

DIVISION OF CANCER TREATMENT AND DIAGNOSIS

PROGRAMS AND INITIATIVES (2013-2017)

NATIONAL CANCER INSTITUTE

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ACRONYMS

AACR – American Association for Cancer Research	BRD – Biospecimen Research Database
AAPM – American Association for Physicists in Medicine	BRISQ – Biospecimen Reporting for Improved Study Quality
ABTC – Adult Brain Tumor Consortium	BRMs – biological response modifiers
ACG – Agreement Coordination Group	BRN – Biospecimen Research Network
ACR – American College of Radiology	BRP – Biometric Research Program
ACRIN – American College of Radiology Imaging Network	BTB – Biological Testing Branch
ACT – NCTN Accrual Core Team	
ADCC – antibody directed cellular cytotoxicity	caAERS – cancer adverse event reporting system
ADME – absorption, distribution, metabolism, and excretion	CADP – Clinical Assay Development Program
ADTTP – Advanced Development Therapeutics Training Program	caDSR – NCI Cancer Data Standards Registry and Repository
AERS – Adverse Event Reporting System	caHUB – NCI Cancer Human Biobank
AFRRI – The Department of Defense Armed Forces Radiobiology and Research Institute	CALGB – Cancer and Leukemia Group B
AHRQ – Agency for Healthcare Research and Quality	CAM – complementary and alternative medicine
ALCHEMIST – Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial	CAP – Corrective Action Plan
ALL – acute lymphoblastic leukemia	CBC – Chemical Biology Consortium
allo HCT – allogenic hematopoietic cell transplantation	CBCTR – NCI Cooperative Breast Cancer Tissue Resource
AML – acute myeloid leukemia	CBIIT – NCI Center for Biomedical Informatics and Information Technology
APEC – Asia Pacific Economical Collaboration	CCCT – NCI Director’s Coordinating Center for Clinical Trials
ARRA – American Recovery and Reinvestment Act of 2009	CCOP – Community Clinical Oncology Program
ASCO – American Society of Clinical Oncology	CCR – Center for Cancer Research
ASIGS – American Society for Image Guided Surgery	CCSS – Childhood Cancer Survivor Study
ASPR – Office of the Assistant Secretary for Preparedness and Response	CCTG – Canadian Cancer Trials Group
ASTRO – American Society for Radiation Oncology	CDE – NIH Common Data Elements Repository
ATR – ataxia telangiectasia mutated and Rad3-related kinase	CDK – cyclin-dependent kinase
ATRF – Advanced Technologies Research Facility	CDMS – Clinical Data Management System
5-aza-T-dCyd – 5-aza-4'-thio-2'deoxyctidine	CDP – Cancer Diagnosis Program
	CDR – Comprehensive Data Resource
BARDA – Biomedical Advanced Research and Development Authority	CDRH – FDA’s Center for Devices and Radiological Health
BBRB – Biorepositories and Biospecimen Research Branch	CDUS – Clinical Data Update System
BDP – Biopharmaceutical Development Program	CEP – Career Enhancement Program
BEBPs – biospecimen evidence-based practices	CGCB – Clinical Grants and Contracts Branch
BEMT – Biobank Economic Modeling Tool	CGH – NCI Center for Global Health
BIGSFP – Biomarker, Imaging, and Quality of Life Studies Funding Program	cGLP – current Good Laboratory Practice
BMT-CTN – Blood and Bone Marrow Transplant Clinical Trials Network	cGMP – current Good Manufacturing Practice
BPV – Biospecimen Preanalytical Variables Program	CHTN – Cooperative Human Tissue Network
BRB – Biological Resources Branch	CI/CACMS – Cancer Institute of China Academy of Chinese Medical Sciences
	CIB – Clinical Investigations Branch
	CIB – Consortium for Imaging and Biomarkers
	CIBMTR – Center for International Blood and Marrow Transplant Research
	CIN – Cancer Immunotherapy Network
	CIP – Cancer Imaging Program

CIRB – Central Institutional Review Board
CISC – Clinical Imaging Steering Committee
CIT – NIH Center for Information Technology
CITN – Cancer Immunotherapy Trials Network
CLIA – Clinical Laboratory Improvement Amendments
CM – Chinese Medicine
CMC – chemistry, manufacturing, and control
cMET – hepatocyte growth factor receptor
CMS – Center for Medicare and Medicaid Services
CNS – central nervous system
COG – Children’s Oncology Group
COSC – Central Operations and Statistical Office
COTS – commercial “off the shelf”
CPTAC – NCI Clinical Proteomic Tumor Analysis Consortium program
CR – complete response
CRADA – Cooperative Research and Development Agreements
CRC – NIH Clinical Research Center
CRCHD – NCI’s Center to Reduce Cancer Health Disparities
CrD PTMA – Career Development Project Team Member Applications
CrDL – Career Development Letter of Intent
CRF – Case Reporting Form
CROB – Clinical Radiation Oncology Branch
CROs – contract research organizations
CRS – Center for Research Strategy
CRT – 3D-conformal radiation therapy
CRTA – Cancer Research Training Award
CSB – Computational and Systems Biology Branch
CTAC – Clinical and Translational Research Advisory Committee
CTB – Clinical Trials Branch
CTCs – circulating tumor cells
ctDNA – circulating tumor DNA
CTEP – Cancer Therapy Evaluation Program
CTEP-AERS – CTEP-Adverse Event Reporting System
CTEP-ESYS – CTEP Enterprise Database
CTEP-IAM – CTEP-Identity and Access Management
CTMS – clinical trial management service
CTOIB – Clinical Trials Operations and Informatics Branch
CTRP – Clinical Trials Reporting Program
CTSU – Cancer Trials Support Unit
CTWG – Clinical Trials Working Group
CUGH – Consortium of Universities for Global Health
DBTB – Diagnostic Biomarkers and Technology Branch
DCEG – Division of Cancer Epidemiology and Genetics
DCIDE – Development of Clinical Imaging Drugs and Enhancers
DCP – Division of Cancer Prevention
DCTD – Division of Cancer Treatment and Diagnosis
DDR – DNA damage repair
DEB – Diagnostics Evaluation Branch
DHS – Department of Homeland Security
DIPG – diffuse intrinsic pontine glioma
DNMT1 – DNA (cytosine-5-)-methyltransferase 1
DOD – U.S. Department of Defense
DOE – U.S. Department of Energy
DOI – Digital Object Identifier
DOTIL – disruptor of telomeric silencing 1-like histone H3K79
DRG – Drug Regulatory Group
DRP – Developmental Research Program
DSC – dynamic susceptibility contrast
DSCB – Drug Synthesis and Chemistry Branch
DTC – Developmental Therapeutics Clinic
DTP – Developmental Therapeutics Program
DWI – diffusion-weighted imaging
EBRT – external beam radiation therapy
ECOG – Eastern Cooperative Oncology Group
ECTN – NCI Experimental Therapeutics Clinical Trials Network
EDC – Electronic Data Capture
EDDOP – Early Drug Development Opportunity Program
EFPIA – European Federation of Pharmaceutical Industries and Associations
EGFR – epidermal growth factor receptor
ELSI – ethical, legal, and social issues of biobanking
EORTC – European Organisation for Research and Treatment of Cancer
EPA – Environmental Protection Agency
ER – Exceptional Responder
ER+ – estrogen receptor positive
ESTRO – European Society for Therapeutic Radiology and Oncology
ESYS – CTEP Enterprise System
FDA – Food and Drug Administration
FDASIA – Food and Drug Administration Safety and Innovation Act
FDG – fluorodeoxyglucose

FES – fluoroestradiol
FFPE – formalin-fixed, paraffin-embedded
FGF – fibroblast growth factor
FISH – fluorescence in situ hybridization
FKI – Fufang Kushing Injection
FLT – 18F-fluorothymidine
FMISO – fluoromisonidazole
FNLCR – Frederick National Laboratory for Cancer Research
FOA – Funding Opportunity Announcement
FTV – functional tumor volume

GB – gigabytes
GBM – glioblastoma multiforme
GCP – Good Clinical Practices
GDC – Genomic Data Commons
GI – gastrointestinal
GM-CSF – granulocyte macrophage colony-stimulating factor
GNMB – transmembrane glycoprotein NMB
GSBT – GliaSite balloon brachytherapy
GTEX – NIH’s Genotype Tissue Expression Project
GU – genitourinary
GVHD – graft versus host disease
GYN – gynecologic

HCS – high content screening
HCT – hematopoietic stem cell transplantation
HER2 – human epidermal growth factor 2
HGF/SF – hepatocyte growth factor/scatter factor
HIV – human immunodeficiency virus
HM – hematologic malignancies
HPV – human papillomavirus
HQT – Huang Qin Tang
HR – hormone receptor
HTS – high throughput screening

IAA – interagency agreement
IAEA – International Atomic Energy Agency
IARC – International Agency for Research on Cancer
IB – Investigator Brochures
IBMTR – International Bone Marrow Transplant Registry
ICCMC – International Consortium for Chinese Medicine and Cancer
ICMIC – In Vivo Cellular and Molecular Imaging Center
IDB – Investigational Drug Branch
IDE – Investigation Device Exemption
IDH-1 – isocitrate dehydrogenase-1
IDSC – Investigational Drug Steering Committee

IGRT – image-guided radiation therapy
IHC – immunohistochemistry
IL-15 – interleukin-15
IMAT – Innovative Molecular Analysis Technologies
IMI – Innovative Medicines Initiative
IMRT – intensity-modulated radiation therapy
IND – Investigational New Drug
IO – immune oncology
IOM – Institute of Medicine
IP – Intellectual Property
IPAD – Integrated Platform for Agents and Diseases
irAEs – immune-related adverse events
IROC – Imaging and Radiology Oncology Core
ISAC – Independent Scientific Advisory Committee
ITB – Information Technology Branch
ITCR – Information Technology for Cancer Research Consortium
ITSA – Integrated Translational Science Award
IWGMI – Interagency Working Group on Medical Imaging
IWRS – Interactive Web Response System

LAPS – Lead Academic Participating Sites
LDHA/B – lactate dehydrogenase-A and B
LDT – laboratory developed tests
LOI – Letter of Intent
Lung-MAP – Lung Master Protocol

MBCCOP – Minority-based Community Oncology Program
Mcl-1 – myeloid cell leukemia-1
MDM2 – murine double minute 2
MDS – myelodysplastic syndromes
MLPCN – Molecular Libraries Probe Production Centers Network
MOA – mechanism of action
MoCha – Molecular Characterization Lab
MPB – Molecular Pharmacology Branch
MPL – Molecular Pharmacology Laboratory
MRI – magnetic resonance imaging
MRT – Molecular Radiation Therapeutics
MSA – Master Service Agreement
MTA – Materials Transfer Agreement
MTD – maximum tolerated dose

NaF – sodium fluoride
NAS – National Academy of Sciences
NASA – National Aeronautics and Space Administration
NCATS – National Center for Advancing Translational Sciences

NCCCP – NCI Community Cancer Centers Program
NCI – National Cancer Institute
NCI-MATCH – NCI Molecular Analysis for Therapy Choice
NCI-MPACT – NCI Molecular Profiling Based Assignment of Cancer Therapy
NCIP – National Cancer Informatics Program
NCORP – NCI Community Oncology Research Program
NCTN – NCI National Clinical Trials Network
NCTVL – National Cancer Target Validation Laboratory
NEXT – NCI Experimental Therapeutics Program
NGS – Next generation sequencing
NHGRI – National Human Genome Research Institute
NHLBI – National Heart, Lung and Blood Institute
NIAID – National Institute of Allergy and Infectious Disease
NIBIB – National Institute of Biomedical Imaging and Bioengineering
NIDDK – National Institute of Diabetes and Digestive and Kidney Diseases
NIH – National Institutes of Health
NIR – near-infrared
NIST – National Institute of Standards and Technology
NLM – National Library of Medicine
NLST – National Lung Screening Trial
NNI – National Nanotechnology Initiative
NP – natural products
NPB – Natural Products Branch
NPNDP – NCI Program for Natural Products Discovery
NSCLC – non-small cell lung cancer
NSFC – National Natural Science Foundation of China
NSET – Nanoscale Science, Engineering, and Technology

OAD – Office of the Associate Director
OAOP – PMB On-line Agent Order Processing
OBRR – Office of Biorepositories and Biospecimen Research
OCCAM – Office of Cancer Complementary and Alternative Medicine
OCPL – Office of Communications and Public Liaison
OEWG – Operational Efficiency Working Group
OPEN – Oncology Patient Enrollment Network
OS – overall survival
OSTP – Office of Science and Technology Policy

PACCT – Program for the Assessment of Clinical Cancer Tests
PADIS – Pharmacodynamic Assay Development and Implementation Section

PAHO – Pan American Health Organization
PARP – poly(ADP-ribose) polymerase
PATS – Protocol Abstraction Tracking System
PBTC – Pediatric Brain Tumor Consortium
PCR – polymerase chain reaction
PD-1 – programmed cell death protein-1
PD – pharmacodynamics
PDAC – Pancreatic Ductal Adenocarcinoma
PDHK1 – pyruvate dehydrogenase kinase 1
PD-L1 – programmed cell death ligand
PDM – patient-derived models
PDQ – Physicians Data Query
PDX – patient-derived xenografts
PET – positron emission tomography
PFS – progression-free survival
PGRN – Pharmacogenomics Research Network
PI3K – phosphoinositide 3-kinase
PI – principal investigators
PIO – Protocol and Information Office
PIRB – Pathology Investigation and Resources Branch
PK – pharmacokinetics
PMB – Pharmaceutical Management Branch
PMI – Precision Medicine Initiative
PMI-O – Precision Medicine Initiative in Oncology
pNET – pancreatic neuroendocrine tumors
PO – Program Officer
POB – Pediatric Oncology Branch
PPTC – Pediatric Preclinical Testing Consortium
PPTP – Pediatric Preclinical Testing Program
PQ – Provocative Question
PR – partial response
PRB – Pharmaceutical Resources Branch
PRESTO – Program and Review Extramural Staff Training Office
PRO – patient reported outcomes
PTGB – Preclinical Therapeutics Grants Branch
PTMAs – Project Team Member Applications

QA – Qualitative Assurance
QC – Quality Control
QIBA – Quantitative Imaging Biomarkers Alliance
QIN – Quantitative Imaging Network

RA – 13-cis-retinoic acid
RAB – Regulatory Affairs Branch
RAC – NIH Recombinant DNA Advisory Committee
RAID – Rapid Access to Intervention Development
rCBV – relative cerebral blood volume

RCC – renal cell carcinoma

RDB – Radiotherapy Development Branch

RECIST – Response Evaluation Criterial in Solid Tumors

REMARK – Reporting Recommendations for Tumor Marker Prognostic Studies

RFA – Request for Applications

RFP – Request for Proposals

RFS – recurrence-free survival

RRP – Radiation Research Program

RRS – Radiation Research Society

RSNA – Radiological Society of North America

RSS – Regulatory Support Services

RT – radiation therapy

SAC – Senior Advisory Committee

SBIR – Small Business Innovation Research

SBRT – Stereotactic Body Radiation Therapy

SCCA – squamous cell cancer of the anal canal

SCLC – small cell lung cancer

SEP – Special Emphasis Panel

SITC – Society for Immunotherapy of Cancer

SNMMI – Society of Nuclear Medicine and Molecular Imaging

SOPs – standard operating procedures

SPECS – Strategic Partnerships to Evaluate Cancer Signatures

SPOREs – Specialized Programs of Research Excellence

SRL – Specimen Resource Locator

SRT – systemic radionuclide therapy

STTR – Small Business Technology Transfer

SUO – Society of Urologic Oncology

TAILORx – Trial Assigning Individualized Options for Treatment

TCGA – The Cancer Genome Atlas

TCIA – The Cancer Imaging Archive

TCM – Traditional Chinese Medicine

T-dCyd – 4'-thio-2'-deoxycytidine

TM – traditional medicine

TMA – tissue microarray

TMIST – Tomosynthesis Mammographic Imaging Screening Trial

TMZ – temozolomide

TPB – Toxicology and Pharmacology Branch

TRIAD – Transmission of Imaging Data

Trk – tropomyosin receptor kinase

TRP – Translational Research Program

TSL – Translational Support Laboratory

TVSL – Target Validation and Screening Laboratory

UICC – Union for International Cancer Control

USAMRIID – U.S. Army Medical Research Institute for Infectious Diseases

UTC – United Therapeutics Corporation

VA – U.S. Department of Veterans Affairs

VHA – Veterans Health Administration

VIEW – Virtual Imaging Evaluation Workspace

WES – whole exome sequencing

WHO – World Health Organization

WMIC – World Molecular Imaging Congress

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PREFACE



DR. JAMES H. DOROSHOW
DIRECTOR, NCI DIVISION
OF CANCER TREATMENT
AND DIAGNOSIS

In these pages, we describe the Programs and Initiatives of the Division of Cancer Treatment and Diagnosis (DCTD), providing a multi-year review of the research activities 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 advances from 2013 through 2017 and outlines important highlights that have helped to improve the diagnosis and treatment of cancer.

One of our greatest challenges is to increase the speed with which new treatments are brought to the millions of Americans with cancer. DCTD has continued efforts to streamline the drug discovery and development process. The NCI Experimental Therapeutics (NExT) Program allows researchers to enter candidate agents into the NCI pipeline at a number of key steps, including: target development or high throughput screening, the facilitation of chemical optimization of potential lead molecules, preclinical toxicology, formulation, development of biologicals, pharmacokinetic/pharmacodynamic assay development, and the initiation of early phase clinical trials. Researchers from academic sites, or from biotechnology concerns, may apply for access to NCI resources and expertise in any of these areas.

Our goal is to facilitate the development of novel molecules that are not a major focus of current pharmaceutical research; several ongoing projects are now undergoing first-in-human clinical trials. The development of the NCI Patient-Derived Models Repository has enhanced access of academic investigators to molecularly- and clinically-characterized patient-derived xenografts and early passage conditionally-reprogrammed cell lines to facilitate development of novel investigational drug combinations and to further the development of molecular criteria for treatment selection.

During the past four years, the efforts of DCTD to improve its national clinical trials program have continued at a rapid pace, including consolidation of the Adult U01 Phase 1 and N01 Phase 2 Programs into a single NCI Experimental Therapeutics Clinical Trials Network (ETCTN). In concert with this reorganization, the NCI made major changes in its existing late stage clinical trials infrastructure, consolidating the ten prior Cooperative Groups into the five members of the NCI National Clinical Trials Network (NCTN). To support these activities, the NCI's single Central Institutional Review Board (CIRB) was expanded to include four Boards to cover early and late stage adult therapy trials, pediatric clinical studies, and cancer prevention investigations. The expanded Cancer Trials Support Unit (CTSU), a unified Medidata Rave clinical trial management system for all network trials, and a revitalized CTEP Clinical Trials Enterprise IT System are now capable of meeting the needs of studies used for FDA registration, and of providing a much enhanced auditing and clinical trial tracking capacity. As expected, the NCTN has been able to rapidly develop, accrue, and complete new generations of genomically-based clinical trials (such as NCI-MATCH) carried out across a national clinical research infrastructure with enhanced research capabilities. Similar results with respect to the initiation of a new generation of early-phase precision oncology studies that incorporate state-of-the-art immunologic and molecular characterization are now a consistent feature of all ETCTN trials.

In addition to these major DCTD efforts, we are providing summaries of recently established priorities and scientific advances across a wide variety of diagnostic and therapeutic domains made possible by the many talented and committed staff members throughout the division. It is my privilege to work with these dedicated individuals.

OVERVIEW

DCTD supports the development of novel diagnostic and therapeutic approaches for cancer by expediting the initial and subsequent large-scale testing of new agents, biomarkers, imaging tests, and other diagnostic and therapeutic interventions (radiation, surgery, immunotherapy) in patients.

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

The **Biometric Research Program (BRP)** provides state-of-the-art expertise in the areas of biostatistics, bioinformatics and computational biology for research areas of the DCTD and other NCI components.

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

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. Among these are nanotechnologies and artificial intelligence methods to extract comprehensive non-visual information from medical images to predict biological and clinical correlates.

The **Cancer Therapy Evaluation Program (CTEP)** functions as DCTD's primary clinical evaluator of new anticancer agents, radiation treatments, and surgical methods. To accomplish this, the program administers the National Clinical Trials Network (NCTN) and the Experimental Therapeutics Clinical Trials Network (ETCTN) along with several specialty networks in immunotherapy, brain tumors, and pediatric cancers.

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 preclinical research materials and pharmacologic services to extramural investigators, and also manufactures new agents in bulk quantities for use in clinical studies conducted under U.S. Food and Drug Administration (FDA) Investigational New Drug applications.

The **Radiation Research Program (RRP)** provides expertise to investigators who perform novel research in radiation oncology, biology, physics and technology, systemic radionuclides and other sources of energy (hyperthermia and photodynamic therapy). The Program also assists in establishing future directions for radiation research related to cancer and normal tissue injury.

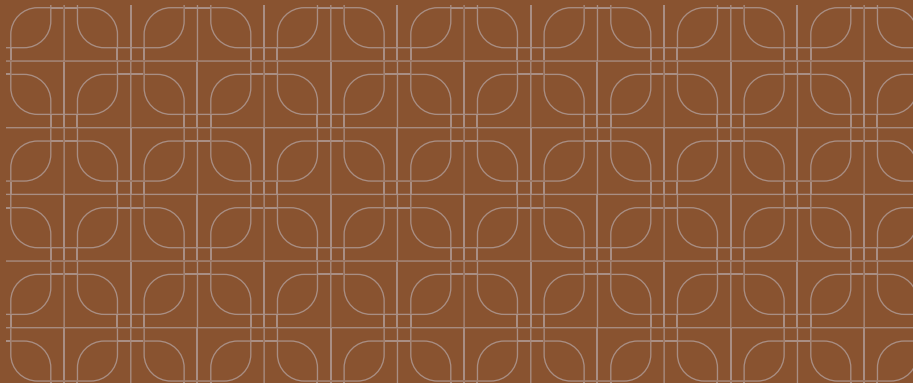
The **Translational Research Program (TRP)** translates novel scientific discoveries from laboratory and/or population studies to the clinic for testing in cancer patients and determines the biological basis for clinical observations.

The **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.

The **Developmental Therapeutics Clinic (DTC)** is located in the NIH Clinical Research Center (CRC) on the Bethesda campus; it works in concert with the Center for Cancer Research to perform early phase clinical trials that include development of pharmacodynamic assays for subsequent use in the extramural community as part of the Experimental Therapeutics Clinical Trials Network (ETCTN).

JAMES H. DOROSHOW

DIRECTOR



Dr. James H. Doroshow has been the Deputy Director for Clinical and Translational Research of the National Cancer Institute since 2011, and the Director of NCI's Division of Cancer Treatment and Diagnosis since 2004. He continues to pursue his own research program as a Senior Investigator in the Developmental Therapeutics Branch of the NCI's intramural Center for Cancer Research. He is the author of over 450 full-length publications in the areas of molecular pharmacology, the role of oxidant stress in tumor cell signal transduction, and novel therapeutic approaches to solid tumors. From 1983 to 2004, Dr. Doroshow was the Chairman of the City of Hope Comprehensive Cancer Center's Department of Medical Oncology and Therapeutics Research, and Associate Cancer Center Director for Clinical Investigation. He has served on the Oncologic Drugs Advisory Committee of the U.S. Food and Drug Administration, the Medical Oncology Board of the

American Board of Internal Medicine, and as Chair of two NIH study sections: Experimental Therapeutics II and Subcommittee A, Cancer Centers. He is currently a member of both the Forum on Drug Discovery, Development, and Translation and the National Cancer Policy Forum of the National Academy of Medicine of the National Academies of Science. He is also the Associate Editor for Oncology of the 25th Edition of the Cecil Textbook of Medicine. Dr. Doroshow received his A.B. degree magna cum laude from Harvard College in 1969 and graduated from Harvard Medical School in 1973. Following an Internal Medicine residency at the Massachusetts General Hospital, he completed a fellowship in Medical Oncology at the Medicine and Clinical Pharmacology Branches of the National Cancer Institute, NIH.

DIVISION OF CANCER TREATMENT AND DIAGNOSIS

Dr. James H. Doroshow
Division Director

Dr. Toby T. Hecht
Deputy Director

Office of Cancer Complementary and Alternative Medicine
Dr. Jeffrey D. White
Office Director

Translational Research Program
Dr. Toby T. Hecht
Associate Director

Cancer Diagnosis Program

Dr. Lyndsay Harris
Acting Associate Director

Biorepository and Biospecimen Research Branch

Dr. Helen Moore
Branch Chief

Diagnostic Biomarkers and Technology Branch

Dr. James V. Tricoli
Branch Chief

Diagnostics Evaluation Branch

Dr. Tracey Lively
Branch Chief

Pathology Investigation and Resources Branch

Dr. Irina Lubensky
Branch Chief

Cancer Imaging Program

Dr. Paula Jacobs
Associate Director

Clinical Trials Branch

Dr. Lalitha Shankar
Branch Chief

Molecular Imaging Branch

Dr. Paula Jacobs
Acting Branch Chief

Image-Guided Intervention Branch

Dr. Robert Nordstrom
Branch Chief

Imaging Technology Development Branch

Dr. Janet Eary
Acting Branch Chief

Nanotechnology Delivery Systems and Devices Branch

Dr. Piotr Grdzinski
Branch Chief

Cancer Therapy Evaluation Program

Dr. Jeffrey Abrams
Associate Director

Clinical Grants and Contracts Branch

Dr. Vikram Devgan
Branch Chief

Clinical Investigations Branch

Dr. Margaret Mooney
Branch Chief

Clinical Trials Monitoring Branch

Mr. Gary Smith
Branch Chief

Investigational Drug Branch

Dr. James Zwiebel
Branch Chief

Operations & Informatics Branch

Dr. Michael Montello
Branch Chief

Pharmaceutical Management Branch

Mr. Charles Hall, Jr.
Branch Chief

Regulatory Affairs Branch

Dr. Jan Casadei
Branch Chief

Developmental Therapeutics Program

Dr. Jerry Collins
Associate Director

Biological Resources Branch

Vacant
Branch Chief

Biological Testing Branch

Dr. Melinda Hollingshead
Branch Chief

Drug Synthesis and Chemistry Branch

Dr. Joel Morris
Branch Chief

ImmunoOncology Branch

Vacant
Branch Chief

Information Technology Branch

Dr. Daniel Zaharevitz
Branch Chief

Molecular Pharmacology Branch

Dr. Beverly Teicher
Branch Chief

Natural Products Branch

Dr. Barry O'Keefe
Branch Chief

Preclinical Therapeutics Grants Branch

Dr. Sundar Venkatachalam
Branch Chief

Toxicology and Pharmacology Branch

Vacant
Branch Chief

Radiation Research Program

Dr. C. Norman Coleman
Associate Director

Radiotherapy Development Branch

Dr. Eric Bernhard
Branch Chief

Clinical Radiation Oncology Branch

Dr. Bhadransain Vikram
Branch Chief

Pharmaceutical Resources Branch

Dr. B. Rao Vishnuvajjala
Branch Chief

Biometric Research Program

Dr. Lisa McShane
Acting Associate Director

Biostatistics Branch

Dr. Boris Freidlin
Acting Branch Chief

Computational & Systems Biology Branch

Dr. Yingdong Zhao
Acting Branch Chief

Additional DCTD information is available at <http://dctd.cancer.gov> and <http://cancer.gov>.

PROGRAMS AND INITIATIVES (2013-2017)

MAJOR INITIATIVES SUPPORTING THE CANCER COMMUNITY



CURRENT RESEARCH EMPHASIS

DCTD supports research across the entire spectrum of areas related to diagnostic and therapeutic approaches to the treatment of cancer. Figure 1 depicts the distribution of the nearly \$976 M in grant funding managed by DCTD in 2016 across the seven Programs with grant portfolios.

FUTURE RESEARCH EMPHASIS

Over the recent past, the NCI has had the opportunity to participate in two major strategic planning programs (the NIH Precision Medicine Initiative and the Beau Biden Cancer Moonshot Initiative) that have identified major areas of research emphasis that are poised for rapid progress. Additional resources for the NCI to support these initiatives have permitted DCTD to make a concerted effort to increase funding for the research community in the following areas of emphasis:

MECHANISMS OF CANCER DRUG RESISTANCE AND SENSITIVITY

- Development of combination targeted and immunotherapies to overcome resistance in clinically relevant models
- Understanding the role of the tumor microenvironment in driving drug and immunotherapy resistance
- Understanding the evolution of therapeutic resistance by longitudinal studies of human tumor biopsies and circulating molecular tumor components

DEVELOPMENT OF IMPROVED PATIENT-DERIVED MODELS TO ENHANCE EARLY PHASE CLINICAL TRIALS

- Development of a consortium of NCI-Designated Cancer Centers to produce and standardize the development and molecular characterization of patient-derived xenograft models of understudied human tumors
- Coordination of testing of novel targeted therapeutic agent combinations in pre-clinical patient-derived xenograft (PDX) trials to develop the rationale for subsequent clinical studies in the NCI's ETCTN

DEVELOPMENT OF CANCER IMMUNOTHERAPY BIOMARKERS

- Development of a laboratory consortium to standardize the methodology for analyzing tumor specimens and associated microenvironmental elements for the

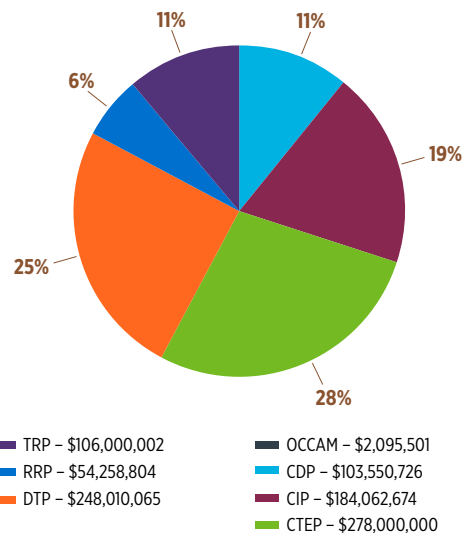


FIGURE 1: DISTRIBUTION OF DCTD 2016 GRANT FUNDING ACROSS PROGRAMS.

expression and interaction of immunomodulatory molecules from patients entered on immuno-oncology clinical trials

- Development of reagents for novel immunobiomarker analytes
- Development of an information system for the storage, evaluation, and sharing of both clinical and immunobiomarker data developed from the clinical samples examined by the consortium for patients entered on immunotherapy clinical trials

NEW CANCER IMMUNOTHERAPY MODEL SYSTEMS

- Utilization of the NCI's Comparative Oncology Network of Veterinary Oncology Centers to conduct clinical trials of immunotherapy agents in spontaneous canine malignancies
- Production of clinical grade canine immunotherapy drugs, as well as reagents for the development of canine immuno-biomarkers, essential for these clinical trials and associated pharmacodynamic investigations

UNDERSTANDING THE MICROENVIRONMENT OF PANCREATIC CANCER TO ENHANCE IMMUNOTHERAPEUTIC OPTIONS

- Understanding the intracellular crosstalk leading to the immunosuppressive microenvironment of pancreatic ductal adenocarcinomas
- Development of a tissue resource for studying the pancreatic cancer microenvironment
- Development of improved antigen selection and biomarker development methods for pancreatic cancer immunotherapy

CURRENT PROGRAMS AND INITIATIVES

NCI'S PRECISION MEDICINE TRIALS

In 2014, NCI launched a series of clinical studies whose overall aim is to use more precise diagnostics to select patients for therapies that target particular molecular abnormalities. These initiatives take advantage of next generation sequencing (NGS) technologies to look for changes in tumor DNA, with some including additional technologies to search for changes in tumor protein levels. By making these studies accessible via NCI's National Clinical Trials Network (NCTN) and Experimental Therapeutics Clinical Trials Network (ETCTN), patients treated at centers large and small, in cities and in rural communities, have access to these new approaches for cancer diagnosis and therapy. The general goals, eligibility criteria, study designs, and planned outcome analyses for each study are described below. Information for physicians is available at the following websites: www.cancer.gov (NCI/clinical trial information) and www.ctsu.org (Cancer Trials Support Unit (CTSU)/Patient Enrollment).

NCI Molecular Analysis for Therapy Choice (NCI-MATCH)

NCI-MATCH, which opened for enrollment in August 2015, is a prospective clinical trial that requires a tumor biopsy before enrollment for the performance of targeted NGS supplemented by immunohistochemical (IHC) or fluorescence in situ hybridization (FISH) assays. The targeted NGS assay, which sequences approximately 250 genes, and the supplemental IHC and FISH are performed in one of four Core Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories. The 250 genes were carefully selected for their alignment with a targeted agent that has demonstrated activity in a human tumor carrying that genetic abnormality. The study reached its accrual goal of screening 6000 patients two years ahead of schedule in May 2017 with a total of 30 targeted agents available in parallel Phase 2 trials conducted under the NCI-MATCH umbrella. The results of NGS assays on freshly biopsied tumors guided the assignment of patients to a treatment option hypothesized to target

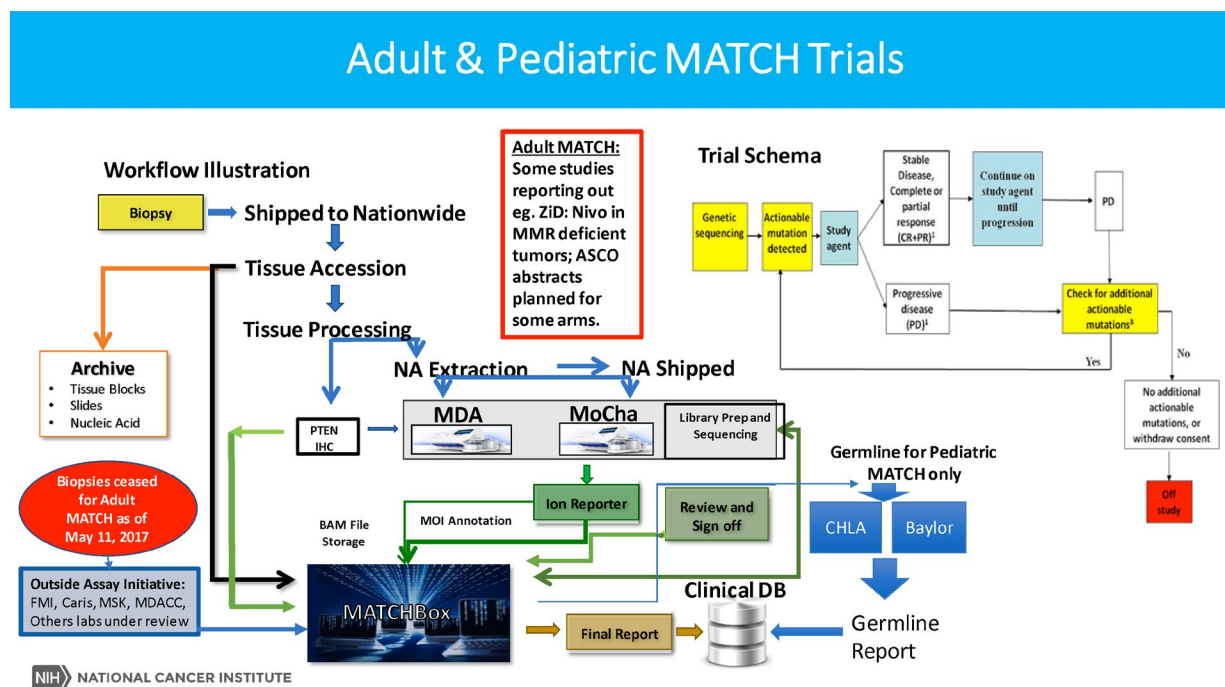
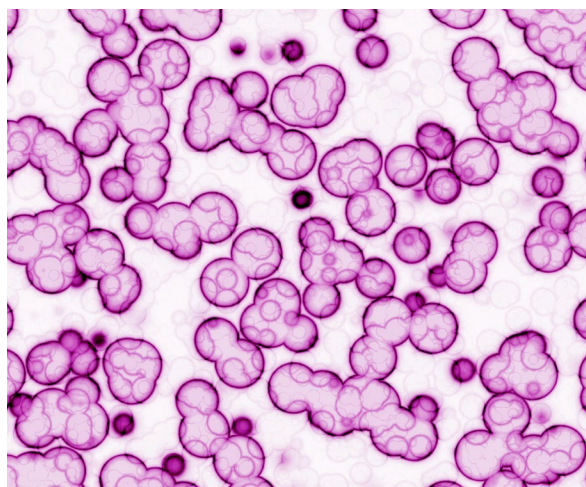


FIGURE 2: NCI-MATCH TRIALS.

Flow chart based on patient tumor mutation analysis and clinical response. Yellow boxes, genomic analysis; blue boxes, clinical decision points; red box, patient taken off trial.



the specific molecular abnormality in their tumor. Agent selection based on the molecular findings of the biopsy was rule driven in the protocol rather than based upon decisions by a tumor board. In the event of more than one mutation or abnormality in a patient's tumor, decision rules were developed to select which genetic abnormality, and therefore treatment option, would predominate.

NCI-MATCH is evaluating Food and Drug Administration (FDA)-approved agents outside of their approved indication, as well as investigational drugs that are not yet approved but have demonstrated evidence of activity against a known target in a specific human tumor. An agent known to be inactive in a certain type of cancer (i.e., BRAF inhibitors of the V600E mutation in colon cancer) is not evaluated in those patients. Conversely, NCI-MATCH also does not compete with currently open NCI-sponsored trials or trials by NCI's pharmaceutical partners. For example, BRAF inhibitors have been shown to be effective in melanomas containing the BRAF V600E mutation, but it is not known if other cancer types with the same mutation are as responsive. Thus, a sarcoma patient with a BRAF V600E mutation, but not a melanoma patient with the same mutation, could receive treatment with a BRAF inhibitor in this study. Similarly, a melanoma patient, but not a breast cancer patient, with a human epidermal growth factor receptor 2 (HER2) amplification could be treated with a HER2-targeted agent.

Eligible patients have to be greater than 18 years of age, have good performance status and adequate organ function, and a solid tumor or lymphoma that has progressed on at least one

standard therapy for metastatic or advanced disease. Patients must be willing and able to undergo a re-biopsy of their tumor before enrolling on the study. Following assignment to a specific study drug based on the molecular abnormality of their tumor, patients are subsequently evaluated for tumor response and progression-free survival (PFS). Each arm of the trial will ultimately have approximately 30 evaluable patients receiving the same agent, all of whom meet the molecular eligibility criteria, but do not necessarily have the same tumor type. Patients whose tumors progress are removed from the study. They and their doctor will receive a report of the molecular analyses performed in the CLIA laboratory, including a list of the genes tested, in the hope that the information may be useful for future treatment choices. Additionally, any patient with progressive disease is eligible for re-biopsy to identify potential new actionable mutations for which another targeted study agent would be appropriate. One goal of NCI-MATCH is to find signals of activity with targeted agents in a wide variety of histologies. Additional follow-up Phase 2 studies are likely to be needed to evaluate any active targeted agent(s) in a larger number of patients with both the precise molecular abnormality and the histologies that showed a good response to determine if and where the agent will be of ultimate value.

NCI-MATCH is available to all members of the four NCTN Adult Groups. ECOG-ACRIN leads the study in partnership with NCI, and it is accessible via the CTSU. The study received 6,397 patient referrals and performed molecular profiling for the 5,962 patients who sent in biopsy samples. With a 93% assay success rate, a total of 992 patients could be

matched to a therapy based on the molecular abnormalities found in their tumors. Due to the high rate of accrual (over 100 patients screened weekly), enrollment occurred more rapidly than expected, and the biopsy phase of the study was closed in May of 2017. An *interim demographic analysis* of the first 795 patients is available.

Outside Assay/Rare Variant Initiative

While the high rate of accrual enabled NCI-MATCH to successfully reach its goal of screening nearly 6,000 patients, there remained arms that were not yet “filled” at that point, particularly in rarer tumors. The Outside Assay / Rare Variant initiative was thus conceived to help complete accrual to those arms using a different mechanism for molecular profiling. During the time that NCI-MATCH has been open, the availability to NGS tumor profiling has expanded through commercial companies and academic laboratories. As many patients are now opting to have their tumor sequenced, the decision was made to work with designated laboratories outside of the NCI-MATCH laboratory network. Two commercial companies (Foundation Medicine Inc. and Caris Life Sciences) and three academic laboratories (MD Anderson Cancer Center, Massachusetts General Hospital and Memorial Sloan Kettering) would notify the ordering physician of patients who are potentially eligible for an NCI-MATCH treatment arm. Additional laboratories are also being recruited to refer patients to NCI-MATCH.

Interested and eligible patients will have their outside assay result confirmed using the NCI-MATCH assay on an archived tissue specimen, preferably from the same tissue that was analyzed by the outside laboratory. Patient enrollment and treatment on the appropriate trial arm, however, will not be delayed pending confirmation.

While the primary goal of this initiative is to enable complete enrollment of the rare variant arms of the NCI-MATCH trial, a secondary outcome is setting the stage for Precision Medicine trials in the future by aligning trials with current practices in the genetic analysis of tumors.

NCI-COG Pediatric MATCH

The NCI-COG Pediatric MATCH trial (Figure 2) is enrolling children with advanced cancers that have progressed or recurred on standard therapy. As in the adult NCI-MATCH

trial, DNA sequencing will be used to identify children and adolescents between the ages of 1 to 21 years whose tumors have a genetic abnormality for which either an approved or investigational targeted therapy exists. Pediatric MATCH is led by the NCTN Children’s Oncology Group and opened for accrual in July of 2017. Patients with all types of solid tumors are eligible for the trial, including central nervous system tumors and non-Hodgkin lymphomas as well as histiocytic disorders, as long as tissue is available from the time of tumor recurrence or progression. In the case of brain stem gliomas, a diagnostic biopsy can be submitted. The trial opened initially with seven treatment arms, with the intention to add several more shortly thereafter. A minimum of twenty patients will be enrolled on each treatment arm, with the ability for expansion if 3 or more responses are observed. Enrollment is expected to be approximately 200-300 patients per year, with the overall goal of screening a minimum of 1,000 pediatric patients.

Several of the treatment arms include agents never before evaluated in children. Discussions with investigators at the NCI, COG and FDA resulted in the decision that inclusion of such agents in Pediatric MATCH could be considered if an adult recommended Phase 2 dose had been identified and upon careful review of the observed adult toxicities. The pediatric patients are monitored closely for these, and other, toxicities. In this way we hope to be able to offer pediatric patients as many targeted agents as possible.

One of the unique aspects of Pediatric MATCH is the submission of peripheral blood at the time of enrollment for germline DNA sequence analysis. If a genetic abnormality is identified in the tumor, the treating physician will be informed whether it was inherited or arose *de novo*, enabling recommendations for genetic testing/genetic counseling to the family.

Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST)

Agents targeting the epidermal growth factor receptor (EGFR) and the ALK-EML4 fusion protein both result in durable responses and an improvement in PFS in patients with advanced lung adenocarcinoma and the appropriate mutation. This study, which began in 2014, examines whether the addition of erlotinib (EGFR inhibitor) or crizotinib (ALK inhibitor) to standard adjuvant therapy, when indicated, in patients with resectable, early-stage lung cancer (stage

1B – 3A) containing the pathognomonic molecular changes will result in improved survival. Screening of eligible patients occurs under a common, screening study (Figure 3). A polymerase chain reaction (PCR)-based assay identifies EGFR mutations, and the FDA-approved break-apart FISH assay is used to reveal ALK fusions. Patients with tumors exhibiting EGFR activating mutations are randomized to receive standard chemotherapy +/- erlotinib and, similarly, patients with tumors exhibiting the ALK fusion are randomized to receive standard chemotherapy +/- crizotinib. Because EGFR mutation and the ALK fusion occur in only 15% and 5% of early stage lung cancer, respectively, an estimated 8,000 patients will need to be screened in order to identify a patient population large enough to power the randomized clinical trials.

Although there is reason to be hopeful that these targeted therapies will improve patient outcomes, their actual contribution to improving survival is unclear. Only an appropriately sized, randomized trial of this type can answer this question definitively. That being said, however, a large percentage of these patients, perhaps half, are unfortunately destined to relapse, so better therapy is indeed necessary. This study enters all patients screened into a registry for long-term follow-up. All screened patients are evaluated with an epidemiologic questionnaire, and tumor samples

from their surgical resection are sent for whole exome sequencing (WES) and other “omic” research tests. All patients are followed until relapse, at which time another tumor sample is procured to evaluate the genomic progression of these treated tumors.

The trial was amended in 2016 to include a third arm using the PD-1 inhibitor, nivolumab, that was proven active in patients with advanced non-small cell lung cancer (NSCLC). Unlike the other two arms of the trial, which are limited to adenocarcinomas, patients with squamous or non-squamous histology are eligible for this arm of the trial. As of the end of 2017, over 2650 patients have been screened for this trial.

Lung Master Protocol (Lung MAP)

This clinical trial design is a novel approach to drug development and regulatory approval as a second-line treatment for advanced squamous cell carcinoma of the lung. Patients whose tumors have progressed after front-line therapy for advanced disease have their treatment selection based upon the molecular profiling results of their tumor from an NGS panel of approximately 250 selected genes. Tumor specimens for profiling can come from a sample derived at diagnosis or at any other point during care. There is no charge to the

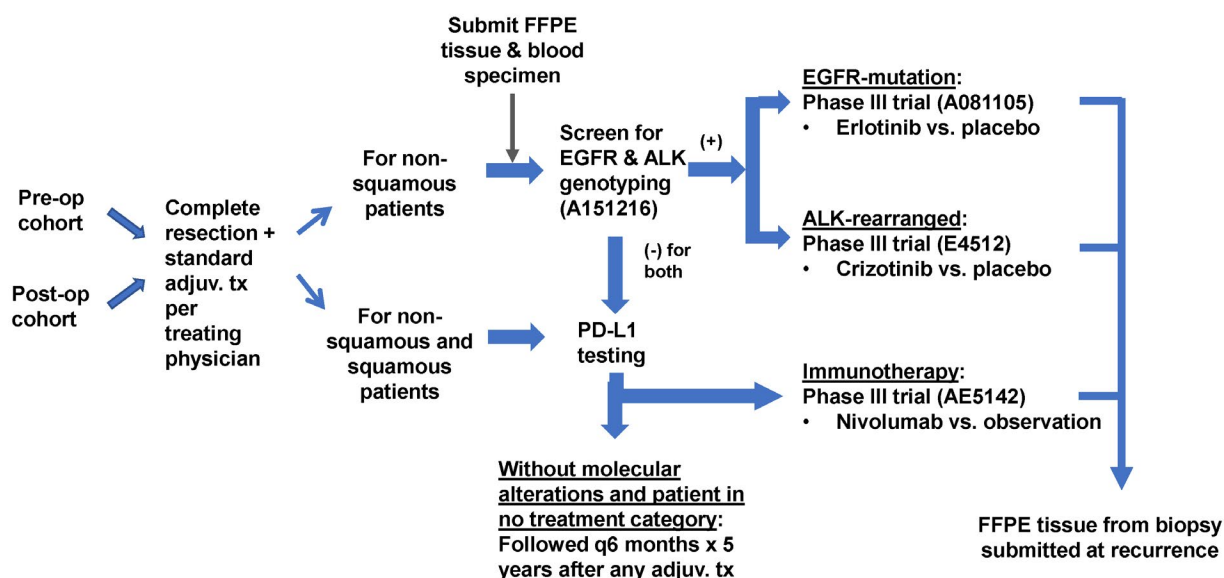


FIGURE 3: ALCHEMIST TRIAL.

Flow diagram based on lung cancer diagnosis and results of gene-specific mutation analysis.

Lung-MAP Schema

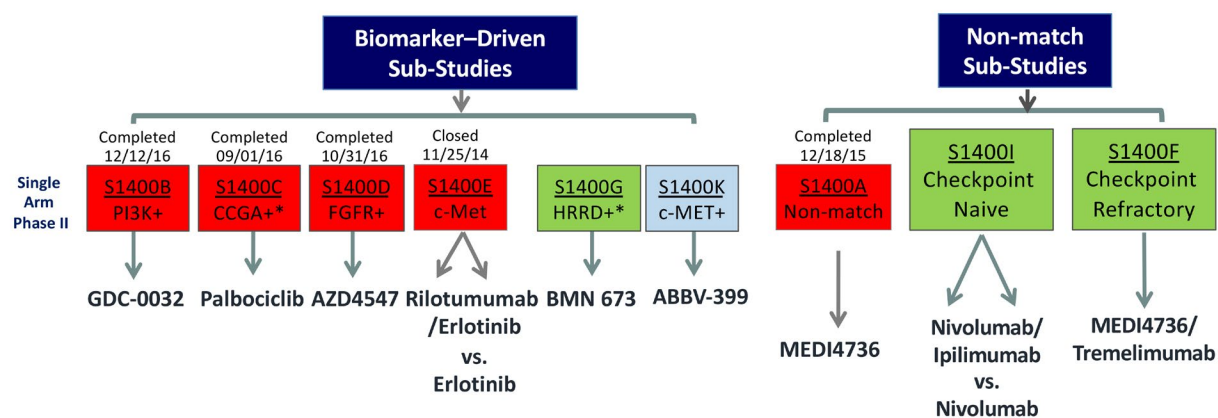


FIGURE 4: FLOW DIAGRAM OF THE LUNG MAP TRIAL WITH DECISIONS MADE ON THE BASIS OF MOLECULAR PROFILING OF AROUND 250 GENES IN THE PATIENT TUMORS.

patient for the molecular profiling, and they are able to obtain their test results if there is progression of their tumor after having received study treatment.

Patients with abnormalities in specific molecular pathways, such as phosphoinositide 3-kinase (PI3K), fibroblast growth factor receptor (FGFR), EGFR, or RAS pathways are treated on a single-arm study with an agent targeting the abnormal pathway. If the patient's tumor profile does not show an abnormality in one of these pathways or their tumor progresses on the targeted therapy, they are eligible to participate in the non-targeted arms of this study, which are currently testing second and third-line immunotherapy regimens.

In view of the relative rarity of these genetic changes, this approach of combining several targeted agents into a single trial represents an efficient way to develop new agents from different companies in the advanced cancer setting by sharing the initial screening expense. The common screening platform effectively allows patients an opportunity to receive a treatment appropriate for their specific tumor and leverages NCI's NCTN to provide accessibility across the United States. SWOG is conducting this study for the NCTN, and it is available via the CTSU. Collaboration between the NCI, SWOG, the Foundation for the National Institutes of Health, the

Friends of Cancer Research, and multiple company partners has enabled the unique framework of this trial design. In addition, FDA has contributed regulatory advice about how best to design and conduct this unique trial. As of the end of 2017, over 1,460 patients have been screened for the trial.

NCI Molecular Profiling Based Assignment of Cancer Therapy (NCI-MPACT)

The goal of this double blind, randomized pilot trial is to establish whether advanced cancer patients who have exhausted standard treatment options with proven benefit, and whose tumors have mutations in one of three genetic pathways (DNA repair, PI3K, or RAS/RAF/MEK), are more likely to derive clinical benefit from treatment with agents targeting their mutated pathway compared to a non-targeted therapy. Each patient is randomly assigned to receive the recommended Phase 2 dose of either a study drug identified to work on their tumor's mutation/aberrant pathway, or an agent from the complementary set not targeting their tumor's specific mutation. The treatment arms are everolimus (PI3K pathway), trametinib (RAS/RAF/MEK pathway), and AZD 1775/carboplatin or veliparib/temozolomide (DNA repair pathway). The objective is to compare the response rate

(complete + partial responses) and/or 4-month PFS of both arms. All patients are biopsied at the time of study entry, and only those with a predefined mutation of interest are enrolled in one of the randomized arms.

The NCI-MPACT trial initially opened at the NCI Developmental Therapeutics Clinic (DTC), within the NIH Clinical Center, to test the feasibility of trial design in 60 patients prior to opening it in the ETCTN at sites across the U.S. In the first 60 patients, 92% of the biopsies were evaluable. At least one actionable mutation was found in 55% of the biopsied patients, and of these patients, 70% started treatment. As of December 2017, this trial has accrued over 191 patients.

In conclusion, these five studies exemplify how NCI is utilizing its ETCTN and NCTN clinical trials networks to conduct large-scale studies that require genetic screening for the detection and targeted treatment of molecular abnormalities that may be infrequent even in common tumors. These NCI-supported networks offer a single registration pathway, a uniform informatics system for data management, and a centralized ethics review board that enable them to perform clinical trials involving specific subsets of patients.

PRECISION MEDICINE INITIATIVE (PMI) – ONCOLOGY SUPPLEMENTS

In 2016, President Obama announced the creation and funding of a Precision Medicine Initiative (PMI) that focused resources in this area for NIH, NCI, and FDA. As part of NCI's contribution to this initiative, DCTD directed the new funding towards expanding its portfolio of genomic-based clinical trials, improving our understanding of resistance to targeted agents and drug combinations, and developing a mechanistic understanding of immunotherapy. The Precision Medicine Initiative in Oncology (PMI-O) was also focused on improving pre-clinical models for evaluating targeted therapeutics. Finally, a major component of this overall effort was the 2016 launch of NCI's Genomic Data Commons (GDC), a data repository that will store and make available complex genomic data to researchers. Molecular data from DCTD-supported clinical trials will be deposited into the GDC in order to foster and encourage data mining and secondary analyses by a broad range of investigators.

To begin this initiative, and to accelerate progress in multiple areas, DCTD announced a series of administrative 1-year supplement awards for 2016. Eligible parent grants for these

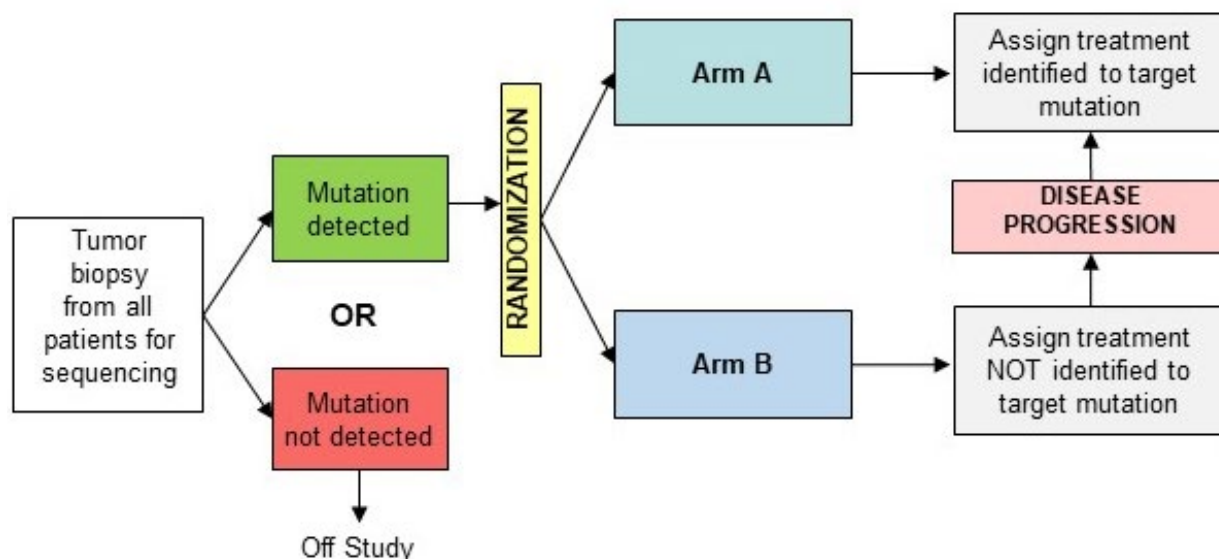


FIGURE 5: SCHEMA FOR THE MULTICENTER NCI-MPACT TRIAL. AN AMENDMENT IS IN PROGRESS THAT WILL ADD AN IMMUNOTHERAPY ARM TO THIS TRIAL FOR ALL PATIENTS WHO DO NOT HAVE A QUALIFYING ACTIONABLE GENETIC MUTATION.

supplements included P30 (Cancer Centers), P50 (SPORES), and UM1 / U10 Cooperative Agreements (ETCTN and NCTN, respectively).

The six scientific areas that were supplemented and the number of supplements provided are listed below:

1. Improvements and Optimization of T-cell Therapies and cGMP Manufacturing Processes for Production of Autologous T-cell Therapy Products Targeting Solid Cancers – 3 awards
2. Biomarker Studies Associated with NCI-supported Clinical Trials of Immunotherapy – 13 awards
3. Mechanisms of Cancer Sensitivity and Resistance to Therapy Utilizing Samples and Information from Human Clinical Trials – 10 awards
4. Administrative Supplements for Research in Canine Immunotherapy via Collaboration of NCI-designated Cancer Centers and Veterinary Medical Colleges – 8 awards
5. Studies of How the Microenvironment of Pancreatic Ductal Adenocarcinoma Affects Immunotherapy – 9 awards
6. Collaborative Research Efforts to Enhance Preclinical Drug Development and Preclinical Clinical Trials Utilizing Patient Derived Xenograft (PDX) Models – 10 awards

In total, 53 awards were made for this supplement initiative from a total of 144 applications.

NCI NATIONAL CLINICAL TRIALS NETWORK (NCTN)

On March 1, 2014, after several years of extensive consultation and coordination with numerous stakeholders, NCI transformed its longstanding Cooperative Group Clinical Trials program into the new **NCTN** for the conduct of large-scale, national oncology treatment and advanced imaging clinical trials in the era of precision medicine.

Recent advances in deciphering the cancer genome that enabled the development of targeted therapies, such as ima-

tinib (Gleevec®), erlotinib (Tarceva®), crizotinib (Xalkori®), and vemurafenib (Zelboraf®), along with the emergence of successful immunotherapies, such as nivolumab (Opdivo®), pembrolizumab (Keytruda®), and ipilimumab (Yervoy®), have fundamentally changed our approach to cancer treatment and have introduced new challenges to performing clinical trials. To effectively treat cancer with targeted therapies, the molecular signature of an individual's tumor must first be diagnosed with sophisticated genetic techniques; only then can an appropriate therapy be selected. Due to the low incidence of certain molecular abnormalities, the development of targeted therapies often requires cancer clinical trials that can screen large numbers of patients with the same or different cancer type to identify those patients whose tumors contain the distinct molecular targets of the therapies being tested. Immunotherapeutic approaches also present a similar challenge in that not all tumor types respond to this approach, and selecting the cancer types most likely to respond is critical for success.

With its state-of-the-art clinical trials infrastructure, the NCTN is poised to implement and complete trials far more rapidly than in the past. For physicians and their patients, important trials will be widely available throughout the country, in large cities and small communities alike. The NCTN has streamlined trial registration, data management, and tumor banking processes. It has a Clinical Trials Support Unit (CTSU) to provide online access to all materials and a central institutional review board (CIRB) to make ethics review easier and less redundant across the country. NCTN offers access to innovative clinical trials that are available for many common and an increasing number of rare cancers. The restructured program also has appeal for industry partners as evidenced by the large number of biotechnology and pharmaceutical companies collaborating on a series of precision medicine trials harnessing next generation DNA and RNA sequencing methods to inform treatment choices. NCTN's resources are ideal for screening large numbers of patients to identify patients whose tumors exhibit the molecular features that may be responsive to new, targeted treatments and/or immunotherapy approaches. In addition, biospecimens collected from patients on these trials may help determine the underlying biological reasons for response and resistance to therapy.

Scientific Oversight Committees

The NCTN Groups propose concepts for new clinical trials, based upon preclinical and early phase research, to the NCI Disease / Imaging Steering Committees, which NCI organized to evaluate and prioritize new clinical trials. Each committee is led by non-governmental co-chairs who are not permitted to hold a leadership position in any of the NCTN Groups, although they can be group members. The remainder of the committee membership consists of NCTN group members selected by each group, representatives of NCI-funded Specialized Programs of Research Excellence (SPOREs) and Consortia, biostatisticians, patient advocates, and NCI disease and biostatistical experts. These committees evaluate and recommend to NCI those concepts most likely to have the highest scientific and clinical impact.

NCTN Organizational Structure

The NCTN includes five U.S. Network groups and the Canadian Collaborating Clinical Trials Network. Membership in an NCTN group is based on criteria as defined individually by each group. Sites can belong to more than one group, and

membership in at least one group allows a site to participate in the trials led by any NCTN group for which their investigators are qualified. Consequently, researchers from the Lead Academic Participating Sites (LAPS), NCI Community Oncology Research Program (NCORP) sites, other academic centers, community practices, and international sites that are full member of a Network group may all enroll patients onto any NCTN trials if the sites meet all trial-specific requirements. In addition, clinical trials led by NCTN Groups may utilize the Imaging and Radiology Oncology Core (IROC) Group and the tissue banks when appropriate to support the scientific needs of the trials.

NCTN Groups and Canadian Collaborating Clinical Trials Network:

- Alliance for Clinical Trials in Oncology
- ECOG-ACRIN Cancer Research Group
- NRG Oncology
- SWOG
- Children’s Oncology Group (COG)
- Canadian Cancer Trials Group (CCTG)

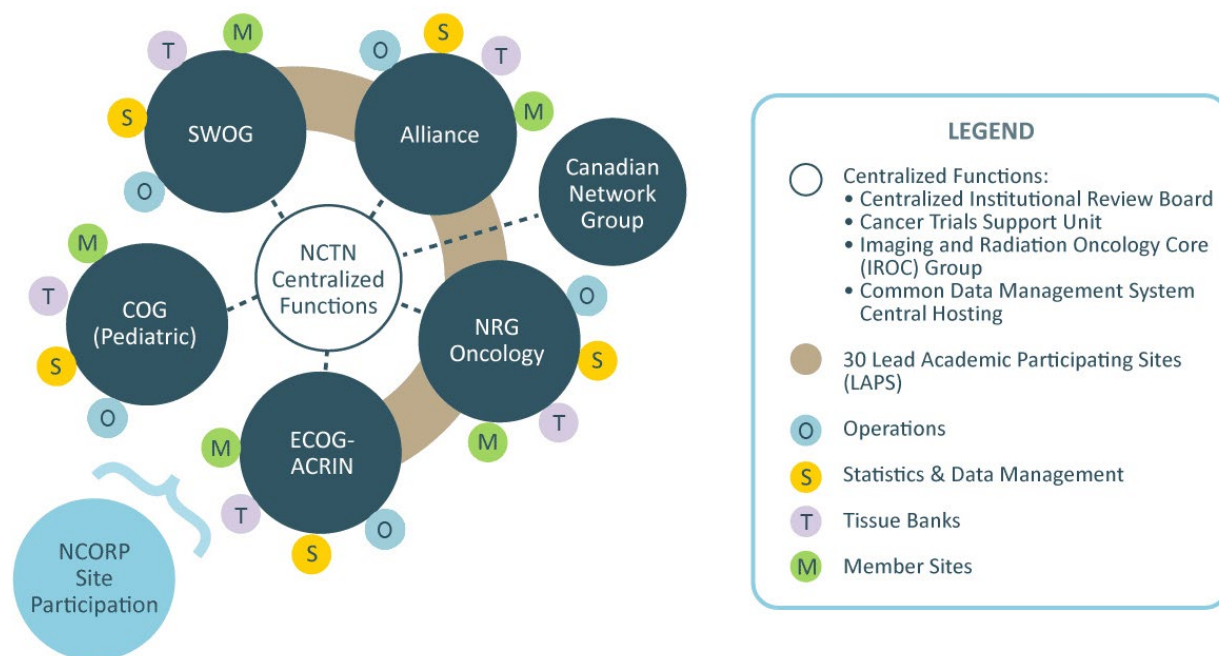


FIGURE 6: NCI NATIONAL CLINICAL TRIALS NETWORK STRUCTURE.

The NCTN Group Operations Centers are responsible for developing new protocols and managing the regulatory, financial, membership, and scientific committees of each group as well as the conduct of the studies the group leads, including safety monitoring. The NCTN Group Statistical Centers are responsible for data management and analysis, manuscript preparation, and study monitoring, in addition to assisting in trial design and development. The Canadian Network Group partners with the U.S. Network Groups in the conduct of select, late-phase, multi-site clinical trials.

Each NCTN Group collects and stores tissue from consented patients in NCTN trials using a harmonized network of tissue banks to facilitate additional research linking outcomes to molecular diagnostics. Standard protocols ensure that the tissues meet the high quality standards required for analysis in the studies. Computerized records of the stored samples contain important deidentified clinical data, such as the patients' treatments, treatment responses, and outcomes. Patients in NCTN trials may also consent to the use of their tissue specimens for studies beyond the NCTN trial in which they are enrolled. The NCTN Tissue Bank Program is also developing a controlled access, web-based data access tool

that will be available in 2018. Researchers, including those not affiliated with the NCTN, will be able to query the availability of specific tissues and request review and approval to obtain tissue samples for translational science studies.

NCTN Sites

Over 2,500 NCTN sites from across the United States enroll patients in clinical treatment trials. These sites are augmented by member sites from the Canadian Collaborating Clinical Trials Network and other international member sites. The map below illustrates the location of U.S. sites.

Community Hospitals and Medical Centers

Many investigators at community hospitals and medical centers participate in NCTN clinical trials. These sites, as well as a number of international sites, either receive research reimbursement for their participation in NCTN trials directly from one of the NCTN Groups with which they are affiliated, or they receive direct awards from the newly developed **NCORP**. NCI's Division of Cancer Prevention (DCP)

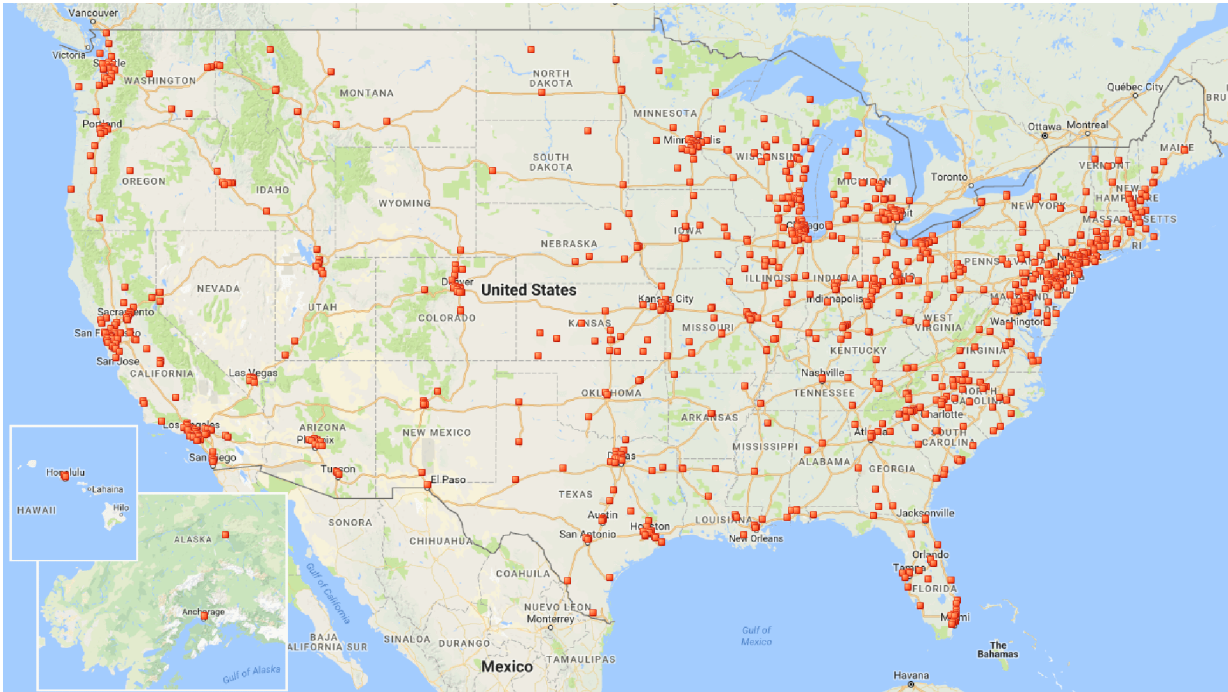


FIGURE 7: NCTN SITES THAT ENROLLED PATIENTS IN 2014.

consolidated their Community Clinical Oncology Program (CCOP), Minority-Based Community Oncology Program (MBCCOP), and NCI Community Cancer Centers Program (NCCCP) into the unified NCORP program for the support of community clinical trial participation.

Lead Academic Participating Sites (LAPS)

Thirty U.S. academic research institutions were selected as LAPS. These sites have fellowship training programs with a demonstrated ability to enroll high numbers of patients onto NCTN trials, as well as to provide scientific leadership in their design and conduct. The LAPS grant component of the NCTN provides additional support to the selected institutions for the increased level of patient data management work required as a result of their high enrollment rate.

The 30 LAPS are:

- Case Western Reserve University – Case Comprehensive Cancer Center
- Dana Farber/Harvard Cancer Center
- Duke Cancer Institute at Duke University Medical Center
- Emory University – Winship Cancer Institute
- Fred Hutchinson Cancer Research Center
- Indiana University Cancer Center
- Johns Hopkins University – Sidney Kimmel Comprehensive Cancer Center
- Mayo Clinic Cancer Center
- Memorial Sloan Kettering Cancer Center
- Norris Cotton Cancer Center at Dartmouth Hitchcock Medical Center
- Ohio State University Comprehensive Cancer Center
- Roswell Park Cancer Institute
- Stanford University – Stanford Cancer Institute
- University of Alabama at Birmingham
- University of California Davis Comprehensive Cancer Center
- University of Chicago Comprehensive Cancer Center
- University of Colorado Cancer Center
- University of Michigan Comprehensive Cancer Center
- University of North Carolina Lineberger Comprehensive Cancer Center
- University of Oklahoma – Stephenson Cancer Center
- University of Pittsburgh Cancer Institute
- University of Southern California – Norris Comprehensive Cancer Center
- University of Texas MD Anderson Cancer Center
- University of Texas Southwestern Medical Center – Harold C. Simmons Cancer Center
- University of Utah – Huntsman Cancer Institute
- University of Wisconsin Carbone Cancer Center
- Vanderbilt University Medical Center – Vanderbilt Ingram Cancer Center
- Washington University at St. Louis – Siteman Cancer Center
- Wayne State University Barbara Ann Karmanos Cancer Institute
- Yale University – Yale Cancer Center

Integrated Translational Science Awards

The NCTN contains a translational component, consisting of seven academic institutions funded through an Integrated Translational Science Award (ITSA) to support teams of translational scientists. These teams use innovative genetic, proteomic, and imaging technologies to help identify and qualify potential predictive biomarkers of response to therapy that the NCTN Groups can incorporate into future clinical trials. These awards leverage ongoing work in the investigators' laboratories, which is often supported in part by other NCI grants, to assist the NCTN Groups to bring new laboratory discoveries into clinical trials. These laboratories employ cutting-edge technologies that characterize tumors and identify changes in tumor biology in response to treatment that may help explain mechanisms of treatment resistance.

The seven ITSA-funded institutions are:

- Children’s Hospital of Philadelphia
- Cold Spring Harbor Laboratory Cancer Center
- Emory University – Winship Cancer Institute
- Montefiore Medical Center
- Ohio State University Comprehensive Cancer Center
- University of North Carolina Lineberger Comprehensive Cancer Center
- Washington University at St. Louis – Siteman Cancer Center

Imaging and Radiation Oncology Core (IROC)

To help monitor and ensure quality in trials that involve new imaging modalities and/or radiation therapy, the NCTN established a consolidated IROC to assist NCTN Groups using these modalities in their trials. The consolidation of these activities under the leadership of a centralized core team improves efficiency and optimizes the use of these resources by the entire network. This unique Quality Assurance (QA) entity brings together imaging QA leaders and specialists into a single, coordinated program designed to

support the NCTN and other NCI-sponsored groups and networks to carry out rigorous oncologic multi-center clinical trials. Within the context of NCI-sponsored trials, the IROC is tasked to provide:

- Scientific expertise in advanced medical imaging, radiotherapy, and information technology to support establishment of appropriate QA procedures
- Consultation to the NCTN Groups in the development of research protocols early on in the process to assist with hypothesis generation and trial design that can be supported by effective QA programs
- Resources for the efficient collection, qualification, analysis, archive and transfer of images, radiotherapy plans and associated clinical data
- Qualification and credentialing policies and to help ensure the delivery of appropriate protocol-specified radiotherapy and advanced imaging

Medical officers and program directors of the Clinical Trials Branch (CTB) of DCTD’s Cancer Imaging Program developed the IROC RFA for imaging. CTB continues to be involved in its operations and advises IROC as a member of the IROC Advisory Committee.

NCTN Statistics

Phase	Grant Year 1 (3/1/2014 to 2/28/2015) Studies/Screened/Accrued	Grant Year 2 (3/1/2015 to 2/28/2016) Studies/Screened/Accrued	Grant Year 3 (3/1/2016 to 2/28/2017) Studies/Screened/Accrued	Grant Year 4 (3/1/2017 to 2/28/2018) Studies/Screened/Accrued
Phase 1	13 / 0 / 155	6 / 0 / 158	7 / 3 / 77	5 / 23 / 65
Phase 2	95 / 221 / 2,606	110 / 767 / 2,673	114 / 967 / 2,620	105 / 565 / 2,548
Phase 3	84 / 1,150 / 13,119	80 / 1,841 / 11,157	75 / 1,730 / 11,506	80 / 1,912 / 12,349
Other/Pilot	7 / 268 / 379	7 / 1,859 / 1,876	7 / 5,746 / 2,669	6 / 3,219 / 1,300
Total	199 / 1,639 / 16,259	203 / 4,467 / 15,864	203 / 8,446 / 16,872	196 / 5,719 / 16,262
Total # Unique Patients	17,246	18,553	22,089	17,298

TABLE 1: TOTAL NUMBER OF NCTN TREATMENT & ADVANCED IMAGING TRIALS OPEN TO RECRUITMENT, NUMBER OF PATIENTS SCREENED ON STUDY, AND NUMBER OF PATIENTS ACCRUED TO THE INTERVENTION FOR EACH YEAR OF THE NCTN GRANT.

