DIVISION OF CANCER TREATMENT AND DIAGNOSIS

PROGRAMS AND INITIATIVES (2018-2019)

NATIONAL CANCER INSTITUTE

DIVISION OF CANCER TREATMENT AND DIAGNOSIS

PROGRAMS AND INITIATIVES (2018-2019)

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ACRONYMS

AACR – American Association for Cancer Research

AAPM – American Association for Physicists in Medicine

ABTC – Adult Brain Tumor Consortium

ACG – Agreement Coordination Group

ACR – American College of Radiology

ACRIN – American College of Radiology Imaging Network

ACT – NCTN Accrual Core Team

ADCC – antibody directed cellular cytotoxicity

ADME – absorption, distribution, metabolism, and excretion

ADTTP – Advanced Developmental Therapeutics Training Program

AERS – Adverse Event Reporting System

AFRRI – The Department of Defense Armed Forces Radiobiology and Research Institute

AHRQ – Agency for Healthcare Research and Quality

ALCHEMIST – Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial

ALL – acute lymphoblastic leukemia

allo HCT – allogenic hematopoietic cell transplantation

AML – acute myeloid leukemia

APEC – Asia Pacific Economic Collaboration

ARRA – American Reinvestment and Recovery Act of 2009

ASCO – American Society of Clinical Oncology

ASIGS – American Society for Image Guided Surgery

ASPR – Office of the Assistant Secretary for Preparedness and Response

ASTRO – American Society for Radiation Oncology

ATR – ataxia telangiectasia mutated and Rad3-related kinase

ATRF – Advanced Technologies Research Facility

5-aza-T-dCyd – 5-aza-4'-thio-2'deoxycytidine

BARDA – Biomedical Advanced Research and Development Authority

BBRB – Biorepositories and Biospecimen Research Branch

BDP – Biopharmaceutical Development Program

BEBPs – biospecimen evidence-based practices

BEMT – Biobank Economic Modeling Tool

BIQSFP – Biomarker, Imaging, and Quality of Life Studies Funding Program

BMT CTN – Blood and Bone Marrow Transplant Clinical Trials Network

BPV – Biospecimen Preanalytical Variables Program

BRD – Biospecimen Research Database

BRISQ – Biospecimen Reporting for Improved Study Quality

BRN – Biospecimen Research Network

BRB – Biological Resources Branch

BRMs – biological response modifiers

BRP – Biometric Research Program

BTB – Biological Testing Branch

caAERS – cancer adverse event reporting system

CADP – Clinical Assay Development Program

caDSR – NCI Cancer Data Standards Registry and Repository

caHUB – NCI Cancer Human Biobank

CALGB – Cancer and Leukemia Group B

CAM – complementary and alternative medicine

CAP – Corrective Action Plan

CBC – Chemical Biology Consortium

CBCTR – NCI Cooperative Breast Cancer Tissue Resource

CBIIT – NCI Center for Biomedical Informatics and Information Technology

CCCT – NCI Director's Coordinating Center for Clinical Trials

CCR – Center for Cancer Research

CCSS – Childhood Cancer Survivor Study

CCTG – Canadian Cancer Trials Group

CDE – NIH Common Data Elements Repository

CDK – cyclin-dependent kinase

CDMS – Clinical Data Management System

CDP – Cancer Diagnosis Program

CDR – Comprehensive Data Resource

CDRH – FDA's Center for Devices and Radiological Health

CDUS – Clinical Data Update System

CEP – Career Enhancement Program

CGCB – Clinical Grants and Contracts Branch

CGH – NCI Center for Global Health

cGLP – current Good Laboratory Practice

cGMP – current Good Manufacturing Practice

CHTN – Cooperative Human Tissue Network

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
CR – complete response
CRADA – Cooperative Research and Development Agreement
CRC – NIH Clinical Research Center
CRCHD – NCI's Center to Reduce Cancer Health Disparities
CRDC – Cancer Research Data Commons
CrD PTMA – Career Development Project Team Member Applications
CRF – Case Reporting Form
CROB – Clinical Radiation Oncology Branch
CRO – contract research organization
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 System
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
DOT1L – 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
ETCTN – NCI Experimental Therapeutics Clinical Trials Network
ECOG – Eastern Cooperative Oncology Group
EDDOP – Early Drug Development Opportunity Program
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
ESYS – CTEP Enterprise System
FDA – Food and Drug Administration
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

GPNMB – transmembrane glycoprotein NMB

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

HR – hormone receptor

HTS – high throughput screening

IAA – interagency agreement

IAEA – International Atomic Energy Agency

IARC – International Agency for Research on Cancer

IB – Investigator Brochure

IBMTR – International Bone Marrow Transplant Registry

ICCMC – International Consortium for Chinese Medicine and Cancer

ICDC – Integrated Canine Data Commons

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 Application

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 – Informatics 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

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 – 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
NPNPD – 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 – On-line Agent Order Processing
OBBR – 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 1
PDM – patient-derived models
PDQ – Physicians Data Query
PDX – patient-derived xenografts
PEP-CTN – Pediatric Early Phase Clinical Trials Network
PET – positron emission tomography
PFS – progression-free survival
PI3K – phosphoinositide 3-kinase
PI – principal investigator
PIO – Protocol and Information Office
PIRB – Pathology Investigation and Resources Branch
PK – pharmacokinetics
PMB – Pharmaceutical Management Branch
PMI – Precision Medicine Initiative
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
PRO – patient reported outcomes
PTGB – Preclinical Therapeutics Grants Branch
PTMA – Project Team Member Application
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 Criteria 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
SCLC – small cell lung cancer
SEP – Special Emphasis Panel
SITC – Society for Immunotherapy of Cancer
SNMMI – Society of Nuclear Medicine and Molecular Imaging
SOP – standard operating procedure
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

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

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 a major component of the National Cancer Institute (NCI). Though not meant to be a complete inventory of the Division's activities, this report covers advances from 2018 through 2019 and outlines important highlights that have helped to improve the diagnosis and treatment of cancer both nationally and internationally.

During the current reporting period, DCTD scientific and administrative staff brought to fruition several new programs to enhance our understanding of both novel diagnostic and therapeutic approaches that have been supported by the Beau Biden Cancer Moonshot Initiative. These include the formation of research consortia to:

- probe molecular mechanisms of cancer drug sensitivity and resistance

- develop a broad range of molecularly characterized patient-derived cancer models from diverse populations that can be used to interrogate the activity of new anticancer drugs as single agents and combinations

- develop new cancer immunotherapy models using canines with spontaneous tumors that possess intact immune systems which may be more closely reflective of human malignancies

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- study the immunologic microenvironment of patients with pancreatic cancers that have, to date, not been readily amenable to novel therapies focusing on modulation of the immune system

- develop, standardize, and apply a comprehensive panel of immune-oncology biomarkers to clinical trials supported by the NCI and through industry collaborations.

From 2018-2019, these complex scientific networks, all linking multiple academic institutions, were successfully launched, produced novel scientific insights, and have improved our understanding of the therapeutic mechanisms that are essential for success in the treatment of patients with 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 several critical steps, including target development or high throughput screening, the facilitation of chemical optimization of potential lead molecules, preclinical toxicology, formulation, development of biologicals, or 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 projects that have proceeded through the NExT pipeline have been licensed to pharmaceutical and biotechnology concerns for clinical evaluation. Many of these agents are now undergoing first-in-human clinical trials at the NCI and in the broader cancer clinical research community; several are making excellent progress toward eventual approval by the US Food and Drug Administration.

During 2018-2019, DCTD's previous efforts to improve the efficiency of its national clinical trials programs have proven remarkably fruitful. 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 now meet the needs of studies used for FDA registration and provide an enhanced auditing and clinical trial tracking capacity. With these tools, the NCI's National Clinical Trials Network (NCTN) rapidly develops, accrues, and completes new generations of genomically-based clinical trials (such as NCI-MATCH, NCI-COG Pediatric MATCH, ALCHEMIST, Lung-MAP) 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 biomarkers are a consistent feature of all NCI's Experimental Therapeutics Clinical Trials Network (ETCTN) trials.

In addition to these major DCTD efforts, we are providing summaries of other recently established priorities and scientific advances across a wide variety of diagnostic and therapeutic domains that have been made possible by the many talented and committed scientific and administrative staff members throughout the Division. It is my continuing privilege to work with such 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 cancer 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 anti-cancer 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 manufactures new small molecules and biologics in bulk quantities under GMP conditions 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)** in the NIH Clinical Center on the Bethesda campus works in concert with the NCI 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).

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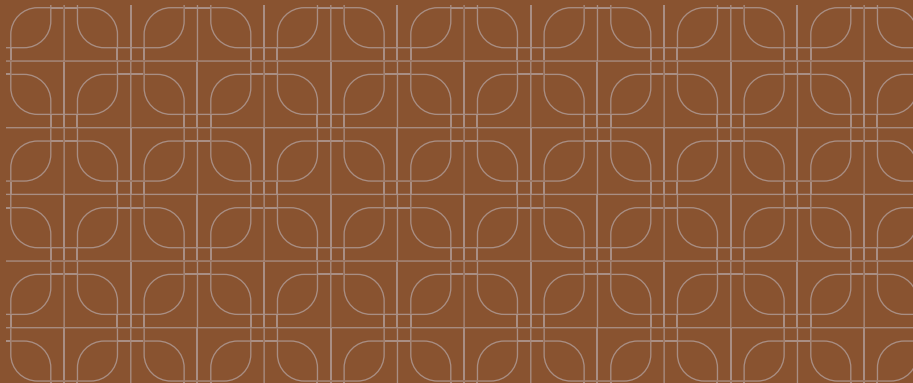
Dr. James H. Doroshow has been the Deputy Director for Clinical and Translational Research of the National Cancer Institute since 2011, and the Director of NCI's Division of Cancer Treatment and Diagnosis since 2004. He continues to pursue his own research program as a Senior Investigator in the Developmental 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.

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Additional DCTD information is available at https://dctd.cancer.gov and https://cancer.gov.

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 $903,400,894 in grant funding managed by DCTD in 2019 across the six Programs and one Office 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

- Developing 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

- Developing a consortium of NCI-Designated Cancer Centers to produce and standardize the development and molecular characterization of patient-derived xenograft (PDX) models of understudied human tumors

- Coordinating testing of novel targeted therapeutic agent combinations in preclinical PDX trials to develop the rationale for subsequent clinical studies in the NCI's Experimental Therapeutics Clinical Trials Network (ETCTN)

DEVELOPMENT OF CANCER IMMUNOTHERAPY BIOMARKERS

- Developing a laboratory consortium to standardize the methodology for analyzing tumor specimens and

associated microenvironmental elements for the expression and interaction of immunomodulatory molecules from patients entered on immuno-oncology clinical trials

- Developing reagents for novel immunobiomarker analytes

- Developing an information system for the storage, evaluation, and sharing of both clinical and immuno-biomarker data developed from the clinical samples examined by the consortium for patients entered on immunotherapy clinical trials

NEW CANCER IMMUNOTHERAPY MODEL SYSTEMS

- Using the NCI's Comparative Oncology Network of Veterinary Oncology Centers, conduct clinical trials of immunotherapy agents in spontaneous canine malignancies

- Producing 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

- Developing a tissue resource for studying the pancreatic cancer microenvironment

- Developing improved antigen selection and biomarker development methods for pancreatic cancer immunotherapy

FIGURE 1: DISTRIBUTION OF DCTD 2019 GRANT FUNDING ACROSS PROGRAMS.

Legend:
- TRP – $78,313,295
- RRP – $54,606,647
- DTP – $206,108,782
- OCCAM – $5,836,015
- CDP – $115,156,373
- CIP – $139,633,272
- CTEP – $303,746,510

Pie chart percentages: 9%, 6%, 23%, 1%, 13%, 15%, 33%

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 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 ETCTN, people 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 the largest precision medicine trial in history. The goal of NCI-MATCH is to determine if treatment based on a tumor's genetic abnormality matched to a molecular targeted agent is effective for treating tumors, regardless of their tumor type. The ECOG-ACRIN Cancer Research Group, part of NCTN, and DCTD's Cancer Diagnosis Program (CDP) are leading the trial, with assistance from DCTD's Cancer Therapy Evaluation Program (CTEP), Biometric Research Program (BRP), and additional committees.
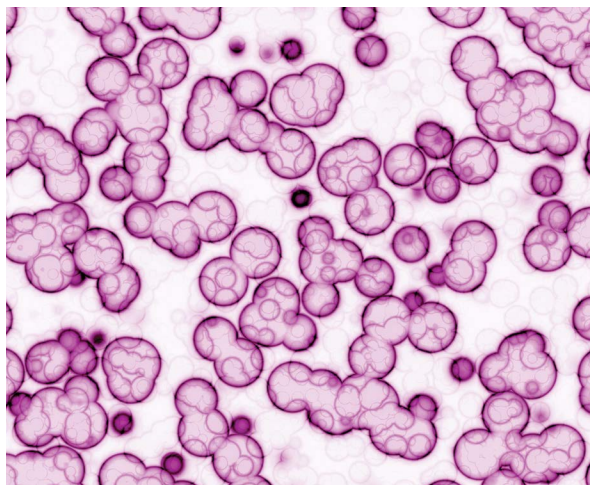
The first part of the trial was the screening and enrollment phase, which required the prospective collection of a fresh tumor biopsy followed by targeted NGS and immunohistochemical (IHC) assays performed in one of four Core Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories. The 250 genes in the NGS panel were carefully selected based on the targeted genetic abnormalities in human tumor cells responsive to the trial agents. People could be enrolled under the NCI-MATCH Master protocol umbrella if their tumor contained a genetic abnormality that was the therapeutic target in one of the 24 study arms open at that time. Agent selection based on the molecular findings of the biopsy was rule-driven using a software called MATCHBOX, not by a tumor board. In the event of more than one mutation in a tumor, the MATCHBOX decision rules were used to select which genetic abnormality, and therefore treatment option, would be chosen (Figure 2). The NCI-MATCH study reached its accrual goal of screening 6,000 patients 2 years ahead of schedule; however, additional patients continue to be enrolled and treated on various arms of the trial (see Outside Assay/Rare Variant Initiative, page 8).

NCI-MATCH Assay Workflow

Biopsy → **Shipped to MDACC (Central Pathological Lab)**

Tissue Accession

Tissue Processing → **Archive**
- Tissue Blocks
- Slides
- Nucleic Acid

PTEN IHC   **NA Extraction**

20ng FFPE DNA
10ng FFPE RNA

4 Lab Network   **MDACC**   **MGH**   **MoCha**   **Yale**   **NGS Library Prep and Sequencing**

Ion Reporter   **Review and Sign off**

BAM File Storage   MOI Annatation

MATCHBox

Treatment Selection Final Report → **Clinical DB**

FIGURE 2: NCI-MATCH ASSAY WORKFLOW WITH MATCHBOX.
Flow chart based on patient tumor mutation analysis and selection process including MATCHBOX.

NCI-MATCH uses 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 tumor. In some trial arms where a tumor type already has FDA approval for the agent being used, or where the agent is known to not be effective, individuals with those tumor types are excluded. For example, BRAF inhibitors are not given to patients with colon cancer with the V600E mutation as they are known to be ineffective in that setting. In addition, NCI-MATCH does not compete with currently open NCI-sponsored trials or trials by NCI's pharmaceutical partners.

Eligible participants must be greater than 18 years of age, have good performance status, adequate organ function,

and a metastatic solid tumor, lymphoma, or myeloma that has progressed on all standard therapy or where no standard therapy exists. Patients assigned to a study arm are evaluated for tumor response and progression-free survival (PFS). Each arm of the trial will have approximately 31 evaluable patients receiving the same agent, all of whom meet the molecular eligibility criteria. Patients whose tumors continue to progress despite the treatment they are receiving are removed from the study to pursue other options. They and their doctor will receive a report of the molecular analyses performed in the CLIA laboratory that includes 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.
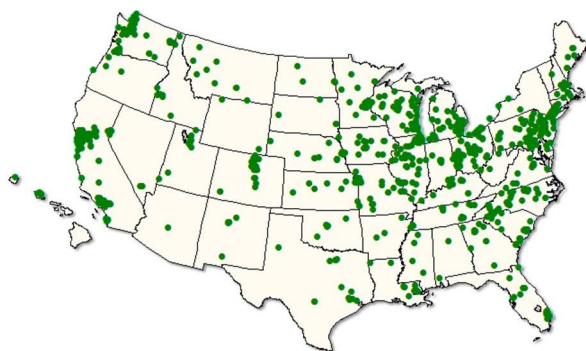
FIGURE 3: NCI-MATCH SITES.

NCI-MATCH is open at more than 1,100 sites in the US across the four adult NCTN Groups and the NCI Community Oncology Research Program (NCORP) and is accessible via the CTSU. (Figure 3). The initial screening phase of the trial received 6,391 patient referrals (Central Screening Cohort; Table 1) and performed molecular profiling for the 5,548 participants who sent in biopsy samples. With a 93% assay success rate, 987 people were matched to a therapy based on the molecular abnormalities found in their tumors and the available study arms. The high rate of accrual (more than 100 people screened weekly) led to the closure of the initial screening phase of the study in May 2017.

	Central Screening Cohort	Designated Laboratory Referral Cohort	Total
Enrolled for Screening	6391	524	6915
Screen	5548	519	6067
Assigned to Treatment	987 (18%)	451 (87%)	1438
Enrolled on Treatment Arm	686 (70%)	374 (84%)	1060

TABLE 1: NCI-MATCH ENROLLMENT.

While the high rate of accrual enabled NCI-MATCH to successfully reach its goal of screening nearly 6,000 people with cancer, several arms had not completely accrued, particularly those with agents targeting rare mutations. The Outside Assay/Rare Variant Initiative was conceived to help complete accrual to those arms using a different mechanism to obtain molecular profiling. During the time that the screening phase of the NCI-MATCH trial was open, NGS tumor profiling became widely available through commercial companies and some academic laboratories. As many people with cancer were then opting to have their tumor sequenced as a component of routine care, specific laboratories outside

of the NCI-MATCH laboratory network were designated as qualified to refer people to the trial. 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) engaged in a cooperative agreement to work with NCI-MATCH to notify ordering physicians if their patient was potentially eligible for an NCI-MATCH treatment arm.

Once the pilot Outside Assay/Rare Variant Initiative demonstrated the ability to accrue patients with rare mutations, additional laboratories were approved to increase the number of people referred for these rare variant arms. Thirty laboratories comprise the Designated Outside Laboratory Network and provide the only path to NCI-MATCH trial enrollment. The molecular profiling is confirmed by the NCI-MATCH assay, preferably from the same tissue that was analyzed by the outside laboratory. Patient enrollment and treatment on the appropriate trial arm are not delayed pending confirmation, and patients whose profiling is not confirmed can stay on that arm of the study. Those patients referred to NCI-MATCH through this mechanism and eligible for assignment to a treatment arm had a higher enrollment rate compared to patients randomly screened and found eligible in the initial phase of the trial, (84% vs 70%, respectively) (Designated Laboratory Referral Cohort; Table 1). NCI-MATCH now has 38 study arms, a subset of which remain open, and one additional study remains to be added (Table 2).

Status of NCI-MATCH: 38 Arms	
12	Findings repported
8	In follow up
7	Enrollment suspended
10	Open to enrollment
1	Pending IRB approval

TABLE 2: 2019 STATUS OF THE 38 NCI-MATCH ARMS.

Table 3 details the results of NCI-MATCH arms that have been published as of 2019. Several studies met their primary endpoint, suggesting that this agent was worth pursuing in further studies. As with any clinical trial, even those arms not meeting their primary endpoint provide valuable information, both molecular and clinical data. Examples are rare tumors that responded to the agent or certain types of mutations that were more likely to respond. Each patient enrolled on NCI-MATCH contributes important information useful in the design of better cancer treatments.

Select NCI-MATCH Treatment Arms with Findings

Drug	Target	Arm	ORR	Publication/Status
Ado-trastuzumab emtansine	HER2 amplifications	Q	8%	Jhaveri KL, *Ann Onc*, onlineahead of print 08-27-19
Afatinib	HER2 activating mutations	B	2.7%*	Bedard PL, AACR 2019 Annual Mtg
AZD1775	BRCA1 or BRCA2 mutations	Z11	3.2%	Kummer S, AACR 2019 Annual Mtg
AZD4547	FGFR pathway aberrations	W	8%	Chae YK, *JCO*, ASCO 2018 Annual Mtg
Capivasertib	AKT mutations	Y	23%*	Kalinsky KM, EORTC-NCI-AACR 2018 Mtg
GSK2636771	PTEN expression or loss by IHC	P	0%	Janku FM, *Ann Oncol*, ESMO 2018 Mtg
	PTEN mutations/deletions	N	5%	
Nivolumab	dMMR status	Z1D	24%*	Azad NS, J Clin Oncol, 38 (3), 214-222 2020 Jan 20
Palbociclib	CCND1, 2, or 3 amplifications and Rb protein expression by IHC	Z1B	0%	Clark AS, AACR 2019 Annual Mtg
Taselisib	PIK3CA mutations	I	0%	Krop IE, *JCO*, ASCO 2018 Annual Mtg
Trametinib + Dabrafenib	BRAF V600E or V600K mutations	H	33%	Salama AKS, ASCO 2019 Annual Mtg

TABLE 3: RESULTS OF NCI-MATCH ARMS THAT HAVE BEEN PUBLISHED AS OF 2019.

The goal of the NCI-MATCH trial, the largest study of its kind, is 'signal-finding' – to identify if a drug could shrink or stabilize tumors containing the targeted genetic mutation, with the intent for those agents to eventually be studied further in larger, more definitive clinical trials. It has already met, and continues to further, this goal. It also demonstrated that broad tumor sequencing and subsequent selection of therapy could be performed in a timeframe consistent with the needs of clinical care, and that screening patients' tumors in this way could identify a therapeutically targeted genetic mutation in a significant proportion of cases (37.6%). However, the trial also demonstrated that in a research setting, clinical trial eligibility and availability of treatment arms reduced this number to 17.8% when only 24 NCI-MATCH treatment arms were initially open to enrollment to match these mutations. In the 'real world,' this implies that existence of drugs targeting tumor mutations will largely be the rate-limiting step to using a precision medicine test to guide therapeutic options.

The encouraging initial results of NCI-MATCH have prompted strategies to develop additional precision medicine clinical trials. Follow-up Phase 2 studies will 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 promising response to determine if and where the agent will be of greatest utility. In addition, combination trials may be suggested in MATCH studies with

limited activity to overcome drug resistance. These studies are just now being developed as the NCI takes precision medicine to the next level with unique approaches to cancer treatment using immunotherapies and combination therapies and treating people diagnosed with rare tumor types (See NCI's Future Precision Medicine Trials, below). The close collaboration between clinicians, researchers, regulators, pharmaceutical companies, and most importantly patients with cancer, will be necessary to meet these challenges and undertake these crucial initiatives.

NCI-COG Pediatric MATCH

The NCI-COG Pediatric MATCH trial is enrolling children with advanced cancers that have progressed or recurred on standard therapy. As in the adult NCI-MATCH trial, DNA sequencing identifies those children and adolescents between the ages of 1 to 21 years of age 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 (COG) and opened for accrual in July of 2017. Participants with all types of solid tumors are eligible for the trial, including central nervous system (CNS) tumors and non-Hodgkin lymphomas as well as histiocytic disorders, if 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 and was expanded shortly thereafter to ten. A minimum of 20 patients is enrolled on each treatment arm, with the ability for expansion if 3 or more responses are observed. Enrollment averages around 30 patients per month, with the overall goal of screening a minimum of 1,500 pediatric participants.

There are several unique aspects to Pediatric MATCH. Four of the ten treatment arms include agents never evaluated in children. Discussions with investigators at the NCI, COG, and FDA resulted in the decision that such agents could be considered for inclusion only after careful review of the observed toxicities in adults and if an adult recommended Phase 2 dose had been identified. The pediatric patients are monitored closely for these, and other, toxicities. This approach allows Pediatric MATCH to evaluate many more therapeutic agents than would otherwise be available to children. In addition, peripheral blood, which is a source of germline DNA, is sequenced for every ndividual enrolled. Treating oncologists can thereby determine if a genetic abnormality identified in the tumor was inherited or arose *de novo*, enabling recommendations for genetic testing/genetic counseling to the family (Figure 4).

Results of an interim analysis for Pediatric MATCH, presented at the 2019 American Society of Clinical Oncology Annual Meeting, revealed that 24% of the 422 children and adolescents screened had genetic alterations amenable to treatment with an investigational targeted agent on Pediatric MATCH. This is significantly higher than the 10% rate projected when the study was developed. This study is successfully facilitating the evaluation of targeted therapies in molecularly defined people with a wide spectrum of childhood solid tumors. The most common diagnoses, as of December 2019, are sarcomas (50%) (particularly bone sarcomas) and CNS tumors (24%).

FIGURE 4: PEDIATRIC MATCH SCHEMA.

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 progression free survival (PFS) in people with advanced lung adenocarcinoma and the appropriate mutation. The ALCHEMIST trial, which began in 2014, examines whether the addition of erlotinib (EGFR inhibitor) or crizotinib (ALK inhibitor) to standard adjuvant therapy, when indicated, in people 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 5). For patients with non-squamous cell lung cancer, EGFR genotyping is performed by sequencing of exons, and ALK FISH is performed using the Vysis break-apart probe. People with tumors exhibiting EGFR activating mutations receive standard chemotherapy +/- radiation and are then randomized to erlotinib or observation. Similarly, patients with tumors exhibiting the ALK fusion are randomized to receive crizotinib after completion of standard chemotherapy +/- radiation. 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 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. However, a large percentage of these patients, perhaps half, are unfortunately destined to relapse, so better therapy is 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. Patients are followed for 5 years or until relapse, at which time there is an option of performing another tumor sample to evaluate the genomic progression of these treated tumors.
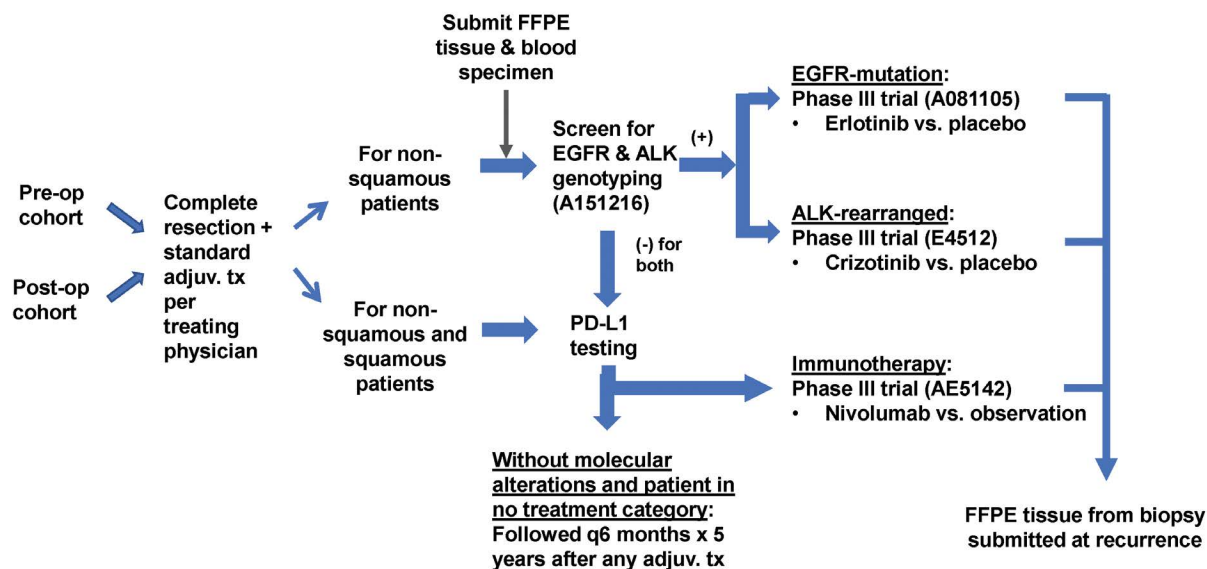
FIGURE 5: ALCHEMIST TRIAL.
Flow diagram based on lung cancer diagnosis and results of gene-specific mutation analysis.

