

Analysis of gene expression data using BRB-ArrayTools, Simon R, Lam A, Li MC, Ngan M, Menendez S, Zhao Y. *Cancer Informatics*, 2007;3:11–17. <http://www.ncbi.nlm.nih.gov/pubmed/19455231>

BRB-ArrayTools data archive for human cancer gene expression: a unique and efficient data sharing resource, Zhao Y and Simon R. *Cancer Informatics*, 2008;6:9–15. <http://www.ncbi.nlm.nih.gov/pubmed/19259398>

Combining positional scanning peptide libraries, HLA-DR transfectants and bioinformatics to dissect the epitope spectrum of HLA-class II cross-restricted CD4+ T cell clones, Sospedra M, Zhao Y, Giulianotti M, Simon R, Pinilla C, Martin R. *Journal of Immunological Methods*, 2010;353:93–101. <http://www.ncbi.nlm.nih.gov/pubmed/20036243>

Lymphoma Genomics

Diffuse large B-cell lymphoma subgroups have distinct genetic profiles that influence tumor biology and improve gene-expression-based survival prediction,

Bea S, Zettl A, Wright G, Salaverria I, Jehn P, Moreno V, Burek C, Ott G, Puig X, Yang L, Lopez-Guillermo A, Chan WC, Greiner TC, Weisenburger DD, Armitage JO, Gascoyne RD, Connors JM, Grogan TM, Braziel R, Fisher RI, Smeland EB, Kvaloy S, Holte H, Delabie J, Simon R, Powell J, Wilson WH, Jaffe ES, Montserrat E, Muller-Hermelink HK, Staudt LM, Campo E, Rosenwald A; Lymphoma/Leukemia Molecular Profiling Project. *Blood*, 2005;106:3183–3190.

<http://www.ncbi.nlm.nih.gov/pubmed/16046532>

Molecular diagnosis of Burkitt's lymphoma,

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. *New England Journal of Medicine*, 2006;354:2431–2442.

<http://www.ncbi.nlm.nih.gov/pubmed/16760443>

Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways,

Lenz G, Wright GW, Emre NCT, Kohlhammer H, Dave SS, Davis RE, Carty S, Lam LT, Shaffer AL, Xiao W, Powell J, Rosenwald A, Ott G, Muller-Hermelink HK, Gascoyne RD, Connors JM, Campo E, Jaffe ES, Delabie J, Smeland EB, Rimsza LM, Fisher RI, Weisenburger DD, Chan WC, Staudt LM. *Proceedings of the National Academy of Sciences of the United States of America*, 2008;105:13520–13525.

<http://www.ncbi.nlm.nih.gov/pubmed/18765795>

Stromal gene signatures in large B-cell

lymphomas, Lenz G, Wright G, Dave SS, Xiao W, Powell J, Zhao H, Xu W, Tan B, Goldschmidt N, Iqbal J, Vose J, Bast M, Fu K, Weisenburger DD, Greiner TC, Armitage JO, Kyle A, May L, Gascoyne RD, Connors JM, Troen G, Holte H, Kvaloy S, Dierickx D, Verhoef G, Delabie J, Smeland EB, Jares P, Martinez A, Lopez-Guillermo A, Montserrat E, Campo E, Braziel RM, Miller TP, Rimsza LM, Cook JR, Pohlman B, Sweetenham J, Tubbs RR, Fisher RI, Hartmann E, Rosenwald A, Ott G, Muller-Hermelink HK, Wrench D, Lister TA, Jaffe ES, Wilson WH, Chan WC, Staudt LM; Lymphoma/Leukemia Molecular Profiling Project. *New England Journal of Medicine*, 2008;359:2313–2323.