*The NCTN replaced the former Cooperative Group program on March 1, 2014. These figures show the number of studies, number of patients screened on study, and number of patients who received the study intervention for the first four grant years of the NCTN. The unique number of patients includes those who were screened on study and / or received the study intervention.

Year Approved for Indication	Drug	Sponsoring Organization	Cancer Site
2004	Letrozole	NCIC Clinical Trials Group (Canadian Cancer Trials Group)	Breast
2004	Oxaliplatin	North Central Cancer Treatment Group (Alliance for Clinical Trials in Oncology Group)	Colorectal
2004	Taxotere	SWOG	Breast
2004	Nelarabine	Children's Oncology Group	Leukemia
2006	Bevacizumab	Eastern Cooperative Oncology Group (ECOG-ACRIN Cancer Research Group)	Colorectal. Lung
2006	Trastuzumab	National Surgical Adjuvant Breast and Bowel Project, North Central Cancer Treatment Group (NRG Oncology, Alliance for Clinical Trials in Oncology Group)	Breast
2006	Dasatinib	SWOG	CML
2006	Sunitinib	ECOG	Renal Cell
2007	Lapatinib	North Central Cancer Treatment Group, Cancer and Leukemia Group B (Alliance for Clinical Trials in Oncology Group)	Breast
2008	Imatinib mesylate	American College of Surgeons Oncology Group (Alliance for Clinical Trials in Oncology Group)	Gastrointestinal stromal tumor
2009	Bevacizumab	Cancer and Leukemia Group B (Alliance for Clinical Trials in Oncology Group)	Renal Cell
2014	Bevacizumab	Gynecologic Oncology Group (NRG Oncology)	Cervix
2015	Dinutuximab	Children's Oncology Group	Neuroblastoma
2017	Lenalidomide	Alliance for Clinical Trials in Oncology Group	Multiple myeloma
2017	Midostaurin	Alliance for Clinical Trials in Oncology Group	AML
2017	Cabozantinib	Alliance for Clinical Trials in Oncology Group	Renal cell
2018	Bevacizumab	NRG Oncology	Ovarian

TABLE 2: SELECTED NCTN TRIALS SUPPORTING FDA-APPROVED INDICATIONS.

Compressing Timelines for Development of CTEP-supported Cancer Treatment Trials

The Operational Efficiency Working Group (OEWG) was established in 2005 to advise the NCI on (i) strategies to identify institutional barriers that prolong the time from initial approval of a study proposal to opening the study for patient enrollment, and (ii) to develop solutions to help overcome these barriers. This collaborative effort included representatives from the CTEP-supported clinical trials network programs (both early and late-phase networks), Cancer Centers, and other NCI Programs and Divisions. The OEWG established specific protocol development guidelines based on study phase. Phase I and Phase 2 studies now have a target development timeline (i.e., the time from initial review of the study proposal to opening of the study to patient enrollment) of 210 days. Phase 3

studies have a target development timeline of 300 days. Trials not activated within 450 and 540 days, respectively, are automatically disapproved.

Funding was provided to network sites for new staff positions to monitor the protocol development process and institute strategically planned conference calls between NCI staff and its investigators to quickly resolve any timeline bottlenecks. CTEP's Clinical Trials Operations and Informatics Branch (CTOIB) also developed a web-based service for investigators with 24/7 online access to information about the status of their protocols during the review/approval and protocol development process.

Following institution of the OEWG timeline processes in April 2010, development times for Phase 1-2 studies between April 2010 and May 2012 decreased by 18.3% from the his-

torical median. The initial experience with Phase 3 studies, although more limited, demonstrated a 45.7% decrease from the historical median¹. It is anticipated that with more experience, continued reduction in protocol development timelines will be achieved. A new initiative to further speed up trials conducted in the ETCTN will provide drafts of initial protocols based on the objectives, goals, and background for the study set out by the principal investigators, incorporating all of the standard template language required by the NCI's Central IRB. It is expected that standardized protocol authoring will shorten the timeline for opening an early phase study by two to three months.

Stopping Guidelines for Slow Accruing Clinical Treatment Trials

Guidelines were also developed by NCI to monitor accrual to CTEP-supported cancer treatment trials after studies are opened for patient enrollment. These guidelines were first developed for Phase 3 trials based on the historical experience of 239 CTEP-sponsored Phase 3 trials initiated on or prior to 2000 that were open for more than 15 months. Overall trial success was judged by whether the final trial accrual was over 80% of projected. Based on development of a validated model from historical experience, a cut-off of less than 20% of the projected accrual by quarters 5 and 6 after study opening was selected as the basis for termination of a study due to poor accrual. These guidelines were instituted in 2010 to monitor accrual on all Phase 3 trials and to close a trial if this minimum level of accrual is not reached. Aggressive early interventions are instituted if it appears that a Phase 3 trial is at risk of not meeting this accrual milestone. Additional monitoring of the study continues throughout its accrual phase with appropriate interventions made as needed if accrual appears too slow.

A similar process was undertaken by NCI to establish stopping guidelines for CTEP-supported early phase clinical trials (i.e., Phase 1, 1/2, and 2 trials). These early phase studies are monitored through completion of quarter 2 accrual, and a Corrective Action Plan (CAP) is developed if the study has accrued less than 50% of the total patients at that time. Study accrual rates are re-evaluated 6 months after the implementation of the CAP to ensure the accrual rate is adequate, and if not, the study may be closed. As with Phase 3 trials, aggressive early interventions are instituted if it appears a trial is at



risk of not achieving adequate accrual to complete the study in the time projected by the investigators.

NCI EXPERIMENTAL THERAPEUTICS CLINICAL TRIALS NETWORK (ETCTN)

Since the early 1970s, CTEP has managed an early phase experimental therapeutics program that has contributed to the clinical development of many anticancer agents. Through this program, hundreds of agents, both conventional and immunologic, have been made available for collaborative development. CTEP currently holds approximately 100 Investigational New Drug Applications (INDs) for investigational agents. Effective development of these agents requires a systematic development plan for Phase 1 and pilot trials, followed by Phase 2 trials that, it is hoped, will conclude in definitive Phase 3 trials. NCI has formed partnerships with the pharmaceutical industry, academic institutions, and individual investigators for the early clinical evaluation of innovative cancer therapies. In 2014, the ETCTN was created to evaluate these therapies using a coordinated, collaborative, and inclusive team-based approach to early phase experimental therapeutic clinical trials.

The objectives of the ETCTN are to:

- Conduct early clinical trials of NCI-IND agents in high priority areas of unmet medical need
- Ensure efficient and timely activation and conduct of these clinical trials

¹ Abrams JS, et al; *J Natl Cancer Inst* 2013 Jul 3;105(13):954-9

- Integrate preclinical findings using clinical samples for biomarker analysis
- Promote collaboration among institutions and investigators
- Integrate molecular characterization, pharmacology, cancer biology, and imaging into clinical trials

ETCTN clinical sites (Figure 8) participate in the Phase 1 and Phase 2 Programs, which are supported by NCI UM1 grants and cooperative agreements as supplements to the existing UM1 grants, respectively. By integrating Phase 1 and Phase 2 Program activities and administrative operations under the UM1 structure, ETCTN awardees have the flexibility to expand Phase 1 studies quickly upon the detection of early activity.

The development of a robust infrastructure to support the conduct of trials in the network has been critical to the success of the ETCTN. The components of the ETCTN infrastructure are depicted in Figure 9 and described in greater detail below.

Program Infrastructure

1. CTEP-Identity and Access Management (CTEP-IAM)

Investigators and Associates register for an account that enables access to the other applications (CTSUS, OPEN/IWRS, Rave, CTEP Enterprise).

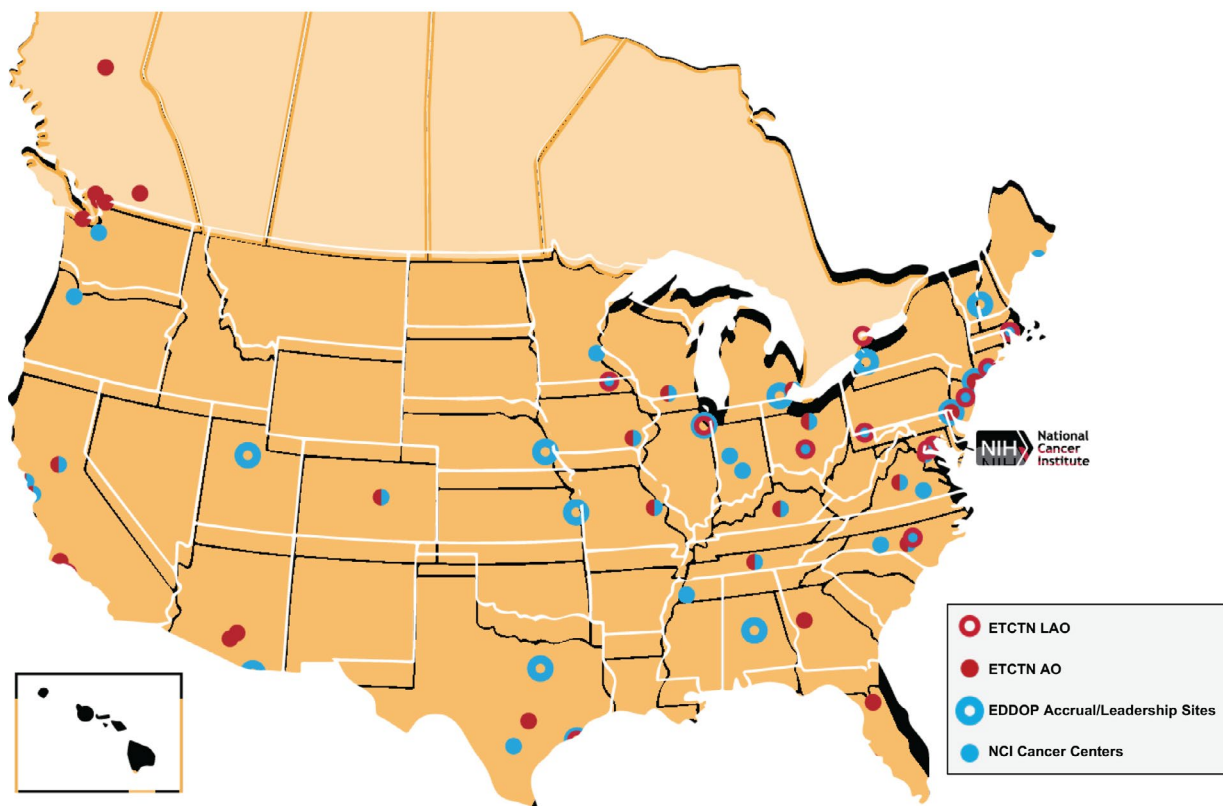


FIGURE 8: ETCTN PHASE 1 AND PHASE 2 PROGRAM SITES.

LAO = Lead Academic Organization; AO = Academic organization; EDDOP = NCI Early Drug Development Opportunity Program

2. **Cancer Trials Support Unit (CTSU)**
Provides a variety of services, including a roster of institutions and medical personnel; website support for posting of protocols and other information; and links to other services (OPEN/IWRS, Rave).
3. **NCI Central Institutional Review Board (CIRB)**
Conducts IRB review of most early-phase NCI-sponsored trials, including ETCTN studies.
4. **Oncology Patient Enrollment Network (OPEN)/Interactive Web Response System (IWRS)**
Linked applications for patient enrollment (OPEN), slot reservations, and cohort management (IWRS). Data are automatically transferred to Medidata Rave.
5. **Medidata Rave**
An application for data entry, data analysis, and clinical trial management.
6. **CTEP Enterprise System**
An application for integrated clinical trials management and reporting, including Serious Adverse Event (SAE) reporting through the CTEP-Adverse Event Reporting System (CTEP-AERS); ordering of investigational agents; trial monitoring/audits; and Operational Efficiency Working Group (OEWG) reporting.
7. **Regulatory Support Services (RSS)**
Serves as a centralized repository for regulatory documents associated with all NCI-supported multi-center clinical trials. The RSS provides a streamlined and comprehensive approach to collecting and maintaining site registration, person, and institution documentation essential to the management of clinical trials.

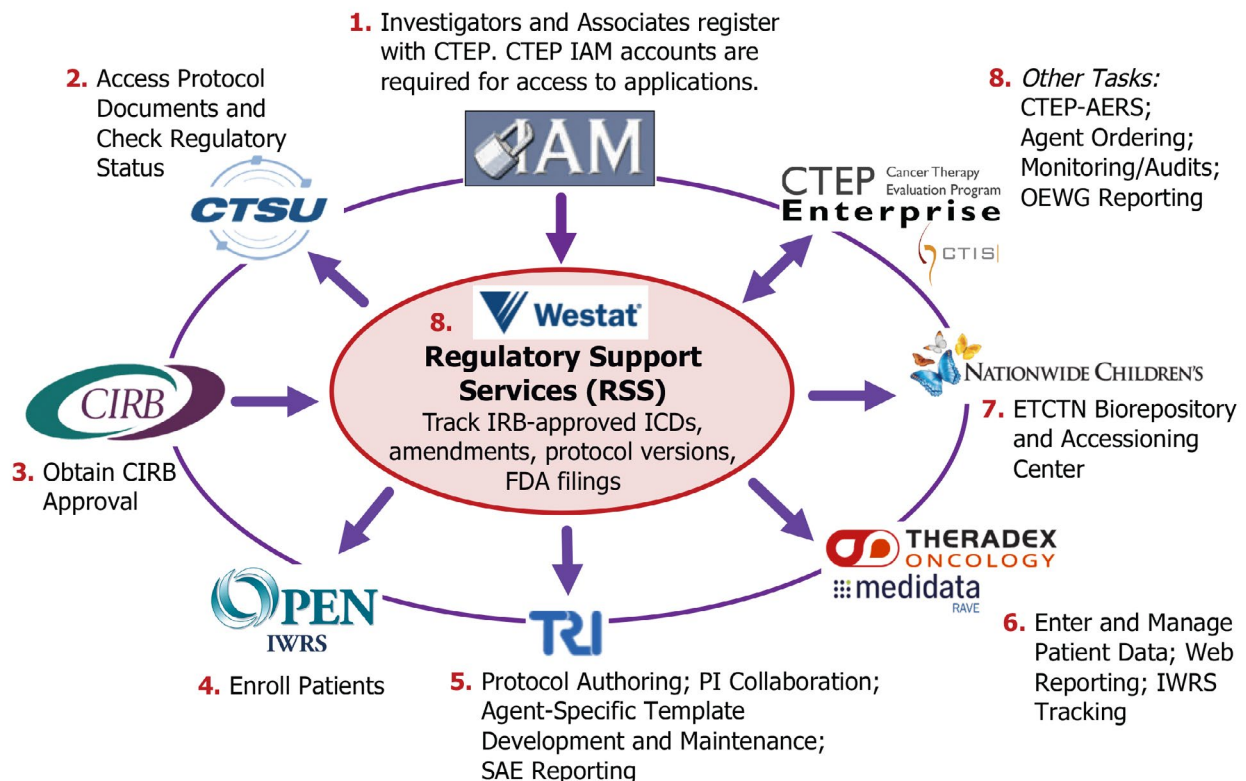


FIGURE 9: CENTRALIZED SUPPORT SERVICES FOR ETCTN.

IT data software systems provide the necessary infrastructure to support the access and reporting requirements for NCI-supported clinical trials.

Activity Summary

From 2013 to 2017, investigators submitted 376 letters of intent (LOI); 109 of these were submitted in response to four mass solicitations issued in 2013 and 2014. During this time-period, the following occurred within CTEP-sponsored early-phase trials:

- Twelve ETCTN project teams were implemented with 14 agents, another 14 agents went through limited drug development.
- 455 PTMA applications were received, 110 were approved.
- 94 of 376 (25%) LOI submissions were approved for protocol development.
- Thirty-two studies were administratively completed (12 were Phase 1 trials).
- Seventy-eight trials were completed (45 were from Phase 1 studies).
- 117 trials were closed to accrual or accrual and treatment (74 were Phase 1 studies).
- Other studies completed or closed were pilot studies, Phase 1/2 investigations, or early Phase 2 studies that fit within the scope of the work performed using ETCTN UM1 grant funding.

Currently, there are 88 active trials (includes ETCTN and legacy U01) of 52 investigational agents and 54 combinations with one or more NCI investigational agents. The CTEP Phase 1 or 1/2 trials account for 60% of Phase 1 trials (excluding pediatric studies) performed under NCI sponsorship.

The agent classes studied under the ETCTN include novel agents that target relevant cancer cell signaling pathways, as well as essential cellular machinery involved in the regulation of cell survival and apoptosis, proliferation, and differentiation. Agents include inhibitors of cancer stem cells, tyrosine kinases, epidermal growth factor receptor, angiogenesis, mTOR, cell cycle progression, histone deacetylases, the proteasome, heat shock proteins, poly(ADP-ribose) polymerase (PARP), angiotensin 1 and 2, as well as some novel cytotoxic agents. Types of agents under evaluation include small molecules, antibodies, antibody–drug conjugates, vaccines, and an oncolytic virus.

The ETCTN also includes studies of special populations (organ dysfunction), novel study designs (accelerated titration, isotonic design, continual reassessment method, and

other various randomized designs), and unique translational efforts [pharmacodynamic (PD), pharmacokinetic (PK), NGS]. Ongoing program endeavors include the molecular characterization of all patients as appropriate, increasing consortium collaboration through the ETCTN, and taking a team-based scientific approach to the development of experimental therapeutics projects, as described above.

NCI Early Drug Development Opportunity Program (EDDOP)

Beginning in 2016, investigators from certain NCI-designated Cancer Centers not affiliated with the ETCTN may submit LOIs and, if approved, receive full ETCTN support to conduct the clinical trial. Non-ETCTN NCI Cancer Centers will also be able to compete for administrative supplements to enroll patients on select ETCTN Phase 2 trials. As of December 2017, 15 non-ETCTN NCI Cancer Centers have successfully competed for EDDOP supplements to their Cancer Center grants.

Notable Recent CTEP-Sponsored Early Phase Trials

Protocol 9434: Radiochemotherapy plus 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (Triapine, 3-AP, NSC #663249) in Advanced-Stage Cervical and Vaginal Cancers

Principal Investigator: Charles Kunos, M.D., Ph.D. The Case Western Reserve University, Case Comprehensive Cancer Center

This single-arm Phase 2 trial assessed triapine-cisplatin-radiation treatment in women newly-diagnosed with advanced-stage II-IV uterine cervix cancer. The experimental therapeutic drug, triapine, compared to hydroxyurea, has been established as a 1000x more potent inhibitor of ribonucleotide reductase, a rate-limiting enzyme responsible for new DNA precursors used by the cancer cell for proliferation or repair. Triapine added to standard-of-care cisplatin and radiation treatment resulted in profoundly beneficial cancer cell death as evidenced by clinical examinations and by metabolic radiology imaging. Results indicated stabilization or response in 96% of patients, which was interpreted as a potential major improvement in the management of uterine cervix cancer. A randomized Phase 2 trial in the NCTN is now underway.

Protocol 9825: A Randomized Phase 2 Study of Combination Cediranib and Olaparib Versus Olaparib Alone as Recurrence Therapy in Platinum-sensitive Ovarian Cancer

Principal Investigator: Joyce Liu, M.D., Dana-Farber Cancer Center

This randomized, open-label, Phase 2 study evaluated the activity of olaparib monotherapy compared with combination cediranib and olaparib in women with ovarian cancer with measurable platinum-sensitive, relapsed, high-grade serous or endometrioid disease or those with deleterious germline BRCA1/2 mutations (gBRCAm). The combination of cediranib and olaparib significantly extended PFS by 8.7 months compared to olaparib alone in recurrent platinum-sensitive ovarian cancer. Moreover, patients with germline wild-type BRCA1/2, who were not expected to benefit from the PARP inhibitor olaparib, experienced significant benefit when treated with the drug combination. This combination is now being studied in larger Phase 3 and Phase 2/3 trials in patients with platinum-sensitive and platinum-resistant ovarian cancer, respectively.

Protocol 9673: A Multi-Institutional Phase 2 Study of Nivolumab in Refractory Metastatic Squamous Cell Carcinoma of the Anal Canal

Principal Investigator: Cathy Eng, M.D., MD Anderson Cancer Center

The incidence of squamous cell cancer of the anal canal (SCCA) continues to rise annually in the US. About 20% of patients will develop metastatic disease, which lacks a consensus approach to treatment. SCCA is largely driven by immune evasion of human papillomavirus (HPV)-specific CD8 and CD4 T cells that promote oncogenesis. In this NCI-sponsored multicenter Phase 2 trial, patients with previously treated refractory metastatic SCCA, but immunotherapy naïve, were enrolled in a Simon two-stage design trial. Patients received intravenous nivolumab [3 mg/kg] every 2 weeks, with optional pre-treatment and on-treatment collection of tissue biopsies and plasma samples for measuring immune biomarkers and HPV/p16 status. Ultimately, 37 patients were enrolled, with a median age of 56 years, of which 33 patients were evaluable for response. Seven

(21%) patients had a partial response (PR), and 19 (58%) patients had stable disease. Ten patients (including one who is HIV-positive) remain on study. The median PFS was 4.1 months. Single agent nivolumab demonstrated very promising activity, was well tolerated, and will lead to further evaluation of immune checkpoint therapy in metastatic SCCA.

Protocol 9204: A Phase 1/1b Study of Ipilimumab in Patients with Relapsed Hematologic Malignancies after Allogeneic Hematopoietic Cell Transplantation

Principal Investigator, Matthew S. Davids, M.D., Dana-Farber Cancer Center

Loss of donor-mediated immune anti-tumor activity may permit relapse of hematologic malignancies (HM) after allogeneic hematopoietic cell transplantation (allo HCT). This NCI-sponsored, Phase 1/1b multicenter, investigator-initiated study was conducted to determine the safety and assess the efficacy of ipilimumab in patients with relapsed HM after allo HCT. Patients received initial courses of ipilimumab at 3.0 mg/kg or 10.0 mg/kg every 3 weeks for 4 doses with additional doses every 3 months for up to 1 year in patients with demonstrated clinical benefit. A total of 28 patients were enrolled. Immune-related adverse events (irAEs) were observed in six patients (21%), including one fatal event, and graft versus host disease (GVHD) was observed in four patients (14%). No responses were observed at the 3.0 mg/kg dose level. However, of the 22 patients receiving 10.0 mg/kg, five (23%) achieved complete response (CR), two (9%) achieved PR, and six additional patients (27%) had decreased tumor burden. CRs occurred in four patients with extramedullary acute myeloid leukemia (AML) and one patient with myelodysplastic syndromes (MDS)/AML. Durable responses were observed in several histologic subtypes, including extramedullary AML. Clinical responses were associated with *in situ* leukemic infiltration of cytotoxic CD8+ T cells, decreased activation of regulatory T cells, and expansion of T effector subpopulations in the peripheral blood. The trial showed that repeated administration of ipilimumab is feasible in patients with recurrent HM after allo HCT, with early promising signs of efficacy, though immune-mediated toxicity and GVHD can occur. These promising response rates and/or survival outcomes have opened new areas for further exploration.

SPECIALIZED PROGRAMS OF RESEARCH EXCELLENCE (SPORE)

The **SPOREs** are a cornerstone of the NCI's efforts to promote collaborative, interdisciplinary translational research. Funded through the P50 or U54 grant mechanisms and managed by the Translational Research Program (TRP), SPORE funding supports state-of-the-art, investigator-initiated translational research contributing to improved prevention, early detection, diagnosis, and treatment of cancer.

In each SPORE, this goal is achieved by:

- Focusing on a specific organ site, a group of highly related cancers, or cancers that are linked by a common activation pathway or other novel cross-cutting themes that have potential for innovation and high scientific impact
- Supporting research projects that have the potential to result in new and diverse approaches to the prevention, early detection, diagnosis, and treatment of human cancers
- Encouraging cross-fertilization between various biomedical disciplines by requiring a minimum of three diverse translational research projects per program and involving both basic and clinical or applied scientists in each research project
- Requiring a dedicated pathology and/or biospecimen specialized resource core to ensure access to clinical materials
- Supporting a developmental research program to promote pilot projects of cutting-edge research (basic, clinical, or translational)
- Supporting a career enhancement program to promote the transition of early-stage or established investigators to translational cancer research in the proposed organ site

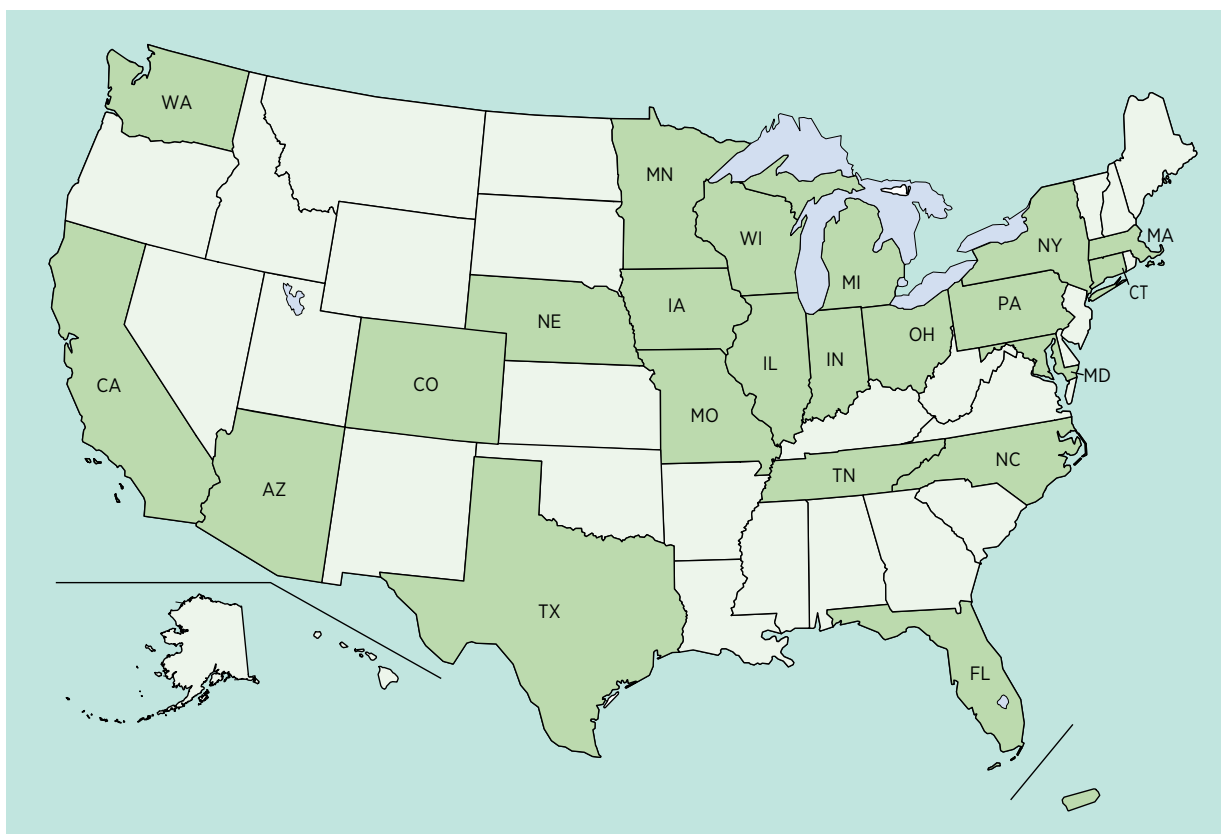


FIGURE 10: STATES WITH ACTIVE SPORE GRANTS IN FISCAL YEAR 2016.

A total of 54 funded SPOREs are located in 22 states within 32 institutions and one consortium (darker green).

- Requiring collaboration among other SPOREs and across NCI-funded networks to promote translational advancement
- 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 input and advice from patient advocates and the advocate community

SPOREs are located at academic centers or consortia in 22 states across the United States. Each SPORE is required to have a Biospecimen/Pathology Core facility to collect, annotate, and store patient biospecimens for use in translational research. SPOREs are strongly encouraged to have a priority plan for sharing these samples with other cancer research entities, including NCI programs. For example, SPOREs have provided over 1,500 tumor and control samples to [The Cancer Genome Atlas \(TCGA\)](#), a collaboration between NCI and the National Human Genome Research Institute (NHGRI), that has generated comprehensive, multi-dimensional maps of the key genomic changes in 33 types of cancer.

TCGA analysis of these samples led to a number of studies focusing on the identification of molecular markers and drivers of tumor growth. Furthermore, pancreatic cancer SPOREs at the University of Nebraska and Johns Hopkins University have established sophisticated processes through their Rapid Autopsy Programs that allow the acquisition and preservation of biospecimens within 1-3 hours of death. These state-of-the-art procedures minimize postmortem degradation and thus facilitate reproducible downstream analysis. These SPORE investigators will be working with DCTD to provide Standard Operating Procedures (SOPs) for the handling of biospecimens to generate patient-derived xenografts (PDXs) in mice.

Several SPORE program investigators have also accessed the drug development resources provided by the [NCI Experimental Therapeutics \(NExT\) Program](#) to help support cGMP manufacture and IND-directed toxicology studies of their novel investigational agents. For example, the University of Alabama, MD Anderson, and Duke Brain SPOREs and Johns Hopkins University Cervical Cancer SPORE have partnered with NExT to develop biologic agents that are currently being tested in the clinic.

Some SPORE investigators are performing correlative studies on clinical trials of therapeutic agents being developed by DCTD's Cancer Therapy Evaluation Program (CTEP). These clinical trials involve agents where CTEP holds the FDA-approved IND. For example, investigators from the Mayo Clinic Ovarian Cancer SPORE have participated in two CTEP-sponsored clinical trials to investigate the efficacy of the PARP inhibitor veliparib in combination with either topotecan or floxuridine.

Finally, SPORE investigators collaborate with and/or include NCI intramural investigators on their research team. One example is the Developmental and Hyperactive Ras Tumor SPORE that consists of a team of investigators from several different institutions, including Dr. Brigitte Widemann from the NCI intramural program. Dr. Widemann provides clinical trial leadership on a project focused on defining characteristics of plexiform neurofibromas that influence response in clinical trials testing targeted therapies in this disease.

NCI EXPERIMENTAL THERAPEUTICS (NExT) PROGRAM

Overview

NCI is working on multiple fronts to develop more patient-specific and effective therapies for cancer. One initiative, the [NExT Program](#), combines the extensive DCTD expertise in cancer treatment with the dynamic intramural research resources of the Center for Cancer Research (CCR) and the NIH Clinical Center. The discovery engine of this program is the [Chemical Biology Consortium \(CBC\)](#). The NCI established this collaborative network, comprised of Dedicated and Specialized Centers, with a broad range of capabilities (including high-throughput screening (HTS), bioinformatics, medicinal chemistry, and structural biology) to support early-stage drug discovery. Subsequent late-stage, IND-enabling studies utilize the resources of the Division's Developmental Therapeutics Program (DTP), which has successfully brought new small molecule and biologic anti-cancer agents into the clinic over the past two decades. The NExT Program also develops molecular imaging agents with support from DCTD's Cancer Imaging Program (CIP), and proof-of-mechanism PD assays through the efforts of the PD Assay Development and Implementation Section (PADIS) of the [Frederick National Laboratory for Cancer Research \(FNLCR\)](#), for application in NCI-supported early phase

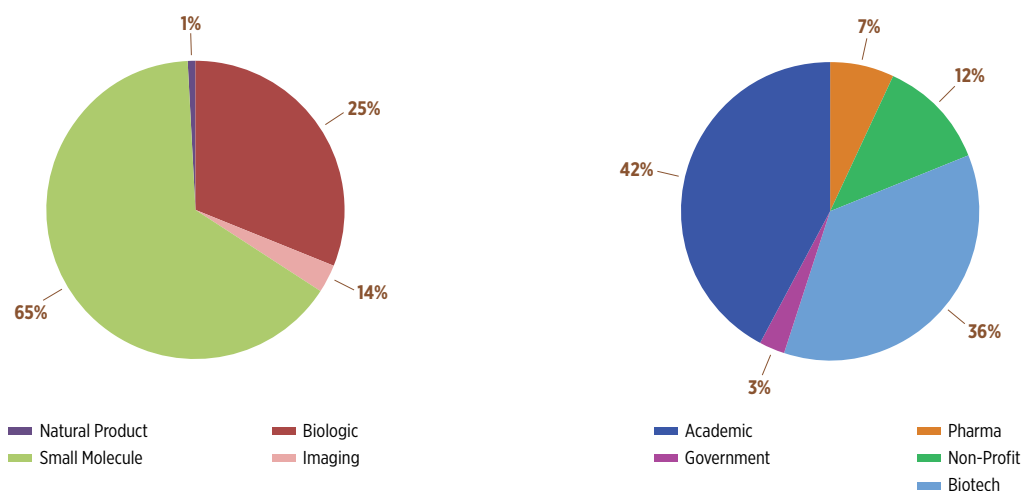


FIGURE 11: NExT PORTFOLIO STRATIFIED BY AGENT CLASSIFICATION AND CATEGORY OF SUBMITTING INSTITUTION.

clinical trials. Finally, early phase clinical trials are performed in the NCI Developmental Therapeutics Clinic (DTC) or institutions funded through grants managed by CTEP. These coordinated activities, described in greater detail below, enable incorporation of cutting-edge technologies into every step of the NExT drug discovery and development continuum, increasing the potential for successful clinical evaluation of new target- and mechanism-based therapies.

Drug discovery and development projects enter the NExT pipeline on a competitive basis and are focused on unmet needs in cancer treatment that are not adequately addressed by the private sector. Of vital importance to the success of this initiative is the careful selection of projects and rigorous evaluation of the portfolio in order to progress the most promising concepts toward the clinic. A Special Emphasis Panel (SEP), composed of outside experts who evaluate all incoming NExT applications, is also charged with assisting the NCI in a yearly strategic portfolio evaluation and prioritization process. This periodic external assessment of a project's relevance, performance, and impact in relation to stated objectives, ensures that resources are used effectively.

Since its inception in late 2009 through December of 2017, the NExT program has received over 670 applications and has an acceptance rate of nearly 15%. Approximately 32% of all applications received were requests for CBC (early drug discovery) resources. The distribution of projects entering the pipeline by agent class and category of submitting institution is highlighted in Figure 11. The pie charts include early (CBC) and late stage (IND-enabling) discovery, as well as development (early clinical evaluation) projects accepted into the program.

Although molecular imaging projects comprise a small segment (3%) of the projects accepted into the NExT pipeline, all biomedical imaging modalities in late discovery phase have progressed to clinical trial evaluation. These include a number of disease-targeted contrast agents and radiopharmaceuticals: (i) a prostate specific membrane antigen positron emission spectroscopy (PET) tracer for prostate tumor imaging (PI: Peter Choyke, NCI CCR), (ii) panitumumab conjugated to the fluorescent dye IR800 (PI: Eben Rosenthal, University of Alabama at Birmingham) for fluorescence assisted head and neck surgery, (iii) LUM015, a cathepsin-activatable fluorescent probe (PI: David Kirsch, Duke University) being evaluated for fluorescence assisted sarcoma and breast cancer surgery and (iv) a near-infrared (NIR) fluorophore (PI: John Frangioni, Beth Israel Deaconess Medical Center) for fluorescence assisted resection and exploration.

Several biologic agents produced by the NExT Program also advanced into clinical trials. The first, ganitumab, entered the NExT Program as a supply of bulk drug substance donated by Amgen. NCI subsequently performed the final sterile filtration, vialing, release testing, QA/QC and stability testing to support a multi-site pediatric Ewing sarcoma trial open through COG in the US and Canada. The remaining projects originally came to NCI under the Rapid Access to Intervention Development (RAID) Program, and continued their progress to clinical trials under the NExT program. NCI manufactured two genetically engineered oncolytic viruses, PVS-RIPO and AdDelta24-RGD, that show promising activity in patients with glioblastoma multiforme. In combination with bevacizumab to control cerebral edema, PVS-RIPO is being studied in a low-dose Extended Phase I Trial. FDA granted Breakthrough Therapy Designation in May 2016 for PVS-RIPO, and an application to FDA for an Orphan

Drug indication is in review. Orphan Drug Designation was given to AdDelta24-RGD in October 2014. Ch11-1F4, a chimeric amyloid-reactive monoclonal antibody, is entering Phase 2 trials in patients with primary amyloidosis (and has already demonstrated therapeutic efficacy), and the Tet-CMV peptide shows potential for reducing cytomegalovirus (CMV) infection during bone marrow transplant, and is also entering Phase 2 clinical trials.

First-in-human trials of Z-endoxifen, the active metabolite of tamoxifen that does not require activation by CYP2D6 (which is non-functional in 20% of women with breast cancer), are now being completed. First-in-human studies for 4'-thio-2'-deoxycytidine (T-dCyd), a DNA (cytosine-5-)-methyltransferase 1 (DNMT1) inhibitor discovered by Southern Research Institute, are in progress in the Developmental Therapeutics Clinic. 5-aza-4'-thio-2'-deoxycytidine (5-aza-T-dCyd), an analogue of T-dCyd, is efficacious in distinct tumor types and received IND and IRB approval in November 2017. A novel class of compounds targeting mutant isocitrate dehydrogenase 1 (IDH-1) discovered by the National Center for Advancing Translational Sciences (NCATS) Chemical Genomics Center was found to be just as efficacious in preclinical studies as another small molecule discovered by Agios, Inc. that recently entered clinical trials. Due to the competitive landscape, NCI has decided to look for a company interested in out-licensing the agent rather than continuing to expend funds for its further development. Three additional small molecule projects are in the

late stage of lead optimization and are anticipated to enter candidate selection toward the end of 2017. The inhibitors target the metabolic enzyme lactate dehydrogenase-A and B (LDHA/B), the anti-apoptotic myeloid cell leukemia-1 (Mcl-1) protein, and the AAA ATPase p97 protein thought to play an important role in the degradation of misfolded proteins. An updated list of current projects in the pipeline is available on the [NExT website](#).

Origin of the NExT Discovery Pipeline

The NCI introduced the RAID Program in 1998 as a vehicle to provide researchers with access to IND-enabling resources for investigator-driven clinical trials; the NCI provided translational expertise and preclinical service contracts at no cost to the researcher. Until incorporation into the NExT program in 2009, the RAID Program pursued 139 projects. IND-enabling studies were done for 30 small molecules and 33 biological agents, of which 15 and 24, respectively, entered clinical trials. The efforts behind two small molecules culminated in FDA approval (Pralatrexate, 2009; Omacetaxine, 2012). A similar program for imaging agents, Development of Clinical Imaging Drugs and Enhancers (DCIDE), was initiated in 2002 and was managed by CIP. Of the 10 formal applications, five reached clinical trials with IND-directed toxicology studies supported by NExT: F-18 FACB, Cu-64-ATSM, In-111 Annexin, F-18 Flurocholine, and F-18 DCFCB (a current NExT project). One of these, F-18 ACBC, received FDA approval for prostate cancer (Axumin®) in 2016.

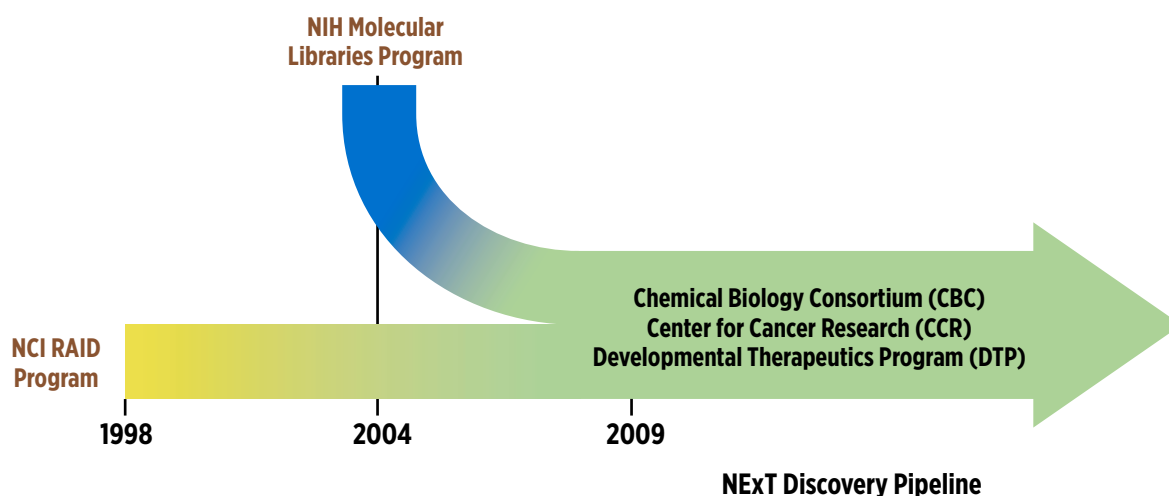


FIGURE 12: THE ORIGIN OF THE DISCOVERY PORTION OF THE NExT PIPELINE.

Initiated in 2009, the Discovery arm of the NExT Program had its origins in the NIH Molecular Libraries and the NCI RAID Programs. The CBC is the main resource for early discovery activities, DTP supports late discovery / pre-clinical development activities, and CCR provides scientific support for both early and late discovery activities.

The NExT Program was created to consolidate existing translational programs across NCI into a single discovery-development pipeline analogous to the multidisciplinary best practices model used successfully in the pharmaceutical industry (see Figure 12). The CBC, created to fill the early drug discovery void at the NCI, was modeled after and capitalized on the significant NIH Common Fund investment in the Molecular Libraries Program² and the Molecular Libraries Probe Production Centers Network (MLPCN). The CBC discovery module of NExT differs from the Molecular Libraries Program in that it maintains confidentiality of the findings until appropriate patents are filed. This is critical to the success of the projects in that it allows NExT applicants and/or the NCI to develop an Intellectual Property (IP) space that encourages downstream investment in the technologies developed through the Consortium and most critically helps enable commercialization of any eventual investigational agents or FDA-approved drugs.

Chemical Biology Consortium (CBC)

Probing cancer's complex network of signaling pathways requires cutting-edge chemical tools, the discovery of which often exceeds the capabilities of an individual laboratory or, for that matter, an individual research university. NCI's CBC is designed to be a flexible network of scientists working to increase the flow of early-stage drug candidates into the development pipeline. This network, which includes participants from government, academia, and industry, focuses on the identification and synthetic optimization of novel chemical leads for drug discovery. The foundation of the Consortium is a task-oriented approach to addressing challenging projects with clear objectives, deadlines, and milestones. By adopting pharma's multidisciplinary drug discovery best practices, the CBC empowers academic and biotech investigators with the much needed capabilities and resources to drive their agents toward clinical development.

Funds from the America Recovery and Reinvestment Act (ARRA) of 2009 enabled NCI to rapidly assemble the infrastructure to support the CBC, including acquisition of a secure central database, mobilization of a small molecule repository at Evotec, and subsequent procurement of a diverse collection of commercial compounds to support High Throughput (HTS) / High Content Screening (HCS).

The pilot phase of the CBC network (2009 – 2015) consisted of 12 Comprehensive and Specialized Centers (Figure 13, upper panel) supported through contractual agreements with Leidos Biomedical Research, Inc. (Leidos Biomed) under its prime contract with the NCI as the Operations and Technical Support Services Contractor supporting the FNLCR. During this period, the CBC performed HTS against ten individual targets, with four of these projects advancing into hit-to-lead chemistry campaigns, three of which subsequently progressed to lead optimization. Routine *in vitro* absorption, distribution, metabolism, and excretion (ADME) profiling (through an interagency agreement (IAA) with the Walter Reed Drug Metabolism and Disposition Center) and structural biology resources were recruited in 2014 to support the medicinal chemistry activities in the Consortium. As several projects advanced toward preclinical evaluation, it became apparent that specialized *in vivo* support activities and increased capacity beyond what was currently available would be required to advance these projects.

The CBC was revised and extended in the spring of 2016 after successfully recompeting the Request for Proposals (RFP) through Leidos Biomed. Changes in the program addressed the need for additional support in all stages of the drug discovery process by expanding beyond the original 12 Centers to 22 Dedicated and/or Specialized Centers (Figure 13, lower panel). Each Dedicated Center provides technical expertise in all of the drug discovery stages. Collaborating under a Master Service Agreement (MSA) mechanism, the Dedicated Centers are provided with base funding sufficient to maintain the infrastructure and staff necessary to provide constant support for CBC projects, which ultimately reduces administrative costs and ensures greater continuity in participation. The Specialized Centers have technical expertise in specific areas, e.g. structural biology, *in vivo* pharmacology, and animal models for proof-of-concept efficacy studies, which broaden the capabilities of the Consortium. Consortium-wide activities are also supported by contract research organizations (CROs), such as Quintara Biosciences (PD analysis), Oncolead (cell line profiling), and Human Metabolome Technologies, Inc. (*in vitro* metabolomics). Specialized Centers and/or CROs are brought into project teams on an ad hoc basis when incorporation of their particular expertise is needed to advance the science and decision-making process.

² For more information, see <https://commonfund.nih.gov/molecularlibraries/index>

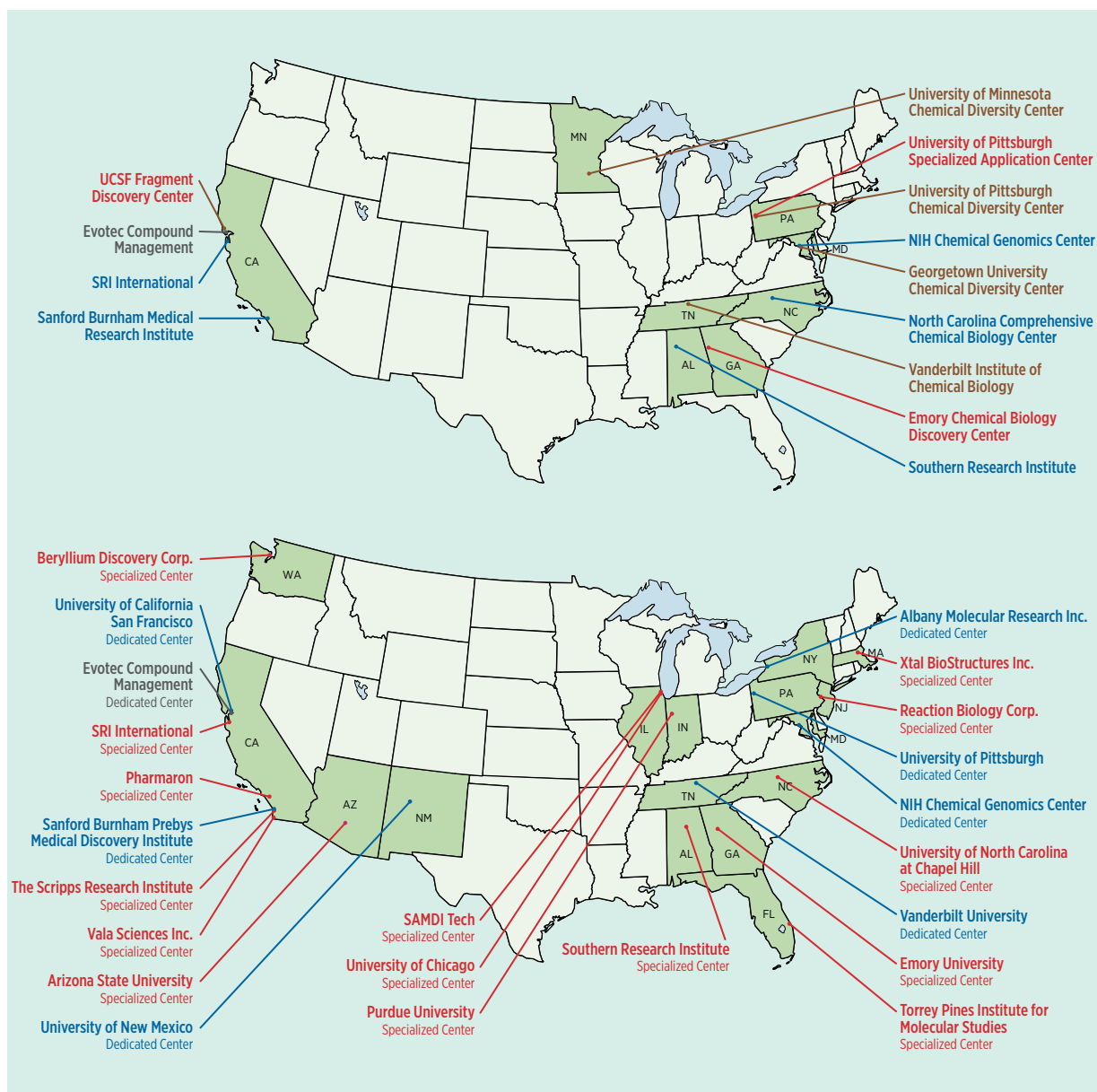
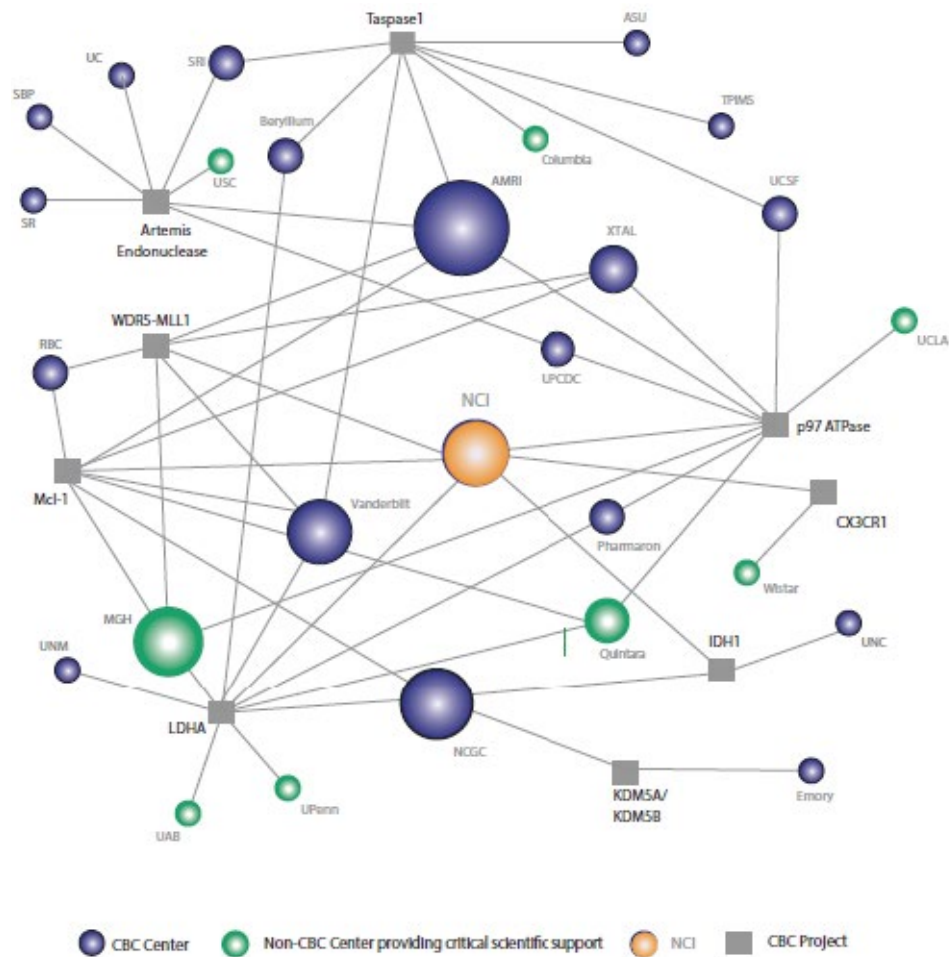


FIGURE 13: EVOLUTION OF CBC NETWORKS.

Upper Panel: The pilot phase of the CBC Network consisted of five Comprehensive Chemical Biology Screening Centers (blue), four Chemical Diversity Centers (brown), and three Specialized Application Centers (rust). Lower Panel: The phase 2 CBC Network is comprised of seven Dedicated Centers (blue) and 15 Specialized Centers (rust). Evotec Inc. (grey) is the CBC compound repository.

The collaborative nature of the CBC is captured in the graphical display of the “CBC Interactome” (Figure 14). Typically, each project engages two or more centers to select the optimal resources and expertise for carrying out the initial

milestones. This interactome evolves as the scientific needs of the projects change during progression to the clinic. The NCI also supports funding of investigators (either applicant principal investigators (PI) or scientific experts) outside



The size of the sphere representing the CBC and non-CBC Centers are proportional to the number of projects being worked on.

<p> AMRI: Albany Medical Research Institute ASU: Arizona State University Beryllium: Beryllium Discovery Corporation Columbia: Columbia University Emory: Emory University Chemical Biology Discovery Center MGH: Massachusetts General Hospital NCGC: NCATS Chemical Genomics Center NCI: National Cancer Institute Centers Pharmaron: Pharmaron Inc. Quintara: Quintara Discovery RBC: Reaction Biology Corporation SBP: Sanford Burnham Prebys Medical Discovery Institute SR: Southern Research SRI: SRI International </p>	<p> TPIMS: Torrey Pines Institute for Molecular Studies UAB: University of Alabama Birmingham UC: University of Chicago UCLA: University of California Los Angeles UCSF: University of California, San Francisco UNC: University of North Carolina UPDC: University of Pittsburgh Chemical Diversity Center UPenn: University of Pennsylvania USC: University of Southern California Vanderbilt: Vanderbilt University Center for Cancer Drug Discovery Wistar: Wistar Institute XTAL: XTAL Biostructures, Inc. </p>
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FIGURE 14: CBC CENTER INTERACTOME AROUND CURRENT PROJECTS WITHIN THE PORTFOLIO ILLUSTRATES THE LEVEL OF COLLABORATION INVOLVED IN ADVANCING PROJECTS. SCIENTISTS FROM NON-CBC CENTERS WITH EXPERTISE IN SPECIFIC AREAS ARE RECRUITED TO PROJECTS AS NEEDED.

the Consortium for project related activities. For example, NExT applicants Chi Van Dang (Abramson Cancer Center, University of Pennsylvania) and Michael Lieber (Keck School of Medicine, University of Southern California) are not only contributing intellectually as the biological experts, but also perform experiments in their laboratories that provide data critical to the progression of their LDHA/B and Artemis Endonuclease projects, respectively. Non-applicant investi-

gators Tsui-Fen Chou (University of California, Los Angeles) and Victor Darley-USmar (University of Alabama at Birmingham) were recruited to project teams as a result of their unique technical capabilities to perform critical experiments and provide scientific input for the p97 and LDHA/B projects, respectively. The contributions of NCI (CCR or DCTD) or Leidos Biomed laboratories and staff to individual projects are not included in this graphic representation.

DCTD Program Support to NExT

Investigative Toxicology Program

The goals of the Investigative Toxicology Program, within DTP's **Toxicology and Pharmacology Branch (TPB)**, are to generate insights about the cellular toxicity of compounds, apply this insight to characterize and aid in the selection of drug candidates, and introduce mechanism-based *in vitro* screens. The program provides investigative toxicology deliverables to the extramural scientific community by serving the immediate needs of the NExT portfolio. The program's services include:

- Profiling early adverse effects for high-priority organ systems using both *in vitro* and *in vivo* assays
- Generating data to describe biologically qualified pathways that are mediating mechanisms of toxicity for classes of approved agents
- Generating data that qualify semivalidated *in vitro* systems for screening opportunities

The program offers a functional toxicogenomics data resource that provides a multitude of methodologies for assessing mRNA for the characterization of molecular changes in vital organs (heart, lung, liver, kidney, bone marrow) induced by marketed anticancer agents, investiga-

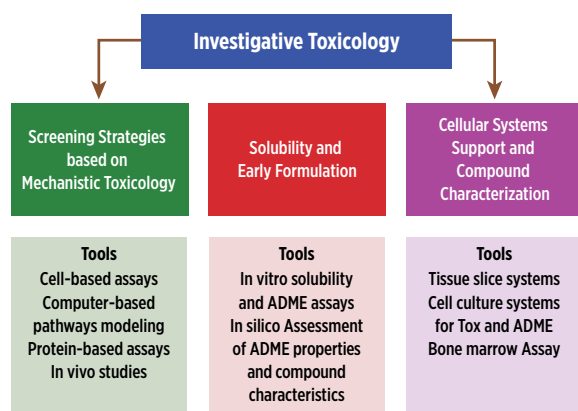


FIGURE 15: ACTIVITIES AND ASSOCIATED EXPERIMENTAL TOOLS PERFORMED BY THE INVESTIGATIVE TOXICOLOGY PROGRAM IN SUPPORT OF NExT PROJECTS.

tional agents, and combinations. Most preclinical toxicology data generated to characterize investigative agents are unpublished and are generally not available as a public data resource.

Pharmacokinetic Laboratory

The Pharmacokinetic (PK) Laboratory at FNLCR analyzes samples from preclinical and clinical trials. Samples from patients on protocols in the DTC, as well as at approved extramural sites, are sent to the PK Laboratory for analysis of systemic exposure to the drug and its metabolites. For earlier-stage projects, the PK Laboratory investigates the metabolism of compounds *in vitro*, including the development of methods for measuring incorporation of bases into DNA. The laboratory then works closely with DTP's **Biological Testing Branch (BTB)** to conduct PK and metabolic studies in mice to provide information about the feasibility of achieving concentrations relevant to activity in cell culture, as well as the potential roles for active or toxic metabolites.

Imaging Drug Group

Molecular imaging has an enormous impact on the 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 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 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, which integrated the activities of several trans-NCI imaging drug activities into one decision-making committee. In doing so, the Imaging Drug Group subsumed the DCIDE program

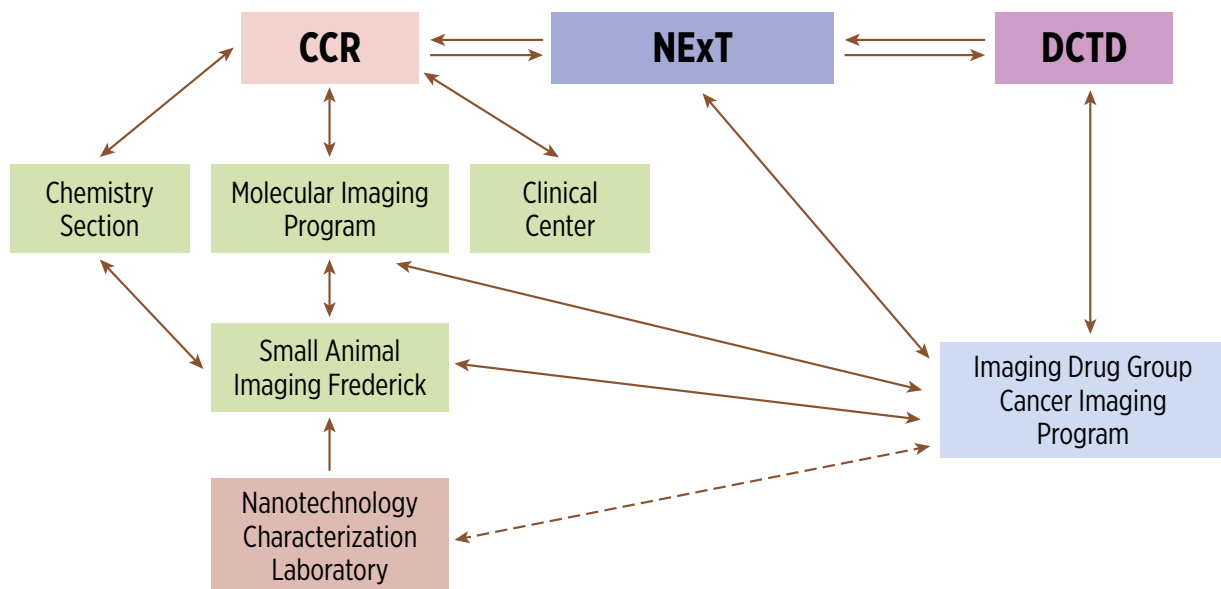


FIGURE 16: IMAGING DRUG DEVELOPMENT AT NCI.

and formed bridges to other important programs in NCI's CCR and DCTD. The Imaging Drug Group also acted in an advisory role with CCR's Molecular Imaging Program and the Small Animal Imaging Program, as well as the Nanotechnology Characterization Laboratory, which are all part of the FNLCR.

The Imaging Drug Group 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.

The NExT Program has now assumed the responsibilities and resources of the Imaging Drug Group and provides an excellent mechanism to bridge the gap between new discovery in imaging drugs and delivery of new agents to cancer patients.

NCI PATIENT-DERIVED MODELS REPOSITORY (PDMR) PROGRAM

In 2013, NCI began development of a national **Patient-Derived Models Repository (PDMR)** to serve as a resource for public-private partnerships and for academic drug discovery efforts. PDMs, such as patient-derived xenografts (PDX) and cell lines, are thought to more closely reflect human tumor biology than established cell lines due to their low passage number, and thus are potentially more predictive models than traditional cancer cell lines. The PDMs being developed for the repository are derived from either tumor tissue or circulating tumor cells (CTCs) and are propagated both *in vitro* using 2D or 3D cell culture systems and *in vivo* via passaging in mice as PDXs. The NCI PDMR currently distributes to research groups viable PDX tumor fragments for implantation in mice, as well as cellular fractions such as DNA, RNA, and fragments that can be used for protein extraction. The publicly available website (<https://pdmr.cancer.gov>) houses a PDM database interface that provides access to the extensive molecular characterization information and patient clinical and social history for all models. A key goal of the NCI PDMR effort has been to establish and make publicly available a set of SOPs for all aspects of PDM creation, propagation, and quality control.

Both conditionally-reprogrammed cell lines, organoid cultures, and cancer-associated fibroblasts are also prepared from matching patient and PDX samples; these cultures are now being finalized for distribution.

Patient specimens for model development are collected from consenting patients with cancer at the NCI Clinical Center, NCI-designated Cancer Centers, and ETCTN and NCORP cooperative groups, through two NCI-sponsored tissue procurement research protocols stating that their biomaterial may be used for the generation of PDMs. In addition, NCI is working with external groups through several NCI funding opportunities who have (1) their own previously established early-passage PDX models, (2) access to rapid-autopsy tumor material, or (3) viably cryopreserved patient material collected under IRB-approved protocols, that with the proper material transfer agreements (MTAs) could be released to the NCI PDMR for further propagation and distribution to the scientific community.

The NCI PDMR is an active member in the recently established PDX Development and Trial Centers Research Network (PDXNet). In addition, PDMR data are being used in the Cellular Level Pilot project for the Joint Design of Advanced Computing Solutions for Cancer (JDACS4C) program. This is a collaboration between NCI and the Department of Energy (DOE) to simultaneously accelerate advances in precision oncology and computing by building predictive computational models using experimental biological data derived from PDX and other preclinical models.

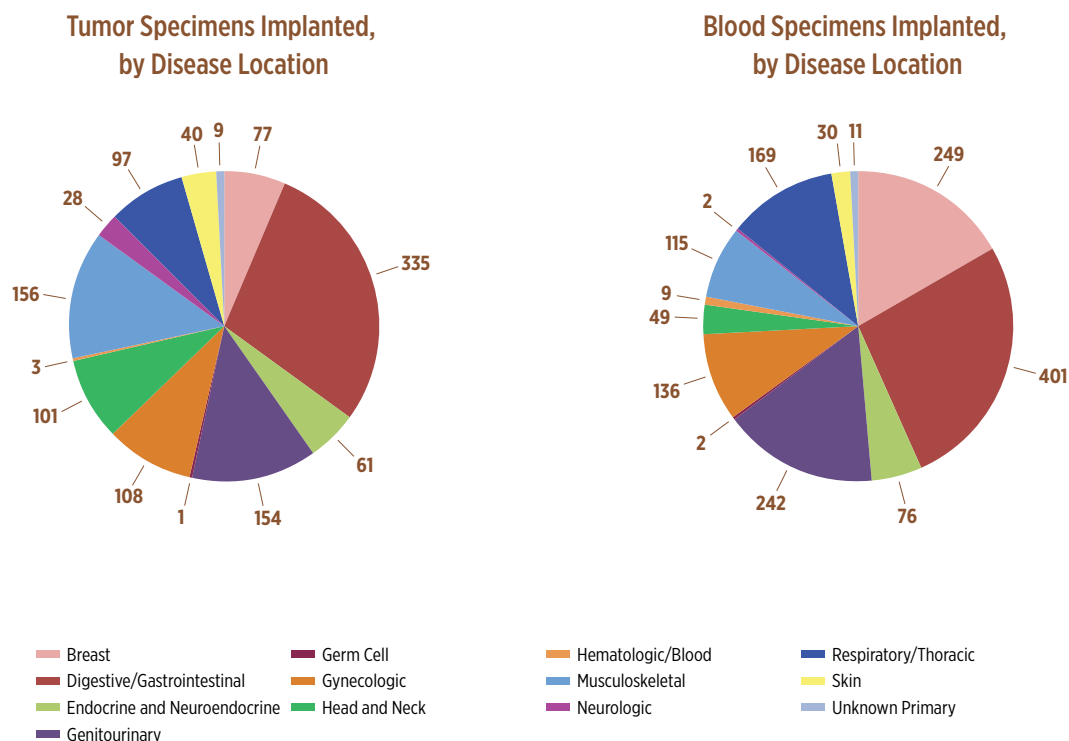
The targeted goal is to develop and make available more than 1,000 unique, quality controlled, early passage, molecularly characterized PDMs that can serve as standardized reagents, enabling comparison of research results across laboratories. Ideally, the PDMR will have 50 unique PDX models for each common tumor type to capture the disease heterogeneity present in the population, provide a representative molecular landscape, and allow in-depth preclinical trial efforts by the research community. In addition to common cancers, the PDMR is also focusing on creating models for less prevalent cancer types that are under-represented in the research model space, such as prostate cancer, small cell lung cancer, and sarcomas, as well as developing models from racial and ethnic minorities. In the past 4 years, the NCI PDMR has received and processed over 6,000 specimens received from more than 4,000 unique patients covering a variety of malignancies (Figure 17).

The NCI PDMR is also undertaking preclinical drug studies using PDXs developed in this program, including the preclinical replication of the NCI-MPACT clinical trial. The PDMR continues its efforts to establish standard procedures for “high-throughput” preclinical testing with rolling enrollment of >80 PDX models against five standard agents; results from this study enable assessment of how closely PDX model responses align with what is observed clinically with this subset of standard-of-care agents.

PHARMACODYNAMIC ASSAY DEVELOPMENT AND IMPLEMENTATION SECTION (PADIS)

DCTD established PADIS at the FNLCR to support the first clinical trial of an investigational agent performed under an Exploratory IND. The objective of the “Phase 0” trial was to provide quantitative evidence for drug activity on the intended target in patient tumors when given at microdoses, quantities well below the anticipated maximum tolerated dose. The underlying principle of the PADIS laboratory is that the application of methods used for blood analysis in the clinical diagnostics industry could be applied to measuring drug activity in patient tissue biopsies. The first assay developed under the Phase 1 program, an immunoassay performed on tumor biopsy extracts to measure inhibition of PARP1/2 by ABT-888, was widely adapted in support of clinical trials in the U.S. and has been licensed by NIH to a small business for commercial development and marketing.

Assays are nominated for development on the basis of compounds in the NExT Program undergoing pre-clinical development or Phase 1 trials to be conducted in the NCI ETCTN. Once an assay is developed by PADIS, it must be analytically validated to ensure that it is accurate within specified parameters and can repeatedly produce the same results over time (and sometimes at different locations). Following validation, the assay is tested on clinical specimens to demonstrate its ability to work on those sample types, and if useful, is transferred to the National Cancer Target Validation Laboratory (NCTVL), an FNLCR laboratory located on the Bethesda campus, to support clinical trials in the DTC and allied medical centers. In addition, the SOPs associated with each clinical assay are made available through a publicly accessible web site, and training classes are provided at FNLCR to interested investigators. For certain assays, calibrators and test reagents may also be made available to support NCI-sponsored trials.



Total Specimens Received	6326
Total Number of <u>Unique</u> Patients	4244
Total Specimens with PDXs at \geq P0 or with Confirmed Growth:	2661
Subtotal: Tumor (pie chart)	1170
Subtotal: Blood (pie chart)	1491
Unique Patients with PDXs at \geq P0 or with Confirmed Growth:	1880

FIGURE 17: NUMBER OF TUMOR (LEFT) AND CTC (RIGHT) SPECIMENS, BY DISEASE LOCATION, THAT ARE CURRENTLY UNDERGOING MODEL DEVELOPMENT AT THE NCI PDMR. SPECIMENS ARE DISCONTINUED IF NO TUMOR GROWTH IS SEEN IN PASSAGE 0 (P0) AFTER 300 DAYS.

In order to bring quantitative methodology to bear on analysis of patient specimens, PADIS brings new technologies on line, often with specific test modifications, software script development, and custom instrumentation. Initial applications of these methods in clinical trial support are performed in PADIS, and lessons learned are used to provide protocols more generally applicable (less requirement for specialized instrumentation and software) in NCTVL and the NCI clinical trials network laboratories. Recently, PADIS has focused on the development of multiplex assays capable

of simultaneously measuring numerous analytes to assess drug target engagement and the PD consequences of drug activity.

Finally, PADIS also serves as an NCI resource for assessing the proposed mechanism of action of new compounds entering the NEXt program when an assay is appropriate for measuring the intended target or cellular pathway. These assays can often be applied to both *in vitro* as well as *in vivo* mouse studies of the compounds of interest.

The following are representative of the assays developed to date:

Apoptosis Multiplex Biomarker Panel. Development of a quantitative, multiplexed (14 biomarkers), validated immunoassay panel for assessing activation of the intrinsic cellular apoptosis pathway. The test is run on extracts from 18-gauge core biopsies, using calibrators and controls developed in PADIS, and is performed on the Luminex platform. A commercially available, research-use-only assay kit was released in June of 2013. The kits are sold by BioRad under the trade name Bio-Plex Pro® RBM Multiplex.

Glycolytic Activity Assay Panel. Development and fitness-for-purpose testing of a quantitative three-biomarker panel (hexokinase 2, PKM2, and lactate dehydrogenase A) designed to assess glycolytic pathway activity.

DNA Damage Repair (DDR) Pathway Activation. In-house development of multiplex assays to survey DNA repair pathway activation on pathology slides from tissue biopsies, including ERCC1, Wee1, pHH3, Ki-67, and others. The multiplex of four DNA repair markers (pS343Nb1s, γ H2AX, pT1989ATR, and RAD51) has completed fitness-for-purpose testing in a mouse xenograft model, and clinical readiness testing. A surprising finding from this work was a high degree of heterogeneity in activation of the repair pathway in different cells in the same tumor, in both pre-clinical models and clinical specimens from patients in DCTD trials.

MET Immunofluorescence Multiplex Assays. Successful application of two different multiplex assays for cMET (hepatocyte growth factor receptor) on tumor biopsies from the CTEP 8880 (pazopanib) clinical trial. Specific membrane staining of pY1235-MET and total MET has been demonstrated in clinical specimens reported to have high pMET and total MET expression levels by the MET quantitative sandwich immunoassay. An important and unusual aspect of this work was the demonstration of concordance of two quantitative assays, one performed on tissue extracts and one on slides from tissue blocks, providing a detailed look at the occurrence, distribution, and activation of this critical protein in tumors.

Circulating Tumor Cells (CTCs). Four methods were developed for the detection, purification, enumeration, and characterization of CTCs in blood as a source for measuring

PD effects on cancers where biopsies cannot be obtained, and enabling more frequent testing of drug effect. This represents the most extensive exploration of this technology in the NCI. Assays for γ H2AX and p16 were developed to monitor the activity of DNA damaging agents and DNA methyl transferase inhibitors.

Extensive studies using the CellSearch technology on 381 patients enrolled in NCI-sponsored clinical trials demonstrated that more than half of patients had no detectable CTCs using the anti-Epcam capture methodology, even though all of the patients had advanced, disseminated carcinomas. A microfluidic dielectrophoresis-based, antibody-independent CTC isolation technology called ApoStream® that can isolate live CTCs from both epithelial and non-epithelial cancers was developed, validated, and brought on line to isolate CTCs from NCI patient clinical specimens and assist in evaluation of PD effects of new anticancer agents. Proof of isolation of CTCs from sarcoma patients was obtained using a FISH assay for a tumor-specific driver gene rearrangement. Detection of CTCs from advanced cancer patients was achieved using automated image acquisition and analysis on the Nikon/Definiens platform developed for biopsy analysis. Isolation and characterization of CTCs from patients with disseminated carcinomas and sarcomas was implemented in several clinical trials.

Epithelial to Mesenchymal Transition Assay. Multiplex assays have been developed to permit simultaneous demonstration and quantitation of the expression of E-cadherin and vimentin in solid tumor biopsies and CTCs. These studies have been noteworthy for quantitating the transition (often in a single cell) from an epithelial to a mesenchymal phenotype following short-term targeted agent therapy in patients with resistance to treatment.

Patents:

- PCT Application No. PCT/US2014/059759, filed October 8, 2014, entitled “Antibodies that specifically bind ataxia telangiectasia-mutated and RAD3-related kinase phosphorylated at position 1989 (pT1989 ATR) and their use”
- U.S. Patent Application No. 62/138,825, filed March 26, 2015, entitled “ANTI-CD133 MONOCLONAL ANTIBODIES AND RELATED COMPOSITIONS AND METHODS”

THE CANCER IMAGING ARCHIVE (TCIA)

Much cancer imaging research requires access to large, standardized, purpose-built imaging collections. In 2010, the Cancer Imaging Program (CIP) leveraged its long-term investment in the development of imaging curation and archiving technology to initiate a funded service that would fill the unmet needs of cross-disciplinary image researchers for network access to clinical images. In response to an announced Request for Proposals, the [Electronic Radiology Laboratory](#) at Washington University in St. Louis was selected to host the TCIA service. The contract was moved to University of Arkansas for Medical Sciences in 2016. Over 74 datasets of computed tomography, magnetic resonance imaging, positron emission imaging, x-ray mammography, and radiation therapy planning imaging studies currently reside in the archive. There are more than 500 peer-reviewed publications based upon these TCIA-hosted data (Figure 18).