ALCHEMIST was amended in 2016 to include a new trial using the PD-1 inhibitor, nivolumab, after it was proven active in patients with advanced non-small cell lung cancer (NSCLC). Unlike the other two trials, which are limited to people with non-squamous cell lung cancer, patients with squamous or non-squamous histology are eligible for the nivolumab trial. As of the end of 2019, more than 5,300 people have been screened for ALCHEMIST, and the PD-1 inhibitor trial closed to accrual in October 2019 after enrollment of 935 participants.

Lung Master Protocol (Lung-MAP)

The clinical trial design for this initiative is a novel approach to drug development and regulatory approval in the evaluation of biomarker-driven therapies and immunotherapies in people with previously treated non-small cell lung cancer (NSCLC). The Lung-MAP study is an umbrella protocol containing both a screening and a clinical trial component (Figure 6). Patients whose tumors progress on current therapy or who receive therapy for stage IV or recurrent NSCLC are eligible to participate in the screening component. The clinical trial component consists of biomarker-driven studies evaluating drug that interacts with a particular biomarker and non-match studies evaluating therapies without any of the study biomarkers. While included within the umbrella protocol, these "sub-studies" are independently conducted and analyzed. The protocol is modular to allow for the addition of new sub-studies of interest. A common biomarker-profiling platform is used for determining if a patient is eligible for the biomarker-driven studies.

The Lung-MAP trial originally opened in June 2014 for second-line treatment of patients with stage IV or recurrent squamous lung cancer. In 2019, the study expanded to allow people with all histologic types of previously treated stage IV or recurrent NSCLC. Progress in the development of immunotherapies led to a change in the landscape and a subsequent expansion of Lung-MAP. The non-matched category of sub-studies now includes combination immunotherapy agents that are either FDA approved or still investigational; however, they may also include small molecule agents or other modalities for which there is a scientific rationale for combining with an immunotherapy agent. All novel combinations continue to be selected through sound scientific rationale, supported whenever possible and appropriate by *in vivo* model systems, to demonstrate anti-cancer activity and preliminary assessments of their clinical tolerability when co-administered. The expansion allowing for all histologic types of NSCLC applies to all the sub-studies. patients with tumors that do not match one of the currently active drug-biomarker combinations (i.e., "non-match") will either be assigned to the non-match sub-study for immunotherapy-naïve patients or to a sub-study evaluating immunotherapy combinations for patients previously treated with immunotherapy.

NCI's Future Precision Medicine Clinical Trials

Following the successful design and implementation of NCI-MATCH, NCI is planning three successor precision medicine trials in areas of unmet clinical need.

LUNGMAP Screening Protocol		
Clinical Trial Component		
S1400VCP	**S1900BDSS**	**S1800NMIO**
	"S1900" symbolizes sub-studies that are all NSCLC histologies and Biomarker Driven.	"S1800" symbolizes sub-studies that are all NSCLC histologies, non-match immunotherapies.
Legacy S1400 S1400 A-E | S1400G | S1400F | S1400I | S1400K	**S1900A** Biomarker Driven LOH/BRCA pos	**S1900 "X"** Future Biomarker driven	**S1800A** Non-Match IO Relapsed/Refractory	**S1900 "X"** Future Non-Match IO combo

🫁 LUNG-MAP

FIGURE 6: DIAGRAM OF THE LUNG-MAP TRIAL.

ComboMATCH

*Combo*MATCH will test combinations of targeted drugs supported by preclinical studies. The goal is to overcome drug resistance to single-agent therapy through the development of genetically directed targeted agent combinations. NCI and the ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) are developing this trial. An overall Master Control Document, managed by ECOG-ACRIN, and several treatment arms (subprotocols) will be organized into 'cassettes' that will have four to six treatment arms. The master protocol will contain rules for assigning people to treatments and other guidelines. Each of the five NCTN Groups will manage a single cassette. Patients with cancer will be referred to this trial from the Designated Laboratory Network, established as part of the outside assay/rare variant initiative in NCI-MATCH, if routine next generation sequencing (NGS) of their tumor reveals a qualifying alteration(s).

MyeloMATCH

*Myelo*MATCH is an umbrella trial that will test treatments for acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). The speed at which new, effective, and tolerable treatment options for these cancers are identified must accelerate. The focus of this trial will be to match AML molecular subtypes to therapies in people of different age and fitness groups. SWOG will lead the trial, which will complete patients' genetic screening through routine bone marrow biopsy. NCI's Molecular Diagnostic Network (MDNet), an NCI-funded network of laboratories, will perform these molecular tests. MDNet will perform all the molecular and cellular biomarker assays on the new three precision medicine trials for the purpose of assigning patients to treatment.

iMATCH

The goal of this trial is to evaluate patients' immunologic profiles and then segregate the patients into different immunotherapy treatment groups based on tumor histology and biomarkers. iMATCH will start as a pilot study with two strata, each consisting of 60 people. Participants will undergo immune profiling using molecular assays to calculate their tumor mutation burden and tumor inflammation scores. The goal of the pilot is to establish the feasibility of testing and allocation to individual treatment groups. MDNet will support the laboratory testing, SWOG will lead the central protocol, and all other NCTN Groups will be developing and leading sub-protocols.

PRECISION MEDICINE INITIATIVE AND THE CANCER MOONSHOT℠

In 2016, DCTD had the opportunity through the Precision Medicine Initiative to fund pilot projects in areas identified as gaps in our understanding of anti-cancer drug and biological agent development, as well as in the identification of biomarkers and the mechanisms of drug resistance. Patient-derived xenografts (PDXs) in mice and immuno-competent companion canines with spontaneous tumors would provide insightful information towards the clinical development of a drug, or combination of agents, in patients with specific cancers.

NCI approached this by requesting the submission of proposals for a one-year administrative supplement to existing Cancer Centers Support Grants (CCSGs; P30s) and, in some cases, other grant and cooperative agreement mechanisms such as SPOREs (P50s), Program Project Grants (P01s), the ETCTN (UM1s), and clinical trials networks and consortia. Focused areas of precision oncology were delineated, and the request was for proposals to conduct pilot or preliminary studies with the potential to lead to more intensive, longer-term studies funded by RFAs or contracts in the future.

The seven focal areas of precision oncology requested, evaluated, and funded were:

- molecular characterization and nucleic acid sequencing of biospecimens obtained from ETCTN clinical trials

- improvement and optimization of T cell therapies and cGMP manufacturing processes to produce autologous T cell therapy products targeting solid cancers

- the study of mechanisms of cancer sensitivity and resistance to therapy utilizing samples and information from human clinical trials

- biomarker studies associated with NCI-supported trials of immunotherapy

- collaborative research efforts to enhance preclinical drug development and preclinical trials using PDX models

- studies of how the pancreatic ductal adenocarcinoma microenvironment affects immunotherapy

- research in canine immunotherapy via collaboration between NCI-designated cancer centers and veterinary medical colleges

The results from these pilot studies encouraged DCTD to issue funding opportunity announcements in five areas of research the following year. These new studies, which became part of the Cancer Moonshot[SM], included the:

- Mechanisms of Cancer Drug Resistance and Sensitivity Network (DRSN)

- Cancer Immune Monitoring and Analysis Centers - Cancer Immunologic Data Commons (CIMAC-CIDC) Network

- Patient-Derived Xenograft (PDX) Development and Trial Centers Research Network (PDXNet)

- Pancreatic Cancer Microenvironment Network (PaCMEN)

- Canine Cancer Immunotherapy Trials Network (PRE-CINCT)

Patient-Derived Xenograft Development and Trial Centers Research Network (PDXNet)

PDXNet comprises centers of excellence that have developed PDX models on a large scale to address the challenges of cancer precision medicine. Increasing the effectiveness of cancer therapy requires honing the assignment of treatments to those cancer indications in which they have the best outcome. As more targeted agents become available, and tumor subtypes are further defined, researchers must prioritize and test optimal combinations of agents in increasingly narrow tumor subsets in early phase clinical trials. New preclinical methods are needed to test novel agents against hundreds of potential tumor subtypes, and in multiple combinations, to identify the most promising strategies for clinical evaluation. Patient-derived models, such as PDXs and patient-derived organoids (PDOs), offer the potential to better represent human tumor biology, in comparison to established cell lines due to their low passage number. Therefore, patient-derived models may serve as better predictive models of tumor response to therapeutic approaches.

PDXNet was formed in 2017 through the issuance of three Cancer Moonshot[SM] funding opportunity announcements (Table 4). DCTD administers four PDX Development and Trial Centers (PDTCs; U54: CA-17-003) with a total annual cost of $5,000,000, one PDXNet Data Commons and Coordinating Center (PDCCC; U24: CA-17-004) with $1,000,000 in total annual operating costs, and an additional $1,000,000 annual cost for administrative supplements (PA-18-498 and PA-19-174) to support the access of non-PDXNet NCI-funded investigators to PDXNet resources. The Center for Cancer Health Care Disparities administers two additional PDTCs (U54: CA-17-032) for the use of patient-derived models from racial and ethnic minority populations to explore the biological reasons behind disparate cancer therapy outcomes in these patient populations. PDXNet sites interact with the NCI Patient Derived Models Repository (PDMR) at the Frederick National Laboratory for Cancer Research (FNLCR) to augment the creation, characterization, and distribution of PDX models to the research community (Figure 7).

The primary objective of PDXNet is the performance of large-scale trials that test therapeutic strategies in models representing the molecular diversity of histologies in a context that can lead to feasible clinical validation of the experimental results. Testing of agents for which NCI holds the IND is emphasized, since these are readily available for clinical evaluation in the NCI Experimental Therapeutics Clinical Trials Network (ETCTN).

In addition to pursuing the research interests of individual grantees, PDXNet investigators collaborate on projects to advance PDX science. One collaborative project involved treatment of the same PDX models with a single agent to evaluate the reproducibility of drug response in PDX models across all PDTC centers. A second project involved multiple methods to determine potential genomic evolution over serial passages to evaluate PDX tumor stability in the context of multiple centers. Both projects required data harmonization and sharing by the PDTCs and coordination by the PDCCC.

Activity Code	PI(s)	Grant Title	Lead Institution
U54	Ramaswamy Govindan (contact); Shunqiang Li; Li Ding	Washington University PDX Development and Trial Center	Washington University
U54	Meenhard Herlyn	Rational Approaches to Melanoma Therapy	The Wistar Institute
U54	Jack Roth (contact); Funda Meric-Bernstam	University of Texas PDX Development and Trial Center	University of Texas MD Anderson Cancer Center
U54	Alana Welm (contact); Bryan Welm; Michael Lewis	PDX Trial Center for Breast Cancer Therapy	University of Utah
U54	Chong-Xian Pan (contact); Luis Carvajal-Carmona; Moon Chen	University of California Minority Patient-Derived Xenograft (PDX) Development and Trial Center (UCaMP) to Reduce Cancer Health Disparities	University of California-Davis
U54	Nicholas Mitsiades	Minority PDX Development and Trial Center: Baylor College of Medicine and MD Anderson Cancer Center Collaboration on Mechanistic Studies to Dissect and Combat Health Disparities in Cancer	Baylor College of Medicine
U24	Jeffrey Chuang (contact); Brandi Davis-Dusenbery	Data Coordination Center for PDX Net	The Jackson Laboratory

TABLE 4: U54 AND U24 PDXNET AWARDS.
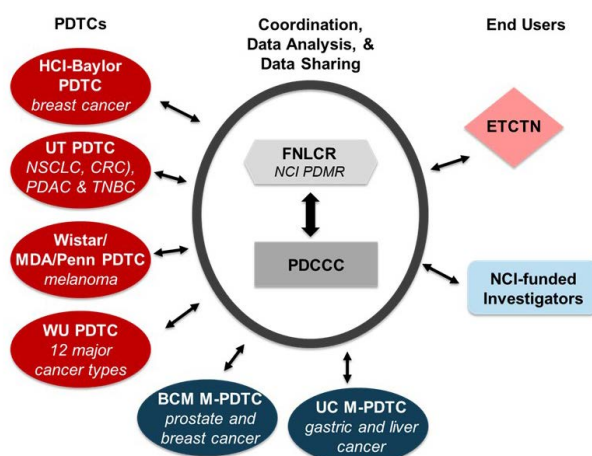
FIGURE 7: PDX DEVELOPMENT AND TRIAL CENTERS NETWORK (PDXNET).
HCI=Huntsman Cancer Institute; UT=University of Texas, MD Anderson Cancer Center; MDA/Penn=MD Anderson/University of Pennsylvania; WU=Washington University, St. Louis; BCM=Baylor College of Medicine; UC=University of California, Davis.

Mechanisms of Cancer Drug Resistance and Sensitivity Network (DRSN)

The DRSN, part of the Cancer Moonshot[SM,] is a network of centers formed to conduct preclinical research focused on innovative strategies to understand and combat mechanisms of tumor resistance (intrinsic or acquired) and to exploit tumor sensitivity to anti-cancer therapies. The overarching goal of the DRSN is to develop preclinical data to support novel concepts in cancer drug resistance that have a feasible path for clinical validation. The DRSN centers use sophisticated laboratory techniques, preclinical models, and human-derived biospecimens to study methods of overcoming clinical cancer drug resistance.

The DRSN comprises (a) five U54 Drug Resistance and Sensitivity Centers (DRSCs) awarded in 2018, (b) two administrative supplements awarded in 2018 to fund collaborative projects with specific DRSCs, and (c) three supplements awarded in 2019 (Figure 8). The research efforts of each DRSC are based on two or three well developed and interrelated research projects (Table 5).

MGH / MIT / Broad Institute DRSC (PI: Corcoran)

1. Overcoming adaptive resistance in cancers with RAS pathway activation

2. Surmounting the heterogeneity of acquired resistance to receptor tyrosine kinase inhibition

3. Identifying and overcoming resistance to immune check-point inhibition

MSKCC / University of Washington / Fred Hutchinson Cancer Research Center DRSC (PI: Sawyers)

1. Resistance in castration resistant prostate cancer caused by androgen receptor (AR) pathway reactivation

2. Reversing resistance caused by lineage plasticity through epigenetic therapy

3. Combination trials with kinase inhibitors to prolong response to AR therapy

Mayo Clinic (Arizona & Rochester) / University of Minnesota DRSC (PI: Stewart)

1. Develop a high throughput drug screening platform for myeloma cell lines

2. Develop correlations between immunomodulatory drug response *in vitro* and *in vivo* with mutational profiles and expression signatures

3. Develop gene expression profiles to identify gene expression signatures that predict response to four proteosome inhibitors

OHSU DRSC (PI: Tyner)

1. Genetics and signaling of drug resistance in acute myeloid leukemia (AML) cell lines, xenografts, and primary patient samples

2. Impact of leukemia microenvironment on response to targeted therapies in AML

3. Drug combinations to enhance sensitivity and circumvent resistance

UCSF / Stanford University DRSC (PI: Bivona)

1. Characterize and therapeutically suppress residual disease during targeted therapy in non-small cell lung cancer

2. Define and interrogate the molecular and cellular basis of resistance and residual disease in lung cancers treated with current immunotherapies, including PD-1 and PD-L1 antibodies

Funding Opportunity	Grant/Project Title	Institution	Principal Investigator(s)
Drug Resistance and Sensitivity/Research to Identify and Treat Cancer Sensitivity or Resistance to Anticancer Therapy (CA-17-009)	Overcoming Drug Resistance in Multiple Myeloma	Mayo Clinic/University of Minnesota	Alexander Keith Stewart
	Tumor Intrinsic and Microenvironmental Mechanisms Driving Drug Combination Efficacy and Resistance in AML	Oregon Health & Science University	Jeffrey Tyner
	An Integrated Translational Approach to Overcome Drug Resistance	Massachusetts General Hospital/ Massachusetts Institute of Technology/ Broad Institute	Ryan Corcoran; Keith Flaherty
	The MSKCC-UW/Fred Hutch Prostate Cancer Drug Resistance and Sensitivity Center	Memorial Sloan Kettering Cancer Center/University of Washington/ Fred Hutchinson Cancer Research Center	Charles Sawyers
	Bay Area Team Against Resistance: Overcoming Resistance to Tyrosine Kinase Inhibitors in Epidermal Growth Factor Receptor Mutant Non-Small Cell Lung Cancer	University of California, San Francisco / Stanford University	Trever Bivona; Calvin Kuo
Administrative supplements to NCI grant and cooperative agreement awards to support collaborations with the Drug Resistance and Sensitivity Network (DSRN) (PAR-18-752)	Analysis of drug responses in BRAF(V600E)-driven lung cancer by single cell RNA-Seq	Huntsman Cancer Institute	Martin McMahon
	Exploiting RB1 deficiency for the treatment of lethal neuroendocrine prostate cancer	Roswell Park Comprehensive Cancer Center	David Goodrich
Notice of Special Interest: Administrative Supplements to Support Collaborations with the Drug Resistance and Sensitivity Network (DRSN) (NOT-CA-19-032)	Combined Natural Killer Cell and Targeted Drug Therapy to Treat AML	University of California, San Diego	Dan Kaufman
	The Role of CD86 in Multiple Myeloma	Emory University	Lawrence Boise
	University of Texas PDX Development and Trial Center	University of Texas MD Anderson Cancer Center	Jack Roth

TABLE 5: U54 DRSN AWARDS AND ADMINISTRATIVE SUPPLEMENT AWARDS.
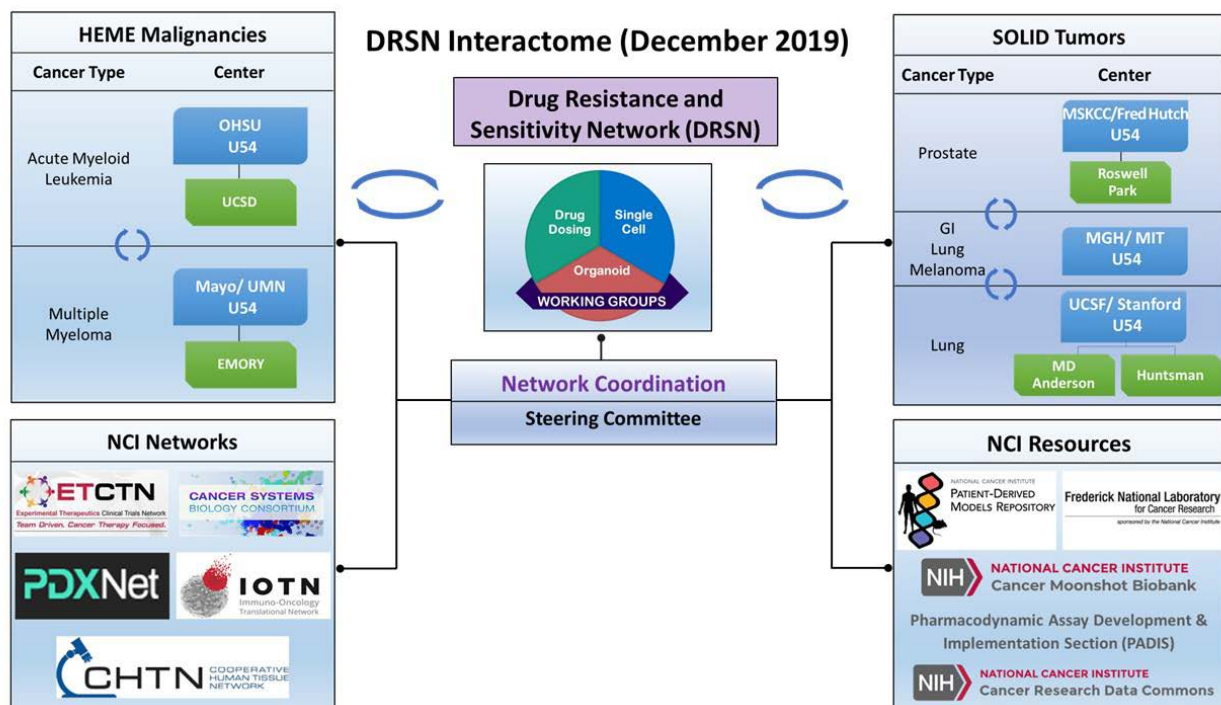
FIGURE 8: DRUG RESISTANCE/SENSITIVITY NETWORK SCHEMA.

Cancer Immune Monitoring and Analysis Centers – Cancer Immunologic Data Commons (CIMAC-CIDC) Network

The CIMAC-CIDC Network is a Cancer Moonshot[SM] initiative launched in September 2017. This network was established to address the critical importance of improving management of cancer in people receiving immunotherapy by identifying biomarkers for optimizing immunotherapeutic strategies.

CIMACs, CIDC, and clinical trial investigators design and conduct analyses correlating biomarkers with clinical data, including outcomes, from immunotherapy trials led by a range of NCI trial organizations (Figure 9). Specifically, each

CIMAC encompasses a multidisciplinary group with basic, translational, clinical, and computational research expertise and provides a wide range of state-of-the-art analyses for genomic, phenotypic, and functional characterization of responses of people treated in NCI-funded early-phase immunotherapy trials using analytically validated and standardized platforms. The CIDC facilitates the network activities in the areas of:

- optimizing data collection methodologies suitable for immune-related biomarkers
- integrating clinical and assay data
- building a biomarker database platform for secondary use by the larger immuno-oncology community

The CIMAC-CIDC Network and Collaborating Clinical Trials
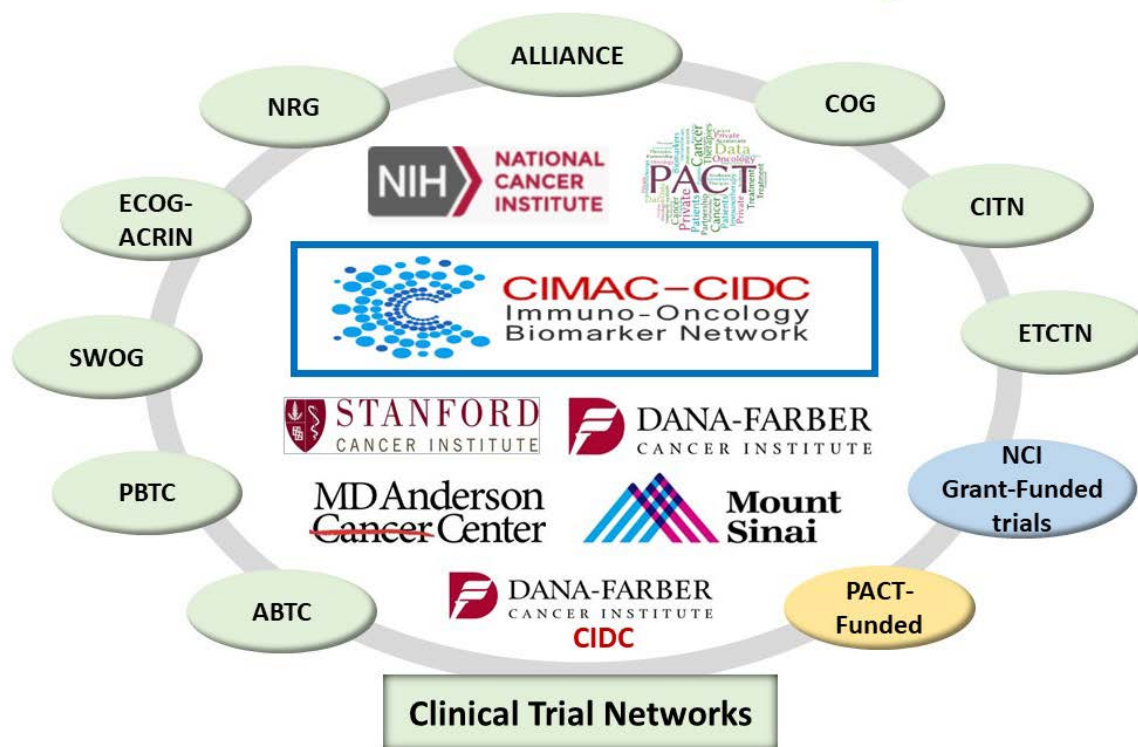
FIGURE 9: CENTERS IN THE CIMAC-CIDC, NCI AND PACT CLINICAL TRIALS NETWORKS.
CITN=Cancer Immunotherapy Trials Network; ETCTN=Experimental Therapeutics Clinical Trials Network; ABTC=Adult Brain Tumor Consortium; PBTC=Pediatric Brain Tumor Consortium; SWOG, ECOG-ACRIN, NRG, Alliance, and COG are members of the NCI Clinical Trials Network.

In February 2018, through the efforts of the Foundation for the NIH (FNIH), the CIMAC-CIDC Network formed a collaboration with the Partnership for Accelerating Cancer Therapies (PACT), a public-private partnership involving 12 leading biopharmaceutical companies, the NIH, and the FDA. PACT provides support for the CIMAC-CIDC infrastructure as well as correlative analyses in clinical trials, including NCI, academic, or industry-sponsored trials that focus on immunotherapy agents or their combinations.

The long-term goal of the CIMAC-CIDC-PACT Network is to develop a database of molecular signatures that define immune response categories to correlate with the clinical outcomes of immunotherapy in cancer. Collectively, the outcome of the network research should lead to the identification of biomarkers with translational potential for optimizing therapeutic strategies and improving outcomes of treatment for people with cancer.

In response to RFA-CA-17-005, four academic centers were awarded grants totaling $47,833,708 to form the CIMACs. In response to RFA-CA-17-006, one academic site was awarded $5,785,000 in grant funding to generate and maintain the CIDC (Table 6).

Activity Code	PI(s)	Grant Title	Lead Institution
U24	Catherine Ju-Ying Wu (contact); Frank Stephen Hodi	Cancer Immune Monitoring and Analysis Center	Dana-Farber Cancer Institute
U24	Sacha Gnjatic	High-Dimensional Immune Monitoring of NCI-Supported Immunotherapy Trials	Icahn School of Medicine at Mount Sinai
U24	Ignacio Wistuba (contact); Gheath Al-Atrash; Cara Haymaker	Translational Cancer Immune Monitoring and Analysis Center	University of Texas MD Anderson Cancer Center
U24	Holden Maecker (contact); Sean Curtis Bendall	Immune Monitoring and Analysis of Cancer at Stanford	Stanford University
U24	Xiaole Shirley Liu (contact); Ethan Cerami	Cancer Immunologic Data Commons	Dana-Farber Cancer Institute

TABLE 6: U24 CIMAC-CIDC AWARDS.