<http://www.ncbi.nlm.nih.gov/pubmed/19038878>





2010 Program
Accomplishments

Office of Cancer Complementary and Alternative Medicine

OVERVIEW

Within the Office of the Director (OD) of the National Cancer Institute (NCI), the Office of Cancer Complementary and Alternative Medicine (OCCAM) was established in 1998 to:

- Collaborate with the National Institutes of Health (NIH) National Center for Complementary and Alternative Medicine (NCCAM) on phase 3 clinical trials on shark cartilage and other complementary and alternative medicine (CAM) therapies
- Improve NIH's information resources on CAM
- Develop a better relationship with the CAM community
- Coordinate and expand, but not necessarily manage, the CAM-relevant research grant activities in the areas of prevention, diagnosis, treatment, and symptom and side effect management
- Track NCI's CAM research expenditures

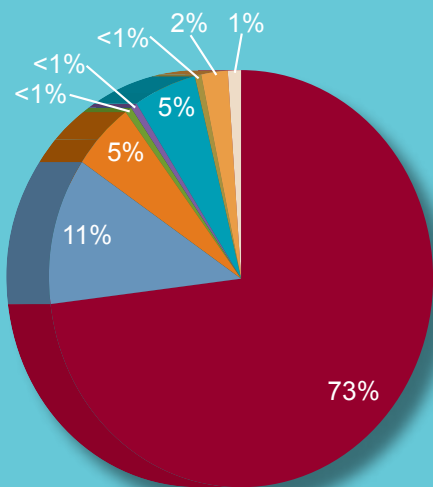
In 2007, the NCI director moved OCCAM into the Division of Cancer Treatment and Diagnosis (DCTD).

CAM continues to be a topic of importance to the U.S. Congress, as indicated by hearings such as the one on integrative medicine that was convened in February 2009. This event coincided with the Institute of Medicine's summit on the same topic.

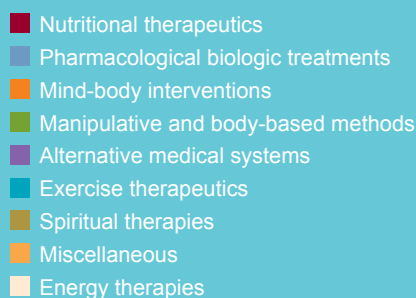
BACKGROUND

Mission

The mission of OCCAM is to improve the quality of care for cancer patients, as well as those at risk for cancer and those recovering from cancer treatment, by contributing to the advancement of evidence-based CAM practice and the sciences that support it, as well as the availability of high-quality information for the health care community, researchers, and general public.



NCI CAM Research by Category, Fiscal Year 2009



JEFFREY D. WHITE, DIRECTOR

Jeffrey D. White, M.D., graduated from Cornell University with a B.S. degree in Applied and Engineering Physics in 1979 and received an M.D. degree from Howard University in 1984. He completed a residency in internal medicine in 1987 and fellowships in oncology and hematology in 1990 at the Washington Hospital Center in Washington, D.C.



Dr. White joined the NCI Metabolism Branch in 1990 as a Medical Staff Fellow. In the Metabolism Branch, he performed laboratory research in immunology and molecular biology and coordinated the development and administration of phase 1 and 2 clinical trials with unmodified and radiolabeled monoclonal antibody constructs.

From 1995 to 1998, Dr. White also served as an oncology consultant to the director of the NIH's Office of Alternative Medicine. In October 1998, he was chosen to serve as director of the newly created NCI OCCAM. The office was formed to augment the activities of the different divisions at NCI that were already supporting CAM research. OCCAM continues to promote and support research and generation of quality information on the various disciplines and modalities associated with the CAM field as they relate to the diagnosis, prevention, and treatment of cancer.

NCI Definitions of CAM-Related Terms

Complementary and alternative medicine (CAM): Any medical system, practice, or product that is not thought of as standard care

Complementary medicine: A CAM therapy used along with standard medicine

Alternative medicine: A CAM therapy used in place of standard treatments

Integrative medicine: An approach that combines treatments from conventional medicine and CAM for which there is some high-quality evidence of safety and effectiveness

History

OCCAM was initially established within the NCI OD (1998–2007) to increase the number and quality of CAM research projects within the NCI portfolio. The office was created not to serve as a central CAM grant management program for all NCI CAM grants, but rather to provide expertise in CAM. After a congressional inquiry about the amount of funding for CAM research at NCI, a reliable system of reporting these figures was created. A competitive, peer-reviewed supplement program was established and implemented to support pilot projects, with the

ultimate goal of increasing the number of R01 research projects on CAM and building CAM research expertise within the NCI-designated Cancer Centers. The following six centers were funded:

1. Johns Hopkins University
2. University of Medicine and Dentistry, New Jersey
3. Wake Forest University
4. University of California at San Francisco
5. University of Chicago
6. University of Colorado

OCCAM also assisted with the development of Physician Data Query (PDQ®) CAM summaries for patients and health professionals.