More than three quarters of the datasets also have some associated metadata, such as demographics, outcomes, therapy, pathology slides, and genomic and proteomic data. The archive has data from more than 36,000 patients and includes over 31 million individual images. Each month more than 8,000 individual users download a cumulative total of approximately 25 terabytes (TB) of data from the archive (Figures 19 & 20, respectively). Both figures illustrate the effect of removing even trivial barriers to use, such as no longer requiring login credentials or simplifying the download of entire datasets. The archive sets the stage for real-time, multi-institutional image accessibility that could support protocol stratification strategies for a variety

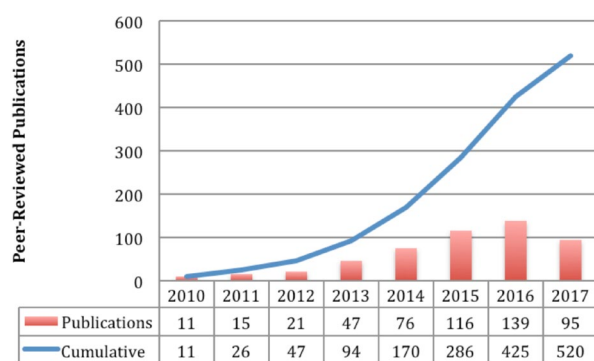


FIGURE 18: PUBLICATIONS BASED ON TCIA DATA SINCE INCEPTION.

of adaptive trials and enable cross-disciplinary research on response measurement fundamentals and analysis reproducibility studies.

Submission and De-identification. Since TCIA contains a large repository of open-access clinical imaging data, robust methodologies and tools were developed and implemented to ensure the protection of Private Health Information while preserving the scientific utility of the data. Thus, further refinement and testing of advanced, standards-based tools were performed to enable the de-identification of medical image data for public consumption. In collaboration with the Radiological Society of North America, a Clinical Trial Processor tool was modified to incorporate current de-identification guidelines from Digital Imaging and Communications in Medicine. The significance of that advance was acknowledged in an editorial, and the methodology has proven its value by being incorporated in numerous institutional laboratories. CIP provides full research-focused de-identification services and makes its tools and knowledge base available to the community. TCIA is the only data repository recognized by *Nature* at this time for inclusion of human imaging scans.

Full Support for Image Submission and Curation.

TCIA has developed extensive procedures to transmit, de-identify and quality assess the medical images submitted to the archive and is staffed with curation experts who review and mount the submitted images.

Easy Access to Purpose-Built Image Collections. TCIA maintains full documentation and meta-data for each of its collections, as well as a help desk and dedicated support staff.

Imaging-Genomics Research Support. A major goal of the TCIA service is to collect and make accessible the clinical images corresponding to the patients who were genomically characterized by TCGA such that researchers could explore the connectivity of cancer-image phenotypes using emerging publicly accessible -omic data. Data hosted in TCIA have allowed researchers across the world to publish *new scientific findings*. Of particular note, the CIP Informatics team has coordinated six volunteer research teams focusing on tumor-specific, TCGA-related phenotype-to-genotype science explorations. These voluntary, non-funded teams regularly hold teleconferences to share ideas. Twenty-one TCGA-matched imaging collections (8 of which have over 100 cases) have been generated from data submitted by mul-

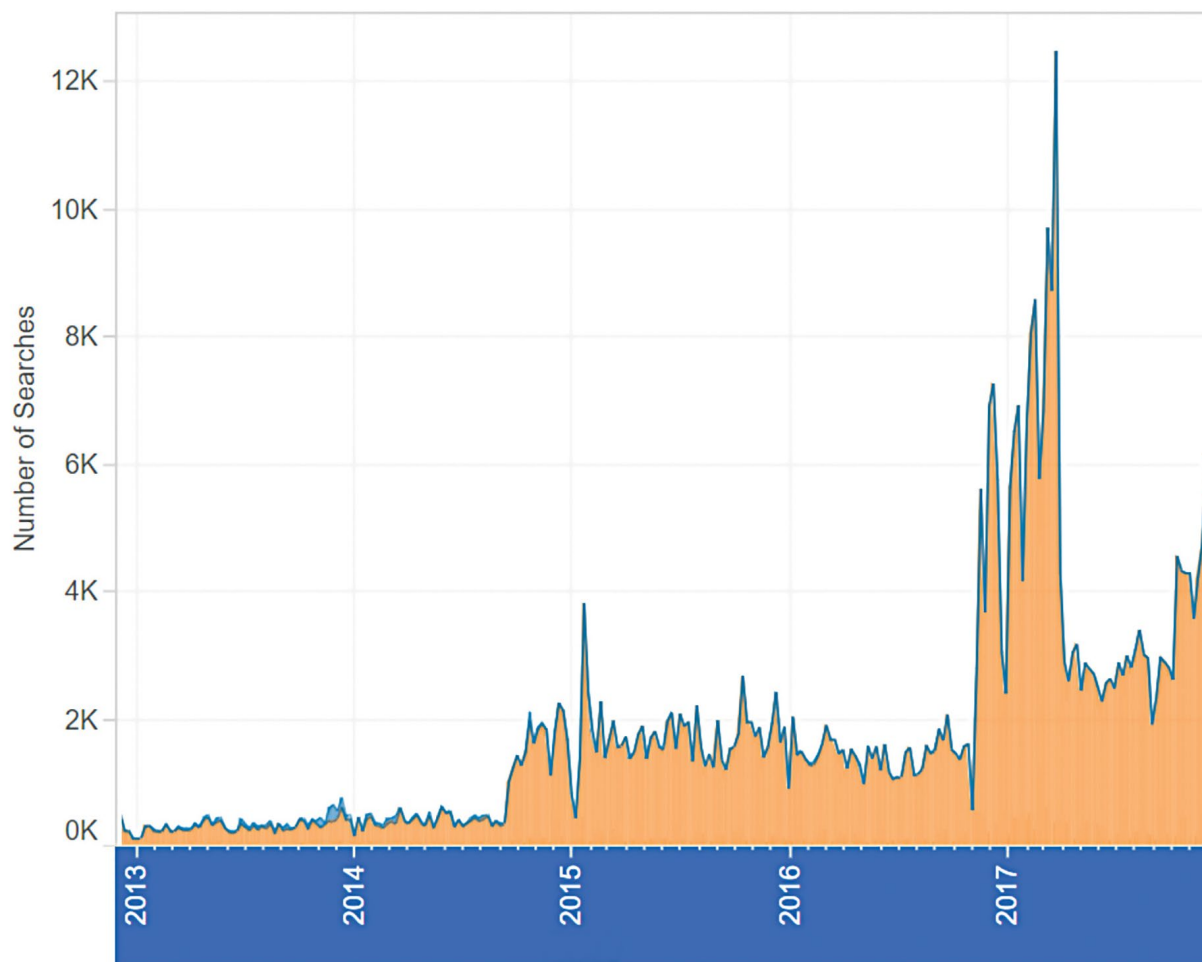


FIGURE 19: NUMBER OF DATABASE SEARCHES FROM 2013-2017. THE LARGE INCREASE IN SEPTEMBER 2014 COINCIDES WITH A DECISION TO NO LONGER REQUIRE AN ID AND PASSWORD TO SEARCH THE DATA.

multiple institutions and are available to these teams. TCIA will be collecting images that have proteomic, as well as genomic, clinical, and pathological data as part of the major effort of CPTAC and the APOLLO project.

Quantitative Imaging Network (QIN) Support. TCIA facilitates data sharing among CIP’s growing QIN. Ten QIN collections are currently hosted on TCIA, and that number is expected to grow with the network activities. In several instances, this data sharing is supporting cross-institutional algorithm validation bilaterally or as part of pilot challenges.

National Lung Screening Trial (NLST) Data Portal. An additional use of the archive has been its availability to

absorb and join the images from the two arms of the NLST trial from both the American College of Radiology Imaging Network (ACRIN) and the Lung Screening Study group. TCIA hosts the full NLST image set with clinical metadata using restricted access, along with a specially developed query tool that supports filtering on associated clinical data parameters. Infrastructure to support associated digital histopathology is being developed.

Community Awareness Building. TCIA has become a vital resource known throughout the cancer imaging community. TCIA provides regular updates on social networks, and CIP hosts meetings focused on imaging and genomics research during the annual meetings of the Radiological Society of

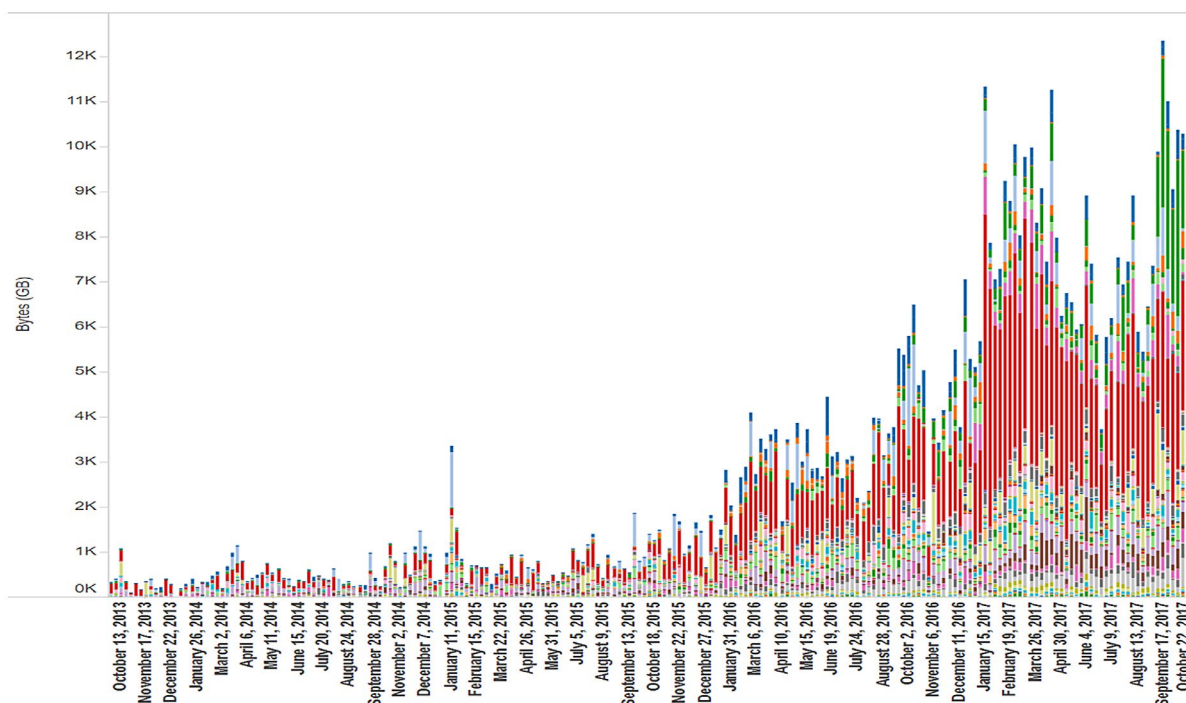


FIGURE 20: DOWNLOADS IN GB OVER THE TIME 2013-2017. THE LARGE INCREASE IN JANUARY 2016 COINCIDES WITH CHANGES IN THE WEB SITE TO MAKE DOWNLOADING ENTIRE COLLECTIONS MORE CONVENIENT.

North America to stimulate interest and cross-fertilize ideas. TCIA is an officially recognized repository for leading cancer imaging journals and has led the field in developing technology to apply Digital Object Identifiers (DOI) to imaging collections, which facilitate the publication and re-use of hosted data. TCIA is a registered publication and is in the process of getting PubMed to index the individual collections (all of which already have an assigned DOI) so that individuals who contribute data will have a way to cite their contribution as a publication and list it on their CVs.

INNOVATIVE MOLECULAR ANALYSIS TECHNOLOGIES (IMAT)

The NCI *Innovative Molecular Analysis Technologies (IMAT)* Program was launched in 1998 to support the development and validation of technologies that offer dramatically new capabilities for molecular and/or cellular analysis and the targeting of cancer-relevant biology. IMAT takes a high-risk, high-reward approach to supporting early-stage technology development, in particular the type of meritorious applications that are often considered too much of a

stretch to put them within the range supported through more traditional competitions for NIH funding. IMAT offers two stages of support based on the maturity of the concept, with a separate track available to small business entities.

- Early technology development to encourage exploratory/developmental research:
 - “Innovative Molecular Analysis Technology Development for Cancer Research (R21)”
 - “Innovative and Early-Stage Development of Emerging Technologies in Biospecimen Science (R21)”
- Development beyond the initial phase of emerging technologies:
 - “Validation and Advanced Development of Emerging Molecular Analysis Technologies for Cancer Research (R33)”
 - “Validation and Advanced Development of Emerging Technologies in Biospecimen Science (R33)”

IMAT has also partnered with the NCI SBIR Program to encourage research in the small business community through the “Innovative Molecular Analysis Technology Development for Cancer Research and Clinical Care (R43/R44)” announcement.

During FY16, IMAT supported 74 projects, of which 34 were new (excluding IMAT-SBIR). A broad variety of technologies were supported through these announcements, including (but not restricted to) technologies for novel drug delivery and targeting capabilities, sample preparation and preservation, clinical point-of-care analysis, multi-modal high resolution spectroscopy, high-throughput ‘omic’ screening, novel biosensors, biomimetic 3D cell culture, and drug screening.

The technologies developed through IMAT enhance the ability of the research community to investigate cancer etiology and proliferation, improve detection capabilities, develop diagnostic methods and treatment strategies, conduct population-scale studies, address and reduce disparities in clinical care, and assist in clinical decision-making.

THE CANCER IMMUNOTHERAPY TRIALS NETWORK (CITN)

The **Cancer Immunotherapy Trials Network (CITN)** was established in late 2010 and is funded through a U01 Cooperative Agreement award for the design and conduct of early phase cancer therapy trials utilizing the most promising immunotherapy agents. The network comprises 32 member clinical sites and a Central Operations and Statistical Office (COSC).

The CITN has activated a total of 11 clinical trials, of which seven have already completed accrual; however, patients are still undergoing post-treatment monitoring to assess the outcome, and in some instances the trial has progressed to an expansion phase. Key examples of such trials include:

- A Phase 1 study of recombinant IL-15 in adults with advanced solid tumors
- A Phase 2 study of CDX-1401, a dendritic cell targeting NY-ESO-1 vaccine, in patients with malignant melanoma pre-treated with rCDX-301, a recombinant human Flt3 ligand
- A Phase 2 randomized study of MK-3475 (Pembrolizumab) in patients with advanced Merkel Cell carcinoma that

provided the basis for FDA approval of Pembrolizumab for this indication

- A Phase 2 study of MK-3475 (Pembrolizumab) for the treatment of relapsed/refractory Mycosis Fungoides/Sezary Syndrome
- A Pilot study of the immunological effects of neo-adjuvant INCB024360, an inhibitor of the immunosuppressive enzyme indoleamine 2,3 dioxygenase (IDO), in patients with epithelial ovarian, fallopian tube or primary peritoneal carcinoma

Results from the Merkel Cell trial have revealed remarkable clinical responses in the first 26 patients who received a single dose of Pembrolizumab: objective clinical responses (CR or PR) were observed in 14 of 25 evaluable patients (56%) (Nghiem PT, 2016).

The remaining five clinical trials are still actively accruing patients:

- A randomized Phase 2 study of the cytokine interleukin-7 (IL-7) in prostate cancer after sipuleucel-T vaccine therapy
- A Phase 1 study of a novel IL-15R/IgG1 fusion complex for patients with advanced solid tumors
- A Phase 1 study of INCB024360, an inhibitor of the immunosuppressive enzyme IDO, in combination with a peptide vaccine for melanoma patients
- A Phase 1 study of an agonistic anti-CD40 antibody for patients with pancreatic cancer
- A Phase 1 study of the PD1 checkpoint blockade inhibitor Pembrolizumab in patients with human immunodeficiency virus (HIV) and relapsed/refractory malignant neoplasms

CHILDHOOD CANCER SURVIVOR STUDY (CCSS)

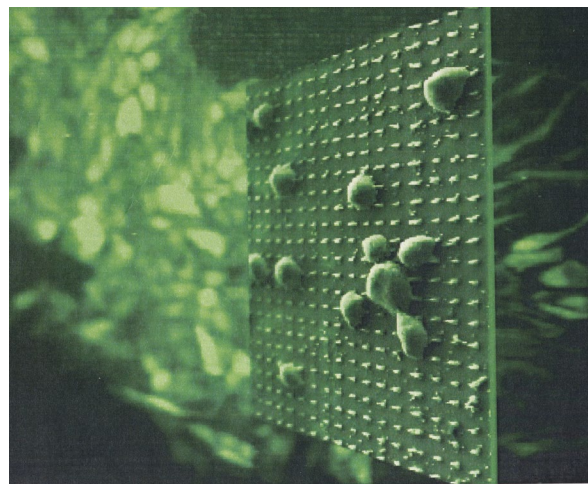
The **Childhood Cancer Survivor Study (CCSS)** was established in 1994 as a multi-institutional, multi-disciplinary collaborative research resource funded through the U24 mechanism to systematically evaluate long-term outcomes among children diagnosed with cancer between 1970 and 1986 who survived five or more years from diagnosis. With the recent successful expansion of the cohort to include survivors diagnosed and treated from 1987-1999, the CCSS now spans three decades and is the world’s



largest established open resource for survivorship research, consisting of 36,000 childhood cancer survivors and approximately 5,000 of their siblings.

Major accomplishments of the CCSS are:

- Extensive use by the research community resulting in 309 published or in press manuscripts now cited over 13,000 times, 262 abstracts accepted or presented, 49 investigator-initiated grants totaling \$46 million, and seven randomized clinical trials.
- Collaborations with other researchers in the field, including the NCI-funded brain tumor SPORES and the NCTN.
- Research demonstrated that by the time childhood cancer survivors reached age 20, 16% experienced a severe and life threatening health condition compared to 3% of their siblings. By age 50, 51% of survivors experienced a severe or life-threatening health condition compared to only 19% of siblings.
- Research demonstrated that even when women were treated with lower doses of radiation to large volumes of breast tissue for childhood cancer, breast cancer risk was higher than previously recognized. By age 45, about 15% of these women developed breast cancer, which is similar to that of BRCA1 mutation carriers and much higher than the general population (4%).
- A study of late effects in long-term survivors of standard risk acute lymphoblastic leukemia (ALL) found that the



incidence of long-term side effects was low. This enables oncologists to reassure patients/families that cure of their child's cancer is not accompanied, in most cases, by a diminished quality of life.

NCI DEVELOPMENTAL THERAPEUTICS CLINIC (DTC)

The **DTC** focuses on the incorporation of pharmacodynamic (PD) endpoints—direct measurements of drug effect on target molecules and/or pathways within a tumor—into the early development of new cancer agents to assess whether they are reaching the tumor and modulating the biology in accordance with their mechanism(s) of action (MOA). These data inform decisions about the clinical activity of the agents, as well as the design of subsequent trials, through targeted patient selection, improved scheduling of agents, or novel combinations. DTC physicians collaborate closely with other clinical and preclinical colleagues to develop new PD assays specific to the clinical trial design and oncologic agent being evaluated. Of note, DTC conducted the first oncology Phase 0 trial under FDA's 2006 guidance on Exploratory IND—a low-dose non-therapeutic trial with PD modulation as the primary end point—with the poly (ADP-ribose) polymerase inhibitor veliparib (ABT-888) in patients with advanced malignancies. At any one time, 15-20 early-phase clinical trials are being conducted in the DTC to facilitate the development and clinical evaluation of novel cancer therapeutics, combinations, or dosing regimens for subsequent application in the ETCTN.

Tissue Procurement/Correlative Pharmacodynamic Support Studies

- Tissue procurement protocol for the Developmental Therapeutics Clinic, NCI

Phase 1 trials

- Combination of the Heat Shock Protein-90 (HSP-90) inhibitor onalespib (AT13387) and the cyclin-dependent kinase (CDK) inhibitor AT7519 in patients with advanced solid tumors
- Veliparib (ABT-888), an oral PARP inhibitor, and VX-970, an ATR inhibitor, in combination with cisplatin in patients with refractory solid tumors
- 4'-thio-2'-deoxycytidine (T-dCyd) in patients with advanced solid tumors
- AZD1775 (MK-1775), a Wee1 inhibitor, in patients with advanced refractory solid tumors
- Combination of bortezomib and clofarabine in adults with relapsed solid tumors, lymphomas, or myelodysplastic syndromes
- Combination of nilotinib and paclitaxel in adults with relapsed solid tumors
- Z-Endoxifen in adults with refractory hormone receptor-positive breast cancer, desmoid tumors, gynecologic tumors, or other hormone receptor-positive solid tumors
- Indenoisoquinolines, LMP400 and LMP776, in adults with relapsed solid tumors and lymphomas
- Pharmacokinetic study of belinostat (an HDAC inhibitor) in solid tumors and lymphomas in patients with varying degrees of liver dysfunction
- Oral 5-fluoro-2'-deoxycytidine with oral tetrahydrouridine in patients with advanced solid tumors

Phase 2 trials

- NCI-MATCH: The use of targeted therapy directed by genetic testing in patients with advanced refractory solid tumors and lymphomas
- MPACT: Molecular Profiling-based Assignment of Cancer Therapy for patients with advanced solid tumors
- A multi-histology study of 5-fluoro-2'-deoxycytidine with tetrahydrouridine (FdCyd + THU)
- Patients with metastatic alveolar soft part sarcoma are randomized to either sunitinib or cediranib monotherapy, with cross-over at disease progression
- Cabozantinib (XL184), a dual inhibitor of MET and VEGFR, in patients with metastatic refractory soft tissue sarcoma
- Vorinostat in subjects with locally advanced, recurrent, or metastatic adenoid cystic carcinoma
- TRC 102, a DNA damage repair inhibitor, plus temozolomide in patients with relapsed solid tumors and lymphomas
- Cediranib (AZD2171) in patients with alveolar soft part sarcoma

TABLE 3: ACTIVE CLINICAL TRIALS IN DTC ([HTTPS://DTC.CANCER.GOV/TRIALS/SEARCH.HTM](https://dctc.cancer.gov/trials/search.htm))

DTC plays a prominent part in NCI's **Precision Medicine Initiative (PMI)** through its role in leading the multicenter **NCI-MPACT** trial in collaboration with the Molecular Characterization Lab (MoCha) and the ETCTN to evaluate the implementation of real-time molecular profiling and its role in guiding cancer treatment decisions. DTC also participates in **NCI-MATCH**, a national clinical trial that analyzes each patient's tumor in search of genetic abnormalities for which there are targeted therapies available. Additionally, DTC has expanded the tumor types in which it conducts clinical research to include rare tumors, such as

alveolar soft part sarcoma, adult soft tissue sarcoma, desmoid tumors, and tumors associated with mutant *BRCA1* or *BRCA2* genes (Table 3).

Having pre-treatment and post-treatment biopsy tissue of sufficient quality to measure drug effect is a critical component of PD-based clinical evaluation. With a preponderance of PD endpoint trials requiring biopsy material in the DTC (PD expansion of Phase 0/1 trials, MPACT and NCI-MATCH), there is a major collaborative effort between the DTC and the NIH Clinical Center interventional

radiologists to improve the quality and quantity of biopsy tissue collected for research. A workshop was organized by the above members in 2017 to discuss approaches to increase the success rate of biopsy collection and disseminate best-practices to the clinical cancer community. Monthly dialogues continue to improve the quality of specimens obtained both at various NCI clinics and throughout the NCI-funded clinical research networks.

DTC staff also capitalize on their co-localization with other outstanding researchers within the **NIH Clinical Center** by establishing collaborations with investigators within NCI, as well as other NIH institutes. They have collaborated with the National Heart, Lung and Blood Institute (NHLBI) in a Phase I trial evaluating both solid tumors and hematologic malignancies. Several trials are ongoing in collaboration with the **NCI Pediatric Oncology Branch (POB)** to allow them to enroll children on DTC-sponsored adult trials, and for DTC to provide care to adult patients enrolled on POB trials. Investigational imaging agents have also been incorporated into several trials to address efficacy and MOA via collaboration with **Radiology and Imaging Sciences** investigators.

In recognition that the increasing complexity of early-phase clinical trials and the development of novel therapeutic agents requires physicians with special skills, DCTD developed the Clinical Oncology **Advanced Developmental Therapeutics Training Program (ADTTP)** to provide advanced training for medical oncologists through their close interaction with DTC investigators. DTC also offers training on an elective basis to the NCI's medical oncology fellows interested in learning more about early phase drug development.

NCI PROGRAM FOR NATURAL PRODUCTS DISCOVERY (NPNPD)

The inconceivably diverse array of molecules that define all life processes form an incredible pool from which new drugs can be discovered. As of 2012, natural product pharmacophores represent >50% of all approved anticancer drugs. Despite the success of mining nature for drugs, large pharmaceutical companies have drastically limited their recent efforts in natural product (NP) discovery. There are many reasons for this trend, including technological difficulties in screening crude NP extracts in a high throughput manner,

and the difficulty of resupply of the original material from which the active compound(s) was purified.

The NCI has outstanding expertise and unique resources in the area of NP, including one of the world's largest and most diverse public NP extract libraries. The chemical diversity contained within this NP library, based on reports of natural product libraries and their sources, is immense and simply cannot be matched by the small molecule libraries currently being screened by most researchers. The **NCI NP Repository** currently consists of crude extracts that have mainly been screened to identify active agents using the NCI-60 cell panel. As a result, the clinically-proven therapies for cancer that have thus far emerged are generally cytotoxic molecules effective at killing cancer cells. Building on this success, we are establishing an **NCI Program for Natural Products Discovery (NPNPD)**, which will create an enhanced pre-fractionated library suitable for high-throughput targeted screens, previously recalcitrant to crude NP extracts, and enhance the efficiency of subsequent NP chemistry efforts to discover new molecules that specifically modulate targets within biological pathways central to human disease. The overarching goal of the NPNPD is to implement new technologies towards increasing the scope and efficiency of NP drug discovery. This program is an exceptional opportunity for NCI to facilitate discovery not only for cancer, but across all disease states; promote multi-disciplinary, intramural-extramural collaboration; and uncover new biological frontiers.

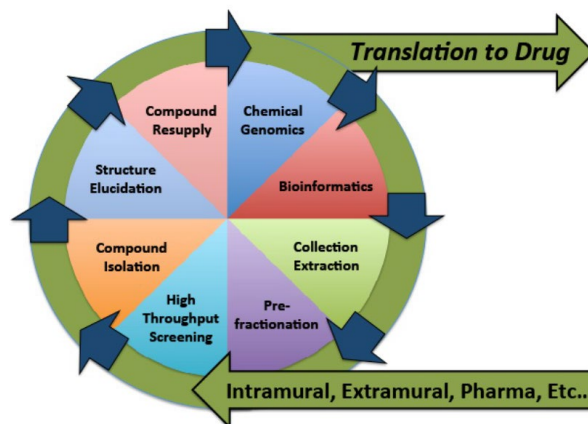


FIGURE 21: COMPONENTS OF THE NCI NATURAL PRODUCTS PROGRAM.

The NPNPD will house the infrastructure necessary to enable NP discovery, including:

- the NCI NP collection of biomaterials
- extraction and prefractionation to create an enhanced NP library amenable to modern high-throughput targeted screening technologies
- analytical resources (isolation, structure elucidation) to support screening centers and expedite hit-to-lead efforts
- resources for resupply of active molecules for translational development into validated lead compounds
- a database and bioinformatics platform to integrate source organism, activity, structural, and chemical genomic data that will improve efficiency and spur further discovery

Discovery programs based in NIH Institutes, universities, medical centers, and Pharma, irrespective of disease, will be allowed to submit requests for access to these resources, as well as the chemistry expertise available in various NCI programs to turn a “hit” into a validated lead compound. The end-product will be structurally defined, validated lead molecules ready for translation. In addition, discoveries made within the NPNPD will push basic science in both chemistry and biology by providing exciting targets for total synthesis and novel compounds that illuminate the underlying biology.

NCI FORMULARY

The **NCI Formulary** is a public-private partnership whose purpose is to provide academic investigators with rapid access to agents for cancer clinical trial use, particularly, for combination trials involving agents from multiple collaborating pharmaceutical companies. As genomic sequencing data become mainstream in cancer therapy, requests for and access to multiple targeted agents for the conduct of clinical research studies are becoming more common. The NCI Formulary will support an efficient mechanism to provide pharmaceutical collaborators’ agents to academic clinical researchers, with the goal of improving the clinical trial implementation process for investigator-initiated and sponsored trials.

To develop the Formulary, DCTD has negotiated with 9 companies to supply 27 agents to date using specific NCI Formulary Clinical Cooperative Research and Development

Agreements (CRADAs). The NCI Formulary CRADAs will provide academic investigators with access to the collaborators’ proprietary agents, thus eliminating the often lengthy agent access process that occurs between individual investigators and pharmaceutical collaborators. Agents within the NCI Formulary are made available to investigators at NCI-designated Cancer Centers for the conduct of pre-clinical research, as well as clinical trials under investigator-held INDs. The NCI clinical trial infrastructure will facilitate conduct of the trials, from proposal submission and timely review by the collaborating pharmaceutical companies, to agent distribution, serious adverse event submission, and clinical data reporting, while providing a coordination mechanism between the clinical investigators and the pharmaceutical collaborators. A clinical Material Transfer Agreement between NCI and the Cancer Center will formalize the expectations of each party.

Initiation of the NCI Formulary began in January 2017.

Negotiations with Pharmaceutical collaborators for additional agents are proceeding actively. Use of agents from the NCI Formulary, the number of trials implemented and completed, the timeliness of completion of these trials, and the overall benefit of these trials on the agent development process will be monitored and evaluated.

EXPLORING THE HORIZON

Exploring the Horizon is a collaborative trans-NCI series created in the summer of 2015 by DCTD and developed by an inter-divisional planning committee. The goal of *Exploring the Horizon* is to foster interactions among program staff throughout NCI’s diverse Divisions, Offices, and Centers through the identification of common interests, enhanced communication about scientific priorities, current research, and possible collaborative opportunities. The first forum brought together 12 program directors from across NCI’s five extramural Divisions to create a cohesive overview of ongoing research in cancer metabolism, specifically focusing on what is known about the role of mutant isocitrate dehydrogenase 1/2 (IDH1/2) as an oncoprotein driving tumorigenesis in various cancers. The different presentations painted a “story” of mutant IDH in cancer biology, including the role of the microbiome, early detection biomarkers, diagnosis and imaging, treatment (both preclinical and clinical studies), and epidemiology studies. This collaborative

effort illustrated how a single topic could integrate information from biochemistry, cancer biology, imaging, drug development, patient stratification, clinical trials, and early epidemiology studies—fields that span the NCI portfolio.

The forum continued in 2017 with a two-part series on *Back Translation: Expecting One Thing and Getting Another*, which examined unique and unexpected clinical trial outcomes in the NCI research portfolio and how further laboratory and population studies clarified the results. Part 1 of the series defined this concept in a story titled, Targeting EGFR—An Iterative Process between Laboratory, Clinic, and Population Studies. The examples explored in Part 1 uncovered biological insights gained from both EGFR inhibitor clinical trial outcomes and population studies and how these insights opened up new avenues of research and guided future clinical trial design. Part 2 continued with back translation stories on overcoming BRAF inhibitor resistance with novel drug combinations, understanding diet and cancer, and how patient derived models can be best incorporated in back translation studies. Ultimately, the 2017 series demonstrated the critical importance of designing clinical trials to facilitate the iterative process of back translation given that unexpected clinical trial outcomes can be the most informative ones.

NCI EXCEPTIONAL RESPONDERS INITIATIVE

Phase 1 clinical trials are primarily designed to evaluate the safety, rather than the efficacy, of an investigational agent. For agents targeting cancer, these trials are performed in patients whose cancers have progressed despite having received treatment with either the standard of care or investigational agents further along in clinical development, and typically enroll patients regardless of their tumor type. Phase 2 studies assess activity of a treatment in patients with a particular cancer type. Preliminary data show that up to 10% of patients on early clinical trials unexpectedly have complete (CR) or partial (PR) responses. This may occur even in trials in which the drugs are not further developed because they show insufficient activity, which is often defined as less than 10% of patients responding to treatment. Responses to a standard treatment that are more robust than typical are also sometimes observed. The *Exceptional Responder (ER) Pilot study* is designed

to investigate the underlying reason(s) that the tumors in such patients responded to a particular therapeutic regimen. The study is available through the [CTSU](#).

An ER, as described in this pilot study, is a patient who has one of the following:

- a CR to a systemic treatment in which the expected CR rate is < 10%
- a PR that lasts at least 6 months and is observed in < 10% of patients treated with that agent
- either a CR or PR that lasts three times longer than the median response duration documented in clinical trials

In this study, physicians electronically submit proposed cases without any patient identifying information. Patients may have been treated with either standard or investigational agents, and must be able to provide informed consent or meet conditions for waiver of consent. The submitter must have access to tumor tissue from before the observed ER, and this tissue must meet quantity and quality thresholds. A committee of laboratory and clinical experts determines whether each case meets the criteria of a potential ER under this initiative. If so, the submitter is requested to proceed with implementing the ER trial at their site, submitting additional clinical information into NCI's confidential Medidata Rave database, and shipping of relevant biological specimens to a central biospecimen core resource (Nationwide Children's Hospital) along with a signed material transfer agreement. Pathologists at the biospecimen core resource review the specimen, isolate and then ship DNA and RNA to the sequencing and characterization center at Baylor College of Medicine for whole exome and RNA sequencing. If enough material is present, some is also shipped to Foundation Medicine, which is collaborating with NCI in this study, for deeper sequencing of a targeted gene panel to potentially identify alterations present in only a small population of cells in the tumor. Data (clinical and laboratory) will be placed in a controlled access database (Genomic Data Commons) for use by other investigators. Analysis working groups, composed of ER pilot study scientists and the case submitter (if he/she wants to participate) review the data and attempt to correlate the molecular findings with the potential mechanism of action of the drug(s) the patient received.

Since the study began in August 2014, approximately 478 cases have been internally reviewed, 221 have been provisionally accepted, specimens from 105 cases have been shipped for sequencing, and analysis reviews are in progress. Breast cancer (24 cases), lung cancer (32 cases), colon cancer (25 cases), other gastrointestinal cancer (34 cases), and ovarian cancer (14 cases) are the most commonly submitted, but other rarer cancers, including melanoma, pancreatic, head/neck, brain, prostate, sarcomas, and others have also been received. Having reached the initial goal of obtaining sequence data from 100 cases in this pilot, additional cases are no longer being sought. It is encouraging that several ERs to standard treatments have been submitted. The feasibility of obtaining retrospective tissue samples suitable for sequencing has already been demonstrated. As we approach the end of the pilot study, we are assessing whether this type of research could result in the development of diagnostic assays that will better inform which patients would be most responsive to a particular treatment, and conversely which treatment might provide the best outcome for an individual patient.

PROVOCATIVE QUESTION INITIATIVE

The **Provocative Question (PQ) Initiative** was introduced in 2011 by then NCI Director Dr. Harold Varmus. The intention was to engage the cancer research community to propose challenging, unsolved questions in the field that might now be addressed in light of advances in our understanding of the underlying biology of cancer and the development of more advanced technologies.

Since 2013, DCTD staff have been actively engaged in (1) workshops for the generation of new questions, (2) the Executive Committee activities that refine and rephrase questions for precise understanding and clarity, (3) the Program Committee that broadly oversees the application process and review, and (4) the Question Teams that focus on individual questions, define and determine responsiveness, and assign applications to specific Program Officers.

In FY17, 411 applications were received in response to the twelve issued PQs, of which at least 40% of the questions related to the mission of DCTD. Twelve of the 46 awards issued, 28% of the awarded R01s and 41% of the awarded R21s, were assigned to DCTD program portfolios, where the progress of these grants is being closely monitored.

RECALCITRANT CANCER RESEARCH ACT OF 2012

The Recalcitrant Cancer Research Act of 2012 requires the NCI to develop scientific frameworks for progress in research against cancers with a five-year survival of less than 20% and which cause more than 30,000 deaths per year in the United States. In response to this Congressional authorization, the NCI selected Pancreatic Ductal Adenocarcinoma (PDAC) and Small Cell Lung Cancer (SCLC) as the focus of this effort. Two workshops were held for both Federal and non-Federal experts in the field to discuss and agree upon specific initiatives for each of these deadly cancers. Since 2014, DCTD has been working across the NCI with the Division of Cancer Prevention (DCP), the Office of the NCI Director's Coordinating Center for Clinical Trials (CCCT), and the Center for Research Strategy (CRS), as well as across the NIH (with NIDDK), to implement new directions in research for the PDAC and SCLC initiatives.

In 2016, DCTD held two immunotherapy workshops—one specifically on the subject of immunotherapy of PDAC—defining the precise obstacles that need to be overcome to make progress in the field, and detailing what resources and strategies the NCI could provide to address and break through the barriers to success.

In the area of SCLC, DCTD issued Program Announcements together with DCP for cooperative agreements to form consortia to study (1) the therapeutic development and mechanisms of resistance of SCLC, and (2) innovative approaches to the prevention and early detection of SCLC. A funding plan was developed for the consortium, which includes a single coordinating center for the funded sites.

In the area of PDAC, DCTD issued a request for supplements to fund grants studying PDAC to (1) expand studies to include the microenvironment of pancreatic tumors in order to enhance the possibility of using immunotherapy approaches for this disease, and (2) provide specimens from “rapid autopsy” programs to create patient-derived xenograft models.

DCTD also worked with DCP to issue a Program Announcement to form a Pancreatic Cancer Detection Consortium, which would conduct research to improve the detection of early stage PDAC and characterization of its precursor lesions. Three grants have been funded.

In addition to funding opportunities, DCTD, CCCT, and CSR staff are members of Action Planning Groups for both PDAC and SCLC. Their role is to interact with working groups of the [Clinical and Translational Research Advisory Committee \(CTAC\)](#) and keep them informed about progress being made within various SCLC and PDAC research initiatives.

NCI R21 PROGRAM: TRANSLATIONAL AND CLINICAL EXPLORATORY RESEARCH

An [R21 Funding Opportunity Announcement \(FOA\)](#) was issued in 2016 for translational and clinical exploratory research in DCTD and DCP. This trans-divisional exploratory grant mechanism is particularly suitable for high risk, high reward projects.

The scope of work appropriate for this FOA includes:

- early clinical studies
- correlative studies and biomarker development
- target and agent discovery and development
- model development and analysis

The first receipt date for this FOA was in July 2016. Of the 375 grant applications received, the majority of the 18 that were eligible for funding involved immunotherapy and epigenetic studies, and 16 were assigned to Program Officers in DCTD. In FY17, a total of 596 applications were received, 524 of which were assigned to DCTD Program Officers. Of the 35 funded in FY17, 28 were assigned to DCTD for management (Table 4).

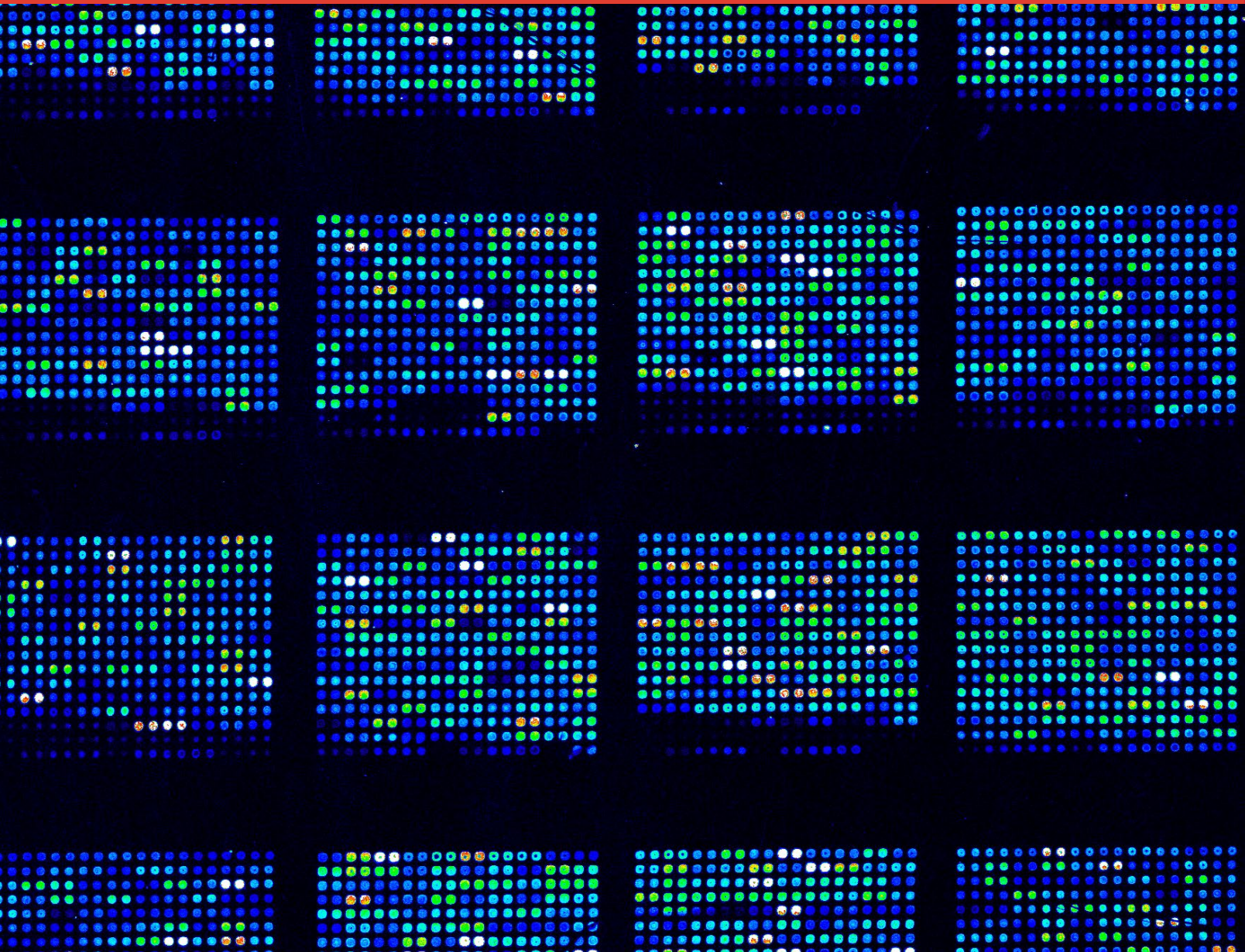
Division	Program	# awards	# applications	Success Rate (%)
DCTD	DTP (PTGB)	9	224	4
	DTP (BRB)	7	92	7.6
	CTEP	1	26	3.8
	CIP	4	50	8
	CDP	5	75	6.7
	RRP	2	39	5.1
	OCCAM	0	18	0
	SUBTOTAL	28	524	5.3

TABLE 4: FY17 DISTRIBUTION OF NCI R21 GRANT APPLICATIONS ACROSS DCTD

This significant number of R21 applications clearly demonstrates the enthusiastic support of the extramural clinical / translational research community, and indicates that the R21 appears to be a popular mechanism for short-term, exploratory grants.

PROGRAMS AND INITIATIVES (2013-2017)

BIOMETRIC RESEARCH PROGRAM





OVERVIEW

The **Biometric Research Program (BRP)** is the statistical and computational biology component of DCTD. It provides leadership for DCTD programs in these areas, and conducts research in clinical trials methodology, biostatistics, computational biology, and bioinformatics.

In addition to collaborating and consulting with DCTD and the Center for Cancer Research (CCR) investigators, BRP investigators conduct self-initiated research. This has enabled BRP 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. BRP does not have a grant, cooperative agreement, or contract portfolio and does not sponsor or fund extramural research.

The major areas of BRP research encompass:

- Efficient clinical trial designs
- Integrating genomics in clinical trials
- Biomarkers in clinical trials
- Computational and systems biology of cancer
- Bioinformatics resources for the research community

STRUCTURE AND FUNCTION

BIostatISTICS BRANCH

Statisticians in the **Biostatistics Branch (BB)** are each designated to collaborate with specific colleagues in other DCTD programs to assist with all major DCTD activities, including clinical trials, drug discovery, molecular diagnostics, and biomedical imaging. It is the philosophy of BRP that statisticians must be deeply involved in a research area to make important scientific contributions in that area and to provide appropriate statistical guidance and oversight for DCTD and NCI activities. In addition to their statistical expertise, BRP statisticians are knowledgeable in cancer therapeutics and are assigned duties by cancer type so that they develop a fundamental understanding of clinical issues relevant to their areas of responsibility.

BRP statisticians have advisory and oversight responsibilities through their interactions with other NCI programs, including:

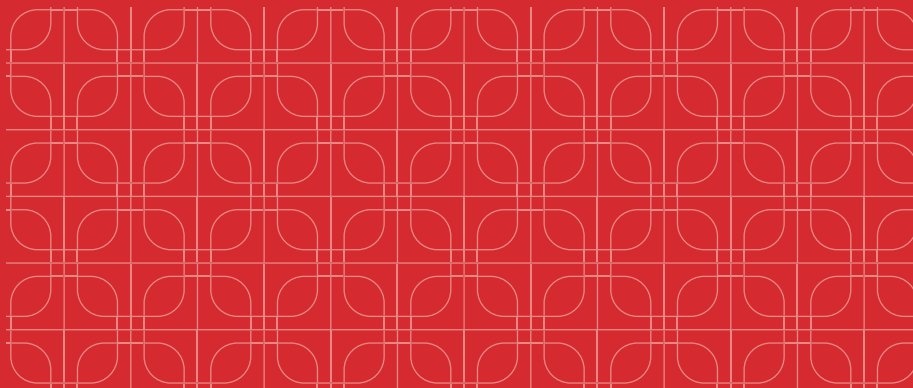
- Reviewing concepts and protocols for all DCTD-sponsored clinical trials
- Serving as liaison to NCI clinical trial network group statistical centers
- Participating with NCI and extramural scientists in drug development strategy groups and protocol development teams
- Serving on data monitoring committees and assuring adherence to procedures established for the NCI-sponsored clinical trials network
- Serving on Intergroup Clinical and Correlative Science Review Committees
- Reviewing correlative science and cancer imaging protocols submitted by the NCI clinical trial network groups

BRP statisticians work closely with other DCTD programs as collaborators on program initiatives and research projects. Example collaborations include:

- Participation in the development of molecular and imaging biomarkers to aid in clinical decision making
- Collaboration on the planning and conduct of extramural programs for the development and application of molecular and imaging diagnostics technology
- Engagement in the design, conduct, and data analysis for NCI program-sponsored projects that aim to address research questions of broad interest to the scientific community, such as systematic reviews of clinical trials in a particular disease area, inter-laboratory assay comparability studies, or systematic reviews of technical performance of imaging procedures
- Oversight of the development and operation of a Web-based data archive to store and enable ethically appropriate sharing of data generated in completed NCI-sponsored clinical trials for which primary analyses have been published
- Facilitating the linkage of imaging and genomic databases and collaboration on analyses of the linked data to evaluate the clinical validity of the measurements

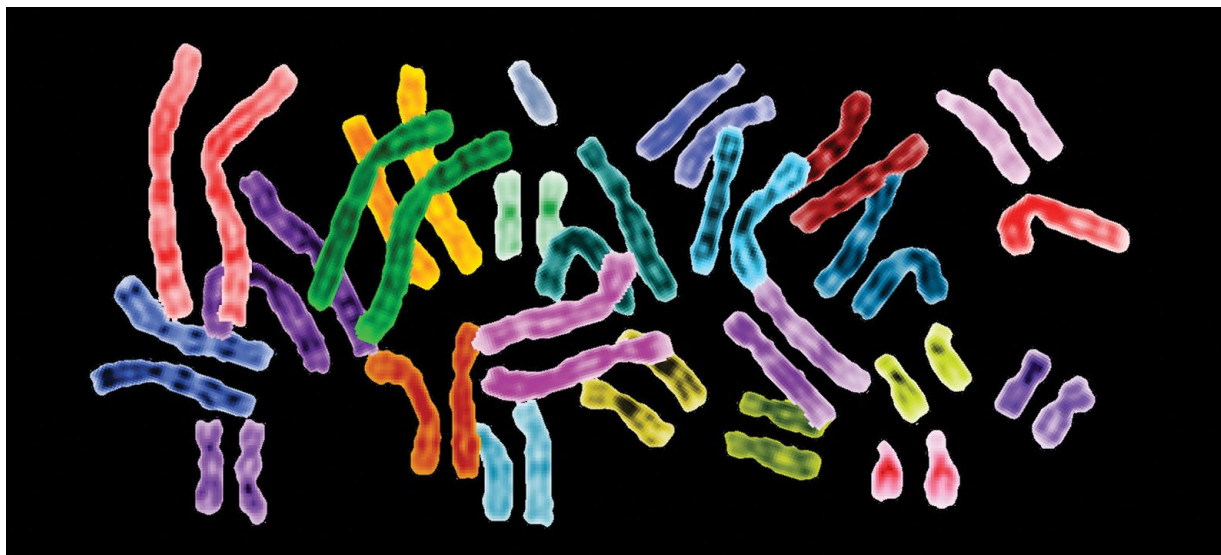
LISA MEIER MCSHANE

ACTING ASSOCIATE DIRECTOR



Lisa McShane, PhD, is Acting Associate Director of BRP. Dr. McShane holds a doctoral degree in statistics from Cornell University in Ithaca, New York. She is internationally recognized for her expertise in cancer biomarkers and precision medicine cancer clinical trials. In 2013, she was elected Fellow of the American Statistical Association for her outstanding statistical contributions to development of clinical tests for personalized medicine, international efforts to improve the quality and reproducibility of tumor marker research, exceptional ability to communicate statistical principles to cancer researchers, and distinguished service to the statistics profession. She is a coauthor of more than 100 statistical and biomedical papers and the book “Statistical Design and Analysis of DNA Microarray Investigations.” Her statistical research interests include biomarker-driven clinical trial design, analysis methods for high-dimensional omics data, multiple comparisons methods, surrogate endpoints, measurement error adjustment methods, and biomarker assay analytical performance assessment. She co-led efforts to develop “Reporting guidelines for tumor marker prognostic studies (REMARK)” and “Criteria for the use of omics-based predictors in clinical trials.”

Dr. McShane joined the National Cancer Institute in 1995 after spending a few years as a mathematical statistician at the National Institute of Neurological Disorders and Stroke. Since joining NCI she has specialized in cancer biomarker and omics research. She was appointed Chief of the Biostatistics Branch of BRP in 2015, and Acting Associate Director of BRP in 2017. Dr. McShane has served on journal scientific advisory and editorial boards, Institute of Medicine committees, and American Society of Clinical Oncology panels and committees that developed guidelines for *HER2* and hormone receptor testing in breast cancer, *EGFR* mutation testing in lung cancer, and use of tumor biomarkers in early stage breast cancer. Her scientific contributions have had a major impact on the design, conduct, analysis, and reporting of cancer biomarker studies and precision medicine clinical trials and have helped to bring high quality biomarker and omics tests into the clinic to improve patient care and outcomes.



BRP statisticians additionally collaborate with CCR intramural clinical branches (neuro-oncology, urologic oncology, metabolism, pediatric oncology, molecular imaging, and pathology). They serve as principal statisticians for multiple NCI intramural early phase clinical studies and provide expertise for clinical, laboratory, and imaging study design and analysis, including analysis of data generated by novel and state-of-the-art imaging modalities and genomic, transcriptomic, proteomic, and other omics technologies.

Collaborations and contributions of BRP statisticians extend beyond NCI to activities arising from NCI partnerships with other stakeholders, including external research groups, advocacy and professional organizations, journals, other NIH institutes, and government agencies. Examples of such activities include:

- Membership on committees convened by professional and scientific societies and charged with the development of clinical practice and molecular testing guidelines, and standards for the design, analysis, reporting, and ethical conduct of biomedical research
- Serving as a study statistician for national precision medicine trials, such as MPACT and NCI-MATCH, which is conducted through a partnership between NCI and the ECOG-ACRIN clinical trials group
- Participating in initiatives conducted collaboratively across government agencies, such as NIH, Centers for Disease Control and Prevention (CDC), FDA, and the

National Institute of Standards and Technology (NIST), to promote best practices for drug, biomarker, and imaging modality development

- Participating in international working groups to standardize or harmonize methods for measurement of laboratory and imaging biomarkers and clinical endpoints

BRP statisticians also maintain active research programs for the development of new biostatistical methodology for clinical trials, preclinical drug development, and development and evaluation of molecular diagnostics and cancer imaging. These statistical research programs are motivated and informed by the wealth of statistical issues that BRP statisticians encounter in their collaborations with other NCI programs. BRP statisticians are internationally recognized for their expertise, which covers a broad range of topics encompassing statistical design and analysis of clinical trials, including biomarker-driven and adaptive clinical trials; statistical approaches for assessment of surrogate endpoints; methods for development and evaluation of prediction models; statistical techniques for analysis of high-dimensional omics data; analysis of analytical and technical performance for laboratory assays and imaging devices. Examples of ongoing statistical methodology research programs include the following:

- Matching biomarker-driven clinical trial designs to level of evidence of a biomarker

- Examination of nonparametric estimation of cumulative distribution functions
- Evaluating microsimulation to inform treatment decisions for prostate cancer
- New analysis strategies for competing risks survival data
- Assessment of the efficiency and ethics of certain types of adaptive clinical trial designs
- Adaptive methods for development of prognostic models
- Modeling of drug synergism and antagonism observed in preclinical drug screening studies, particularly those utilizing patient-derived xenografts
- Statistical approaches to evaluate the clinical validity of image-based biomarkers in the presence of measurement error due to technical variation in imaging assessments

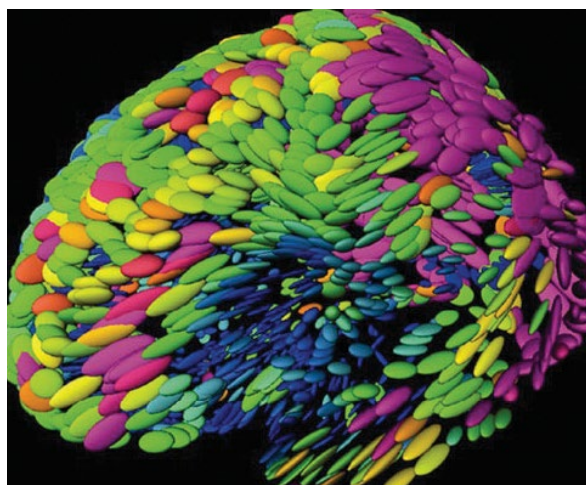
COMPUTATIONAL AND SYSTEMS BIOLOGY BRANCH

The objective of the **Computational and Systems Biology Branch (CSB)** is to provide DCTD and NCI with a tightly integrated group of scientists knowledgeable in cancer biology, drug pharmacology, genomics, computational and systems biology, and bioinformatics, and to train young investigators to do research that spans cancer biology and computational biology. The CSB has investigators with backgrounds and expertise in computational biology, cancer biology, structural chemistry, genetics, bioinformatics, pharmacology and computer science. They also have expertise in the management and analysis of genome-wide tumor characterization data of all types. They use this knowledge to provide biologically and medically meaningful interpretations of genomic alteration data, for using transcriptional pharmacodynamics data for understanding resistance mechanisms, and for identifying biomarker candidates. The branch also designs and develops large-scale bioinformatics systems that empower the community of cancer biologists worldwide to effectively utilize genome-wide tumor characterization data and to perform genomics driven clinical trials.

These systems include the following examples:

- **BRB-ArrayTools** for the analysis of DNA microarray gene expression profile data, particularly in the development and validation of gene expression-based prognostic or predictive signatures. The software is targeted to biologists and has been distributed on request to more than 15,000 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.
- **BRB-SeqTools** was released in 2017 for the analysis of next-gen DNA and RNA sequencing data. The system provides a front-end to BRB-ArrayTools for pre-processing RNA-SEQ data for gene expression analysis. It also provides variant analysis, with special filtering capabilities for the processing of tumor samples grown in nude mice.
- **NCI Transcriptional Pharmacodynamics Workbench (TP-Workbench)**, targeted for release in 2018, will be a web-based system providing biologists and pharmacologists with extensive detailed tools for the analysis of the genome-wide transcriptional response of treating the NCI-60 cell lines with 15 drugs of various mechanisms of action.
- **GeneMed** and **Portable GeneMed** are bioinformatics systems for supporting the conduct of multi-drug basket clinical trials in which treatment selection is based on the genomic alterations in the tumor. The system serves as a communication hub among the tumor sequencing center, the clinic, the study leadership, the data coordinating center and the statistician. This system is currently used in real time for clinical trials conducted both in the NIH Clinical Center and nationwide in NCI's Experimental Therapeutics Clinical Trials Network (ETCTN).

The CSB conducts a postdoctoral training program in cancer computational and systems biology and bioinformatics. BRP has hosted visitors from several countries on short and extended visits for training and research in the use of genomics in cancer research.



Areas in which CSB research has recently focused include the following:

- Development of analytically validated computational pipelines for clinical-grade, high-throughput DNA sequencing
- Development of a bioinformatics system for therapeutic clinical studies in which drug selection is based on the genomic variants in an individual's tumor
- Utilization of whole-exome sequencing of tumor cell line panels for understanding the genomic basis of therapeutic activity, resistance, and synergism
- Development of methods for the analysis of tumor DNA sequencing studies for elucidating the evolutionary history of the tumor, and development of methods for analysis of whole-exome, single-cell DNA sequencing of multiple cells from the same tumor for understanding intra-tumor heterogeneity

FUTURE DIRECTIONS

In upcoming years, BRP plans to focus on the following activities:

- Development and application of statistical and computational 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 computational methods for enhancing the understanding of oncogenesis with massively parallel sequencing, whole-genome characterization technology, and systems biology approaches
- Development and application of statistical and computational methods for using genomic data to elucidate the early steps of tumor pathogenesis and to identify key molecular targets for cancer prevention, early detection, and therapy
- Development of novel statistical designs and analysis methods for enhancing the effectiveness of cancer clinical trials and for expediting the development of technology of potential importance for biomedical investigation
- Development of a bioinformatics system that empowers cancer biologists and pharmacologists to utilize whole genome tumor characterization data to identify resistance mechanisms, predictive biomarkers, and innovative combinations and treatment plans

PROGRAMS AND INITIATIVES (2013-2017)

CANCER DIAGNOSIS PROGRAM





OVERVIEW

The mission of the **Cancer Diagnosis Program (CDP)** is to enable and promote precision cancer medicine by improving the diagnostics for, and thereby the treatment of, cancer. CDP accomplishes this by effectively moving new scientific knowledge about biomarkers into clinical practice. This national program stimulates, coordinates, and funds resources and research on diagnostics and improved technologies to better characterize cancers, to guide the choice of treatment, and to evaluate response to treatment. The overarching goals of CDP are to:

- Support development of the most effective *in vitro* diagnostic tools to optimize treatment decision making
- Encourage research on the clinical utility of biomarkers for clinical practice
- Facilitate translational research by supporting the collection of research biospecimens and sharing of previously collected biospecimens for research
- Develop best practices and tools to improve the quality of biospecimen collection

CDP has been instrumental in the implementation of two of NCI's current precision medicine trials: **NCI-MATCH** (Molecular Analysis for Therapy Choice) and **NCI-COG Pediatric MATCH**, by bringing together a network of laboratories that are Centers for Medicare & Medicaid Services (CMS) approved under the Clinical Laboratory Improvement Amendments (CLIA) to molecularly profile patients' tumors. Along with the ECOG-ACRIN Cancer Research Group, part of the NCTN, CDP and the Cancer Therapy Evaluation Program (CTEP) led the development of NCI-MATCH and coordinated committees working on appropriate treatments, logistics, ethical and other issues. CDP also partners with NCI's Center for Cancer Genomics in the **Exceptional Responders Initiative**, which invited clinicians to submit cases and tumors from patients who had an exceptional response to their chemotherapy treatment (targeted or standard chemotherapy). These tumors undergo extensive molecular profiling in an attempt to find potential molecular reasons for the patient's exceptional response. The data may provide the seeds to eventually identify other patients with similar molecular profiles who may also respond very well to a given treatment. CDP's efforts have also been crucial for the collection of the normal tissues used for **NIH's Genotype Tissue Expression Project (GTEx)**. The GTEx data have proven useful as normal expression controls in the

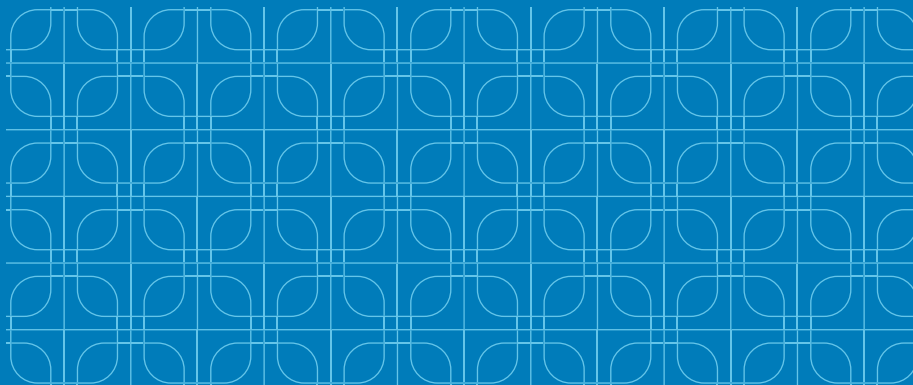
profiling of the Exceptional Responders tumors. The genome sequencing and gene expression data produced by GTEx is used extensively by cancer researchers. CDP's initiatives over the past several years have contributed significantly to progress in the field of biomarker development and clinical application. CDP is now building on lessons learned and scientific advances achieved in large and small molecular biomarker research, as well as from the pilot Clinical Assay Development Program (CADP). Current research directions focus on the transition of research assays of potentially useful biomarkers derived from new molecular insights into assays that are validated for clinical use.

In order to be useful for patient therapy, insight into the molecular features of a cancer that correlate with its behavior or responsiveness to a particular treatment must be developed into a reliable assay. This involves several steps, the first of which is the development of a research assay that uses human tissues or other biospecimens likely to be used in clinical practice. This assay must then undergo *analytic validation* to confirm that it is reliable, robust, and accurate for its intended clinical use. Analytically validated assays must then be *clinically validated* to ensure that the result of the assay can be correlated with the clinical condition for which it is intended to be used. Finally, and most importantly, the assay needs to be studied for its *clinical utility* to demonstrate that use of the assay provides more benefit to a patient or group of patients than not using the assay in clinical care. In order to realize the promise of precision medicine, or treatment individualized to the patient's particular, molecularly characterized tumor, careful validation of the molecular assays that will allow this type of treatment, and clinical trials to assess the clinical utility of this approach, are necessary.

Although the research processes for drug development and approval have been well known for years, the same cannot be said for molecular diagnostics. Clinical researchers in oncology are not trained to develop molecular diagnostics in a rigorous manner. CDP has promoted methods to bridge the gap between drug development and concurrent, accurate, and reliable molecular diagnostic development. CDP works to support all of the activities involved in the development of robust clinical assays: appropriate ethical, legal, and social approaches for engaging patients in research studies; support of basic research and correlative science by making biospecimens (and their attendant clinical data) available for research; promulgation of biospecimen best practices;

LYNDSAY N. HARRIS

ACTING ASSOCIATE DIRECTOR



Lyndsay Harris, MD, is Acting Associate Director of CDP. Prior to coming to NCI, she was Professor of Medicine at Case Western University and Director of the University Hospital's Seidman Breast Cancer Program. Her research in the last 25 years has focused on the development of biomarkers and targeted therapeutics to improve outcomes for breast cancer patients. Her laboratory focused on the use of genomic technologies to develop breast cancer signatures for optimizing therapy selection. She brings experience as a clinician, clinical-trialist and translational researcher, publishing over 120 scientific research articles, and has contributed to the understanding of molecular subtypes of breast cancer and the implication of gene, gene expression, and protein expression profiles on treatment response and resistance. She has held a variety of national and international leadership positions related to cancer clinical trials and translational studies, including co-leader of American Society of Clinical Oncology (ASCO) Breast Cancer Biomarker Guidelines, co-leader of Translational Studies for Breast Committee in Cancer and Leukemia B (CALGB), Breast Committee Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN), Leader of Audit Committee for Pan American Cancer Trials Network and Member of the (Neo) ALTTO International Adjuvant Breast Cancer Clinical Trial Steering Committee. She directed the Tissue, Pathology and Clinical Data Core for the Dana-Farber/Harvard Cancer Center SPORE in Breast Cancer from 2001-2006, and co-led a Project.

As Acting Associate Director, Dr. Harris directs her team in the development of robust prognostic and therapeutic biomarkers through the study of biospecimen science, innovation and technology, pathology evaluation and clinical application of biomarkers. CDP works closely with the Cancer Therapy Evaluation Program (CTEP) to implement biomarkers into clinical trials, and CDP directs the NCI-MATCH (Molecular Analysis for Therapy Choice) and Exceptional Responders Precision Medicine trials.



research related to the effects of biospecimen handling protocols on research data; and grant support for robust translational research, technology, laboratory and quality assurance processes that will lead to more robust clinical assays.

CDP collaborates closely with CTEP to promote the effective integration of biomarker studies and well validated biomarker assays into CTEP-sponsored clinical trials and to implement recommendations of the Clinical Trials Working Group (CTWG), especially through the [NCI Biomarker, Imaging, and Quality of Life Studies Funding Program](#) and the newer [DCTD Biomarker Review Committee](#). These reviews are focused on the development of a fit-for-purpose reliable assay for the intended clinical trial. CDP strongly encourages clinical investigators to collaborate closely with laboratorians, molecular and clinical pathologists, statisticians, and others to bring biomarker guided clinical trials to reality.

CDP also supports earlier stages of biomarker discovery research and clinical assay development through an actively managed portfolio of investigator-initiated research project grants. Nearly 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.

CDP is actively engaged in the ethical, legal, and social aspects of clinical molecular profiling in tumors and how these new technologies can be expected to affect a patients' perception of their treatment options, or the impact on families/relatives of having molecular information about oneself. CDP informs and participates in discussions of

ethical issues surrounding biospecimen procurement, storage, and use, as well as ethical, legal, and social issues surrounding the generation and public availability of omics data.

Research supported by CDP extends to the development of new technologies: the instruments and analytical methods that provide the technical platforms for innovative diagnostics. CDP scientists keep abreast of emerging technologies and their intersection with cancer molecular science. These development efforts encompass:

- Genomics and next-generation sequencing
- RNA and microRNA expression and sequencing
- DNA methylation and epigenetic regulation
- Proteomics and immunoassays
- Metabolomics and glycomics
- Circulating tumor, nucleic acids, and other analytes
- Assays that demonstrate target engagement by a cancer drug
- Collaboration with experts and programs in functional imaging
- New engineering techniques (e.g. molecular machines, nanotechnology)
- New techniques and access to informatics technology
- Point of care devices for molecular diagnostics
- Diagnostics that are appropriate and effective for use in low and middle income countries

Biospecimens of sufficient quality are essential to the biomarker research and assay development that leads to diagnostic tests. CDP is a critical component of NCI's program to provide cancer biospecimens for research and to develop the biospecimen resources of the future. CDP provides support for two major sources of biospecimens, the [Cooperative Human Tissue Network \(CHTN\)](#) and the [National Clinical Trials Network \(NCTN\) Biospecimen Banks](#), which each year provide thousands of biospecimens with appropriate pathologic and clinical data to researchers across the country. CDP's [Specimen Resource Locator \(SRL\)](#) enables researchers to quickly and efficiently gain access to existing biospecimen resources housed in pathology archives within and outside NCI or NIH funded resources.

CDP also generates standards for biorepository infrastructure through publication of the [NCI Best Practices for Biospecimen Resources](#). The *Best Practices* were most recently updated in 2016 and are utilized internationally. CDP has developed resources to assist cancer patients and members of the general public to understand how tissue specimens are used in research and the importance of tissue donation. As part of efforts to improve research reproducibility, CDP conducts and supports research on the effects of biospecimen pre-analytical variation on molecular testing results. A primary focus is the development of evidence-based procedures for biospecimen collection and utilization, to support assessment of biospecimens for fit-for-purpose use in assays that will be used for prognosis and prediction.

The program supports several biobank initiatives including the Cooperative Human Tissue Network (CHTN), NCTN biobanks and the Moonshot Biobank Initiative that is being developed by the Biorepositories and Biospecimen Research Branch.

STRUCTURE AND FUNCTION

Established as a DCTD program in 1996, CDP strives to improve patient outcomes by effectively moving molecular diagnostics from research 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. The development of accurate and reliable molecular diagnostics that can guide treatment has been difficult, and there is no accepted, uniform path to this goal. CDP concentrates on the development of assays for cancers that have already been diagnosed, rather than on screening assays for identifying the presence of cancer.

The activities of CDP fall into three major categories:

1. Developing, validating, 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

CDP collaborates with programs in the [NCI Office of the Director](#), the [NIH Common Fund](#), the [NIH Personalized Medicine Initiative](#), the [National Institute of Biomedical Imaging and Bioengineering \(NIBIB\)](#), and bioengineering efforts across NIH. A significant challenge is the great quantity of information that can now be generated by various omics technologies. CDP works to validate such technologies for clinical use and collaborates to solve the challenging bioinformatics problems associated with these technologies and their use in patients.

As part of the mission to transition research assays from the laboratory into the clinic, CDP is involved in national and international deliberations of the ethical, legal, and social implications of this work. The topics of these deliberations include the return of research results to participants and the return to patients of secondary or incidental findings from the molecular characterization of their tumors.



BIOREPOSITORIES AND BIOSPECIMEN RESEARCH BRANCH

The lack of standardized biospecimens of known quality has been widely recognized as one of the most significant roadblocks to the progress of cancer research. Biospecimens, their preservation, attachment to clinical data and fitness for use in molecular diagnostics has been a focus of CDP since its inception. Over the past fifteen years, NCI has undertaken an intensive due-diligence process to understand the state of its funded biospecimen resources and the relative quality of biospecimens used in cancer research. This process, which began in 2002 with NCI surveys and community forums, resulted in the establishment of a trans-divisional Biorepository Coordinating Committee and creation of the Office of Biorepositories and Biospecimen Research (OBBR), in 2004 and 2005, respectively, to lead and coordinate a strategic plan to confront and resolve the issues in a stepwise fashion.

OBBR was incorporated into CDP in 2012 as the **Biorepositories and Biospecimen Research Branch (BBRB)** where it continues to provide leadership, tools, resources, and policies in biobanking for the global biomedical research community, to enable translational research and precision medicine for patients. BBRB develops biorepository standards and facilitates biospecimen science studies that form the basis of evidence-based practices to guide clinical cancer research and other biomedical studies. The ultimate goal is to increase the reproducibility of cancer research involving the use of biospecimens.

BBRB activities include the following:

- Development and dissemination of the *NCI Best Practices for Biospecimen Resources*, a foundational document for biobanking that is utilized internationally. The *Best Practices* represent operational standards for all aspects of biobanking, including quality management, governance, legacy planning, biobank economics, and data management.
- Biospecimen research to better understand and mitigate the effects of different collection, processing, and storage procedures on the outcome of molecular analysis conducted for basic research and clinical diagnostics.
- Programs to better understand and improve public engagement in biobanking, including development and dissemination of patient brochures, sponsored research in the ethical, legal, and social issues (ELSI) of biobanking, and incorporation of evolving ELSI approaches and policies into *Best Practices* documents.
- Development and operational management of robust biospecimen collection infrastructures to facilitate major team science initiatives in genomics and biospecimen science.
- International collaborations to coordinate biospecimen science with standards initiatives, and to harmonize biobanking policies and procedures.

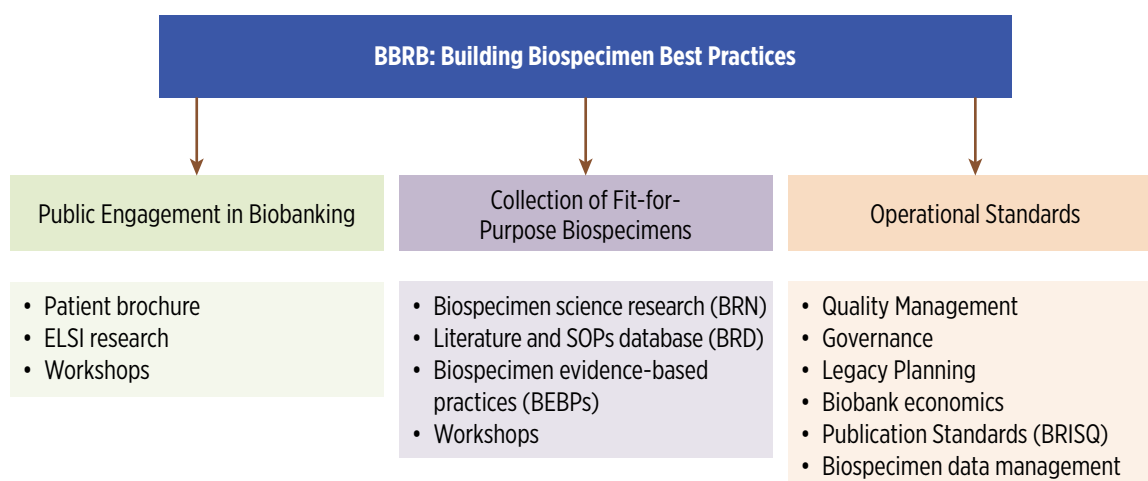


FIGURE 22: BBRB ACTIVITIES DESIGNED TO IMPROVE THE QUALITY OF BIOSPECIMENS AND BIOSPECIMEN RESEARCH.