Pancreatic Cancer Microenvironment Network (PaCMEN)

The PaCMEN consortium consists of five U01 research project grants and one U24 resource center (Table 7). The NCI awarded these grants as a pancreatic cancer-directed initiative in response to the Recalcitrant Cancer Research Act of 2012. The consortium was also integrated into the Cancer Moonshot[SM] initiatives. The intent was to stimulate research to understand the interaction between pancreatic ductal adenocarcinoma (PDAC) and its microenvironment. The grants were preceded by a series of NCI Cancer Center one-year supplements in support of this research.

The goals of the PaCMEN consortium are to:

- study the tumor-microenvironment interactions in PDAC

- discover vulnerabilities in these interactions that could be exploited in the design of immunotherapies

- develop interventions that could lead to improved responses in preclinical models and clinical evaluation either in NCI-based early phase networks or by industry or NCI Cancer Centers

- serve as a hub for the broader research community involved in studies of the PDAC microenvironment

Through the Associate Membership status, several groups joined the consortium and periodically participate in its activities, calls, and meetings. Several collaborative studies evolved from these interactions. The consortium has already published more than 40 scientific papers, including the following topics:

- the angiotensin system as a target to improve immune responses to pancreatic cancer[1]

- real-time genomic characterization of advanced pancreatic cancer that enables precision medicine interventions[2]

- targeting cytokine therapy to the pancreatic tumor microenvironment using PD-L1-specific nanobodies[3]

- the inhibitory effect of macrophage-released pyrimidines on gemcitabine therapy in pancreatic cancer[4]

- broader collaborative efforts[5]

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[1] Pinter M and Jain RK. Sci Transl Med. 2017 Oct 4;9(410).
[2] Aguirre AJ, Nowak JA, Camarda ND, et al. Cancer Discov. 2018 Sept;8(9):1096-1111.
[3] Dougan M, Ingram JR, Jeong HJ, et al. Cancer Immunol Res. 2018 Apr;6(4):389-401.
[4] Halbrook CJ, Pontious C, Kovalenko I, et al. Cell Metab. 2019 Jun 4;29(6):1390-1399.
[5] Balachandran VP, Beatty GL and Dougan SK. Gastroenterology. 2019 May;156(7):2056-2072.

Activity Code	PI(s)	Grant Title	Lead Institution
U01	Vinod Balachandran	Defining Neoantigen Immunodominance for Antigen Selection and Biomarker Discovery in Human Pancreatic Cancer Immunotherapy	Sloan-Kettering Institute for Cancer Research
U01	Howard Crawford	Interrupting Cellular Crosstalk in the Immunosuppressive Microenvironment of Pancreas Cancer	University of Michigan
U01	William Hahn	Systematic Interrogation of the Pancreatic Cancer Microenvironment in Patient-Derived Specimens	Dana-Farber Cancer Institute
U01	Sunil Hingorani	Disrupting the Immune and Drug-Privileged Microenvironment to Improve Immunotherapy	Fred Hutchinson Cancer Research Center
U01	Rakesh Jain	Reprogramming PDAC Tumor Microenvironment to Improve Immunotherapy	Massachusetts General Hospital
U24	Anirban Maitra, Subrata Sen	Pancreatic Ductal Adenocarcinoma Translational Resource Center (PATReC)	University of Texas MD Anderson Cancer Center

TABLE 7: PACMEN CONSORTIUM'S RESEARCH PROJECT GRANTS AND RESOURCE CENTER.

PRECINCT Network for Canine Cancer Immunotherapy Trials and the Integrated Canine Data Commons (ICDC)

Cancers in pet dogs arise spontaneously (as in humans), and dogs have similar genomes, immune responses, environment, and tumor complexity to humans. In 2017, five sites were granted U01 awards to perform canine immunotherapy trials and correlative analyses for the purpose of investigating if dogs are a useful model for informing human cancer research (Table 8). These five sites comprise the PRECINCT Network: **PRE**-medical **C**ancer **I**mmunotherapy **N**etwork **C**anine **T**rials.

Two of the five sites are performing 3-5 pilot clinical trials of immunotherapy combinations with a larger clinical trial planned following selection of the best regimen from the pilot trials. These trials are for osteosarcoma and DLBCL (diffuse large B cell lymphoma), and the pilot trials are near completion. One of the combinations from a pilot trial for osteosarcoma has performed so well that a pediatric clinical trial is planned based on the results. Another two sites are each conducting a single large clinical trial in brain tumors (gliomas), with on target accrual. One glioma site is using an oncolytic virus in combination with an inhibitor (1-Methyl-D-tryptophan) that modifies the immunosuppressive tumor microenvironment. The other site is also using a combination approach, although with a tumor lysate vaccine. The final site is treating lung metastases from osteosarcoma and melanoma with inhaled IL-15 and super-agonist IL-15. In all five grants, correlative analyses to investigate mechanisms of immune response and tumor regression will be undertaken. DCTD staff, the NCI intramural Comparative Oncology Program, colleagues in the Cancer Moonshot Immuno-Oncology Translational Network, and associate members provide input to the sites.

NCI support for canine cancer research is meant to further human cancer research via analysis across the two species. An environment for the storage and analysis of large amounts of various data types is essential to this endeavor. The NCI has therefore initiated an ICDC that will contain clinical trial information and correlative data derived from the PRECINCT Network and the Center for Cancer Research's Comparative Oncology Trials Consortium (COTC), as well as sequencing data from studies supported by P30 grant supplements. The ICDC is a node in the larger NCI human Cancer Research Data Commons (CRDC) and was developed to incorporate genomic, proteomic, imaging, clinical trial, biomarker, population study, cancer model, and immuno-oncology data. Investigators will be able to query across canine and human data sets using a web-based interface (an ICDC Portal is under development) and perform analytical operations using NCI cloud-based resources and tools. The ICDC will serve as a resource for canine researchers to submit and access data related to cancer and will empower the cancer research community to generate new hypotheses that can be tested by comparative analysis in dogs and humans.

The ICDC is currently in the prototype development stage at the FNLCR, guided by a Steering Committee consisting of subject matter experts from the extramural and intramural veterinary and human cancer research communities, as well as staff from the NCI and FNLCR. A Data Governance Advisory Board was established to define the processes for accepting new data submissions, evaluating proposals, and providing to the NCI a recommended prioritization for inclusion in the ICDC. A Best Practices Subcommittee and its specific working groups have also been established to recommend clinical, pathological, immunological, imaging, and sequencing data standards for the ICDC. The group has also worked with a semantics team to ensure the application of standard definitions/language throughout the harmonization and coding processes.

STIMULATION OF CELL-BASED IMMUNOTHERAPY PRODUCTION

Workshop on Cell-based Immunotherapy for Solid Tumors

Cell-based immunotherapies have had remarkable success in the clinic, specifically in the treatment of hematologic malignancies. However, these strategies have had limited efficacy in people with solid tumors. To better understand the challenges involved and how to facilitate further progress in the field, DCTD brought together extramural researchers and NCI staff for a Workshop on Cell-based Immunotherapy for Solid Tumors in December 2018. The goals were to discuss current efforts to apply cell-based immunotherapy to solid tumors, obtain insights into the critical knowledge gaps in the field, and receive recommendations for new NCI initiatives to help address major challenges.

Meeting participants emphasized four main types of challenges in further developing cell-based immunotherapy for people with solid tumors: scientific, clinical, technical, and regulatory. Specific obstacles and research gaps identified during the meeting included:

- Target selection and tumor specificity
- Immune cell trafficking and tumor penetration
- Overcoming the immunosuppressive tumor microenvironment
- Need for improved animal models for preclinical studies
- Lack of clinical trial harmonization
- Challenges of multi-institution trials (data tracking, indemnification, infrastructure support)
- Product inconsistencies due to starting material variability and lack of standardized manufacturing procedures
- Chain of custody and transport logistics for patient material
- Limited availability of GMP manufacturing space and critical resources (vectors, reagents, specialized assays)

Title of Grant	Type of Grant	PI(s)	Institution	Disease under investigation
Optimizing novel immunotherapy combinations targeting the tumor microenvironment in canine spontaneous osteosarcoma	U01	Dow/London	Colorado State University	Osteosarcoma
Enhancing the efficacy of immunotherapy in DLBCL using rational combination approaches	U01	London	Tufts University	DLBCL (diffuse large B cell lymphoma)
Canine Immuno Neurotherapeutics	U01	Chambers	University of Alabama at Birmingham	Glioma
Enhancing NK immunotherapy with first-in-dog trials of inhaled recombinant IL-15 and super-agonist IL-15 in naturally occurring canine cancers	U01	Canter/Rebhun	University of California, Davis	Osteosarcoma, melanoma (lung metastases)
Novel combined immunotherapeutic strategies for glioma: Using pet dogs as a large animal spontaneous model	U01	Pluhar	University of Minnesota	Glioma
Coordinating Center for Canine Immunotherapy Trials and Correlative Studies	U24	Mason/Long	University of Pennsylvania	N/A

TABLE 8: U01 AND U24 CANINE IMMUNOTHERAPY CLINICAL TRIALS AWARDS.

- Regulatory challenges due to limited clinical experience with cell therapies for solid tumors

The workshop allowed NCI to identify these major challenges facing the extramural community, leading to various initiatives to move the cell therapy field forward. A long-term goal of the NCI is to promote greater efficacy and broad-based adoption of cell-based immunotherapies for both hematological and solid tumors.

Cell-based Immunotherapy Supplements

Given the lessons learned at the NCI Workshop on Cell-based Immunotherapy for Solid Tumors and other known challenges in the field of cell therapy, NCI provided supplemental funding to P30 Cancer Center Support Grants and P50 Specialized Programs of Research Excellence (SPORE) Grants for research projects that addressed specific challenges in cell-based immunotherapies for hematological malignancies and solid tumors. The supplements supported developmental and preclinical research projects, although investigators were required to have access to a GMP facility and the ability to later conduct clinical trials of cell-based cancer therapies.

Examples of potential research goals appropriate for these supplements included: identification of new targets for cell-based immunotherapy, improvements in vector manufacturing, improvements in therapeutic immune cell persistence and functionality, optimization of therapeutic immune cell trafficking, reduction in off-tumor toxicities, modulation of the immunosuppressive tumor microenvironment, and strategies to address treatment resistance. To accelerate research progress, supplement awardees are encouraged to meet regularly and discuss opportunities for collaboration.

Supported projects include:

- Image-guided CAR T-cell therapy for neuroblastoma
- Novel antigen discovery for CAR T-cell therapy of multiple myeloma
- Targeted cancer immunotherapy using natural killer cells engineered with a switchable chimeric antigen receptor system
- Adoptive cell therapy using CAR Th9 cells to address antigen loss resistance
- Method development for A2AR gene editing of CAR T-cells to enhance efficacy against solid tumors
- Expansion and persistence of allogeneic therapeutic T-cells by expression of a CD30-CAR

Cell Therapy Production Facility

To address the challenges in cell therapy manufacturing faced by researchers, NCI also began supporting the production of cell-based immunotherapies at Frederick National Laboratory for Cancer Research (FNLCR), making autologous cell therapy products available to intramural and extramural clinical trial investigators. The NCI Biopharmaceutical Development Program (BDP) at FNLCR, operated by Leidos Biomedical Research, Inc., provides centralized manufacturing of cell-based products in a current GMP (cGMP) facility, ensuring consistent and standardized processes and increasing reproducibility across studies. Clinical sites cryopreserve and ship T-cell source material to the BDP facility and, after a 2-week manufacturing and testing process, receive cryopreserved clinical product ready for infusion. This workflow also allows NCI to help manage product chain logistics, which is a significant challenge for investigators (Figure 10).
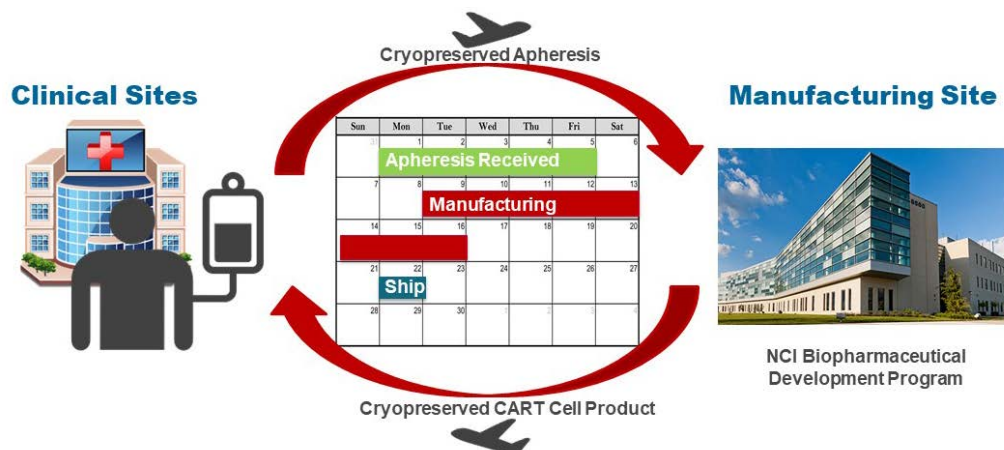
FIGURE 10: OVERVIEW OF BDP/FNLCR CAR-T CELL MANUFACTURING.

Current capabilities at FNLCR include production of CAR T-cells using a closed manufacturing system and lentivirus vector production. Retrovirus vector production processes are in development, and facility renovations are underway to allow for new cell therapy suites to come online in 2021.

FIGURE 11: OPERATION OF PRODIGY BIOREACTORS FOR CELL THERAPY PRODUCTION AT FNLCR.

The U.S. Food and Drug Administration approved an Investigational New Drug application for NCI to begin supporting a multicenter clinical trial of CD33 CAR T-cells in pediatric acute myeloid leukemia, and additional trials are in development. In addition, NCI is planning to collaborate with the National Institute of Standards and Technology, FDA, and other stakeholders to standardize product testing where appropriate.

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. The work of the NCTN continued in 2019 with the successful recompetition of the NCTN grant infrastructure.

Recent advances in deciphering the cancer genome that enabled the development of targeted therapies, such as imatinib (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 people with the same or different cancer type to identify those people 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 implements and completes trials far more rapidly than in the past. For physicians and their patients, important trials are 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 people whose tumors exhibit the molecular features that may be responsive to new, targeted treatments and/or immunotherapy approaches. In addition, biospecimens collected from people 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. and one Canadian Network Group. 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 members of a Network Group may enroll patients onto any NCTN trial if the site meets all trial-specific requirements. In addition, clinical trials led by NCTN Groups may utilize the Imaging and Radiology Oncology Core (IROC) Group (see Radiation Research Program, Assistance to the Cancer Research Community), Integrated Translational Science Awards (ITSAs), and the tissue banks, when appropriate, to support the scientific needs of the trial. The five U.S. NCTN Groups and the Canadian Network are:

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

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 person's 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 Pathology Investigation and Research Branch within DCTD's Cancer Diagnosis Program (CDP) supports the NCTN's specimen banking activities. NCTN clinical trials are uniquely positioned to provide high-quality biologic specimens associated with detailed treatment histories, recurrence data, and careful follow-up from patients over long periods of time. The NCTN Biospecimen Banks consti-

NCI National Clinical Trials Network Structure
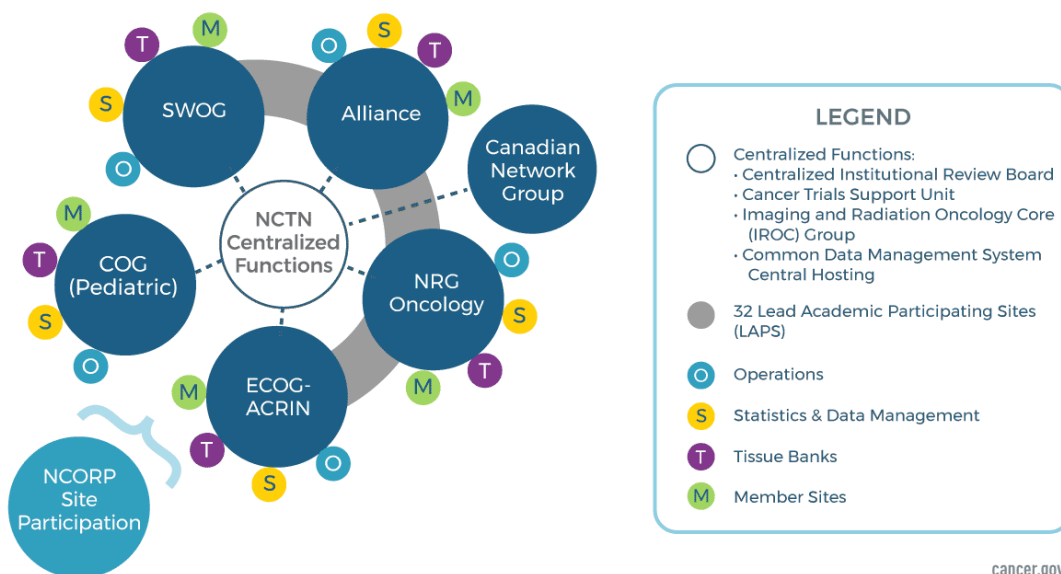
FIGURE 12: NCI NATIONAL CLINICAL TRIALS NETWORK STRUCTURE.

tute a large collection of well-annotated biospecimens from people enrolled on NCTN clinical trials run through the NCTN Groups. The five NCTN Biobanks work closely and effectively with each other, the NCTN Groups, and NCI, and play an integral role in the coordination of requests for specimens and analyses of research results involving biospecimens collected on NCTN trials. These requests are for:

- specimens collected for integral and integrated biomarker studies on trial protocols for the NCTN Group investigators

- "legacy" specimens remaining after the trials are completed and available to both NCTN Group investigators and the research community for correlative studies (approval is based on scientific merit by the NCTN Core Correlative Science Committee (NCTN CCSC) or NCI internal review)

The NCTN Biospecimen Banks developed the NCTN Navigator, a controlled access, web-based data access tool that launched in 2018 to allow researchers, including those not affiliated with the NCTN, to query the availability of specific specimens and request review and approval to obtain them for use in translational science studies. Currently, NCTN specimen collection and processing are being standardized, and harmonized, with informatics implementation, and transparent access procedures to make specimens more widely available for critical research, both within and outside the NCTN.

An update compiled for the NCI Board of Scientific Advisors in 2019 showed that during the period from 2013 to 2017 the NCTN Biospecimen Banks had collected 1,755,886 specimens. They distributed 440,114 specimens (410,248 solid tumors and 29,866 leukemia specimens), and 572 peer-reviewed scientific publications have resulted from the use of NCTN biospecimens and the associated data. During the same period, the NCTN Biospecimen Banks had served a total of 571 investigators; 223 NCTN Group investigators received specimens collected for integral and integrated studies, and 348 investigators received legacy specimens. Legacy specimens were distributed to 220 NCTN Group investigators and 128 non-Group investigators from the scientific community whose research proposals for correlative studies were approved by the NCTN CCSC based on scientific merit.

NCTN Sites

More than 2,200 NCTN sites from across the U.S. enroll patients in clinical treatment trials. These sites are augmented by member sites from the Canadian Network Group and other international member sites. The map in Figure 13 illustrates the location of U.S. sites that enrolled patients in 2019.
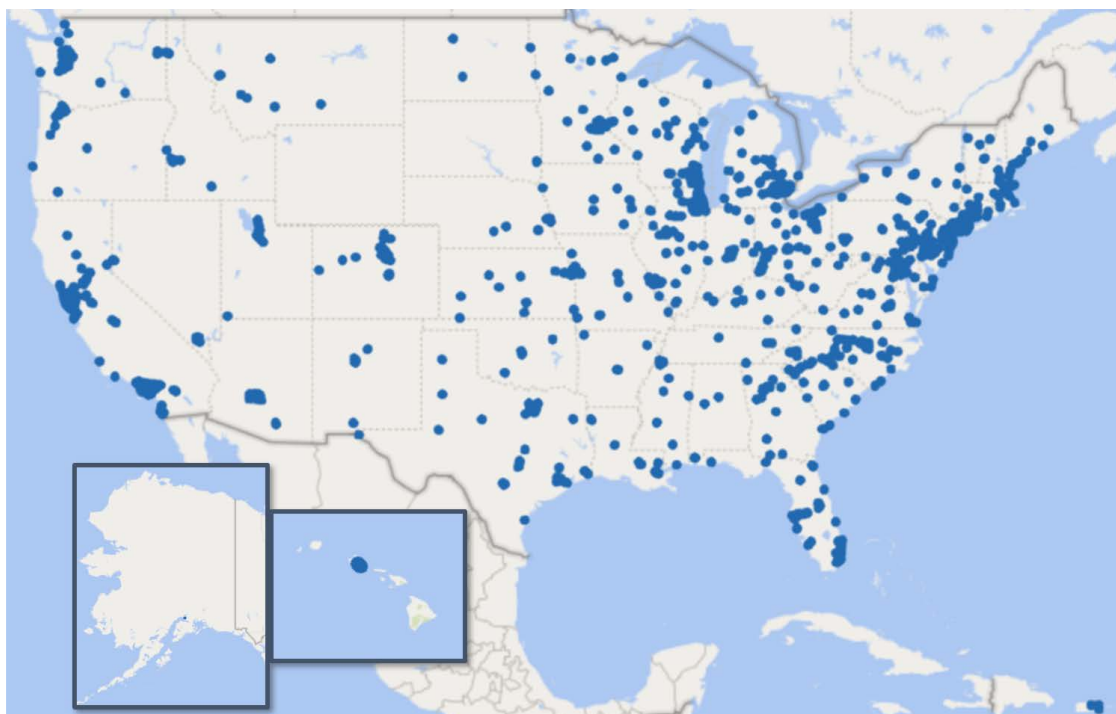
FIGURE 13: NCTN SITES THAT ENROLLED PATIENTS IN 2019.

Community Hospitals and Medical Centers

Many investigators at community hospitals and medical centers participate in NCTN clinical trials. These sites, as well as several 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 NCORP.

Lead Academic Participating Sites (LAPS)

Thirty-two U.S. academic research institutions were selected as LAPS. These sites are academic research institutions with fellowship training programs that have demonstrated their ability to enroll high numbers of patients onto NCTN trials, as well as to provide scientific leadership in trial 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 because of their high enrollment rate.

The 32 LAPS grantees 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
- Johns Hopkins University – Sidney Kimmel Comprehensive Cancer Center
- Mayo Clinic Cancer Center
- Medical College of Wisconsin
- Memorial Sloan Kettering Cancer Center
- Norris Cotton Cancer Center at Dartmouth Hitchcock Medical Center
- Northwestern University – Robert H. Lurie Comprehensive Cancer Center
- Ohio State University Comprehensive Cancer Center
- Roswell Park Cancer Institute
- Sidney Kimmel Cancer Center at Jefferson Health
- 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 Rochester Wilmot 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 (ITSA)

The NCTN contains a translational component, consisting of five academic institutions funded through an 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 five ITSA-funded institutions are:

- Children's Hospital of Philadelphia
- Emory University – Winship Cancer Institute
- Memorial Sloan Kettering Cancer Center
- Ohio State University Comprehensive Cancer Center
- University of North Carolina Lineberger Comprehensive 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 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

NCTN Statistics

Phase	Grant Year 2 (3/1/15 to 2/29/16) Studies/Screened/ Accrued	Grant Year 3 (3/1/16 to 2/28/17) Studies/Screened/ Accrued	Grant Year 4 (3/1/17 to 2/28/18) Studies/Screened/ Accrued	Grant Year 5 (3/1/18 to 2/28/19) Studies/Screened/ Accrued
Phase 1	5 / 0 / 144	6 / 3 / 60	4 / 23 / 47	5 / 11 / 43
Phase 2	88 / 1,049 / 2,531	102 / 1,146 / 2,550	105 / 613 / 2,537	98 / 511 / 2,141
Phase 3	86 / 2,816 / 11,371	80 / 2,639 / 11,381	83 / 2,294 / 10,752	84 / 2,477 / 9,566
Other/Pilot	7 / 1,191 / 1,895	6 / 5,208 / 2,680	4 / 2,868 / 1,315	5 / 2,078 / 1,634
Total	186 / 5,056 / 15,941	194 / 8,996 / 16,671	196 / 5,798 / 14,651	192 / 5,077 / 13,384
Total # Unique Patients	18,699	22,410	17,445	15,162

TABLE 9: TOTAL NUMBER OF NCTN TREATMENT & ADVANCED IMAGING TRIALS.
Enrolled Patients, Number of Patients Screened on Study, and Number of Patients Accrued to the Intervention for Each Year of the NCTN Grant.

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 10: 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 strategies to identify institutional barriers that prolong the time from initial approval of a study proposal to opening the study for enrollment

- 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 timelines based on study phase. Over time, these timelines have been tightened to further increase efficiencies. Phase I and Phase 2 studies now have a development deadline (i.e., the time from initial review of the study proposal to opening of the study to enrollment) of 400 days. Phase 3 studies have a development deadline of 540 days.

Funding is provided to network sites to monitor the protocol development process and participate in strategic conference calls between NCI staff and its investigators to quickly resolve any timeline bottlenecks. CTEP's Clinical Trials Operations and Informatics Branch (CTOIB) also supports 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.

The NCTN/NCORP Data Archive

The NCTN and the NCI Community Oncology Research Program (NCORP) clinical trials network evaluate therapies, diagnostics, and imaging approaches for the treatment, diagnosis, and prevention of cancer. The results of these NCI-sponsored clinical trials improve and lengthen the lives of individuals with cancer. These trials collect a large amount of information on each patient, including:

- clinicopathologic data - demographic and pre-treatment clinicopathologic characteristics

- on-treatment information - treatments received and adverse events

- outcome information - tumor response, quality of life measures, survival, etc.

Although individual trials are designed to provide convincing evidence to address their primary hypotheses, some research and clinical questions can only be answered by much larger datasets consisting of multiple trials. For example, analyzing treatment effects in defined subsets of patients (e.g., patients whose tumors have a specific mutation) or estimating the prevalence of rare adverse events requires pooling data across multiple trials. In addition, these trials frequently collect biospecimens and images from the patients.

The NCTN/NCORP Data Archive (the Archive) structure provides the ability to link the clinicopathologic and outcome data to molecular characteristics of specimens collected from trial participants (e.g., acquired by genomic analysis) and to clinical images. Remaining specimens from completed NCTN trials are catalogued in the NCTN Navigator, which facilitates access to those specimens for investigators with approved correlative science study proposals. Imaging data are made available to investigators through the Cancer Imaging Archive (TCIA). Databases bringing together such rich data sets provide valuable Big Data resources that can be leveraged by additional investigators to generate new biological and therapeutic insights.

The Archive was established in 2017 to be a centralized and controlled-access resource to allow the widest availability of patient-level data from completed Phase 3 NCTN and NCORP trials. The Archive complements other NCI data sharing activities that focus on genomic or imaging data as well as the sharing of specimens. The Archive contains data from NCTN/NCORP Phase 3 trials for which the primary publication was on or after January 1, 2015 or for which the non-primary publication was on or after April 1, 2018. The data submitted to the Archive includes patient-level data sufficient to reproduce the analyses presented in the publications of the trials. This ensures that the data are reliable, "cleaned," and include all key variables used in the publications.