OCCAM was moved to DCTD in 2007. Within DCTD, OCCAM identified three research areas with slight representation within NCI but offering potential for therapeutic advances. Designed to mesh with DCTD goals, these areas focus on:

- Identifying novel therapeutics in the pharmacopeia of traditional medical systems as defined by the World Health Organization
- Using complementary approaches to improve the therapeutic ratio of standard and investigational anticancer therapies
- Research on lifestyle modifications (e.g., diet, exercise, mind–body approaches) for their impact on cancer outcomes (e.g., response to conventional cancer therapy, survival)

PROGRAM ACCOMPLISHMENTS

- Program Announcement: Developmental Projects in Complementary Approaches to Cancer Care and Treatment (R21): Issued three times, the latest version being [PA-09-167](#), and once for R03 grants, [PA-09-168](#). This Program Announcement has increased the amount of high-quality research in CAM supported by NCI while keeping projects integrated in the relevant program portfolios.
 - Source of funded grants for each of the four extramural granting divisions
 - 51% of all NCI's active CAM R21s in fiscal year (FY) 2007 were received in response to this series of announcements
 - More than 120 publications from funded projects
- NCI Best Case Series Program:
 - Only program in the world advertised as willing and interested to review case records of patients treated with unconventional cancer therapies
- Intent is to identify approaches that may warrant NCI-initiated research
- Coordinated NCI and NCCAM monitoring and oversight of a clinical trial of an enzyme treatment for pancreatic cancer. The trial was performed by Columbia University's Herbert Irving Cancer Center and a CAM practitioner, Dr. Nicholas Gonzalez.
 - Nonrandomized, controlled clinical trial compared the effectiveness of gemcitabine-based chemotherapy with that of the "Gonzalez regimen" (i.e., enzyme therapy) in patients whose pancreatic cancer could not be treated with surgery (<http://jco.ascopubs.org/cgi/content/abstract/28/12/2058>)
 - Patients treated with gemcitabine-based chemotherapy survived an average of 14 months; those treated with the Gonzalez regimen survived an average of only 4.3 months
 - In addition, patients treated with chemotherapy reported a better quality of life than those treated with the Gonzalez regimen
- Supported one of the largest and fastest-accruing trials in the history of Eastern Cooperative Oncology Group at that time
 - L-Carnitine for cancer-related fatigue (**Analysis of cytokines in ECOG E4Z02: a phase III randomized study of l-carnitine supplementation for fatigue in patients with cancer**, Rich TA, Fisch MJ, Manola J, Cella D, Ansari B, Koc M, Cruciani R. *Journal of Clinical Oncology*, 2009;27[suppl 15]:9635)



- OCCAM funding necessary for costs not typically incurred with other trials (acquisition of the supplement and placebo were necessary for the trial to be done)
- Survey Results of Cancer Researchers and CAM Practitioners
 - Two unique surveys of the interests and concerns of CAM practitioners and cancer researchers working on CAM topics:
 - **Survey of complementary and alternative medicine practitioners regarding cancer management and research**, Lee CO, Zia F, Olaku O, Michie J, White JD. *Journal of the Society for Integrative Oncology*, 2009;7:26–34.
 - **Survey of cancer researchers regarding complementary and alternative medicine**, Smith WB, Olaku O, Michie J, White JD. *Journal of the Society for Integrative Oncology*, 2008;6:2–12.
 - Results from these surveys helped guide development of a series of conferences and the creation of new database resources for researchers.
- Conferences:
 - **Traditional Chinese Medicine and Cancer Research: Fostering Collaborations, Advancing the Science**: April 10–12, 2006. Purpose: To inform NCI staff about the application of various traditional Chinese medicine (TCM) modalities for cancer prevention, treatment, and symptom management
 - **Cancer Researchers and CAM Practitioners: Fostering Collaborations, Advancing the Science**: October 22–23, 2007.