DIAGNOSTIC BIOMARKERS AND TECHNOLOGY BRANCH

The **Diagnostic Biomarkers and Technology Branch (DBTB)** stimulates and supports research to develop new biomarkers, diagnostic strategies, models, innovative technologies, improved devices, and molecular assay platforms that will lead to better research tools and assist in clinical decision-making. This branch maintains familiarity with novel technologies that may prove useful for precision diagnostics. Significant input from DBTB staff into **NCI's Innovative Molecular Analysis Technologies (IMAT) program**, allows CDP and NCI to develop and support important research into the development and application of new technologies to the diagnosis of cancer. Other specific interests/activities of the branch are to:

- Stimulate research that incorporates new knowledge from cancer biology and tumor-host interactions into cancer diagnosis research
- Support research focused on the development of innovative technologies and devices for use in cancer diagnostics, prognostics and prediction
- Support research to integrate and apply results from biomarker research and technology development into novel platforms for cancer diagnosis, including diagnostics suitable for low and middle income countries and other point of care diagnostics
- Stimulate research focused on the development and implementation of algorithms for analysis of high dimensional data applied to cancer diagnostics, prognostics and prediction
- Stimulate novel interdisciplinary technological research with usefulness for precision cancer medicine

DIAGNOSTICS EVALUATION BRANCH

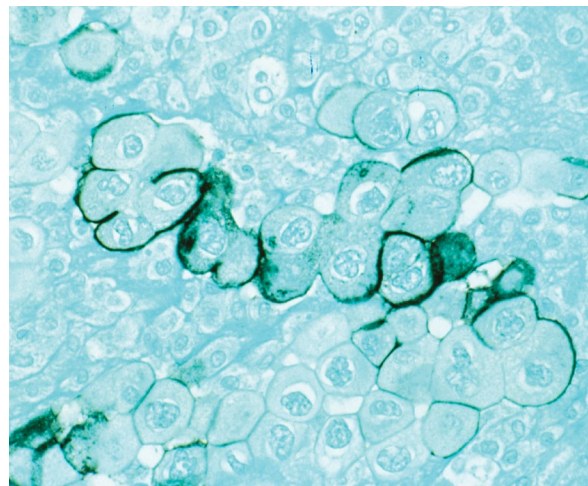
The **Diagnostics Evaluation Branch (DEB)** focuses on the development of predictive and prognostic diagnostic assays from the translational research stage through assessment of their clinical utility. DEB collaborates with CTEP to promote the effective integration of biomarker studies into DCTD's cancer therapy trials as well as to develop appropriate clinical trials that can be used for patients whose tumors have or will be molecularly profiled. Staff review biomarker studies

proposed for inclusion in concepts and protocols for CTEP trials, and considering both the analytic validity and the clinical utility of novel assays, provide recommendations at all stages of trial design. This effort improves the quality of clinical studies and serves CDP's planning processes by enabling staff to identify obstacles to progress in the field. Clinical trials that include investigational biomarker assays, particularly where assays are integral to the trials (e.g. necessary in order for the trial to be performed – such as to choose particular patients based on a molecular profile, or to stratify patients by a molecular characteristic), require time and effort for adequate analytical and/or clinical validation of the assays, thereby posing special challenges to the implementation of NCI's operational efficiency initiatives. Members of CDP's 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. CDP and CTEP currently collaborate to foster research on biomarkers of response to new and novel immune therapies, other targeted therapies and combinations of different therapies.

DEB also keeps abreast of molecular diagnostics and precision oncology needs in the cancer community, and supports collaborative research involving the expertise of clinicians and laboratorians from different universities to develop appropriate molecular assays that can further guide precision medicine. One product of this activity has been the successful **Strategic Partnerships to Evaluate Cancer Signatures (SPECS)**.

DEB activities include:

- Stimulating research to use *in vitro* diagnostics as prognostic markers to improve tumor classification, and predictive markers to improve response to therapy
- Collaborating with other researchers and government agencies to analytically and clinically validate *in vitro* diagnostics and their clinical utility
- Stimulating interdisciplinary research to develop novel assays or novel uses of existing assays that can be used to inform about the behavior or the response of cancers to a particular treatment
- Interacting with other agencies such as FDA and CMS to understand problems in the development of promising assays, particularly those that can be used to identify patients for whom certain treatments could be beneficial



THE PATHOLOGY INVESTIGATION AND RESOURCES BRANCH

The Pathology Investigation and Resources Branch (PIRB) supports the collection and distribution of human biospecimens, pathology investigation to facilitate the discovery of novel molecular features of cancers, and translational and cancer diagnostics research that requires patient biospecimens.

Biomarker discovery research, assay development, and evaluation of clinical utility of assays all depend on the availability of human tumor (or other) specimens for which there is also associated demographic and clinical data. PIRB 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 biomarker research community, providing high-quality human specimens specifically collected and processed to support biomarker discovery and early assay development. This resource collects specimens prospectively, based on the researcher's requirements. The Cooperative Breast Cancer Tissue Resource, initially planned and created by CDP, was the first virtual specimen resource with significant clinical data. They provided the specimens and associated clinical outcome data from breast cancer patients that were used to create statistically designed tissue microarrays for the investigation of prognostic and predictive biomarker hypotheses. These resources, including the Breast Cancer Tissue Microarrays, are still in great demand and are being provided to support prognostic marker research by CHTN.

PIRB also supports NCTN's specimen banking activities; prior to this stable support, collection of valuable specimens

in the context of randomized trials was haphazard at best. Currently, the NCTN tissue collection and processing are being standardized, informatics implemented, and transparent access procedures are making the specimens more widely available for critical research, both within and outside the NCTN.

PIRB activities include the following:

- Development and support of human specimen resources that procure, store, and distribute a variety of biospecimens for research
- Assistance for investigators in locating and acquiring human cancer specimens needed for their research
- Development and administration of the [Specimen Resource Locator \(SRL\)](#), a searchable website that maintains information about existing biospecimen resources
- Support for the NCI Tissue Expediter, an individual who assists investigators in locating appropriate resources as well as identifying potential collaborations
- Provision of pathology expertise and advice on human tissue specimen resources and sample preparation to researchers. PIRB also provides pathology assessment and QA/QC for specimens on CDP/DCTD/NCI scientific initiatives
- Collaboration with investigators to optimize biospecimen quality, identifying best molecular QA/QC methods and overcoming challenges in molecular analysis of human samples
- Support and development of informatics tools to improve access to human biospecimens and associated clinical data in NCI-funded biospecimen resources

CDP GRANTS OVERVIEW

The CDP research portfolio included 218 funded grants during fiscal year 2016. The grant award mechanisms used by CDP and their distribution in terms of research support in 2016 are shown in the accompanying charts.

The predominant mechanism is the individual research project grant (R01), followed by co-operative agreements that support both targeted research and research resources such as tissue banks.

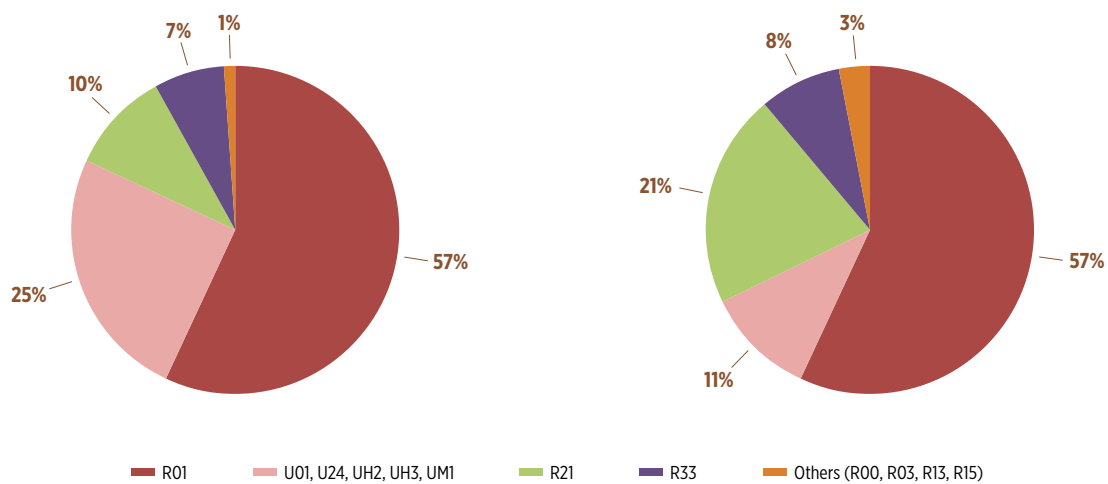


FIGURE 23: DISTRIBUTION OF 2016 GRANT FUNDS (LEFT) AND NUMBERS OF GRANTS (RIGHT) BY MECHANISM.

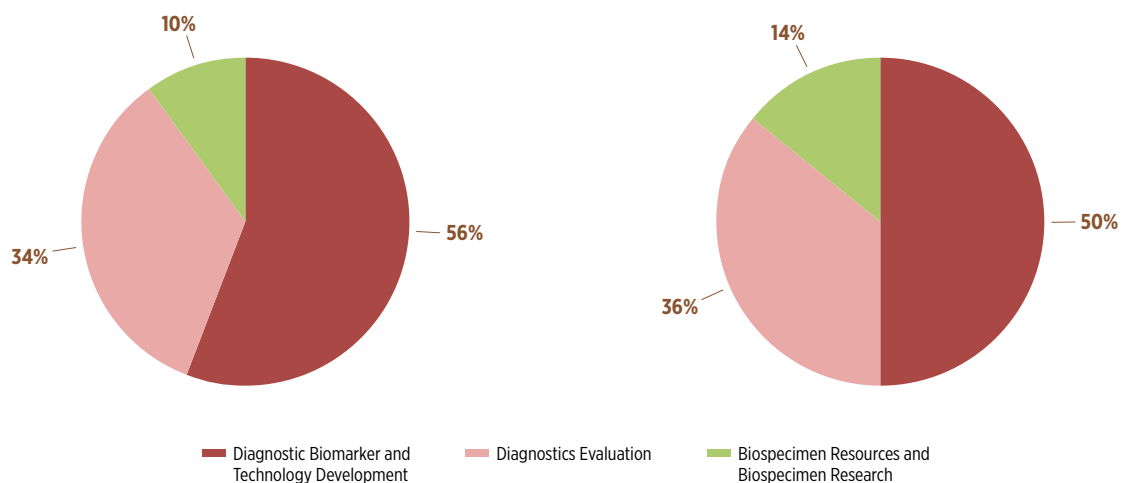


FIGURE 24: DISTRIBUTION OF 2016 GRANT FUNDS (LEFT) AND NUMBERS OF GRANTS (RIGHT) BY RESEARCH AREA.



ASSISTANCE TO THE CANCER COMMUNITY

MOLECULAR CHARACTERIZATION LABORATORY (MOCHA)

The Molecular Characterization Laboratory at the Frederick National Laboratory for Cancer Research (FNLCR) assists with early phases of assay development and transition to clinical laboratory readiness. This laboratory provides genomic characterization of biospecimens obtained from cancer patients in clinical trials sponsored by DCTD. The results are used to (1) identify patients who may benefit from trials of new interventions targeting a specific genetic alteration(s) detected in their tumor, and (2) provide insight into the cellular mechanism(s) of resistance that develop in response to targeted therapies. MoCha also serves as the lead laboratory for the network of CLIA-approved laboratories involved in NCI-MATCH and NCI-COG Pediatric MATCH. These laboratories are responsible for obtaining appropriate biopsies, characterizing the tissue received, isolating nucleic acids, and performing the molecular assays to screen patients for treatment in these targeted therapeutic trials.

PROGRAM FOR THE ASSESSMENT OF CLINICAL CANCER TESTS (PACCT)

Barriers impeding progress in the field of biomarker and assay development include the absence of a well-defined pathway for the development and evaluation of clinical biomarkers, and a lack of standards that assays must meet before being incorporated into trials or clinical practice. Only a small number of molecular assays used in cancer treatment are submitted to the FDA for clearance or approval. Most assays used in clinical practice are laboratory developed tests (LDTs) that can vary in their performance from laboratory to laboratory. If not adequately addressed, such variation in biomarker assessment could delay or diminish the impact of precision oncology. CDP launched the [Program for the Assessment of Clinical Cancer Tests \(PACCT\)](#) to develop a process for moving technologic and cancer biology advances more efficiently and effectively into clinical practice. PACCT is a strategy group composed of scientists from academia, as well as FDA and NCI, with expertise in clinical oncology,

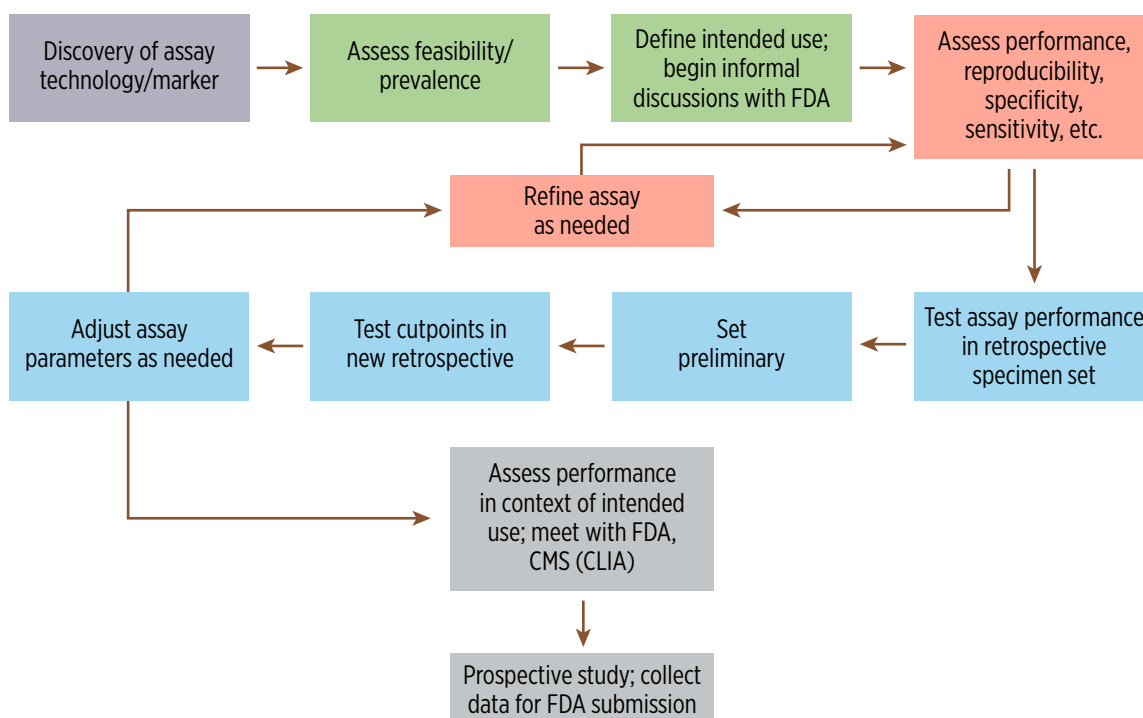


FIGURE 25: THE MARKER DEVELOPMENT PROCESS.

THE TAILORx TRIAL

TAILORx, the first trial launched by PACCT, is testing whether a set of genes whose expression has been shown to be associated with the 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 the National Surgical Adjuvant Breast and Bowel Project, an NCI cooperative group. U.S. Postal Service sales of breast cancer stamps 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.

TAILORx is being carried out as a collaboration between CDP, CTEP, and all of the NCTN Groups that perform breast cancer studies. The trial was launched in the spring of 2006 and completed its testing and accrual of more than 11,000 patients in the summer of 2010. The first major result was published in the *New England Journal of Medicine* in 2015; the analysis indicated that women meeting the trial's entry criteria whose tumors had a low-risk score on the 21-gene panel could safely be treated with hormonal therapy alone. Analysis of the randomized arm of the trial is anticipated in 2018. This trial is expected to have a major impact on the treatment of women with breast cancer.

pathology, basic cancer biology, diagnostics technology and assay development, clinical trials methodology, and statistics. The strategy group establishes working groups to guide the development of specific projects.

PACCT leverages many existing NCI-supported activities to achieve the research goals of improving the creation and use of diagnostics to positively affect patient care.

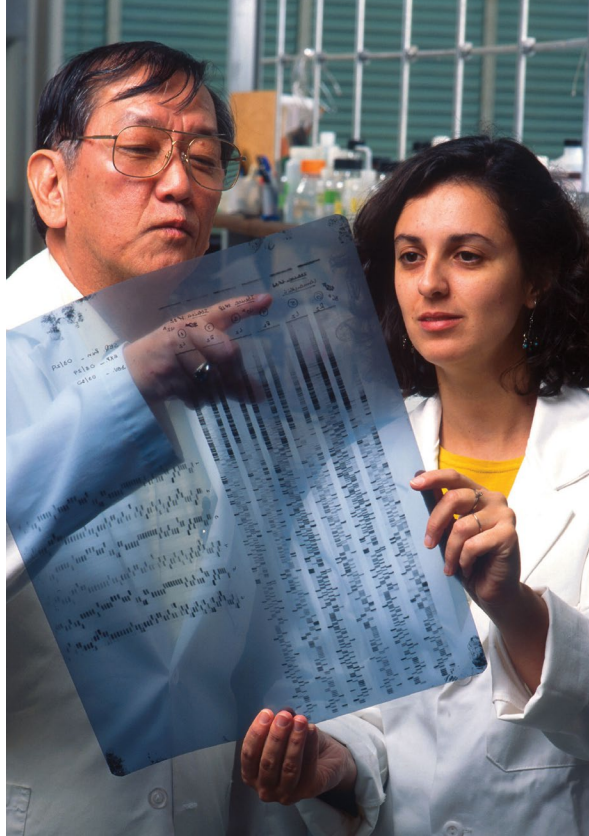
Outcomes include the following:

- Launch of the landmark “Trial Assigning Individualized Options for Treatment” (TAILORx) to evaluate the ability of the OncotypeDX assay to predict benefit from chemotherapy; accrual has been completed, interim analyses have been published, and primary analysis results are expected in 2018
- Publication of the “Reporting Recommendations for Tumor Marker Prognostic Studies” (REMARK) guidelines for reporting tumor marker studies in biomedical journals
- Development of standards for the analytic performance of assays incorporated into clinical trials
- Development of guidelines for the validation of omics assays prior to use in clinical trials
- Discussion and recommendations on how to evaluate the clinical utility of predictive and prognostic assays
- Discussion and recommendations on bringing massively parallel sequencing into clinical use
- Establishment of a major series of international meetings on cancer molecular markers

STRATEGIC PARTNERSHIPS TO EVALUATE CANCER SIGNATURES (SPECS)

SPECS is a cooperative agreement program accelerating progress in moving molecular profiles of tumor tissue from the research setting into clinical practice. New diagnostic tools developed under the SPECS program 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, now cleared by the FDA and commercially marketed as Prosigna™ (NanoString Technologies, Seattle, WA)



- A commercially available mass spectroscopic assay to predict response to epidermal growth factor receptor (EGFR) inhibitors marketed by Biodesix
- An improved risk classifier for adult and pediatric patients with acute lymphoblastic leukemia, now incorporated into clinical trials for assessment of clinical utility
- 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 that is under commercial development for marketing and has been included as an investigational biomarker in clinical trials of ibrutinib

Additional signatures still undergoing clinical validation studies include:

- A molecular signature for aggressive prostate cancer that can be applied to biopsy specimens with minimal amounts of tissue
- Prognostic signatures for squamous cell lung cancer based on mRNA and microRNA expression patterns
- An assay that combines RNA gene expression signatures with gene mutation assessments to identify responders and non-responders to cetuximab therapy in patients with colon cancer

BIOMARKER EVALUATION IN NCI CANCER THERAPY TRIALS

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 also serve as reviewers on the Central Correlative Science Committee for applications to use specimens from the NCTN biospecimen repositories. CDP provides critical biomarker expertise at clinical trials planning meetings and serves on intergroup task forces.

REMARK AND THE EORTC-NCI CANCER MOLECULAR MARKERS COLLABORATIONS

CDP has led an NCI collaboration with the European Organisation for Research and Treatment of Cancer (EORTC), the American Society of Clinical Oncology (ASCO), and the American Association for Cancer Research (AACR) to convene a series of meetings on molecular diagnostics that take place alternately in Europe or the United States and are joined by the regulatory agencies in each continent (European Medicines Agency or the U.S. FDA). These scientific meetings are accompanied by an intense training program in the development of assays for use in clinical trials, attended by junior investigators and taught by experts from government, academia, and industry. The training sessions allow students to develop a plan for assay validation for an intended clinical trial, and hopefully results in the expertise needed for precision medicine clinical trials of the future. At the first



meeting, one resulting international working group focused on the development of guidelines for information that should be included in all publications about tumor markers. The REMARK guidelines were published in several major scientific journals and are now being used by journals as standards for the review of manuscripts on markers.

In 2014 a new collaboration was initiated between NCI, EORTC, the European Medicines Agency, and AACR to develop a new meeting series with a clearer emphasis on drug development. The first meeting in this new series, *Innovations in Biomarkers and Cancer Drug Development* was held in Brussels, Belgium in 2016 and attracted more than 200 participants.

CLINICAL ASSAY STANDARDIZATION

Members of CDP are acknowledged experts in the fields of clinical cancer research, engineering, biology of cancer, assay methodology and 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.

CDP, with the PACCT strategy group, has initiated proactive efforts to improve the standardization and reliability of newer assays entering into clinical practice. Projects have focused on how to evaluate the clinical utility of predictive and prognostic assays and to ensure that assays being evaluated in clinical trials or being used in clinical practice can be performed with sufficient reproducibility and minimal laboratory-to-laboratory variation. This is

critical for dissemination of clinical laboratory tests into community practice.

CDP staff served on an international subcommittee that was formed to assess the current state of reproducibility of Ki67 assessments across different laboratories. Results from the first phase of the study showed a concerning lack of concordance of Ki67 assessments on a common set of specimens among eight laboratories regarded as experts in assessment of Ki67. These results were published (McShane, 2013) and prompted efforts to develop a web-based training tool to standardize and harmonize Ki67 scoring. CDP statisticians were involved in developing the training system and analyzing the data. They also helped to design a second international reproducibility study to assess whether harmonization efforts were successful. These results (Polley MY, 2015) showed that after calibrating to a common scoring method via the web-based tool, laboratories could achieve high inter-laboratory reproducibility in Ki67 scoring on centrally stained tissue microarray slides, but some clinically important discrepancies persisted. Future work will be needed to extend this approach to clinical use.

Additional projects directed by CDP and PACCT have included participation in international efforts to standardize quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR) assays to detect and measure BCR-ABL fusion gene transcripts in blood, in order to monitor for the molecular recurrence of chronic myelogenous leukemia after treatment, and efforts in the area of measurement of minimal residual disease, using various analytes and platforms.



BIOSPECIMEN ACCESS FOR THE CANCER RESEARCH COMMUNITY

Cooperative Human Tissue Network (CHTN)

The **CHTN** is not a bank for the storage of tissues, but provides access to human tissue for basic and translational research scientists in 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 conduct the retrieval, preservation, and delivery of specimens obtained from surgical resections and autopsies according to protocols defined by the investigator. Quality assurance review on all biospecimens is conducted by the board-certified anatomic pathologists. Since its establishment, CHTN has provided over a million high-quality specimens from a wide variety of organ sites to several thousand investigators. CHTN also produces and distributes sections of tissue microarrays constructed from multiple tissue types with several disease-specific designs.

Tissue procurement through 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. As such, about 80% of the investigators using CHTN samples are academic researchers, and the majority of them use the samples for their ROI grant funded projects. In addition, a large number of patents have cited the CHTN.

Tissue Microarrays for Breast Carcinoma and Colorectal Carcinoma

CDP, together with the **NCI Cooperative Breast Cancer Tissue Resource (CBCTR)**, has developed progression and prognostic tissue microarrays (TMAs), along with associated pathological and clinical outcome data, providing high statistical power to assist investigations of prognostic biomarkers in breast cancer and colorectal carcinoma.

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 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. **Application and access procedures** are available online through the CHTN.

National Clinical Trials Network Banks

The **NCTN Biospecimen Banks**, formerly the Cooperative Oncology Group Banks, 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 or assay clinical validation studies on uniformly treated patient populations. PIRB has supported these banks through U24 grant awards to the Oncology Groups and ensured that the banks implement best practices such as common data structures and standardized collection and storage practices. After the reorganization of nine Cooperative Oncology Groups into five NCTN Groups in March, 2014, the NCTN biorepositories were also reorganized and are now supported by five U24 grants with Biospecimen Bankers/Pathologists as PIs. The NCTN Group Banking Steering Committee was established with representatives from all the NCTN banks/groups and NCI to lead and implement a harmonization of SOPs and a process for fair access to specimens. Investigator requests for “legacy” banked specimens and research proposals are reviewed for scientific merit by the NCTN Core Correlative Science Committee. If proposals receive favorable reviews, specimens with clinical, treatment, and outcome data can be made available to researchers through collaborative arrangements. NCI and the NCTN Group Banking Steering Committee are currently working on an improved informatics system, and common application and review processes are being developed to improve access to specimens by the broader research community.

The Specimen Resource Locator (SRL)

Finding appropriate tissue resources for translational research can be very difficult for an investigator. The SRL database was designed to help researchers locate resources that might be able to provide the samples needed for their studies. This publicly searchable database includes information about biospecimen banks and sample procurement services. The specimens and samples come from non-commercial sources, either NCI or non-NCI-funded resources. Investigators can search the database and gain access to thousands of specimens of various tumor, organ, and preservation methods.

In the event a researcher is unsuccessful in finding the appropriate specimen resource through the SRL, they may contact the [NCI Tissue Expediter](#) and speak with a scientist who can further assist them. The NCI Tissue Expediter can also assist researchers to identify potential collaborators. NCI and NCI's SRL do not oversee or take responsibility for the content, quality, or data of the specimen collections or resources participating in the SRL.

NIH GENOTYPE TISSUE EXPRESSION (GTEx) PROGRAM

BBRB coordinated tissue acquisition for the [NIH Common Fund's Genotype Tissue Expression \(GTEx\) Program](#), which is studying human gene expression and regulation in multiple normal tissues with a focus on the expression of quantitative trait loci and their potential disease associations. BBRB staff worked in partnership with the [Frederick National Laboratory for Cancer Research \(FNLCR\)](#) to develop the infrastructure capable of delivering large quantities of high-quality and annotated tissues from postmortem and organ donor cases for genomic analysis. The same infrastructure was customized for collection of tumor tissues for BBRB's [Biospecimen Preanalytical Variables \(BPV\) Program](#), and is now being utilized for biospecimen collections to support the [NCI Clinical Proteomic Tumor Analysis Consortium \(CPTAC\)](#).

Biospecimen collections for GTEx were completed in late 2015, with biospecimens from almost 1,000 postmortem donors, and the program is now planning and implementing

a legacy plan for the remaining biospecimens and all associated biospecimen and clinical data. Residual biospecimens are now available to researchers outside the GTEx program; sample requests can be made at the [GTEx Portal](#). An extensive set of GTEx public resources has been developed and released to the research community, including a full set of the SOPs guiding the project and an online library of histological images that correspond to the clinical, DNA and RNA sequencing, and expression quantitative trait loci data now available at dbGaP. More than 200 scientific publications have been generated thus far from the molecular data derived from the GTEx biospecimens (Keen J, 2015). An associated study of the ethical, legal, and social implications of the GTEx project was also conducted, with findings relevant to ongoing work in engaging research participants (GTEx Consortium, 2013; Carithers LJ, 2015; GTEx Consortium, 2015).

GTEx Standard Operating Procedures (SOPs)

NCI released to the public a [compendium of SOPs](#) that are currently guiding the successful collection of normal human biospecimens for the NIH GTEx project. NCI released these SOPs in order to provide transparency about the biospecimen collections that NCI is conducting and to enable high quality biospecimen collection by others in the research community.

The GTEx Symposium: All Things Considered

The "Genotype Tissue Expression (GTEx) Symposium: All Things Considered — Biospecimens, Omics Data, and Ethical Issues" was a 2-day symposium held on the NIH campus on May 20-21, 2015. Topics included an overview of the GTEx program, the biospecimen challenges for GTEx, establishing the approach for GTEx prospective collections, new systems that were developed to implement the program, ethical, legal, and social implications research within the program, and scientific outcomes from the GTEx Project thus far. An archive of [Day 1](#) and [Day 2](#) of the GTEx Symposium can be viewed online. An annual meeting open to the research community was initiated in 2013, and the final GTEx Project Community Scientific Meeting was held on June 28, 2017 in Rockville, MD.



- Development of a searchable website of the existing biospecimen literature, the *Biospecimen Research Database (BRD)*

Biospecimen science activities are continuing in BBRB through the following coordinated activities:

- The *Biospecimen Preanalytical Variables (BPV) Program* that is examining the effects of key biospecimen preanalytical factors in formalin-fixed, paraffin-embedded (FFPE) and frozen tissues on genomic and proteomic research data (e.g., DNA and RNA sequencing)
- Expansion of the BRD to include an international collection of established SOPs for biospecimen collection, processing, and storage
- Development and distribution of literature annotated, evidence-based procedural documents — *Biospecimen Evidence-Based Practices (BEBP)*
- A new Cooperative Agreement grants program to integrate biospecimen science studies into clinical assay development in order to improve the reproducibility and utility of clinical biomarker assays utilized in therapeutic clinical trials

BIOSPECIMEN RESEARCH NETWORK (BRN)

The *Biospecimen Research Network (BRN)* was initiated to systematically address the impact of specific variables in individual specimen types on molecular data from different analysis platforms. Differences in preanalytical procedures (e.g. procurement, processing, shipping, storage) are potentially a large component of the inability of other researchers to reproduce biomarker findings. The goal of the BRN is to address these issues by sponsoring, conducting, and collaborating on biospecimen science studies to assess the effects of pre-analytical factors on the outcome of genomic and proteomic studies conducted for clinical diagnosis and cancer research purposes. By communicating the results of such research to the scientific community, and incorporating the data into biospecimen evidence-based practices for the collection, processing, storage, and analysis of biospecimens, BBRB aims to significantly improve the quality and reproducibility of NCI-funded biospecimen-based research. The first phase of the BRN program concluded in 2015.

BRN program activities included:

- A public outreach effort to define issues around human specimen research and identify the most pressing needs for human analyte standardization, including an annual *BRN Symposium*
- *Sponsored research* in biospecimen science that resulted in numerous publications and stimulated growth of this new area of science

TOOLS AND GUIDANCE FOR BIOBANKING

NCI Best Practices for Biospecimen Resources

After an extensive due diligence process, BBRB (then OBBR in the NCI OD) published the *First-Generation Guidelines for NCI-Supported Biorepositories in the Federal Register* (71 FR 25184) and on the OBBR website, where public comments were requested. The *Guidelines* were subsequently revised on the basis of public comment and input from content experts and renamed the *NCI Best Practices for Biospecimen Resources*.

The *NCI Best Practices* do not comprise detailed laboratory procedures, but rather represent salient guiding principles that define state-of-the-science biospecimen resource practices, promote biospecimen and data quality, and support adherence to ethical and legal requirements. The recommendations are intended to be adapted, as appropriate, based on the mission and scientific needs of individual biospecimen

resources. Although adoption of the *NCI Best Practices* is voluntary, the outlined principles support the goal of optimizing biospecimens for cancer research. Notably, the College of American Pathologists has recently launched a Biorepository Accreditation Program based on the *NCI Best Practices*.

The revised 2016 edition includes (i) recommendations based on the most recent research, guidance and standards for collecting, processing and storing specimens, (ii) informatics practices in recognition of the phasing out of the caBIG and caGRID programs, and (iii) literature references. The Ethical, Legal and Policy Best Practices was also updated based on more recent guidance concerning (i) informed consent for genomics research, (ii) the return of research results, and incidental findings, (iii) genomic data sharing, and (iv) community engagement.

Online Library of Standard Operating Procedures (SOPs) for Biobanking

An online library of SOPs related to biospecimen collection, processing, and storage was created within the *NCI Biospecimen Research Database (BRD)*. The BRD is a free and publicly accessible database that contains peer-reviewed primary and review articles, and now SOPs, in the field of human biospecimen science. The goal of BRD is to share information and increase collaboration on evidence-based biospecimen practices, and ultimately to increase research reproducibility. The project is international in scope.

Biobank Economic Modeling Tool

Biospecimens and biospecimen resources are integral to the advancement of basic and clinical research, and play an important role in precision medicine. NCI conducted a survey on the economics of biobanking and released the *Biobank Economic Modeling Tool (BEMT)*. BEMT is a publically available, web-based financial planning tool for biobanks designed to enhance understanding of the economic considerations involved in initiating, operating,

and maintaining a biobank, thereby assisting with long-term financial planning and cost recovery.

Open source versions of biobanking software and vocabulary utilized in NCI programs

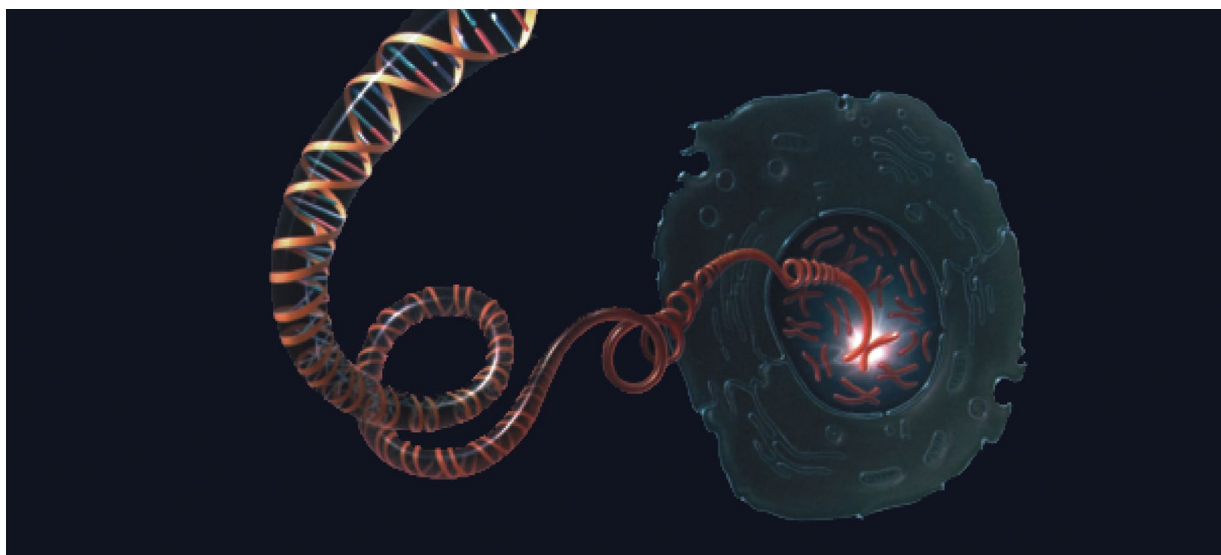
NCI's *Comprehensive Data Resource (CDR)* is a distributed web-based system that manages and maintains multi-dimensional data models on biospecimens. CDR was developed and is currently utilized to collect biospecimen and clinical data on biospecimens collected from cancer patient donors and post-mortem donors, for the NCI BPV and NIH GTEx programs. A simplified version known as "*CDR Lite*" has also been released as open source software.

Biobanking and clinical data terminology utilized in the GTEx and BPV programs has been independently reviewed and released for public use in the *NCI Cancer Data Standards Registry and Repository (caDSR)* and the *NIH Common Data Elements (CDE) Repository*.

PATHOLOGY EVALUATION OF TISSUE SPECIMENS FOR RESEARCH

PIRB provides pathology evaluation of tissue specimens for use in research methodologies (ex. Next Generation Sequencing (NGS) assays, molecular testing, and pharmacodynamic immunoassay development) and assay validation by the Pharmacodynamic Assay Development and Implementation Section (PADIS), National Clinical Target Validation Laboratory (NCTVL), and Molecular Characterization Laboratory (MoCHA), all part of the FNLCR. The assessment includes confirmation of diagnosis, evaluation and annotation of Aperio-scanned images of the H&E and immunohistochemical stained slides for tumor content and viable tissue, as well as QA/QC of tissue specimens.

PIRB also offers pathology support and expertise in collaboration with other NCI divisions and NIH institutes.



FUTURE DIRECTIONS

BIOMARKER SUPPORT FOR IMMUNOTHERAPY

Immunotherapy has been successful in a subset of patients with particular malignancies, and holds the promise of therapeutic potential in other tumors. In January 2016, DCTD convened a workshop engaging immune-oncology (IO) leaders to provide insight into the critical challenges in the field, and to advise NCI on new directions and initiatives that will facilitate coordinated efforts and expedite progress in cancer immunotherapy. The participants represented academia, industry, and the NCI intramural programs and covered a range of in-depth discussions from basic science, to translational research, to clinical investigation and databases/informatics.

Overall, the workshop participants concluded that NCI should play a central role in providing strong support in high priority areas. In addition to support for basic research and training for new investigators in cancer immunology, key recommendations for NCI related to immunotherapy biomarker development included:

- Strengthening the infrastructures of research centers to enable biomarker-rich early clinical trials and translational studies

- Facilitating biomarker studies through support for biobanking and assay development or standardization
- Development of a common platform for the collection of and access to immune-related biomarkers, in addition to clinical and genomic data

PRECLINICAL AND CLINICAL MOLECULAR CHARACTERIZATION FOR DEVELOPMENTAL THERAPEUTICS

CDP plans to enhance and adapt the laboratory resources developed at FNLCR to focus on assay development and tumor characterization for the DCTD clinical trials program. DCTD supports several clinical trials networks to develop investigational drugs for cancer. These drugs often are of interest because of their activity against biological targets that are abnormal in cancer. However, the molecular mechanism(s) of action is often not known with certainty, and it is rarely known which molecular abnormalities could serve as eligibility criteria to predict response or resistance. Therefore, obtaining whole exome sequencing, RNA sequencing, and potentially other molecular characterization on specimens from patients participating in these trials should be informative in this regard. One objective of early phase trials is to determine the dose at which the drug engages the relevant cellular mechanisms. The laboratories at FNLCR (MoCHA

and PADIS) will produce robust assays that are well characterized and documented by SOPs so that the assays can be transferred to a clinical laboratory as needed to support drug studies.

The broad aim is to accelerate time to appropriate drug approval, or to abandoning development of unsuccessful drugs, by identifying indicators of drug action, response, and resistance biomarkers from preclinical models, by using robust, well characterized assays to investigate specimens retrospectively from DCTD-sponsored clinical studies. In addition, and where feasible, a goal is to develop analytically validated pharmacodynamic and predictive assays to be used as integrated and/or integral assays in a GLP- or CLIA- certified clinical assay laboratory network in NCI-sponsored precision medicine studies. These assays will inform whether the intended molecular target has been engaged by the investigational treatment. These activities will also be helpful in developing rational combination therapies for cancer (e.g. combining two targeted agents, or targeted agents and immune checkpoint inhibitors).

CIRCULATING TUMOR NUCLEIC ACIDS

For a number of years, it has been known that tumor cells can often be detected in the bloodstream, and diagnostic tests have been devised to enumerate and characterize these cells. More recent reports indicate that genetic material derived from tumor sites can also be identified in the blood of cancer patients. These studies have demonstrated the potential of this genetic material to be used as a source of screening patients through so called “liquid biopsy” for actionable somatic mutations. This approach permits screening of virtually all patients, even those whose tumor sites would introduce significant risk for needle biopsy. In addition, it has been reported that the use of serial assessment of circulating tumor DNA (ctDNA) is feasible for the determination of treatment response and disease progression. Additional uses for assessment of circulating nucleic assays include monitoring of treatment effect or recurrence, monitoring for the

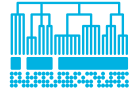
development of actionable resistance mutations, and potential detection of target engagement by novel therapeutics.

CDP plans to approach this opportunity in two ways. First, it will pursue an ongoing research program at FNLCR. The laboratory will assess current methods available for collection, shipment, and purification of ctDNA from blood or urine, examine methods to identify many somatic mutations in ctDNA using next-generation sequencing, and ultimately develop a full clinical grade assay to identify and/or monitor actionable somatic mutations in patient body fluids. Second, CDP will work with outside investigators and FDA to develop strategies to demonstrate the clinical utility of ctDNA-based diagnostic tests in clinical decision-making for cancer patients. A first step was taken in October 2016, when CDP hosted a workshop on this topic.

BIOETHICS AND SCIENCE IN BIOBANKING

Publications are in preparation from ongoing BBRB research initiatives in the ethical, legal, and social implications of biobanking. These include the results of studies that have been embedded in the GTEx programs. These studies investigate the attitudes and understandings of biospecimen donors and the families of deceased donors towards research biospecimen donation and engagement in research including return of research results. The GTEx study also investigates community attitudes about biospecimen donation and actively engages diverse Community Advisory Boards in the preparation of training materials for consenting personnel.

A new CDP initiative in biospecimen science is working to advance clinical biomarker assay development within the NCTN and ETCTN. Grantees for a new FOA will be awarded in 2017 and 2018 and together will form a network of investigators to solve molecular assay challenges when utilizing small biopsies, including tissue cores and needle biopsies. An additional, trans-NCI initiative is in the planning stages and will investigate and mitigate the challenges in utilization of clinical FFPE biospecimens for RNA sequencing analysis.



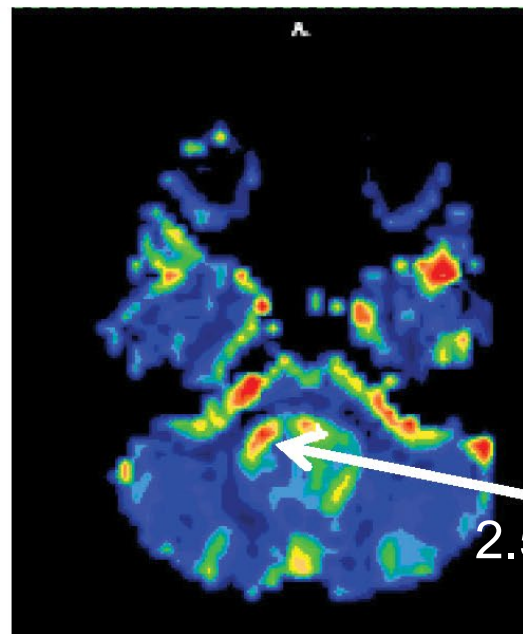
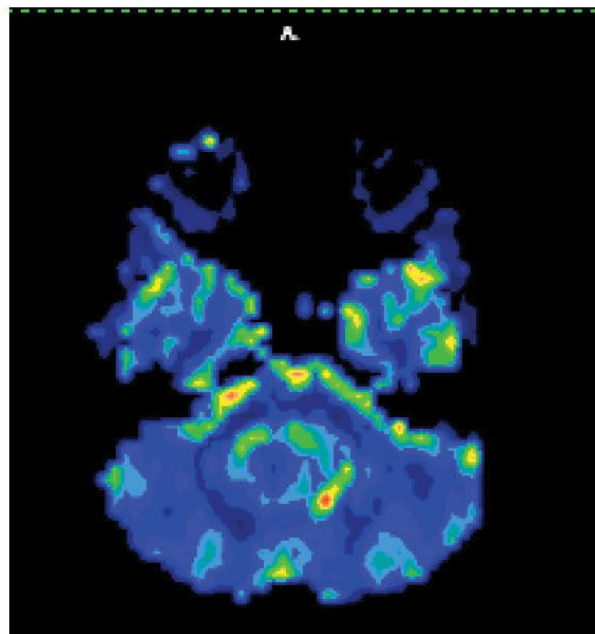
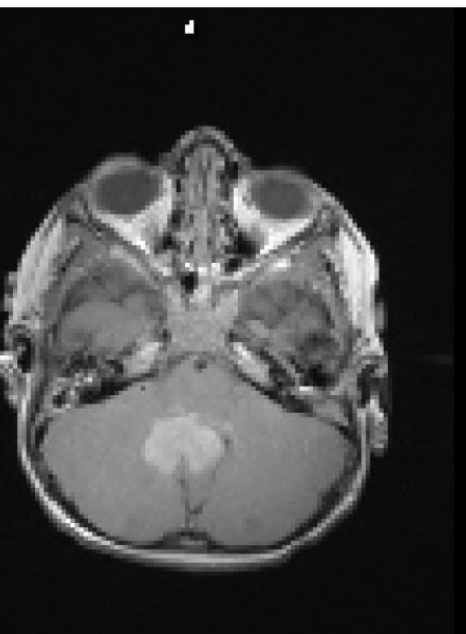
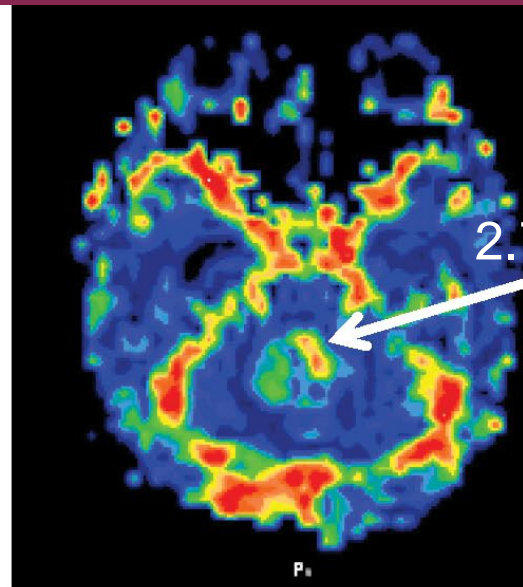
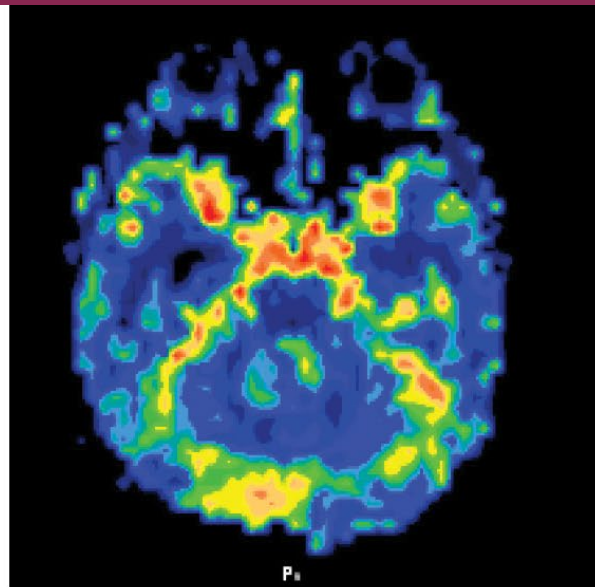
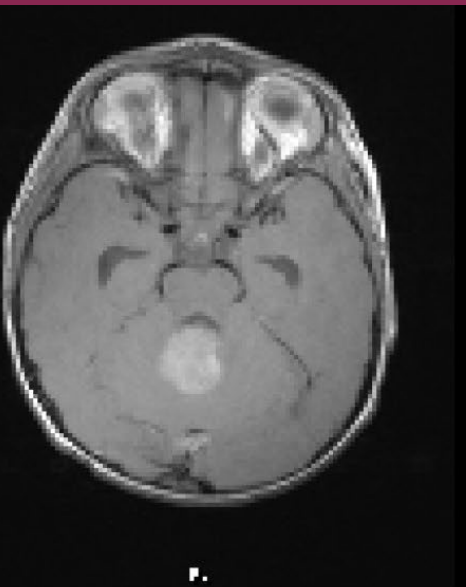
PROGRAMS AND INITIATIVES (2013-2017)

CANCER IMAGING PROGRAM

T1 + gadolinium

rCBF

rCBV





OVERVIEW

The Cancer Imaging Program (CIP) of DCTD 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 applications
- Imaging interventions in cancer

Imaging is an enabling scientific discipline combining methods in advanced technology and complex analysis to provide the ability to extract spatial and temporal information from *in vivo* systems. Imaging enables interrogation of intact biological systems across the spectrum from subcellular to macroscopic levels and from discovery research to clinical decision making. In the last decade, major advances have been made in our understanding of tumor systems, in large part due to advanced imaging capability. The utility of imaging has grown beyond anatomic imaging to include functional and molecular domains. These enhancements have opened new opportunities for imaging in areas such as pharmacodynamics (PD), image-guided interventions, and immunotherapy,

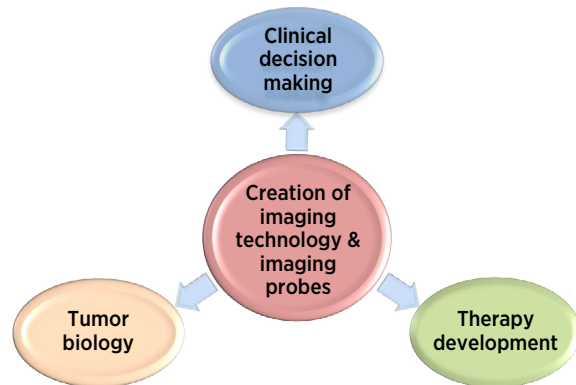


FIGURE 26: ROLE OF IMAGING TECHNOLOGIES IN UNDERSTANDING BASIC TUMOR BIOLOGY, THERAPEUTIC DEVELOPMENT AND INFORMING CLINICAL DECISIONS.

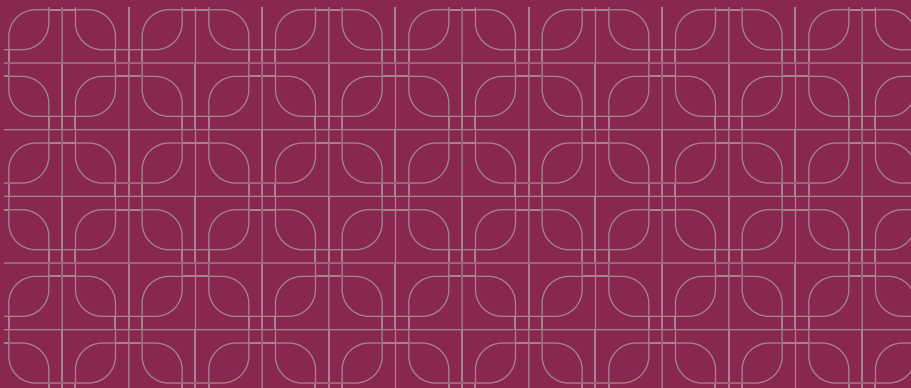
leading to improved standard of care. There is growing interest in combining information gained from imaging methods with information from genomic and proteomic analyses in order to increase the body of knowledge about cancer and its progression or response to therapy.

Because of its successes, 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, to visualize and quantify the physiological, PD, cellular, or molecular processes in living tissues. This is being aided by advances in artificial intelligence (AI), data extraction and processing for building and testing predictive models of cancer development, metastasis, and response to therapy. Connections to archives of clinical, genomic, and proteomic data are essential to this progress.

Advanced imaging is critical for fundamental improvements in the care of cancer patients. As NCI continues to guide the discovery of new molecular signatures and cellular pathways of cancer, success can be achieved only by understanding how these processes integrate into complex biological systems. Only then can we begin to develop effective therapies with lower morbidity. The challenge in medical imaging research is to continue to deliver sophisticated and integrated imaging methodologies to provide insight into the complex,

PAULA M. JACOBS

ASSOCIATE DIRECTOR



Paula M. Jacobs, PhD, joined NCI after 30 years in the pharmaceutical and medical device industries, where she was a key developer of ultrasmall superparamagnetic iron oxide drugs as magnetic resonance imaging agents and iron replacement therapeutics. She became Deputy Associate Director of DCTD responsible for CIP in 2009, Acting Associate Director in 2011, and Associate Director in 2012. Her efforts for NCI have been focused on lowering the scientific, logistical, and regulatory barriers to investigational use of positron emission tomography radiopharmaceuticals for therapeutic drug development by facilitating access to Investigational New Drug (IND) filings and by overseeing research to develop labeled drugs for clinical and preclinical use, particularly for optical imaging agents used to assist surgeons to make complete resections. Another effort is focused on wide-ranging aspects of standardization and quantitative imaging techniques, and a third focus is on genome-imaging correlations. Dr. Jacobs serves on three NCI Experimental Therapeutics (NExT) committees to review and manage the projects chosen for development. She oversees a radiochemistry laboratory and radiopharmacy at the Frederick National Laboratory for Cancer Research that provides preclinical and early clinical radiopharmaceuticals in support of therapeutic drug development.

Dr. Jacobs earned her undergraduate degree in chemistry at the Massachusetts Institute of Technology and graduate degrees at Tufts University and Northeastern University. Her postdoctoral training was at Northeastern University, the Massachusetts Institute of Technology, and Peter Bent Brigham Hospital/Harvard Medical School.

Her industrial experience began at Clinical Assays, a division of Baxter Travenol that manufactured *in vitro* radioimmunoassays, where she was responsible for process improvements in radioactive tracer synthesis, technical product maintenance, product and process improvements, and manufacturing of all reagents used in the company's products. At Seragen, a small biotechnology firm, she was General Manager, with profit and loss responsibility for a division that developed, manufactured, and marketed prostaglandin, leukotriene, and small protein immunoassays. Subsequently, she joined Advanced Magnetics as Vice President, Development, to help chart a new course for this small biomedical products company. She was responsible for the development of iron oxide magnetic contrast agents from laboratory synthesis through IND submissions, including design of pharmacology, toxicology, and clinical studies. She served as international liaison for technology transfer to licensees, worked with independent physicians in the United States and abroad to develop physician IND trials in magnetic resonance imaging, and collaborated with academic researchers in a variety of preclinical investigations.

Dr. Jacobs has published papers in the areas of organic chemistry, inorganic chemistry, magnetic resonance imaging, positron emission tomography (PET), neuro-oncology, and nephrology.



heterogeneous, and dynamic biologic system that constitutes cancer. Even more of a challenge is to integrate this wealth of information to understand, manipulate, and defeat cancer through prevention and therapeutic intervention.

Imaging is critical to increasing our understanding of subcellular structural and molecular interactions executed by the proteome-to-cell microenvironment and cell-cell interactions through complex signaling and transfer processes. Imaging currently provides information at several places across the genotype-to-phenotype continuum. At one extreme, imaging is being applied to evaluate subcellular structure and biology, including protein-protein interactions and compartmentalization within unique intracellular microenvironments. At another extreme, macro-level imaging is used clinically to evaluate cancer phenotypic changes and characterizing changes in the cancer microenvironment.

In the next decade, CIP-sponsored research will continue to contribute to the basic understanding of various cancers by creating novel methods to enhance the clinical role of imaging in noninvasive diagnosis, help identify disease subsets for effective treatment in patients, improve disease staging and treatment monitoring, and play a pivotal role for imaging in development of new therapies. Correlation of medical images with genomic and proteomic data will be critical in precision medicine, particularly where obtaining tissue samples is difficult, such as in recurrent disease or multiple metastatic deposits.

As part of its mission, CIP plays a critical role in the activities of NIH and NCI, contributing to the integration of imaging with emerging technologies, such as nanotechnology, cancer genomics, proteomics, and high-throughput screening and big data challenges. In addition to funding projects in key areas, CIP supports researchers by providing pooled resources and developing protocols that encourage the sharing of data, samples, and results.

CIP 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 and 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 are being developed through extramural research support that highlights extensive collaborations among biologists, 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. Medical images contain much more information than is obvious to the naked eye, and radiomics approaches using structured computer-extracted features and AI are yielding increasing insights. Similar approaches employing complex cell systems have already revealed unanticipated network connectivity when these systems are perturbed with drugs with the potential to lead to refined models to be used in drug development for predicting not only target response but also toxicity. Translation of these research results to clinical practice is likely to depend heavily on collaboration with ongoing research in nanotechnology.

CIP STRATEGIC GOALS

- Encourage investigators to design and apply imaging to better understand tumor microenvironment and biochemistry.
- 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 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 precision medicine.
- In collaboration with the Food and Drug Administration (FDA), reduce barriers to full clinical implementation of imaging agents and devices.

HISTORICAL NOTE

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

STRUCTURE AND FUNCTION

CIP unites researchers from disciplines as diverse as radiology, nuclear medicine, bioengineering, biology, genomics, chemistry, computer science, informatics, and physics in a team science 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 activities and responsibilities can be divided into six broad areas:

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

Through this organizational structure, CIP supports extramural investigators in academia and private industry as they create and apply the next generation of imaging technologies, including molecular probes, imaging devices, new contrast agents, and image-guided therapies to cancer problems.



MOLECULAR IMAGING BRANCH

The goal of *in vivo* cancer molecular imaging supported 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 IND applications and encouraging suppliers for noncommercial 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 and the Molecular Imaging Clinic in the NIH Clinical Center

CLINICAL TRIALS BRANCH

CIP supports clinical trials in several ways:

- Awarding grants and contracts to extramural investigators for exploratory trials
- Advising and providing a strategic roadmap for imaging research in the extramural imaging community via a leadership role in the Cancer Imaging Steering Committee (CISC)
- Providing guidance for NCI-sponsored clinical trials through review of protocols sponsored by the Cancer Therapy Evaluation Program (CTEP) that have imaging as a scientific objective

- Helping to promote standardization of imaging used in NCI-sponsored clinical trials by helping to establish and advise the Imaging and Radiation Oncology Core (IROC) as part of the National Clinical Trials Network (NCTN)
- Overseeing development of imaging in trials done through NCI's early phase Experimental Therapeutics Clinical Trials Network (ETCTN)
- Developing trial-related informatics
- Promoting the development of radiomics based clinical support tools

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 INTERVENTION BRANCH

The Image-Guided Intervention Branch (IGIB) promotes the integration of imaging, informatics, and interventional methods to address diverse clinical challenges such as directed biopsy, image-guided tumor ablations, dimensionality of scale, and targeted drug delivery. IGIB is heavily involved in image augmentation probe development and supports research in probes, tissue markers, and delivery vectors for applications where imaging plays a significant role in clinical decision making.

By its very nature, image-guided interventions (IGI) encompass all aspects of imaging; from disease detection and therapy planning to response assessment and disease recurrence monitoring. Central to the IGI mission is contributing to the therapy delivery process. The therapy can be surgery, radiotherapy, cryotherapy, targeted drug therapy, or any of many cancer treatments. Imaging in this process can be with or without exogenous agents or probes intended to augment the image. Combinations of imaging methods such as optical/MRI or ultrasound/MRI are often appropriate for image guidance during therapy.

IMAGING TECHNOLOGY DEVELOPMENT BRANCH

The Imaging Technology Development Branch (ITDB) 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. The integration of informatics with imaging is an important activity of the branch.

NANODELIVERY SYSTEMS AND DEVICES BRANCH

The Nanodelivery Systems and Devices Branch (NSDB) was formed in 2017. Initially known as the Office of Nanotechnology Research in the Center of Strategic Scientific Initiatives within the office of the NCI Director, this program was established in 2007 to support the development of nanomaterials and nanotechnology enabled devices for clinical applications in cancer diagnosis and treatment. It was the first program to fund large scale cooperative research in this area of medicine. Within its initial embodiment, it focused on the development of technology platforms that were seeking appropriate cancer applications. The program has matured and evolved into defining relevant biological and clinical problems that serve as a driver for the implementation of suitable nanotechnologies. Since the beginning of the program,

several technologies developed under the Nanotechnology Alliance funding have reached a level warranting the initiation of clinical trials.

Due to the increased technological maturity and progression of several technologies to the clinical stage, the decision was made to transition the program into DCTD. Although the new branch resides organizationally within CIP, its activities will extend beyond nano-imaging to also include novel *in vitro* diagnostics and therapeutics benefiting from the incorporation of nanotechnologies. The experience and expertise of the staff in managing cooperative agreement network programs will enable NSDB to serve as a focal point for nanotechnology-based grant and contract activities within DCTD and NCI. The NSDB will continue in its prior role supporting and overseeing the [Nanotechnology Characterization Laboratory \(NCL\)](#) in Frederick National Laboratory for Cancer Research for the characterization of nanomaterials, and will participate in supporting the [Small Animal Imaging Program \(SAIP\)](#) activities involving nanomaterials.

CIP GRANTS OVERVIEW

The CIP research portfolio included 417 funded grants during fiscal year 2016, totaling \$184 million. The grant award mechanisms used by CIP and their distribution in terms of research support in 2016 are shown in the accompanying chart. The predominant mechanism is the individual research project grant (R01), followed by cooperative agreements (U01).

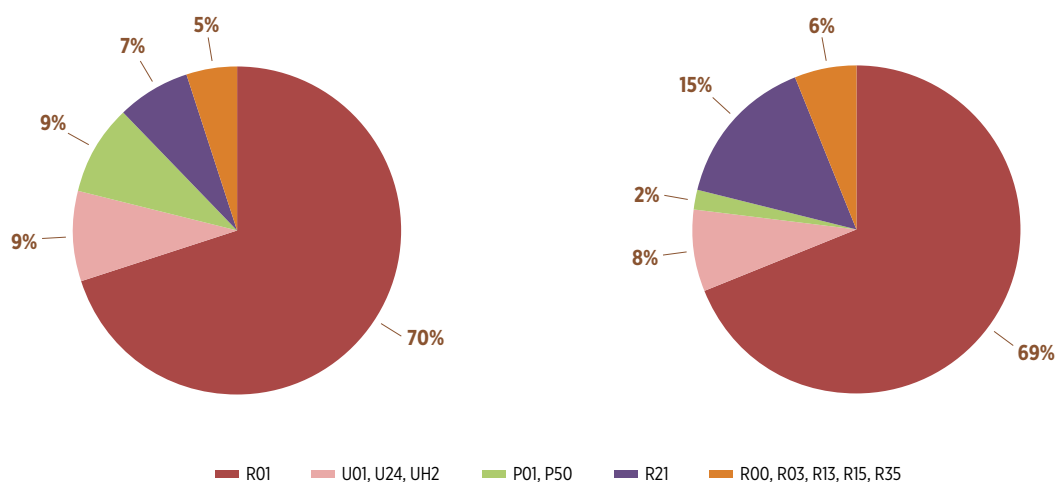


FIGURE 27: DISTRIBUTION OF 2016 GRANT FUNDS (LEFT) AND NUMBERS OF GRANTS (RIGHT) BY MECHANISM.

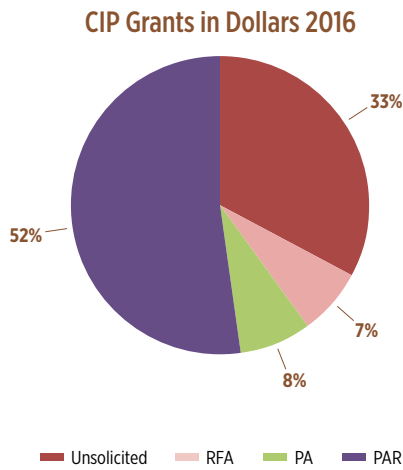


FIGURE 28: DISTRIBUTION OF CIP 2016 RESEARCH FUNDS BY SOLICITATION MECHANISM.

Because of the specialized nature of imaging research, CIP has developed a number of funding initiatives that encourage applications in specific areas. Figure 28 shows the breakdown of funded grants by mechanism/initiatives.

ASSISTANCE TO THE CANCER COMMUNITY

CIP 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 the Center for Cancer Research, which is providing the infrastructure for early clinical trials of imaging probes, and DCTD, which is providing expertise in drug development.

SPECIALIZED INITIATIVES

Extramural funding of research related to imaging at NCI includes traditional P01, R01, R21, and other investigator-initiated grants. Several specialized initiatives have been developed or re-issued during this time period to address unmet needs in the field. They include initiatives in all of the areas that CIP is involved. CIP initiatives cover the full spectrum of research efforts, from basic research to clinical trials. These programs serve a variety of needs in the cancer

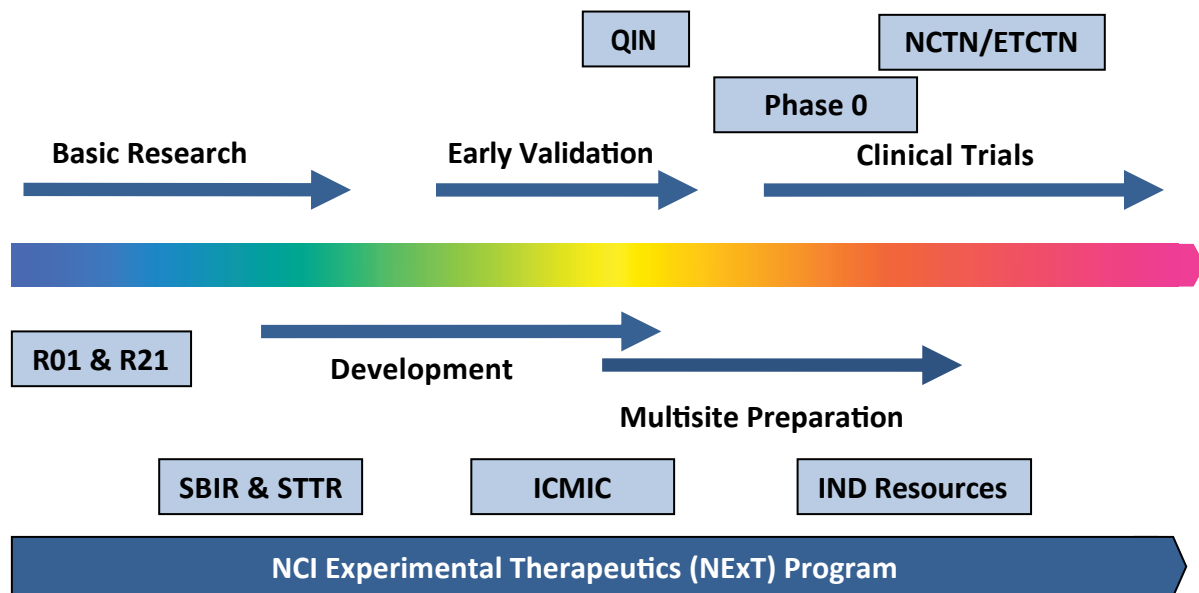


FIGURE 29: IMAGING RESEARCH SPECTRUM AND KEY CIP PROGRAMS.

ICMIC = In Vivo Cellular and Molecular Imaging Centers; QIN = Quantitative Imaging Network; SBIR = Small Business Innovation Research; STTR = Small Business Technology Transfer

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. Others use specialized grant mechanisms, such as U01, P50, and U24, suited for their positions in the research pipeline.

- **Early Phase Clinical Trials in Image-Guided Interventions (R01).** PAR-17-167: The overall goals of this initiative are to provide support for clinical trials in preliminary evaluation of safety and efficacy of imaging agents, as well as assessment of imaging systems, image processing, image-guided therapy, and contrast kinetic modeling. As many such preliminary evaluations are early in development, this FOA will provide investigators with support for pilot (Phase I and II) cancer imaging clinical trials, including patient monitoring and laboratory studies. It provides funding for the immediate conduct of Phase 0, 1, or small Phase 2 clinical trials that are designed and developed to facilitate completion within the 3-year funding period. This FOA supports novel uses of known/standard clinical imaging agents and methods as well as the evaluation of new agents, systems, or methods. The imaging and image-guided intervention (IGI) investigations, if proven successful in these early clinical trials, can then be validated in larger studies through competitive R01 mechanisms, or through clinical trials in the [Specialized Programs of Research Excellence \(SPOREs\)](#), [Cancer Centers](#) and/or the NCI's [National Clinical Trials Network](#).
- **Image-Guided Drug Delivery in Cancer (R01).** PAR-16-044: The Imaging-Guided Drug Delivery initiative encourages innovative translational research in the development of quantitative *in vivo* imaging characterization of imaging-guided drug delivery in cancer, including characterizations of the target, delivery validation, and therapy response. This initiative supports 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 imaging-guided drug delivery technology into the clinic are appropriate for this initiative. A goal of this research is the development of minimally invasive or noninvasive “theranostic” (combined therapeutic and diagnostic) approaches to cancer in order to optimize the therapeutic ratio and to provide quantitative imaging evaluation of therapy. These grants also support the development of techniques to identify and modulate features of

the tumor microenvironment 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, and resulted in 12 pending applications. This initiative was developed in collaboration with the NCI Alliance for Nanotechnology in Cancer.

- **Imaging and Biomarkers for Early Detection of Aggressive Cancer (U01).** PAR-16-089: Collaboration with Division of Cancer Prevention: The purpose of this program is to: (a) invite researchers to submit collaborative research project (U01) applications to improve cancer screening, early detection of aggressive cancer, assessment of cancer risk and cancer diagnosis aimed at integrating multi-modality imaging strategies and multiplexed biomarker methodologies into a singular complementary approach, and (b) establish a Consortium for Imaging and Biomarkers (CIB) to perform collaborative studies, exchange information, share knowledge, and leverage common resources. The research will be conducted by individual multi-disciplinary research teams, hereafter called Units. All Units are expected to participate in collaborative activities with other Units within the Consortium.
- **Quantitative Imaging Network (U01).** PAR-17-128 and PAR-17-129: This cooperative agreement program seeks to bring quantitative methods to clinical imaging to reduce the bias and variance seen in the variety of imaging devices available in the clinical setting. The program also works to create software tools to extract quantitative information from clinical images and apply robust analyses to predict or measure response of tumors to therapies in clinical trials. Progress toward applying decision support tools in clinical trials as correlative tools is gaining speed and soon the network will be testing tools in several National Clinical Trial Network (NCTN) trials.
- **Academic-Industrial Partnerships for the Development and Validation of *in vivo* Imaging Systems and Methods for Cancer Investigators (R01).** PAR-17-093: In collaboration with the Radiation Research Program and the Cancer Diagnosis Program, this initiative encourages applications from research partnerships formed by academic and industrial investigators to accelerate translation of either preclinical or clinical *in vivo* imaging systems and methods that are designed to solve a cancer problem. The proposed imaging system or methods may include



single or multi-modality *in vivo* imaging and spectroscopy systems, image-guided and drug delivery systems, image analysis, and related research resources. Translational development and methods optimization for a targeted cancer problem is emphasized.

- **Academic-Industrial Partnerships for Translation of Technologies for Cancer Diagnosis and Treatment (R01).** PAR-15-075: Collaboration with the Cancer Diagnosis Program and the National Institute of Biomedical Imaging and Bioengineering, this initiative encourages applications from research partnerships formed by academic and industrial investigators, to accelerate the translation of technologies, methods, assays, or devices, and/or systems for preclinical or clinical molecular diagnosis or *in vitro* imaging that are designed to solve a targeted cancer problem. Funding may be requested to enhance, adapt, optimize, validate, and translate the current commercial systems, next-generation systems, quality assurance and quality control, validation and correlation studies, quantitative imaging, and related research resources. Basic research or actual commercial production are not supported.
- **Oncology Co-Clinical Imaging Research Resources to Encourage Consensus on Quantitative Imaging Methods and Precision Medicine (U24).** PAR-16-385: Collaboration with the Division of Cancer Prevention and the Division of Cancer Biology: The purpose of this program is to invite Cooperative Agreement (U24) applications to develop research resources that will encourage a consensus on how quantitative imaging methods are optimized to improve correlation of results for co-clinical trials. The scientific goals of this FOA are to: (a) perform the appropriate optimization of the pre-clinical quantitative imaging methods, (b) implement the optimized methods in the co-clinical trial, and (c) populate a web-accessible research resource with all the data, methods, workflow documentation, and results collected from the co-clinical investigations.
- **Advanced Development of Informatics Technologies for Cancer Research and Management (U24, U01, R21).** PAR-15-331, PAR-15-332, PAR-15-333, PAR-15-334: Collaboration with NCI's Center for Biomedical Informatics and Information Technology: The purpose of this series of programs is to support advanced development and enhancement of emerging informatics technologies to improve the acquisition, management, analysis, and



dissemination of data and knowledge across the cancer research continuum, including cancer biology, cancer treatment and diagnosis, cancer prevention, cancer control and epidemiology, and/or cancer health disparities. Each separate program in this series focuses on emerging informatics technology, defined as one that has passed the initial prototyping and pilot development stage, has demonstrated potential to have a significant and broader impact, has compelling reasons for further improvement and enhancement, and has not been widely adopted in the cancer research field.

IMAGING INFORMATICS

The informatics activities of CIP address major challenges to the acceleration of cancer imaging research. CIP established and supports [The Cancer Imaging Archive \(TCIA\)](#) to address both the lack of readily accessible, large, curated clinical image collections and the barriers to interinstitutional sharing of image data.

IN VIVO CELLULAR AND MOLECULAR IMAGING CENTERS

The *In Vivo* Cellular and Molecular Imaging Center (ICMIC) P50 grant program, established in 1999, completed the final year of funding in 2016 with PAR 09-157. When the ICMIC program was established, molecular imaging was in its infancy. During the 16 years of NCI funding through the ICMICs, the power and potential of molecular imaging has been realized, and is now being integrated into scientific projects spanning discovery sciences through to clinical applications.

The highly successful ICMIC program supported interdisciplinary scientific teams conducting cutting-edge cancer molecular imaging research. ICMIC grants supported:

- Innovative cancer molecular imaging research projects
- Unique core facilities
- Initiation of pilot research in promising new directions
- Interdisciplinary career development opportunities for investigators who were 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:
 - Investigation into 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

MOLECULAR 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. In 2009, the intramural Molecular Imaging Clinic was established to provide a dedicated research infrastructure for such trials. This facility is engaged in performing multiple Phase 0 and 1 imaging studies, including some with radiopharmaceuticals supplied by the radiopharmacy at the Frederick National Laboratory for Cancer Research (FNLCR) that was developed in collaboration by CIP during the same period.

Three IND drugs are currently being supplied to the NIH Clinical Center: 16α - ^{18}F Fluoro- 17β -estradiol, ^{89}Zr Panitumumab, and ^{18}F DCFBC.

Institution	Principal Investigator
Emory University	Carolyn Meltzer
Johns Hopkins University	Zaver Bhujwala
Massachusetts General Hospital	Ralph Weissleder
Memorial Sloan-Kettering Cancer Center	Steven Larson/Ronald Blasberg
Stanford University	Sanjiv Gambhir
University of California, Los Angeles	Harvey Herschman
University of California, San Diego	Robert Mattrey
University of Michigan	Brian Ross
Vanderbilt University	John Gore
MDACC/Washington University	David Piwnica-Worms/Sam Achilefu

TABLE 5: INSTITUTIONS / INVESTIGATORS FUNDED THROUGH THE IN VIVO CELLULAR & MOLECULAR IMAGING CENTERS



FIGURE 30: FACILITY FOR THE SYNTHESIS OF RADIOPHARMACEUTICALS FOR CLINICAL INVESTIGATIONS.