Policies and agreements were developed for the Archive to make trial data widely available while protecting patient confidentiality, the data rights and intellectual property rights of the pharmaceutical companies for trials conducted under collaborative agreements, and the intellectual investments of the trial investigators. To protect patient confidentiality, Network groups deidentify trial data before submission to the Archive. A Data Use Agreement, required for each request for trial data, protects the data and intellectual property rights of pharmaceutical companies, as defined in NCI and/or Network Group Collaborative Agreements. Prior to trial data being made available in the Archive, pharmaceutical companies are given a six-month review period to assess whether time will be needed for a regulatory filing. The intellectual investment of the trial investigators is ensured by requiring Archive submission of trial data only after the trial results have been published. To ensure widespread availability of the Archive data to investigators, no scientific review of proposals is required. All trial data sets submitted to the Archive have an accompanying data dictionary that describes each variable. DCTD statisticians and contractors ensure that submitted datasets and dictionaries are understandable to researchers who were not intimately involved in the conduct of the trials.

A web-based, semi-automated system is used to handle the submission of trial data from the Network groups and subsequent requests for trial data from investigators. This includes processes for:

- Network groups to submit trial data and dictionaries to the Archive

- quality review for the submitted data and documentation

- pharmaceutical company review

- implementation of blinded patient codes that enable the linkage of clinicopathologic and outcome data in the Archive to other NCI resources that contain patient-level genomic data, biomarker data, and/or images

- registration of investigators who wish to view and request data in the Archive

- obtaining signatures on Data Use Agreements

- providing data Access for registered users whose requests have been administratively approved.

In addition, a link between the Archive and Project DataSphere was created, enabling requests for Archive trial data to be made through the Project DataSphere platform, thereby expanding public awareness of data available in the Archive.

Data from 110 trials have been submitted to the Archive, which collectively include individual-level data on over 95,000 people with cancer. Of these trials, 39 have specimens listed in NCTN Navigator, and one has imaging data in TCIA. There are more than 550 registered users of the Archive across the world. Sixty-eight requests for data from the Archive have been fulfilled, which have resulted in five published papers and four abstracts, with a variety of other manuscripts in preparation and submitted for publication.

NCTN Navigator

Most oncology biospecimens lack extensive clinical annotation and outcomes data. The biospecimen collections developed from cancer clinical trials conducted by the NCTN are highly annotated with carefully collected clinical data, including outcome data. The NCTN Navigator Clinical Trials Specimen Resource fills a gap by providing the research community access to these high-quality, clinically annotated specimens and associated clinical data from a variety of NCTN cancer trials that can be used to test clinically important hypotheses.

The Navigator inventory currently includes specimens from large adult treatment trials from which the primary outcome data have been reported. Specimens from newly completed trials are added on a rolling basis. Specimens from large NCTN pediatric trials are expected to be added in 2020. As of December 2019, the Navigator inventory includes more than 140 trials with more than 1,000,000 specimens across disease areas and treatment types.

Investigators interested in conducting research using specimens from NCTN trials can visit the Navigator website and readily explore the available specimens through the query tool. Any investigator interested in obtaining access to specific specimens from the Navigator inventory must submit a brief letter of intent (LOI) detailing the specimens in which they are interested. The LOI is not reviewed for scientific merit but rather serves to determine the availability of the specimens and associated data. If the LOI is found to be feasible, an investigator then submits a more extensive proposal describing their research project. NCTN Core Correlative Sciences Committees, comprised of NCI and extramural experts in oncology, laboratory science, translational medicine, pathology, statistics, biobanking, and patient advocacy perform a scientific review and prioritization of the proposals to ensure optimal use of these irreplaceable clinical trial biospecimens.

Since the launch of Navigator in April 2018, more than 80 LOIs have been submitted. Approximately three-quarters were deemed feasible, and most of those were followed by protocol submissions. A list of approved proposals, including those processed before Navigator launched, is publicly available.

NCI EXPERIMENTAL THERAPEUTICS CLINICAL TRIALS NETWORK (ETCTN)

Since the early 1970s, DCTD's Cancer Therapy Evaluation Program (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). 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 phase 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

- 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 14) 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 (Figure 15 and below) to support the conduct of trials in the network has been critical to the success of the program.

Experimental Therapeutics Clinical Trials Network
Lead Academic (12) and Affiliated Organizations (41 sites)
Experimental Drug Development Opportunities Program (15)

FIGURE 14: ETCTN PHASE 1 AND PHASE 2 PROGRAM SITES.
LAO = Lead Academic Organization; AO = Academic Organization; EDDOP = NCI Early Drug Development Opportunity Program.

ETCTN Central Infrastructure Support
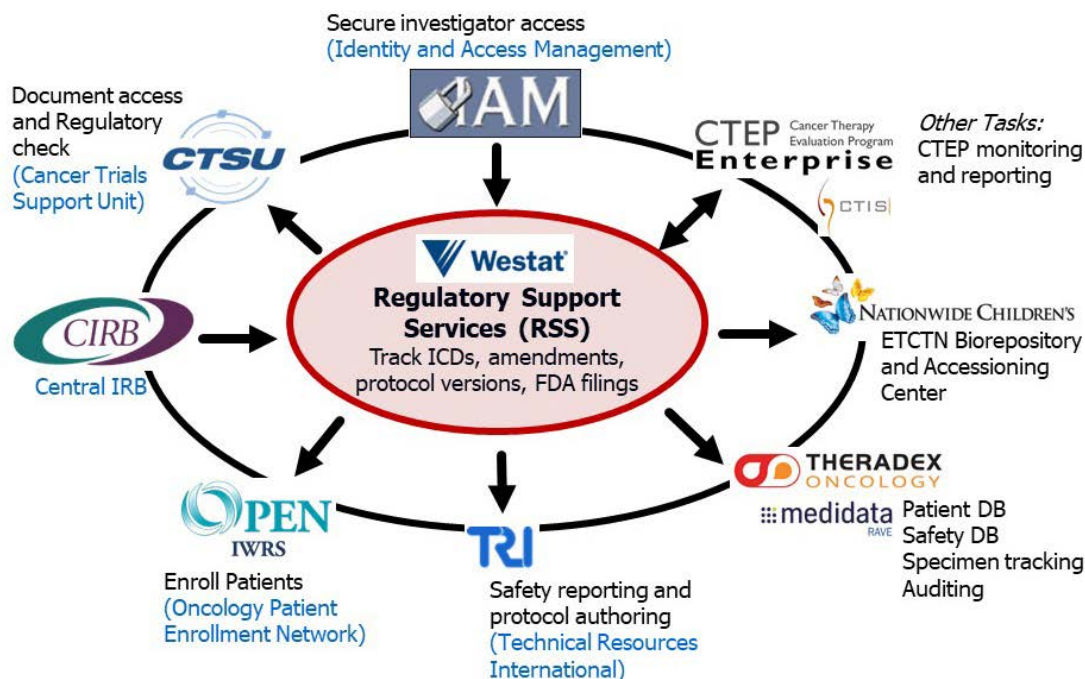
FIGURE 15: CENTRALIZED SUPPORT SERVICES FOR ETCTN.

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

Program Infrastructure

1. **CTEP-Identity and Access Management (CTEP-IAM)**
   Investigators and Associates register for an account that enables access to the other applications (CTSU, OPEN/IWRS, Rave, CTEP Enterprise).

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. **ETCTN Biorepository and Accessioning Center**
   The ETCTN Biobank collects, processes, and stores high-quality human biospecimens from enrolled people with cancer. The ETCTN Biobank also provides up-to-date maintenance of specimen inventory and distribution of specimens to qualified, NCI-approved trial investigators and research laboratories.

8. **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.

Activity Summary

From 2018 to 2019, investigators submitted 174 letters of intent (LOI). During this reporting period, the following occurred within CTEP-sponsored early-phase trials:

- Nine ETCTN project teams were implemented with nine agents, and another five agents went through limited drug development.

- 330 Project Team Member Applications were received, and 104 were approved to serve on CTEP project teams.

- 96 of 174 (55%) LOI submissions were approved or approved on-hold for protocol development.

- Twelve trials were administratively completed or completed (two were Phase 1 studies).

- 28 trials were closed to accrual or closed to accrual and treatment (eight 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.

There are 89 active trials (including ETCTN and ETCTN transition trials) of 48 investigational agents and 69 combinations with one or more NCI investigational agents. The CTEP Phase 1 or 1/2 trials account for 61% 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 PI3 kinase, tyrosine kinases, epidermal growth factor receptor, fibroblast growth factor receptor, angiogenesis, mTOR, cell cycle progression, histone deacetylases, the proteasome, heat shock proteins, and poly (ADP-ribose) polymerase (PARP). New agent classes that are now part of the CTEP drug development program include oncolytic viruses, radiopharmaceuticals, antitumor vaccines, antibody drug conjugates and cellular therapies.

The ETCTN also includes studies of special populations (organ dysfunction), novel study designs (accelerated titration, isotonic design, continual reassessment method, Bayesian optimal interval design and other randomized designs), and unique translational efforts (pharmacodynamic, pharmacokinetic, Next Generation Sequencing). 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)

The EDDOP program commenced in 2016 to make the ETCTN infrastructure more widely available to clinical investigators and consists of programs for study leadership and accrual. In the study leadership program, investigators from any NCI-designated Cancer Centers not affiliated with the ETCTN may submit clinical study proposals for NCI-IND agents. If approved, the investigator will receive full ETCTN support to conduct the clinical trial in the ETCTN and in their cancer center. In the accrual program, non-ETCTN NCI Cancer Centers can compete for administrative supplements to their NCI Cancer Center Support Grants (P30) to enroll patients on select ETCTN Phase 2 trials. As of December 2019, 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 9944: Gemcitabine Hydrochloride Alone or With M6620 in Treating Patients With Recurrent Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

Principal Investigator: Panagiotis Konstantinopoulos; Dana-Farber – Harvard Cancer Center

   This randomized Phase 2 trial studies how well ATR kinase inhibitor M6620 (M6620) and gemcitabine hydrochloride work compared to standard treatment with gemcitabine hydrochloride alone in treating people with ovarian, primary peritoneal, or fallopian tube cancer that has come back after a period of improvement. M6620 may stop the growth of tumor cells by blocking an enzyme needed for cell growth and may also help gemcitabine hydrochloride work better. Gemcitabine hydrochloride stops the growth of tumor cells by blocking their

growth and repair, but it is not yet known whether adding ATR kinase inhibitor M6620 to standard treatment with gemcitabine hydrochloride is more effective than gemcitabine hydrochloride alone in these patients.

Protocol 10104: Cabozantinib S-malate and Nivolumab in Treating Patients With Advanced, Recurrent, or Metastatic Endometrial Cancer

Principal Investigator: Stephanie Lheureux; University Health Network Princess Margaret Cancer Center

This randomized Phase 2 trial studies how well cabozantinib s-malate and nivolumab work in treating people with recurrent or advanced/metastatic endometrial cancer. Cabozantinib may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth, and the immunotherapy, nivolumab, may help the body's immune system attack the cancer by interfering with its growth and spread. Giving cabozantinib and nivolumab may work better in treating endometrial cancer.

National Clinical Laboratory Network (NCLN)

The ETCTN conducts early phase clinical trials of investigational anti-cancer agents, and these are arguably the most important trials in which to understand the pharmacodynamic (PD), genomic, transcriptomic, and proteomic underpinnings of outcomes in clinical trials. While the ETCTN is well-positioned to conduct these clinical trials, robust and reliable laboratory assays are needed to perform molecular characterization and PD studies. These are often "high-complexity" assays requiring a combination of specialized specimen collection and preparation, measurement expertise/experience, and test instrumentation to be successful and reliable. Many components of these molecular assay pipelines are not readily available to most investigators or are not operating under rigorous best practices. The NCLN was established to provide centralized, robust assays and expanded support for ETCTN studies. The NCLN will perform validated assays using certified operators and following harmonized SOPs, to include genomic characterization by means of next-generation sequencing technology and sophisticated, highly quantitative and reproducible multiplex PD assays on immunofluorescence and immunoassay platforms.

An NCLN Genomics laboratory was established at MD Anderson Cancer Center. When fully operational, it will perform NGS-based assays in a manner fully harmonized with the Molecular Characterization Laboratory at the Frederick National Laboratory for Cancer Research (FNLCR). These assays will include a targeted sequencing panel for tumor DNA, whole exome sequencing, RNAseq, and sequencing of circulating DNA on the Illumina platform. Two multiplex pharmacodynamic assays will also be established in the NCLN. A quantitative immunofluorescence assay for γ-H2AX and pNBS1 with β-catenin segmentation is being set up at MD Anderson using the SOPs developed by the PADIS group at FNLCR. The Molecular Pathology Laboratory Network, an independently owned company, established the multiplex apoptosis panel for analysis of tumor biopsy extracts by quantitative immunoassay on the Luminex platform. As additional assays undergo development and validation at FNLCR, they may be added to the NCLN test menu.

The NCLN also includes a dedicated biorepository at Nationwide Children's Hospital in Columbus, Ohio, which receives, processes, and distributes the samples collected on the ETCTN clinical trials, again according to reproducible and standardized SOPs. The centralized support for these complex assays will permit comparisons of assay results across trials, which is an advantage for those ETCTN project teams that conduct several trials of the same agent in different combinations and clinical settings.

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 people with advanced malignancies. At any one time, 25+ 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 applica-

tion in the NCI Experimental Therapeutics Clinical Trials Network (ETCTN). More than 300 patients with cancer were referred to DTC last year, predominantly from their primary physicians, and more than 170 patients were enrolled onto trials. The referral base for the early phase trials is predomi-

nantly from the continental US; however, for specialty trials, like alveolar soft part sarcoma (ASPS), the referral base is international. Referrals from other NCI Center for Cancer Research (CCR) clinics on campus has increased over the last few years.

Tissue Procurement/Correlative Pharmacodynamic Support Studies
• Tissue procurement protocol for the Developmental Therapeutics Clinic, NCI
Phase 1 trials
• Veliparib (ABT-888), an oral PARP inhibitor, and M6620, 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
• Phase I Study of Recombinant Interleukin 15 in Combination with Checkpoint Inhibitors Nivolumab and Ipilimumab in Subjects with Refractory Cancers
• A Phase I Study of Indenoisoquinoline LMP744 in Adults With Relapsed Solid Tumors and Lymphomas
• Phase IB Combination Study of Copanlisib and Nivolumab in Advanced Solid Tumors and Lymphomas
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
• DURVA+ : Evaluation of the Safety and Pharmacodynamics of Anti-PD-L1 Antibody MEDI4736 (durvalumab) in Combination with Chemotherapy in Patients with Advanced Solid Tumors
• 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
• A Phase 2 Study of Anti-PD-L1 Antibody (Atezolizumab) in Alveolar Soft Part Sarcoma
• 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
• DART: Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors
• Phase II Trial of the γ-secretase Inhibitor PF-03084014 in Adults with Desmoid Tumors/Aggressive Fibromatosis
• Phase II Trial of the MEK1/2 Inhibitor Selumetinib (AZD6244 hydrogen sulfate) in Adults with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas
• A Phase 2 Trial of The MEK Inhibitor Selumetinib (AZD6244 Hydrogen Sulfate) in Combination with the mTOR Inhibitor Sirolimus for Patients with Unresectable or Metastatic Malignant Peripheral Nerve Sheath Tumors
• A Phase 1b Study of Nivolumab in Patients with Autoimmune Disorders and Advanced Malignancies (AIM-NIVO)

TABLE 11: ACTIVE CLINICAL TRIALS IN DTC.

DTC plays a prominent part in the Precision Medicine Initiative® (PMI) through its role in leading the multicenter NCI-MPACT trial. This collaboration with the Molecular Characterization Laboratory (MoCha), located at the Frederick National Laboratory for Cancer Research, and the ETCTN was designed to evaluate the implementation of real-time molecular profiling and determine its feasibility in guiding cancer treatment decisions. DTC also participates in NCI-MATCH, a national clinical trial that analyzes each person'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 ASPS, adult soft tissue sarcoma, desmoid tumors, and tumors associated with mutant *BRCA1* or *BRCA2* genes (Table 11). In the last two years, DTC has entered the field of immunotherapy with a primary focus on exploring the changes of the tumor environment during PD1/PDl1 therapy.

Having pre-treatment and post-treatment biopsy tissue of adequate 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. Monthly dialogues continue to improve the quality of specimens obtained both at various NCI clinics and throughout the NCI-funded clinical research networks. Several workshops and publications elucidate the process and the improved PD specimens/results (Ferry-Galow, 2018).

DTC staff also capitalize on their co-localization with other outstanding researchers within the NIH Clinical Center by establishing collaborations with other investigators. They have joined 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 enable the enrollment of children onto DTC-sponsored adult trials, and for DTC to provide care to adults enrolled on POB trials. Investigational imaging agents have also been incorporated into several trials to address efficacy and MOA via collaboration with NIH Radiology and Imaging Sciences investigators. The most recent collaboration built upon NIH's Rare Tumor Initiative, with trials in development to offer treatment options for people with rare tumors.

Recognizing that the increasing complexity of early-phase clinical trials and the development of novel therapeutic agents require 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. DTC is well known in the NIH Summer Internship Program, having had summer interns for the last 5 years with active participation in the annual NIH Poster Day every August.

PHARMACODYNAMIC ASSAY DEVLOPMENT AND IMPLEMENTATION SECTION (PADIS) AND MOLECULAR CHARACTERIZATION LABORATORY (MOCHA)

PADIS

DCTD established PADIS at the Frederick National Laboratory for Cancer Research (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 tissue biopsies from patients with cancer. 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 based on compounds in the NCI Experimental Therapeutics (NExT) Program undergoing preclinical development or Phase 1 trials to be conducted in the NCI Developmental Therapeutics Clinic (DTC) or the Experimental Therapeutics Clinical Trials Network (ETCTN). Once PADIS develops an assay, 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 NIH 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. This approach is applied to pre-clinical and clinical tissue and blood specimens for both extraction and image-based assays.

To bring quantitative methodology to bear on analysis of patient specimens, PADIS brings new technologies online, 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. Currently, PADIS is 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.

Recently PADIS has actively engaged in the implementation of a National Clinical Laboratory Network (NCLN) that can provide specimen analysis for patients enrolled in DCTD-sponsored clinical trials. Extraction- and image-based biopsy analyses have been deployed, and additional assay transfers are planned, including PD assays for circulating tumor cells (CTCs).

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.

- The three assay subpanels have been harmonized with the NCLN laboratory MPLN, Maryville, TN. These assays are available to ETCTN trials through NCLN.

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.

Clinical implementation of signaling pathway multiplex biomarker (for drugs targeting PI3k, AKT, mTORC, MEK, ERK, RAF, RAS).

- Signaling multiplex involving five panels were developed and validated for fitness-to-purpose and converted into kits produced by commercial vendors.

  Panel-1: AKT1, AKT2, AKT3, rpS6

  Panel-2: pT308-AKT1, pT309-AKT2, pT305-AKT3, pS235-rpS6

  Panel-3: pS473-AKT1, pS474-AKT2, pS472-AKT3, pS240/244-rpS6

  Panel-4: ERK1, ERK2, MEK1, MEK2,

  Panel-5: pS218/S222-MEK1, pS222/S226-MEK2, pT202/Y204-ERK1, pT185/Y187-ERK2

- In collaboration with Dr. Brigitte Widemann from the Center for Cancer Research, clinical readiness of all panels was demonstrated in core and skin biopsies from people with neurofibromatosis type-1 (NF1) and inoperable plexiform neurofibromas (PN).

- Further application of Panels 1-3 is awaiting completion of accrual of paired patient biopsies in NCI 10131: A Phase 1 Study of AZD8186 in Combination with Docetaxel in Patients with *PTEN* Mutated or *PIK3CB* Mutated Advanced Solid Tumors, Potentially Amenable to Docetaxel.

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, γH2AX, 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 preclinical models and clinical specimens from patients in DCTD trials. In response to this
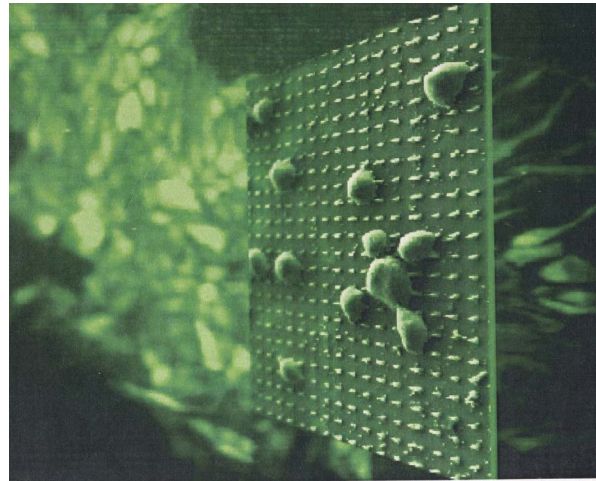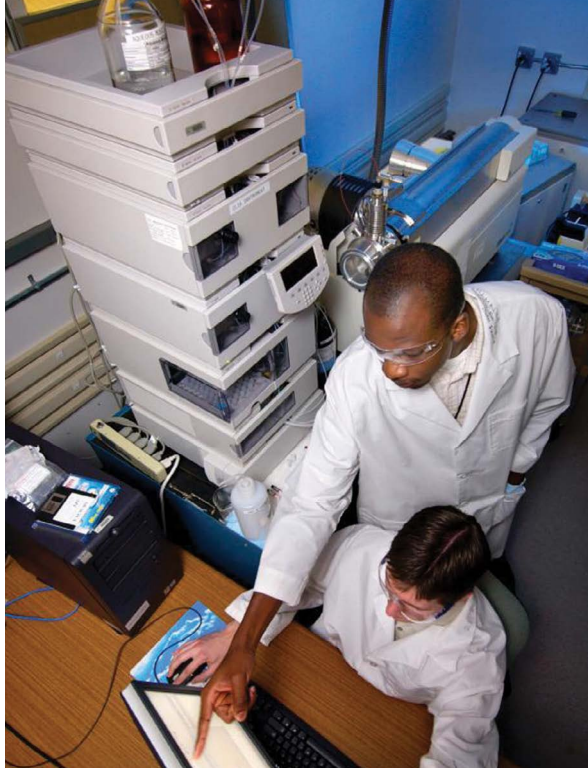
discovery, PADIS developed and clinically validated a multiplex for determination of cell cycle state for application on patient biopsies, to be used in conjunction with the DDR assay, to aid in understanding PD of new agents and combinations. The initial DDR multiplex was deployed in support of a DTC trial of the Wee1 Kinase inhibitor (AZD6244).[6]

As a further consequence of these studies, PADIS researchers developed an assay that combines colocalization of cleaved (activated) Caspase 3 with pS133 H2Ax as an accurate method to assess drug-induced apoptosis in clinical biopsy specimens and distinguish those cells from pS133 H2Ax expression induced as a DNA damage response (Wilsker, 2019; Dull, 2018).

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 (Srivastava, 2018)

Circulating Tumor Cells. 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 for enabling more frequent testing of drug effect. This represents the most extensive exploration of this technology in the NCI. Assays for γH2AX 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 had no detectable CTCs using the anti-Epcam capture methodology, even though all 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 patients with sarcoma was obtained using a FISH assay for a tumor-specific driver gene rearrangement. Detection of CTCs from patients with advanced cancer 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.[7,8]

Epithelial to Mesenchymal Transition Assay. Multiplex assays have been developed to permit simultaneous demonstration and quantitation of the expression of E-cadherin, beta-catenin,

[6] Do Khanh, Wilsker D, Ji, et al. Phase I Study of Single-Agent AZD1775 (MK-1775), a Wee1 Kinase Inhibitor, in Patients With Refractory Solid Tumors. J Clin Oncol. 2015 Oct 20;33(30):3409-15.

[7] Balasubramanian P, Kinders RJ, Kummar S, et al. Antibody-independent Capture of Circulating Tumor Cells of Non-epithelial Origin with the ApoStream® System. PLoS One. 2017 Apr 12;12(4):e0175414.

[8] Wang L, Balasubramanian P, Chen AP, et al. Promise and Limits of the CellSearch Platform for Evaluating Pharmacodynamics in Circulating Tumor Cells. Semin Oncol. 2016 Aug;43(4):464-75.

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 people with resistance to treatment. Combining this assay with tumor-specific markers such as PSA, and stem cell markers, such as CD133, provides a powerful method for determining the transitional state of cells in tumor biopsies or CTCs (Navas, 2018; Navas, 2019).

T-Cell Activation Panel (TCAP1) Multiplex assay for Immuno-Oncology. PADIS has developed a 5-channel multiplex assay for monitoring T-cell activation initiated by checkpoint inhibitor therapies (CTLA-4 and PD-L1 inhibitors). The multiplex assay measures phosphorylation levels of CD8-zeta, ZAP-70, and SHP-2 in CD8 cells. In tumor biopsy specimens, distribution of CD8 cells within tumor vs mesenchyme, and along tumor margins is also measured.

A peripheral blood PhosFlow assay for the TCAP1 multiplex has also been developed for Flow cytometry analysis of CD8 and CD4 cell activation. The PhosFlow assay has been deployed within the DTC for analysis of clinical specimens to demonstrate utility and Clinical Readiness of the assay.

MoCha

MoCha at FNLCR assists with early phases of assay development and transition to clinical laboratory readiness. MoCha's clinical laboratory is Clinical Laboratory Improvement Amendment (CLIA)-certified, performing multiple analytically validated next-generation sequencing (NGS) assays in support of DCTD clinical studies and precision medicine initiatives. To support the clinical trials, MoCha has built a strong group consisting of histotechnologists, molecular biologists, quality assurance specialists, bioinformaticians, scientific project/program managers, scientists, and molecular pathologists. MoCha aims to improve clinical outcomes by providing a comprehensive assessment of key cancer-related genes in people's tumors.

MoCha collaborates with NCI to coordinate the activities and manage the NGS laboratory network that includes external subcontractors (Massachusetts General Hospital, MD Anderson Cancer Center, Yale University, Dartmouth College, and Nationwide Children's Hospital) and MoCha's CLIA laboratory. This network supports the NGS activities for the NCI Molecular Analysis for Therapy Choice (NCI-MATCH) Clinical Trial (CTEP-EAY131) and the NCI–Children's Oncology Group (COG) Pediatric MATCH Clinical

Trial (APEC1621SC). After concluding the screening of the initial 6,000 patients for NCI-MATCH in 2017, MoCha and the MATCH NGS Laboratory Network began to support the NCI-MATCH Archival Initiative, a correlative research proposal under NCI-MATCH. This study aims to determine whether "fresh" biopsies are required for precision medicine studies by assessing the concordance between treatment assignments based on molecular data using fresh biopsies (baseline specimens) compared to archival specimens. MoCha also continues to play a central role in reviewing applications for laboratory membership in the NCI-MATCH Designated Outside Laboratory Network, as well as in the administration of a qualification study given to all laboratories as part of the outside laboratory application process. To date, the Designated Outside Laboratory Network has contributed nearly 400 patients, demonstrating the feasibility of enrolling rare cancer arms.

NCI-COG Pediatric MATCH has screened more than 400 patients so far and, ultimately, may screen about 1,000 pediatric patients for somatic and germline mutations. As part of this support effort, MoCha has contracted with Nationwide Children's Hospital as the biorepository and preanalytical laboratory. Additional contracts have been established with Children's Hospital Los Angeles and Baylor College of Medicine for germline reporting. A germline validation study was completed to enable germline testing. Dartmouth and MD Anderson Cancer Center are subcontracted to support NGS for NCI-COG Pediatric MATCH alongside MoCha.