Purpose: To foster interaction and dialogue between CAM practitioners and cancer researchers and to inform NCI staff about issues related to the implementation of research projects involving collaborations between CAM practitioners and cancer researchers

- **Botanicals and Cancer Research: Clinical Trials**: July 15–16, 2009. Purpose: To bring together experts in the botanical field to participate in workshop activities designed to assess the state of the science of botanicals



as potential cancer treatments, with a focus on anticancer drug development through clinical trials

- Research resources
 - Cancer CAM Researchers Directory
 - A directory of cancer CAM researchers to assist networking with others who have similar or related research interests
 - Cancer CAM Funding Database
 - Nonfederal funding is often needed to back preliminary research that aids in providing proof of concept required to acquire larger-scale grants from NIH
 - Nonfederal funding is difficult to locate or identify, thus can be a barrier to obtaining federal funding for foundational or exploratory research
- OCCAM provides content expertise on CAM for patient education materials and other NCI publications, including the *NCI Cancer Bulletin*
- Center for Cancer Research
 - Study of anticancer activity and immune-stimulating effects of SQF, a mixture of herbs often used at Guang An Men hospital in Beijing, China, to decrease the side effects of chemotherapy
 - Institutions: Guang An Men hospital and Laboratory of Molecular Immunoregulation at NCI-Frederick
 - Use of a murine model of inflammatory breast cancer to assess the impact of the herbal formula on the function of myeloid immunosuppressive cells
 - Oral administration of SQF alone significantly inhibited tumor development in the 4T1 murine breast cancer model
 - Combination of SQF and Taxol showed a small additive effect
 - SQF combined with gemcitabine produced synergistic inhibition of tumor growth and reduction in gemcitabine-induced toxicity; >40% of mice remained tumor free after combination therapy
 - Phytochemical research on prostate cancer stem cells
 - Identification of molecular targets and predictive biomarkers for dietary colon cancer prevention
- Division of Cancer Prevention—Community Clinical Oncology Program
 - OCCAM staff members serve as reviewers on concept and protocol

COLLABORATIONS

Interdivisional Collaborations

- NCI's [Annual Report on Complementary and Alternative Medicine](#) (available each year from FY 2005 to 2008)—OCCAM produces these reports in collaboration with all NCI divisions and the OD to highlight CAM research, training, and communication activities at NCI.
- Office of Communications and Education
 - With the former Office of Liaison Activities (currently the Office of Advocacy Relations), OCCAM developed and posted questions regarding the PDQ® cancer CAM information summaries (patient versions) to solicit feedback

review committees when a proposed trial addresses a CAM topic. Expertise is provided on medical oncology research and CAM content.

Intradivisional Collaborations

DCTD Natural Products Branch (NPB), Developmental Therapeutics Program (see “International Collaborations”)

Interagency Collaborations

- NIH Clinical Center: OCCAM supports the Infectious Diseases and Immunogenetics Section in the Department of Transfusion Medicine for a project exploring the combined effect of an herbal mixture (PHY906) with irinotecan in a xenograft model of colorectal cancer.
- NCCAM; National Heart, Lung, and Blood Institute; NIH Office of Research Services; and NIH Recreation and Welfare Association: OCCAM helped support NIH Yoga Week, held May 19–23, 2008, to educate NIH employees and the public about the potential benefits of yoga.
- NCCAM: Two cooperative agreement applications from an NCCAM Request for Applications were funded by NCI:
 - International Center for the Evaluation of East Asian Botanicals for Cancer (grant number 1U19CA128534)
 - Institutions: Harvard University, Chinese University of Hong Kong, Hong Kong Baptist University
 - Objectives and outcomes:
 - Establish and maintain a library of authenticated TCM botanical extracts for scientific evaluation
 - International Center of Traditional Chinese Medicine for Cancer (Grant number 1U19CA121503)
 - Institutions: Partnership between the University of Texas MD Anderson Cancer Center and the Cancer Hospital, Fudan University in Shanghai, China
 - Grant supports ongoing investigation of:
 - Herbal and natural treatments that target cancer and related symptoms
 - Acupuncture for dealing with some side effects of cancer treatment
 - Biobehavioral effects of Qigong and other mind-body-based interventions
 - Grant studies/outcomes:
 - Clinical trial of huachansu (a TCM therapy derived from sterilized toad skin extract) in patients with advanced hepatocellular carcinoma, non–small-cell lung cancer, and pancreatic cancer (**Pilot**