SYNTHESIS OF AGENTS

Radiopharmaceuticals are essential components of our program. 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.

CIP manages both radiochemistry and radiopharmaceutical facilities at FNLCR. The radiochemistry laboratory brings in research imaging agents to establish and validate their preparation, after which they are used in pre-clinical studies or transferred to the radiopharmacy for human use. The radiopharmacy at FNLCR is compliant with the FDA Code of Federal Regulations Title 21, Part 212 pertaining to cGMP production of PET drugs, for the production and compounding of radiopharmaceuticals.

Examples of compounds explored for such use include: ^{59}Fe , ^{18}F -AMT, ^{89}Zr - and ^{111}In -Cetuximab, ^{18}F -DCFBC, ^{18}F -FES, ^{18}F -FLT, ^{18}F -ICMT-11, ^{18}F -Lapatinib, ^{18}F -ML-10, ^{89}Zr -, ^{111}In -, and NIR-Panitumumab, Reactive Oxygen Species Tracer FDHE, and ^{89}Zr - and ^{111}In -Trastuzumab.

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:

- [¹⁸F]Fluorothymidine, targeted to areas of increased proliferation
- [¹⁸F]Fluoromisonidazole, targeted to hypoxic tissues
- 16α-[¹⁸F]Fluoro-17β-estradiol, targeted to estrogen receptors
- [¹⁸F]Sodium fluoride, accumulating in areas of increased osteogenic activity
- [¹¹¹In]Trastuzumab, targeted to HER2-expressing cancers
- [⁸⁹Zr]Panitumumab, targeted to cancers expressing epidermal growth factor receptor (HER1)
- Ferumoxytol, an iron oxide nanoparticle for magnetic resonance imaging (MRI)
- [¹⁸F]Fluorodeoxycytidine, targeted to areas of increased DNA synthesis
- [¹⁸F]DCFB, targeted to prostate specific membrane antigen
- Hyperpolarized [¹³C]Pyruvate, targeted to areas of increased metabolism

NCI's first IND for an imaging agent, [¹⁸F]fluorothymidine, was filed in 2004, while the most recent, C-13 hyperpolarized pyruvate, was acquired from General Electric in 2015. To facilitate further clinical research on these imaging drugs by the research community, a subset of the documents filed in several of these INDs 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 U.S. FDA. CIP provides a letter to cross-reference the NCI IND file at the FDA for pharmacology, toxicology, dosimetry, and previous human experience.

In addition, CIP has developed a process that authorizes qualified academic sites to manufacture and supply short-lived radiopharmaceuticals for NCI-sponsored clinical trials under the NCI-held IND. This effort has expanded the number of sites that can participate in the trials of advanced imaging agents while assuring that the drug is equivalent across sites, a serious concern with the necessary decentralized manufacturing.

CLINICAL TRIALS

Although Phase 0 and imaging feasibility studies can be performed in the Molecular Imaging Clinic 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 the Eastern Cooperative Oncology Group (ECOG)-American College of Radiology Imaging Network (ACRIN), a group under NCI's NCTN structure that has imaging as one of its foci. Another mechanism for inclusion of imaging in therapy trials is by supplements to trials being funded through other NCTN Groups. These efforts are discussed further below.

Early-Phase Clinical Trials in Imaging and Image-Guided Interventions

CIP sponsors an R01 Program Announcement with special review, PAR-14-166, which was released March 28, 2014. This initiative, led by CTB program staff, is designed to support clinical trials conducting preliminary evaluation of the safety and efficacy of imaging agents and imaging-guided interventions, among other indications. Compared with its predecessor, the R21 Early Phase Trials (PAR-11-216), the R01 Early-Phase Clinical Trials Program Announcement has refined its purpose and primarily provides funding for the immediate conduct of Phase 0, 1, or small Phase 2 clinical trials that are designed and developed to facilitate completion within the 3-year funding period. This Program Announcement is designed to fill the gap for projects that seek to obtain



early information about an imaging agent or imaging-guided intervention. 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 the NCTN.

American College of Radiology Imaging Network (ACRIN): 15 Years of Progress in Oncologic Imaging Clinical Trials

CIP established **ACRIN** to provide a flexible, responsive Cooperative Group for the systematic study of novel and maturing imaging technologies in clinical trials. Managed by CTB, ACRIN is a clinical trials network made up of affiliated investigators at more than 200 academic and community-based facilities in the United States and internationally. ACRIN's research encompasses the full range of medical imaging investigation, from landmark cancer screening trials to evaluating imaging biomarkers and novel imaging technologies in Phase 2 and 3 trials. Working together, CTB and ACRIN have provided a standard for ensuring clinical trial compliance, implementation, data collection, monitoring, and reporting (e.g., safety data, accrual reports, study status, protocol deviations, unanticipated problems, or final data), to achieve trial completion. Together with some of the world renown scientists and clinicians, an Imaging Science Advisory Committee, Early Diagnosis and Detection Science group, as well as cancer-specific disease committees were formulated. CTB staff participate on these committees and also served on ACRIN's Data Safety and Monitoring Board.

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. Several trials are among the highest-profile clinical trials in NCI's portfolio, and a majority of trials involve collaboration with therapy cooperative groups or industries, as illustrated in the following paragraphs. The Network has published over 300 papers and developed standard operating procedures and a corresponding guideline for qualifying the 58 clinically focused NCI-designated Cancer Centers as Centers of Quantitative Imaging Excellence in addition to training young radiologists as imaging researchers.

In May 2012, ACRIN merged its oncology research program with ECOG, a membership-based research organization whose large-scale cancer treatment clinical trials for major diseases have changed the standard of care for cancer patients. The new ECOG-ACRIN Cancer Research Group designs and conducts clinical research along the cancer care continuum, with a focus on diagnostic, therapeutic, preventive, and biomarker-driven trials.

CTB recognizes that the ability to understand how we harness the novel developments in medical imaging (imaging agent, devices, etc.) is perhaps best illustrated through clinical studies that potentially lead to incremental improvements in standard of care practices and/or the technological advances that promise to improve human health and quality of life standards. Thus, a few ACRIN trials that have been completed are highlighted below.

ACRIN 6657: Functional MRI Techniques for Measuring Breast Tumor Response

Breast cancer is genetically and clinically heterogeneous, which makes it challenging to identify effective patient-specific therapies. Although mortality due to breast cancer in the United States has decreased, more than 40,000 women in the United States still die from this disease each year. Further decreases in mortality will require therapeutic options that target biologic properties of tumors and can be delivered early enough in the disease course to make a clinical difference.

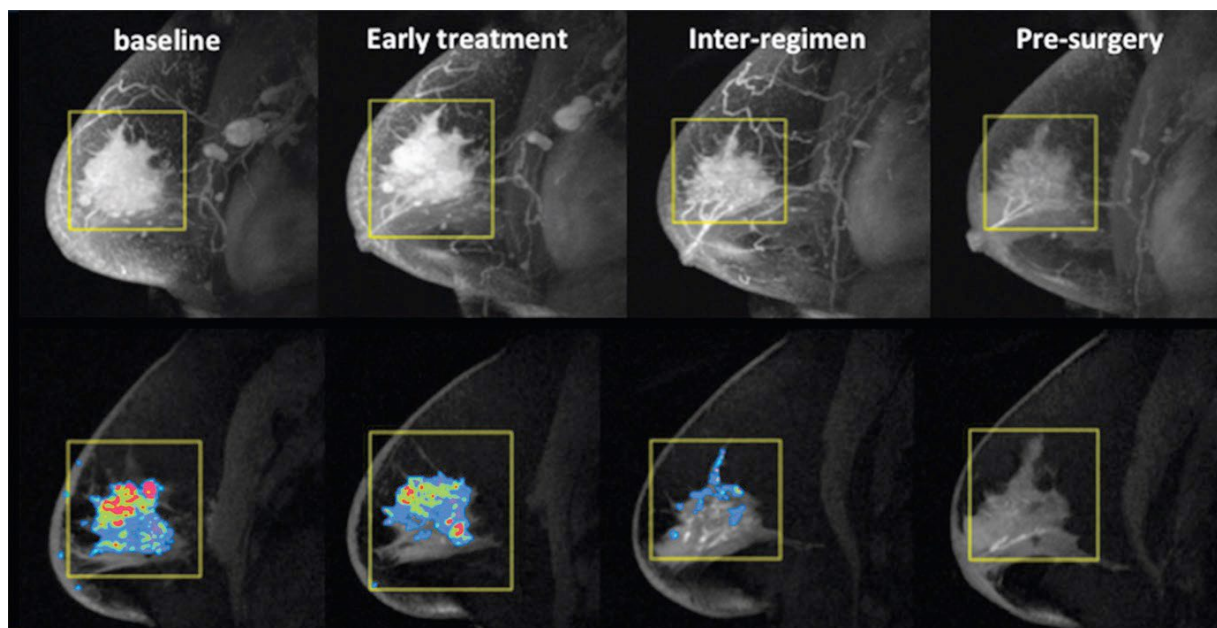


FIGURE 31: LONGITUDINAL MR IMAGES AND FTV MAPS.

Maximum intensity projection images (top row) and corresponding FTV maps (bottom row) for a patient with an excellent clinical response and disseminated residual disease. FTV measurements were 48.5 cm³, 35.4 cm³, 5.6 cm³, and 0 cm³ for baseline, early treatment, inter-regimen, and pre-surgery time points, respectively (shown from left to right).

MRI of the breast is a sensitive method for assessing both tumor morphology and physiology. The most common technique for functional assessment of breast tissue is based on DCE-MRI and involves the serial acquisition of MR images before, and at multiple points following intravenous injection of gadolinium contrast agent. In this particular multi-center trial, functional DCE-MRI was used to assess breast tumor response to neoadjuvant chemotherapy and to predict recurrence-free survival (RFS) by measuring the functional tumor volume (FTV).

As shown below, the FTV values measured by MR imaging predict RFS for patients who receive neoadjuvant chemotherapy for breast cancer. Models combining MRI, histopathology, and breast cancer subtype demonstrated the strongest predictive performance in this study. FTV predictive performance also differs among breast cancer subtypes defined by hormone receptor (HR) and HER2 status; exploratory Kaplan-Meier analyses found significant survival differences in the HR-positive/HER2-negative and HER2-positive subtypes.

In addition, the use of this DCE-MRI technique to assess tumor responsiveness to two drug candidates, a veliparib-

carboplatin drug combination, yielded promising results in the I-SPY2 trial for treating triple negative breast cancer patients.

Recently, these same investigators also looked at the potential of using diffusion-weighted imaging (DWI) for determining breast cancer response. DWI is an alternative MRI technique that can be used to measure the mobility of water molecules *in vivo*. DWI is sensitive to tissue characteristics such as cell density, membrane permeability, and microstructure. As such, DWI provides different, but complementary, biologic information about tumors and their response to treatment. The data from this ACRIN 6698 trial, a sub-study of the I-SPY-2 trial, is currently being analyzed to determine whether the use of DW-MRI improves response determination.

ACRIN 6677: A MRI Marker for Predicting Improvements in Overall Survival in Recurrent Glioblastoma

Each year, 17,000 patients are newly diagnosed with primary brain tumors, with glioblastoma multiforme (GBM) being the most common and most aggressive malignant primary brain tumor. For patients with glioblastoma, surgical resection followed by chemoradiation with concomitant

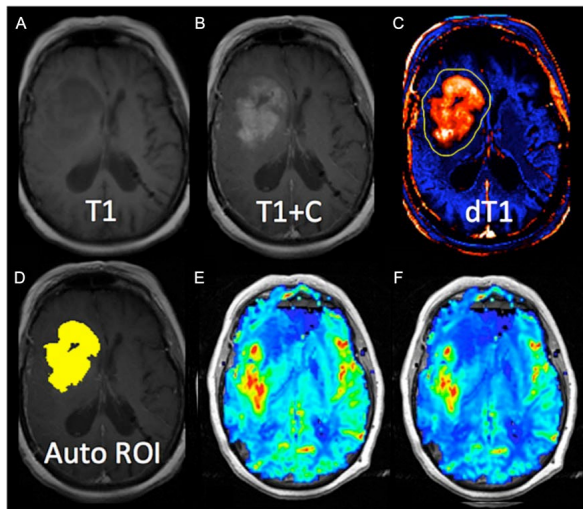


FIGURE 32: EXAMPLE RESULTS FROM A REPRESENTATIVE CASE.

Shown are (A and B) the pre- and postcontrast T1-weighted images, (C) the delta T1 (dT1) map, (D) an image with the automatically determined ROI highlighted in yellow, and (E and F) the normalized and standardized RCBV maps from the same slice.

and adjuvant temozolomide (TMZ) is the current standard of care. In early studies, patients treated with bevacizumab demonstrated an improved rate of progression-free survival (PFS) at 6 months compared with historical controls in clinical trials with no improvement in overall survival (OS). The challenge therefore is to be able to predict which patients are most likely to derive benefit from anti-angiogenic treatment. For this purpose, standard anatomic imaging methods are proving insufficient. The study goal was to determine whether changes in relative cerebral blood volume (rCBV) derived from dynamic susceptibility contrast (DSC) MRI are predictive of OS in patients with recurrent GBM when measured at 2, 8, and 16 weeks after treatment initiation.

This study represents the first multicenter trial to demonstrate that rCBV can serve as a useful biomarker for the prediction of response to anti-angiogenic therapy. Specifically, a rCBV that decreases from baseline, measured at either 2 or 16 weeks post treatment initiation, predicted a clear improvement in OS for patients. Thus, this trial was able to show that changes in rCBV, as demonstrated on a DSC MRI scan, is predictive of survival in patients with recurrent GBM who were treated with bevacizumab.

ACRIN 6687: Therapeutic Response Evaluation of Bone Metastases in Prostate Cancer Patients

Prostate cancer clinical research is challenged by the lack of validated disease response endpoints for bone metastases. Bone scintigraphy is not a quantitative measure, and response to therapy is impossible to describe outside of the detection of new lesions. As a result, prostate cancer trials have focused on endpoints such as OS and radiographic PFS, rather than

response to therapy. These endpoints require significant patient numbers and follow-up and may not be practical for widespread use in the clinic because of the inability to offer a real-time assessment of treatment response to the patient. For these reasons, ACRIN embarked on this multicenter, cooperative group, prospective imaging biomarker trial to evaluate the utility of PET for determining response to therapy.

This research study evaluated a newer imaging technique, 18F-Sodium Fluoride (NaF) PET, that takes advantage of the fact that the tracer NaF is very sensitive for detecting changes in bone osteogenic activity. The study looked at how repeatable the NaF PET scans are before treatment, and performed scans after standard chemotherapy or hormone-directed treatment. The results demonstrated that this imaging approach was able to identify dasatinib treatment response in castrate-resistant prostate cancer bone metastases. It also confirmed that changes in 18F-fluoride uptake in bone metastases correlated with accepted criteria for radiographic PFS. This information could be used to develop better ways to measure prostate cancer bone lesions. In turn, this could be used to better evaluate treatment effects of standard chemotherapy and other new drugs being developed to treat prostate cancer.

Collaboration with CTEP

As a member of the 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.

The following clinical trials involved imaging agents supported by CTEP and CIP:

PBTC N12 – Phase 2 Study of Fluoro-Thymidine (FLT) for PET Imaging of Brain Tumors in Children

Though rare, brain tumors are the most common solid tumor in children and is the leading cause of death from cancer in children. In the U.S., approximately 20,500 new cases of brain tumors are diagnosed per year, and of these, approximately 10% are diagnosed in children. While these brain tumors can

be evaluated by conventional imaging such as CT or MRI, these anatomy-based scans often are neither as powerful nor as useful as functional imaging modalities such as PET scans. Being performed by the **Pediatric Brain Tumor Consortium (PBTC)** with funding from the FDA, this study evaluates a promising radioactive PET imaging agent called 18F-fluorothymidine (FLT), which is thought to be superior to the standard 18F-fluorodeoxyglucose (FDG) used currently in clinical practice, and is the first multi-center study to study this agent in the pediatric population.

RTOG 1106 / ACRIN 6697 – Randomized Phase 2 Study of Individualized Adaptive Radiotherapy Using During-Treatment FDG PET/CT and Modern Technology in Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer death in the U.S. and worldwide, with an estimated 222,520 new cases of and 156,176 deaths related to this disease in the U.S. in 2010. Radiation therapy (RT) is the principal mode of treatment for lung cancer patients who are medically inoperable or have disease that is not amenable to surgical resection. Despite the proven efficacy of RT, many patients do not respond as expected, and it is thought that one of the contributing factors to this observed RT resistance is the hypoxic micro-environment that tumors create around themselves in the body. Therefore, if areas of hypoxia in the tumor can be detected early, increasing the focal radiation dose to the hypoxic area can compensate for the resultant radiation resistance. This clinical trial attempted to improve RT with two kinds of PET scans: 1.) a standard FDG PET to see if mid-therapy response as determined by the scan can be used to escalate the radiation dose to areas that are not responding well; 2.) an investigational PET agent 18F-FMISO to see whether areas of hypoxia visualized by this agent can serve as a prognostic biomarker for eventual response to therapy.

EAI141 – Early Assessment of Treatment Response in Acute Myeloid Leukemia Using Fluoro-Thymidine (FLT) PET/CT Imaging

Acute myeloid leukemia (AML) is a devastating liquid cancer that is typically initially treated by a strong induction chemotherapy aimed at wiping out the patient's bone marrow, followed by consolidation treatment with either more chemotherapy or stem cell transplantation. Currently, there is a need to develop better tools to assess the effectiveness of the induction chemotherapy. Based on promising pre-clinical experiments in mice and early first-in-human studies, EAI141 tests in a multi-center setting the hypothesis that the investigational PET agent FLT can

be used to predict the success of induction chemotherapy more accurately and at an earlier time point compared to the current practice of a bone marrow biopsy, which can give false results due to sampling errors and is an uncomfortable procedure for the patient.

EAI142 – Fluoro-Estradiol (FES) PET Imaging as a Predictive Biomarker for Hormonal Therapy in Women with Metastatic Breast Cancer

One of the standard treatment options for patients with breast cancer is the use of estrogen hormonal therapy in patients with estrogen-receptor positive (ER+) tumor. However, not all patients with ER+ disease will respond to hormonal therapy due to intrinsic resistance mechanisms, such as tumor heterogeneity (not all metastatic breast cancer cells have the same level of ER expression). Sampling of all tumors via biopsies in the body is not feasible, especially in cases of multiple metastatic tumors, and there is currently no method in standard practice that can give this information. EAI142 attempts to see whether an investigational PET agent, 18F-fluoroestradiol (FES), can be used to provide accurate ER status information on all tumors in the entire body non-invasively. While previous single-center trials using FES PET have been promising, EAI142 is the first to evaluate FES PET in a large-scale, multi-center setting that will generate part of the data needed for eventual FDA approval of this agent.

A021302 – Impact of Early FDG PET Scan on Pre-operative Therapy for Locally Advanced Gastric Cancer

Patients with locally advanced gastric cancer can often have improved clinical outcomes with surgical resection if adjuvant therapy is added to the treatment course prior to surgery. However, it is currently not known how much of a response effect the added adjuvant therapy provides and for which patients this effect will be seen. Previous studies have shown that patients who have an improved PET scan done with standard FDG tend to benefit the most from adjuvant therapy. In this study performed by the NCTN group Alliance, the investigators directly test the hypothesis that the FDG PET scan can be used to identify patients who have not benefitted from the adjuvant therapies that they have received, so that additional, more aggressive salvage adjuvant therapy can be given prior to undergoing surgical resection. The goal is to see whether patients who did not initially respond to adjuvant therapy, as identified by the FDG PET scan, can be given salvage adjuvant therapy so that their post-surgical clinical outcomes can be as good as those who had initially responded.



9604 – Perfusion CT as a Predictive Biomarker in Advanced Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine tumors (pNET) are rare cancers thought to arise from the pancreatic islet cells. These tumors have been found to induce high amounts of new blood vessel growth nearby with high degrees of neo-vasculature. This study being performed by the N01 Phase 2 Consortium member MD Anderson aims to see whether pNETs can be effectively treated with ziv-aflibercept, a drug that disrupts the neo-vasculature and blood supply built by these tumors. Embedded within this trial is a correlative imaging subcomponent that examines whether vascular parameters (such as tumor blood flow, tumor blood volume, and mean blood transit time) obtained by a specialized perfusion CT can serve as predictive biomarkers for eventual response to the therapy agent. Funding for this specialized perfusion CT is provided through the Imaging Option in the N01 Phase 2 Consortium, which is made available to members of the Consortium through the efforts of CTB.

PBTC 047 and other Brain Tumor Trials with MR Imaging

Approximately 200 new cases of diffuse intrinsic pontine glioma (DIPG) are diagnosed each year in the U.S. DIPG is a devastating disease with no current effective therapy and low survival in the first few years of life. Different immunotherapy agents are currently being evaluated in clinical trials for DIPG and other brain tumors. Surgery and radiation therapy are not options for children with DIPG and are often not fully curative for other brain tumors. CIP board certified medical officers provide review of MRI scans for orphan diseases such as DIPG and plexiform neurofibromas. CIP collaborates with Pediatric Radiologists and the Children's Oncology Group (COG) in developing more optimal means of tumor burden assessment.

In order to determine areas of the body affected by immunotherapy following clinical trial participation, CIP is working with the Laboratory of Pathology and Pediatric Neuro Oncology Branch in the Center for Cancer Research to complete a limited autopsy where some imaging guidance can be performed. For both children and adults, CIP has helped develop much needed standardized imaging protocols, which has enabled the comparison of imaging data between centers and improvements to patient care.

EA1151 - Tomosynthesis Mammographic Imaging Screening Trial (TMIST)

The debate on the relative risks and benefits of breast cancer screening has recently increased. Some experts prefer to both detect cancers that will never harm patients (overdetection) and provide false positive results so as not to miss detecting clinically important tumors earlier with the belief that this will reduce overall breast cancer mortality. This is based on earlier randomized clinical trials that showed a mortality benefit from screening mammography, however these studies were done before the era of modern digital mammography or tomosynthesis, and prior to current treatment paradigms. EA1151 is a randomized trial of the two most commonly used mammography screening technologies, tomosynthesis and digital mammography, designed to evaluate whether these newer technologies produce a stage shift through earlier detection of the most aggressive tumors, detect additional cancers that may not be dangerous, and provide measurements of the diagnostic accuracy of the currently available technologies in women undergoing state-of-the-art treatments.

Clinical Imaging Steering Committee (CISC)

The CISC was established in December 2010 as a forum for the extramural imaging and oncology communities to provide strategic input to NCI regarding its significant investment in imaging activities in clinical trials. CISC membership includes imaging representatives from each of the NCTN Groups and other NCI-sponsored networks, as well as other clinicians, translational scientists, biostatisticians, and patient advocates.

The roles of the CISC are:

- To identify and promote the “Best Science” by evaluating the design and prioritization of Phase 3 and large Phase 2 trials focused primarily on cancer imaging
- To serve as a forum for the extramural imaging and oncology communities to provide NCI with strategic input on managing our significant investment in imaging associated with clinical trials
- To provide other steering committees with valuable expertise for the evaluation of therapeutic concepts and discussions that include an imaging component

CTB has primary responsibility for the scientific proceedings of the CISC and acts as the main liaison between the CISC and the rest of the NCI, including CTEP and other NCTN Disease-Specific Steering Committees.

Imaging Biomarker Evaluation through the Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP)

BIQSFP is a funding program designed to assist NCTN and NCORP Groups with inclusion and implementation, where appropriate, of important biomarker component studies in their clinical trials. The goal is to ensure that the most important, scientifically meritorious biomarker, imaging, or quality of life studies are funded and initiated in a timely manner. A number of clinical trials with an imaging biomarker subcomponent have been approved and funded through the BIQSFP program, including:

- A Phase 3 randomized trial for newly diagnosed high risk leukemia to evaluate whether standard of care MRI can be used to help detect the presence of osteonecrosis in patients treated with clofarabine (AALL1131)
- A Phase 3 study in metastatic prostate cancer to evaluate the performance of Tc99m-MDP bone scans in comparison to F18-NaF PET scans (A031201)
- A large Phase 2 study in breast cancer to see whether the PET imaging done with the hypoxia agent F18-FMISO correlates with clinical outcomes or other markers of hypoxia (9881)

- A large Phase 2 study in lymphoma that evaluates whether F18-FLT PET scans can be used as an early response evaluation biomarker

CTB played an integral part in writing the BIQSFP funding announcement, and continues to support BIQSFP imaging research by serving as reviewers for submitted applications and contributing to the revised BIQSFP application template.

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 (FDG) PET in the assessment of tumor response in clinical trials. CIP is also supporting the development of a proposal for an infrastructure to support the implementation of RECIST—an FDA-acknowledged imaging methodology for clinical trial endpoints where noninvasive imaging is required to track tumor change over time.

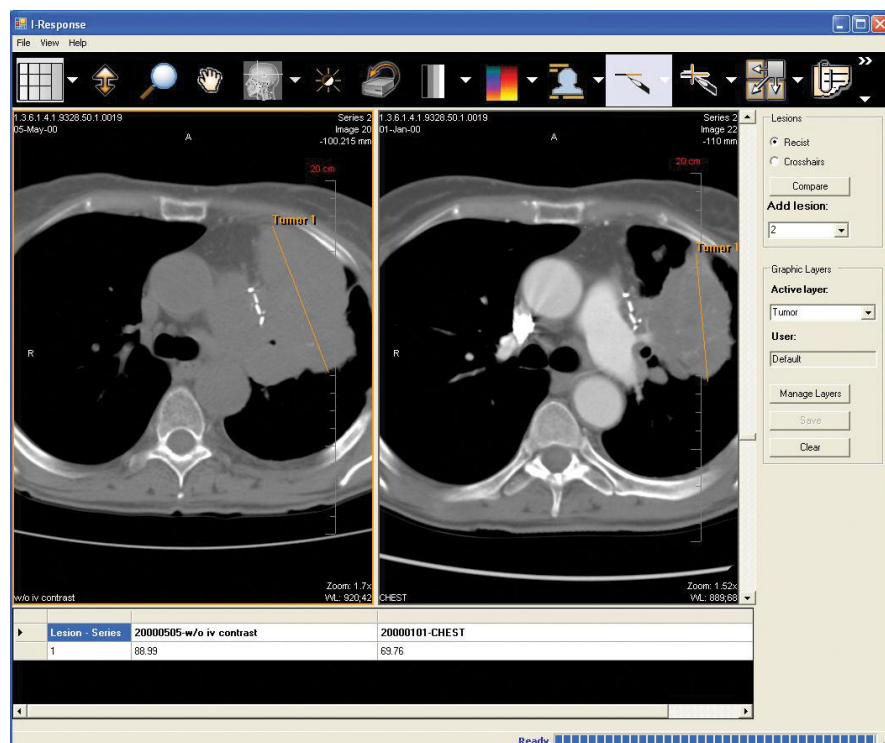


FIGURE 33: RECIST MEASUREMENTS TAKEN ON A LUNG TUMOR AT TWO DIFFERENT TIMES.



For the Agency for Healthcare Research and Quality (AHRQ), CIP staff members have served as reviewers for Centers for Medicare and Medicaid Services (CMS)-related evaluation of the application for Medicare reimbursement for FDG 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 FDG 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 to and opportunities for enhanced participation in international trials.

Medical Monitor for Imaging IND Agents

CIP currently holds INDs for the following eight investigational imaging agents and acts as the regulatory sponsor for NCI-funded trials that use these agents:

- [18F] Sodium Fluoride
- [18F] FLT
- [18F] FMISO
- [18F] FES
- [89Zr]-panitumumab
- [18F] DCFBC
- Hyperpolarized [13C] Pyruvate
- Ferumoxytol

Medical officers in CTB serve as the medical monitor on record for these agents and have the responsibility of reviewing and collating all adverse events deemed related to these investigational agents. CTB officials also assist in the preparation and filing of annual reports to the FDA.

Clinical Trial Informatics

CTB supports the application and development of informatics technology in the conduct of imaging clinical trials, via participation in projects and committees both internal and external to NCI. CTB provides crucial clinical input to these endeavors ensuring that the informatics technology being developed can achieve real-world application for use by imaging clinical trialists. These projects often have wide impact affecting both internal NCI processes and the extra-

mural research community. Contributions of CTB to these projects include:

- The National Cancer Informatics Program (NCIP): contributes clinical perspective to discussion of NCIP informatics activities and representation on the Imaging Informatics Working Group
- Clinical Trials Reporting Program (CTRP): works with CTRP to develop imaging-appropriate terminology and abstraction rules so that clinical trials involving imaging can be more accurately reported
- Medidata RAVE Electronic Data Capture (EDC) and Clinical Data Management System (CDMS): medical officers from CTB provided clinical imaging input and were heavily involved with the customization and integration phase of Medidata-RAVE as it was being developed for NCI use
- NCI-CDISC Imaging Case Report Form (CRF) template project: CTB medical officers made significant contributions to the writing and editing of CRFs meant to capture data relative to imaging components in clinical trials
- Input to other trans-DCTD informatics projects: CTB staff assisted with the development of the new CAERS system for adverse event reporting and upgrades to the existing Protocol Abstraction and Tracking System (PATS system)

QUANTITATIVE IMAGING NETWORK (QIN) FOR THE MEASUREMENT OF THERAPY RESPONSE

Quantitative imaging encompasses the process of extracting measurable feature information from medical images for assessment of normal or the severity, degree of change, or status of a disease, injury, or chronic condition relative to normal. The goal of the quantitative process is to create the condition where clinical imaging scanners perform as measurement instruments, delivering reliable and reproducible information concerning a patient's health. To support this endeavor, CIP established the [Quantitative Imaging Network \(QIN\)](#) in 2008 to promote the development and clinical validation of data collection methods and software tools for clinical decision making in oncology. To date, 27 research teams, shown in Figure 34, participate as members of the network, and five others are active as associate members. The network is expanding internationally to include associate members from India and Europe. The multidisciplinary

teams include oncologists, radiologists, imaging specialists, medical physicists, computer informatics scientists, and others. An Executive Committee consisting of the principal investigators from each of the teams oversees the direction and external interactions of the network. External interactions include discussions and presentations to professional societies, cancer centers, global health initiatives, and collaborations with clinical groups, such as NCTN and the other clinical cooperative groups.

The teams in QIN are studying non-small cell lung cancer, cancers of the central nervous system, breast cancer, and hepatocellular carcinoma, among others. Using single- and multisite clinical trials, these teams are applying a variety of imaging modalities to make quantitative measurements of tumor response to therapies, such as drug or radiation treatments. The network is developing algorithms that could eventually become clinical tools to help oncologists make decisions about cancer treatment pathways for

individual patients. At present, data are being collected and curated in TCIA. In addition, a number of demonstration projects are under way across the network to evaluate data analysis methods across different imaging platforms and commercial vendors.

QIN is moving rapidly from a posture of discovery and development into one of validation and deployment. Tools designed to locate, isolate, and extract information about tumors from medical images are being subjected to critical tests called challenges. A number of common function tools are tested against a dataset of images where outcome is known, but withheld from the challenge participants. Challenge results indicate which tools have potential for further clinical testing. In addition to validating tools and methods on an individual basis, QIN is also evaluating pipeline processes, where the output from one tool is used as the input to the next, providing sequential information to support clinical decision making.

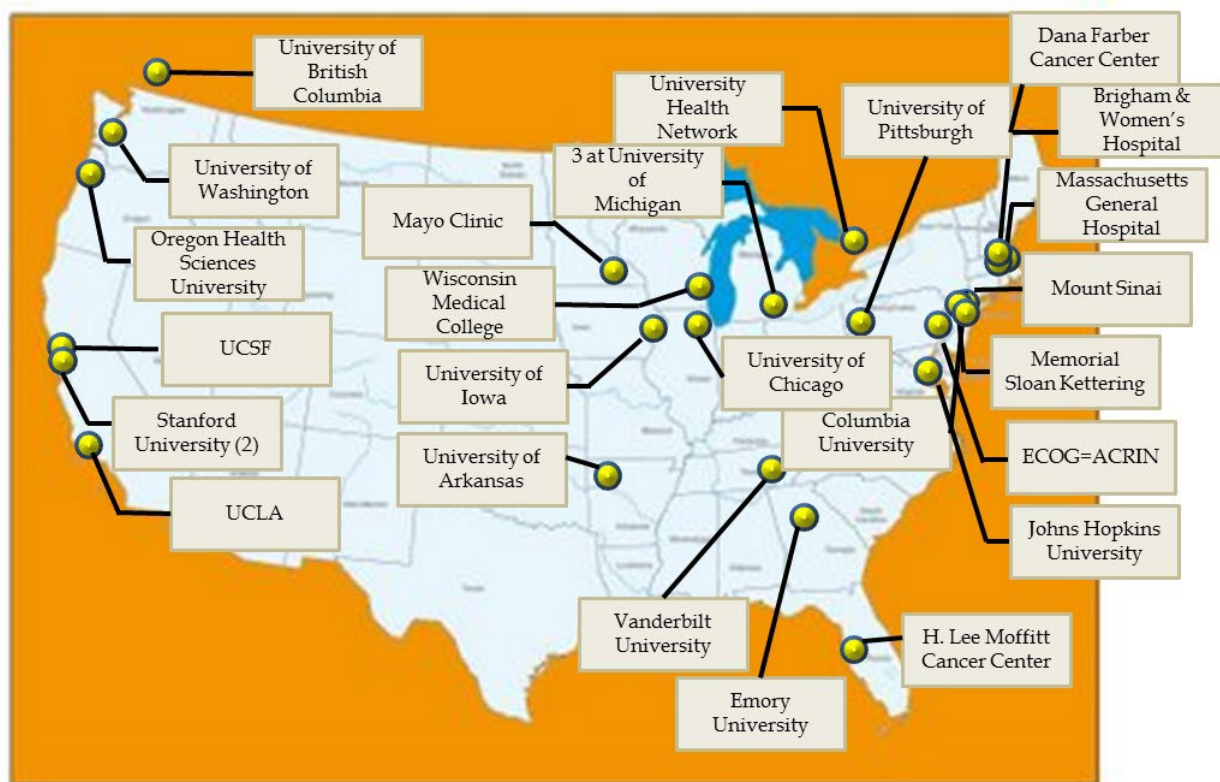


FIGURE 34: GEOGRAPHICAL DISTRIBUTION OF QIN TEAM MEMBERS.



Network Organization

Networks are generally organized to create avenues for communication and collaboration among its members, and the value of a network can be measured by the degree of collaboration experienced by the participants. Collaboration can be difficult, however, when teams are focused on different technical challenges. Therefore, it is important to explore activities of common interest that cut across the goals of each technical team/institution and to create a mechanism for emphasizing these common interests.

QIN has achieved these goals through the use of cross-institutional working groups. The organizational diagram of the network is shown in Figure 35. The Executive Committee guides the overall direction of the network, and the working groups are the links that bring the network together. Consensus among its members is important when establishing policies and network activities. Each technical team is required to participate in each of the separate working groups. As a result, each working group is a microcosm of the entire network, and each working group is focused on a specific challenge in quantitative imaging.

The working groups and their focus areas are:

- **Clinical Trial Design and Development:** Methods for moving software tools into clinical trials, including those developed by the network; fostering strong connections with clinical trial groups, such as NCTN.
- **Data Acquisition:** Problems associated with reducing bias and variance in image data collection; phantom circulation among QIN teams to determine sources of error in the various imaging scanners and analysis of results.
- **Bioinformatics and Data Sharing:** Quantitative imaging methods rely on firm informatics infrastructure to support tool comparison, data archiving and visualization, annotation, and statistical methods. This working group considers all of the projects being conducted within the network and plans for informatics support for them.
- **PET/CT Working Group:** Specific issues in PET/CT data processing
- **MRI Working Group:** Specific issues in MRI data processing

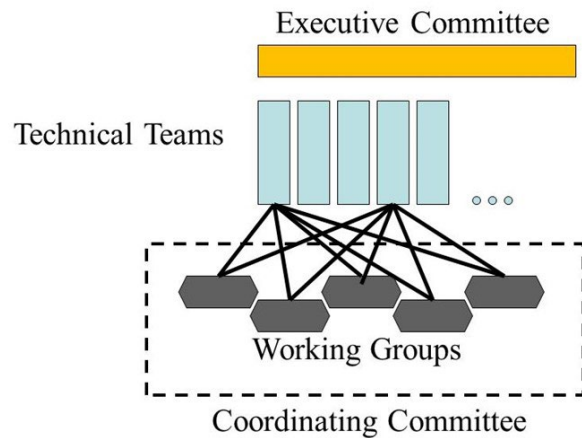


FIGURE 35: ORGANIZATION OF THE QIN.

An important characteristic of each working group is that the leadership is chosen from within the group, not by the leadership of the individual research teams. Each working group selects a chair and co-chair to run the monthly teleconference meetings and to set the priorities for the group, which gives a strong sense of ownership to each working group for the projects undertaken. Most of the projects deal with important comparisons of quantitative imaging methods within the purview of the group. For example, the PET/CT group has completed a study of various methods used to segment tumor locations in images.

Network Highlights and Progress

Quantitative imaging is an important contributor to precision medicine and offers diagnostic methods based on molecular and/or mechanistic information to understand the causes, pathogenesis, and pathology of cancer. By rapid and precise measurement of response to therapy, quantitative imaging can stratify patients for appropriate interventions. However, quantitative imaging can only have value as a reliable method in this arena if it is embedded in the clinical workflow. Therefore, the major goal of QIN is to translate software tools and methods from development to clinical validation and deployment.

Moving from discovery and development of clinical decision support tools to their final validation is a complex process. To relate tool performance to the desired clinical outcome, the clinical outcome must be known; however, clinical outcomes data are often missing or of limited value in retrospective

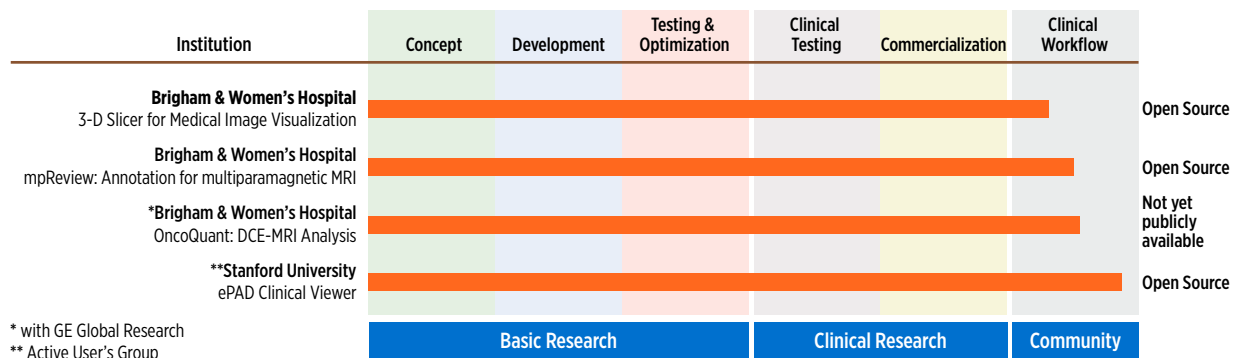


FIGURE 36: PROGRESS OF QIN TEAMS TOWARD CLINICAL WORKFLOW.

datasets, and can be difficult to acquire if prospective data are used. In either case, sufficient data must be available to make an accurate assessment of the performance characteristics of the tool or method.

A recent review of QIN research teams shows that steady progress is being made to bring clinical decision support tools closer into the clinical workflow. Figure 36 shows how three classes of research teams (early stage, middle stage, and late stage in the network) are progressing in translational efforts. The scale considers basic research to include concept, development, and optimization; clinical research to include clinical testing or validation and commercialization; and the final stage to include clinical workflow in the community. Not surprisingly, the early stage teams (fewer than 2 years in the network) are making progress through the basic research tasks, middle-stage research teams (3 or 4 years in the network) have moved past basic research and are working to validate tools or methods, and teams with years of network experience are intent on building collaborations with industrial partners for commercialization.

Several QIN teams are moving their clinical support tools beyond the clinical validation and testing stage into clinical workflow. Figure 37 shows that the efforts by Brigham and Women's Hospital and Stanford University to move software tools into clinical workflow are succeeding. In the case of Brigham and Women's, their 3-D Slicer program is being expanded through their QIN participation to include medical image visualization and annotation for multiparametric MRI studies. With industrial participation in their project, the team is overcoming translational challenges. Stanford

University has been working on ePAD, a portable iPad device with a number of software tools useful in clinical decision support. Many of the functions within the ePAD device are tools developed by other QIN network members.

Future Directions for QIN

QIN is increasing its efforts to bring clinical decision support tools to clinical utility. This involves a close interaction with NCTN and other organizations focused on clinical trials. Outreach has already begun with the ECOG-ACRIN group and the Alliance group, both working on numerous clinical trials. A dialogue with IROC, the coordinated program designed to support NCTN efforts in imaging and radiotherapy, is providing avenues for QIN members to begin inserting tools into imaging trials. The next few years will be important for the QIN and its attempts to translate tools and methods designed to predict or measure response to therapy during clinical trials.

ONGOING STRATEGIES IN IMAGING – NATIONAL STRATEGIC PLANS, INITIATIVES, & ROADMAPS

The CTB team is actively engaged in the following activities designed to establish national strategic plans and an NCI-specific roadmap to advance the field of medical and biomedical imaging. By serving as lead representatives, CTB staff are able to define and develop avenues leading to the discovery of the next scientific breakthroughs and foster the transfer of new technologies into the product development pipeline while focusing on key societal needs/priorities.

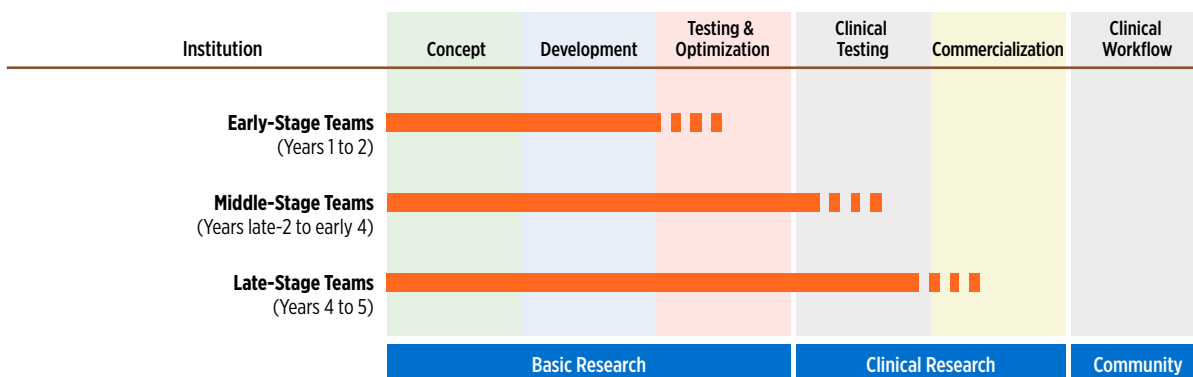


FIGURE 37: SEVERAL PROJECTS IN QIN ARE PARTICIPATING IN CLINICAL WORKFLOW.

National Nanotechnology Initiative 2.0

The **National Nanotechnology Initiative (NNI)** is a collaboration of twenty Federal agencies and Cabinet-level departments with shared interests in nanotechnology research, development, and commercialization. These agencies recognize that the ability to understand and harness the novel phenomena that occur at the nanoscale is already leading to revolutionary new materials, devices, and structures for the diagnosis and treatment of cancer. These advances promise to improve human health and quality of life.

Every three years the NNI agencies are required to develop/update the NNI Strategic Plan. This document represents a consensus among NNI agencies on the high-level goals and priorities of the initiative and on specific objectives to be pursued over at least the next three years. The purpose of the Strategic Plan is to catalyze achievement in support of the goals and vision of the NNI by providing guidance for agency leaders, program managers, and the research community regarding the planning and implementation of Federal Nanotechnology research and development (R&D) investments and activities.

A CTB program staff member currently serves as the co-Chair of the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of NNI and works with the Office of Science Policy in the NIH Office of the Director to define opportunities and national priorities. Based on a recent NIH-wide portfolio analysis, technical developments

at the intersection of nanotechnology and imaging represent an opportunity to plan for the future in this field. The focus will be on the creation of grand challenges and new initiatives that support fundamental discovery, foster innovation of new materials, and accelerate the clinical translation of existing nanomedicine for cancer management.

Interagency Working Group On Medical Imaging (IWGMI)

Established in 2015 by the National Science and Technology Council (NSTC) Committee on Science, the **IWGMI** was created in response to **Senate Report 113-181 FY2015**, which called for the establishment of “a Medical Imaging Subcommittee [MIS] to coordinate Federal investments in imaging research.” Following the group’s first meeting on July 9, 2015, the IWGMI, which included representation from the Executive Office of the President (Office of Management and Budget, Office of National Drug Control Policy, and Office of Science and Technology Policy) and membership from a number of NSTC departments and agencies, developed a roadmap for the full scope of medical imaging research and development in the U.S. Some of the functions of the IWGMI were to:

- Improve coordination and collaboration of Federal Agency R&D agendas on medical imaging
- Identify cross-cutting national priorities that would benefit from medical imaging research outcomes

- Develop a strategic roadmap for research and development of medical imaging technologies and integration of science and technology advancements into clinical implementation
- Liaise with, respond to, and provide expert information to the Office of Science and Technology Policy (OSTP) and other NSTC groups on relevant issues of national concern involving medical imaging and related technologies

CTB staff, along with CIP's Associate Director, supported this effort through a collaboration with the NIH National Institute of Biomedical Imaging and Bioengineering (NIBIB) and the National Institute of Standards and Technology (NIST), who served as inaugural co-chairs of the IWGMI. The IWGMI published its *final report* in December 2017.

SPECIALIZED WORKSHOPS

Community Engagement with Professional Societies

CIP staff work continuously with the major professional societies of medical imaging in the U.S. to understand and help support current areas of need and interest in medical imaging research. Medical Officers and Program Directors from CTB work directly with societies representing the various imaging modalities essential to cancer imaging, including the Radiological Society of North America (RSNA), the Society of Nuclear Medicine and Molecular Imaging (SNMMI), and the World Molecular Imaging Congress (WMIC). Examples of community outreach activities with professional societies include:

- Membership and participation of CIP/CTB in various initiatives organized by Quantitative Imaging Biomarkers Alliance (QIBA) of RSNA
- Offering consultation to the SNMMI on seeking regulatory approval for novel PET agents such as fluorocholine and fluorothymidine
- Giving presentations on relevant medical imaging and regulatory issues at plenary and other scientific sessions at the society Annual Meetings

- Membership in the Research Committee of the European Society of Radiology and the Imaging Committee of the EORTC

Immune Modulation Therapy and Imaging: What can we do in clinical trials now?

Immunotherapy is rapidly becoming a successful strategy in treating malignancies. NCI is investing a large percentage of its resources to evaluate the role of various immunotherapies – either alone or in combination with other cytotoxic or cytostatic therapies. Assessment of tumor response with anatomic imaging and with the standard RECIST criteria has not been very helpful in patients receiving immunotherapy. Therefore, CIP is actively pursuing alternative methods of tumor response assessment in this setting. SNMMI partnered with CIP to conduct this workshop on May 2, 2016. A *meeting report* was published by the *Journal of Nuclear Medicine* (Shields AF, 2017).

NCI-ASIGS-WMIS Workshop on Regulatory Pathways for Clinical Use of Optical Methods and Exogenous Targets for Cancer Detection

On May 4, 2016 officials from NCI, the FDA, members of the American Society for Image Guided Surgery (ASIGS) and the World Molecular Imaging Society (WMIS) discussed consensus methods for FDA-directed human testing and approval of investigational optical imaging devices and contrast agents for surgical applications. The specific goals of this workshop were to present FDA's approval requirements and expectations for studies of new devices and drugs, alone and in combination, in the context of optical surgical navigation, and to provide clarity to the research community for the purpose of improving the data submitted to FDA and accelerating the regulatory process. This workshop was created in response to the community's request to further the rapid development of optical and image-guided imaging technologies, which is an activity that falls within CIP's purview of facilitating the clinical evaluation of promising methodologies that can improve cancer care.



Response Evaluation Criteria in Solid Tumors (RECIST) Working Group (2006-present)

The RECIST criteria is a set of voluntary, international standards, which is the *de facto* method by which the response to an intervention (such as a novel cancer therapeutic drug) is being evaluated in the majority of cancer-related clinical trials performed today. RECIST is based on statistically validated work and analysis that categorizes responses to therapy based on changes in tumor size as measured with anatomical imaging modalities, such as a CT or MRI scan. The criteria were originally published in February 2000 by an international collaboration that included EORTC, NCI, and the National Cancer Institute of Canada, and were revised to RECIST 1.1 in 2009. Having a set of standardized, validated response evaluation criteria such as RECIST enables comparative analysis across studies and allows medical imaging data to be used as a surrogate endpoint in clinical trials. Medical Officers of CTB participated in this international collaboration and are committee members who produced RECIST. Moreover, CTB is leading the next version update to RECIST, and CTB Medical Officers have been co-chairs on the RECIST FDG PET Working Group from 2007 to the present, including the most recent revisions of the RECIST criteria issued in 2015.

QuIC-ConCePT (Quantitative Imaging in Cancer: Connecting Cellular Processes with Therapy) Consortium

The Innovative Medicines Initiative (IMI), a unique partnership between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA), has awarded a grant to the QuIC-ConCePT Consortium to study imaging biomarkers for anti-cancer drug development. QuIC-ConCePT is coordinated by AstraZeneca and managed by the EORTC. Staff from CTB serve in an advisory role to QuIC-ConCePT by being active members of the Independent Scientific Advisory Committee (ISAC).

FUTURE DIRECTIONS

Clinical imaging in cancer will continue to be transformed by novel devices, new methods for displaying and using images, and highly targeted imaging agents capable of isolating even the smallest tumors for characterization. Holographic images coupled with 3-D printing will give surgeons the opportunity to visualize deep seeded tumors in difficult anatomical location before surgery begins. Imaging probes that remain dormant in the bloodstream until reaching the tumor site will suddenly activate to isolate the tumor location. Functional imaging methods will signal the activity of natural immune response to tumors. Nanobot devices, molecularly engineered structures capable of performing intercellular tasks, guided through image control will be able to alter damaged cellular communication pathways to prevent disease before it begins. Implanted devices will be capable of detecting and eliminating circulating tumor cells before metastasis can take place. Such feats will be possible if imaging is teamed with the needed biological, chemical, and engineering technologies.

As imaging technologies and capabilities move toward these novel goals, tasks for the immediate future include improving methods that will support precision medicine. Major emphasis will be placed on improved methods for directed biopsy, support for clinical studies of imaging agents for tumor augmentation, and quantitative methods to extract phenotype information from tumors, including artificial intelligence techniques. It is critical to address the issue of co-correlation at vastly different physical scales and the integration of 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 our understanding of human cancer and improving patient outcomes.

Additional challenges in imaging technology development will include methodologies for translating new imaging concepts into the clinical workflow, requiring consensus on standards, quality management activities, and continued dialogue with the FDA. Improvements in imaging capabilities will continue to be a central focus for technology development, but methods for translation will be emphasized in future support.

PROGRAMS AND INITIATIVES (2013-2017)

CANCER THERAPY EVALUATION PROGRAM





OVERVIEW

The Cancer Therapy Evaluation Program (CTEP) coordinates the clinical treatment program of 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 resources may be utilized 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 direct the monitoring of greater than 800 cancer treatment clinical trials conducted throughout the nation. These trials are funded by more than 40 cooperative agreements and contracts, and involve about 20,000 patients annually. This level of activity makes CTEP the largest publicly funded clinical trials organization in the United States. The program is responsible for many of the major studies that have improved cancer treatment over the last three decades. The trials are conducted by clinical trials networks of U.S. and international members, within which are contained both considerable scientific expertise and accrual capability. The trial networks, supported in whole or in part by CTEP, are aligned as shown in the accompanying diagram.

STRUCTURE AND FUNCTION

CTEP staff comprise physicians, scientists, nurses, pharmacists, and other specialists. By offering support and expertise to extramural investigators, 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 167 Investigational New Drug (IND) applications for new agents, primarily through Cooperative Research and Development Agreements (CRADAs) with pharmaceutical partners, thereby providing latitude to extramural investigators during early-phase trials to explore new schedules, doses, and proof-of-concept/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 (comprising the Phase 1 and 2 programs shown in the diagram below) adds significantly 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 rare tumors. In addition, a particular

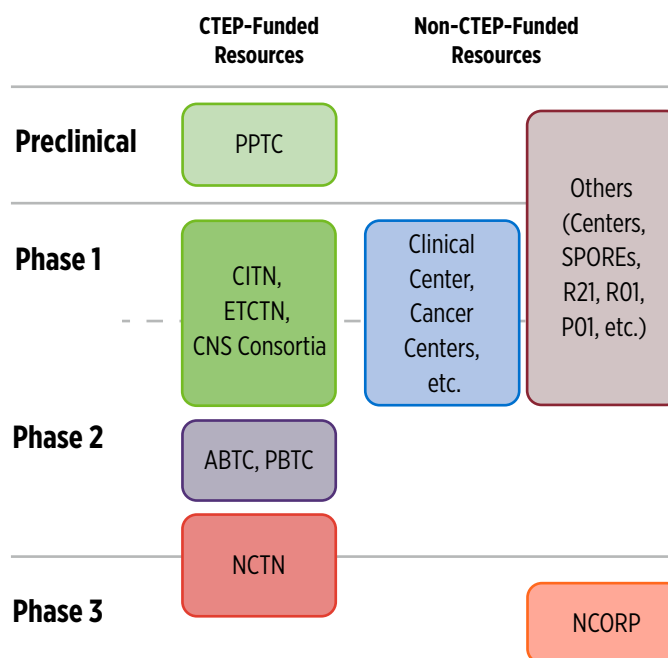


FIGURE 38: NCI FUNDED CLINICAL TRIALS NETWORK.

ABTC = Adult Brain Tumor Consortium; CITN = Cancer Immunotherapy Network; CNS = central nervous system; ETCTN = Experimental Therapeutic Clinical Trials Network; NCORP = National Community Oncology Research Program; NCTN = National Clinical Trials Network; PBTC = Pediatric Brain Tumor Consortium; SPOREs = Specialized Programs of Research Excellence; R01, R21, P01 are research project, exploratory/developmental research, and program project grants.

JEFFREY S. ABRAMS

ASSOCIATE DIRECTOR



Jeffrey S. Abrams, MD, has led CTEP as Associate Director since June 2007. 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 and was responsible for the direction of the NCI Clinical Trials Cooperative Group program. As Associate Director, Dr. Abrams supervises a staff that collectively oversees, reviews, and coordinates more than 150 active Phase 3 trials and more than 700 early-phase trials in all varieties of cancer and all modalities of treatment. 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 the implementation of NCI's Central Institutional Review Board. Dr. Abrams' achievements have been recognized by numerous NIH Director and Merit Awards, and he is the author of over 100 publications in the field of breast cancer and clinical trials and numerous book chapters.

CTEP STRATEGIC GOALS

- Develop predictive diagnostics in tandem with new agents to enable precise targeting to those patient populations most likely to benefit from the agents
- Conduct controlled Phase 2 and 3 trials with the goal of determining the best treatment approach for a particular cancer or molecular subtype

niche filled by CTEP in recent years involves early combination trials with experimental agents from two or more companies. CTEP has forged 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. Over 50 novel combinations of targeted investigational agents have entered into clinical trials sponsored by CTEP in recent years.

When promising signals of biologic activity are seen in Phase 2 trials performed by CTEP's early-trials networks, the NCI National Clinical Trials Network (NCTN) is prepared to move these ideas into controlled, randomized, Phase 3 trials.

Transitioning from Phase 0 to Phase 3 studies requires a full complement of clinical trials services that reside in CTEP's seven branches.

INVESTIGATIONAL DRUG BRANCH

The **Investigational Drug Branch (IDB)** is responsible for coordination and oversight of clinical trials of new chemotherapeutic and biological antitumor investigational agents that aim to evaluate their pharmacokinetic (PK), pharmacodynamic (PD), and antitumor efficacy. IDB oversees a portfolio of 52 investigational agents, nearly all of which are developed under agreements with biotechnology and pharmaceutical companies. IDB staff evaluate agents for potential clinical development by NCI, initiate drug development plans, review study proposals, and oversee the conduct and analysis of data from trials conducted under CTEP INDs. IDB's primary role is the acquisition of novel agents from the pharmaceutical industry in order to assist in their further development via CTEP's Phase 1 and Phase 2 clinical trials programs, which in 2014 were combined to form the Experimental Therapeutics



Clinical Trials Network (ETCTN). Staff meet regularly with pharmaceutical companies, serve on NCI drug development committees, and interact with investigators in academia and industry, as well as FDA regulatory staff. A major focus of CTEP drug development is exploration of the combinatorial utilization of investigational and approved drugs based upon a strong mechanistic rationale and supportive preclinical data. NCI is well positioned as a leader in testing novel combinations because of the large number of agents for which it holds the IND and its long tradition as a safe haven for IP, thereby permitting different companies to overcome industry barriers to co-development of agents.

CLINICAL INVESTIGATIONS BRANCH

The **Clinical Investigations Branch (CIB)** is responsible for the scientific coordination and oversight of definitive, practice-changing clinical trials of innovative oncology treatments and advanced imaging, including complex, preliminary, and definitive precision medicine trials. These mostly randomized, Phase 2 and 3 studies include investigations of single-agent or multiple-agent targeted therapies or combined modality interventions, including surgical and radiation therapy with chemo-, biologic- and immuno-therapies, in the treatment of cancer for adult, adolescent, and pediatric populations, conducted nationally by the extramural scientific community:

- **NCI National Clinical Trials Network (NCTN)**
- **Pediatric and Adult Brain Tumor Consortia (PBTC / ABTC)**
- **Pediatric Phase 1 Consortium**
- **Pediatric Preclinical Testing Program (PPTP)**

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

- The Cancer Trials Support Unit (CTSU), which provides centralized patient enrollment 24 hours a day, 7 days a week, as well as administrative and regulatory support for trial conduct
- The Central Institutional Review Board (CIRB) for adult and pediatric NCTN trials
- The Cancer Diagnosis Program (CDP) regarding the collection, banking, and use of clinical biospecimens in

conjunction with validated data from multi-institutional clinical trials

- The Center for Coordinating Clinical Trials (CCCT) on identifying and prioritizing clinical trials for disease-related research
- Other NIH and NCI programs, such as the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN), co-sponsored by NCI and the National Heart, Lung, and Blood Institute (NHLBI)
- Other international clinical trial organizations on treatment trials

CLINICAL GRANTS AND CONTRACTS BRANCH

The Clinical Grants and Contracts Branch (CGCB) manages a multidisciplinary clinical research portfolio that is concentrated in the areas of clinical oncology and surgical oncology. These program areas are focused on the development of investigative clinical agents, related correlative studies, novel treatment regimens, clinical and surgical methods development, pharmacogenomics, clinical trial related bioethics, and clinical trial design. The CGCB supports investigator-initiated therapeutic research projects as well clinical trials networks and consortia.

In 2016, the CGCB managed 194 active grants totaling \$144 million, including 124 (\$55 million) Research Project grants (R01), 27 (\$64 million) Program Project grants (P01) and 10 (\$14 million) cooperative agreements (U01/U24/U10/U54/UM1). The distribution of grant award mechanisms in CGCB's portfolio, in terms of cancer type, is shown in Figure 39.

CGCB staff is composed of Program Officers (POs) who manage the scientific, technical, administrative, and fiscal aspects of CTEP's extramural clinical research portfolio consisting of grants and cooperative agreements. POs are responsible for, but are not limited to, the following activities:

- Ensuring that research project grants and cooperative agreements are scientifically and programmatically sound, and technically appropriate
- Identifying areas of scientific gaps and/or overlap
- Discovering new areas of scientific investigation
- Developing plans to exploit promising new therapeutic agents, modalities, and treatment strategies

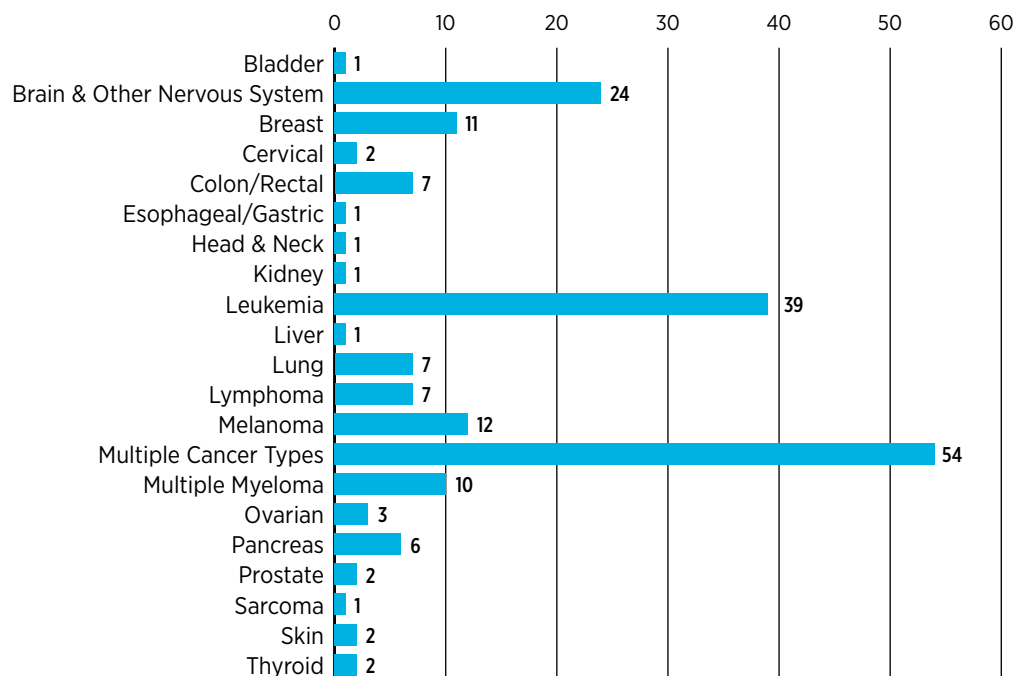


FIGURE 39: DISTRIBUTION OF CTEP 2016 AWARDS BY CANCER TYPE.

- Providing assistance, information, guidance, and advice to the scientific community
- Managing CTEP UM1- and U01-funded consortia, such as the ABTC, the BMT CTN, and the Cancer Immunotherapy Trials Network (CITN)
- Ensuring regulatory compliance
- Ensuring that research project progress is adequate to meet project goals/objectives
- Stimulating interest in scientific areas relevant to clinical and surgical oncology
- Evaluating merit and mission relevance of research proposals

REGULATORY AFFAIRS BRANCH

The **Regulatory Affairs Branch (RAB)** is comprised of two groups, the Agreement Coordination Group (ACG) and the Drug Regulatory Group (DRG), both of which function to facilitate the development of promising anti-cancer drugs as identified via the NCI Experimental Therapeutics (NExT) Program. The ACG begins this process by developing and

negotiating a CRADA with an industry partner, as a foundation for the co-development of an agent. A CTEP-specific CRADA template with standard, non-negotiable clauses is used to reduce negotiation time. More recently, the ACG has been responsible for fostering pharmaceutical collaboration for three DCTD initiatives, the **NCI-Molecular Analysis for Therapy Choice (NCI-MATCH)** and **NCI-COG Pediatric-MATCH** precision medicine studies, as well as the **NCI Formulary** (See Major Initiatives Supporting the Cancer Community, pg. 42). Other types of agreements put in place to support our IND studies include Material Transfer Agreements (for nonclinical studies), Clinical Trial Agreements (e.g., NCI-MATCH study), International Agreements, Memoranda of Understanding, and Data Use Agreements (See “Assistance to the Cancer Community” below).

As part of the co-development process, CTEP takes on the role of IND sponsor, and all the responsibilities required by FDA. The DRG within RAB is responsible for filing the necessary INDs to support all clinical trials under the auspices of a CRADA. Moreover, this group is responsible for ensuring that these studies are in compliance with FDA regulations. Currently, there are 167 IND applications used to support



our ETCTN and NCTN trials. IND-related activities include Safety Reporting (expedited and annual reporting), new protocols and amendments, and responses to FDA queries. In addition, DRG coordinates End-of-Phase 2 meetings between the FDA and CTEP-NCTN-Pharma for all studies intended to support a new indication or label change. DRG also plays a central regulatory role regarding investigational biomarker assays used in conjunction with investigational drugs. Specifically, this group ensures that pertinent Investigation Device Exemption (IDE) regulations are followed for those studies utilizing investigational, treatment-determining assays. In addition, meetings with FDA's Center for Devices and Radiological Health (CDRH; e.g., Pre-submission meetings) are coordinated through this group.

PHARMACEUTICAL MANAGEMENT BRANCH

The **Pharmaceutical Management Branch (PMB)** is a unique resource for experimental and investigational oncology agents in support of DCTD clinical research efforts by providing the extramural community with specific pharmaceutical services, regulatory oversight, and administrative support. PMB pharmacists manage the more than 150 investigational agents and deliver appropriate guidance to thousands of sites within the United States and around the world, requiring that they remain current on the latest advances in oncology practice.

CLINICAL TRIALS MONITORING BRANCH

The **Clinical Trials Monitoring Branch (CTMB)** manages quality assurance and quality control of the following:

- Early phase clinical trials (Phase 0, Phase 1, and Phase 2 studies) conducted by the ETCTN
- Late phase clinical trials (Phase 2 and Phase 3 studies) conducted by the NCTN
- Prevention trials sponsored by the Division of Cancer Prevention (DCP)

CTMB is responsible for establishing standards for quality assurance activities and for overseeing the on-site auditing activities to assure the integrity of the data, patient safety, and compliance with protocol requirements and Good Clinical Practices (GCP). CTMB also provides education to clinical research sites that are experiencing performance issues.



Accomplishments (01/01/2013-11/30/2017)

- 4,446 Cooperative Group/Network Group audits reviewed
- 239 Non-Network Group audits reviewed
- 156 Cancer Center Site Visits coordinated and performed
- 86 Children's Oncology Group (COG) Phase 1 Consortium audits conducted by the clinical trial management service (CTMS) and reviewed by CTMB staff
- 137 Phase 1 and Phase 2 Protocols assigned for CTMS monitoring involving 1,878 patient enrollments
- 292 CTMS Phase 1/Phase 2 audits conducted by the CTMS and reviewed by CTMB staff
- 7 special response audits with independent radiologic review of cases
- All new studies assigned for CTMS monitoring since 2014 are built in Medidata Rave
- Since 2014, all Phase 2 studies conducted through the ETCTN have data management, including study build and monitoring by CTMS
- Development and deployment of a web-based module to facilitate the review of clinical trial data by IDB Drug Monitors and Principal Investigators, including tools for aggregate data analysis within and across studies using the same agent

CLINICAL TRIALS OPERATIONS AND INFORMATICS BRANCH

The Clinical Trials Operations and Informatics Branch (CTOIB) improves protocol development and conduct by providing efficient business practices, informatics tools, as well as central review of clinical trials for human safety and protection, and process evaluation methods. CTOIB includes the Protocol and Information Office (PIO), the CTEP Enterprise System (ESYS), the NCI CIRB, the CTSU and a quality improvement program. CTOIB also supports process evaluation and data-analysis efforts for the NCTN systems. This includes using surveys and marketing analyses for the development and application of systematic accrual practices to aid challenging trials and evaluation of NCI programs, including the CIRB.

CTEP GRANTS OVERVIEW

The CTEP research portfolio includes 263 active grants and cooperative agreements totaling approximately \$278 million during fiscal year 2016. The award mechanisms used by CTEP and their distribution in terms of number of awards and funding in 2016 are shown in Figure 40. The predominant mechanism, in terms of funding, is the Cooperative Agreement (U10), followed by the Program Project grant (P01) and Research Project grant (R01). In terms of numbers of grants, the Research Project grant (R01) is the mechanism most utilized in CTEP's portfolio.

ASSISTANCE TO THE CANCER COMMUNITY

CTEP-SPONSORED PHASE 2 TRIALS LEADING TO PIVOTAL TRIALS

A number of CTEP-sponsored Phase 2 studies have led to pivotal clinical trials. Examples include the following:

- The randomized Phase 2 trial of cabozantinib versus sunitinib in metastatic renal cell carcinoma (RCC) led to the pivotal METEOR trial (NCT01865747).¹ This comparison of cabozantinib to everolimus was the basis for the 2016 FDA approval of cabozantinib in patients with advanced RCC who had received prior anti-angiogenic therapy.
- Phase 2 trial of cabozantinib in endometrial carcinoma (NCT01935934) leading to the pivotal CTEP-sponsored Phase 3 CARE trial of cabozantinib vs. adriamycin in recurrent/metastatic endometrial cancer.
- Randomized Phase 2 trial (NCT01143402) in metastatic uveal melanoma demonstrated marked improvements in PFS with selumetinib monotherapy relative to temazolo-mide or dacarbazine.² These results led to the pivotal Phase 3 SUMIT trial (NCT01974752) of selumetinib + dacarbazine compared to dacarbazine alone.³ Unfortunately, the improvements in PFS and OS observed in the earlier trial were not reproduced.

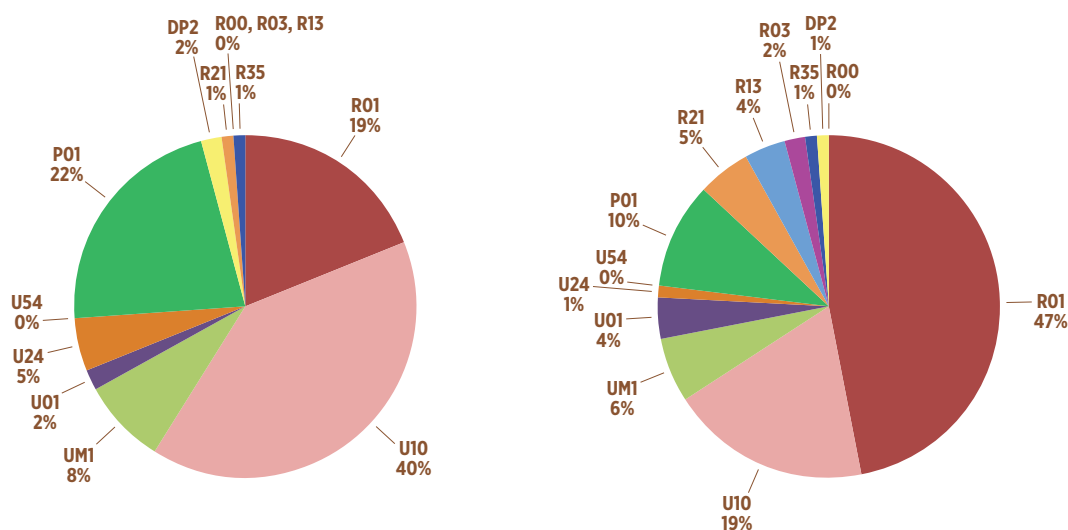
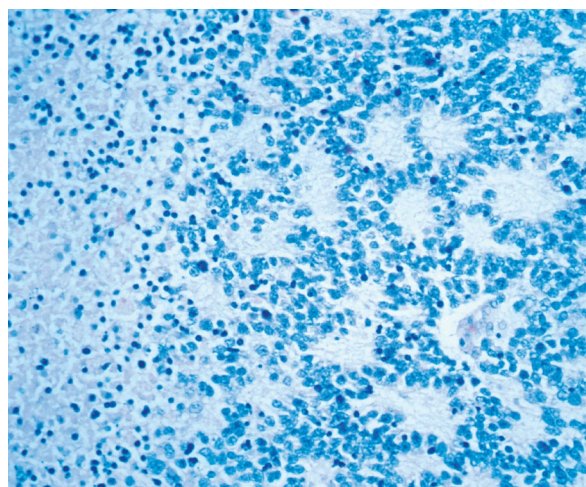


FIGURE 40: DISTRIBUTION OF CTEP 2016 GRANT FUNDS (LEFT) AND NUMBERS OF GRANTS (RIGHT) BY MECHANISM.

¹ Choueiri TK, et al; *Lancet Oncol* 2016 Jul;17(7):917-27

² Carvajal RD, et al; *JAMA* 2014;311(23):2397-2405

³ Carvajal RD, et al; *BMC Cancer* 2015 Jun 10;15:467



- Randomized Phase 2 study (NCT01116648) of combination cediranib and olaparib versus olaparib alone in ovarian cancer⁴ has led to two pivotal trials: one in platinum-sensitive (NCT02446600) and the other in platinum-refractory (NCT02502266) ovarian cancer.

- Initiation of projects that interrogate the large CTEP Phase 1 database containing data from thousands of patients enrolled in CTEP clinical trials

FOSTERING CAREER DEVELOPMENT OF JUNIOR CLINICAL INVESTIGATORS

The Career Development LOI (CrDL) program is designed to facilitate career development by providing a competitive advantage for junior investigators submitting LOIs. The program provides mentoring in the LOI development and review process, including expert commentary on clinical trial proposals. Of the several hundred CrDLs submitted since the program's inception, approximately 30% have been approved. Moreover, virtually all members of CTEP Drug Development Project Teams are junior faculty/mentor pairs. CrDLs have been submitted through all funding mechanisms, reflecting broad acceptance of the CrDL process.

Ten to twenty fellows and junior faculty from institutions around the country rotate at CTEP each year, during which they participate in:

- CTEP review of LOIs and protocols
- Scientific presentations by biotechnology and pharmaceutical companies seeking CTEP collaboration

CLINICAL TRIALS PROGRAM

NCI National Clinical Trials Network (NCTN)

See Major Initiatives Supporting the Cancer Community, pg. 12

In 2016, investigators from COG presented their results for newly diagnosed children with high-risk neuroblastoma. ANBL0532 was designed to test whether intensifying therapy using two back-to-back phases of myeloablative chemotherapy (tandem) would improve 3-year event-free survival. A total of 652 patients were enrolled with 355 randomized to either single or tandem autologous stem cell transplants. The children treated with the tandem transplants had a superior 3-year event-free survival of 63% as compared to 49% for those children who received a single transplant.