Given its extensive experience in the precision medicine arena, the MoCha laboratory was chosen to support the development of the 'Molecular Diagnostics Network' (MDNet) that will support three large Precision Medicine trials that are under development. The three initiatives (ComboMATCH, iMATCH, MyeloMATCH) each require extensive development of genomic assays that need to be customized for each study due to the broad variation in disease types and molecular targets. The MoCha laboratory has already begun validation of genomics assays designed for each initiative.

The MoCha clinical laboratory also supports NCI's Molecular Profiling-Based Assignment of Cancer Therapy (MPACT) for Patients with Advanced Solid Tumors Clinical Trial (CTEP Protocol #9149). This study recently reopened to recruitment after a planned pause for analysis, and it is now screening patients using the Oncomine™ Comprehensive Assay version 3 assay. To date, more than 350 patient samples have been sequenced.

The MoCha CLIA laboratory has begun support of the NCORP Tissue Procurement Protocol (CTEP Protocol

#10231). The protocol aims for 150 people with paired biopsies before and after treatment, with each person receiving an Oncomine™ clinical report. This clinical trial known as the 'NCORP Pilot Trial' is a precursor to the Cancer Moonshot[SM] Biobank that aims to recruit approximately 800 pre/post biopsy specimens from patients on standard-of-care therapy. The specimens will also be tested with the Oncomine™ panel producing a clinical report of variants with careful annotation that the treating physician can choose to use for clinical care. The MoCha laboratory is responsible for managing all aspects of this project in close collaboration with DCTD's Cancer Diagnosis Program.

The MoCha laboratory has provided invaluable support and advice to the Cancer Moonshot[SM] project, CIMAC-CIDC (Cancer Immune Monitoring and Analysis Centers – Cancer Immune Data Commons), whose role is to perform immunologic biomarkers on specimens from NCI's National Clinical Trial Network studies. Because of their extensive experience in this area, MoCha has taught the CIMAC investigators optimal approaches to validation and harmonization of their assays to ensure reproducibility across the Network. In addition, they provided their genomic services to perform some of these harmonization experiments. The success of the CIMAC-CIDC Network is partly attributable to MoCha's involvement in this initiative.

The MoCha CLIA NGS and Histology laboratories are currently working to develop assays for MGMT (O-6-Methylguanine-DNA Methyltransferase) immunohistochemistry screening and a methylation assay based on reverse-transcription polymerase chain reaction in support of DTC studies. In addition, the MoCha CLIA NGS laboratory has recently begun a collaboration with the University of Maryland to review the commercially available Oncomine™ Myeloid Assay's clinical utility for potential use in future DTC studies. MoCha continues to keep NCI DCTD apprised of the progress of these development efforts.

Research and Development Activities

MoCha's Research and Development (R&D) group is involved with developing new technologies and has established robust research assays to support genomic characterization in blood and several tumor tissue types. MoCha's R&D group is directly involved in NCI's Patient-Derived Models Repository (PDMR) project. The goal of the project is to establish approximately 1,000 patient-derived models and make tumor material and associated genomic data from these models freely available to the research community for preclinical and other studies. In support of the project, MoCha generates all RNA sequencing and whole-exome sequencing data. The MoCha histopathology group also confirms the histopathology of all models and performs an immunohistochemical characterization of selected models of interest. In addition, efforts include the genomic characterization of models derived from rare and recalcitrant tumor types.

Other activities have included evaluating and optimizing cutting-edge assays, sequencing platforms, and data analysis methods. For example, the 10x Genomics Single Cell Sequencing platform and an assay to identify RNA fusions have been evaluated and are under development for formal implementation. Collaboration between MoCha laboratory staff and bioinformaticians has resulted in the ability to successfully evaluate genomic characteristics, such as tumor mutational burden (TMB), copy-number variants (CNVs), single-nucleotide variants (SNVs), and insertions/deletions (indels), using minimal amounts of starting material. Other activities include implementation of novel technologies, e.g., transitioning R&D sequencing assays from the Illumina® HiSeq 2500 sequencing platform to the newest Illumina sequencing instrument, the NovaSeq™ 6000. This required substantial testing and optimization but is an important step to increase both data output and sample throughput while decreasing sequencing times and overall cost.

MoCha has collaborated with two groups to evaluate and characterize NGS quality control standards. These materials will prove invaluable in the field by providing universal materials and guidelines that can be used to accurately determine assay performance. A partnership with the Foundation for the National Institutes of Health focuses on circulating tumor DNA (ctDNA) reference standards. Another project with Friends of Cancer Research specifically evaluates TMB reference standards.

The advantage of MoCha having both a CLIA-accredited clinical laboratory and an R&D laboratory is the ability to easily convert research-grade assays into clinical assays for care of people with cancer. The groups have collaborated on several projects aimed at identifying predictive biomarkers and understanding treatment response and resistance in tumors. Currently, the MoCha R&D and CLIA laboratories are collaborating to develop a clinical grade ctDNA assay, the Illumina TruSight Oncology 500. The assay is expected to support studies from the DTC, as well as other NCI-sponsored trials. MoCha has also been selected to receive over 4,000 NCI-MATCH blood samples as part of a correlative proposal to characterize ctDNA from NCI-MATCH.

MoCha has also established a network NGS laboratory as part of the NCLN to provide genomic support for ETCTN trials. The network NGS laboratory is currently located at MD Anderson Cancer Center and performs whole-exome and RNA sequencing. Setting up this Network has taken advantage of MoCha's extensive experience in harmonization and validation experiments for whole-exome and RNA and ctDNA sequencing workflows. As part of the NCLN, MoCha has subcontracted with Nationwide Children's Hospital as the biorepository and preanalytical laboratory for the ETCTN.

MoCha Leadership

MoCha senior leadership:

- participates in meetings such as the Association for Molecular Pathology, United States and Canadian Academy of Pathology, American Association for Cancer Research, and American Society of Clinical Oncology meetings

- shares experiences in clinical assay development, bioinformatics pipelines, and NGS application/assay design in clinical trials and studies

- stays abreast of the latest advancements by others in the field

The director of MoCha serves as one of the principal investigators for the MPACT, NCI-MATCH, and NCI-COG Pediatric MATCH clinical trials. In addition, members of MoCha are frequently invited to U.S. Food and Drug Administration/Center for Devices and Radiological Health workshops and roundtables for discussions about precision medicine and genomics.

SPECIALIZED PROGRAMS OF RESEARCH EXCELLENCE (SPORES)

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 alteration 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 SPORE and involving both basic and clinical or applied scientists in each research project

- Requiring a dedicated biospecimen/pathology 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 or theme

- 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 or are completed during the funding period

- Encouraging input and advice from patient advocates and the advocate community

SPOREs are located at academic centers or consortia in 20 states across the United States (Figure 16). Each SPORE is required to have a Biospecimen/Pathology Core facility to collect, annotate, and store 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 many 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. SPORE investigators have contributed over 135 fresh primary and metastatic tumor samples to the NCI Patient-Derived Models Repository (PDMR), have worked with this repository to develop several SOPs for shipping and handling of both cryopreserved and fresh human tissue, and have developed numerous PDX models derived from individual cases.

Several SPORE program investigators have accessed the drug development resources provided by the NCI Experimental Therapeutics (NExT) Program to help support cGMP manufacture and investigational new drug (IND)-directed toxicology studies of their novel investigational agents. For example, the NExT Program supported the Duke University Brain SPORE manufacturing of a cGMP lot of the oncolytic virus, PVS-RIPO, and conducted IND-directed safety studies in cynomolgus monkeys. Early results of the Phase 1/2 trial demonstrated that PVS-RIPO is safe to use in people with glioblastoma multiforme (GBM) and showed evidence of anti-tumor activity. Ongoing trials are also showing promising results with up to 8 years survival. The Mayo Clinic, Rochester Breast SPORE collaborated with NExT Program for the use of NCI's decitabine-derived compounds. This collaboration has led to preclinical work *in vitro* and in animals,

and the potential development of a Phase 2 clinical trial in triple negative breast cancer at Mayo Clinic, Rochester.

SPORE investigators are also 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, the MD Anderson Cancer Center Ovarian SPORE has obtained support from CTEP to sponsor STAR, a trial to determine the efficacy of sequential therapy with olaparib and AZD1775, a Wee1 inhibitor.

Finally, SPOREs have expanded to include research in cross-cutting themes, such as pediatric cancer and cancer health disparities. The Developmental and Hyperactive Ras Tumor SPORE, which consists of a team of investigators from several institutions and the NCI intramural researcher, Dr. Brigitte Widemann, focuses on treatment and survival of children and adults with Rasopathy disorders. TRP has also partnered with NCI's Center to Reduce Cancer Health Disparities (CRCHD) to develop the P20 SPORE Planning Grants, which supports investigators developing translational research programs in cancer health disparities. It is expected that research programs developed by the P20 awards should be competitive with other applications for a full P50 SPORE, addressing cancer health disparities as a cross-cutting theme.
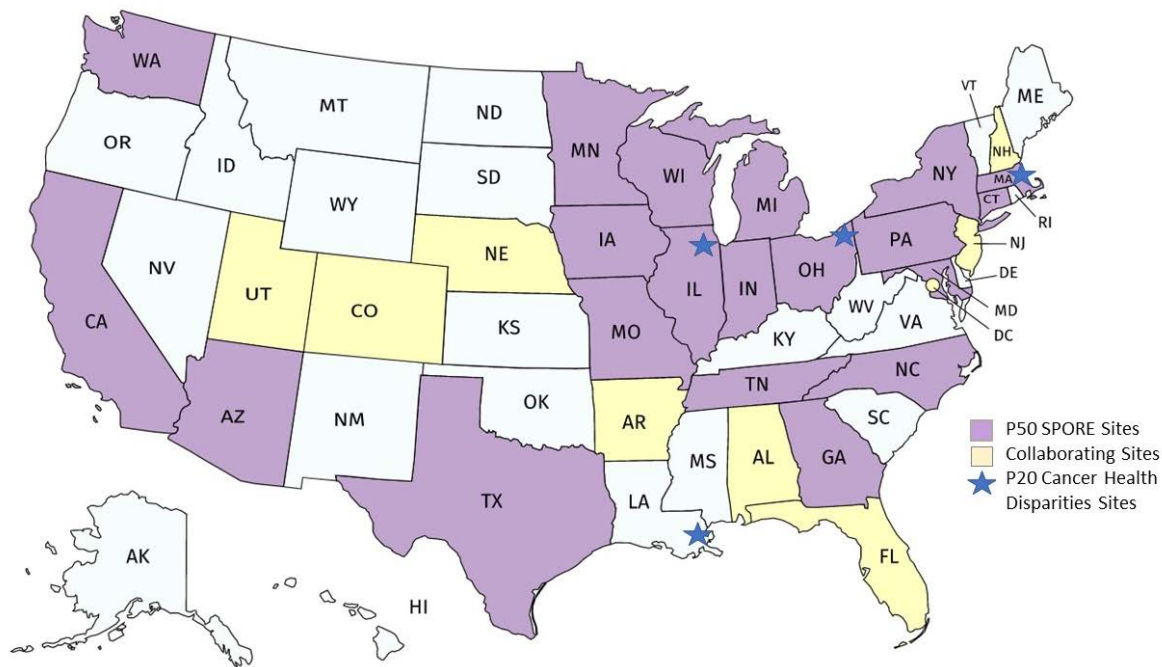
FIGURE 16: STATES WITH ACTIVE SPORE GRANTS IN FISCAL YEAR 2019.
Fifty-four funded SPOREs are located in 20 states within 30 institutions and collaborate with institutions in 8 additional states, including the District of Columbia. Four P20 SPORE Planning Grants in cancer health disparities are also funded in represented states, including Louisiana.

SPORE Scientific Accomplishments

SPORE researchers have been highly productive from 2018-2019 and have published more than 2,400 publications with relative citation ratios (RCRs) as high as 77 in leading journals. Several SPORE scientific accomplishments are highlighted in Table 12.

Institution	Organ Site	Summary
University of California, Los Angeles	Brain	**Neoadjuvant Anti-PD-1 Immunotherapy Promotes a Survival Benefit with Intratumoral and Systemic Immune Responses in Recurrent Glioblastoma.** *Nat Med.* **2019 Mar;25(3):477-486.** A randomized, multi-institution clinical trial evaluated immune responses and survival following neoadjuvant and/or adjuvant therapy with intravenous pembrolizumab (PD-1 blockade) in 35 patients with recurrent, surgically resectable glioblastoma (GBM). Neoadjuvant pembrolizumab was associated with upregulation of T cell- and interferon-γ-related gene expression.
Dana-Farber Cancer Institute	Breast	**Association of Cell-Free DNA Tumor Fraction and Somatic Copy Number Alterations with Survival in Metastatic Triple-Negative Breast Cancer.** *J Clin Oncol.* **2018 Feb 20;36(6):543-55.** Investigators evaluated somatic copy number alterations in metastatic triple negative breast cancers (TNBCs) relative to paired primary tumors and primary TNBCs in publicly available data sets. Results indicated that prespecified cell-free DNA tumor fraction threshold of $\geq$ 10% was associated with significantly worse metastatic survival, independent of clinicopathologic factors.
Baylor College of Medicine	Breast	**CAR T Cell Therapy for Breast Cancer: Harnessing the Tumor Milieu to Drive T Cell Activation.** *J Immunother Cancer.* **2018 May 10;6(1):34.** Chimeric antigen receptor (CAR) T cells were directed against mucin1 (MUC1) co-expressed with an inverted cyto-kine receptor linking the IL4 receptor exodomain with the IL7 receptor endodomain (4/7ICR). This combination transformed the IL4 signal into one that would enhance the anti-tumor effects of CAR T cells at the tumor site leading to T cell expansion, tumor control, in vivo persistence, and memory formation.
Johns Hopkins University & Mayo Clinic, Rochester	Gastrointestinal	**Detection and Localization of Surgically Resectable Cancers with a Multi-analyte Blood Test.** *Science.* **2018 Feb 23;359(6378): 926-930.** Investigators developed a blood test called CancerSEEK that can detect eight cancer types (ovary, liver, stomach, pancreas, esophagus, colorectum, lung, and breast) by assessing the levels of circulating proteins and mutations in cell-free DNA. This test was positive in a median of 70% of the eight cancer types and had sensitivities ranging from 69-98% in five cancer types (ovary, liver, stomach, pancreas, and esophagus).
MD Anderson Cancer Center	Gastrointestinal	**TAS-120 Overcomes Resistance to ATP-Competitive FGFR Inhibitors in Patients with FGFR2 Fusion-Positive Intrahepatic Cholangiocarcinoma.** *Cancer Discov.* **2019 Aug;9(8):1064-1079.** The irreversible pan-FGFR inhibitor TAS-120 was efficacious in four patients with FGFR fusion positive intrahe-patic cholangiocarcinoma (ICC) who developed resistance to the ATP-competitive FGFR inhibitors BGJ398 or Debio 1347.
University of Pittsburgh	Head & Neck/ Thyroid	**Analytical Performance of the ThyroSeq v3 Genomic Classifier for Cancer Diagnosis in Thyroid Nodules.** *Cancer.* **2018 Apr 15;124(8):1682-1690.** A DNA- and RNA-based next-generation sequencing assay, ThyroSeq v3, was evaluated for differentiating between malignant lesions and benign lesions using 238 tissue samples and 175 fine-needle aspirates (FNA) with known surgical follow-up. ThyroSeq v3 demonstrated high accuracy for detecting all common types of thyroid cancer and parathyroid lesions with a sensitivity of 98.0%, specificity 81.8%, and accuracy 90.9% in the FNA validation set.
UT Southwestern Medical Center	Kidney	**Phase I Dose-Escalation Trial of PT2385, a First-in-Class Hypoxia-Inducible Factor-2α Antagonist in Patients with Previously Treated Advanced Clear Cell Renal Cell Carcinoma.** *J Clin Oncol.* **2018 Mar 20;36(9):867-874.** First-in-human study of PT2385 was conducted to characterize the safety and efficacy of PT2385 dose in clear renal cell carcinoma patients. PT2385 was well tolerated, with anemia (grade 1 to 2, 35%; grade 3, 10%), peripheral edema (grade 1 to 2, 37%; grade 3, 2%), and fatigue (grade 1 to 2, 37%; no grade 3 or 4) being the most common treatment-emergent adverse events.

Institution	Organ Site	Summary
Washington University, St. Louis	Leukemia	**An "Off-the-Shelf" Fratricide-resistant CAR-T for the Treatment of T cell Hematologic Malignancies.** *Leukemia.* **2018 Sep;32(9):1970-1983.** A fratricide (self-killing)-resistant "off-the-shelf" CAR-T (UCART7) targeted CD7+ T cell malignancies and lacked both CD7 and T cell receptor alpha chain expression. UCART7 demonstrated efficacy against human T cell acute lymphoblastic leukemia (T-ALL) cell lines and primary T-ALL in vitro and in vivo without the induction of xenogeneic graft-vs.-host disease.
University of Colorado Cancer Center	Lung	**Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children.** *N Engl J Med.* **2018 Feb 22;378(8):731-739.** A unique cell line was generated and used in the screen for Larotrectinib, an agent exhibiting antitumor activity in patients with TRK fusion-positive cancer. Larotrectinib was approved by the FDA for solid tumors with NTRK gene fusions in November 2018.
City of Hope	Lymphoma	**CAR T Cells Targeting BAFF-R Can Overcome CD19 Antigen Loss in B Cell Malignancies.** *Sci Transl Med.* **2019 Sep 25;11(511).** Investigators developed humanized, second-generation CAR T cells against B-cell activating factor receptor (BAFF-R), non-CD19. BAFF-R-CAR, but not CD19-CAR, T cells demonstrated antitumor effects against an additional CD19 antigen loss primary PDX in vivo.
Mayo Clinic, Arizona	Myeloma	**Long-Term Follow-up of Monoclonal Gammopathy of Undetermined Significance.** *N Engl J Med.* **2018 Jan 18;378(3):241-249.** Investigators studied 1384 patients in Minnesota, in whom monoclonal gammopathy of undetermined significance (MGUS) was diagnosed at the Mayo Clinic from 1960 through 1994. Significant differences were noted in the risk of progression between patients with immunoglobulin M (IgM) MGUS and those with non-IgM MGUS, with shorter survival noted for MGUS patients compared to controls.
Roswell Park Cancer Institute	Ovarian	**Rapid Construction of Antitumor T-cell Receptor Vectors from Frozen Tumors for Engineered T-cell Therapy."** *Cancer Immunol Res.* **2018 May;6(5):594-604.** Investigators constructed a T-cell receptor (TCR)-expressing library from specimens that contain antigen-specific T cells, including frozen tumor biopsies. The engineered peripheral T-cells from the library-derived TCR-gene demonstrated antitumor effects in a tumor xenograft model.
Memorial Sloan-Kettering Cancer Center	Sarcoma	**Novel SS18-NEDD4 Gene Fusion in a Primary Renal Synovial Sarcoma.** *Genes Chromosomes Cancer.* **Epub 2019 Oct 21;59(3):203-208. doi: 10.1002/gcc.22814.** The study reports a primary renal synovial sarcoma with a novel gene fusion and unusual morphology. The patient was a 35-year-old female, and a definitive diagnosis of synovial sarcoma was made only subsequently to RNA-sequencing, which revealed a novel SS18-NEDD4 gene fusion.
Washington University, St. Louis	Pancreatic	**Agonism of CD11b Reprograms Innate Immunity to Sensitize Pancreatic Cancer to Immunotherapies.** *Sci Transl Med.* **2019 Jul 3;11(499).** A CD11b agonist (ADH-503) reduced the number of tumor-infiltrating immunosuppressive myeloid cells and, in turn, improved T cell immunity and effectiveness of check point inhibitors in previously unresponsive pancreatic ductal adenocarcinoma models.
University of Michigan & Fred Hutchinson Cancer Center	Prostate	**Inactivation of CDK12 Delineates a Distinct Immunogenic Class of Advanced Prostate Cancer.** *Cell.* **2018 Jun 14;173(7):1770-1782.e14.** Inactivating mutations of both alleles of the CDK12 gene defined a distinct subtype of metastatic castration-resistant prostate cancer.
Weill Cornell Medicine	Prostate	**N-Myc-mediated Epigenetic Reprogramming Drives Lineage Plasticity in Advanced Prostate Cancer.** *J Clin Invest.* **2019 Jul 1;130:3924-3940.** These studies outline a potential mechanism by which overexpression of N-Myc and its subsequent binding to DNA induced epigenomic and transcriptomic reprogramming in prostate cancer. The result was a castration-resistant, lineage-plastic phenotype that gives rise to neuroendocrine prostate cancer.

TABLE 12. EXAMPLES OF SPORE ACCOMPLISHMENTS 2018-2019.

NCI PATIENT-DERIVED MODELS REPOSITORY (PDMR) PROGRAM

In 2013, NCI began development of a national PDMR to serve as a resource for public-private partnerships and for academic drug discovery efforts. Patient-derived models (PDMs), such as patient-derived xenografts (PDXs) and cell lines, are thought to reflect human tumor biology more closely than established cell lines due to their low passage number, and thus are potentially more predictive models than traditional cancer cell lines which have been passaged in vitro for decades. The PDMs being developed for the repository are derived from tumor tissue from people with cancer and are propagated both *in vitro* using 2D or 3D cell culture systems and *in vivo* via passaging in mice as PDXs. The PDMR currently distributes:

- Viable PDX tumor fragments for implantation in mice

- Cellular fractions such as DNA and RNA

- Tumor fragments that can be used for protein extraction

- 3D organoid models (PDOrg)

- 2D *in vitro* cell cultures (early passage tumor cell lines [PDCs] and/or cancer associated fibroblasts [CAFs])

The publicly available PDMR database provides access to extensive molecular characterization information and clinical and social history for all models. A key goal of the PDMR effort has been to establish and make publicly available a set of SOPs for all aspects of PDM creation, propagation, and quality control.

Specimens for model development are collected from consenting people with cancer at the NCI Clinical Center, NCI-designated Cancer Centers, the NCI Experimental Therapeutics Clinical Trials Network (ETCTN), and the NCI Community Oncology Research Program (NCORP) through two NCI-sponsored tissue procurement research protocols allowing the patient biomaterial to be used for the generation of PDMs. In addition, NCI is working with external groups through several NCI funding opportunities who have:

- their own previously established early-passage PDX models

- access to rapid-autopsy tumor material

- viably cryopreserved patient material collected under Institutional Review Board (IRB)-approved protocols,

that with the proper material transfer agreements (MTAs) could be released to the PDMR for further propagation and distribution to the scientific community

The PDMR is an active member in the 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 collaboration between NCI and the Department of Energy (DOE) aims 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 of the PDMR 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 pre-clinical trial efforts by the research community. In addition to common cancers, the PDMR is also focusing on the creation of 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 6 years, the PDMR has received and processed over 8,400 specimens received from more than 5,200 patients covering a variety of malignancies (Figure 17). In addition, the PDMR has distributed over 1,000 vials of material to investigators in the pharmaceutical industry and academia, at major cancer centers across the United States.

The PDMR is also undertaking preclinical drug studies using PDXs developed in this program. An earlier effort using five standard of care agents against over 76 PDX models demonstrated response to these agents in the appropriate histology and at a similar percentage as that seen in the clinical setting. A large preclinical trial evaluating 56 novel therapeutic combinations in PDXs of rare cancers (mesothelioma, osteosarcoma, Hurthle cell cancer, etc) is ongoing to identify new therapeutic approaches for treating people with these tumors.

Tumor Specimens Implanted, by Disease Location

Legend:
- Breast
- Digestive/Gastrointestinal
- Endocrine and Neuroendocrine
- Genitourinary
- Germ Cell
- Gynecologic
- Head and Neck
- Hematologic/Blood
- Musculoskeletal
- Neurologic
- Respiratory/Thoracic
- Skin
- Unknown Primary

Pie values: 7, 211, 501, 78, 162, 1, 200, 126, 9, 156, 26, 181, 124
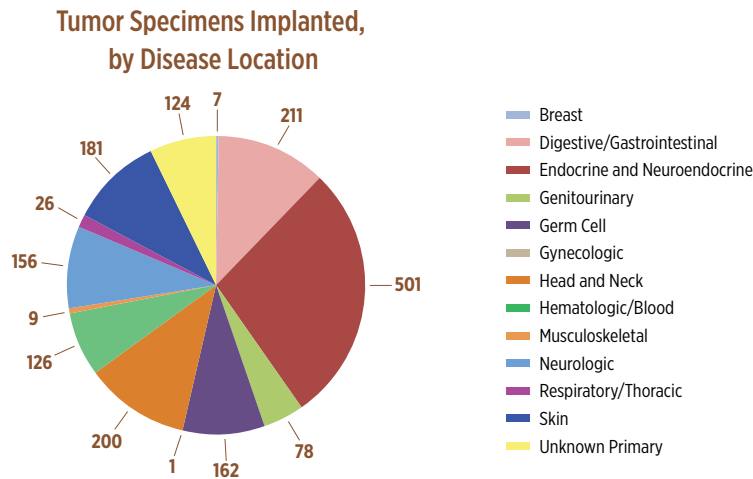
Blood Specimens no longer implanted after late 2016. Currently used for germline characterization.

Total Specimens Received	8419
Total Number of <u>Unique</u> Patients	5252
Total Specimens with PDXs at ≥P0 or with Confirmed Growth:	1790
Tumor (pie chart)	**1782**
CTCs (confirmed PDX out of >2800 implants)	**8**
Unique Patients with PDXs at ≥P0 or with Confirmed Growth:	1680
Total discontinued specmens:	6739

FIGURE 17: PDMR MODEL DEVELOPMENT.

Number of Tumor 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. Circulating tumor samples from blood samples shipped overnight had a <0.01% take rate, so model derivation is no longer attempted from those specimens.

THE CANCER IMAGING ARCHIVE (TCIA)

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 hosted at the University of Arkansas for Medical Sciences that would fill the unmet needs of cross-disciplinary image researchers for open access to clinical images. More than 111 datasets of computed tomography, magnetic resonance imaging, positron emission imaging, x-ray mammography, digitized histopathology slides, and radiation therapy planning imaging studies are currently available in TCIA. There are at least 800 peer-reviewed publications based upon these TCIA-hosted data (Figure 18), and more are likely as most of the collections are completely open and available for public use.

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Publications	5	10	16	38	46	83	130	141	160	226
Cumulative	5	15	31	69	115	198	328	469	629	855
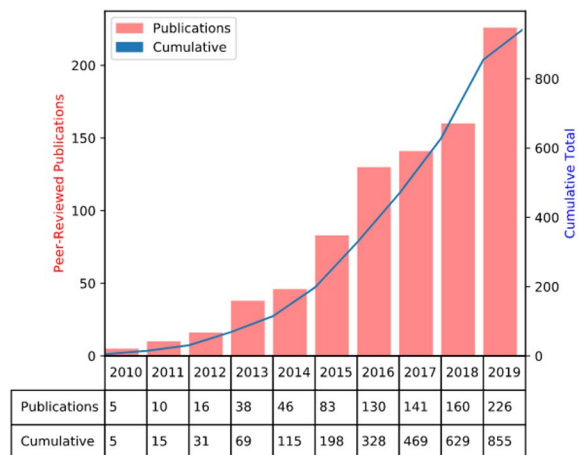
FIGURE 18: PUBLICATIONS BASED ON TCIA DATA SINCE INCEPTION.