study of huachansu in patients with hepatocellular carcinoma, non-small cell lung cancer, or pancreatic cancer, Meng Z, Yang P, Shen Y, Bei W, Zhang Y, Ge Y, Newman RA, Cohen L, Liu L, Thornton B, Chang DZ, Liao Z, Kurzrock R. *Cancer* 2009;115:5309–5318)

- Acupuncture to prevent prolonged postoperative ileus—Qigong for women with breast cancer



- NCI/NCCAM/U.S. Food and Drug Administration fellowship: First trans-agency CAM oncology fellow allows expertise to be gained in cancer CAM research, policy, and regulatory affairs, as well as clinical investigation

International Collaborations

- OCCAM and NPB research collaboration with Kunming Institute of Botany (KIB), China
 - Memorandum of Understanding signed between KIB, Academy of Sciences and NCI in October 2008
 - KIB supplied novel natural products derived from plant specimens, while DTP screened them in NCI's system of 60 human cancer cell lines
- OCCAM and NPB research collaboration with State Key Laboratory of Chemistry for Natural Products in Guizhou Province, China
 - Memorandum of Understanding signed between State Key Laboratory of Chemistry for Natural Products in Guizhou Province, China, and NCI in March 2010
 - State Key Laboratory will supply novel natural products derived from plant specimens, while DTP screened them in NCI's system of 60 human cancer cell lines
- Fellowships/guest researchers:
 - OCCAM has provided support for two postdoctoral fellows from China:
 - From Guang An Men hospital in Beijing, China
 - Consecutively joined investigators from the Laboratory of Molecular Immunoregulation

at NCI-Frederick to explore the anticancer activity and immune-stimulating effects of SQF

- OCCAM hosts a guest researcher from M-mu Cancer Center in the East West Neo Medical Center of Kyung Hee University in Seoul, Korea, to learn clinical research skills to take back to her institution

FUTURE INITIATIVES

Because industry and academia are not likely to invest in the development of botanical and dietary supplement compounds that may increase the effectiveness of chemotherapy agents, OCCAM will contribute to this area of research. Patient information materials on CAM and cancer have increased, but a need remains for tailored patient education. OCCAM will develop evidence-based patient education resources. A clinical research program is planned:

- Translational research with medicinal botanicals and bioactive food components that have a strong preclinical research base and meet one of the above areas of special interest will be further explored, both in the laboratory and the clinic
- Phase 1 and 2 studies will be designed and implemented through the DTP Clinic for those compounds possessing the most convincing preclinical evidence for anticancer activity
- Investigation and development of novel complementary approaches to the treatment of cancer will be an objective

SELECTED PUBLICATIONS

Gemcitabine sensitivity can be induced in pancreatic cancer cells through modulation of mir-200 and mir-21 expression by curcumin or its analogue CDF, Ali S, Ahmad A, Banerjee S, Padhye S, Dominiak K, Schaffert JM, Wang Z, Philip PA, Sarkar FZ. *Cancer Research*, 2010;70:3606–3617.

<http://www.ncbi.nlm.nih.gov/pubmed/20388782>

Impacts of baicalein analogs with modification of the 6th position of A ring on the activity toward NF-kappaB-, AP-1-, or CREB-mediated transcription, Huang ST, Lee Y, Gullen EA, Cheng YC. *Bioorganic & Medicinal Chemistry Letters*, 2008;18:5046–5049.

<http://www.ncbi.nlm.nih.gov/pubmed/18722769>

Liquid chromatography/mass spectrometry analysis of PHY906, a Chinese medicine formulation for cancer therapy, Ye M, Liu SH, Jiang Z, Lee Y, Tilton R, Cheng YC. *Rapid Communications in Mass Spectrometry: RCM*, 2007;21:3593-3607.