In view of these results, tandem transplant has now become the standard therapy for children with high-risk neuroblastoma. In the next high-risk neuroblastoma study (ANBL1531), this regimen will be compared against the European approach for myeloablative therapy and against a treatment arm using the targeted radioactive agent ¹³¹I-MIBG during the first phase of therapy (induction) followed by tandem transplant.

⁴ Liu JF, et al; *Lancet Oncol* 2014 Oct;15(11):1207-14

Cooperative Research and Development Agreements (CRADAs)

The establishment of an Alternate Technology Development Coordinator position within RAB in 2011 markedly enhanced CTEPs ability to execute agreements associated with clinical trials. Following are the numbers and types of agreements for 2013–2017:

- CRADAs Executed: 67
- Total Active CRADAs: 98
- CTAs Executed: 19
- Total CTAs: 46
- International Agreements Executed: 9
- Total International Agreements: 17
- INDs Filed: 109
- IND Portfolio: 167
- IND Amendments (per year): 658 Protocol Amendments, 30 New Protocols, 194 Expedited Safety Reports, and 115 Annual Reports
- CRADA, IND, and Sponsor Inspection Support: Anti-GD2 MoAb ch14.18 (FDA-approved March 2015)

IP and Biomarker Development

In order to facilitate precision medicine trials such as NCI-MATCH, as well as biomarker driven targeted therapy, DCTD has developed collaboration agreements with language that facilitates diagnostic assay company access to data and materials by clarifying the rights to data and IP for the pharmaceutical collaborators as well as the diagnostic company. As described in the [CTEP IP Option to Collaborator](#), diagnostic assay companies must provide a pharmaceutical collaborator the biomarker rights to a research use and label use license if the collaborator is required to use an assay, for marketing of the agent or regulatory filings, that was developed using data or specimens collected under the scope of a CTEP study. In return, the diagnostic company retains the rights to any improvements or developments related to the proprietary assay that is

being used to support or select patients for that clinical trial. Biomarker and clinical outcome data are shared per the multiparty data provisions of all agreements in order to allow both the collaborators and diagnostic companies any further development of their proprietary products.

NCI Drug Development Project Teams

Highly ranked drug development proposals submitted through the NCI Experimental Therapeutics (NExT) Program require the assembly of an NCI Drug Development Project Team to design the scope of NCI's initial multi-institutional, multi-disciplinary drug development plan for the proposed agent(s). In order to identify the appropriate team members, CTEP solicits and reviews Project Team Member Applications (PTMAs) from investigators in CTEP's clinical trial networks. The Project Team members are selected based upon their qualifications and the expertise they can provide to the Project team. They will determine which clinical trials will be conducted across the CTEP clinical trials network sites, and how best to approach critical translational studies.

Extramural investigators included on the Project Teams may fill one or more of the following roles:

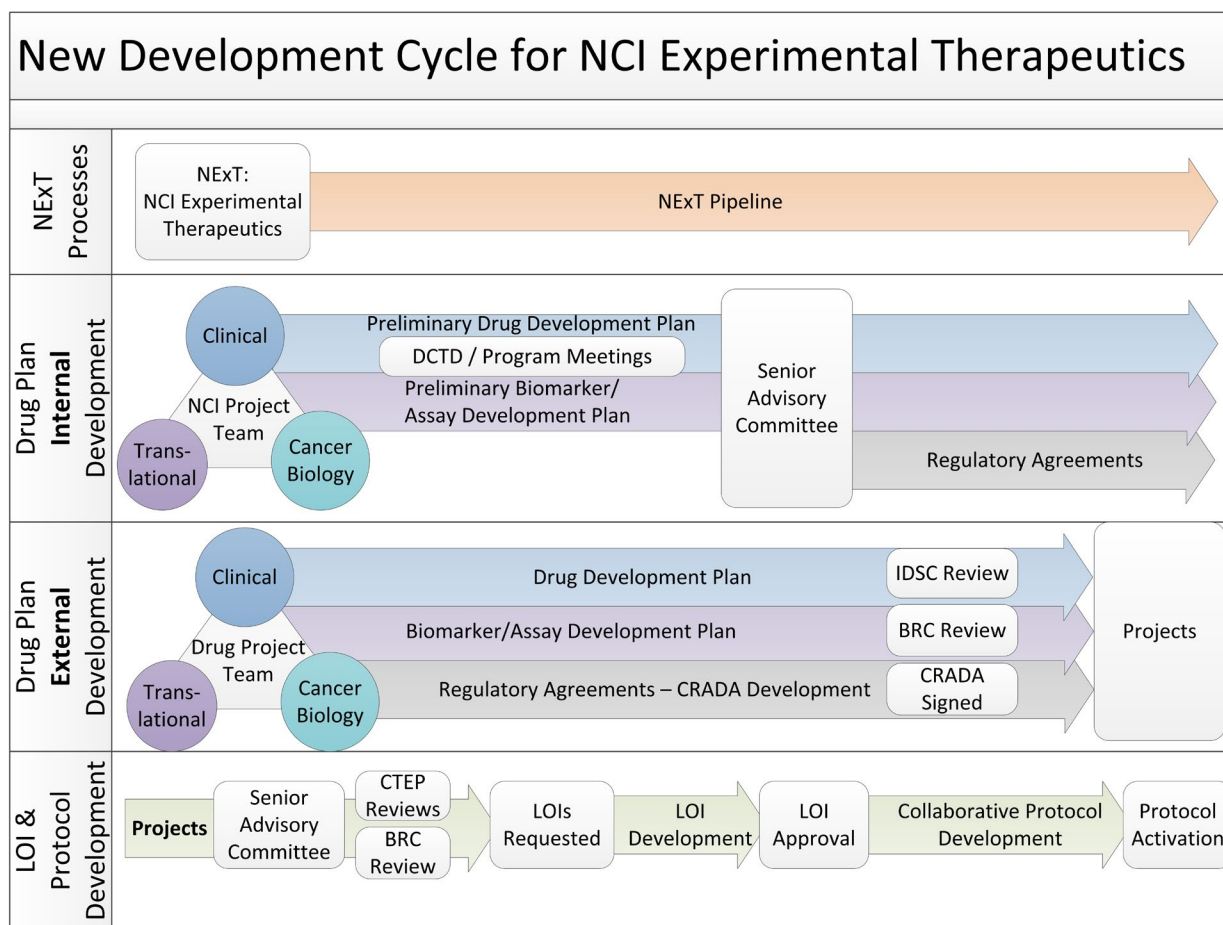
- **Clinician scientists** lead the clinical trials recommended by the NCI Drug Development Project Team and create protocol study committees for execution of these studies. These trials can be conducted through any of the clinical trials networks managed by CTEP. Junior investigators and their mentors are encouraged to submit Career Development Project Team Member Applications (CrD PTMAs), similar to the CrDL process.
- **Translational scientists** provide guidance on prioritization of biomarkers for the studies under development, including recommendations for technologies and platforms that meet increasingly stringent requirements for integral and integrated biomarkers.
- **Basic scientists** provide scientific guidance for the study design based on the mechanism of action of the investigational agent, and help prioritize the clinical study choices based on published literature and unpublished data. Basic scientists on the team



will have access to the agents in order to conduct additional laboratory studies deemed important for supporting the proposed clinical trial(s) of the agent.

Once convened, the NCI Drug Development Project Team meets regularly over a 6-8-week period in order to finalize the drug development plan for presentation to the Investigational Drug Steering Committee (IDSC). Upon approval of

the project development plan and the requisite funding by the NEXt Senior Advisory Committee (SAC), the clinician and translational scientists on the Project Team submit LOIs to CTEP. CTEP subsequently makes the agent available to qualified investigators, contingent on approval from the agent applicant. Network and non-network sites not on the Project Team may submit unsolicited LOIs for clinical trials or request the agent for nonclinical studies (Figure 41).



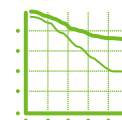
CRADA: Cooperative Research and Development Agreement **IDSC:** Investigational Drug Steering Committee **BRC:** Biomarker Review Committee

FIGURE 41: WORKFLOW FOR THE PROJECT TEAM-DRIVEN APPROACH TO NCI CLINICAL TRIALS.

Listed below are the Drug Development Project Teams assembled since implementation of this concept in 2014 through 2017.

Year	Agent	Mechanism of Action	Target
2014	AT13387 (Onalespib lactate)	poly(ADP-ribose) polymerase (PARP) inhibitor	HSP90
	AZD-9291 (Osimertinib)	3rd generation inhibitor of mutated epidermal growth factor receptor (mEGFR)	mEGFR
	VX-970	Inhibitor of ataxia telangiectasia mutated and Rad3-related (ATR) kinase	ATR
2015	CO-1686 (Rociletinib)	3rd generation inhibitor of mEGFR	mEGFR
	MPDL3280A (Atezolizumab)	Designed to target programmed cell death ligand (PD-L1) expressed on tumor and infiltrating immune cells, and prevent binding to programmed cell death protein-1 (PD-1) and B7.1	PD-L1
	MEDI-4736 (Durvalumab)	A human monoclonal antibody directed against PD-L1. Signals from PD-L1 help tumors avoid detection by the immune system	PD-L1
2016	T-VEC	Herpes simplex virus type 1-derived oncolytic immunotherapy designed to selectively replicate within tumors and produce granulocyte macrophage colony-stimulating factor (GM-CSF) to enhance systemic antitumor immune responses	Oncolytic Virus
	AMG-232	Inhibitor of murine double minute 2 (MDM2) signaling	MDM2
	Anetumab ravtansine	A fully human IgG1 monoclonal antibody directed against the cell surface glycoprotein mesothelin and conjugated to the maytansinoid DM4 with potential antineoplastic activity	IgG1 Antibody
2017	Copanlisib	A phosphoinositide 3-kinase (PI3K) inhibitor with potential antineoplastic activity	PI3K
	CB-839	Glutaminase inhibitor, oncology metabolomics	Glutaminase
	Ixazomib	Proteasome inhibitor	proteasome
	Pevonedistat	NEDD8ylation inhibitor	NEDD8
	M3814	DNA-PKcs inhibitor, DNA Repair	DNA

TABLE 6: NCI DRUG DEVELOPMENT PROJECT TEAMS (2014-2017)



CTEP has also acquired agents that, due to a very limited drug development plan, have not required a Drug Development Project Team. Those agents are listed in the following table.

Year	Agent	Mechanism of Action	Target
2014	AMG-102 (Rilotumumab)	Inhibit the hepatocyte growth factor/scatter factor (HGF/SF)	HGF/MET
	AMG-337	Specific inhibitor of the Met receptor	cMET
	CDX-011 (Glembatumumab vedotin)	Transmembrane glycoprotein NMB (GPNMB)-targeted antibody drug conjugate	GPNMB
	SGI-110 (Guadecitabine)	Dinucleotide antimetabolite of a decitabine linked via phosphodiester bond to a guanosine, with potential antineoplastic activity	DNMT
	VXc-984	A novel DNA-protein kinase (PK) inhibitor	DNA-PK
2015	AZD8186	An inhibitor of the beta isoform of PI3K	PI3K
	CDX-1127 (Varlilumab)	Fully human monoclonal antibody that targets CD27	anti-CD27-mAb
	KW-0761 (Mogamulizumab)	Defucosylated humanized IgG1 mAb against C-C chemokine receptor 4 (CCR4)	anti-CCR-mAb
2016	LOXO-101	An orally available, tropomyosin receptor kinase (Trk) inhibitor, with potential antineoplastic activity	pan TRK
	Pinometostat	DOT1-like (Disruptor of telomeric silencing 1-like), histone H3K79 methyltransferase (DOT1L) inhibitor	DOT1L
	Tazemetostat	An orally available, small molecule selective and S-adenosyl methionine (SAM) competitive inhibitor of histone methyl transferase EZH2, with potential antineoplastic activity.	EZH2
	Savolitinib	An orally bioavailable inhibitor of the c-Met receptor tyrosine kinase with potential antineoplastic activity	MET
2017	GSK525762 (I-BET-762, GSK525762A)	Binds to the acetylated lysine recognition motifs on the bromodomain of BET proteins, thereby preventing the interaction between the BET proteins and acetylated histone peptides.	BET
	TAK-243	A cell permeable small molecule inhibitor targeting ubiquitin-activating enzymes (UAE, also known as E1 enzymes).	UAE

TABLE 7: NCI AGENTS WITH LIMITED DRUG DEVELOPMENT (2014-2017)

NCI Investigational Drug Steering Committee (IDSC)

The recommendation of NCI's Clinical Trials Working Group, which reviewed the national clinical research enterprise, formed the basis for establishment of the NCI IDSC in November 2005. The IDSC is composed of a steering committee and nine task forces. Members of the IDSC include the principal investigators of NCI's early drug development grants and contracts, representatives from the NCTN, a patient advocate, biostatisticians, and NCI staff.

The goals of the IDSC are to:

- Provide external strategic input into the prioritization of Phase 1 and 2 trials for new agents, including review of the drug development plans proposed by the NCI Drug Development Project Teams
- Increase transparency of the prioritization process
- Optimize clinical trial designs to improve efficiency of early-phase therapeutics

Registration of Clinical Trial Site Research Staff

More than 23,000 physician investigators are registered with PMB to participate in clinical investigations, of which approximately 20,000 (87%) are domestic and 3,000 (13%) are international researchers. In addition, approximately 53,300 trial-associated health care professionals are also registered. The help desk manages more than 55,000 inquiries and communications annually in support of the registry. Registration is accomplished via the newly developed and implemented NCI Registration and Credential Repository database, which documents that the appropriate education, training and qualification of research staff required to conduct DCTD-sponsored and funded research are obtained and current.

Additional activities include:

- An average of 25,000 investigational agent shipments annually authorized in support of DCTD-sponsored and supported trials worldwide. Of these, approximately 24,000 are distributed to domestic clinical trial sites.
 - Blinded study/patient-specific supply order shipments: approximately 3,500 annually (for 18 blinded, placebo-controlled and patient-specific supply clinical trials accruing patients)
 - Open-label study standard order shipments: 21,500 annually
- Specialized resources to support shipment of agents to international clinical trial sites. Over the past five years, agents were successfully shipped to clinical trial sites in the following countries: Australia, Canada, Hong Kong, Israel, Japan, South Korea, New Zealand, South Africa, Singapore, and Taiwan.
- Specialized resources to support randomized, placebo-controlled and patient-specific supply clinical trials. The development, implementation, support, and monitoring of blinded and patient-specific clinical trials require development of specialized computer programming for each trial to ensure that the pertinent active agent or placebo supply is delivered to patients in a timely manner. There are currently 18 blinded trials eligible to accrue patients and two more in development.
- Investigator Community Service-Support Projects:
 - Website—Provides the investigator and associated community valuable and time saving online tools to meet regulatory requirements.

- PMB After Hours—An e-mail address where investigators and research staff can send questions 24/7/365, which is particularly helpful for sites outside the continental United States. Routine response time is within one business day. More than 10,000 e-mails in addition to 7,000 telephone inquiries are addressed annually.
- Maintenance and Distribution of Investigator Brochures—IBs contain confidential and essential information required by the investigator and research staff to develop and conduct clinical investigations. PMB has implemented a secured, password-protected web-based module utilizing authentication factors to allow access to authorized recipients.
- Creation of a library of training videos that support site education for investigational agent management and reinforce PMB policies and procedures. These are accessible through the NCI YouTube channel and PMB website.
- Implementation and enhancement of an interactive PMB On-Line Agent Order Processing (OAOP) module. OAOP allows investigators and research staff to order investigational agents and track their shipment, access stock recovery notifications and IBs.
- Re-design of registration website and resources to support the implementation of the NCI Registration and Credential Repository.
- Facilitated development of website in support of the NCI Formulary.
- Meet regulatory requirements to support agent distribution processes for IND Exempt clinical investigations.

Protocol and Information Office

The PIO collects, processes, tracks, and monitors all protocol-related information between CTEP and its extramural collaborators, as well as with other CTEP and NCI programs to:

- Facilitate the development and conduct of quality clinical trials in the most efficient and expeditious manner possible
- Minimize the administrative burden related to clinical trial development, conduct, and management on CTEP staff and the extramural community



- Capture protocol-related keywords and milestones into CTEP ESYS to assist with CTEP decision making
- Promote, inform, and educate all concerned parties regarding NCI programs, policies, and objectives related to clinical trial development, conduct, and management

Item	2013	2014	2015	2016	2017
LOIs	130	230	128	114	111
Concepts	57	68	65	64	68
New protocols	165	163	144	130	157
Protocol revisions	283	159	172	136	369
Protocol amendments	1034	1466	907	838	781

TABLE 8: ITEMS PROCESSED BY THE PROTOCOL AND INFORMATION OFFICE (2013–2017)

CTEP Enterprise System

The CTEP ESYS is a 29-application system that fosters broad investigator participation, patient safety, and scientific advancement. Specifically, it facilitates clinical trial conduct and management by:

- Capturing data and translating it into a usable and streamlined format to address scientific, safety, regulatory, and administrative requirements of clinical trials
- Eliminating data redundancy throughout the oncology community through integrated data systems
- Improving communication between CTEP and its collaborators
- Assuring the security and confidentiality of proprietary and patient information
- Supporting broad patient access to clinical trials

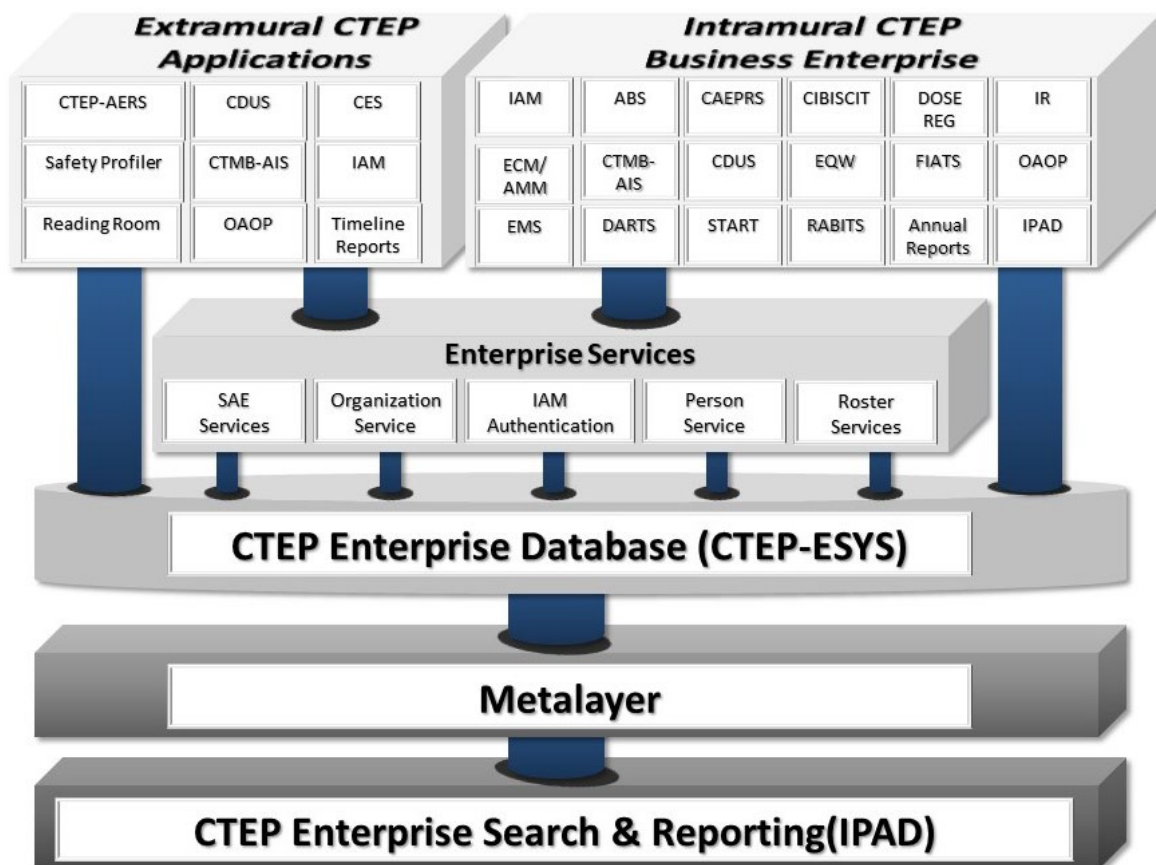


FIGURE 42: SCHEMATIC DIAGRAM OF THE CTEP-ESYS INTEGRATION INTO THE LARGER IT INFRASTRUCTURE THAT SUPPORTS THE NCI CLINICAL TRIAL SYSTEM.

- Expediting the protocol development and review process within both clinical trial organizations and reviewing bodies

Because many of the sub-CTEP ESYS applications were developed more than 10 years ago, it is currently undergoing modernization from both a technical and operational perspective. Tools are being upgraded to broaden their use for diagnostic imaging, cancer prevention, and cancer control. Additional flexibility is being incorporated to support evolving scientific needs, including translational research, precision medicine, and other genomic initiatives. Software upgrades will ensure that CTEP ESYS applications remain secure, flexible, and relevant with technology, operational, and scientific advancements.

The CTEP ESYS contains data on:

- 10,872 LOIs
- 1,581 Concepts
- 22,483 Protocols
- 1,225,987 Patients
- 1,641,487 Expedited and routine adverse events
- 185,060 Expedited adverse event reports submitted to NCI (original AE reports + amendments)

The CTEP ESYS contains several systems (new and enhanced) used for submitting and tracking clinical trial information to CTEP:

1. **CTEP Adverse Event Reporting System (CTEP-AERS)**—Used by members of the external community to inform IND sponsors and the FDA of serious adverse events occurring during trials. Current CTOIB activities related to adverse event reporting include continued customization of CTEP-AERS. This includes integrating Rave with CTEP-AERS to allow Rave users to submit reports of serious adverse events while using Rave, as well as updating tools used by CTEP to track, review, and assess adverse event reports and submit them to the FDA within the regulatory timeframes.
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. Recent CTOIB activity

related to CDUS is the integration of CDUS and the Oncology Patient Enrollment Network (OPEN), which sends real-time patient demographic information to CTEP-ESYS.

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. CTOIB is currently working with NCI's Center for Biomedical Informatics and Information Technology to extend the usage of Identity Access Management to include the NIH Lightweight Directory Access Protocol to provide all CTEP ESYS users with true single-sign-on capability.
4. **NCTN & ETCTN Restructure**—The Cooperative Group program under NCI was restructured in response to the NCTN and its goals. As a result, the nine Cooperative Groups were merged to form four Adult and one Pediatric Network organizations. Changes to the CTEP Enterprise included adding a new organization status, providing the ability to transition and abstract protocols, ship drugs, enter adverse events, track patient accrual and monitor studies for the newly formed network organizations. The new organization status helped preserve the protocol information associated with legacy Cooperative Group organizations in the CTEP-ESYS for query and reporting purposes. Enhancements were made across the enterprise systems to support the new 3-tiered organization rostered structure. A central roster validation service was developed to maintain and verify Grant Package Roles across multiple systems (ECM, RSS and CCOP-SYS), which increased collaboration and accuracy of information.
5. **Study Abstraction Review & Tracking System (START)**—The Study Abstraction Review and Tracking System provides CTEP the ability to enter, modify, and retrieve data on study documents such as LOIs, concepts, protocols, revisions, and amendments received from researchers conducting clinical trials. START tracks these documents as they move through the protocol lifecycle, from review and approval to activation and completion. The legacy protocol abstraction system, PATS, was re-engineered with a technology upgrade to a more scalable service-oriented platform that will support integration, configuration and enhanced security. An NCI BRIDG compliant database design was implemented to



enable data exchange with other sources. Data abstraction capabilities were enhanced to support streamlined workflows for protocol approval, reduce duplication of data abstraction, enable better tracking and reporting of OEWSG timelines, study status, related studies (precision medicine), actual and planned accrual.

- 6. Registration and Credentialing Repository (RCR)**—The Registration and Credentialing Repository (RCR) is an online application used for the collection and management of NCI annual registration documents to ultimately generate an on-demand site- and protocol-specific registration report, based on study activities assigned on the trial's Delegation of Tasks Log (DTL) that span the history of the study and meets FDA regulations. Information collected through the RCR includes elements from the NCI Biosketch, FDA Form 1572, the FDA Financial Disclosure Form and the NCI Shipping Information Form. It complies with 21 CFR Part 11.
- 7. CTMB Audit Information System (AIS)**—CTMB-AIS is the audit information system used to schedule and perform audits at sites conducting CTEP sponsored studies. The technology stack of AIS was updated to integrate SSO, improve security and enable integration with other CTEP-ESYS applications to include IAM, RCR, START and web services. One of the major enhancements was the implementation of site monitoring capability for a specific protocol and Targeted Source Document Verification (TSDV) integration, which enables source data verification in RAVE and provides transparency for audit activities.

- 8. Integrated Platform for Agents and Diseases (IPAD)**—IPAD serves as a search engine for anyone seeking information contained within the CTEP ESYS, which allows for customized queries that can be saved and exported as needed along with access to protocol-related documents linked within the CTEP ESYS. Several major enhancements were made to IPAD to meet NCI's reporting and data analysis capabilities. The NIH AD/PIV Card login option was implemented, enabling CTEP IAM account holders who also have NIH accounts to login to IPAD. New accrual fields (Screening vs. Intervention) and reports were implemented to support the analysis of accrual performance on more complex precision medicine trials.
- 9. Central Enterprise Services (CES)**—CES consists of multiple web services developed to support the exchange, sharing, and integration of clinical trial data with systems that are internal and external to the CTEP ESYS. These services have replaced manual processes to share data, reduced duplication of effort and increased data quality and standardization. Two new services were implemented, and existing services were enhanced. One of the new services was developed to send CTEP trial registration and accrual data to NCI's Clinical Trial Reporting Program (CTRP) for all CTEP studies. The Central Accrual Service (CAS) was implemented to provide planned and actual accrual data to IPAD, AIS, and other external consumers. Study service enhancements added new data elements and additional operations to support integration and data retrieval.

10. **CTEP Clinical Oncology Research Enterprise (CORE)**—The CTEP CORE was established to increase collaboration and represent an integrated solution across

multiple IT systems and contractors. CTEP CORE will support evolving and more complex science, emphasize harmonization, and streamline integration.

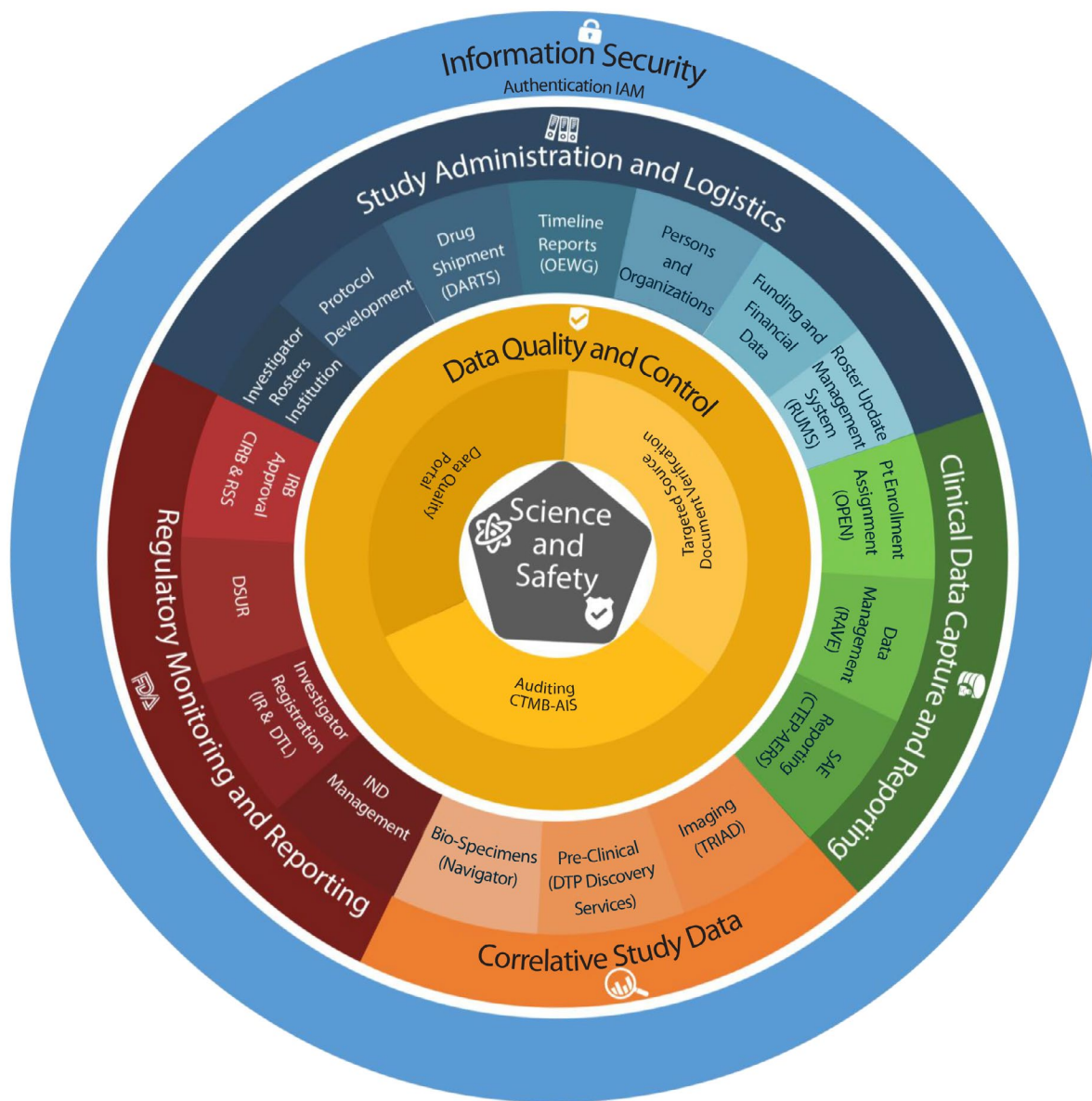


FIGURE 43: CTEP CLINICAL ONCOLOGY RESEARCH ENTERPRISE (CORE).
Provides secure, flexible and scalable operational infrastructure to a robust clinical trials program.



Cancer Trials Support Unit and CTSU-Flex Programs

The **Cancer Trials Support Unit (CTSU)** increases physician and patient access to NCI-sponsored clinical trials, reduces the regulatory burden on investigators participating in clinical trials, and streamlines and standardizes trial data collection and reporting.

The CTSU works in tandem with ESYS to simplify admittance to NCI-funded clinical trials for qualified clinical sites and support the conduct of those clinical trials. CTSU membership provides access to a wide range of assistance for eligible investigators, including patient enrollment and data-collection services. The CTSU website also offers a listing of active CTSU-supported clinical trial protocols, displays accrual information, and provides links to study abstracts.

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 in collaborative trials annually
- Diminished the regulatory and administrative burden for trial enrollment, handling more than 10,000 IRB approvals (initial, continuing, and amendments) each month
- Provided standardized data management services for multiple Phase 3 clinical trials
- Initiated the **Oncology Patient Enrollment Network (OPEN)**, a Web-based registration system providing the

ability to enroll patients on a 24/7 basis in trials occurring at any NCTN location 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 ETCTN trials supported by IDB, cancer control and symptom management trials sponsored by the NCI DCP, and trials initiated by Specialized Programs of Research Excellence (SPORE) investigators. Since its inception, the CTSU-Flex program has supported approximately 40 clinical trials and contributed more than 3,100 enrollments to trials led by NCTN Groups, cancer centers (including the NIH Clinical Center and NCI Community Oncology Research Program (NCORP) research bases) and various consortia and networks.

NCI Central Institutional Review Board

The **NCI CIRB** helps reduce the administrative burden on local IRBs and investigators while continuing a high level of protection for human research participants. The CIRB, with one centralized review, enables investigators to enroll patients into network trials significantly faster than when employing the traditional method of assessment, which requires trial investigators in each site to obtain approval from a local IRB.

In the past several years, the CIRB has expanded both its scope and service. The 2013 initiation of the Adult Early Phase Emphasis CIRB was followed in 2015 by the Cancer Prevention and Control CIRB. Now, with four Boards, nearly

all of the clinical trials conducted via the NCTN, the ETCTN, the NCORP and the DCP Phase I-II Prevention Consortia programs are reviewed by the CIRB. Thus, all study phases, treatment modalities, participant ages, cancer diagnoses, related conditions, and interventions across the entire cancer continuum can be coordinated. In 2014, the CIRB reviewed 39 new studies. In the years 2015, 2016, and 2017, the following numbers of new studies were reviewed: 69 (NCI-MATCH counted as one study), 68, and 96, respectively. The CIRB continues to meet the established review timelines in spite of this dramatic increase in volume.

A total of 533 signatory institutions, representing 1,932 sites, are currently enrolled in the CIRB. This constitutes 86% of the NCTN, 100% of the ETCTN, and 93% of the NCORP institutions. The total number of protocols opened through the CIRB by institutions since its inception in 2001 is over 10,000.

In addition:

- The CIRB implemented (2014) a new ‘independent’ model, with the CIRB serving as the ‘IRB of record’ for enrolled institutions. The benefits of this model occur at the local research sites where administrative burden

is reduced. According to one survey respondent, “It has allowed the research associate staff more time for tracking studies and focus on carrying out the actual research, rather than being bogged down in paperwork.”

- A multi-year effort with the Veteran’s Administration (VA) recently culminated in an agreement that allows VA institutions conducting NCI trials to enroll in the CIRB. This complex negotiation required the VA to change their policy precluding reliance on external IRBs.
- The CIRB underwent its first routine FDA inspection in February 2015, with no findings and no issues identified. A 3-day site visit by the Association for the Accreditation of Human Research Protection Programs resulted in a December 2015 award of Full Accreditation for 5 years. These findings serve to reinforce the program’s credibility and promote trust among its relying institutions.

Common Network-Wide Clinical Data Management System

Medidata Rave is a standard Clinical Data Management System (CDMS) deployed by NCI in the Spring of 2012 across its clinical trial networks to improve operational

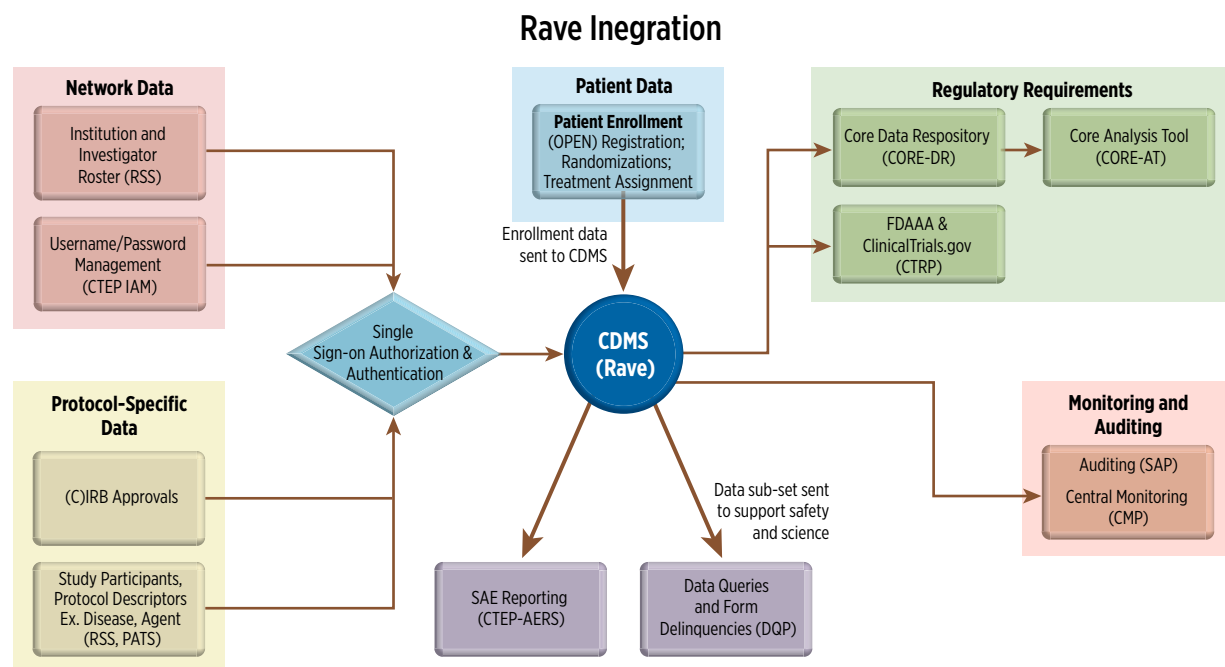


FIGURE 44: INTEGRATION OF THE METADATA RAVE CLINICAL DATA MANAGEMENT SYSTEM (CDM) INTO THE NCI CLINICAL TRIALS IT INFRASTRUCTURE.



efficiency, patient safety, and scientific advancement. Rave is integrated with multiple NCI applications, including the Cancer Therapy Evaluation Program Identity and Access Management (CTEP-IAM) Single Sign-On (SSO), Oncology Patient Enrollment Network (OPEN), Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS), Data Quality Portal (DQP), Site Audit Portal (SAP), Central Monitoring Portal (CMP), and Core Data Repository (CORE-DR). Future integrations will support specimen tracking and site performance evaluation (using the auditing and central monitoring data).

The goals of using a common CDMS and related systems, are to improve efficiency of multi-center trial operations through communication, elimination of duplicative effort, and the development and use of standard systems and processes, for trial sponsors and participating sites. With the standard

CDMS, NCI has been successful in facilitating a consistent adoption of Medidata Rave within the NCTN community, and it is now providing a broad package of support to users as they conduct clinical trials using Medidata Rave within the NCI Enterprise Systems environment.

Protocol Tracking System

To support recommendations from the Operational Efficiency Working Group to improve timelines for protocol development, CTOIB is opening its services to 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 has helped CTEP and its investigators to reduce protocol development timelines by more than 75% in some cases.

Protocol Tracker

Document Tracker

Track LOIs/Concepts/Protocols Sequential View Gantt View

Document Number: LOI XXXXX
Status: [Consensus Review sent to PI](#)
Status Date: 02/21/2011
Principal Investigator: John Smith
Lead Organization: Group ABC
Associated INDs: 1111, 2222
Associated Agents: AAA1, BBB2

Document Milestones	Milestone Date	LOI/Concept/Protocol
Stage 1a: Initial LOI Consensus Evaluations		
LOI received	04/01/2010	LOI
IDB reviewed	04/7/2010	LOI
PRC reviewed	04/8/2010	LOI
Consensus Review completed	04/15/2010	LOI
Consensus Review sent to PI	04/15/2010	LOI

Tracking results provided by Document Tracker 04/22/2010 4:36 P.M. ET

NOTICE: This is for tracking the Protocol Development Timelines.

National Cancer Institute

FIGURE 45: CTOIB'S PROTOCOL TRACKER.

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 primarily sponsors pediatric clinical trials through the NCTN COG. Additional pediatric trial consortia include the **Pediatric Preclinical Testing Consortium (PPTC)**, the **COG Phase 1/Pilot Consortium**, and the **Pediatric Brain Tumor Consortium (PBTC)**.

Pediatric Preclinical Testing Consortium (PPTC)

The **PPTC** systematically tests novel anticancer agents against pediatric preclinical models to develop datasets that can assist clinical researchers in selecting the agents and combination therapies that are most likely to be effective for childhood solid tumors and leukemias. The PPTC builds upon the 10 years of experience achieved through the Pediatric Preclinical Testing Program (PPTP), during which approximately 80 anticancer agents were systematically studied, providing the preclinical data that supported the advancement of a number of these agents into pediatric clinical testing. Equally importantly, the PPTP identified agents with limited activity for which focused pediatric development could be deferred absent additional rationale. The PPTC began its 5-year funding period in the second half of 2015 and has already developed agreements with companies and research institutes for evaluating 15 agents, some of which have initiated testing. Research Triangle Institute (RTI) serves as the Coordinating Center for this international consortium, which consists of the following research programs for the *in vivo* testing of agents using patient-derived xenograft (PDX) models:

- Osteosarcoma Research Program led by Richard Gorlick, MD (Albert Einstein College of Medicine; New York, NY)

- Sarcoma and Renal Tumors Research Program led by Peter Houghton, PhD, (Greehey Children's Cancer Research Institute; San Antonio, TX)
- Brain Tumor Research Program led by Xiao-Nan Li, MD, PhD (Texas Children's Hospital; Houston, TX)
- Neuroblastoma Research Program led by John Maris, MD (Children's Hospital of Philadelphia; Philadelphia, PA)
- Acute lymphoblastic leukemia (ALL) Research Program led by Richard Lock, PhD (Children's Cancer Institute; Sydney, Australia)

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 completed and published (or publicly presented) include:

- ADVL1011: Phase 1 dose escalation study of Ruxolitinib in children with solid tumors that defined the Phase 2 dose as 50 mg/m²/dose BID.⁵ An ALL Phase 2 study (AALL1521) is currently open to accrual to further study Ruxolitinib.
- ADVL1013: Phase 1 study of MK-2206 that evaluated two separate schedules of this AKT inhibitor. The recommended pediatric Phase 2 dose of MK-2206 was determined to be 45 mg/m²/dose every other day or 120 mg/m²/dose weekly. The pharmacokinetics (PK) appeared linear over the dose range studied.⁶
- ADVL1211: Phase 1 study of Cabozantinib. Based upon dose-limiting toxicities in cycle 1, during later cycles, and PK data from this Phase 1 study of Cabozantinib, the recommended dose for pediatric patients with solid tumors was determined to be 40 mg/m².⁷ In addition, based on the results of this Phase 1 trial, a Phase 2 study of cabozantinib is under development (ADVL1622).

⁵ Loh M, et al; *Pediatric Blood and Cancer* 2015; 62(10):1717-24

⁶ Fouladi M, et al; *Pediatric Blood and Cancer* 2014 Jul;61(7):1246-51

⁷ Chuk M, et al; *J Clin Oncol* 32:5s, 2014 (suppl; abstr 10078)



- **ADVL1212:** This Phase 1 study combining the targeted agent crizotinib with cytotoxic chemotherapy agents simultaneously evaluates different chemotherapy backbones as well as new formulations of crizotinib. Parts A and B of the study of crizotinib oral solution in combination with chemotherapy were presented at ASCO 2015.⁸ Building upon ADVL1212 and the previous Phase 1 study of single agent crizotinib (ADVL0912), crizotinib is also being evaluated in combination with chemotherapy in newly diagnosed patients with anaplastic large-cell lymphoma (AHNL12P1), and the Neuroblastoma Disease Committee is planning to incorporate crizotinib into an upcoming Phase 3 trial (ANBL1531).
- **ADVL1314:** The results of this Phase 1 study of eribulin mesylate were presented at ASCO 2016.⁹ The recommended Phase 2 dose was determined to be 1.4 mg/m² IV Days 1 and 8 of a 21-day cycle. This dose was well tolerated in children with relapsed or refractory solid tumors. The expansion cohort is continuing to accrue, and PK analysis is pending completion of this accrual. Phase 2 studies of eribulin mesylate are in early stages of development.

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 in children with brain tumors. A focus of the consortium is conducting the first in children studies of agents that directly target recurring genomic lesions in pediatric brain tumors, as illustrated by the following clinical trials:

- **PBTC-025 & PBTC-032:** Phase 1 and 2 studies, respectively, of vismodegib.¹⁰ The Phase 2 study included a cohort of patients selected for activation of the sonic hedgehog (SHH) pathway and identified a minority of patients who achieved an objective response to vismodegib.
- **PBTC-029:** Phase 1 and 2 studies of the MEK inhibitor selumetinib (AZD6244) in children with recurrent or progressive pilocytic astrocytoma. Activity was observed in patients with BRAF activation through either its fusion to a nearby gene or containing a point mutation(s). The Phase 2 expansion continues the trial in a selected cohort of patients.
- **PBTC-036:** Phase 1 study of imetelstat, an oligonucleotide that binds to the template region of the RNA component of telomerase, thereby inhibiting its enzymatic activity. While the PBTC demonstrated that imetelstat inhibited intratumoral and PBMC telomerase activity, the agent proved too toxic in children with recurrent CNS tumors at the schedule studied. Hence, if telomerase is to be targeted, other agents will need to be pursued.¹¹

⁸ Greengard E, et al; *J Clin Oncol* 33, 2015 (suppl; abstr 10058)

⁹ Schafer E, et al; *J Clin Oncol* 34, 2016 (suppl; abstr 2567)

¹⁰ Robinson GW, et al; *J Clin Oncol* 2015;33:2646-54

¹¹ Salloum R, et al; *J Neurooncol* 2016 Sep;129(3):443-51

- PBTC-022: Phase 1 study of cediranib, a potent and relatively selective VEGF receptor inhibitor. The PBTC identified a recommended Phase 2 dose of 32 mg/m²/day, but found that chronic treatment with cediranib was not well tolerated in children with brain tumors.¹²

Major NCI-Supported Multisite Initiatives

Adult Brain Tumor Consortium

The **Adult Brain Tumor Consortium (ABTC)** is a multi-institutional consortium that is supported through a UM1 Cooperative Agreement. The consortium performs innovative, multidisciplinary Phase 1/2 clinical trials that focus predominantly on adult patients with grade IV gliomas (glioblastoma multiforme; GBM). The ABTC is composed of a Central Operations office located at Johns Hopkins University, plus 11 premier institutions across the United States. Since its inception in 2009, the ABTC has completed more than 18 pilot and Phase 1/2 clinical trials and accrued more than 750 patients. These studies have resulted in more than 40 peer-reviewed publications. Currently, 13 studies are in progress with an expected accrual of more than 250 additional patients. Some recent representative ABTC studies include:

- NABTT 2105: Determination of the maximum tolerated dose (MTD) of GliaSite balloon brachytherapy (GSBT) followed by conventional external beam radiation therapy (EBRT) in newly diagnosed GBM patients.¹³
- NCT00979862: Does the addition of cilengitide (an integrin inhibitor with anti-invasive and antiangiogenic properties) safely block infiltrative tumor growth and enhance the efficacy of cediranib in patients with recurrent GBM.¹⁴
- Evaluation of the Safety and Benefit of Phase I Oncology Trials for Patients with Primary CNS Tumors: a review of patients with recurrent HGG enrolled onto ABTC trials of single-agent, cytotoxic or molecular agents from 2000 to 2008.¹⁵

ABTC has demonstrated that clinical trials are not only possible in this challenging tumor type, but provide an important treatment option for patients faced with this refractory tumor.

¹² Kieran MW, et al; *Childs Nerv Syst* 2015;31:1433-45

¹³ Streiff M, et al; *J Neuro Oncol* 2015 Sep;124(2):299-305

¹⁴ Gerstner ER, et al; *Neuro Oncol* 2015 Oct;17(10):1386-92

¹⁵ Gounder MM, et al; *J Clin Oncol* 2015 Oct 1;33(28):3186-92

¹⁶ Cui B, et al; *Blood* 2016 Dec 22;128(25):2931-2940

¹⁷ Salzar et al; *Nature Immunol* 2016; 17:1352-1360

¹⁸ McClanahan F, et al; *Blood* 2015; 126:212-221

Chronic Lymphocytic Leukemia Research Consortium

The **Chronic Lymphocytic Leukemia Research Consortium** is a premier example of translational science activity. 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 ultraconserved noncoding RNAs in human CLL relative to normal lymphocytes. MicroRNA34a, which is induced by activation of TP53, is involved in posttranscriptional silencing of the gene encoding the zeta-associated protein of 70 kilodaltons (ZAP-70). A mouse model of CLL developed under this P01 has permitted the evaluation of the capacity of lenalidomide to reverse the defective immunologic synapse observed in patients with CLL. Further, the expression of Ror1 was recently shown to be directly correlated with CLL disease progression.¹⁶ Of particular interest, AD-ISF35 gene therapy induces anti-ROR1 autoantibodies in patients. Several promising drugs, including flavopiridol, 9-(2-phosphorylmethoxyethyl)guanine, GS-9219, beta-phenylethyl isothiocyanate, and XIAP antagonists, are also in development in this highly interactive P01. The role of the immune microenvironment has also been a focus of the P01, and in particular how CLL cells regulate the adoptive T cell response in the tumor milieu. CLL cells appear to induce defective T cell mobility, which is reversible by lenalidomide and is linked to impaired cytoskeletal dynamics.¹⁷ Further, a CLL mouse model study demonstrated that treatment with an anti-PD1 agent results in reversal of CLL-induced immunosuppression.¹⁸

Myeloproliferative Disease Research Consortium

The **Myeloproliferative Disease Research Consortium** is an international consortium of medical centers established in 2005 under the P01 mechanism. It consists of five core centers conducting six projects, and 22 ancillary sites. All are served by three shared resource cores. Its function is to conduct basic research in Philadelphia-negative myeloproliferative diseases—in particular, polycythemia vera and primary myelofibrosis—and to design and perform new clinical trials in these diseases. Six protocols have been activated in the consortium, and three are in various stages of accrual. A



recently published study¹⁹ from the consortium showed that 1) a thrombopoietin receptor antagonist depletes myelofibrosis hematopoietic stem and progenitor cells²⁰ and 2) the inflammatory cytokine lipocalin-2 is elaborated by myelofibrosis myeloid cells, resulting in a cascade of events ultimately creating a dysfunctional microenvironment.²¹

Major Co-Funded Networks

Blood and Marrow Transplant Clinical Trials Network

The **BMT CTN** utilizes the U01 funding mechanism to conduct large, multi-institutional clinical trials in hematopoietic stem cell transplantation (HCT) and evaluate promising therapies for the treatment of hematopoietic malignancies and nonmalignant disease. The network is composed of 20 core clinical centers and a data coordinating center. The network is supported by a partnership between NCI and NHLBI.

The BMT CTN was renewed in September of 2017, for its fourth 7-year period, to fund 20 transplant centers and the central Data Coordinating Center. Since inception, the BMT CTN has launched 46 protocols, either alone or in collaboration with NCTN. It has completed 33 trials, enrolling more than 10,200 patients from more than 125 transplant centers across the U.S. The number of new protocols launched and

patients accrued in the last five years alone are 18 and 4800, respectively, with 13 protocols still open for accrual at the end of 2017. The BMT CTN has also established a research repository containing more than 350,000 biospecimens.

The most recent BMT CTN clinical trials have provided the following important insights:

- A study in collaboration with the AIDS Malignancy Consortium revealed that autologous transplant should be considered the standard of care for patients with relapsed/refractory HIV-associated lymphoma who meet standard eligibility criteria.²²
- In collaboration with the Cancer and Leukemia Group B (CALGB) in the NCTN, a study demonstrated that patients older than age 60 with acute myeloblastic leukemia (AML) in the first complete remission can benefit from the graft-versus-leukemia effects of allogeneic HCT using a reduced intensity, non-myeloablative conditioning regimen (RIC). Outcomes were similar to younger patients.²³
- A study testing the best conditioning regimen for all adult patients with AML / myelodysplastic syndrome (MDS) showed that standard myeloablative conditioning, not RIC, should be considered standard of care.²⁴

¹⁹ Wang X, et al; *J Clin Invest* 2012;122(11):3888–3899

²⁰ Wang X, et al; *Blood* 2016; 127:3398–3409

²¹ Lu M; *Blood* 2015; 126:972–982

²² Alvarnas J, et al; *Blood* 2016;128:1050–1058

²³ Devine SM, et al; *J Clinical Oncol* 2015;33:4167–4175

²⁴ Scott et al; 2015 Dec; Abstract and oral late-breaking presentation, ASH 57th Annual Meeting

Center for International Blood and Marrow Transplant Research

The Center for International Blood and Marrow Transplant Research (CIBMTR) was formed in 2004 as a merger of the International Bone Marrow Transplant Registry (IBMTR) and the research division of the National Bone Marrow Donor Registry. It is funded by a U24 grant with co-funding from NHLBI and the National Institute of Allergy and Infectious Diseases (NIAID). The CIBMTR collects baseline and outcomes data from consecutive patients transplanted at centers throughout the world to advance hematopoietic stem cell transplant therapy.

The CIBMTR database includes:

- 480,000 HCT recipients, an increase of 70,000 submissions since 2013, from over 420 transplant centers worldwide (over 55 countries)
- Information for 100% of the allogeneic transplants done in the US (as this is mandated by law), 25% of the allogeneic transplants done outside the U.S., and 80% of auto transplants

The CIBMTR has a proven system for facilitating the utilization of its database for research projects via 15 scientific/research working committees, as well as collaborations with government agencies, professional groups, international partners, and patient organizations.

Cancer Immunotherapy Trials Network

See “Major Initiatives Supporting the Cancer Community”
Page 38

Development of a New NCI Informed Consent Document Template

Tension exists between the requirement to provide adequate information about a cancer clinical trial in an informed consent document and the need to keep the document concise to maximize readability and comprehension. All too often, the informed consent document has been viewed by sponsors as a legal tool to limit investigator and site liability rather than, as originally proposed in the *Belmont Report*, part of a process to ensure that the key ethical principles for human experimentation—autonomy, beneficence, and justice—are

respected.²⁵ There is concern that the balance has tipped in favor of comprehensiveness instead of comprehension.

In 1997, the NCI developed and promulgated an informed consent boilerplate document, known as the NCI Informed Consent Template, for use by its Clinical Trials Cooperative Group Program and others. Although the informed consent template has certainly made NCI-sponsored trial consent forms more harmonious, the length of the consent forms grew over the ensuing years to the point where there is now concern that readability and comprehension have been compromised. To address the problem, an NCI Planning Committee took on the challenge of revising the NCI Consent Form Template to result in more concise consent forms that still accurately capture the required explanations and elements of informed consent. Five working groups comprising internal and external stakeholders from across the scientific, academic, regulatory, and advocacy communities, including representation of clinical trialists and individuals with expertise in institutional review boards, were tasked with revising the template, resulting in shorter consent forms being launched in 2013. The forms are currently being revised to incorporate new language reflecting recent advancements in precision medicine and the need to collect biospecimens from which genetic information is obtained. A compliance review of the 2013 template also identified several sections where the responses often deviated from the template, indicating the need for modifications to more clearly capture the submitted information. Examples of such sections include those dealing with patient costs, additional tests and the collection of biospecimens for biobanks. Once the proposed updates have been widely reviewed and modified with stakeholder input, the revised template will be released for use, with the overall goal of continuing to have a concise and patient-friendly document that facilitates patient decision-making.

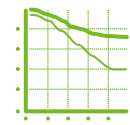
NCI Clinical Trials Quality Assurance Program

The Clinical Trials Monitoring Branch is responsible for managing quality assurance and quality control of the Phase 1, Phase 2, and NCTN clinical therapeutic trials sponsored by DCTD and of prevention trials sponsored by the Division of Cancer Prevention.

This program includes:

- Establishing standards for evaluating the conduct of research and the reporting of audit findings

²⁵Sharp SM, et al; *Am J Clin Oncol* 2004;27(6):570–575



- 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 GCP 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, NCTN Groups, NCORPs, Cancer Centers, and all other institutions conducting clinical research trials sponsored by CTEP and NCI. The program provides oversight and coordination of audit procedures for international sites participating in CTEP or DCTD clinical trials.

Organization/Type of Study	Audits	Protocols	Patient Cases
Phase 1/2 studies	292	137	1878
Cooperative Groups/NCTN	4,446	700	26,293
Cancer Centers and single institutions	156	198	2,086
Groups/Non-NCTN	239	106	1,404
COGC	86	28	694

TABLE 9: AUDIT STATISTICS (2013-2017)

New Initiatives and Recent Accomplishments

- In April 2012, CTEP's clinical data management system, Medidata Rave, was launched for early-phase clinical trials. Medidata Rave has replaced a variety of electronic and paper-based data capture systems that were used by the groups for many years and establishes a common clinical data management system (CDMS) across the NCTN, NCI-funded networks, and the Early Therapeutics Program. In an effort to make the transition from paper-based reports, and coinciding with the deployment of Medidata Rave, IDB and CTMB staff have been collaborating closely with Theradex (an NCI contractor) to develop and deploy a Web-based reporting system that will provide IDB staff with 24/7 access to clinical data. The system will include modules for patient demographics, protocol compliance, and reporting of adverse events, as well as an end-of-study module. Together representatives from IDB and CTMB staff have also been actively engaged in the development of electronic case report forms for the collection of genomic and PD data.
- In February 2014, CTMB issued revisions to the Guidelines for Auditing of Clinical Trials for Cooperative Groups, CCOP Research Bases, and the Cancer Trials Support Unit (CTSUs).
- In September 2016, CTMB deployment of a web-based module to facilitate the review of clinical trial data by IDB Drug Monitors and Principal Investigators, including tools for aggregate data analysis within and across studies using the same agent.

Accrual Assessment and Interventions

NCI analyzed Phase 3 trials activated between 2000 and 2007 and found that 26.7% of their 149 non-pediatric treatment trials had insufficient accrual (accruing less than 90% of projected goal).²⁶ To address slow accrual proactively, NCI organized the NCTN Accrual Core Team (ACT), which includes representatives from Network Groups, NCORPs, LAPs, patient advocates, and NCI offices. The team's mission is to provide an inclusive forum to work collaboratively to raise awareness, enhance patient enrollment, and increase site participation and accrual to NCTN and NCORP trials. The ACT meets monthly via conference calls and provides NCTN and NCORP trial leaders the opportunity to present trials with challenging or complex issues and receive Network ACT input and support for improving accrual. Additionally, smaller Task Force Groups within the overall ACT have breakout sessions to address an identified accrual concern, such as developing templates to help in the creation of patient-friendly materials or identifying strategies to minimize the number of eligibility requirements listed for a trial.

Thus far, interventions to facilitate accrual have included educational and promotional efforts, including the use of NCTN-wide webinars to highlight trials and social media and other promotional efforts to increase awareness and understanding of the importance of clinical trials. In addition, groups have amended trials to adjust patient eligibility requirements, streamline the steps needed for trial activation, and reduce complexities. Trial accrual is monitored quarterly to evaluate progress and assess the need for further support. CTEP Early Stopping Guidelines for Slow Accruing Trials are used to determine whether further survey or accrual interventions are needed to avoid closure due to inadequate accrual. These efforts are also responsive to recommendations made by NCI's Clinical Trials Working Group and the IOM Report "A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program."

²⁶Korn EL, et al; *J Clin Oncol* 2010;28(35):197-201

FUTURE DIRECTIONS

CTEP will focus on four key areas over the next 5 years:

1. Expand efforts in targeted therapeutics and immunotherapy in early-phase trials.
2. Assist in the ongoing evolution of the NCTN Groups into a highly integrated system capable of performing cutting-edge, definitive trials with molecularly targeted agents.
3. Improve development and accrual timelines for Phase 1-3 trials.
4. Increase contributions to the mentoring of the next generation of clinical investigators.

Expand targeted therapeutics and immunotherapy in early-phase 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 metastasis. Translating scientific discoveries into clinically effective and safe interventions will require CTEP to:

- Continue to serve as the key clinical facilitator for the newly created 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.
- Develop early trials in the ETCTN that are highly translational in which all patients entering trials have their tumors profiled for specific molecular targets.
- 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 Patient Characterization Centers and the Center for Cancer Genomics.

Assist in the ongoing evolution of the NCTN Groups into an effective mechanism for cutting-edge, definitive trials that precisely characterize patient populations:

- Assist with funding from the Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP) for these trials.
- Aid in the development of the Translational Centers in the NCTN.
- Collaborate with the NCTN and industry in trial designs and public-private partnership agreements.

Improve timelines for developing and accruing to large Phase 2 and 3 trials:

- Monitor and track 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:

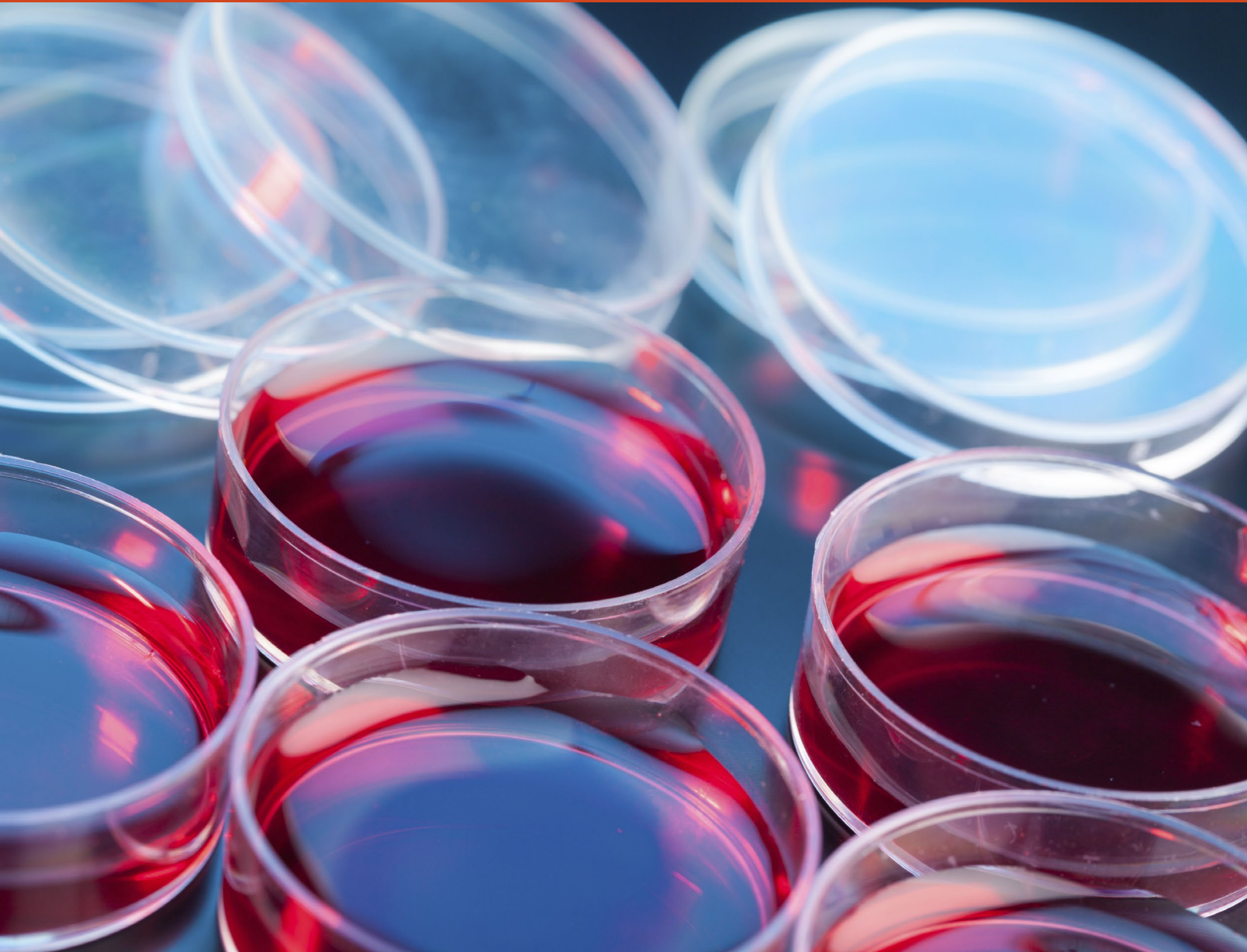
- Expand the CTEP fellowship program, whereby U.S. oncology fellows spend 1–3 months at CTEP participating in protocol review.
- Increase attendance from U.S. fellows at CTEP's Early Drug Development Meetings.
- Continue the CrDL program for new fellows.
- Continue annual meetings of the American Society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

A number of intra- and interdivisional collaborations are underway or in the planning stages:

- Increased integration of imaging and correlative sciences into CTEP clinical trials
 - With the DCTD Cancer Imaging Program, incorporation of molecular imaging in CTEP trials of IND agents carried out in the ETCTN
 - With the DCTD Molecular Characterization Laboratory, DNA sequencing of patient tumors to identify actionable genetic abnormalities
- 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

PROGRAMS AND INITIATIVES (2013-2017)

DEVELOPMENTAL THERAPEUTICS PROGRAM





OVERVIEW

The mission of the Developmental Therapeutics Program (DTP) is to facilitate the discovery and preclinical development of novel therapeutic agents by providing services, resources, and leadership to the academic and private-sector research communities worldwide. Created by Congress in 1955 as the Cancer Chemotherapy National Service Center, DTP manages and oversees a large research grant portfolio, and is a resource for the generation of preclinical information and research materials, including vial and plated compounds, tumor cells, cell extracts, natural products extracts and compounds, as well as bulk and formulated drugs, necessary to support Investigational New Drug (IND)-directed studies. As shown on page 130, DTP has historically been directly involved in the discovery or development of many of the anticancer therapeutics on the market today. The pharmaceutical sector is currently responsible for the bulk of activity surrounding anticancer therapeutics development; however, DTP continues to be involved in the development of selected agents.

In addition, DTP has expanded its efforts as a provider of various forms of cancer drug discovery infrastructure to the broader extramural cancer research community, including:

- Materials:
 - Samples of individual compounds for research use
 - Large plated sets of compounds for high-throughput screening (HTS)
 - Manufacturing and development of biopharmaceuticals, such as monoclonal antibodies, cytokines, and viral vectors and cancer vaccines
 - Genomically and transcriptionally characterized established tumor cell lines and extracts (DNA, RNA)
 - Natural product crude extracts and fractions
- Datasets and data mining tools:
 - Data from *in vitro* screening of “open” compounds submitted by investigators
 - Web-based databases of historical screening records
 - Data mining tools, such as COMPARE, and the molecular targets program
- Grants: Over 800 active grants managed in 2017
- Resources for a robust discovery and development infrastructure:

- Compound libraries, chemical synthesis, and structure-activity modeling
- Preclinical efficacy testing *in vitro* and *in vivo*
- Natural product collection, extraction, and characterization
- Pharmaceutical optimization, formulation, and manufacturing under current Good Manufacturing Practice (cGMP) for both small molecule and biological therapeutic agents
- Pharmacology and toxicology testing under current Good Laboratory Practice (cGLP)
- Preparation and review of technical documents for IND applications to the U.S. Food and Drug Administration (FDA)

Extramural and intramural investigators can access DTP discovery and development resources through the [NCI Experimental Therapeutics \(NExT\)](#) program.

STRUCTURE AND FUNCTION

DTP is functionally organized into nine branches under the oversight of the Office of the Associate Director.

OFFICE OF THE ASSOCIATE DIRECTOR

The Office of the Associate Director (OAD) organizes and coordinates activities across DTP to expedite the discovery and pre-clinical development of new anti-cancer therapeutic agents. In addition, there are broader NCI activities involving DTP staff and support that are also managed by the OAD, including the following in 2013-2017:

- Organization of a five-session PRESTO (Program and Review Extramural Staff Training Office) training program, which was offered to NCI extramural grant program directors and review staff. This training covered DTP’s broad research resources for supporting the discovery and pre-clinical development of small molecules, natural products, and biological anti-cancer therapeutic agents. The goal of this training program is to encourage Program staff to inform their grantees to utilize these government resources to facilitate their research and promote awareness of DTP and NExT capabilities.

JERRY M. COLLINS

ASSOCIATE DIRECTOR



Jerry M. Collins, PhD, is an internationally recognized pharmacologist who has been closely associated with NCI's drug development efforts for more than 30 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 Developmental Therapeutics Program in DCTD 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). He received his bachelor's degree from Drexel University and his master's and doctoral degrees from the University of Pennsylvania. He has authored or co-authored more than 200 papers in the field of clinical pharmacology, primarily emphasizing the applications of pharmacokinetic (PK) and pharmacodynamic (PD) principles in the field of cancer. His current work also includes extending these principles with PET imaging.

- The COMBO drugs project is a joint effort among DTP and DCTD's Office of the Director, Cancer Diagnosis Program (CDP), Biometric Research Program (BRP), and Cancer Therapy Evaluation Program (CTEP) that is supported by the DTP OAD and other DTP branches: the Biological Testing Branch (BTB) conducts studies *in vivo*, the Molecular Pharmacology Branch (MPB) conducts studies in cell culture, the Drug Synthesis and Chemistry Branch (DSCB) provides drug supply, the Information Technology Branch (ITB) provides data management, and the Toxicology and Pharmacology Branch (TPB) provides external contractor management.

PRECLINICAL THERAPEUTICS GRANTS BRANCH

The Preclinical Therapeutics Grants Branch (PTGB) manages the biochemistry and pharmacology grants portfolio within DTP. PTGB grants support preclinical research related to therapeutic intervention, including chemistry, natural products, mechanisms of drug action, pharmacology, toxicology, and the co-development of drugs and biomarkers to support the new era of precision medicine with emphasis on the modulation of targets and pathways that drive tumors, consistent with the goal of accelerating the discovery, development, and evaluation of agents to treat cancer. PTGB manages more than 550 active extramural investigator-initiated research grants, and provides counsel to hundreds more potential applicants each year. The PTGB analyzes the portfolio to identify areas of innovative drug discovery and development that would benefit from focused support and develops new initiatives and funding opportunity announcements to encourage greater extramural participation in those innovative areas.

MOLECULAR PHARMACOLOGY BRANCH

The Molecular Pharmacology Branch (MPB) provides mechanistic understanding of drug responses in patient-derived models that influence research on anticancer therapeutics. A major focus is on improving the treatment of recalcitrant, rare, and neglected cancers through interactions and collaborations with the cancer research community and other NCI laboratories. In support of this mission, MPB oversees the work of several laboratories at FNLCR that use state-of-the-art molecular characterization and mechanism-of-action techniques to identify therapeutic targets and genomic vulnerabilities, screen potential new agents, and develop potential therapeutic combinations.



Target Validation and Screening Laboratory

The Target Validation and Screening Laboratory (TVSL) is dedicated to screening targets and cell lines in an effort to identify new drugs and disease sensitivity to investigational agents. TVSL has developed in-house expertise, automation, instrumentation, and an information technology infrastructure to carry out screening campaigns with a diverse array of molecular and cell-based assay technologies applied to large chemical libraries. TVSL has assembled and is characterizing disease-based cell line panels focused on challenging cancers for response to standard and investigational anticancer agents with the goal of uncovering previously unrecognized sensitivities and potential new targets for therapeutic intervention.

The TVSL is currently engaged in developing methods to use complex 3D cell spheroids (described below) to assay the response of several recently developed patient-derived conditionally-reprogrammed cell lines to more than 300 compounds in 7-day and 12-day exposures. Complex spheroid screening is being pursued to evaluate new molecules developed by the [Chemical Biology Consortium](#) in the NExT Program, as well as in studies of novel, investigational-investigational agent combinations in advance of early phase clinical trials conducted by CTEP.

Functional Genomics Laboratory

The Functional Genomics Laboratory (FGL) studies drug mechanism(s) in detail, applying leading-edge gene manipulation technology (deletion and insertion) to drug mechanism of action studies. MPL collaborates with computational biologists and statisticians to identify deregulated cellular processes utilizing patient-derived models and omic databases to inform therapeutic choices, and develop testable mechanistic hypotheses suitable for clinical trial evaluation. Currently, MPL is examining the molecular basis for the differences in drug sensitivity among individual patient-derived xenograft (PDX) models and is conducting *in vitro* studies to validate drug targets and to explore the therapeutic potential of the targets that appear promising.

Translational Support Laboratory

The Translational Support Laboratory (TSL) contributes broadly to collaborative projects through its performance of detailed cell-based studies. A major tenet of cancer therapeutics is that combinations of anticancer agents with different mechanisms of action and different toxicities may be effective treatment regimens. Evaluation of drug combinations in cell culture may be used to identify opportunities and assess risk of additive/synergistic toxicity. Currently, TSL is engaged

in developing 3D cell culture models, including tumor, endothelial, and stromal cells in mixed culture spheroids. These models are being used for detailed studies in TSL and screening campaigns by TVSL.

BIOLOGICAL TESTING BRANCH

The Biological Testing Branch (BTB) provides oversight and technical direction to evaluate the *in vivo* activity of new chemotherapeutic agents, including the development and implementation of new models for drug discovery and testing. To accomplish this, BTB is responsible for:

- Implementing and managing a program to develop PDX models for distribution to the research community as tools for cancer target discovery as well as drug discovery and development
- 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
- Providing support for preclinical *in vivo* pharmacokinetic and pharmacodynamics studies across the DCTD drug development effort
- Maintaining a repository of experimental animal and human tumor cell lines for use in research performed by DTP and extramural investigators

COLLABORATIVE EFFORTS BETWEEN BTB AND THE PHARMACODYNAMICS PROGRAM

BTB provided the preclinical animal model support for the development and validation of numerous clinical assays, using the establishment of methodologies for collecting and stabilizing tumor biopsies for subsequent analysis. These assays and projects included assays for inhibition of DNA methylation, the γ -H2AX assay, the c-Met assay, the HIF1 α assay, the Mer kinase assay, the EMT immunofluorescence assay, the preclinical development of T-dCyd, the PARP inhibitors project, the development of multiplex immunofluorescence assays, the calf intestinal alkaline phosphatase assay, the topoisomerase 1 complex assay, and the apoptosis 15-plex panel.