More than three quarters of the datasets also have associated supporting data, such as demographics, outcomes, therapy, image analyses, pathology images, genomic, and proteomic data. TCIA maintains the documentation and meta-data for each of its collections and provides a help desk staff to assist with questions about the data from the research community. The archive has data from more than 46,000 patients and includes more than 45 million individual images. Each month, more than 15,000 unique users visit the site and download approximately 60 terabytes (TB) of data from the archive (Figure 19).
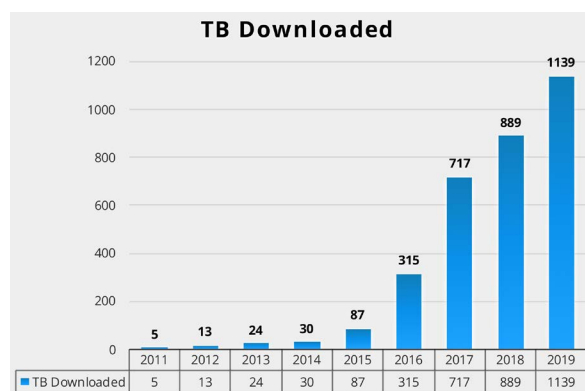
FIGURE 19: TCIA DISTRIBUTION TO RESEARCHERS (DATA DOWNLOADS).

The archive sets the stage for real-time, multi-institutional image accessibility that could support protocol stratification strategies for a variety 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, protection of Private Health Information while still preserving the scientific utility of the data is critical. TCIA has developed robust tools and 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 publish the submitted images. Further refinement and testing of advanced, standards-based tools are routinely performed to enable more efficient de-identification of medical image data for public consumption. TCIA provides full research-focused de-iden-

tification services and makes its tools and knowledge base available to the scientific community.

Crediting Data Generators for Data and for Data Reuse

To enhance research reproducibility and validation, and to encourage data submissions from academic researchers, TCIA freely provides standards-based Digital Object Identifiers (DOIs) for each of its data collections and to researchers using customized data cohorts. The DOIs are frequently used to reference data in peer-reviewed publications, support data-use tracking, and provide authorship citations for use in academic CVs.

Imaging-Proteogenomics Research Support

TCIA is part of two major NCI programs that are collecting medical and pathological images matched to proteomic, as well as genomic, clinical, and pathological data. For the Clinical Proteomic Tumor Analysis Consortium (CPTAC), TCIA has collected and hosts more than 1,500 patients' histopathology images, 400 patients' radiology images, and coordinates a special interest group that meets monthly to support cross-disciplinary research across imaging and omic data. TCIA's leadership participation in the Applied Proteogenomics OrganizationaL Learning and Outcomes (APOLLO) network, a collaboration between NCI, the Department of Defense (DoD), and the Department of Veterans Affairs, has allowed extension of TCIA's data curation and collection capacity to the VA's research Precision Oncology Project. It has successfully supported multiple pilot data collection activities and will be the imaging data collection and characterization portal for the APOLLO 5 prospective data collection. TCIA collected and hosts radiological imaging from The Cancer Genome Atlas (TCGA), along with the results of characterization and analysis work done by TCIA-TCGA imaging phenotype research groups.

Quantitative Imaging Network (QIN) Support

TCIA facilitates data sharing among CIP's growing QIN. Eleven 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-in-

stitutional 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 images from both arms of the NLST trial from 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.

NCI National Clinical Trials Network (NCTN) Support

In 2019 TCIA received funding to expand its data collection services to support the NCTN. Imaging data associated with NCTN trials are being centralized and de-identified under a subcontract with the Imaging Radiation Oncology

Core (IROC). The TCIA team has documented its curation procedures and trained IROC staff to apply them. Trial image datasets will then be shipped to TCIA for final review and linked with clinical data hosted in the NCTN/NCORP Data Archive.

Preclinical Imaging Support

Although not a major focus for TCIA, it also hosts some high value preclinical image collections. These include studies of specialized phantoms, devices that permit standardization of quantitative imaging parameters across instruments and site, as well as imaging studies of patient-derived xenograft models from the NCI Patient-Derived Models Repository and canine clinical trial data from the Canine Immunotherapy Trials Network.

Community Awareness Building

TCIA has become a vital resource known throughout the global cancer imaging community (Figure 20).

Country	Acquisition Users ↓
	165,517 % of Total: 100.00% (165,517)
1. United States	55,415 (32.53%)
2. China	21,144 (12.41%)
3. India	16,979 (9.97%)
4. Japan	8,051 (4.73%)
5. United Kingdom	5,426 (3.18%)
6. Germany	4,131 (2.42%)
7. Canada	3,833 (2.25%)
8. South Korea	3,498 (2.05%)
9. France	3,041 (1.78%)
10. Brazil	2,884 (1.69%)
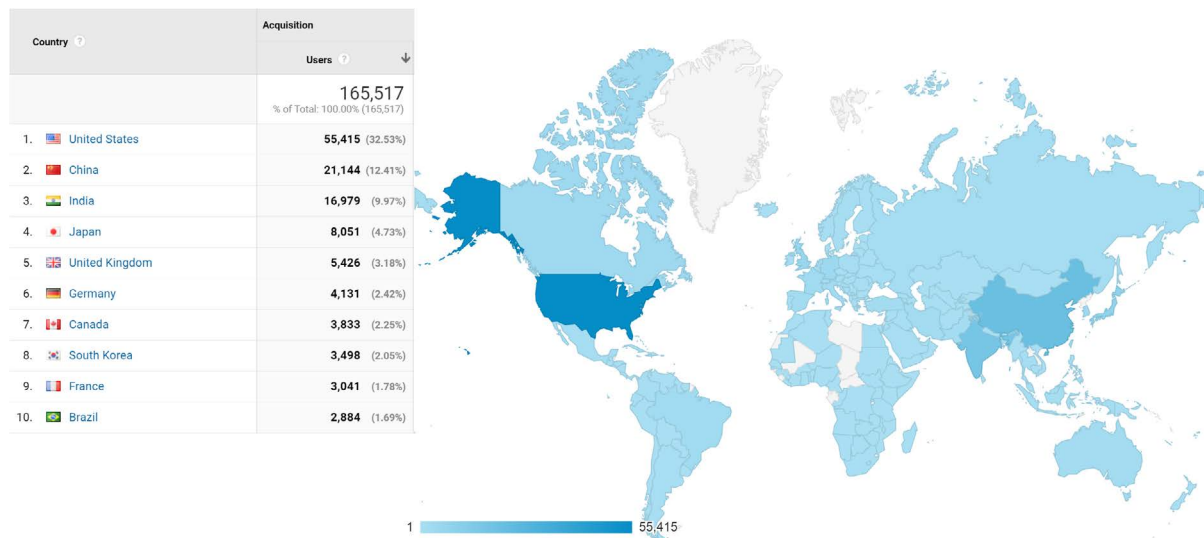
FIGURE 20: GLOBAL ACCESS TO TCIA.
Shading indicates relative number of unique users visting TCIA in 2019.

Approximately one third of TCIA users are from the U.S. and Canada, one third from China, India, Japan, and Korea, and the remaining third from the rest of the world. TCIA provides regular updates on social networks, and CIP hosts a wide variety of TCIA-centric sessions during annual meet-ings of the Radiological Society of North America to stim-ulate interest and cross-fertilize ideas. TCIA is an officially recognized data repository for leading journals such as those of the Nature Group. The number of users accessing TCIA datasets each year continues to grow (Figure 21).

Total Users

	2011	2012	2013	2014	2015	2016	2017	2018	2019
Total Users	2956	10814	21350	22830	32517	47936	79398	109965	164528
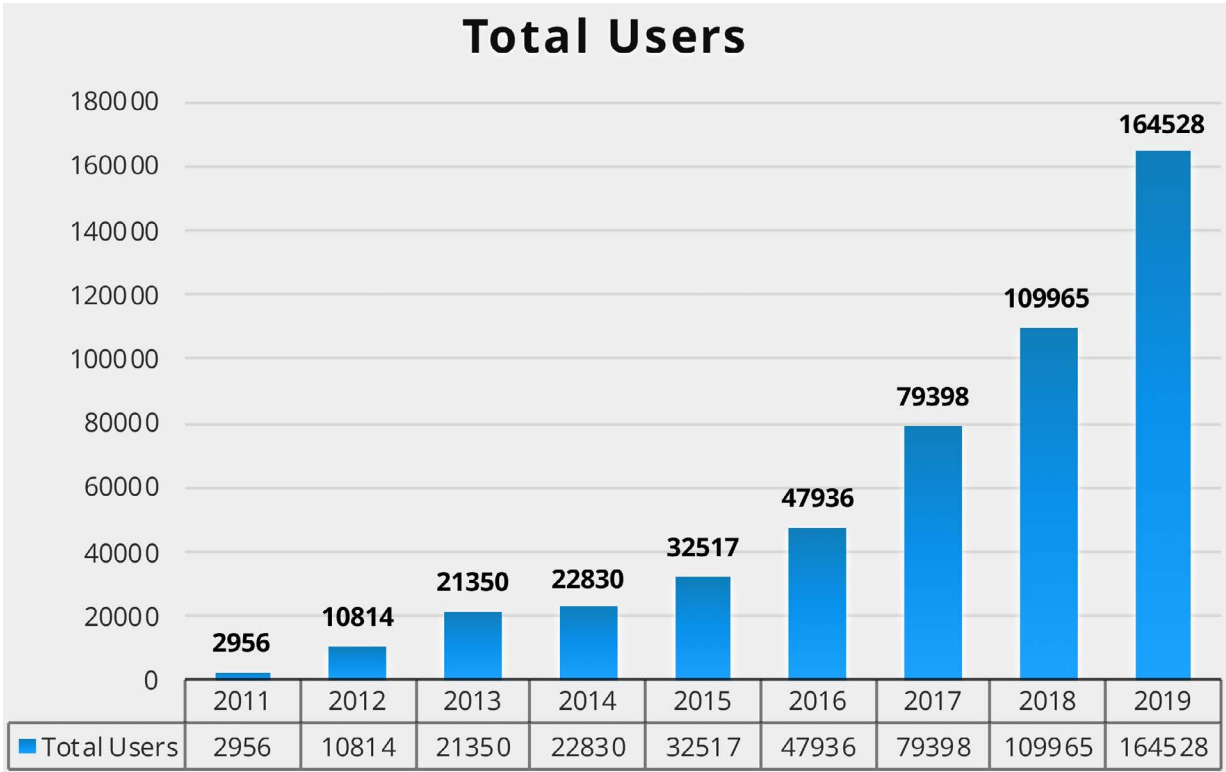
FIGURE 21: ACCESS TO TCIA.
The total number of users accessing the TCIA continues to grow.

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 DCTD'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 pharmacodynamic (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 clinical trials. Finally, early phase clinical trials are performed in the NCI Developmental Therapeutics Clinic (DTC) or the NCI Experimental Therapeutics Clinical Trials Network. 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 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, the NExT Program has received more than 800 applications (over 130 during this reporting period) and has an overall acceptance rate of nearly 15%. Approximately 33% 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 22. The pie charts include early (CBC) and late stage (IND-enabling) discovery, as well as development (early clinical evaluation) projects accepted into the program.
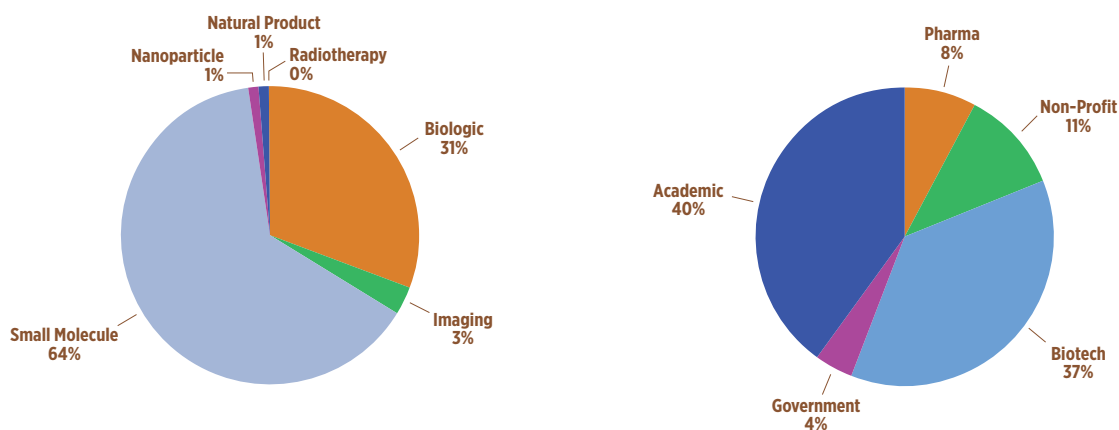
FIGURE 22: NExT PORTFOLIO STRATIFIED BY AGENT CLASSIFICATION AND CATEGORY OF SUBMITTING INSTITUTION.

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 several disease-targeted contrast agents and radiopharmaceuticals:

- A prostate specific membrane antigen positron emission spectroscopy (PET) tracer for prostate tumor imaging (PI: Peter Choyke, NCI CCR). The completed trial included 116 people, and the results are available.

- Panitumumab conjugated to the fluorescent dye IR800 (PI: Eben Rosenthal, University of Alabama at Birmingham, now at Stanford) for fluorescence assisted head and neck surgery. Six trials are underway for fluorescence assisted surgery: two in head & neck carcinoma, one each in pancreatic adenoma, lung tumors, pediatric brain tumors and adult brain tumors

- LUM015, a cathepsin-activatable fluorescent probe (PI: David Kirsch, Duke University) being evaluated for fluorescence assisted sarcoma and breast cancer surgery. The agent has been acquired by Lumicell, Inc, and seven trials are ongoing for fluorescence assisted surgery in breast, prostate, peritoneal surface, and brain cancers.

- A near-infrared (NIR) fluorophore (PI: John Frangioni, Beth Israel Deaconess Medical Center) for fluorescence assisted resection and exploration. This agent is being developed by Curadel, LLC. Phase 1 and 2 trials have been performed in Europe for delineation of ureters during abdominal surgery. A targeted derivative with the Cyclic Arg-Gly-Asp (cRDG) peptide, a selective ligand for the $\alpha v \beta 3$ integrin receptor which has an important role in human metastasis and tumor-induced angiogenesis, is in oral cancer surgery trials, also in Europe.

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 the Children's Oncology Group 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 people 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 and Orphan Drug Status. Orphan Drug Designation was given to AdDelta24-RGD in October 2014. Two additional RAID/NExT oncolytic viruses that were manufactured by NCI, HSV-M032 and HSV-C134, are currently in phase I clinical evaluation for glioblastoma at UAB. Ch11-1F4, a chimeric amyloid-reactive monoclonal antibody, is entering Phase 2 trials in people 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. Both agents are in commercial development following successful technology transfer from NCI/FNLCR.

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 completed. First-in-human studies for two DNA (cytosine-5-)-methyltransferase 1 (DNMT1) inhibitors discovered by Southern Research Institute - 4'-thio-2'-deoxycytidine (T-dCyd) and 5-aza-4'-thio-2'-deoxycytidine (5-aza-T-dCyd), an analogue that displayed preclinical efficacy in distinct tumor types - are being performed in the NCI DTC. 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 was approved by FDA in 2018. Due to the competitive landscape, NCI is looking for a company interested in out-licensing the agent rather than continuing to fund its further development. In addition, three small molecule projects have recently progressed to the late stage of preclinical development:

- An inhibitor targeting the anti-apoptotic myeloid cell leukemia-1 (Mcl-1) protein has been out licensed to Boehringer Ingelheim

- An inhibitor targeting the metabolic enzymes lactate dehydrogenase-A and B (LDHA/B) is under licensing discussions with pharma partners

- An inhibitor targeting the AAA ATPase p97 protein, thought to play an important role in the degradation of misfolded proteins, is entering clinical trials.

NExT Discovery Pipeline
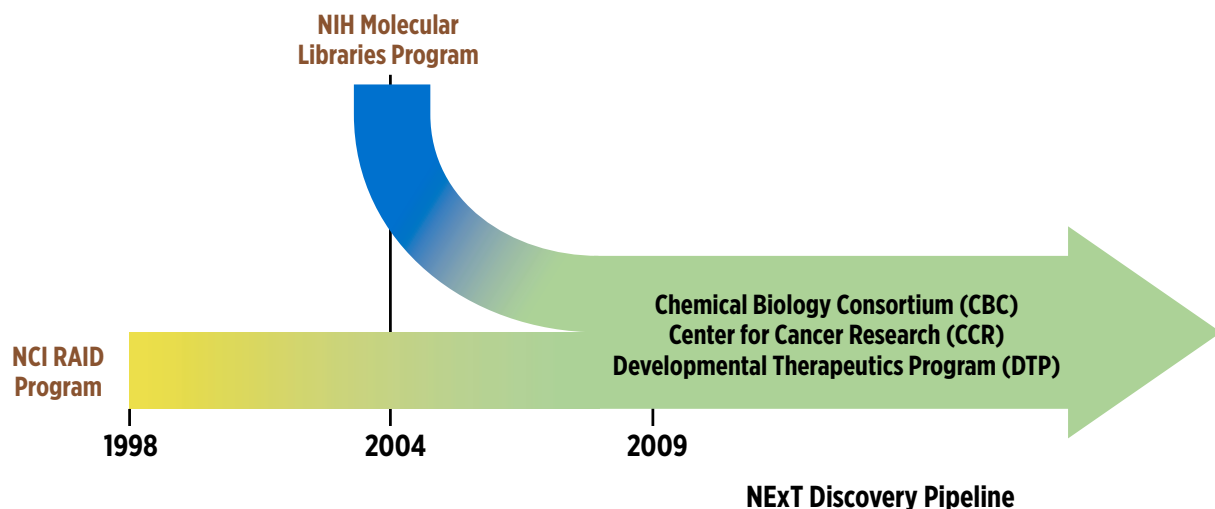
FIGURE 23: THE ORIGIN OF THE DISCOVERY PORTION OF THE NExT PIPELINE.
Initiated in 2009, the Discovery arm of the NExT Program had its origins in the NIH Molecular Libraries and the NCI RAID Programs. The CBC is the main resource for early discovery activities, DTP supports late discovery / pre-clinical development activities, and CCR provides scientific support for both early and late discovery activities.

The NExT Program, within the CBC, is also investigating inhibitors of additional cancer therapeutic targets, including β-catenin, a central nexus for the Wnt signaling pathway, and a target heretofore considered to be undruggable. 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 RAID/NExT: F-18 FACBC, Cu-64-ATSM, In-111 Annexin, F-18 Fluorocholine, and F-18 DCFBC. One of these, F-18 FACBC, received FDA approval for prostate cancer (Axumin®) in 2016.

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 (Figure 23). 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 Program 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 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). Collaborating under a Master Service Agreement (MSA) mechanism, the Dedicated Centers are provided with base funding sufficient for maintaining the infrastructure and staff necessary to provide constant support for CBC projects, ultimately reducing administrative costs and ensuring 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 Pharmaron (PD analysis), Reaction Biology (assay development), and Xtal BioStructures (structural biology and biophysical studies). Specialized Centers and/or CROs are brought into project teams on an ad hoc basis when incorporation of their expertise is needed to advance the science and decision-making process.

The collaborative nature of the CBC is captured in the graphical display of the "CBC Interactome" in Figure 25.
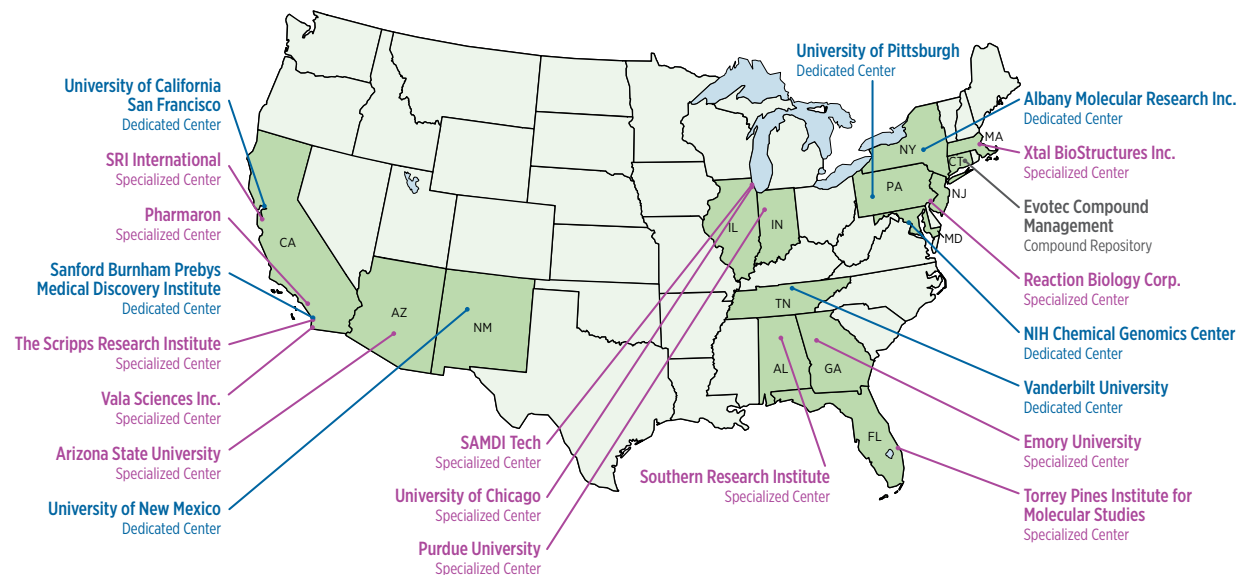
FIGURE 24: EVOLUTION OF CBC NETWORKS.
The CBC Network comprises seven Dedicated Centers (blue) and 15 Specialized Centers (purple). Evotec Inc. (grey) is the CBC compound repository.
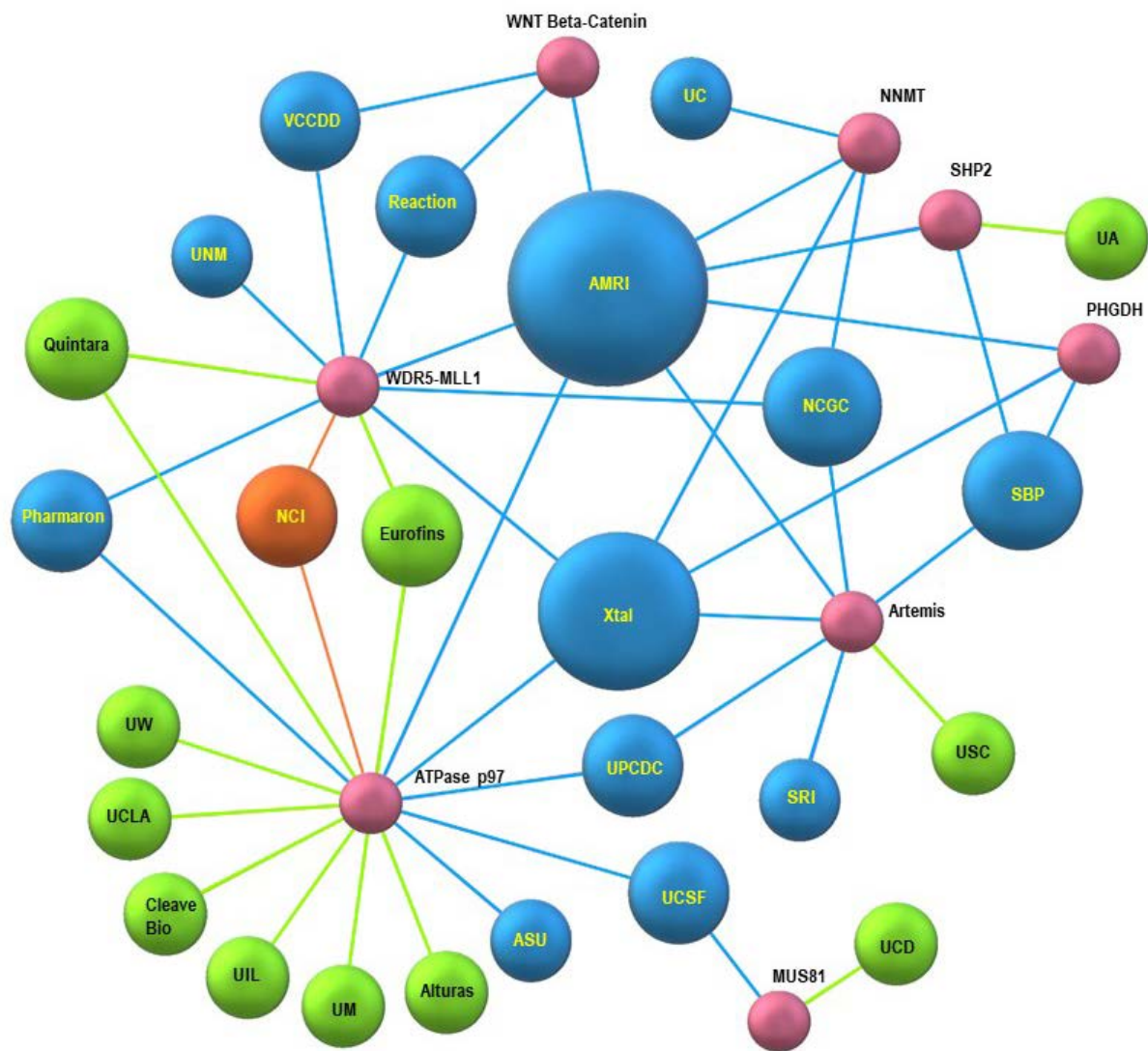
FIGURE 25: CBC CENTER INTERACTOME.
Current projects within the portfolio illustrate the level of collaboration involved in advancing projects. Scientists from non-cbc centers with expertise in specific areas are recruited to projects as needed. Current projects: artemis, atpase p97, mus81, nnmt, phgdh, shp2, wdr5-mll1, wnt β-catenin.

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 Consortium for project related activities. For example, NExT applicants Stephen Fesik (Vanderbilt University) and Michael Lieber (Keck School of Medicine, University of Southern California) are not only contributing intellectually as the target experts, but also perform experiments in their

laboratories that provide data critical to the progression of their WDR5 and Artemis Endonuclease projects, respectively. Non-applicant investigators Tsui-Fen Chou (University of California, Los Angeles) and Victor Darley-Usmar (University of Alabama at Birmingham) were recruited to project teams because 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 Laboratory (ITL)

The objectives of the ITL, within DTP's Toxicology and Pharmacology Branch (TPB), are to identify and advance mechanistic understanding of potential toxicity of therapeutic agents that come into the NExT pipeline. The program provides investigative toxicology deliverables to the extramural scientific community by serving the immediate needs of the NExT portfolio.