<http://www.ncbi.nlm.nih.gov/pubmed/17944003>

Induction of apoptosis by [8]-shogaol via reactive oxygen species generation, glutathione depletion, and caspase activation in human leukemia cells, Shieh PC, Chen YO, Kuo DH, Chen FA, Tsai ML, Chang IS, Wu H, Sang S, Ho CT, Pan MH. *Journal of Agricultural and Food Chemistry*, 2010;58:3847–3854.

<http://www.ncbi.nlm.nih.gov/pubmed/20163181>

Increased growth inhibitory effects on human cancer cells and anti-inflammatory potency of shogaols from *Zingiber officinale* relative to gingerols, Sang S, Hong J, Wu H, Liu J, Yang CS, Pan MH, Badmaev V, Ho CT. *Journal of Agricultural and Food Chemistry*, 2009;57:10645-10650.

<http://www.ncbi.nlm.nih.gov/pubmed/19877681>

Electro-acupuncture to prevent prolonged postoperative ileus: a randomized clinical trial, Meng ZQ, Garcia MK, Chiang JS, Peng HT, Shi YQ, Fu J, Liu LM, Liao ZX, Zhang Y, Bei WY, Thornton B, Palmer JL, McQuade J, Cohen L. *World Journal of Gastroenterology*, 2010;16:104–111.
<http://www.ncbi.nlm.nih.gov/pubmed/20039456>

Pilot study of huachansu in patients with hepatocellular carcinoma, nonsmall-cell lung cancer, or pancreatic cancer, Meng ZQ, Garcia MK, Chiang JS, Peng HT, Shi YQ, Fu J, Liu LM, Liao ZX, Zhang Y, Bei WY, Thornton B, Palmer JL, McQuade J, Cohen L. *Cancer*, 2009;115:5309–5318.
<http://www.ncbi.nlm.nih.gov/pubmed/19701908>

Phase II designs for anticancer botanicals and supplements, Vickers, AJ. *Journal of the Society*

for Integrative Oncology, 2009;7:35–40.
<http://www.ncbi.nlm.nih.gov/pubmed/19476733>

Results of a diet/exercise feasibility trial to prevent adverse body composition change in breast cancer patients on adjuvant chemotherapy, Demark-Wahnefried W, Case LD, Blackwell K, Marcom PK, Kraus W, Aziz N, Snyder DC, Giguere JK, Shaw E. *Clinical Breast Cancer*, 2008;8:70–79.
<http://www.ncbi.nlm.nih.gov/pubmed/18501061>

Pancreatic proteolytic enzyme therapy compared with gemcitabine-based chemotherapy for the treatment of pancreatic cancer, Chabot JA, Tsai WY, Fine RL, Chen C, Kumah CK, Antman KA, Grann VR. *Journal of Clinical Oncology*, 2010;28:2058–2063.
<http://www.ncbi.nlm.nih.gov/pubmed/19687327>





2010 Program
Accomplishments

APPENDIX

DIVISION OF CANCER TREATMENT AND DIAGNOSIS STAFF ROSTER

Office of the Director

Dr. James Doroshov	Division Director
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Mr. David Ricks	Senior Financial Analyst [Contractor]
Dr. Krishnendu Roy	Expert
Mr. David Segal	Information Technology Officer
Ms. Sonjia Shorts	Secretary to the Deputy Director
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Ms. Gina Uhlenbrauck	Science Writer [Contractor]

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Resources Development Branch

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Cancer Disparities Research Partnership

Vacant	Chief, Oncology Outreach
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Dr. Igor Kuzmin	Health Scientist Administrator/Program Director
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Dr. Boris Freidlin	Mathematical Statistician
Dr. Sally Hunsberger	Mathematical Statistician
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Dr. Edward Korn	Mathematical Statistician
Mr. Ming-Chung Li	Biostatistician [Contractor]
Dr. Ezhou Long	Bioinformatics Statistical Analyst [Contractor]
Dr. Lisa McShane	Mathematical Statistician
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Mr. Michael Ngan	System Administrator [Contractor]
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NIH Publication No. 12-7911
Printed December 2012