APPROVED CANCER TREATMENT DRUGS DEVELOPED WITH DTP INVOLVEMENT

2015	Dinutuximab (Unituxin, NSC 764038)	1979	Daunorubicin (NSC 82151)
2012	Omacetaxine (homoharringtonine, NSC 141633)	1978	Cisplatin (cis-platinum) (NSC 119875)
2010	Eribulin (NSC 707389)	1977	Carmustine (BCNU) (NSC 409962)
	Sipuleucel-T (NSC 720270)	1976	1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosurea (CCNU) (NSC 9037)
2009	Romidepsin (NSC 630176)	1975	Dacarbazine (NSC 45388)
	Pralatrexate (NSC 713204)	1974	Doxorubicin (NSC 123127)
2004	Cetuximab (NSC 632307)		Mitomycin C (NSC 26980)
2003	Bortezomib (NSC 681239)	1973	Bleomycin (NSC 125066)
1998	Denileukin diftitox (NSC 697979)	1970	Floxuridine (FUDR) (NSC 27640)
1996	Polifeprosan 20 with carmustine implant (NSC 714372)		Mithramycin (NSC 24559)
	Topotecan (NSC 609699)		Mitotane (o-p'-DDD) (NSC 38721)
1995	All-trans retinoic acid (NSC 122758)	1969	Cytarabine (ARA-C) (NSC 63878)
1992	2-Chlorodeoxyadenosine (NSC 105014)		Procarbazine (NSC 77213)
	Paclitaxel (NSC 125973)	1967	Hydroxyurea (NSC 32065)
	Teniposide (NSC 122819)	1966	Pipobroman (NSC 25154)
1991	Fludarabine phosphate (NSC 312887)		Thioguanine (NSC 752)
	Pentostatin (NSC 218321)	1964	Melphalan (NSC 8806)
1990	Hexamethylmelamine (NSC 13875)		Actinomycin D (NSC 3053)
	Levamisole (NSC 177023)	1963	Vincristine (NSC 67574)
1989	Carboplatin (NSC 241240)	1962	Fluorouracil (NSC 19893)
1988	Ifosfamide (NSC 109724)	1961	Vinblastine (NSC 49842)
1987	Mitoxantrone (NSC 301739)	1959	Cyclophosphamide (NSC 26271)
1983	Etoposide (NSC 141540)		Thiotepa (NSC 6396)
1982	Streptozotocin (NSC 85998)	1957	Chlorambucil (NSC 3088)



DRUG SYNTHESIS AND CHEMISTRY BRANCH

The Drug Synthesis and Chemistry Branch (DSCB) is responsible for the following activities in support of the discovery and development of novel anti-cancer agents:

- Worldwide scientific liaising with universities and industries to stimulate the submission of a wide variety of synthetic compounds and pure natural products for *in vitro* anti-cancer screening
- Managing the acquisition, synthesis, storage, inventory, documentation, and distribution of chemical samples for research purposes to NIH and external investigators
- Acquisition of pre-clinical and clinical anti-cancer small-molecule chemotherapeutics for evaluation in various cell-line screens and testing *in vivo*, including PDX models
- Synthetic and medicinal chemistry resources and expertise in support of NExT development and discovery projects
- Collaboration with DTP's Natural Products Branch (NPB) for identification of novel chemical scaffolds, as well as development of synthetic methods to generate further supplies for active compounds that have been isolated from natural product extracts

External Synthesis Contracts	<ul style="list-style-type: none">• Supports NExT project Initiatives• Synthesis of benchmark clinical and preclinical candidates
NCI Chemical Repository	<ul style="list-style-type: none">• Manages new compounds submitted by extramural researchers• Distribution of compounds for intramural and extramural research activities
Laboratory of Synthetic Chemistry	<ul style="list-style-type: none">• Supports NExT discovery / development projects• Provides chemical synthetic enablement expertise and service, across DCTD, including natural products

FIGURE 46: CHEMISTRY SUPPORT FOR DCTD.

NATURAL PRODUCTS BRANCH

The primary responsibility of the Natural Products Branch (NPB) is the acquisition of crude natural product materials from terrestrial and marine environments for the preparation of crude extracts to be screened in various intramural and extramural screening programs, including the NCI-60 Cell Line Screen. For example, a set of 100,000 extracts was pro-

vided to an extramural team of investigators to be screened in their biologic HTS assay as part of a NExT project. NPB also oversees the operations of the Natural Products Support Group at FNLRCR, which conducts isolation and chemical identification of active components from various crude extracts that are positive in *in vitro* and *in vivo* anticancer screens, as well as scale up for production of active compounds to support pre-clinical and early clinical evaluation.

BIOLOGICAL RESOURCES BRANCH

The Biological Resources Branch (BRB) supports research in biotechnology-based therapies and provides resources to develop potential leads for the treatment of cancer and related conditions. Classes of therapeutic agents includes recombinant proteins, monoclonal antibodies, genetically modified viruses, bacteria and mammalian cells, peptides, and oligonucleotides. These entities may function as cytokines, growth factors, vaccines, adjuvants, or other immune-modifying 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:

1. Peer-reviewed, grant-supported, investigator-initiated discovery

The active BRB-managed grant portfolio consists of over 150 grant awards (R01, R03, R15, R21, and P01) focusing on the discovery, testing, and development of biotechnology-based products including immunotherapy agents for the treatment of, and vaccination against, cancer. The portfolio also includes therapeutic model development and the study of therapeutic mechanisms of action. This grant portfolio has a notable history of supporting concepts that successfully compete for further development in programs like NExT.

2. Access to consistent and high-quality reliable reagents for detailed preclinical studies

A preclinical repository was established in 1988 to acquire, usually by donation, and distribute well-characterized biological reagents to extramural investigators to provide more robust preclinical studies and therapeutic concept development. Surplus production materials from projects within the Biopharmaceutical Development Program (BDP) are also provided to the community through this repository. See “BRB Preclinical Repository”

3. Preclinical product development, cGMP manufacturing, testing and release of biologic material for IND-directed pre-clinical studies through Phase 3 clinical trials

BRB directs projects in the BDP located at FNLRCR.

TOXICOLOGY AND PHARMACOLOGY BRANCH

The Toxicology and Pharmacology Branch (TPB) provides essential toxicology and pharmacology data and expertise for drugs, biologics, and imaging agents in development for clinical trials. TPB manages external contractors for the generation of toxicology data (e.g. ADME, dose range finding and IND-directed toxicology studies) that are an essential component of filing an IND application with the FDA. TPB also provides toxicology expertise to the extramural community, creating tailored preclinical strategies and study designs for safety assessment. TPB staff guide studies at all stages of product development, from early and rapid *in vitro* or *in vivo* characterization to optimize clinical candidate selection through PK, PD, and safety studies across species to support IND-filing and clinical use in humans.

PHARMACEUTICAL RESOURCES BRANCH

The Pharmaceutical Resources Branch (PRB) provides comprehensive pharmaceutical services to various DCTD programs and other parts of NCI and NIH. The primary objective of PRB is to supply high-quality chemical substances and formulated products for use in preclinical studies and human clinical trials. PRB accomplishes this objective through the management of external contractors. Most of the generated data are submitted to the FDA in support of an IND.

The major contract areas managed by PRB staff include:

- Chemical Resources. Small-scale synthesis, including probe runs, process optimization, and large-scale GMP synthesis ranging from relatively short syntheses of one to two steps to complicated and challenging multistep syntheses.
- Analytical. Development of validated assays to certify the purity, identity, and quality of test agents according to FDA guidelines and industry standards. For bulk chemical substances of all lots, the branch also prepares specifications for release of bulk chemical substances for IND-directed cGLP toxicology studies and manufacturing of clinical supplies.
- Pharmaceutical Research and Development. Development of dosage forms suitable for use in human clinical trials and evaluation of salts, non-aqueous solvents,

and surfactants, with emphasis on newer techniques to improve solubility or stability (emulsions, prodrugs, and complexation). Evaluation of dosage forms for chemical content, activity in rodent models whenever possible, and feasibility for manufacture on production scale.

- Pharmaceutical Production. Management of a pharmaceutical production contract for parenteral drug products, including freeze-dried, emulsion, and liquid-filled dosage forms. PRB also produces capsules and tablets for oral use, and has the capability to produce creams and gels for topical use. Production is carried out with adherence to strict cGMP guidelines and regular inspections of the production facilities are performed by the U.S. FDA, the United Kingdom Medicines and Healthcare Products Regulatory Agency (the U.K. equivalent of FDA), and other European regulatory authorities.
- Shelf-Life Surveillance. Stability programs are established for each clinical batch of drug to certify potency, identify degradation products, and other aspects as required. Testing schedules are carried out according to FDA and other guidelines.

INFORMATION TECHNOLOGY BRANCH

The Information Technology Branch (ITB) provides scientific computing support and development for DTP and other programs in DCTD. ITB staff work to understand and translate the specific needs with regard to data capture, storage, searching and analysis 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 making available to the research community both DTP data as well as the requisite analysis tools, such as COMPARE. ITB works to ensure that data analyses are driven by the science and not by software limitations.

DTP GRANTS OVERVIEW

The DTP research portfolio included 721 funded grants with a total budget of ~\$252 million during fiscal year 2016. DTP's grants portfolio covers various aspects of the discovery and pre-clinical development of small molecule and biological

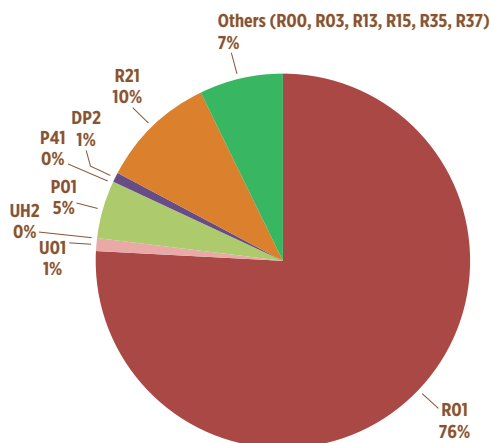


FIGURE 47: DISTRIBUTION OF DTP 2016 GRANT FUNDING BY MECHANISM.

therapeutic agents, such as drug discovery screen assays and models, medicinal chemistry, mechanism of actions, biomarkers, cGMP production, and immunotherapy. The grant award mechanisms used by DTP and their distribution in terms of research support in 2016 are shown in the accompanying graphs and charts. The predominant mechanism is the individual research project grant (R01), followed by exploratory phase grants (R21).

Funding Mechanism	Number of Grants	Total Cost
R01	398	\$ 152,400,229
U01	3	\$ 1,982,390
P01	7	\$ 12,169,288
DP2	1	\$ 2,377,500
R21	105	\$ 19,911,749
R00	12	\$ 2,965,505
R03	12	\$ 944,886
R15	15	\$ 5,650,661
R35	4	\$ 3,564,884
R37	1	\$ 294,818
Total	558	\$ 202,261,910

TABLE 10: FY16 SMALL MOLECULE GRANTS PORTFOLIO

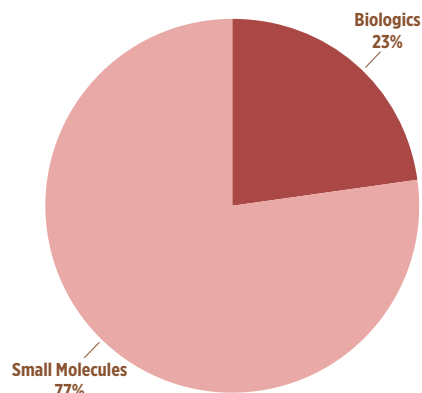


FIGURE 48: DISTRIBUTION OF DTP 2016 FUNDED GRANTS BY THERAPEUTIC AGENT CLASS.

In 2016, the grants portfolio administered by DTP's PTGB contained 558 grants with a total budget of ~\$202 million that support all aspects of small molecule anticancer drug discovery and treatment strategies, including drug design, selective targeting of therapeutic agents, development of new preclinical models for drug discovery, biomarker development for assessing treatment response, and understanding, preventing, and overcoming drug resistance. Meanwhile, the biologics grant portfolio administered by BRB contains 163 grants with a total budget of ~\$50 million that supports concept discovery and development in nonclinical models and laboratory studies conducted in parallel with ongoing clinical trials.

Funding Mechanism	Number of Grants	Total Cost
R01	115	\$ 39,481,143
R21	35	\$ 2,846,625
R15	4	\$ 1,652,593
R03	3	\$ 239,250
P01	3	\$ 4,053,666
UH2	1	\$ 198,360
R00	1	\$ 249,000
P41	1	\$ 1,081,184
Total	163	\$49,801,821

TABLE 11: FY16 BIOLOGICAL GRANTS PORTFOLIO

ASSISTANCE TO THE CANCER RESEARCH COMMUNITY

NCI-60 CELL LINE SCREEN

The NCI-60 Cell Line Screen provides an initial evaluation of the activity of potential anticancer agents. The screen includes cell lines representing nine cancer types: leukemia, melanoma, lung, colon, brain, ovary, breast, prostate, and kidney. The aim of the screen is to identify synthetic compounds and natural product samples, as well as selected biologicals and combinations, showing selective growth inhibition or cell killing of particular tumor cell lines. The NCI-60 cell lines have been thoroughly characterized biologically and molecularly through the [Molecular Targets](#) initiative. There have been more than 200 peer-reviewed publications citing the NCI-60 Cell Line Screen over the past five years. While many of the reports are medicinal chemistry, drug response, and compound studies, an increasing number of publications center on gene expression, genomics, and the development of gene signatures. Other prominent topics include mutation analyses, proteomics, development of bioinformatics methods, biomarkers, microRNAs, metabolomics, epigenetics, and pathways analyses.

The NCI-60 Cell Line Screen consists of a three-step process that starts with a single concentration screen against all 60 cell lines. Agents showing activity are further evaluated across a five-log-concentration range. Agents demonstrating a dose response are then retested in a confirmatory five-concentration assay.

During FY2015, the NCI-60 Cell Line Screen laboratory:

- Performed single-concentration testing on more than 5,700 new synthetic compounds and 7,400 natural product extracts from NPB.
- Tested 888 synthetic compounds and 756 natural product extracts in the five-concentration screen.

As an additional service to the extramural research community, 50 vials of frozen cell pellets were prepared from each of the 60 cell lines for distribution to approved Molecular Targets investigators providing molecular characterization of the cells.

IN VIVO MODEL DEVELOPMENT AND TESTING

Over the past five [2013 – 2017] years, BTB has assessed more than 308 synthetic molecules, 160 natural product extracts, and 20 unique vehicle formulations for determination of maximum tolerated dose in preparation for *in vivo* efficacy studies. It also conducted 64 hollow-fiber assays with 250 unique new molecules or natural product extracts to test for *in vivo* activity, of which 37 agents met the traditional criteria for activity. BTB conducted 397 xenograft studies assessing the antitumor activity of small-molecules and natural product extracts, as well as of agent combinations. These represent more than 75 unique human tumor xenograft models. During this timeframe the branch received over 6300 patient samples (blood or tumor) for implantation into mice to generate patient-derived xenograft (PDX) models. Over 300 PDX models have been created and cryopreserved (>200 vials/model) for distribution through the [NCI Patient-Derived Models Repository \(PDMR\)](#). Presently there are 110 models available to the research community through the PDMR. The branch has conducted 190 studies using PDXs to assess efficacy or to collect samples for pharmacodynamic endpoint determinations.

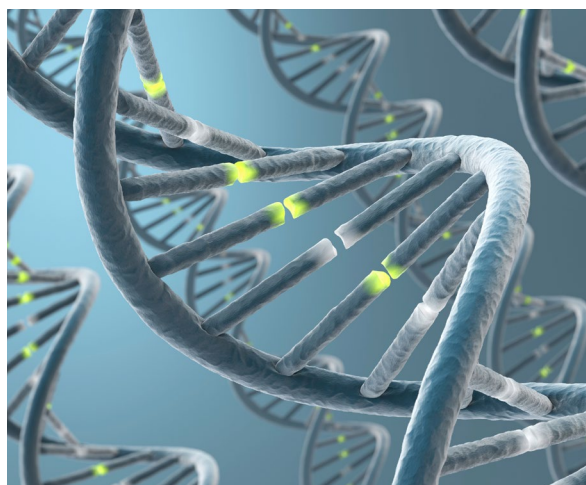
These efforts were facilitated by a major change to their experiment management and data capture system, going to a commercial “off the shelf” (COTS) software package, which was integrated into the larger DTP data systems by ITB, including the systems that allow suppliers to access the results of tests on their compounds.

TUMORS, CELLS, CELL LINES, AND MICE

BTB prepares and ships 300–350 orders annually, representing a distribution of more than 2,000 vials of cells, tumor fragments, and cell pellets to individual investigators in the scientific community. The branch also isolated mRNA at serial passages 1, 4, and 10 from more than 100 unique human tumor xenografts for Affymetrix gene expression profiling. The [MicroXeno Project](#) raw data for these profiles are web-accessible to the research community.

COLLECTION AND DISTRIBUTION OF SYNTHETIC COMPOUNDS

DSCB maintains a [repository](#) of synthetic compounds and pure natural products that are available to investigators for non-clinical research purposes. The Repository collection is



a uniquely diverse set of more than 200,000 compounds that have been either submitted to DTP for biological evaluation, as part of a chemistry effort under a NExT project, or synthesized under DTP auspices.

Year	No. of New Submitted Compounds (NSCs)	No. of Compounds Shipped	No. of Plates Shipped**
2013	6,989	24,682	2,138
2014	4,298	20,290	1,991
2015	5,560	22,190	1,912
2016	6,441	23,619	1,846
2017*	6,846	21,414	1,765

* As of 11/30/2017

** Plates include approved oncology drugs set, structural diversity set, mechanistic diversity set, and natural products set.

TABLE 12: DISTRIBUTION AND PROCUREMENT SUMMARIES (2013–2017)

ACQUISITION OF SMALL-MOLECULE ONCOLOGY AGENTS

As part of its mission, DSCB acquires samples of investigational oncology agents, comprised primarily of targeted small molecules currently in clinical and/or preclinical anticancer studies. These compounds are provided for evaluation in the NCI-60 Cell Line Screen, as well as to other DCTD programs, such as PADIS and the Molecular Pharmacology

Lab in MPB, and to investigators in NCI's CCR. As oncology treatment moves toward personalized targeted therapeutic agents, the various DCTD human tumor cell line panels are an ideal community-wide tool for further understanding of the disease targets of new agents. All DCTD panel cell lines were thoroughly characterized at the molecular level under the **Molecular Target Program**, with both in-house and crowd-sourced characterization, including exome sequence mutations, SNPs, DNA methylation, metabolome, mRNA, microRNA, and protein expression. This molecular characterization dataset enables interrogation of patterns of growth inhibition by the investigational drug set looking for characteristics of the cell lines that determine sensitivity. It is anticipated that comparison between drug sensitivity profiles from this data set could lead to the elucidation of common mechanistic targets or pathways, associations with potential response biomarkers, the confirmation of mechanism of action or identification of novel mechanisms, and the uncovering of unexpected “off-target” activities.

DSCB is in the process of developing open-source web-based online tools to enable data analysis for this set, including an improved version of **COMPARE**, which provides for the identification of compounds and/or genes that have highly correlated response patterns for any selected ‘seed’ compound. Solid samples (5 mg) of most FDA-approved oncology drugs, as well as a plated set of the most current FDA-approved drugs, are available for transfer to external investigators without cost for non-clinical research purposes through the **DSCB repository**.

LABORATORY OF SYNTHETIC CHEMISTRY

DSCB provides synthetic and medicinal chemistry resources and expertise in support of NExT development and discovery projects. DSCB resources and expertise include: iterative drug design and synthesis, synthetic method development and process synthesis development. Recent NExT projects utilizing DSCB resources include:

- 1. Preclinical development of T-dCyd: a New Epigenetic Agent:** DNMT1 is a maintenance methyltransferase that contributes to the hypermethylation and silencing of tumor suppressor genes. In addition, DNMT1 also has roles independent of its methyltransferase activity, and its knockout causes decreases in cell viability that are preceded by events consistent with activation of DNA damage response. Southern Research Institute submitted a NExT proposal for assistance in the preclinical development of 4'-Thio-2'-deoxycytidine (T-dCyd), an agent that they found depletes DNMT1 both *in vitro* and *in vivo* in tumor cells. In non-small cell lung cancer (NSCLC) NCI-H23 xenograft studies, treatment with T-dCyd resulted in the inhibition of tumor growth with concomitant DNMT1 depletion at well tolerated doses. Given the significant compound supply needs consistent with preclinical development, DSCB developed an efficient process for the synthesis of the clinical candidate, T-dCyd, and that of a close analog, 5-aza-T-dCyd.
- 2. Silvestrol:** Investigators at Ohio State University came to NCI, originally through the RAID Program, seeking assistance in the preclinical development of silvestrol, a natural product isolated from the plant *Aglaia foveolata*, which had been found to have anti-cancer activity. In order to further evaluate the potential of this natural product in large scale animal models and potentially human clinical trials, DSCB undertook the preparation of multi-gram quantities of silvestrol through total synthesis, using previously reported methodology as the template for the scale-up work.

NATURAL PRODUCTS REPOSITORY

Located at FNLCR, the **Natural Products Repository** is one of the largest and most diverse collections of natural products in the world, housing nearly 230,000 extracts from more than 80,000 plants, more than 20,000 marine organisms collected

from more than 35 countries, and more than 30,000 extracts of diverse bacteria and fungi. The Natural Products Repository Program was initiated by NPB in 1991 to maximize the potential of the plant, microbial, and marine invertebrate extracts derived from the raw materials that were collected for NPB. NPB continues to establish collaborative programs through the signing of a **natural product collaboration agreement** or **letter of collection** with qualified research organizations in source countries for the screening of natural product extracts for activity against cancer and human disease, and the pre-clinical and clinical development of active agents meeting NCI selection criteria. From 1996, these extracts have been made available to organizations and investigators interested in exploring their potential in any disease related to NIH interests. Materials are provided for only the costs of shipment.

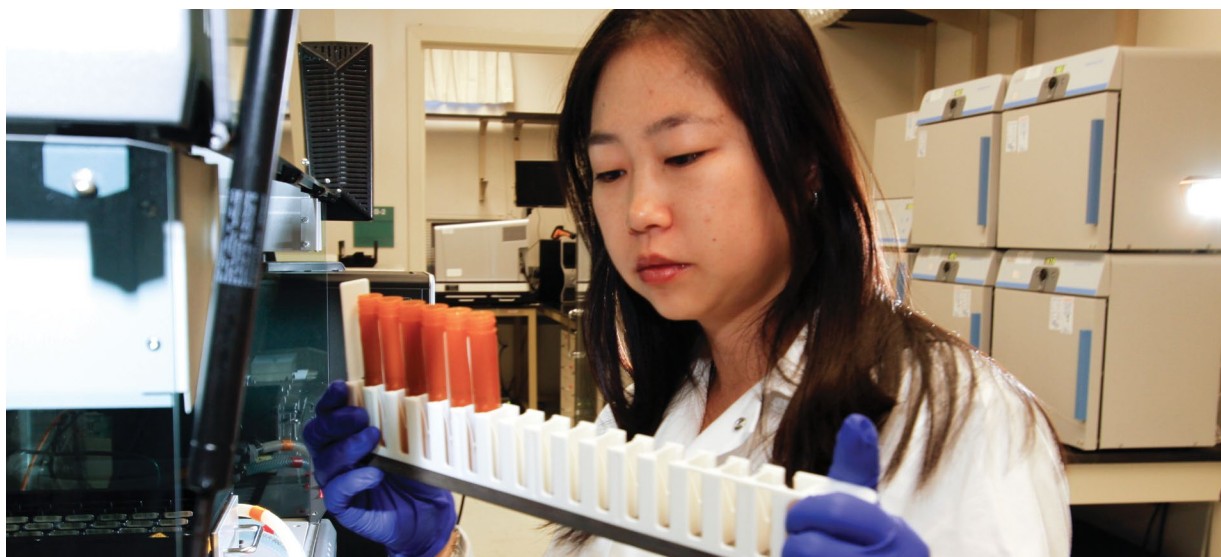
Year	Vials	Plates	Total Extracts	Cultures
2013	4667	131	16,195	0
2014	3637	439	42,269	0
2015	630	2025	178,885	25
2016	788	667	59,531	0
2017	531	493	43,919	1

TABLE 13: SHIPMENTS MADE BY NPB TO NON-DCTD INVESTIGATORS AND COLLABORATORS (2013-2017)

A significant number of samples (>100 vials per year) are shipped to the NCI Center for Cancer Research (CCR) Molecular Targets Laboratory for chemical evaluation of DCTD's Natural Products Repository extracts identified as active in targeted assays based on CCR-designated molecular targets. In addition to CCR efforts, NPB has >100 current material transfer agreements with extramural researchers to investigate various aspects of the bioactivity and chemical diversity of DCTD's Natural Products Repository extracts.

Marine Collections

NPB successfully negotiated a new agreement based on a Letter of Collection with the Australian Institute of Marine Sciences to obtain more than 3,000 individual marine invertebrate specimens and more than 6,000 marine microbe



cultures for use by NCI. NPB will extract the relevant samples, and the resulting extracts will be split between NCI and Australian research institutions.

NPB also completed collections of marine invertebrates from the waters of Thailand through a Memo of Understanding between the Thai government, Chulabhorn Research Institute (CRI), and NCI. These samples were extracted in the Natural Products Support Group (NPSG), and the resulting 210 extracts were tested for activity in the NCI-60 Cell Line Screen. Eight active extracts were selected for compound isolation and structure elucidation in NCI. The results of these studies were presented to Her Royal Highness Princess Chulabhorn Mahidol at a meeting hosted at NCI at Frederick between officials of the Thai government and NCI. Extracts from these collections will be split between NCI and CRI and made available to researchers in both countries.

Plant Collections of Opportunity

Although contracts for collections of plants have not been funded by NCI since 2004, NPB has been successful in finding other pathways to continue the acquisition of these materials. One such collection is of plants used in traditional Chinese medicine (TCM).

Traditional Chinese Medicinal Plants. This fully annotated library of plant materials was obtained through collaboration

with DCTD's Office of Cancer Complementary and Alternative Medicine, Harvard University, Beijing University of Chinese Medicine, and Hong Kong Baptist University. These plants had been collected under TCM-defined conditions from sites where the original plants were collected for the ancient TCM monographs approximately 1,000 years ago. Five-hundred-gram samples of each part of the collection have been ground, extracted, and tested in the single-dose NCI-60 Cell Line Screen. Screening plates of these extracts have now been made available to researchers through the [NP Repository website](#) for testing in other assay systems.

Microbial Collections

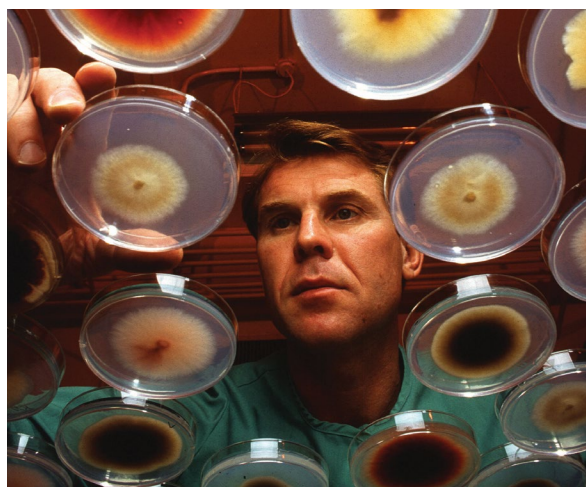
In 2016 NPB gained access to a new fungal library through a contract with Leidos Biomedical, Inc. and the University of Oklahoma Institute for Natural Product Applications and Research Technologies (INPART) to obtain recently collected soil fungi from the United States for culture at NCI. These fungi have been collected through a citizen science collection program sponsored by the University of Oklahoma. The contract is scheduled to bring up to 4,000 new, taxonomically typed, non-duplicative fungi to NCI every year. NCI will culture the fungi and extract the cultures to yield a new microbial extract library for natural product research. It is anticipated that this contract will extend for several years and bring significant new chemical diversity to the NPB screening library.

Natural Products Support Group (NPSG)

The NPSG extracts samples of natural products for testing in the NCI-60 Cell Line Screen, provides a compound plating support service for all drugs and natural products entering the NCI-60 queue, and conducts research to characterize and purify extracts showing promising screening results. These tasks include:

- Preparation of all samples (natural-product extracts or fractions, purified natural products, and synthetic compounds) for the one- and five-dose NCI-60 Cell Line Screens and the *in vivo* hollow-fiber and xenograft tests run by BTB.
- Management and maintenance of in-house computerized systems, including the successful integration of two state-of-the-art Tecan robotic systems that materially improved the liquid handling systems and output. The output of this part of the NPSG can be seen in the quantity of the screening numbers reported on a weekly basis covering the NCI-60 Cell Line Screen.
- Purification and identification of active materials (both natural and synthetic) from within DCTD whose chemical structures require independent confirmation.
- Isolation, curation, and subsequent growth of microbes isolated as a result of collaboration with the U.S. Department of Agriculture's Noxious Weeds Research Unit based on the Fort Detrick campus and more recently with the University of Oklahoma.
- Development of new bioinformatics analysis tools (self-organizing maps) to aid in the prioritization of extracts for compound isolation based on large data sets of biological, taxonomic, geographic, and chemical data.
- Creation of a pre-fractionated library of partially-purified extracts from the NCI National Products Repository. This library is expected to be much more amenable to use in modern screening programs and is expected to contain approximately 1,000,000 samples.

NPSG has continued the isolation and structure elucidation of active compounds from extracts selected by DTP data review group. As a result of close cooperation between the *in vivo* testing laboratories of BTB and NPSG, and using the



newly installed bioinformatics prioritization principles and pre-fractionation strategies, 30 extracts were selected for research in November 2015. Those projects have now all been completed, and 11 active samples have been scheduled for *in vivo* testing in suitable mouse models. Overall, since January 2015, 124 individual chemical characterization projects have been pursued by the NPSG and brought to completion by identification of the compound or class of compounds responsible for the cytotoxicity of the extract.

CGMP MANUFACTURING AND FORMULATION

PRB produces clinical supplies and chemistry, manufacturing, and control (CMC) data to support INDs sponsored by DCTD. Several new clinical candidates are currently in advanced IND development stages. The branch synthesized several distinct compounds ranging in batch sizes of grams to multi-kilograms, often manufacturing additional batches as the need arose. PRB also validated high-pressure liquid chromatographic (HPLC) analytical methods that were developed for several distinct compounds in advanced development, with individual lots undergoing complete analytical assessment and release for advanced preclinical studies (IND directed) and/or use in preparing clinical dosage forms. In addition, PRB prepared a number of batches of parenteral dosage forms, including freeze-dried and liquid-filled products. Oral dosage forms (mostly capsules) of several compounds have been prepared in multiple batches and strengths to accommodate dosing needs in ongoing clinical



CLINICAL SUPPLIES RECENTLY PROVIDED BY PRB FOR NEW OR ONGOING TRIALS

- Z-Endoxifen
- T-dCyd (4'-thio-2'-deoxycytidine)
- Aza-T-dCyd (5-aza-4'-thio-2'-deoxycytidine)
- IPdR (5-iodo-2-pyrimidinone-2'-deoxyribose)
- LMP-400
- LMP-776
- LMP-744
- FdCyd/THU (5-fluoro-2'-deoxycytidine / tetrahydrouridine)
- PU-H71
- DMS-612
- 1-MT
- Fenretinide
- Safingol
- TRC102
- Phenformin

trials. Shelf-life studies were conducted at several points each year on an average of 80 distinct batches of drug products. Pre-formulation and formulation work was performed to identify the conditions required for preparing suitable and stable formulations, with the results transferred to the manufacturers of the clinical dosage forms for preparation of actual clinical supplies. Several lots of GMP bulk drugs were synthesized, requiring quality-control release testing of each batch. Formulations and/or new size configurations were developed, and sterile injectable and capsule dosage forms were manufactured as appropriate for each drug.

INVESTIGATIVE TOXICOLOGY LABORATORY

The Investigative Toxicology Laboratory, overseen by TPB, generates insights about the cellular toxicity of compounds. Better characterization of mechanisms of toxicity aids in the selection of drug candidates through the design of mechanism-based *in vitro* screens. Thus, DCTD is better able to achieve its programmatic goals in drug development, and to support the underserved area of toxicology of anticancer agents. Generation and publication of baseline information on *in vitro* assays and biomarkers that may be used to advance research are critical for expanded utilization of well-established *in vitro* assays by the community of toxicological scientists.

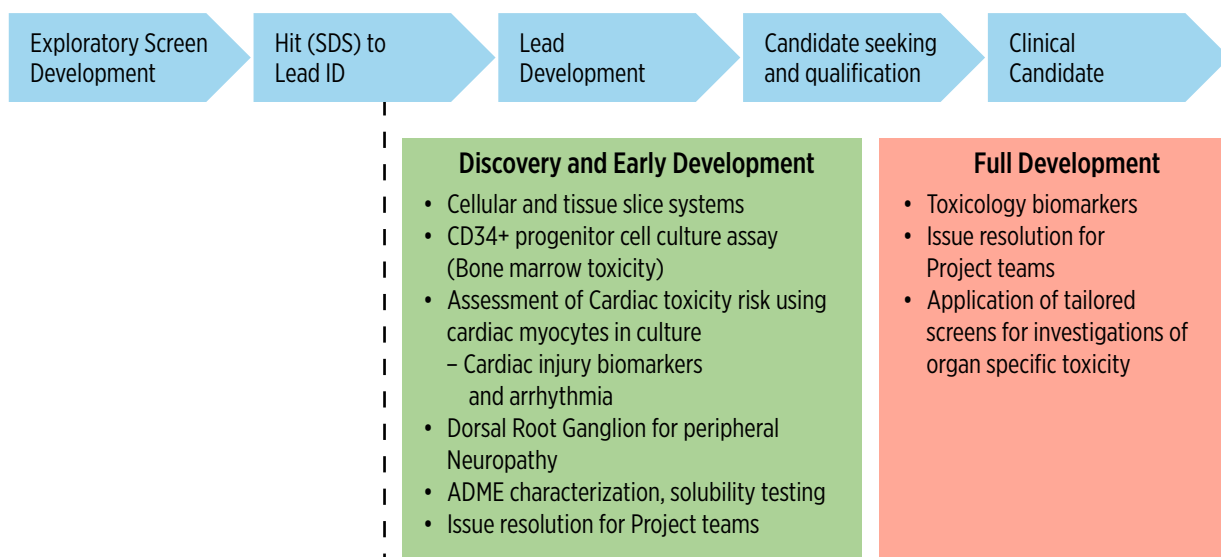


FIGURE 49: INVESTIGATIVE TOXICOLOGY ACTIVITIES IN SUPPORT OF DRUG DEVELOPMENT.

THE BIOPHARMACEUTICAL DEVELOPMENT PROGRAM

The BDP was established in 1993 for the purpose of manufacturing biologicals at pilot scale for first-in-human, proof-of-concept studies; however, production levels now support preclinical development studies, Phase 1 and 2, or selected Phase 3, clinical trials. The BDP is located in the Advanced Technologies Research Facility (ATRF), a state-of-the-art FNLCR research facility with 55,000 ft² occupied by BDP laboratory, GMP manufacturing, and fill-finish suites. The GMP facility contains separate upstream bioprocessing and purification trains for mammalian and bacterial products, plus a separate set of isolated suites for viral vector production. The BDP facility has often served as a site for the FDA's biologics inspectors training program, and maintains cGMP compliance through audits by qualified independent contractors.

Technical expertise and specialized capabilities in BRB and BDP primarily support the production of biologic agents targeting cancer; however, the BDP is frequently engaged in collaborations outside of cancer with the following other government programs:

- National Institute of Allergy and Infectious Diseases (NIAID) and the U.S. Army Medical Research Institute for Infectious Diseases (USAMRIID) for vaccine development in infectious diseases

- National Center for Advancing Translational Sciences (NCATS) for rare and neglected disease treatments
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) for approaches to abort the autoimmune course of early type 1 diabetes

In addition, staff expertise is frequently sought for advice or training by a range of programs outside DCTD that are involved in drug development:

- Source Evaluation Groups or Special Emphasis Panels reviewing grant applications and contract proposals for non-NCI initiatives
- Steering committees for new NIH programs in infectious disease or nanotechnology applications
- New biopharmaceutical programs and academic institutions in developing countries for in-plant training of their senior staff
- New foreign production plants collaborating with NIH requiring the conduct of site visits

Since 2012, 31 different BDP products have been used in IND-supported clinical trials. In that interval, BDP released 10 new GMP clinical lots in addition to master cell banks, control lots, diluents, and other associated products. BDP provides quality control, quality assurance, and regulatory support for its products, including technical packages for



FIGURE 50: ADVANCED TECHNOLOGIES RESEARCH FACILITY (ATRF) IN FREDERICK, MD.



FIGURE 51: cGMP FILL/FINISH ACTIVITY AT THE BDP, FNLCR.

pre-IND meetings with FDA; CMC documents for IND applications; post-filing technical and regulatory assistance, as well as on-going stability studies for the duration of their use in clinical trials. The following are some of the most significant milestones for BDP products during this reporting period (2013 – 2017):

Ch14.18 (dinutuximab/Unituxin). Ch14.18 is based on an anti-GD2 murine monoclonal antibody (mAb) discovered in the laboratory of Dr. Ralph Reisfeld, a BRB grantee and holder of a DTP-sponsored U01 Collaborative Agreement. BDP manufactured several versions of the antibody (e.g., murine, human, the murine/human chimeric, and a human14.18-IL-2 recombinant fusion protein) as part of this project. In the largest clinical effort, BDP manufactured 11 clinical lots of ch14.18 to support Children’s Oncology Group (COG) clinical trials in high-risk neuroblastoma combining ch14.18 with IL-2 and GM-CSF to boost Antibody Directed Cellular Cytotoxicity (ADCC), and 13-cis-retinoic acid (RA). After significant improvement in median disease-free survival was shown in a planned interim review of the randomized Phase 2 trial, NCI sought a commercial partner with whom they could license the manufacturing of this agent. Although United Therapeutics Corporation (UTC) became NCI’s CRADA Partner in 2010, BDP continued to provide most of the clinical material under the original IND trial and worked with UTC extensively in technology transfer activities while UTC established its large-scale commercial manufacturing process. In 2015, UTC received commercial licenses under Orphan Disease indications in the U.S. from FDA and in the EU from EMA for ch14.18 (now called dinutuximab, or

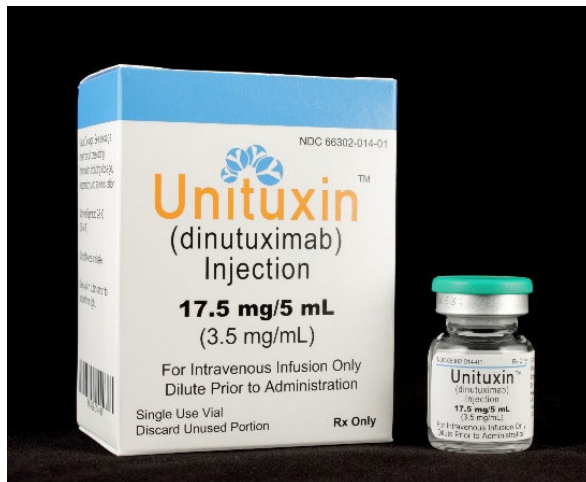


FIGURE 52: Ch14.18 WAS ADVANCED FROM A GRANTEE RESEARCH LABORATORY INTO CLINICAL TRIALS AND EVENTUALLY TO A COMMERCIAL PARTNER THROUGH NCI ASSISTANCE.

Unituxin), based on the COG trial results using BDP product and several comparability studies between BDP and UTC product. FDA also awarded UTC a Rare Pediatric Priority Review Voucher, under the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA). After more than 1,000 children had been treated in the U.S., Canada, Australia, and New Zealand, the last BDP product was withdrawn from clinical use in March 2015.

PVS-RIPO. PVS-RIPO, a modified poliovirus, was developed in the laboratory of Dr. Matthias Gromeier, who submitted a development proposal to the RAID/NExT program requesting NCI assistance in the GMP manufacturing of this agent as a potential treatment for recurrent Glioblastoma Multiforme (GBM) by direct intra-tumoral infusion. Under a research grant in the BRB portfolio, Dr. Gromeier and colleagues at Duke University Medical Center are evaluating the mechanistic hypothesis that in addition to direct tumor cell killing, infection with a low dose of PVS-RIPO elicits inflammatory events that mediate anti-neoplastic effects through host-mediated immune responses. Based on promising results observed in the first 23 patients treated with a low-dose infusion, the FDA provided a “Breakthrough Therapy Designation” in May 2016, whereby the FDA will provide accelerated review of regulatory submissions, and work closely with the IND Sponsor during product development. Three trial subjects are currently disease-free more

than three years after treatment. An IND amendment to extend the study to enroll subjects with Pediatric Glioblastoma was submitted to the FDA and reviewed by the NIH Recombinant DNA Advisory Committee (RAC) in 2016. BDP released a new lot of PVS-RIPO in 2016 that is sufficient to treat more than 1,400 additional subjects in support of the expanded studies.

Tet-CMV Peptide Vaccine. Tet-CMV (CMVPepVax) is a peptide vaccine, developed in the laboratory of Dr. Don Diamond at the City of Hope (COH) Cancer Center, to prevent CMV virus infections that cause major morbidity in the setting of hematopoietic cell transplant (HCT) procedures. The peptide, a T-helper epitope linked to a CMV pp65 HLA *0201 restricted epitope (Tet-CMV), is used in combination with CpG 7909 adjuvant that was donated by Pfizer. Results from the controlled Phase I study using BDP material were published in *The Lancet Hematology* in early 2016 showing a positive effect on CMV viremia and relapse-free survival. BDP released a new clinical lot in 2015 to support a multi-institution Phase 2 trial. In 2016, COH licensed the vaccine (named CMV PepVax) to Fortress Biotech (formerly Coronado Biosciences) who will work closely with BDP to transfer the technology in anticipation of taking over future production.

Ganitumab. Ganitumab is an anti-IGF1R monoclonal antibody that was being developed by Amgen, and for which COG and NCI-CTEP had planned a Phase 2 clinical trial in Ewing Sarcoma. In early 2013 Amgen terminated their development of the product; however, Amgen provided technical information to NCI in April 2013, and donated bulk drug substance to NCI in September 2013 for the COG trial and other clinical research under a CRADA. BDP established assays for quality control (QC) of the bulk drug substance and finished products to meet requirements established in a January 2014 pre-IND meeting with FDA. The first lot (3,652 vials) of BDP filled material was released in September 2014, and the clinical trial opened in December 2014 at 175 COG institutions. Canadian sites opened in June 2015. Enrollment of subjects increased faster than expected, and Amgen donated additional bulk drug substance that was filled (8,719 vials) in January 2016. This was QC tested and released by BDP in June 2016 to avoid interruption in subject accrual. Accrual was completed without interruption in November 2016.

A second NCI trial is planned in the NIH Clinical Center. NantBio has recently licensed Ganitumab from Amgen and will be responsible for future drug supply.

Interleukin-15. Interleukin-15 (IL-15) was co-developed by the intramural laboratory of Dr. Thomas Waldmann at NCI. A high priority agent for immunotherapy researchers, BDP began the project with an R&D grade IL-15 expressing *E. coli* clone provided by Dr. Waldmann, and was able to develop a master cell bank from which scale-up manufacturing of GMP material could be performed. Toxicology material was released in June 2008, and the first clinical lot was produced in March 2009. Eight clinical lots (> 35,000 vials in total) have been produced, including three lots (~20,000 vials) funded by the American Recovery and Restoration Act (ARRA). In the current reporting interval, clinical trials have been underway in the extramural Cancer Immunotherapy Treatment Network (CITN), CCR, and individual grant-supported extramural centers. BDP-manufactured IL-15 is also available through the BRB Preclinical Repository for R&D purposes. Since this R&D material is closely similar to the BDP clinical material, investigators have developed preliminary data using this material to support regulatory filings for clinical trials. Therapeutic combinations with IL-15 are now in development at CITN to improve adoptive cell therapy (T cells and natural killer cells) and at NCI (Dr. Waldmann) to improve monoclonal antibody strategies.

Ch11-1F4 monoclonal antibody. Dr. Alan Solomon of the University of Tennessee developed a murine antibody (mu 11-1F4O) that recognized AL amyloid deposits (see figure below) and cleared deposits of human amyloid placed subdermally in a mouse model. Dr. Solomon's proposal to generate a chimeric antibody clone was accomplished by a BDP subcontractor under the NExT Program. BDP manufactured a GLP lot of murine 11-1F4 antibody for toxicology studies. The murine antibody was then used for an I-124 PET study in humans that was funded by an FDA Orphan Drug Grant. Striking images of amyloid deposits were demonstrated.¹ The murine antibody has also generated images that demonstrate before-and-after effects of standard therapy (melphalan +/- stem cell infusion). BDP manufactured a 50 gm lot of chimeric antibody that is being used in a **Phase 1 clinical trial** that opened in 2014. An interim analysis presented at the American Society of Hematology meeting in December

¹ Wall JS, et al; *Blood* 2010;116:2241-44



AL11 λ

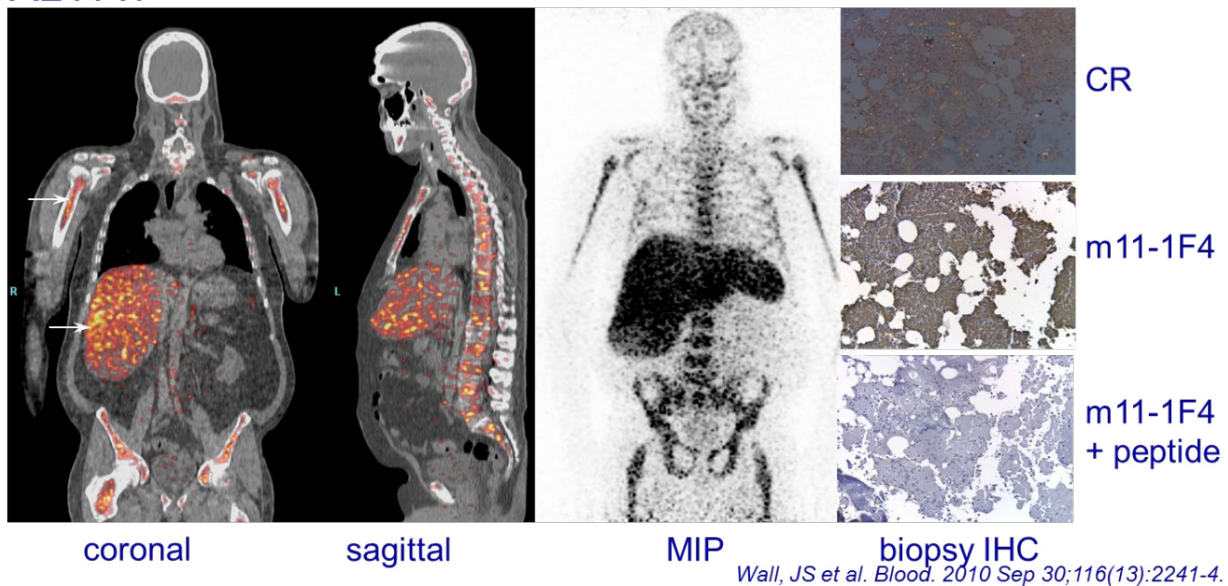


FIGURE 53: CO-LOCALIZATION OF 124I-M11-1F4 WITH HEPATOSPLENIC AND BONE AL AMYLOID.

2015 showed biomarker and organ response evidence of single-dose antibody effects on amyloid deposits. The antibody has been tolerated through six dose levels up to 500 mg/m² administered IV in a single dose. The trial was taken to a multiple weekly-infusion phase that will provide groundwork for a possible Phase 2 study in the SWOG cooperative group. BDP is now in the process of manufacturing an additional 700 gm of Ch11-1F4 in preparation for a Phase 2 study.

BRB PRECLINICAL REPOSITORY

- The BRB Preclinical Repository distributes bulk cytokines, monoclonal antibodies, cytokine standards, and other highly sought research reagents to academic investigators at no cost except for shipping expenses.
- Since 1996, more than 68,000 vials of different reagents have been shipped domestically and internationally to over 3,000 scientists. In recent years, the repository has provided an average of 2,900 vials/year through approximately 180 shipments.
- One of the most popular BRB Repository requests is the NIH collection of Recombineering Bacteria Strains and Plasmid Vectors that investigators use to create new molecular entities for further study or manufacturing.
- Agents developed and manufactured under NCI-sponsored programs recently made available through the repository include ch14.18 and 1A7 monoclonal antibodies, Ad-CCL21 chemokine, MPL adjuvant, and IL-7, IL-12, and IL-15 cytokines.
- The initial repository inventory was significantly augmented with thousands of vials of cytokine standards from the United Kingdom's National Institute of Biological Standards and Control for distribution to U.S. investigators and 80,000 vials of recombinant human IL-2 from industry.
- BRB negotiates with companies and investigators to obtain, by donation or at reduced cost, new materials to enrich the repository's supply of reagents. Many donated lots are expired commercial clinical materials that are retested or re-vialled by BDP to enable distribution of high-quality reagents for research and development use only.
- Agents are provided to the research community.



IT ENHANCEMENTS FACILITATING INTERACTIONS WITH THE RESEARCH COMMUNITY

Support for *In Vivo* Screening. BTB has made a major change to their experiment management and data capture system, going to a commercial “off the shelf” (COTS) software package. This package is central to the efficiency of BTB’s contributions to the NCI Patient-Derived Models Repository. ITB integrated the new software into the larger DTP data systems, including the Compound Submission System (see below) that allows suppliers to access the results of tests on their compounds.

Support for Combination Studies. DCTD has invested significant effort in looking at combinations of agents in the NCI-60 Cell Line Screen, as well as in panels of sarcoma and NSCLC cell lines. ITB has created computer systems to capture, store, and report the data generated to the scientific community, as demonstrated via the [NCI ALMANAC](#).

Compound Submission / Ordering System. A web-based [Compound Submission / Ordering System](#) collects the information necessary to process compound submissions to the [NCI-60 Cell Line Screen](#). The system also creates an electronic Material Transfer Agreement (NCI_Receiving Form) for each submission. This is a change from the past, where suppliers either completed a written agreement that applied to all submissions, or went without any agreement at all. The

online form also allows submitters to follow the progress of their compounds through screening and to access data as the assays are completed. This application handles more than 600 submissions per month.

The [DCSB Repository](#) can be accessed via a [web interface](#) to request samples of individual compounds or plated sets of compounds with an electronic Material Transfer Agreement (NCI_Shipping Form) that is automatically generated and routed, minimizing paperwork and processing time. This application handles about 20 requests per week with an average of about 15 compounds per request.

Further modification of the standard online submission application implemented above enabled the Chemical Biology Consortium (CBC) Centers to register and request compounds with NSC numbers within minutes using the [NExT/CBC Compound Submission](#) form. This application handles about 200 submissions per month.

Molecular Targets. The results of this effort by more than 300 laboratories worldwide to molecularly characterize the NCI-60 Cell Lines are made available for data mining through the web-based [Molecular Target Program](#) interface. These activities have included the characterization of 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 the last three years, more than 15,000 measurements in 18 projects have been publicly released. The largest contribution to this total was from an effort to sequence the exome of all the cell lines.

FUTURE DIRECTIONS

DTP will continue to provide services and resources to the academic and private sector worldwide to facilitate the discovery and development of new cancer therapeutic agents. Over the next five years, DTP plans to focus on the following three key areas:

Enhance the support for extramural immuno-oncology discovery and development

In response to the rapid progress in anti-cancer immunotherapy research, DTP recently established the **Immuno-Oncology Branch** to support peer-reviewed research projects in areas of emerging interest. Among these areas are small molecule immunomodulators, 3-dimensional organ and tumor systems consisting of multiple cell types and structural components, and the role of the tumor microenvironment or the crosstalk between tumor and the microenvironment as one of the modes of action for immune-oncology. DTP grant staff will continue to conduct portfolio analyses to identify research gaps for new initiatives,

develop new funding opportunities and recommend funding levels to stimulate and facilitate the translational research of immunotherapy. In addition, DTP staff will explore opportunities to provide valuable resources to the immuno-oncology community, for instance, by acquiring and distributing well-characterized reagents.

Enhance the support for extramural therapeutic product developers

In 2016, DTP staff developed the **Experimental Therapeutics Consultation Service** of the NExT program. With the submission of a simple online form, extramural investigators can request a consultation with DTP's drug development experts on critical path activities for preclinical development of new therapeutics, including nonclinical safety and good manufacturing processes for small molecules, biologics, and imaging agents. Ultimately, investigators are encouraged to consider applying to the NExT program to request access to NCI resources for performing the activities discussed if they do not have the capabilities themselves.

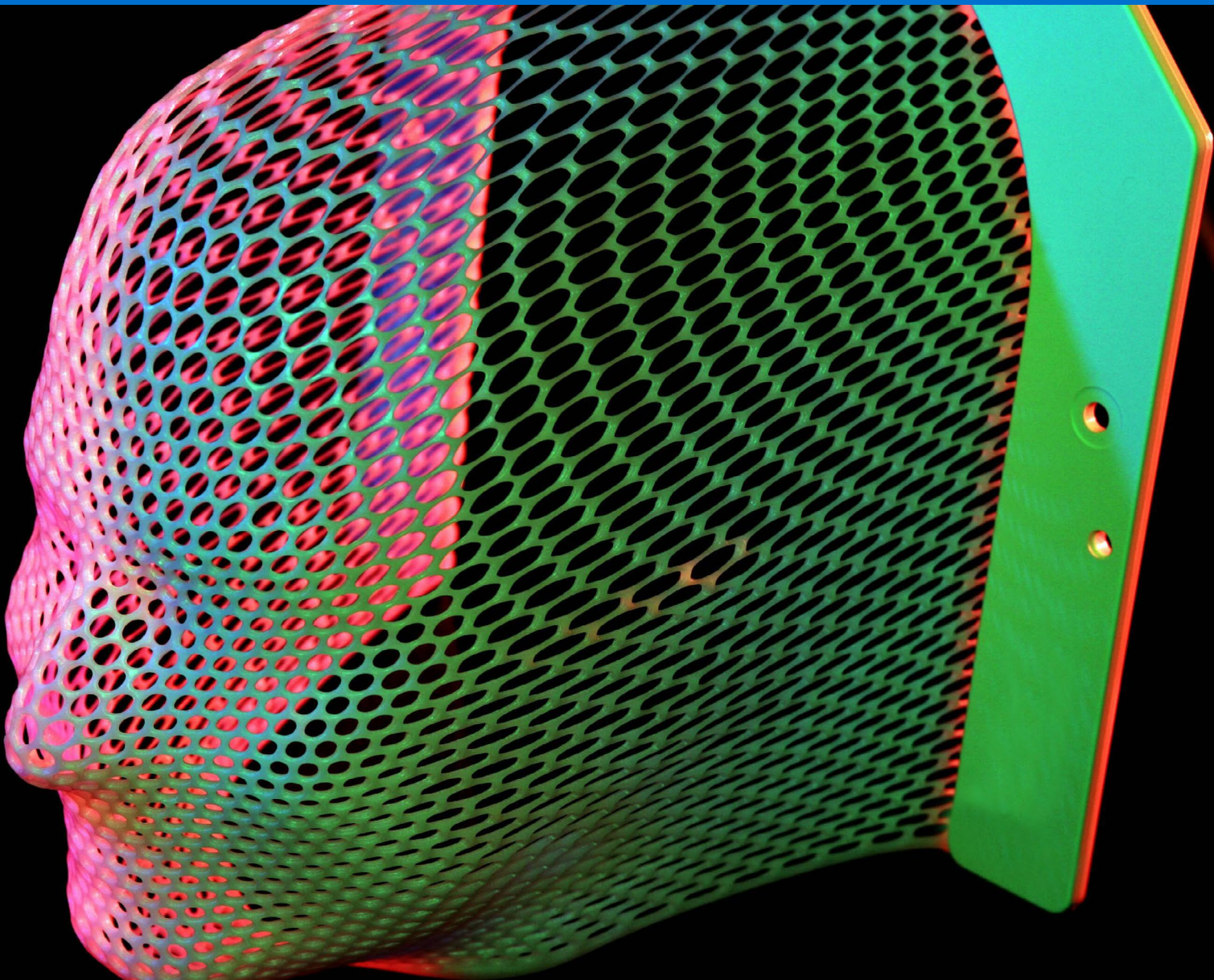
In addition, DTP staff will continue to support the best translational research based on peer review and clinical need, catalyze interactions among scientists, educate the scientific community on peer review and grant policy changes, inform grantees about DCTD drug development services such as NExT, and organize workshops. DTP staff will continue their involvement in the NExT program, serving as team members of working group committees and providing contract-based resources for approved projects where appropriate.

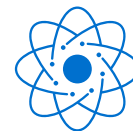
Enhance the support for natural products drug discovery

NPB has undertaken a new effort to accelerate the discovery of new bioactive compounds from extracts in the **NCI Natural Products Repository**. This effort, termed the **NCI Program for Natural Products Discovery (NPNPD)**, is a joint endeavor between CCR and DCTD to create an approximately 1,000,000 sample partially-purified natural product library for screening by CBC centers and other extramural institutions. NPB will also work with these centers in the isolation and structure elucidation of active natural products.

PROGRAMS AND INITIATIVES (2013-2017)

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 biology, innovative technology, electronic data acquisition and analysis, image-guided therapy, particle radiation therapy (RT; protons, carbon ions, and others), multimodality cancer treatment, immunology, systemic radionuclide therapy (SRT), non-ionizing radiation (hyperthermia, ultrasound, photodynamic therapy), outreach to the underserved and global cancer care, and health, medical, and societal response to threats from nuclear and radiological disasters, potentially including terrorism. With its research base in basic biology, physics, and 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 palliative care. The **Radiation Research Program (RRP)** is the sole program focused on therapeutic radiation sciences within the extramural programs of NCI.

As part of ongoing efforts to stimulate research in RT and radiation biology, RRP staff provide support for basic, translational, and clinical RT research within DCTD by:

- Providing expertise to investigators and potential grantees who perform cutting-edge research with radiation and other forms of energy
- Helping to organize and lead the RT research community in establishing priorities for the future direction of radiation research, including interagency cooperation and collaboration
- Developing and promoting collaborative efforts among extramural investigators for both preclinical and clinical investigations, including the evaluation of systemic agents that can be used in combination with radiation
- Evaluating the effectiveness of radiation research being conducted by NCI grantees
- Advising NCI-funded clinical trial groups and the Cancer Therapy Evaluation Program (CTEP), DCTD regarding scientific priorities and quality assurance in clinical studies with RT
- Developing unique models and capabilities to help and mentor medically underserved communities in the United States and worldwide to access cancer clinical trials and care

- Serving as the NCI liaison and advisor on the mitigation of radiation injury to normal tissue and the development of biomarkers for radiation injury in programs addressing radiological and nuclear terrorism in the National Institute of Allergy and Infectious Diseases (NIAID) and the Office of the Assistant Secretary for Preparedness and Response (ASPR) within the Department of Health and Human Services (HHS)
- Working and coordinating with professional societies to publicize research efforts and findings in radiation oncology and biology

RRP coordinates its activities with other radiation research efforts at NCI, in particular the Division of Cancer Biology (DCB), the Division of Cancer Control and Population Sciences (DCCPS), the Center for Cancer Research's (CCR) Radiation Oncology Branch and Radiation Biology Branch, and the Division of Cancer Epidemiology and Genetics (DCEG), as well as NIH, other federal agencies, and national and international research organizations. RRP also serves as a focal point for extramural investigators who are concerned with clinically related radiation oncology and biology research.

STRUCTURE AND FUNCTION

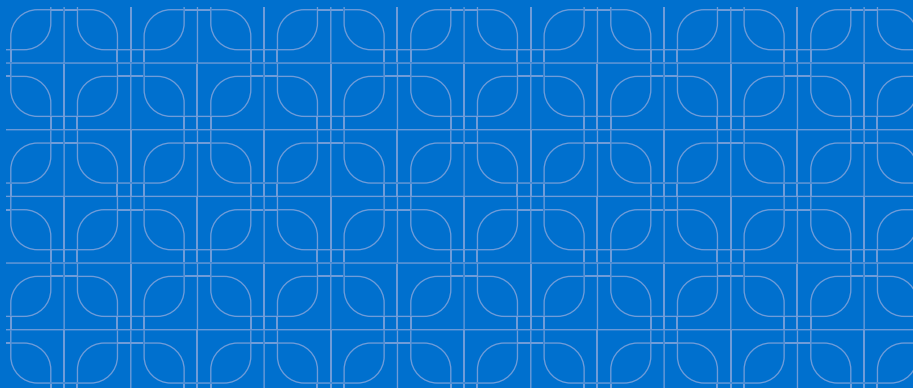
RRP is divided into two branches and one coordinating activity:

1. Radiotherapy Development Branch (RDB)
2. Clinical Radiation Oncology Branch (CROB)
3. Molecular Radiation Therapeutics (MRT)

The primary responsibility of RRP is to the grantees and contractors of NCI and NIH. In fiscal year 2016 (FY16), RRP administered over 430 grant applications (including approximately 130 funded research projects from this and preceding years). In addition to conducting grants management, RRP staff members advise on and act as reviewers for grants and contracts submitted to the U.S. Department of Defense (DoD) and consult on radiation issues with program staff in NIAID, the Biomedical Advanced Research and Development Authority (BARDA), and the National Aeronautics and Space Administration (NASA).

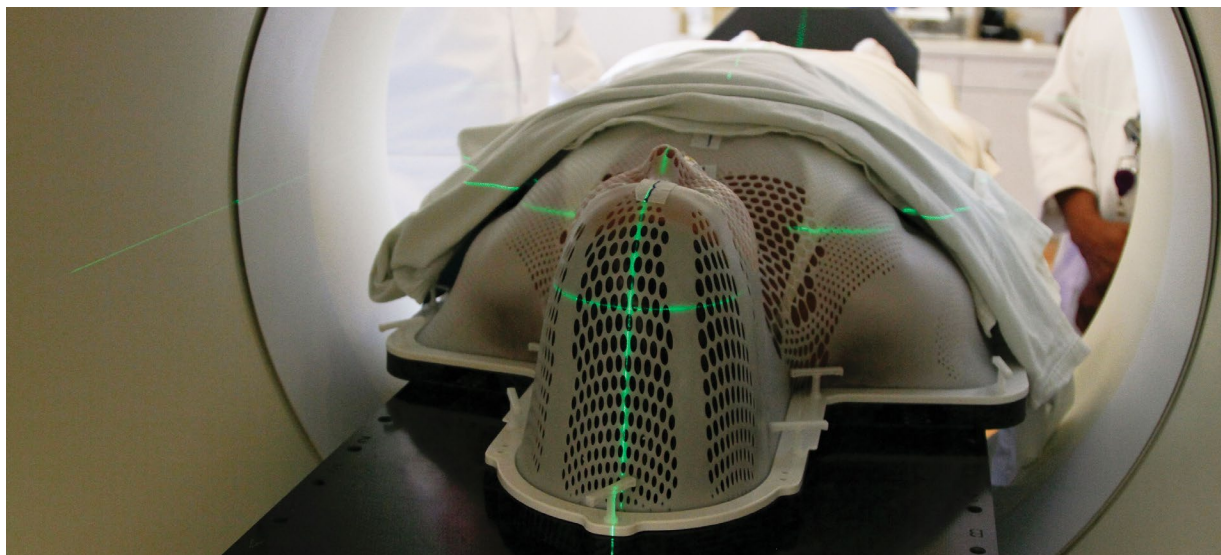
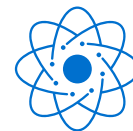
C. NORMAN COLEMAN

ASSOCIATE DIRECTOR



C. Norman Coleman, MD, is Associate Director for RRP, a Senior Investigator in the Radiation Oncology Branch of the NCI intramural CCR, and a Senior Medical Advisor in the Office of ASPR in HHS. He 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 Associate Director of NCI's Radiation Research Program, Branch Chief and Senior Investigator in the Radiation Oncology Branch in the Division of Clinical Sciences (now part of the CCR) and Chief of the virtual Radiation Oncology Sciences Program that also included the Radiation Biology Branch. He served as Chief of the Radiation Oncology Branch from 1999 until 2004, at which time he began working in the Office of

Public Health Emergency Preparedness at HHS. He has written extensively in his field and has won numerous awards, including the 2005 Gold Medal Award from the American Society for Radiation Oncology (ASTRO). In 2011 he received the Service to America Homeland Security Medal from the Partnership for Public Service for his contributions to developing the health and medical response for radiological/nuclear disasters and his service in Japan during their nuclear power plant crisis in 2011. In 2015 he received a Doctor of Science degree, Honoris Causa from his alma mater, the University of Vermont, for his contributions to science and society. He is the 2016 recipient of the Failla Award from the Radiation Research Society (RRS) for his many scientific and professional contributions to the fields of radiation oncology and radiation biology. Dr. Coleman is a Fellow of the American College of Physicians, the American College of Radiology (ACR), ASTRO, and the American Society of Clinical Oncology (ASCO).



RADIOTHERAPY DEVELOPMENT BRANCH

RDB is responsible for the overall coordination of RRP's research portfolio, which encompasses a broad range of topics that includes:

- Development and implementation of advanced technologies for the production and delivery of radiation, including protons and heavier charged particles (in collaboration with RRP's CROB)
- Combination of RT with molecular-targeted treatment and immunotherapy
- Preclinical and clinical development of multi-modality cancer therapy including diagnosis, predictive and prognostic biomarkers, treatment, and long-term outcomes/toxicity
- Radiation-inducible molecular changes in both tumor and normal tissues that can be exploited to improve outcomes with drugs and immune modulators
- Radiation modifiers, including sensitizers and protectors, and radiation-nanotechnology
- Normal tissue injury and treatments to prevent or mitigate these injuries
- Systemic targeted radionuclide therapy, including radioimmunotherapy
- Non-ionizing radiation-based therapies such as photodynamic therapy and hyperthermia

RDB and CROB collaboratively manage grants that deal with image-guided RT (IGRT) and the physics of basic radiation track (beam) structure and radiation chemistry. RDB

also organizes workshops highlighting the importance of understanding biology in RT, including the tumor micro-environment, DNA repair (in collaboration with DCB), and the role of immunity in radiation responses. The workshops addressed overarching issues in radiation research, such as the future of radiation biology research, precision medicine, particle and systemic radionuclide therapies, reproducibility of preclinical translational research, often in collaboration with national radiation related clinical and research professional societies such as ASTRO, SNMMI, and RRS. RDB also collaborates with NCI's Center to Reduce Cancer Health Disparities (CRCHD) on issues relating to the accrual of underserved populations to cancer clinical trials.

CLINICAL RADIATION ONCOLOGY BRANCH

CROB manages the clinical and translational research grant portfolio in radiation oncology and nuclear medicine, the technical and physical aspects of radiation research, and the development of new therapeutic approaches.

In addition to managing grants, CROB devotes a substantial effort to supporting NCI, NIH, HHS, and government-wide activities, such as technology development and assessment, comparative effectiveness research, and the application of precision medicine. The staff, with their knowledge of radiation biology and therapeutic interventions, work extensively with other organizational entities in DCTD, NCI, NIH and even within other government agencies, to assist them in their mission:

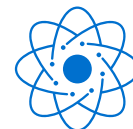
- **CTEP and CIP**
Assisting with their cooperative clinical trial groups and early-phase trials consortia

- **The Coordinating Center for Clinical Trials (CCCT)**
Working with its steering committees and task forces (e.g., subcommittees on head and neck, thoracic, breast, gastrointestinal, genitourinary, and gynecological malignancies; investigational drugs; and symptom management and quality of life)
- **The NCI Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) programs**
Establishing priorities for programs involving radiation to help bring new treatments and technology to cancer care
- **The National Cancer Informatics Program, the NCI Center for Biomedical Informatics and Information Technology (CBIIT), and the NIH Center for Information Technology (CIT)**
Formulating concepts for demonstration projects using radiation oncology as a platform, including telemedicine with TELESYNERGY®
- **The NCI Center for Global Health (CGH)**
Developing topics for conferences and potential research programs involving RT as a component of global cancer research and care
- **The Information Technology for Cancer Research (ITCR) Consortium**
Helping to promote IT solutions for cancer treatment involving RT
- **NIAID**
Assisting in the identification of opportunities for radiation countermeasure investigators to decrease treatment toxicity in cancer patients and for the development of biomarkers for whole or extensive partial body exposure for use in triage and medical management
- **The Food and Drug Administration (FDA)**
Assisting in identifying needs and opportunities for postmarketing surveillance of devices cleared for use in radiation oncology, and in establishing endpoints and benchmarks for the approval/clearance of new drugs and devices
- **The Agency for Healthcare Research and Quality (AHRQ) and the National Academy of Sciences (NAS)**
Assisting in identifying priorities and opportunities for comparative effectiveness research in cancer
- **The DoD Armed Forces Radiobiology and Research Institute (AFRRI)**
Discussing ways in which cancer clinical trials may help in licensing of radiation countermeasures
- **The Department of Veterans Affairs**
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 other radiation oncology networks, such as the recently formed NRG Oncology Group (merger of the NSABP, RTOG and GOG)
- **Professional societies:** facilitate transition of the most promising, radiation-based, experimental therapies to clinical practice by working with such groups as the Society of Nuclear Medicine and Molecular Imaging (SNMMI), American Association for Physicists in Medicine (AAPM), American Association for Cancer Research (AACR), Society for Immunotherapy of Cancer (SITC), ASTRO and ASCO
- International organizations, such as the International Atomic Energy Agency (IAEA), the International Agency for Research on Cancer (IARC), the World Health Organization (WHO), Union for International Cancer Control (UICC), the Pan American Health Organization (PAHO), and the Consortium of Universities for Global Health (CUGH)
- Assisting countries and provinces with cancer control planning, especially with regard to human and other resources required for improving cancer detection and management using RT and allied treatments

MOLECULAR RADIATION THERAPEUTICS

MRT staff serve as a focal point for promoting collaboration between extramural radiation oncology researchers and the Developmental Therapeutics Program (DTP) and CTEP within DCTD, as well as with intramural investigators in the Radiation Biology and Radiation Oncology Branches of CCR. The focus of MRT activities is to facilitate the development of radiation modifiers for tumor sensitization and to establish assays to better guide clinical trial designs in collaboration with DTP. The MRT staff are also members of NCI's Experimental Therapeutics (NExT) Program projects involving the development of radiosensitizers.

MRT staff coordinate and manage a series of clinical working groups in the areas of brain metastases, colorectal cancer, upper gastrointestinal tract cancer, glioblastoma, sarcoma, thoracic lung cancer, and radiation-immune system. Each working group is comprised of staff from RRP, DTP and



CTEP's Investigational Drug Branch, core investigators from CCR's Radiation Biology and Radiation Oncology Branches, extramural investigators, and industry collaborators. The working groups not only provide a forum for the discussion of pre-clinical and clinical gaps in prospective and active radiation-therapeutic agent combination trials, but also a network of investigators whose radiobiology laboratories are able to perform pre-clinical work in support of clinical trial concepts. Working group investigators undertake:

- 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, orthotopic mouse models, or genetically engineered mouse models
- Determining mechanisms of action of potential radiation modifiers using a variety of molecular and biochemical approaches for biomarker development

RRP GRANTS OVERVIEW

The 2016 RRP research portfolio comprised approximately 121 awarded grants distributed across several areas of radiation research (Figure 54).

The grant award mechanisms used by RRP and their distribution in terms of research support in 2016 are shown in Figure 55. The predominant mechanism is the individual research project grant (R01), followed by exploratory phase grants (R21).

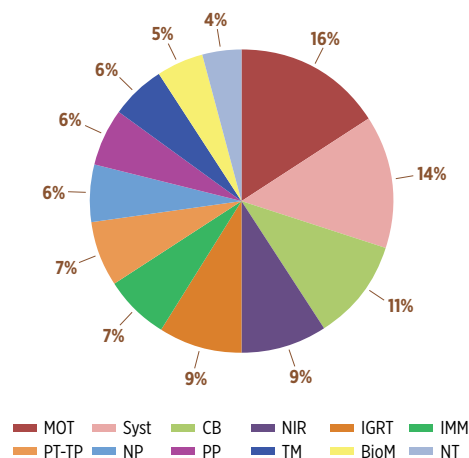


FIGURE 54: DISTRIBUTION OF RRP 2016 GRANTS BY RESEARCH AREAS.

The above graph depicts the distribution of FY16 grants based on the number funded in each of the categories. Molecular targeting of tumor signaling (MOT), Radioimmunotherapy/ systemic radiotherapy (Syst), Cancer Biology and responses to radiation (CB), Non-ionizing radiation (NIR), Therapeutic imaging (IGRT), Immune effects (IMM), Physics and technology (PT-TP), Nanoparticle interventions (NP), Particles and proton radiation (PP), Tumor microenvironment (TM), Biomarkers & predictive assays (BioM), Normal tissue (NT).

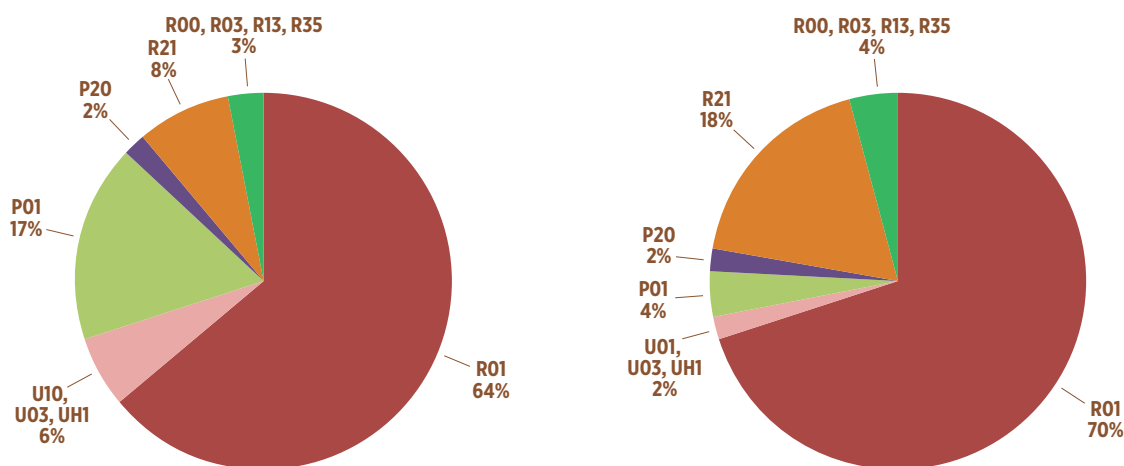


FIGURE 55: DISTRIBUTION OF RRP 2016 GRANT FUNDS (LEFT) AND NUMBERS OF GRANTS (RIGHT) BY MECHANISM.