The laboratory's services include:

- Developing *in vitro* models and assays to generate deeper insight about cellular toxicity of therapeutic agents

- Profiling early adverse effects for high-priority organ systems using both *in vitro* and *in vivo* assays

- Applying mechanism-based approaches to characterize and aid in selection of drug candidates

- Generating data to describe biologically qualified pathways that are mediating mechanisms of toxicity for classes of approved agents

- Detecting target modulation and off-target effects to inform and manage potential safety liabilities
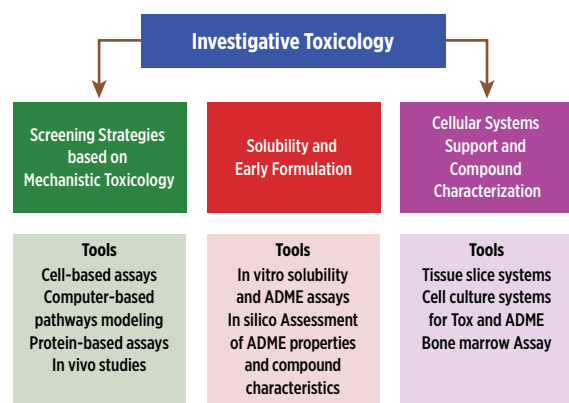
FIGURE 26: ACTIVITIES PERFORMED BY THE INVESTIGATIVE TOXICOLOGY PROGRAM IN SUPPORT OF NExT PROJECTS.

Pharmacokinetic (PK) Laboratory

The PK Laboratory at FNLCR analyzes samples from preclinical and clinical trials. Samples from people 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.

Radioactive Drug and Small Animal Imaging Programs

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, the Imaging Drug Group integrated the activities of several trans-NCI imaging drug activities into one decision-making committee, incorporating the DCIDE program and bridging to other important programs, such as CCR's Molecular Imaging Program and the Nanotechnology Characterization Laboratory.
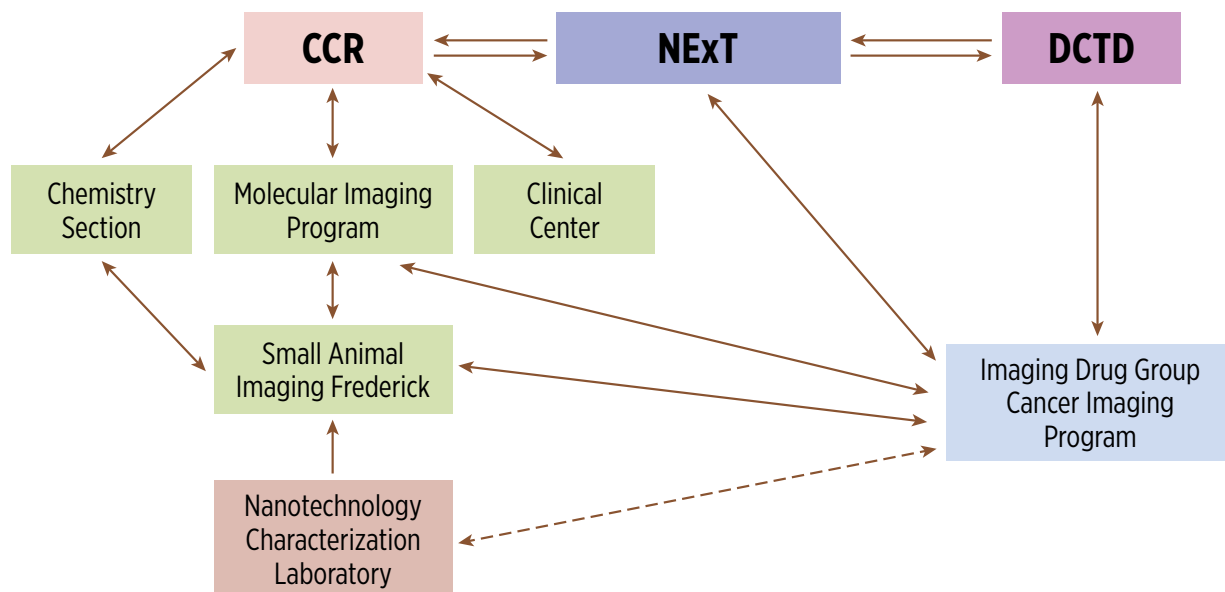
FIGURE 27: IMAGING DRUG DEVELOPMENT AT NCI.

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 people with cancer. As well as evaluating imaging agents that are accepted into NExT, the Radioactive Drug Program together with the Small Animal Imaging Program has assisted in NExT projects by using molecular imaging to confirm therapeutic drug targeting with labeled drugs and animal models with the appropriate target. Independent confirmation of critical targeting is essential prior to a commitment for development.

NCI PROGRAM FOR NATURAL PRODUCTS DISCOVERY (NPNPD)

Natural products (NP) or chemical entities derived from nature have been and continue to be a major source of new drugs and drug leads. This is particularly important in cancer therapy since NP pharmacophores represent >50% of all approved anticancer drugs. The NCI's Natural Products Repository is one of the largest and most diverse collections of plant, marine invertebrate, and microbial biota used for NP-based research. However, in its current form, this resource is comprised of crude extracts that are very difficult to screen in a high-throughput manner and require long and labor-intensive purification steps to identify a single active ingredient.

To fully utilize this unique collection of chemical diversity, the Natural Products Branch (NPB) within DCTD's Developmental Therapeutics Program (DTP) has established the NPNPD, which will create an enhanced pre-fractionated library suitable for high-throughput targeted screens, previously recalcitrant to crude NP extracts. This resource will enhance the efficiency of subsequent NP chemistry efforts to discover new molecules that specifically modulate targets within biological pathways central to human disease. The 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. It will also promote multi-disciplinary, intramural-extramural collaboration and uncover new biological frontiers.

NPB has thus far released 326,000 fractions available in 384-well plates that are publicly accessible, free of charge, and open to screening against any disease target. Operations were moved into a purpose-built automation laboratory at Frederick National Laboratory for Cancer Research (FNLCR), which houses state-of-the art liquid handling, automation, and analytical chemistry equipment. The NPNPD fraction library workflow (Figure 28) required extensive customization of commercially available instrumentation; it encompasses solid phase extraction chromatography, drying, plate generation, and storage, and can produce approximately 16,000 NP fractions per month. Previous sample production throughput at this scale and scope has never been demonstrated.
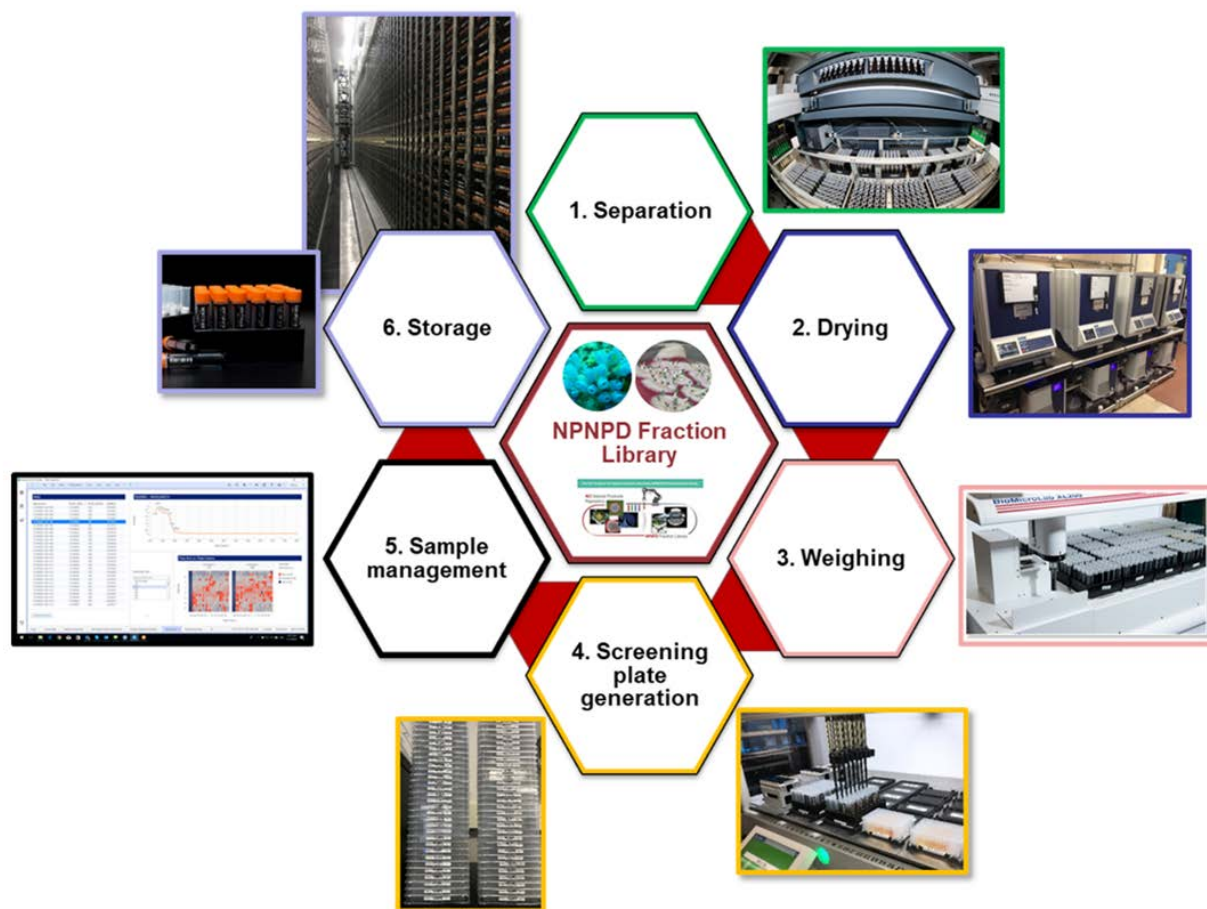
FIGURE 28. NPNPD FRACTION LIBRARY WORKFLOW.

To further support the use of NP samples in high through-put-screening (HTS), methodologies for rapid second-stage active compound purification and identification were developed and validated. Traditionally, in NP-based HTS campaigns, this step is material- and time-consuming as it requires multiple fractionation and screening steps before the identification of the active components. Here, by utilizing multiple high-throughput and high-capacity parallel HPLC systems, the fully automated NPNPD workflow is capable of processing 500 primary hit fractions in a two-week period (Figure 29). Overall, the rapid second-stage purification conserves extract mass, requires much less chemist time, and introduces knowledge of structure early in the isolation workflow, enabling faster turnaround times in NP-based HTS.
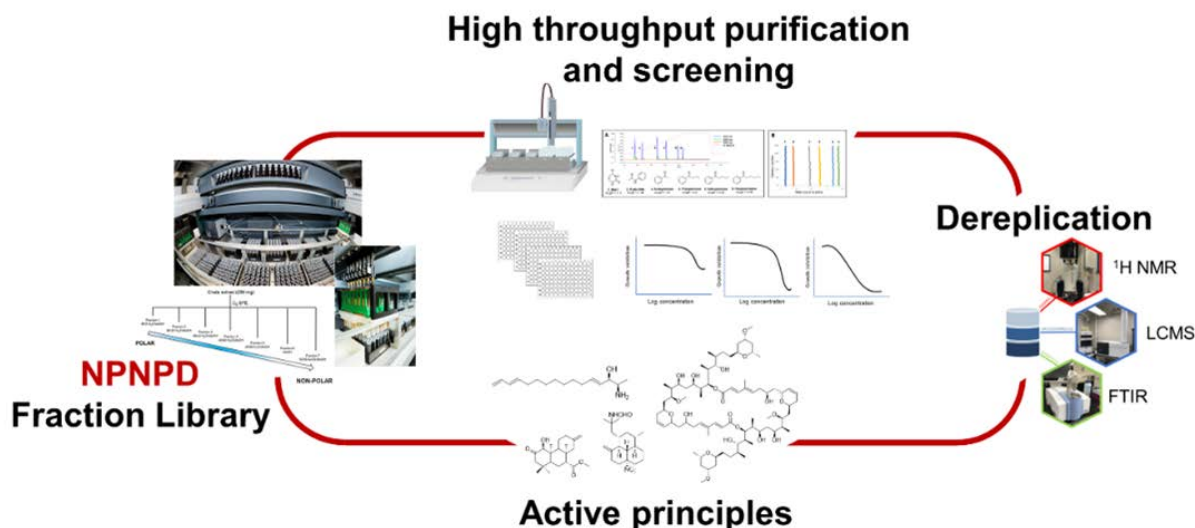
FIGURE 29: FULLY AUTOMATED NPNPD WORKFLOW.
Multiple high-throughput and high-capacity parallel HPLC systems

INNOVATIVE MOLECULAR ANALYSIS TECHNOLOGIES (IMAT) PROGRAM

The NCI 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 Small Business Innovation Research (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 FY19, IMAT supported 89 projects, of which 30 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.

PROVOCATIVE QUESTION (PQ) INITIATIVE

The 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 following 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:

- workshops for the generation of new questions
- Executive Committee activities that refine and rephrase questions for precise understanding and clarity
- the Program Committee that broadly oversees the application process and review
- the Question Teams that focus on individual questions, define and determine responsiveness, and assign applications to specific Program Officers

In FY19, 479 applications were received in response to the 12 issued PQs, of which at least 40% of the questions related to DCTD's mission. Eighteen of the 41 awards issued, 52% of the awarded R01s, and 31% of the awarded R21s, were assigned to DCTD program portfolios, where the progress of these grants is being closely monitored. Of the 3,010 applications received from FY12-FY19 in response to the 92 issued PQs, 823 have been assigned to DCTD Program Officers.

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 or pre-clinical research, particularly for combination trials involving agents from multiple collaborating pharmaceutical companies. As

the use of genomic sequencing data becomes mainstream in cancer therapy, requests for, and access to, multiple targeted agents for the conduct of clinical research studies are becoming more common.

To develop the Formulary, DCTD negotiated with 11 companies to supply 31 agents using specific NCI Formulary Clinical Cooperative Research and Development Agreements (CRADAs). Negotiations for additional agents continue. These CRADAs 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 accessible to NCI main-member Experimental Therapeutics Clinical Trials Network (ETCTN) and NCI National Clinical Trials Network (NCTN) institutions and their investigators in the United States, with a clinical Material Transfer Agreement used to formalize the expectations of each party. The NCI clinical trial infrastructure facilitates 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.

NCI CLINICAL AND TRANSLATIONAL EXPLORATORY/DEVELOPMENTAL STUDIES (R21 CLINICAL TRIALS OPTIONAL)

This funding opportunity supports translational and clinical exploratory research in cancer diagnosis, treatment, imaging, symptom/toxicity, and prevention clinical trials; correlative studies associated with clinical trials; novel cancer therapeutic, symptom/toxicity, and preventive agent development, radiotherapy development activities, and mechanism-driven combinations; innovative preclinical studies. This trans-Divisional exploratory grant mechanism, particularly suitable for high risk, high reward projects, involves DCTD, the Division of Cancer Prevention (DCP), and the Center to Reduce Cancer Health Disparities (CRCHD).

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

- studies to reduce the unequal burden of cancer in diverse populations

Response to the initial issuance in 2018 as PAR 18-020 was remarkable, with more than 1,300 applications submitted (Table 13). Many studies performed in these R21 grants led to high quality peer-reviewed publications, as well as provided the preliminary studies necessary for R01 grant applications. The popularity within the extramural community led to its reissuance in 2019. The first receipt date for PAR 19-356 was in October 2019, wherein 310 grant applications were received. Scientific merit review for these applications was scheduled for early 2020.

PAR 18-020 R21 Grants (over four submission rounds)
1,367 Grants Submitted
96 grants funded
83 were funded within the payline
13 grants were funded beyond the payline, by exception
Success rate = 7%

TABLE 13: PAR 18-020 R21 GRANTS.

NCI CLINICAL TRIALS STEWARDSHIP INITIATIVE

The NIH has embarked on a "New Era of Trust and Transparency in Clinical Trials"[9] by building a better clinical trial enterprise through improved stewardship, accountability, and transparency. In 2016, NIH announced the first series of reforms and initiatives to improve the quality and efficiency of NIH-funded clinical trials focused on a variety of key points along the lifespan of a clinical trial. NIH modified existing, and created new, policies governing research involving human subjects and their participation in clinical trials. These initiatives reengineer the process by which clinical investigators develop ideas for new trials, how NIH reviews and selects clinical trials for support, oversees research progress, and how results are reported to ensure rigor and efficiency in clinical trials.

NCI has taken steps to implement these changes and to achieve more consistency in the conduct and management of clinical trials funded through grants, cooperative agreements, and contracts. This NCI Clinical Trials Stewardship Initiative builds upon NCI's solid foundation of clinical trials stewardship and is led by a committee of NCI representatives from the various Divisions, Offices, and Centers supporting clinical trials. The goal of the initiative is to ensure the:

- Quality of clinical trials
- Safety of research participants
- Reliability of data
- Dissemination of results
- Appropriate stewardship of funds

The role of the NCI Clinical Trials Stewardship Committee (NCTSC) is to oversee and guide the development of our Institute-specific stewardship plan. As part of this plan, the NCTSC identified essential and enhancing elements that were incorporated into clinical trial management and oversight processes performed by NCI staff. Essential elements are those that comply with the updated NIH policies and Federal regulations whereas enhancing elements represent high-quality practices in clinical trial stewardship.

Since the launch of the Initiative, the NCSTC has continuously informed NCI staff and the extramural community of the new practices undertaken, as well as developed resources to assist in the understanding of definitions and policies related to human clinical trials. The NCI continues to provide guidance to the NIH Office of Extramural Research to achieve better consistency in the conduct and management of trials by NIH staff.

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[9] Hudson KL, Lauer MS, Collins FS. *JAMA*. 2016 Oct 4;316(13):1353-1354.

SMALL CELL LUNG CANCER CONSORTIUM (SCLC-C)

The NCI's SCLC-C was created to address all five priorities established by the SCLC Scientific Framework Report and respond to the Recalcitrant Cancer Research Act of 2012, namely to:

- Build better research tools for the study of SCLC by (a) optimizing the collection of tumor tissue specimens representing distinct phases of SCLC, and (b) developing new tumor models that reflect the phases of SCLC found in the clinic

- Expand comprehensive genomic profiling studies of clinically annotated SCLC specimens to improve the basic understanding of the frequency, distribution, and range of molecular abnormalities that exist at diagnosis and following therapeutic relapse

- Investigate new diagnostic approaches for populations at high risk of developing SCLC

- Focus therapeutic development efforts on specific molecular vulnerabilities of SCLC

- Examine mechanisms underlying both the high initial rate of response to primary SCLC therapy and the rapid emergence of drug and radiation resistance following completion of treatment

The SCLC-C consists of national and international leaders that have produced many key publications within the past two years spanning several areas of focus (Table 14). In 2018, the Consortium included one U24 infrastructure grant, seven U01 projects in early detection/diagnosis or therapy, ten additional grants funded by the NCI in SCLC, and NCI intramural investigators focused on the disease.

SCLC-C Milestones	Publications
Molecular classification of SCLC	• Rudin CM et al. Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data. *Nat Rev Cancer*. 2019 May;19(5):289-297. • Yang, D et al. Intertumoral Heterogeneity in SCLC Is Influenced by the Cell Type of Origin. *Cancer Discov*. 2018 Oct;8(10):1316-1331.
New PDX, CDX, GEMM, and cell line models addressing tumor heterogeneity	• Zhou, T et al. A hPSC-based platform to discover gene-environment interactions that impact human β-cell and dopamine neuron survival. *Nat Commun*. 2018 Nov 16;9(1):4815. • Jia, D et al. Crebbp Loss Drives Small Cell Lung Cancer and Increases Sensitivity to HDAC Inhibition. *Cancer Discov*. 2018 Nov;8(11):1422-1437. • Drapkin, BJ et al. Genomic and Functional Fidelity of Small Cell Lung Cancer Patient-Derived Xenografts. *Cancer Discov*. 2018 May;8(5):600-615.
Establishment of new therapeutic targets	• Sen, T et al. Targeting DNA Damage Response Promotes Antitumor Immunity through STING-Mediated T-cell Activation in Small Cell Lung Cancer. *Cancer Discov*. 2019 May;9(5):646-661. • Adeegbe, DO et al. BET Bromodomain Inhibition Cooperates with PD-1 Blockade to Facilitate Antitumor Response in Kras-Mutant Non-Small Cell Lung Cancer. *Cancer Immunol Res*. 2018 Oct;6(10):1234-1245. • Huang, F et al. Inosine Monophosphate Dehydrogenase Dependence in a Subset of Small Cell Lung Cancers. *Cell Metab*. 2018 Sep 4;28(3):369-382.e5.
Novel biomarkers for risk assessment and screening	• Hanash, SM et al. Blood based biomarkers beyond genomics for lung cancer screening. *Transl Lung Cancer Res*. 2018 Jun;7(3):327-335. • Integrative Analysis of Lung Cancer Etiology and Risk (INTEGRAL) Consortium for Early Detection of Lung Cancer et al. Assessment of Lung Cancer Risk on the Basis of a Biomarker Panel of Circulating Proteins. *JAMA Oncol*. 2018 Oct 1;4(10):e182078.
New approaches in immunotherapy	• Ponath, P et al. A Novel, Fully Human Anti-fucosyl-GM1 Antibody Demonstrates Potent In Vitro and In Vivo Antitumor Activity in Preclinical Models of Small Cell Lung Cancer. *Clin Cancer Res*. 2018 Oct 15;24(20):5178-5189. • Chaikovsky, AC and Sage, J. Beyond the Cell Cycle: Enhancing the Immune Surveillance of Tumors Via CDK4/6 Inhibition. *Mol Cancer Res*. 2018 Oct;16(10):1454-1457. • Liu, Y et al. NK Cells Mediate Synergistic Antitumor Effects of Combined Inhibition of HDAC6 and BET in a SCLC Preclinical Model. *Cancer Res*. 2018 Jul1;78(13):3709-3717.

TABLE 14: SCLC-C MILESTONES 2018-2019.

Small Cell Lung Cancer Consortium Meetings (2018-2019)

The SCLC-C held its first NCI meeting on March 15-16, 2018 at the NCI Shady Grove Campus. The topics included molecular pathology, detection, oncogenesis/tumor biology, models, therapeutics, and emerging targets. Among special guests, the NCI welcomed its former director Dr. Harold Varmus, who was awarded a U01 in the Consortium. Dr. Varmus presented research from his U01 on deriving SCLC-like cells from human embryonic cells.

The International Association for the Study of Lung Cancer, the Memorial Sloan Kettering Cancer Center (MSKC-C)-based Resource Center, and the NCI jointly organized the second SCLC-C meeting on April 3-5, 2019 in New York, NY. The planning committee included Julie George (University of Cologne, Germany), Trudy Oliver (University of Utah), Taofeek Owonikoko (Vanderbilt), and J.T. Poirier (MSKCC). Nine sessions defined the current trends in research: pathology, omics, cell of origin, development, and tumor initiation, tumor heterogeneity and tumor expression, platforms of discovery, targeted therapies, biomarkers, immunotherapy, and recent ongoing clinical trials. The keynote presentations were given by patient Montessa Lee, who spoke on breaking the smoking stigma, and Dr. Anton Berns from the Netherlands, who recaptured lessons from the SCLC mouse models. A poster session complemented the presentations.

BIOMETRIC RESEARCH PROGRAM
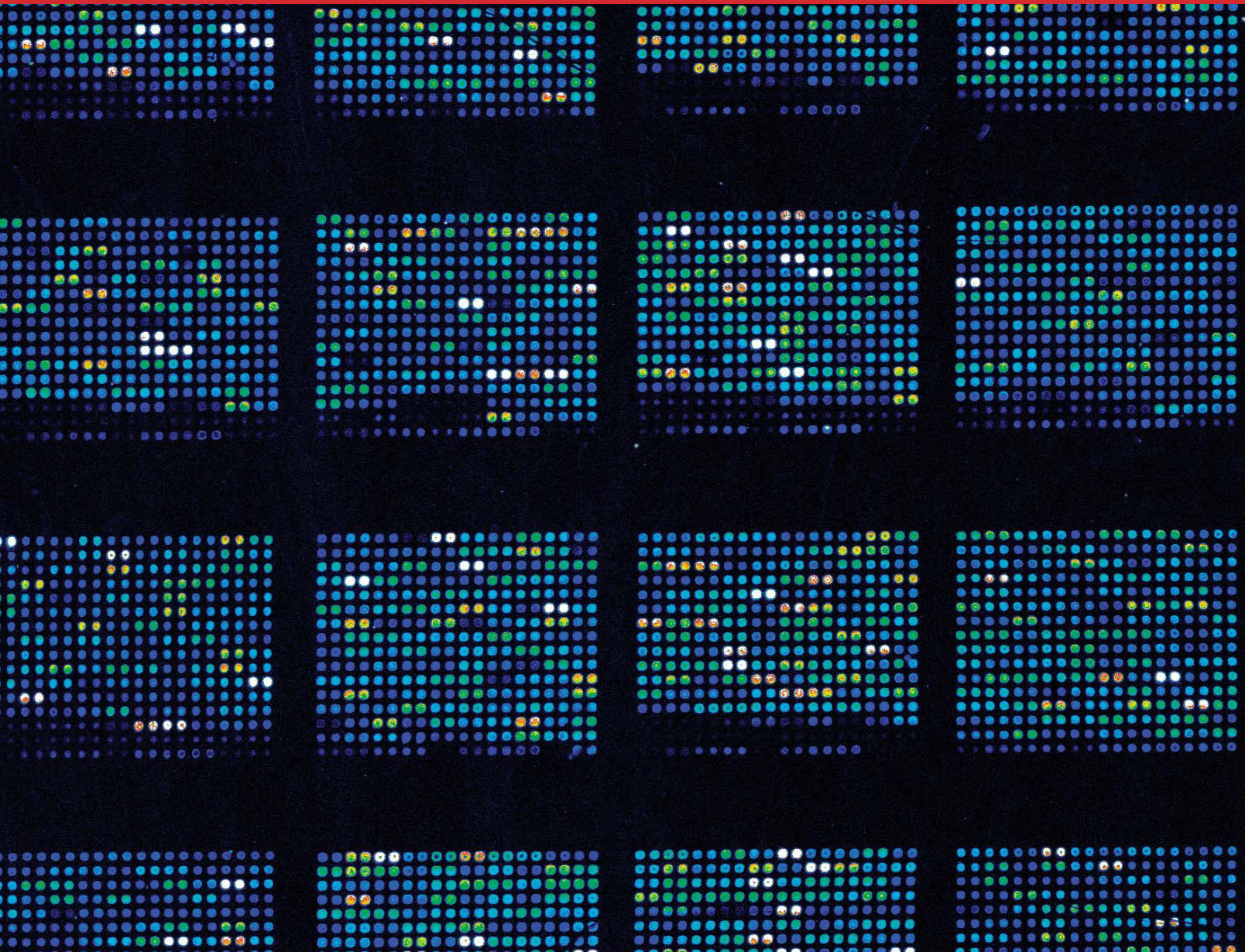
OVERVIEW

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 enables BRP to recruit and retain a world-class research staff, provide high-quality collaboration and consultation with DCTD and NCI scientists, and make major research contributions motivated by important problems in cancer research. BRP conducts a postdoctoral training program in cancer computational and systems biology, bioinformatics, and biostatistics. BRP has hosted visitors including scientists and clinicians from several countries on short

and extended visits for training and research in the use of genomics in cancer research and precision medicine clinical trials. 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:

• Developing efficient/adaptive clinical trial designs

• Integrating genomics and molecular profiling into clinical trials

• Biomarker-driven clinical trial designs for precision medicine

• Computational and systems biology of cancer

• Bioinformatics resources for the research community

LISA MEIER MCSHANE
ASSOCIATE DIRECTOR
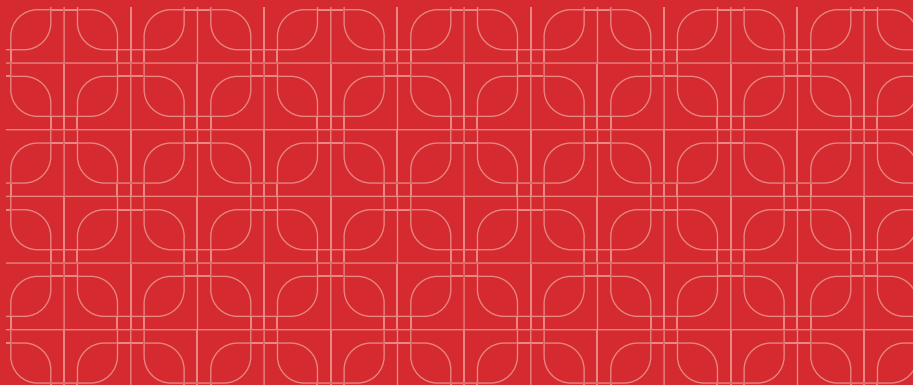
Lisa McShane, PhD, is Associate Director of BRP. Dr. McShane holds a doctoral degree in statistics from Cornell University in Ithaca, New York. She is internationally recognized for her expertise in cancer biomarkers and precision medicine cancer clinical trials. In 2013, she was elected Fellow of the American Statistical Association for her outstanding statistical contributions to the 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 120 statistical and biomedical papers, a dozen book chapters, 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, development of predictive signatures for precision medicine, 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 NCI 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, Acting Associate Director of BRP in July 2017 with full appointment as Associate Director in September 2019. Dr. McShane has served on multiple 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 care and outcomes for people with cancer.