ASSISTANCE TO THE CANCER RESEARCH COMMUNITY

IMAGING AND RADIATION ONCOLOGY CORE (IROC)

The Imaging and Radiation Oncology Core (IROC) provides integrated radiation oncology and diagnostic imaging quality control programs in support of the NCI's National Clinical Trials Network (NCTN), thereby assuring high quality data for clinical trials designed to improve the clinical outcomes for cancer patients worldwide. A major strength of IROC is the ongoing development of an IT infrastructure that fully integrates informatics and quality assurance (QA) services across six IROC QA Centers to enable the easy transmission of imaging and RT data sets for receipt, assessment, validation, and archiving using a common Web portal for all data entry and a common database of imaging and RT QA data. The NCTN Groups and associated investigators seamlessly share and access the data sets, which support trial outcomes analyses.

Previously funded grants were combined in the newly formed NCTN structure to form and provide support for the IROC infrastructure as follows:

IROC Houston QA Center

Located at the MD Anderson Cancer Center, this RT QA Center has experience interacting with approximately 1,800 national and international research sites through its remote and on-site dosimetry quality audits, extensive RT credentialing programs, QA of brachytherapy treatments, and proton clinical trial QA program. Additionally, the center has experience with the design, implementation, and analysis of QA anthropomorphic phantoms for credentialing and maintains the only QA database of radiation oncology sites participating in NCI-sponsored research.

IROC Ohio QA Center

This imaging QA Center is located at The Ohio State University (OSU) Wexner Medical Center and James Comprehensive Cancer Center. Its extensive experience in all aspects

of imaging in oncologic trials includes participation in the Imaging Response Assessment Teams, the Virtual Imaging Evaluation Workspace (VIEW) consortium, and the Oncology Biomarker Qualifying Initiative.

IROC Rhode Island QA Center

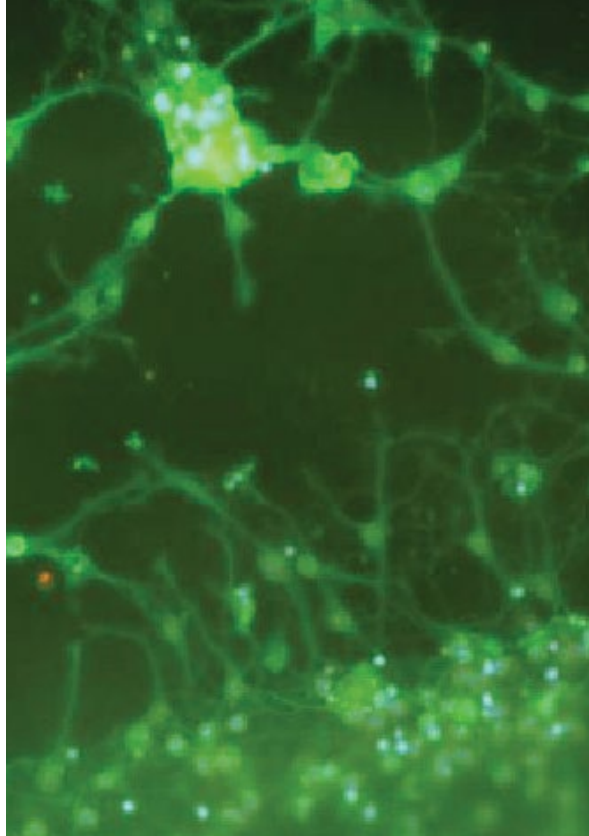
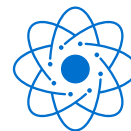
Located in Lincoln, RI and administered through the University of Massachusetts Medical School, this QA center has experience providing real-time, on-site, and remote review of imaging and RT objects (e.g., tumor, lymph nodes and normal tissue organs at risk specified in the study) to prevent research protocol deviations capable of invalidating trial results. It has developed a comprehensive, fully validated informatics infrastructure for acquisition, management, and review of imaging and RT objects. With approximately 3,000 new patients whose data are monitored each year, the IROC Rhode Island QA Center maintains more than 80,000 imaging datasets for 398 protocols from approximately 1,500 participating sites.

IROC Philadelphia (RT) QA Center

Located at the ACR Research Center in Philadelphia, this RT QA center has amassed extensive experience supporting a broad range of RT protocols involving advanced RT modalities, including 3D-conformal RT (CRT), intensity-modulated RT (IMRT), and IGRT. Key strengths of this QA Center include its ability to collaborate with physicists, dosimetrists, and radiation oncologists in developing protocols and credentialing techniques; conduct case reviews using a centralized remote review system; and develop and standardize credentialing for IMRT and lung stereotactic body RT (SBRT).

IROC Philadelphia (Imaging) QA Center

Also located at the ACR Research Center in Philadelphia, this QA Center provides imaging trial support for NCTN studies involving positron emission tomography (PET), magnetic resonance (MR), and computed tomography (CT), and most disease sites. Key strengths include its experience with the VIEW consortium, standardized image management processes, and QA and analysis approaches across the NCTN system.



IROC St. Louis QA Center

Located at Washington University, this RT QA Center has experience developing data exchange formats, data QA processes, and an informatics infrastructure for transmission, receipt, and analysis of imaging and treatment planning data from participating sites. More than 15,000 patient data sets for more than 80 US and international clinical trial protocols have been captured by the center. IROC St. Louis QA Center also has experience developing consensus contouring atlases and supporting secondary analyses.

RADIOBIOLOGY BIOTERRORISM RESEARCH AND TRAINING GROUP

The **Radiobiology Bioterrorism Research and Training Group (RABRAT)** is an informal working group of scientists in government agencies that are involved in all aspects of radiation research, including the Department of Energy (DoE), the normal tissue medical countermeasures development program of NIAID, radiation biology and biodosimetry of AFRRRI (DoD), space radiation and space radiation biology (NASA), BARDA, FDA, and others (see below) interested in radiation sciences and preparedness for radiation accidents and terrorism events. The purpose of RABRAT is to help keep the agencies informed of ongoing activities, to avoid both gaps and duplication of effort, develop synergy among programs, and to discuss training and educational opportunities. RABRAT meets three to four times per year.



WORKSHOP ON UTILIZING THE BIOLOGICAL CONSEQUENCES OF RADIATION THERAPY IN THE DEVELOPMENT OF NEW TREATMENT APPROACHES

RRP convened a workshop on the biological consequences of radiation therapy from September 11-12, 2017 at NCI. Called “Shades of Gy,” this one and a half-day workshop included thought-provoking presentations related to defining what is a biologically meaningful “radiation dose” in the tumor milieu, as well as broadening the concepts of how radiation is an integral part of precision medicine. The workshop’s long-term goal is to build from a combination of well-known reliable models, new cancer biology, and clinical experience to develop new paradigms for clinical cancer care.

In addition to staff from RRP and NCI’s Center for Cancer Research (Radiation Biology Branch and Radiation Oncology Branch), more than 50 U.S. and international workshop attendees from the federal government, large academic centers and hospitals, and industry participated in eight speaker and discussion sessions. The session topics included: Dose-effect models; Biophysics; Endpoints for Relative Biological Effectiveness; Biomarkers and response predictors; Clinician’s perspective on radiation dose; Exploiting biology; and Partial tumor volume radiotherapy. The following are highlights of the discussions:

1. Compelling tumoricidal dose effects beyond the conventional 2 Gy, as each radiation dose can potentially act “as a drug” with unique and exploitable mechanism of action. This pertains to molecular-target therapy and immunotherapy.

2. Utilizing biomarkers of radiation therapy in precision medicine to assess both efficacy and normal tissue damage.
3. Rethinking the target and extent of tumor volume irradiation for maximum curative benefit and avoiding normal tissue toxicity with preservation of organ function.

This workshop sparked discussion of transformational approaches in radiotherapy that will lead to a new era of radiation science and ultimately new approaches to cancer treatment.

FUTURE DIRECTIONS

The role of radiation oncology in the new era of “Precision Medicine” is both broad and critical to advances in cancer care and quality of survival. The ability of radiation to be aimed precisely and accurately greatly enhances our ability to specifically kill cancer cells and enhance immunotherapy. In addition, radiation oncologists and biologists repurpose molecular targeted therapies for use in combination with RT. This can potentially extend the use of a drug that has already undergone clinical development. Given the extent of patient data captured as part of routine RT treatment, working under appropriate safeguards, radiation oncology has robust data sets for patients receiving RT that could provide well curated information in the emerging era of “big data.” 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, RRP approaches its entire portfolio and that of its scientific colleagues as a complex interactive system. Advances in any one area can potentially have an impact on 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 conferences and workshops, program staff strive to lead the field into new areas of opportunity. The broad but highly interrelated fields are:

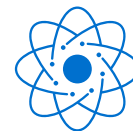
- Accelerator physics
- Basic molecular and cell biology
- Complex tumor biology
- Electronic databases to facilitate comparative effectiveness research and international collaboration

- Immunotherapy
- International collaboration for nuclear safety and terrorism response
- International oncology-based diplomacy
- Molecular imaging and image-guided therapy
- Molecularly targeted therapeutics with radiation
- Normal tissue radiation injury
- Outreach to the medically underserved through technology and mentoring
- Quality assurance for clinical trials
- Radiation biomarkers
- Radioprotectors and mitigators
- SRT

With a staff actively engaged in research planning and conduct through its MRT faculty, collaboration with CCR, NIAID, and ASPR’s BARDA, 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 (see below), new areas of SRT (see below) and immunotherapy (see below), and a means of bringing cancer advances to underserved populations worldwide (see above.)

Radiobiology Education Initiatives

Future progress in the 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. In collaboration with personnel in the Cancer Training Branch of NCI’s *Center for Cancer Training (CCT)*, and ASTRO, an effort is being made to enhance current training in the radiation sciences through the development of supplemental training courses that will incorporate radiobiology, radiation physics, and translational and experimental methodology. The aim is to provide enhanced training in the radiation sciences at a



national level. Support in preparing applications for training programs geared to radiation training is provided on request to extramural investigators. In addition, RRP staff participate in the educational initiatives of national societies and international groups, such as the European Society for Therapeutic Radiology and Oncology (ESTRO). A successful R25E training program at Wayne State University (Detroit, MI) has evolved out of these efforts.

Radiation and Immunotherapy

Radiation oncology is gaining importance in the field of cancer immunotherapy as radiation is used as a component of the vaccine process by causing robust presentation of antigens, including neo-antigens, and hence, augmenting the effects of immunotherapy. This cross-discipline interaction requires (a) mutual in-depth understanding of the disciplines of radiation biology and cancer immunotherapy; and (b) partnership in terms of exchange of resources/materials for pre-clinical and clinical studies. One of RRP's missions is to expand opportunities to expose cancer immunotherapists to the science of radiation oncology/biology. By better understanding the underlying basic science of radiation and immunology, areas of collaboration can be established to develop strategic initiatives that help translate into successful combined modality trials. RRP's MRT staff works with others in DCTD and extramural investigators to establish the Radiation and Immune Modulation Working Group to develop sound multi-center clinical concepts. RRP is currently highlighting the following critical issues that need to be addressed when combining radiation plus immunotherapy: (a) immune-modulation of tumor microenvironment and tumor cells by radiation; (b) effective combinations of radiation and immunotherapy; and (c) biomarkers of opportune immunogenicity after radiation-immunotherapy combinations.

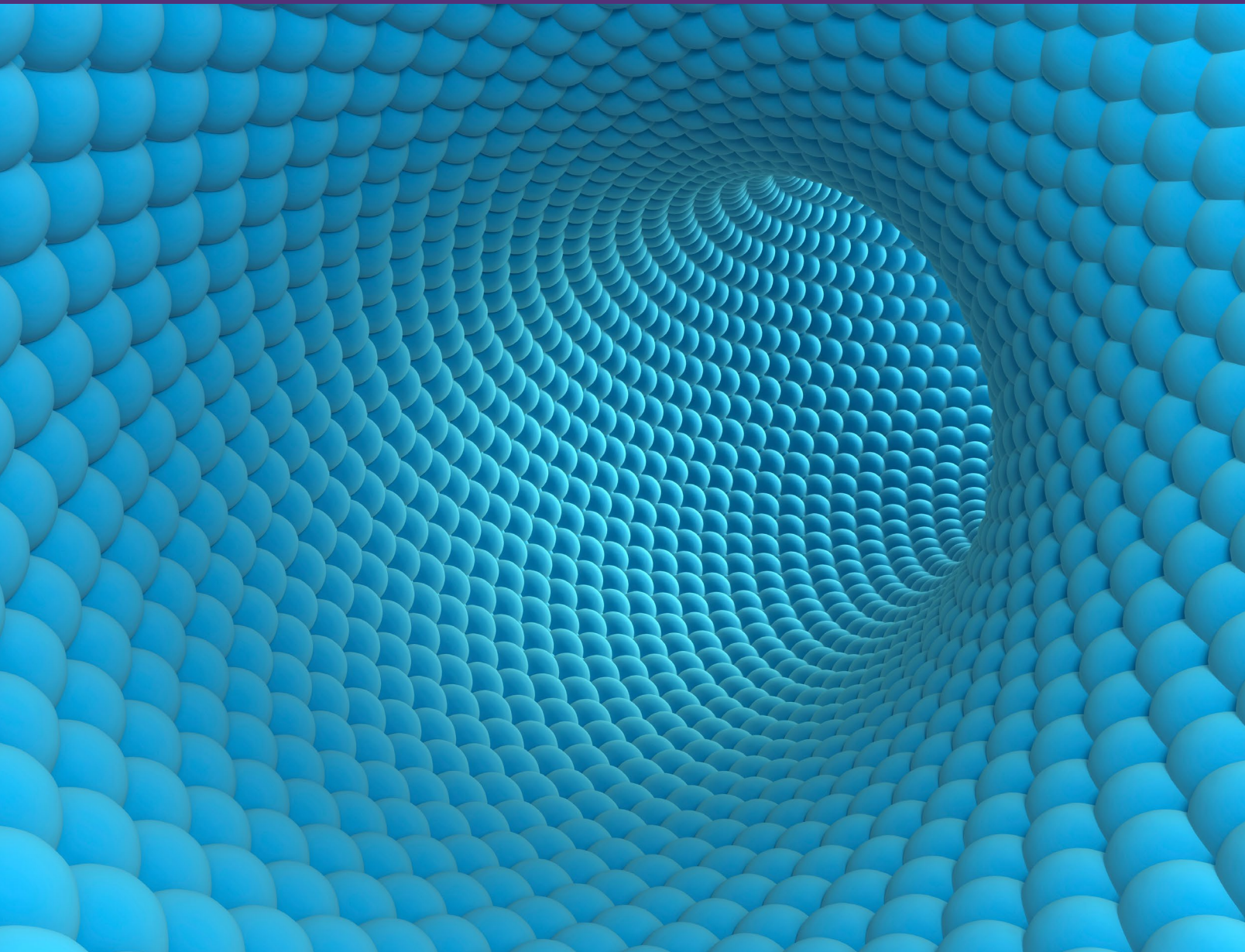
Systemic Radionuclide Therapy

Systemic Radionuclide Therapy (SRT) enables personalized cancer treatment by combining the therapeutic effect of RT with the targeting capability of molecularly targeted agents, such as antibodies used for biologically targeted therapy or immunotherapy. In SRT, a radioactive isotope is attached to an agent that selectively binds to malignant tumor cells, thereby concentrating the radioactively labeled agent at the tumor site and delivering a cumulatively cytotoxic dose to the tumor cells, while normal tissue receives only a minimal diluted dose. This selectivity minimizes toxicity to normal tissues, can increase therapeutic efficacy (therapeutic index), and can reduce overall treatment costs.

Currently available SRT compounds, such as yttrium-90 ibritumomab tiuxetan (linked radioactive chemical, Yttrium-90), iodine I-131 tositumomab (linked to the radioactive isotope iodine-131), and radium-223 dichloride have been developed and approved in the United States for use in the treatment of non-Hodgkin's lymphoma (NHL). Large multicenter trials to study long-term survival are currently underway, but early results indicate that this class of treatments shows tremendous clinical promise. Development of next-generation technologies for cancers other than NHL is crucial, including solid tumors where the clinical need is most acute. To this end, RRP in collaboration with the SNMMI, organized two workshops on the current status and future directions of SRT and initiated a SRT-related request for proposals that was issued by NCI's SBIR Program. As a result, SNMMI established a **Therapy Center of Excellence**, the function of which is to enhance professional networking and education, and SBIR awarded 14 contracts to small companies to stimulate research, development, and commercialization of innovative SRT techniques that could potentially shorten treatment cycles and reduce toxicity to normal tissues.

PROGRAMS AND INITIATIVES (2013-2017)

TRANSLATIONAL RESEARCH PROGRAM





OVERVIEW

The Translational Research Program (TRP) is committed to reducing cancer incidence and mortality and improving survival and quality of life for cancer patients. 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 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
- 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

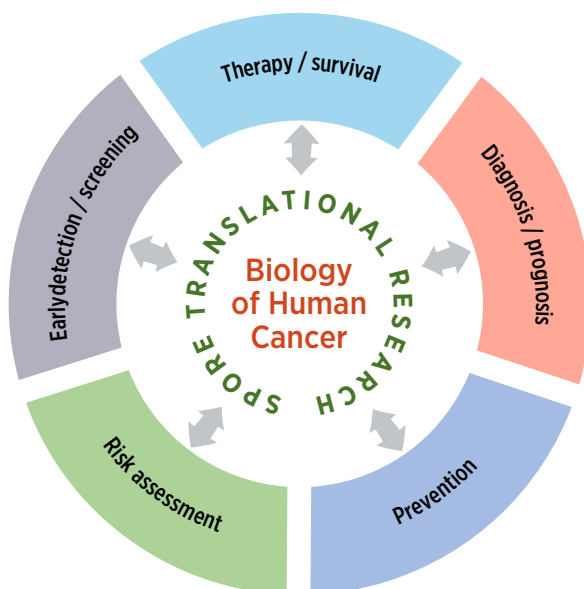


FIGURE 56: TRP FOSTERS A MULTIDIRECTIONAL APPROACH TO TRANSLATIONAL RESEARCH BY COORDINATING INTERDISCIPLINARY INVESTIGATIONS THAT ARE BASED ON THE BIOLOGY OF HUMAN CANCER.

In addition to SPOREs, TRP also manages grants that are part of special initiatives, such as the Provocative Questions Initiative when those grants are translational and are connected to the themes of currently funded SPOREs; the Recalcitrant Cancer Act initiatives; and R50 Research Specialist Career Awards where the applicant is integral to the work of a funded SPORE.

TRP 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 or populations at risk for cancer. TRP's mission is accomplished 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. To that end, TRP engages in the following activities and initiatives:

- Planning, advising, coordinating, evaluating, and supporting the SPOREs, which use the P50/U54 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, other government organizations, and outside organizations to increase cross-fertilization of ideas, leverage resources, reduce duplication, and ensure access of resources to projects and investigators
- Maintaining the Developmental Research Program and the Career Enhancement 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 rare cancers
- Collaborating with the advocacy community who supports translational science in cancer

TOBY T. HECHT

ASSOCIATE DIRECTOR



Toby T. Hecht earned a PhD 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 conducted her postdoctoral research at Yale University in genetics and lymphocyte development before coming to 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 more than 37 years at NIH, 28 of which were spent at 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, now known as the NCI Experimental Therapeutics (NEXT) program. In 2008, Dr. Hecht was chosen to oversee the SPORE program and was made the permanent Associate Director of TRP in 2011. In 2016, she was also selected for the position of Deputy Director of DCTD.

TRP GRANTS OVERVIEW

TRP currently uses the P50 (and the U54) funding mechanism for the SPORE program. In 2016 there were 54 funded SPOREs, covering 18 organ sites and systems and including one signaling pathway-focused grant. Fifty-two of the grants used the P50 mechanism, and the remaining two were funded through a U54.

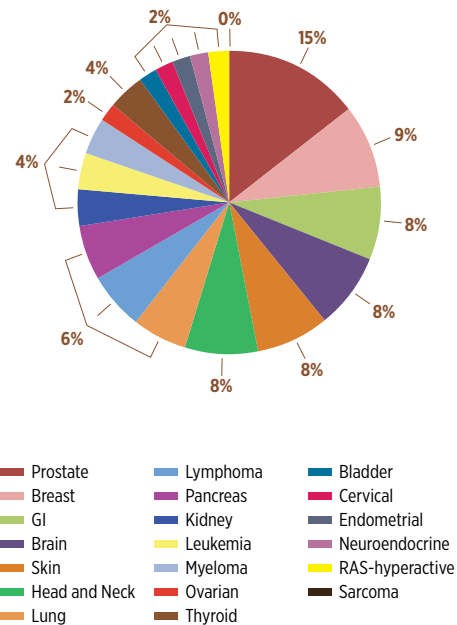


FIGURE 57: DISTRIBUTION OF TRP 2016 SPORE GRANTS ACROSS ORGAN SITES/PATHWAYS.

The 2017 fiscal year TRP research portfolio included 50 funded SPORE grants. In addition, TRP staff currently oversee a relatively smaller number of R21, R01, and R50 translational research grants.



	2013	2014	2015	2016	2017
Breast	5	6	5	5	4
Prostate	7 [#]	6	7	8	9
Lung	3 [#]	3	4	3	3
Gastrointestinal	5	5	4	5 [#]	2
Ovarian	5	3 [*]	4 [#]	2	3
Bladder	1	1	1	1	0
Skin	4	5	4	4	3
Brain	5	5	5	4	5
H&N/Thyroid	4 [*]	4	4	5	4
Lymphoma	3	3	3	3	3
Endometrial	1	1	0	1	1
Cervical	1	1	1	1	1
Kidney	1	0	1	2	2
Leukemia	3	2	2	2	3
Myeloma	2	2	2	2	2
Pancreatic	2 [*]	3	2	3	3
Sarcoma	2	2	1	1	0
Neuroendocrine	0	0	1	1	1
Pediatrics/RAS	0	0	1	1	1
Total SPOREs	56	52	52	54	50

**TABLE 14: DISTRIBUTION OF SPORE GRANTS ACROSS ORGAN SITES/
PATHWAYS IS SHOWN BY YEAR**

Groups of grants containing one (*) or two (#) grants on interim funding are indicated. From 2013-2015 one H&N SPORE was funded by NIDCR; in 2016, three grants were partially funded by NIDCR.

ORGANIZED SPORE WORKSHOPS

BRAIN SPORE WORKSHOPS (2013-2017)

Members of the Brain SPORE teams hosted yearly workshops at their institutions (2013 – Birmingham, University of Alabama, Birmingham; 2014 - San Francisco, University of California, San Francisco (UCSF); 2015 - Houston, MD Anderson Cancer Center (MDACC); 2016 - Boston, Dana-Farber Cancer Institute/Harvard Cancer Center (DFCI/HCC); 2017 – Durham, Duke University). The workshops provided an informal collaborative forum for sharing current data with all Brain SPORE members and the planning of future projects. Collaborations on SPORE projects have originated and been cultivated at the workshops, such as a decade long population study between UCSF and the Mayo Clinic, which has provided new genetic and molecular insights in the classification of gliomas. Another example is the collaboration between DFCI/HCC and MDACC on a SPORE project studying PI3K inhibitors for glioma treatment. Individual project updates were presented, as were representative examples from career enhancement or developmental projects. These workshops provided sufficient time for in depth discussions and included representatives from patient advocacy groups. Another outcome from these workshops was a plan in 2015 for the establishment of an Inter-SPORE Immune Monitoring Consortium aimed at the standardization of protocols for preparing, shipping, and analyzing specimens between SPOREs collaborating on clinical immunotherapy trials.

GASTROINTESTINAL (GI) AND PANCREAS WORKSHOPS (2013-2017)

Two SPORE workshops were held at the NCI Shady Grove campus in Rockville, MD in the areas of GI and pancreas cancer since 2013. In March 2014, a GI and Pancreas cancer SPORE workshop was organized by TRP program staff and Dr. Robert Coffey (Vanderbilt University GI SPORE Principal Investigator (PI)). The following workshop held in July 2015 was organized by TRP staff and Dr. Scott Kern (Johns Hopkins University GI SPORE PI). In October 2017, a third meeting was held in Nashville with coordination between staff and the Vanderbilt University GI SPORE. These workshops started with a session that allowed each SPORE PI to present a general summary of the activities in each of the components of their SPORE. Subsequent sessions were

organized around specific scientific topics of relevance to all or most of the GI/pancreas SPOREs, including:

- genomics/proteomics
- microbiome
- imaging
- cancer detection
- drug discovery
- new therapies

In addition, each workshop included a session on progress in Career Enhancement Program (CEP) and Developmental Research Program (DRP) projects, as well as a session on NCI initiatives. After the final presentation of each session, the session speakers led a discussion to engage all the workshop participants. The SPORE PI-led breakout sessions and opportunities for informal interactions among workshop participants were crucial to discussions related to issues arising in the SPOREs. As an example, one of the break-out groups focused specifically on patient/research advocacy issues.

SKIN SPORE WORKSHOPS (2013-2017)

Skin SPORE teams also alternated hosting the SPORE workshops (2013 – Houston, MD Anderson Cancer Center; 2014 – Tampa, Moffitt Cancer Center; 2015 – Philadelphia, Wistar Institute/University of Pennsylvania; 2016 – Pittsburgh, University of Pittsburgh; 2017 – New Haven, Yale University). The Skin SPORE workshops included presentations of the latest data from individual SPOREs, and covered a wide range of topics such as:

- Molecular Anti-tumor Signaling Inhibitors and Precision Medicine for Melanoma
- Biomarkers in Melanoma Theory
- Patient-derived xenograft (PDX) Models as Potential for Shared Research in Melanoma
- Challenges to Current Immunotherapy: Resistance to anti-PD1-Mechanisms of Resistance
- Sharing Data Handling, Databases, and Datasets Toward Collaborative Inter-SPORE Research

Breakout meetings were convened on prevention strategies, biostatistics, tissue acquisition and sharing, or Inter-SPORE Clinical Trials Collaboration (Rare Disease, Combinations,

Personalized Medicine). The workshops have been the impetus for developing inter-institutional Materials Transfer Agreement (MTA) to allow more seamless interchange of data, human biospecimens, and experimental PDXs. While each institution signs the MTA agreement with NCI as the umbrella organization, individual documents are specifically generated for each product shipped or shared between SPORE organizations.

LUNG CANCER SPORE WORKSHOPS (2013-2017)

From 2013 – 2016 the Lung Cancer SPORE workshops were held in Rockville or Bethesda, MD. The workshop in 2013 was adjacent to the first NCI Workshop on setting priorities in small cell lung cancer (SCLC) research that was organized by the NCI under the leadership of Drs. Harold Varmus and James Doroshow, and chaired by SPORE investigators Drs. John Minna and Charles Rudin. Many lung cancer SPORE investigators actively participated in the SCLC meeting and contributed to a report titled “[Scientific Framework for SCLC](#)” that laid the foundation for three SCLC-focused Program Announcements in 2015. The 2017 workshop was hosted by the Yale University Lung Cancer SPORE in New Haven, CT.

Highlights from the 2013 Workshop:

- Discovery of oncogenic ARAF mutations in lung adenocarcinoma associated with dramatic sorafenib responses
- An integrated analysis of Axl and other mesenchymal targets using data from in The Cancer Genome Atlas
- Epigenetic priming of non-small cell lung cancer (NSCLC) to anti-PD-1 checkpoint inhibitor therapy

Highlights from the 2014 Workshop:

- Phenotypic heterogeneity in SCLC and its implications for treatment
- The concept of afatinib plus cetuximab in tyrosine kinase inhibitor-naive EGFR mutant lung cancer
- EGFR as an early adaptive mechanism of resistance in gene fusion-positive lung cancer
- Predictive biomarkers of response to PDL1 checkpoint inhibition
- Gene connectivity and expression variance in lung cancer, and molecular and clinical features of patients with advanced lung adenocarcinoma from the Lung Cancer Mutation Consortium



Highlights from the 2015 Workshop:

- EGFR kinase domain duplication (EGFR-KDD) - a novel oncogenic driver in lung cancer
- Inhibition or genetic ablation of Focal Adhesion Kinase (FAK) radiosensitizes KRAS lung cancer
- Perspectives on immunotherapy of lung cancer
- Targeting glutamine dependence as a novel therapeutic strategy in NSCLC
- Micropore selection isolates from lung epithelial cells with altered biophysical and metastatic properties
- An mRNA expression signature for classification and grading of NSCLC

Highlights from the 2016 Workshop:

- Report of novel mutations in the receptor tyrosine kinases/Ras/Raf pathway with implications for targeted therapy of lung adenocarcinoma and whole-genome sequence alterations in non-coding regions
- Association of LKB1 loss alone with an inert immune phenotype in adenocarcinomas by comprehensive immunoprofiling
- SCLC cell line screen of drugs and investigational agents with gene and microRNA expression in collaboration with NCI



PROSTATE AND GENITOURINARY (GU) SPORE WORKSHOPS (2013-2014)

In 2013 and 2014 the SPORE investigators conducted workshops in conjunction with the Annual Meetings of the Society of Urologic Oncology (SUO). In 2013, the NCI SPORE SUO Workshop, titled “Bio Marker of Prostate Cancer Aggressiveness,” provided the urologic community with a comprehensive and critical overview of newly discovered and commercially developed markers of prostate cancer aggressiveness. In 2014, the SUO Meeting featured the Bladder SPORE Program and the Kidney SPORE Program, which updated the urologic oncology community on translational research in these GU cancers.

TRP organized the NCI Prostate Cancer Provocative Questions Workshop, held on November 13, 2014. Participants, which included scientific leaders from each of the prostate cancer SPOREs, were experts from across the broad scientific community. This workshop resulted in the inclusion of a new provocative question for the Provocative Question solicitation: PQ – 4, “Why do some closely related tissues exhibit dramatically different cancer incidence?”

In 2014 and 2016, through R13 and U13 funding, NCI/DCTD sponsored the Urological Oncology Research Symposia at the Annual Meeting of the American Urological Association. Prostate and GU SPORE investigators, as well as TRP staff, played key roles in organizing the agenda and actively participate in these symposia.

LEUKEMIA INTER-SPORE MEETING (2014)

A Leukemia Inter-SPORE meeting was held September 8-9, 2014 in St. Louis. The participating leukemia SPORE investigators were from Washington University, St. Louis and MDACC. Each SPORE provided research updates on all of their SPORE projects, including unpublished results. Discussions, resulted in a number of new interactions and collaborations, including agreements to collaborate on joint clinical trials and biomarker trials. Moreover, each SPORE agreed to broadcast a call for Career Enhancement Programs (CEP) applications at Washington University, St. Louis and MDACC in order to broaden mentoring opportunities for CEP applicants and facilitate other collaborations.

HEAD AND NECK CANCER SPORE WORKSHOP (2014)

This workshop was held at the NCI Shady Grove campus in Rockville, MD, and it was hosted by Drs. Thomas Carey from the University of Michigan and Robert Ferris from the University of Pittsburgh. Four sessions of the meeting were focused on novel therapies; human epidermal growth factor receptor 2 (HER) family signaling and targeting, human papillomavirus (HPV), cancer biology, and new targets. Within novel therapies, hyaluronan-cisplatin conjugates, bifunctional anti-EGFR and transforming growth factor-beta (TGF- β) antibodies, iron-oxide-Pc4 nanoparticles, and cetuximab-activated natural killer and dendritic cells were discussed. The HER session covered other pathways such as PI3K, B-Raf/MEK/ERK, EGFR, ROS, and SIRT-1. Four presentations were devoted to HPV-associated cancer, including the unique study of high risk HPV, biomarkers, and outcomes in matched cohorts of head and neck cancer patients positive and negative for human immunodeficiency virus (HIV). Presentations in the last session included an integrative genomic characterization of oral squamous cell carcinoma that identified frequent somatic drivers of this cancer, and lysyl oxidase like-2 as a potential therapeutic target in oral neoplastic diseases.

HEMATOLOGIC MALIGNANCIES SPORE WORKSHOP (2015)

This workshop was held on March 9-10, 2015 at the NCI Shady Grove facility in Rockville, MD. There were approximately 100 participants, including investigators from the Hematologic Malignancies SPOREs, investigators supported

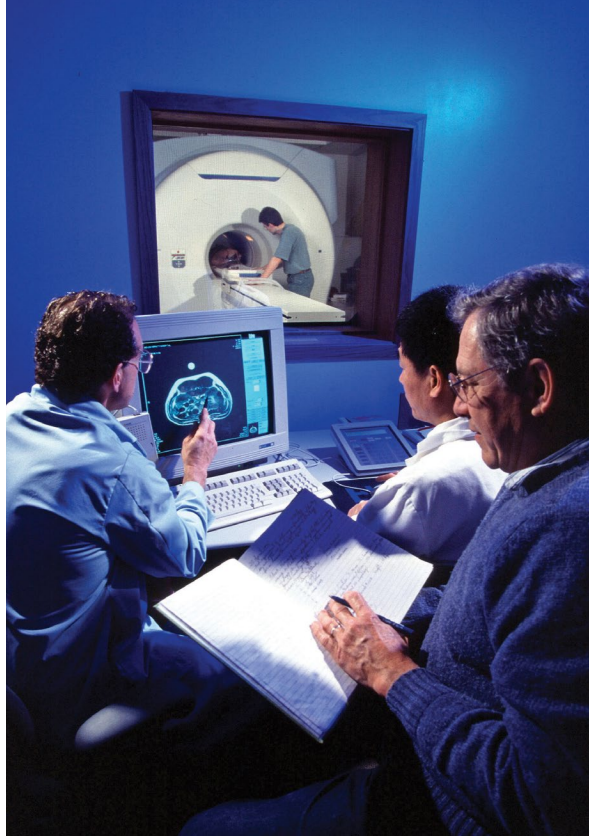
by P01 awards in hematological malignancies, NCI extramural staff, and NCI intramural investigators. The agenda focused on presentations in the general areas of myeloma, lymphoma, and leukemia; however, the sessions overlapped these disease boundaries. Dr. Louis Staudt, NCI, provided the keynote presentation. In addition to the oral presentations, a poster session allowed the participants to interact informally and discuss potential collaborations.

TRANSLATIONAL RESEARCH IN OVARIAN AND GYNECOLOGIC CANCERS WORKSHOP (2016)

On May 4, 2016, members of the translational ovarian and gynecologic (GYN) cancer research communities participated in a **workshop** organized by TRP at the NCI Shady Grove campus in Rockville, MD. The diverse group of 90 attendees included NCI staff, NCI-supported investigators with ovarian, cervical, and endometrial cancer expertise, and patient advocates. The presentations and discussions concentrated on defining obstacles to success in the immunotherapy approach for treating ovarian and GYN cancers, identifying crucial resources to overcome these obstacles, and suggesting ways in which NCI can facilitate progress in this area. Four meeting sessions, totaling 19 presentations, were devoted to the following critical areas of ovarian and GYN cancer translational research: immunotherapy, highlights in ovarian and GYN cancer, PARP Inhibitor-based therapy, early detection in ovarian cancer. The workshop provided a venue to identify new synergies and collaborative opportunities between SPOREs and promoted their interaction with other programs and networks supported by the NCI.

TRANSLATIONAL SCIENCE IN PROSTATE CANCER WORKSHOP (2016)

Members of the prostate cancer translational research community participated in a **workshop** from April 4-5, 2016 at the NCI Shady Grove campus in Rockville, MD. The goal of the workshop was to develop feasible metric- and endpoint-driven studies that will have an impact on the prevention and/or treatment of prostate cancer. The workshop was planned collaboratively by TRP staff and prostate cancer SPORE investigators. Additional workshop attendees and speakers were members of the broad research community, including representatives from the Department of Defense, the Prostate Cancer Foundation, the American Urological Association, the Food and Drug Administration, and the Department of Veterans Affairs. The workshop consisted



of a series of short presentations describing current studies related to the following crucial areas in translational prostate cancer research:

- early detection and active surveillance
- high-risk localized and hormone sensitive metastatic disease
- castration resistant metastatic prostate cancer

Extensive deliberation by the working groups on both days of the workshop resulted in the development of blueprints for specific clinical studies.

HEAD AND NECK/THYROID CANCER SPORE WORKSHOP (2017)

Translational researchers with expertise in head and neck/thyroid cancer and stakeholders from the NCI assembled at the NCI to exchange ideas in this field of research. In collaboration with members of TRP's staff, including Program Director Leah Hubbard, PhD, the following three workshop co-chairs planned the meeting: Robert L. Ferris, MD, PhD, University of Pittsburgh, Jennifer Rubin Grandis, MD, University of California, San Francisco, and Matthew D. Ringel, MD, The Ohio State University.

The **workshop** was divided into the following sessions: Chemoprevention/Premalignancy/Risk Management/Screening; Novel Tumor Targets/Cell Signaling/Cell Autonomous Targets; Treatment Resistance; SPORE HIV Consortium; Translation Models; Immunotherapy/Tumor Microenvironment; and Human Papilloma Virus.

Robust discussions during each session identified several opportunities for future collaboration among SPORE research teams, applicants, and NCI cooperative group members. Some identified future goals included collaboration among Head & Neck and Cervical SPOREs in the area of HPV-related cancer and HIV-infected patients; combination of novel therapeutic HPV vaccine strategies with current head and neck cancer therapies; and standardization of methods used to characterize, maintain, and share head and neck cancer models across SPORE sites, such as cell lines and patient-derived xenografts.

FUTURE DIRECTIONS

Following are descriptions of TRP initiatives planned for future years:

- Encourage research that will enable precision medicine approaches, such as genomic and proteomic-based diagnostic technologies, that will allow cancer patients with specific molecular alterations to receive the most effective treatments
- 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 recalcitrant cancers (not represented above) where additional translational research is warranted
- Advance studies on the dynamic relationship between tumors and cells/mediators in the microenvironment to translational science to make a difference in the diagnosis and treatment of cancer, particularly in the area of immunotherapy
- 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

PROGRAMS AND INITIATIVES (2013-2017)

OFFICE OF CANCER COMPLEMENTARY AND ALTERNATIVE MEDICINE



OVERVIEW

The Office of Cancer Complementary and Alternative Medicine (OCCAM) was initially established within the NCI Office of the Director in 1998 to increase NCI's capacity to attract and manage high quality research on complementary and alternative medicine (CAM) in cancer and improve messaging, accuracy, and usefulness of information products addressing these topics.

OCCAM's work is accomplished by four different organizational components:

- Research Development and Support Program – Solicits and manages a grant portfolio predominantly involving research on CAM and cancer treatment.
- Case Review and Intramural Science Program – Gathers and evaluates information about unconventional cancer therapies to propose next steps and facilitate decisions about therapies warranting NCI-initiated research.

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 treatment

Integrative medicine: An approach that combines treatments from conventional medicine and CAM for which there is some high-quality evidence of safety and effectiveness

- International Research Program – Establishes research collaborations with foreign research organizations predominantly in the areas of natural product and traditional medical product evaluation.
- Office of the Director – Supports the other programs, provides topic area expertise for internal and external contacts, manages communication and education activities

The office was created to provide expertise in CAM for the NCI. In 2007, the NCI director moved OCCAM into DCTD, where it promotes and supports 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. The office also manages a portfolio of grants and other projects evaluating CAM approaches for cancer treatment.

OCCAM identified three research areas with potential for therapeutic advances. Designed to mesh with DCTD goals, these areas focus on:

1. Identifying novel therapeutics in the pharmacopeia of traditional medical systems as defined by the World Health Organization
2. Using complementary approaches to improve the therapeutic ratio of standard and investigational anticancer therapies
3. 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)

MISSION

The mission of OCCAM is to improve the quality of care for cancer patients, 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 and by improving the availability of high-quality information for the health care community, researchers, and the general public.

JEFFREY D. WHITE

DIRECTOR



Jeffrey D. White, MD, graduated from Cornell University with a BS degree in Applied and Engineering Physics in 1979 and received an MD 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, DC.

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.

OCCAM GRANTS OVERVIEW

OCCAM is responsible for overseeing, directing, managing, and evaluating a portfolio of preclinical and clinical cancer treatment research grants, cooperative agreements, and contracts related to the use of various dietary and natural product interventions, mostly in combination with conventional cancer therapies. OCCAM contributes to the coordination of CAM activities across NCI divisions and analyzes NCI's CAM expenditures and research portfolio.

The grant award mechanisms used by OCCAM and their distribution in terms of research support in 2016 are shown in Figure 59. The predominant mechanism is the exploratory phase grants (R21), followed equally by the individual research project grant (R01) and conference grant (R13).

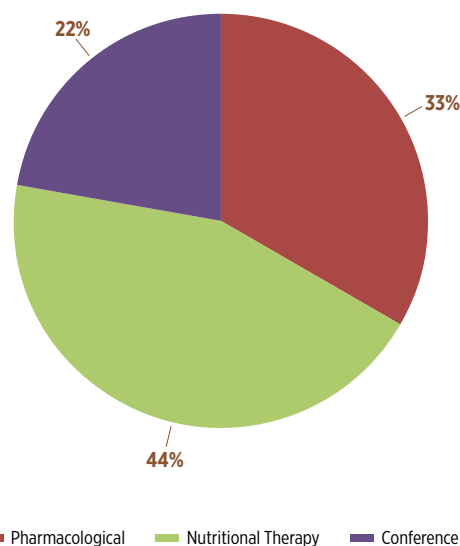


FIGURE 58: PERCENT DISTRIBUTION OF OCCAM FY16 GRANTS BY RESEARCH AREA.

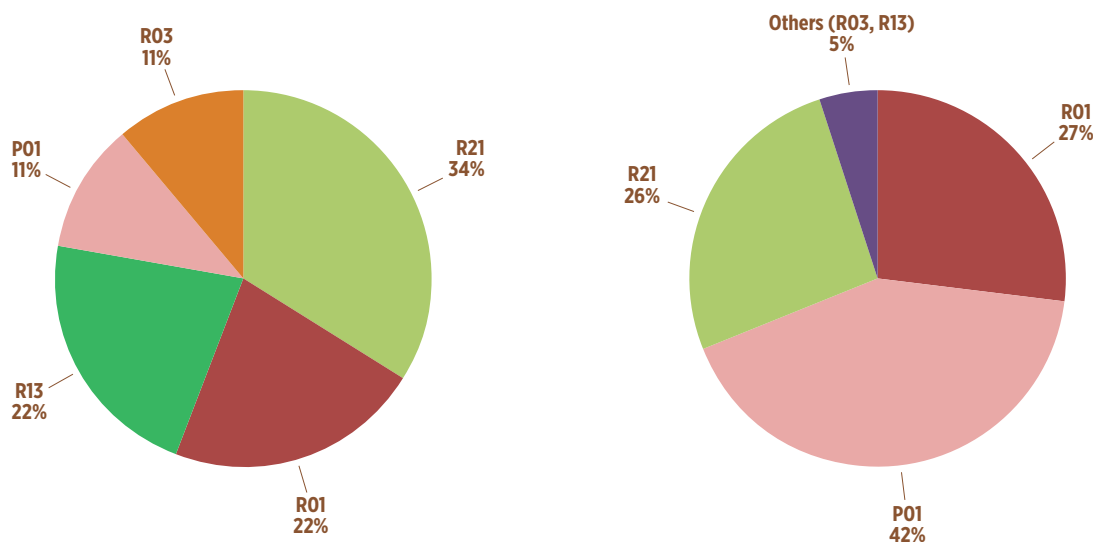


FIGURE 59: DISTRIBUTION OF 2016 GRANT NUMBERS (LEFT) AND FUNDING (RIGHT) BY MECHANISM.

ASSISTANCE TO THE SCIENTIFIC COMMUNITY

HERBAL MIXTURE PROGRAM PROJECT GRANT

NCI's first program project grant (P01) of an herbal mixture (1P01CA154295-01A1), "Chinese Herbal Medicine as a Novel Paradigm for Cancer Chemotherapy," is being led by Principal Investigator Yung-chi (Tommy) Cheng, PhD, of Yale University. In fiscal year 2011, NCI, along with the National Center for Complementary and Alternative Medicine (now the National Center for Complementary and Integrative Health) and the NIH Office of the Director, funded a grant to investigate the effectiveness of PHY906 as a modulator of the chemotherapy drug irinotecan in the treatment of patients with metastatic colorectal cancer. PHY906 is an extract of four herbs based on a formula of traditional Chinese medicine (TCM) known as Huang Qin Tang (HQT). HQT is used as a treatment for gastrointestinal ailments, including diarrhea, nausea, and vomiting. Animal research demonstrated that PHY906 improved the gastrointestinal side effects of irinotecan while simultaneously increasing the drug's anticancer activity.

NCI BEST CASE SERIES PROGRAM

The NCI Best Case Series Program is the only program in the world advertised as willing and interested to review the case records of patients treated with unconventional cancer therapies. The program is administered as a research protocol with approvals from the NCI Special Studies Institutional Review Board and the NIH Clinical Center. The primary objective of the program is to identify unconventional approaches to the treatment of cancer that may warrant NCI-initiated research. Since inception of the protocol, 185 cases have been submitted for review, of which 51 cases have met the eligibility criteria. In 2015, one case series met all eligibility criteria, received favorable reviews from the protocol investigators as well as external reviewers, and was presented to DCTD Leadership for further research recommendations.

PATIENT EDUCATION RESOURCE

In early 2013, OCCAM published an open access online patient education resource, "Talking about Complementary and Alternative Medicine with Health Care Providers: A Workbook and Tips," which has an average of 250 visitors each month. The workbook was created to help patients and their health care providers have meaningful discussions about the use of CAM during and after cancer care.

CONFERENCES

Workshop on Circadian Rhythm and Chronomedicine for Cancer and Other Diseases in the Era of Precision Medicine

This recent 2-day **workshop** from September 27-28, 2017 was led by OCCAM and planned with input from the workshop planning committee. This comprehensive, trans-NIH workshop was also co-funded by NCI's Division of Cancer Prevention, the National Institute of General Medical Sciences, the National Heart, Lung, and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute of Allergy and Infectious Diseases.

Approximately 50 attendees from NIH, academia, and cancer centers participated, with the following diverse expertise: circadian rhythms, circadian clock, sleep research, chronotherapy, cancer therapeutics research, radiation therapy, population and behavior science, cancer biology, molecular biology, computation and mathematical modeling, nutrition, metabolism, obesity and diabetes, the microbiome, the immune system and inflammation, neuroscience, aging and dementia, stem cells, pediatrics, biomarkers, and clinical trials.

The goals were to (1) assess the status of circadian rhythm and sleep research in cancer research, other diseases, and chronotherapy, from basic biology to population, translational, and clinical research, (2) discuss the scientific gaps, needs, and opportunities, (3) provide input to NCI/NIH regarding future initiatives and priority research areas, and (4) to ultimately improve our fundamental understanding of human circadian clock biology and improve translational application in public health, disease diagnosis, prevention, treatment, and health disparities across the lifespan. A white paper is in preparation.

Conference on Microbial-based Cancer Therapy

The first NIH-sponsored, comprehensive **meeting on microbial-based cancer therapy** occurred on July 11-12, 2017. A trans-NCI working group consisting of staff from DCTD, the Division of Cancer Biology, the Division of Cancer Prevention, and the NCI Small Business Innovation Research program planned and supported this important meeting. The

goals of this multidisciplinary conference were to provide a forum for the nearly 300 participants from academia, industry, and the federal government to learn about the recent scientific advances in tumor biology, microbial pathogenesis, cancer immunity, and molecular tools and to develop new scientific collaborations, interactions, and research programs centered around this topic.

The agenda included 19 speakers in sessions on the biology of microbe-tumor interactions, virus- and bacteria-based therapies, translational aspects of microbial-based therapies, and a poster session. Opportunities for microbial-based therapy where conventional therapy is inadequate were highlighted, such as tumor cell dormancy, tumor cells that are not well affected by drugs, hypoxia, or poorly vascularized tumors. In addition, speakers described the complex nature of the microbe-tumor interaction and discussed recent advances in the field.

Future research could involve studying the unique potential of viruses and bacteria to invade, damage, or destroy human cells and induce immune responses to create new, safe, and effective therapeutic approaches. Post-meeting activities include preparation of a white paper by a Working Group, and a possible journal special issue aimed to highlight the clinical potential of microbial-based cancer therapy.

Acupuncture for Cancer Symptom Management

This **conference** was held in the Natcher Conference Center on the NIH Campus from June 16 – 17, 2016. OCCAM staff organized and co-chaired this meeting with invited expert speakers from various academic centers, including Harvard Medical School, Memorial Sloan Kettering Cancer Center, MD Anderson Cancer Center, Moffitt Cancer Center, and University of Zurich. The conference objectives were to:

1. Determine the current evidence of acupuncture in the management of cancer patients, by specifically addressing mechanism of action
2. Determine the specific symptom(s) with the best evidence of response to acupuncture treatment
3. Determine the feasibility of the use of acupuncture in the management of cancer patients, assessing issues such as physician training, reimbursement, disparities, and cost-effectiveness



The conference assessed the current state of the science of acupuncture for cancer symptom management, determined the current gaps in research, and discussed ways to move research forward on a strong scientific foundation. A product of the conference was a [white paper](#) published in a special monograph of *The Journal of the National Cancer Institute (JNCI)*.

The State of the Science: Cancer Complementary and Alternative Medicine Therapeutics Research

On May 25-26, 2016, researchers with expertise in cancer therapeutics research, bioinformatics, computation modeling and databases, clinical trial design, and CAM convened at NIH to discuss the current [state of the science](#). The diverse group of about 70 attendees included individuals from NIH, FDA, academia, cancer centers, and integrative medicine programs. Representatives from the National Natural Science Foundation of China (NSFC) and Chinese medicine (CM) physician scientists from China also participated in the meeting.

The goals of the meeting were to:

- Assess the current status of evidence-based cancer CAM therapeutics research

- Discuss the scientific gaps, needs, and future opportunities of cancer CAM therapeutics research in the era of precision medicine
- Explore solutions for challenges preventing progress in the field
- Provide suggestions to NCI regarding future initiatives and priority areas

This workshop provided a venue to identify new collaborative opportunities among a diverse, international research community. As a result, Beijing University of Chinese Medicine, one of the earliest established traditional Chinese medical universities in China, NSFC, and OCCAM are currently defining several priority areas for collaboration with NCI. A [workshop summary](#) report was published and serves as a guide to future research and provides suggestions regarding future initiatives and priority areas.

Evidence-based Traditional Medicine and Healthcare System in India

This NCI-sponsored Mini Symposium on March 3, 2016 was organized in collaboration with scientists and Ayurveda practitioners on Indian Traditional Medicine from Savitribai Phule Pune University, India (Dr. Bhushan Patwardhan),

George Mason University, VA (Dr. Avinash Patwardhan), and AIM Swasthya, CA (Dr. Namyata Pathak Gandhi).

The main aim was to learn more about the state of evidence-based Indian Traditional Medicine and its practices in India and the United States, and the potential for music and art to help in the management of cancer in patients. The symposium included presentations on the following topics: traditional medicine and healthcare in India, ayurveda (an Indian Traditional Medicine) and cancer, yoga and cancer, and evidence-based traditional medicine-research glimpses, research needs, and areas of potential collaborations.

International Consortium for Chinese Medicine and Cancer (ICCMC)

On November 3, 2014, in Bethesda, Maryland, OCCAM/ NCI and Cancer Institute of China Academy of Chinese Medical Sciences (CI/CACMS) jointly held a meeting to examine the potential utility and feasibility of establishing an International Consortium for Chinese Medicine and Cancer (ICCMC), an international CM and cancer research platform to promote and enhance basic research and clinical trials of combined Western oncology and CM. At the meeting, participants from China, the US, Canada, Australia, and Korea discussed issues in CM and cancer research, treatment and management, including potential mechanisms of action, proof of efficacy, side effects, regulatory issues, and the need for improving the quality of randomized clinical trials of CM treatments and supportive care interventions. This initial planning meeting was followed by a second conference on October 17-18, 2015 in Dalian, China. Since these meetings, staff from OCCAM and CI/CACMS have continued to work with a committee of scientists and practitioners from the US, China, Korea, Australia to establish the ICCMC.

TRAINING

OCCAM has continued educating the next generation in the area of CAM by maintaining a position within their program for a Cancer Research Training Award (CRTA) fellow.

RESEARCH RESOURCES

OCCAM worked with the Natural Products Branch (NPB) within DCTD's Developmental Therapeutics Program (DTP), to establish a library of plant extracts from the pharmacopeia of TCM that is now available. (See section titled "Intradivisional and International Collaborations" below for further details)

COLLABORATIONS

NCI Office of Communications and Public Liaison (OCPL)

The director of OCCAM serves as the Editor-in-Chief of the Integrative, Alternative and Complementary Therapies editorial board of the Physicians Data Query (PDQ) program, which is managed by OCPL. This board produces evidence-based summaries of the literature about various complementary and alternative medicine approaches used by cancer patients.

NCI Center for Cancer Research (CCR)

OCCAM collaborates on a number of projects with NCI's CCR:

- CCR's Laboratory of Molecular Immunoregulation is studying Fufang Kushing Injection (FKI), an herbal mixture containing extracts from *Sophora flavescens* and *Heterosmilaxis Japonica*, for its anticancer effects and ability to decrease cancer-related pain. The study has resulted in findings on FKI's functions to inhibit sarcoma cancer cells' growth both *in vitro* and *in vivo*, and its capability to modulate tumor-induced hyperalgesia in animal models. The molecular mechanism of FKI on pain control is related to signaling through the protein encoded by the transient receptor potential cation channel subfamily V member 1 (TRPV1) gene.
- In CCR's Cancer Stem Cell Section, the Laboratory of Cancer Prevention studied a compound derived from CM – cryptotanshinone – for its inhibitory effects on

prostate cancer stem cells. The study found that cryptotanshinone targets the CD44+, CD24+ subpopulation of LNCaP prostate cancer cells, which represents prostate tumor initiating cells, and also affects total LNCaP cells as well via down-regulation of stemness genes, such as Nanog, OCT4, Sox2, β -catenin, and CXCR4.

- The Laboratory of Cancer Prevention in CCR's Gene Regulation Section has undertaken a comparative analysis of the CM compound berberine used to prevent or treat cancer with mouse models of similar types of cancer. The study has showed that berberine could regulate AMP-activated protein kinase signaling pathways and inhibits colon tumorigenesis in mice. Another study showed that cryptotanshinone can inhibit Stat3 expression and suppresses colorectal cancer proliferation and growth *in vitro*.
- The Signal Transduction Section in CCR's Laboratory of Genitourinary Cancer Pathogenesis uses prostate cancer stem cells and animal models to study CM compounds (such as Gambogic Acid) and extracts (such as FKI) and their inhibition functions on prostate cancer stem cell growth and related mechanisms.

Intradivisional and International Collaborations

OCCAM is working with CDP and the investigators of the Exceptional Responders Initiative (ERI) to investigate various aspects of the lifestyles of patients whose cases have been accrued to this initiative. A substudy to the ERI protocol has been approved by the Central Institutional Review Board that will permit a voluntary survey of these patients about their dietary and physical activity habits, as well as their use of CAM approaches.

Together with DTP's NPB, OCCAM has worked to develop a CM herb library that contains 332 samples of unfractionated extracts from 133 plant species collected from different locations in China. The preliminary assessment of the anti-cancer activity of these extracts has been performed in the NCI-60 human cancer cell line screen. This **CM plant extracts library** and the screening results are accessible to drug discovery

researchers worldwide (academic and non-profit organizations) to investigate CM plants as potential sources of agents for the treatment of human diseases, especially cancer.

OCCAM and NPB have also worked together to collect pure compounds and medicinal herb extracts through international collaborative projects via Memorandum of Understanding (MOU) agreements. Up to 349 pure compounds and 200 extracts have been collected from three institutes in China (Kunming Institute of Botany; Key Laboratory of Chemistry for Natural Products (KLCNP) in Guizhou Province; and Institute of Materia Medica, China Academy of Medical Sciences). Seventy-four pure compounds have been screened on the NCI-60 human cancer cell lines; 14 of them entered to 5-dose screens. More compound screenings on the NCI-60 human cancer cell lines are underway. CCR's Molecular Targets Laboratory has screened 26 compounds on seven cell target assays (GP78, PLK1, NF1, EpCAM, META, SUMO, p38) with certain hits; 152 medicinal herb extracts have been screened on eight cell target assays (GP78, NF1, EpCAM, MALT1, p38, SUMO, TRAIL and META) with certain hits. Hit extracts or compounds will be further tested on cell target assays.

Fellowships and Guest Researchers

Seven international visiting fellows from CI/CACMS have consecutively joined investigators from the Laboratory of Molecular Immunoregulation, Laboratory of Cancer Prevention at NCI's Frederick National Laboratory for Cancer Research, and Laboratory of Genitourinary Cancer Pathogenesis in CCR to explore various CM compounds and extracts for their anticancer activity and immune-stimulating effects (Fufang Kushing Injection - FKI) and cancer prevention activity (berberine, cryptotanshinone - CT, FKI). Five fellows have finished their training and collaborative studies and returned to their original institutes to continue their research. The studied CM compounds and herbal formulations are often used at hospitals in China as standard care to control cancer growth and decrease the side effects of chemotherapy.

FUTURE DIRECTIONS

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 continue to contribute to this area of research.

Planned research activities:

- An interdivisional dialog about diet, physical activity, and stress management after cancer diagnosis, with a focus on interactions of these factors with standard and investigational cancer therapies will be established. The goal of this dialog is to understand past and current research activities on this topic, the extent to which NCI has supported this work, and to identify areas of potential opportunity for program development and action. To date, background literature searches and preliminary portfolio analyses have been performed in preparation for these efforts.
- Translational research with medicinal botanicals and bioactive food components that have a strong preclinical research base and meet one of OCCAM's research priorities of special interest will be further explored both through collaborations with intramural and extramural research laboratories and in the clinical setting.
- The clinical evaluation of various CAM approaches to managing symptoms of cancer will be explored, including nausea, vomiting, xerostomia, fatigue, arthralgias, myalgias, and neuropathy. Opportunities may be considered through DCTD's Developmental Therapeutics Clinic, as well as other clinics within the CCR, NIH Clinical Center, and outside collaborators.
- The ICCMC is being established in collaboration with the CI/CACMS to bring together scientists, CM practitioners, conventional medicine oncologists, and industry to enhance the standards of CM oncology research, integrate CM and Western medicine cancer management, and encourage East-West dialog and collaboration.
- Working with NCI's Center for Global Health and the Office of Global Affairs of HHS, OCCAM is exploring the potential to apply for an Asia Pacific Economical Collaboration (APEC) funding program to form the APEC Traditional Medicine and Cancer Network among APEC economies. This proposal has been submitted to the APEC Health Working group and has received positive responses from other APEC economies, such as Philippines, China, and Chinese Taipei as co-sponsors. The APEC Traditional Medicine and Cancer Network could promote collaborative studies on traditional medicine (TM) and cancer; to share information on TM and cancer care; to establish TM and Cancer Network website/database; to set up standards on TM practice and products; and to promote regulations on the safety, quality, and efficacy of TM products.
- OCCAM plans to develop a concept for system biology of nutritional modulation.
- Funding opportunities and initiatives for mechanistic studies, drug discovery, clinical trials, adverse effects, databases, and computation modeling of CAM in the priority areas suggested in the May 25-26, 2016 workshop, "The State of the Science: Cancer Complementary and Alternative Medicine Therapeutics Research" are being developed.
- International collaborations with funding agencies and organizations in China and other countries, e.g. co-funding with Natural Science Foundation of China, a joint scientific conference, and international centers for cancer complementary and integrative research are being developed and/or explored. The amount and availability of patient information materials on CAM and cancer have increased, but a need remains for tailored patient education. OCCAM will continue developing evidence-based patient education resources.

CAM

OFFICE OF CANCER
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ALTERNATIVE MEDICINE

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PROGRAMS AND INITIATIVES (2013-2017)

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Division Director

Dr. Toby Hecht

Deputy Division Director
Acting Director for Preclinical Research

Dr. Jeffrey S. Abrams

Acting Director for Clinical Research

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Dr. Smitha Antony

Health Science Administrator

Mr. Bill Bray

Senior Operations Director [Contractor]

Dr. Jason Cristofaro

Intellectual Property Program Manager

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Program Manager

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Secretary [Contractor]

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Ms. Jena Kidwell

Program Analyst

Dr. Manu Kohli

Scientific Program Manager [Contractor]

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Secretary to the Division Director

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Science Communications Specialist [Contractor]

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Secretary to the Deputy Director

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Expert

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Information Technology Officer

Mr. Robert Willey

Senior Financial Analyst [Contractor]

Dr. Mickey Williams

Scientific Program Manager [Contractor]

DEVELOPMENTAL THERAPEUTICS CLINIC

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Head, Early Clinical Trials Development

Ms. Debbie Childs

Clinical Research Coordinator [Contractor]

Ms. Pilley Doe

Nurse Specialist

Dr. Robert Meehan

Clinical Fellow

Ms. Nicole Monteiro

Program Specialist

Ms. Nancy Moore

Nurse Specialist

Dr. Geraldine O'Sullivan-Coyne

Staff Clinician

Ms. Mary Quinn

Nurse Practitioner

DCTD NEXT PROGRAM SUPPORT

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Manager, CBC Support Group, Scientific Project Manager [Contractor]

Mr. John Giraldes

CBC, Scientific Project Manager [Contractor]

Dr. Neal Green

CBC, Scientific Project Manager [Contractor]

Ms. Melinda Hohnke

CBC, Program Manager [Contractor]

Dr. Bill Moore

CBC, Scientific Project Manager [Contractor]

Dr. Gordon Stott

CBC, Scientific Project Manager [Contractor]

MEDICAL WRITING & CLINICAL PROTOCOL SUPPORT

Dr. Melanie Simpson

Head, Medical Writing Unit [Contractor]

Dr. Laura Fogli

Medical Writer [Contractor]

Dr. Mariam Konaté

Medical Writer [Contractor]

Dr. Sarah Miller

Medical Writer [Contractor]

Dr. Andrea Voth

Medical Writer [Contractor]

NATIONAL CLINICAL TARGET VALIDATION LABORATORY

Dr. Sherry Yang

Chief

Dr. Karen Gray

Senior Project Manager [Contractor]

Dr. Jiuping (Jay) Ji

Head, Senior Principal Scientist, NCTVL Support Lab [Contractor]

Ms. Donna Ketchum

Research Associate [Contractor]

Dr. Dat Nguyen

Special Volunteer

Ms. Ravi Putvatana

Research Associate [Contractor]

Ms. Huong-Lan Tran

Research Associate [Contractor]

Mr. William Yutzy

Research Associate [Contractor]

Dr. Yiping Zhang

Scientist [Contractor]

PHARMACODYNAMIC ASSAY DEVELOPMENT AND IMPLEMENTATION SECTION

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Head, Senior Principal Scientist, PADIS [Contractor]

Ms. Rachel Andrews

Research Associate [Contractor]

Ms. Anne Book

Research Associate [Contractor]

Mr. Facundo Cutuli

Research Associate [Contractor]

Ms. Angie Dull

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Dr. Katherine Ferry-Galow

Principal Scientist [Contractor]

Ms. Valerie Ficca

Research Associate [Contractor]

Mr. Jeevan Govindharajulu

Bioinformatics Analyst [Contractor]

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Postdoctoral Fellow

Mr. Sonny Khin

Research Associate [Contractor]

Mr. Scott Lawrence

Bioinformatics Analyst [Contractor]

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Senior Scientist [Contractor]

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Principal Scientist [Contractor]

Dr. Lihua Wang

Senior Scientist [Contractor]

Dr. Deborah Wilsker

Scientist [Contractor]

Mr. Weimin Zhu

Research Associate [Contractor]

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Mathematical Statistician

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Mathematical Statistician

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Mathematical Statistician

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Mathematical Statistician

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Mathematical Statistician

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Postdoctoral Fellow

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Mathematical Statistician

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Postdoctoral Fellow

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Dr. Brian Sorg

Program Director

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Deputy Associate Director

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Special Prjects Administrator [Contractor]

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Business Analyst

Dr. G. Craig Hill
Head, Cancer Imaging Support, Medical Affairs Scientist
[Contractor]

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Program Director

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Mr. Justin Stephen Kirby
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Head-GI Cancer Therapeutics

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Head-NCTN Clinical Trials Operations & Scientific
Liaison-Patient Reported Outcomes

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Head-Breast Cancer Therapeutics

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Head-Hematologic Cancer Therapeutics

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Head-Head & Neck, Lung, Mesothelioma, Thymoma,
Thyroid

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Head-GU, Brain Cancer Therapeutics

Mr. Andrew Marshall

Extramural Grants Clerk

Ms. Grace Mishkin

Public Health Analyst

Dr. Nita Seibel

Head-Pediatric Solid Tumors

Ms. Georgia Washington

Extramural Support Assistant

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Associate Branch Chief

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Program Support Assistant

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Clinical Trials Program Coordinator

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Clinical Trials Monitoring Specialist

Ms. Dandre Thornhill

Clinical Trials Monitoring Specialist

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Health Program Specialist

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Head-CIRB Strategy Operations

Ms. Martha Kruhm

Head-PIO

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Senior Behavioral Science Analyst

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Dr. L. Austin Doyle

Senior Investigator

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Program Specialist

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Dr. Jeffrey Moscow

Medical Officer

Dr. Richard Piekarz

Senior Investigator

Dr. Elad Sharon

Medical Officer

Dr. Howard Streicher

Senior Investigator

Dr. Naoko Takebe

Senior Investigator

Ms. Mary Walker

Program Support Assistant

Ms. Rhonda Williams-Robinson

Team Lead, Program Specialist/
Administrative Coordinator

Dr. John Wright

Senior Investigator

PHARMACEUTICAL MANAGEMENT BRANCH

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Branch Chief

Mr. Rodney Howells

Associate Branch Chief

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Senior Clinical Research Pharmacist

Ms. Melizza Ford

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Ms. Arie Gray

Support Services [Contractor]

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Dr. Tali Johnson

Senior Clinical Research Pharmacist

Dr. Ravie Kem

Senior Clinical Research Pharmacist

Dr. Donna Shriner

Senior Clinical Research Pharmacist

Dr. Jennifer Thompson

Senior Clinical Research Pharmacist

Dr. Eileen Wu

Senior Clinical Research Pharmacist

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Associate Chief, Agreement Coordination Group

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Senior Regulatory Affairs Manager

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Specialist, R&D Agreements

Ms. Bhanu Ramineni

Regulatory Affairs Specialist

Dr. Julie Rhie

Pharmacologist, Sr. Regulatory Affairs Scientist

Ms. Karen Said

Executive Assistant

Ms. Lora Spencer

R&D Agreements Advisor

Dr. Jian Zhang

Senior Manager, R&D Agreements

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Associate Director

Dr. Rosemarie Aurigemma
Deputy Associate Director

Mr. Lawrence Anderson
Chemist

Ms. Bernadette Carter
Program Assistant

Dr. Michael Currens
Special Assistant to the Associate Director

Dr. Min He
Special Assistant to the Associate Director

Dr. Brian Peyser
Special Assistant to the Associate Director

Dr. Lawrence Phillips
Chemist

BIOLOGICAL RESOURCES BRANCH

Dr. Rosemarie Aurigemma
Acting Branch Chief

Ms. Dawn Albaugh
Extramural Support Assistant

Ms. Virginia Axline
Program Specialist

Mr. Trevor Broadt
Director, Process Analysis/Quality Control BDP
[Contractor]

Dr. Stephen Creekmore
Special Volunteer

Dr. Douglas Gaum
Director, Quality Assurance, BDP [Contractor]

Ms. Patricia Green
Manager, Budget and Project Control, BDP [Contractor]

Ms. Barbara Kending
Senior Program Coordinator, BDP [Contractor]

Dr. Gautam (George) Mitra
Program & Technical Director and Development Lead,
BDP [Contractor]

Mr. John Roach
Director, Manufacturing, BDP [Contractor]

Ms. Sheryl Ruppel
Director, Regulatory Affairs, BDP [Contractor]

Dr. Rachelle Salomon
Health Science Administrator

Dr. Anthony Welch
Biologist

Dr. Jason Yovandich
Biologist

BIOLOGICAL TESTING BRANCH

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Branch Chief

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Biologist

Ms. Robin Bender

Extramural Support Scientist

Ms. Linda Blumenauer

Animal Scientist

Ms. Michelle Eugeni Crespo

Nurse Specialist

Ms. Lisa Devore

Manager, Animal Production [Contractor]

Dr. Yvonne Evrard

Operations Manager, NCI Patient Derived Models Repository [Contractor]

Ms. Michelle Gottholm-Ahalt

Program Specialist

Ms. Ruth Green

Supervisor, Animal Care Support [Contractor]

Mr. Nathaniel Greenberg

Chemist

Dr. Tara Grinnage-Pulley

Veterinary Medical Officer

Dr. Dianne Newton

Manager, Principal Scientist, In Vivo Evaluation [Contractor]

Ms. Christine Pacula-Cox

Microbiologist

Ms. Annette Stephens

Document Specialist [Contractor]

Mrs. Robin Wright

Extramural Program Assistant

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Branch Chief

Dr. Mark Kunkel

Biologist

Dr. Prabhakar Risbood

Chemist

Dr. Stephen White

Chemist

Mr. Donn Wishka

Chemist

IMMUNO-ONCOLOGY BRANCH

Dr. Connie Sommers

Health Science Administrator

INFORMATION TECHNOLOGY BRANCH

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Branch Chief

Dr. Mark Gunnell

Head, Information Technology Support [Contractor]

Dr. Richard Gussio

Director Research, Commissioned Officer

Dr. Connor McGrath

Head, Computational Drug Development [Contractor]

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Branch Chief

Dr. David Evans

Manager, Principal Scientist, In Vitro Testing
[Contractor]

Dr. Gurmeet Kaur

Biologist

Dr. Annamaria Rapisarda

Manager, Scientist, Molecular Pharmacology

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Branch Chief

Dr. Robert Bahde

Health Science Administrator

Mr. John Britt

Programmer Analyst, IT Manager, Natural Products
Support Group [Contractor]

Mr. Guy Carter

Special Volunteer

Dr. Gordon Cragg

Special Volunteer

Dr. Tanja Grkovic

Chemist, Senior Scientist, Manager, Natural Products
Support Group [Contractor]

Dr. Paul Grothaus

Chemist [Contractor]

Ms. Carol Haggerty

Extramural Support Assistant

Dr. David Newman

Special Volunteer

Dr. Ron Quinn

Special Volunteer

Dr. Sheo Singh

Special Volunteer

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Dr. Shanker Gupta

Pharmacist

Dr. Paul Liu

Chemist

Dr. Esmail Tabibi

Chemist

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Pharmacologist

Dr. Suresh Arya

Biologist

Dr. Weiwei Chen

Health Science Administrator

Dr. Suzanne Forry-Schaudies

Biologist

Dr. Yali Fu

Chemist

Dr. Sudhir Kondapaka

Biologist

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Acting Branch Chief

Ms. Ruoli Bai

Chemist, Tubulin Lab

Dr. David Covell

Computer Scientist

Dr. Ernest Hamel

Senior Disciplinary Scientist, Tubulin Lab

TOXICOLOGY AND PHARMACOLOGY BRANCH

Dr. Joseph Covey

Pharmacologist

Dr. Susan Donohue

Pharmacologist (Function – Toxicologist)

Dr. Sandy Eldridge

Toxicologist

Dr. Liang Guo

Head, Investig. Toxicology Support Lab, LHTP, Senior Principal Scientist [Contractor]

Dr. Eugene Herman

Special Volunteer

Dr. Elaine Knight

Pharmacologist (Function – Toxicologist)

Dr. Dane Liston

Pharmacologist

Dr. James Peggins

Pharmacologist

Dr. Karen Schweikart

Chemist (Function – Toxicologist)

RADIATION RESEARCH PROGRAM

OFFICE OF THE ASSOCIATE DIRECTOR

Dr. C. Norman Coleman

Associate Director

Dr. Bhadrasain Vikram

Deputy Associate Director

Ms. Patricia Angelis

Administrative Support

Dr. Judith Bader

Special Volunteer

Ms. Lang Banh

Administrative Support

Dr. Francis Mahoney

Special Volunteer

Dr. David Pistenmaa

Special Volunteer

Ms. Mary Martha Smith

Program Specialist

Dr. Anil Srivastava

Special Volunteer

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Dr. Bhadrasain Vikram

Branch Chief

Dr. Jeffrey Buchsbaum

Medical Officer

Dr. Jacek Capala

Program Director

Dr. James Deye
Program Director

Dr. Ceferino Obcemea
Medical Physicist

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Branch Chief

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Program Director

Dr. Pataje Prasanna
Program Director

Dr. Rosemary Wong
Special Volunteer

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Dr. Peter Ujhazy
Deputy Associate Director

Ms. Ann Alston
Program Support

Dr. Julia Arnold
Health Scientist Administrator/Program Director

Dr. Andrew Hruszkewycz
Medical Officer/ Program Director

Dr. Leah Hubbard
Health Scientist Administrator

Dr. Igor Kuzmin
Health Scientist Administrator/Program Director

Dr. Steve Nothwehr
Health Scientist Administrator/Program Director

Dr. JoyAnn Phillips Rohan
Health Scientist Administrator/Program Director

Ms. Sharna Tingle
Program Coordinator [Contractor]

Ms. Terese Trent
Extramural Support Assistant

Ms. Tamara Walton
Program Coordinator

OFFICE OF CANCER COMPLEMENTARY AND ALTERNATIVE MEDICINE

Dr. Jeffrey White

Director

Ms. Christina Armstrong

Administrative Program Specialist

Dr. Libin Jia

Science Program Manager

Ms. Gina Nauman

Cancer Research Training Awardee

Dr. Oluwadamilola Olaku

Scientific Program Analyst [Contractor]

Dr. Avraham Rasooly

Health Science Administrator

Ms. Nekesha Rowlett-Thomas

Meeting Coordinator [Contractor]

Dr. Dan Xi

Program Director, Research Development and Support
Program

Dr. Farah Zia

Director, Case Review

PROGRAMS AND INITIATIVES (2013-2017)

DCTD STAFF PUBLICATIONS

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