STRUCTURE AND FUNCTION

BIOSTATISTICS BRANCH

Statisticians in the Biostatistics Branch 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 clinical or preclinical 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 biology and therapeutics, and many of their major duties are assigned 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

- Providing statistical leadership for CTEP Project Team drug development efforts

- Serving on data monitoring committees and assuring adherence to procedures established for the NCI-sponsored clinical trials networks (NCI National Clinical Trials Network (NCTN) and Experimental Therapeutics Clinical Trials Network (ETCTN))

- Serving on Intergroup Clinical and Correlative Science 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:

- Design and implementation of the Myeloid Malignancies Precision Medicine Initiative platform trial (Myelo-MATCH)

- Design and development of combination MATCH (ComboMATCH) and immune MATCH (iMATCH) basket trials

- Design and conduct of the NCI Exceptional Responders Initiative

- Establishment and implementation of the ETCTN Data Safety Monitoring Board (DSMB), including development of the DSMB charter and standard operating procedure.

- 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 technologies

- 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 the Web-based NCTN/NCORP Data Archive to store and enable appropriate sharing of data generated in completed NCI-sponsored clinical trials for which primary analyses have been published

BRP statisticians additionally collaborate with CCR intramural clinical branches (Radiation Oncology Branch, Lymphoid Malignancies Branch, Urologic Oncology Branch and Molecular Imaging Program), the Developmental Therapeutics Clinic, and other NCI divisions. 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, genomic, transcriptomic, proteomic, and other omics technologies, and patient-derived xenograft (PDX) mouse models. BRP statisticians and clinical fellows have collaborated with investigators in the CCR Pediatric Oncology Branch (POB) and NCI Division of Cancer Epidemiology and Genetics (DCEG) Clinical Genetics Branch (CGB). For example, BRP members have collaborated with POB and CGB members to study people with Li-Fraumeni syndrome, including cancer surveillance with whole body magnetic resonance imaging. An additional example is the collaboration between BRP members and POB clinicians to study people with germline neurofibromatosis type 1 (NF-1) mutations and symptomatic plexiform neurofibromas to evaluate how therapeutic interventions (especially MEK inhibitor versus non-MEK therapy) and other factors relate to the likelihood of developing malignant peripheral nerve sheath tumors.

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 NCI-MATCH, which is conducted through a partnership between NCI and the ECOG-ACRIN clinical trials group; and the ALK-positive non-small cell lung cancer trial (NRG-LU003), an innovative biomarker-driven trial conducted in partnership with NRG Oncology clinical trials group

- Providing statistical leadership for establishment of the NCI-MATCH outside assay network and credentialing of new laboratory participants

- Providing statistical leadership and analyses for the Friends of Cancer Research tumor mutation burden harmonization project

- Providing statistical guidance and leadership for Blood Profiling Atlas in Cancer (BloodPAC) and Foundation for the National Institutes of Health ctDNA initiatives

- Leading statistical and bioinformatic analyses for investigation of differences in molecular profiles of tumors from adolescent and young adults compared to those from older adults

- Participating in initiatives conducted collaboratively across government agencies, such as NIH, Centers for Disease Control and Prevention, Food and Drug Administration (FDA), and the National Institute of Standards and Technology, to promote best practices for drug, diagnostics, 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 have been involved in efforts of the Response and Evaluation Criteria in Solid Tumors (RECIST) committee working groups to update RECIST 1.1 to incorporate such advances in treatment as immunotherapy and targeted agents, and in imaging technologies (iRECIST, FDG-PET RECIST, modified RECIST for brain metastasis and RECIST for targeted agents). BRP staff have been the lead statisticians in a multi-year, international working group effort to standardize the measurement of Ki67 proliferation index in breast cancer.

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. The wealth of statistical issues that BRP statisticians encounter in their collaborations with other NCI programs informs and motivates these statistical research 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
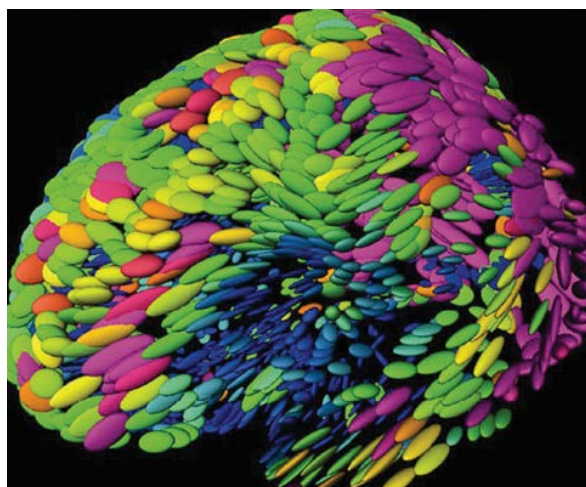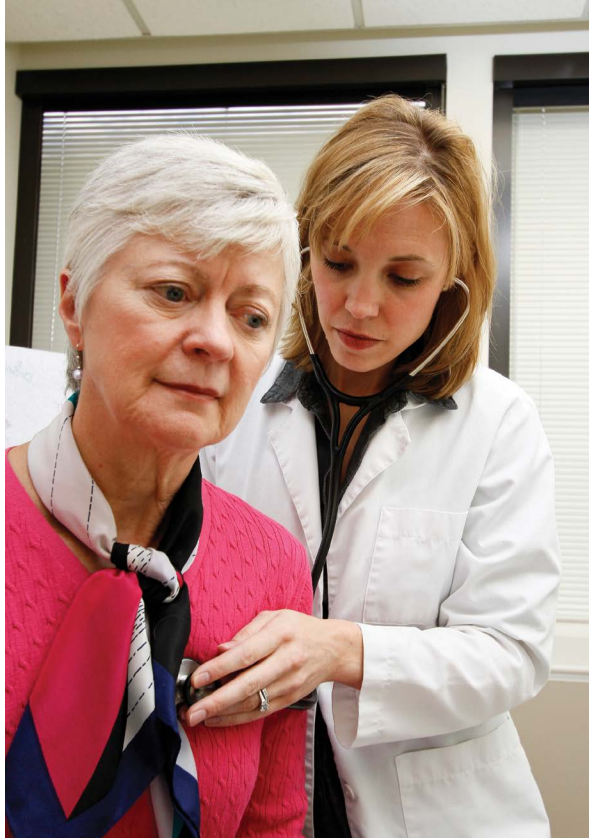
laboratory assays and imaging devices. Examples of ongoing statistical methodology research programs include:

- Improving clinical trial designs for evaluating treatments in the presence of delayed treatment effect, such as is typical for immunotherapies

- Development of new approaches for evaluation of clinical utility of molecular signatures

- Development of methods to enhance therapy predictive signatures by incorporating biological pathway information

- Development of new designs for quantitative assessment of the prognostic and predictive capabilities of biomarker panels

- Improving designs for non-inferiority clinical trials

- Development of new methodology and statistical software for evaluation of inter-observer agreement and diagnostic accuracy

- Development of methods for casual inference in personalized medicine

- Improving methodology for detection and risk-stratification of prostate cancer

- New analysis strategies for competing risks survival data

- Assessment of the efficiency, potential bias, and ethics of certain types of adaptive clinical trial designs

- Assessment of the impact that outcome adaptive randomization could have on subsequent biomarker studies using clinical trial specimens, and development of methods to correct for design-induced bias

- Modeling the efficacy of drug monotherapy, as well as combination therapy synergism and antagonism, observed in preclinical drug screening studies, particularly those utilizing PDXs

- Development of statistical approaches for evaluating 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 (CSB)

The objective of the 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, biostatistics, 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 mean-

ingful 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:

- NCI Transcriptional Pharmacodynamics Workbench (TP-Workbench), released in October 2018, is a web-based system providing biologists and pharmacologists with extensive detailed tools for the analysis of the genome-wide transcriptional response elicited by treating the NCI-60 cell lines with 15 drugs of various mechanisms of action. Analysis results are integrated into a database where additional interactive analysis tools can be applied to explore gene expression modulation by molecular pathway, drug target, and association with drug sensitivity. A manuscript highlighting this unique system was published in the *Cancer Research* at the end of 2018. More than 300 individual researchers across the U.S. and worldwide have visited the publicly available website thousands of times.

- 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 a person's 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 the MPACTv2 clinical trial conducted both in the NIH Clinical Center and nationwide in NCI's ETCTN.

- D3Oncoprint is a standalone software system to visualize and dynamically explore annotated genomic mutation files. It provides access to curated variant lists from CIViC, My Cancer Genome, and FDA-approved drug indication listings to facilitate the use of genomic data for biomedical discovery and application. Its unique feature is a flexible environment to dynamically explore the variant mutation profiles provided as input. The focus on interactive visualization with biological and medical annotation significantly lowers the barriers for interpretation of complex

genomic data by biomedical investigators. A motivation in designing this system is to empower researchers in their translation of collected data sets to biological insights and clinical applications.

- MutSpliceDB is a public resource of splice sites mutations effects, documenting mutation effects on splicing based on manually reviewed RNA-seq BAM files from samples with particular splice site mutations. Accurate interpretation of splice site mutations can influence a person's treatment, and for germline splice site mutations, may be relevant for familial disease predisposition.

CSB members engage in a variety of collaborations critical to the mission of DCTD and NCI. Examples include:

- Computational and bioinformatics support and/or oversight to NCI DCTD preclinical programs and labs, as well as NCI clinical trials, projects, and the national cancer immunotherapy network

- Review of scientific proposals for NCI clinical trials or projects with bioinformatics and computational biology components

- Collaboration with the NCI clinical and preclinical programs to conduct research on mechanisms of carcinogenesis and chemotherapy resistance using whole-exome sequencing and RNA-seq data of tumor cell line panels and PDX models for better understanding the genomic basis of therapeutic activity, resistance, and synergism

Recent CSB methodologic research areas include development of:

- Bioinformatic and computational methods to identify biological pathway signatures and investigate their association with response to specific therapies

- Validation strategies for deep learning applications for drug combination response prediction

- Improved computational approaches to integrate genomic and epigenomic data

- Bioinformatics tools and systems to support genomic variant-based clinical trials and preclinical studies and to enhance the ability to jointly analyze, visualize and interpret clinical, pathological, and genome-wide data

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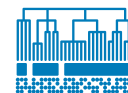
In upcoming years, BRP plans to focus on the following:

- Development and application of statistical and computational methods to facilitate and accelerate the development and clinical evaluation of effective molecularly targeted therapeutics for individual people with cancer and companion diagnostics

- Development and application of statistical and computational methods for derivation of molecular signatures to enhance precision medicine approaches

- 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

CANCER DIAGNOSIS PROGRAM

OVERVIEW

Established as a DCTD program in 1996, the Cancer Diagnosis Program (CDP) strives to improve outcomes for people with cancer 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 to develop information that can aid people with cancer 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.

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 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 All of Us Research Program, the National Institute of Biomedical Imaging and Bioengineering (NIBIB), and many DCTD programs including but not limited to the Cancer Therapy Evaluation Program (CTEP), the Cancer Imaging Program (CIP), and the Biometric Research Program (BRP).

A significant challenge is the large amount 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 with cancer.

Part of CDP's mission 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 define new technologies that best predict response to treatment. The overarching goals of CDP are to:

- Support development of the most effective in vitro diagnostic tools to ensure precise diagnosis and optimize treatment decision making

- Encourage research on the clinical utility of biomarkers to guide 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 creating a network of laboratories that identify potentially eligible cases for the NCI-MATCH trial using centrally vetted next generation DNA sequencing (NGS) assays being conducted in the context of clinical care. The NCI-MATCH Designated Laboratory Network consists of laboratories that are selected by an NCI-MATCH committee that evaluates each group for quality standards, and all laboratories operate under the Clinical Laboratory Improvement Amendments (CLIA) standards to molecularly profile tumors in the clinical setting.

CDP also partners with NCI's Center for Cancer Genomics in the Exceptional Responders Initiative, which invited clinicians to submit cases and tumors from people who had an exceptional response to their chemotherapy treatment (targeted or standard chemotherapy). These tumors undergo extensive molecular profiling to define the molecular underpinnings that lead to an exceptional response. Initial results suggest collection and identification of bonafide exceptional responders is feasible – of 478 cases proposed, 221 were confirmed as exceptional responders. Results of molecular analysis of this cohort may one day provide the knowledge to identify people with similar molecular profiles who may also respond very well to a given treatment.

LYNDSAY N. HARRIS
ASSOCIATE DIRECTOR
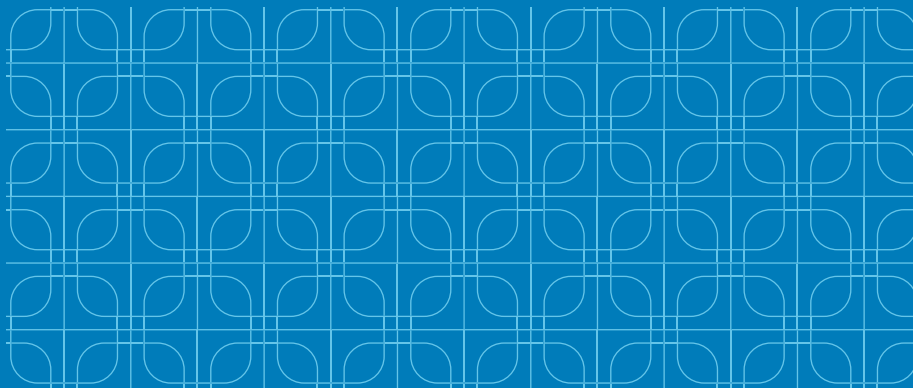
Lyndsay Harris, MD, is Associate Director of CDP. Prior to coming to NCI, she was Professor of Medicine at Case Western University and Director of the University Hospital's Seidman Breast Cancer Program. She has been on faculty at Yale University where she led the Breast Cancer Program, and Dana-Farber Cancer Center where she directed the Tissue, Pathology and Clinical Data Core for the Dana-Farber/Harvard Cancer Center SPORE in Breast Cancer. Her research in the last 25 years has focused on the development of biomarkers and targeted therapeutics to improve outcome for people with breast cancer. 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 to the program, publishing over 140 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. As 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's efforts have also been crucial for the collection of the normal tissues used for NIH's Genotype Tissue Expression (GTEx) Project. The genome sequencing and gene expression data produced by GTEx is used extensively by cancer researchers with a resulting 1876 papers published as of 2019. The GTEx data have proven useful as normal expression controls in the profiling of the Exceptional Responders tumors. CDP has leadership roles in several Cancer MoonshotSM initiatives that aim to accelerate progress in key areas of cancer research. Examples include the Cancer Immune Monitoring and Analysis Centers (CIMAC)-Cancer Immune Data Commons (CIDC) Network. This joint CDP and CTEP effort provides state-of-the-art analyses for genomic, phenotypic, and functional characterization of responses in early phase clinical trials using analytically validated and standardized platforms. In addition, the Cancer Moonshot Biobank aims to provide longitudinally collected biospecimens and associated data to cancer researchers studying resistance and sensitivity to cancer therapeutics.

To be useful for 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 using the assay improves outcomes compared with not using the assay. To realize the promise of precision medicine, treatment individualized to a person's 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 activities involved in the development of robust clinical assays, including:

- Appropriate ethical, legal, and social approaches for engaging people 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, i.e., research related to the effects of biospecimen handling protocols on research data

- 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 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. The recently launched National Clinical Laboratory Network serves the research community by providing access to validated assays to support early-stage clinical trials and teaches other groups how to perform these assays in a rigorous fashion.

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 person's 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 NGS
- 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 access 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. CDP has developed resources to assist patients with cancer and members of the 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.

STRUCTURE AND FUNCTION

CDP's primary mission is to stimulate, coordinate, and fund research for the development of diagnostic and therapeutic biomarkers, novel technologies and biospecimen resources, and science. None of this work would be possible without the strong contributions of each branch in CDP. These include the Biospecimen and Biorepository Research Branch, the Diag-

nostic Biomarkers and Technology Branch, the Diagnostics Evaluation Branch, and the Pathology Investigations Research Branch. Their individual contributions are described below.

BIOREPOSITORIES AND BIOSPECIMEN RESEARCH BRANCH (BBRB)

Researchers' access to biospecimens of known quality, with sufficient annotation, is essential for the progress of cancer research. Biospecimens, their appropriate preservation and annotation, association with high quality clinical data and fitness for use in molecular diagnostics has been a focus of CDP since its inception. In the past two decades, NCI undertook 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 efforts to identify issues and implement solutions.

In 2012, CDP incorporated OBBR as 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. BBRB's goal is to increase the reproducibility of cancer research involving the use of biospecimens. 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. BBRB

also develops and coordinates high quality biospecimen and associated data collection programs for major NCI and NIH research initiatives, including the Cancer MoonshotSM and the GTEx project.

BBRB activities include:

- 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, and data management, along with ethical, legal, and policy best practices

- 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
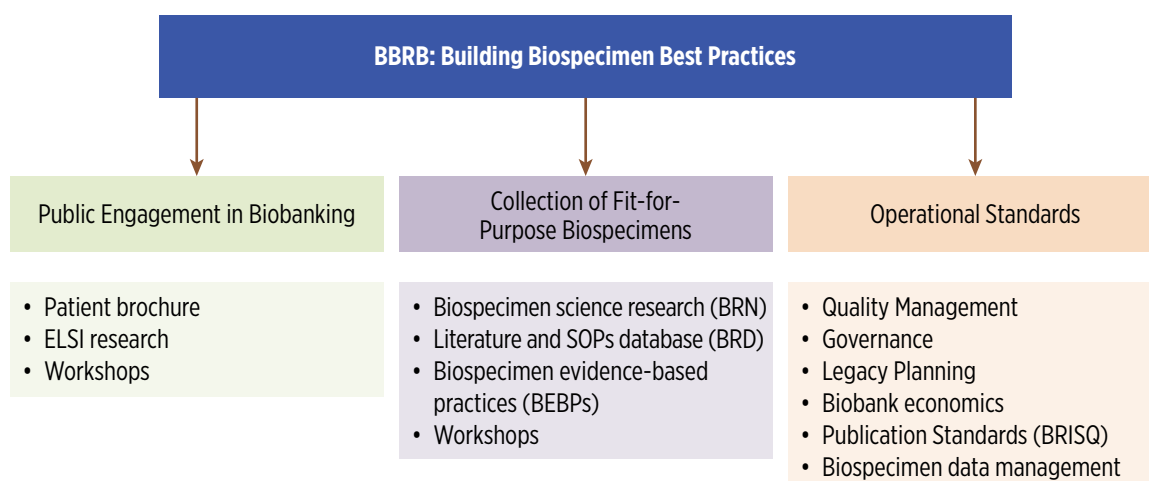
FIGURE 30: BBRB ACTIVITES DESIGNED TO IMPROVE THE QUALITY OF BIOSPECIMENS AND BIOSPECIMEN RESEARCH.

DIAGNOSTIC BIOMARKERS AND TECHNOLOGY BRANCH (DBTB)

DBTB stimulates and supports research to develop new bio-markers, 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 information on novel technologies that may prove useful for precision diagnostics. Significant input from DBTB staff into NCI's Innovative Molecular Analysis Technologies (IMAT) program, the Small Business Innovation Research (SBIR) program and the Academic Industrial Partnership Initiative allow CDP and NCI to support important research in the development and application of new technologies to improve cancer diagnostics. Other specific activities of the branch include:

- Stimulating research that applies new knowledge from cancer biology and tumor-host interactions to facilitate cancer diagnostics research

- Supporting research focused on the development of innovative technologies and devices to use for cancer diagnosis, prognosis, and prediction

- Supporting research to 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

- Stimulating research focused on the development and implementation of algorithms for analysis of high-dimensional data applied to cancer diagnostics, prognosis, and prediction

- Stimulating novel interdisciplinary technological research for use in precision cancer medicine, bridge the gap between innovative ideas and technologies applicable to cancer diagnosis and treatment, and their practical clinical application

- Facilitating the movement of novel technologies toward product development

These efforts are critical to further the development and deployment of novel technologies and methodologies to the practice of biomarker research.

DIAGNOSTICS EVALUATION BRANCH (DEB)

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.

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 was the successful Strategic Partnerships to Evaluate Cancer Signatures (SPECS) program launched in 2004.

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 validate *in vitro* diagnostics analytically and clinically, establishing 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 treatment regimens

- Interacting with other agencies such as the Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS) to understand problems in the development of promising assays, particularly those that can be used to identify people for whom certain treatments could be beneficial

These efforts are critical to facilitating the development of high-quality biomarker assays applied in the clinical setting to ensure optimal care for patients with cancer.
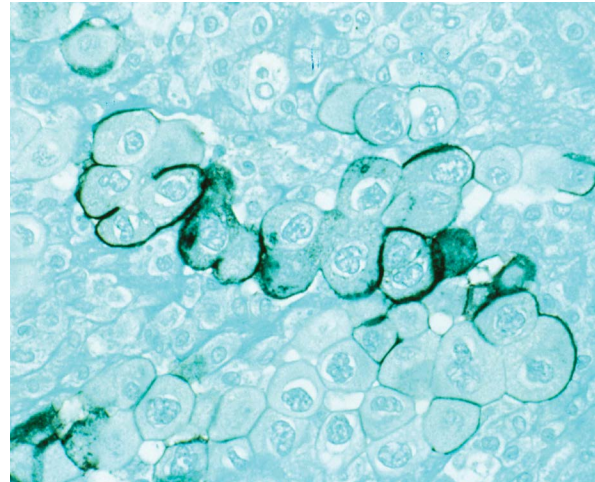
THE PATHOLOGY INVESTIGATION AND RESOURCES BRANCH (PIRB)

PIRB supports the collection and distribution of human bio-specimens, pathology investigation to facilitate the discovery of novel molecular features of cancers, and translational cancer research that requires patient biospecimens.

Biomarker discovery research, assay development, and evaluation of clinical utility of assays depend on the availability of human tumor (or associated) specimens for which there are also associated demographic and clinical data. PIRB has a long history of creative approaches to addressing these needs, including the CHTN, the CDP Cooperative Breast Cancer Tissue Resource , the ETCTN biobanking infrastructure, and working with the NCTN in their specimen banking efforts.

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 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 on human tissue specimen resources and sample preparation for researchers and pathology assessment and QA/QC for 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

- Participation in NCI's IMAT program, particularly in the biospecimen research arm of the initiative

- Support and development of informatics tools to improve access to human biospecimens and associated clinical data in NCI-funded biospecimen resources

- Contribution to the Cancer Moonshot[SM] that provides 'legacy' specimens to investigators that compete successfully for the Moonshot grant award

- Development of optimal biomarker collection processes for the CIMAC-CIDC clinical trials

These contributions are an essential part of the NCI scientific mission to support the research community by providing access to cancer samples that are optimally collected, clinically annotated, and easily accessible.

CDP GRANTS OVERVIEW

The CDP research portfolio included 240 funded grants during fiscal year 2019. The grant award mechanisms used by CDP and their distribution in terms of research support in 2019 are shown in the accompanying charts.

The predominant mechanism is the individual research project grant (R01), then exploratory grants (R21), followed by cooperative agreements that support both targeted research and research resources such as tissue banks.

Legend: ■ R01 ■ U01, U24, U2C, UH2, UH3, UM1 ■ R21 ■ R33 ■ Others (P01, R03, R35, R37, R50)
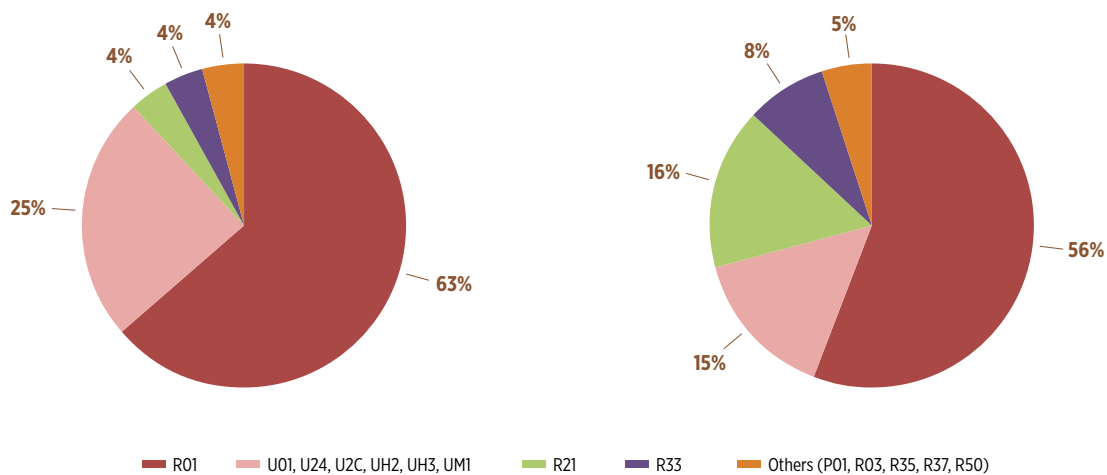
FIGURE 31: DISTRIBUTION OF CDP 2019 GRANT FUNDS (LEFT) AND NUMBERS OF GRANTS (RIGHT) BY MECHANISM.

Legend: ■ Diagnostic Biomarker and Technology Development ■ Diagnostics Evaluation ■ Biospecimen Resources and Biospecimen Research
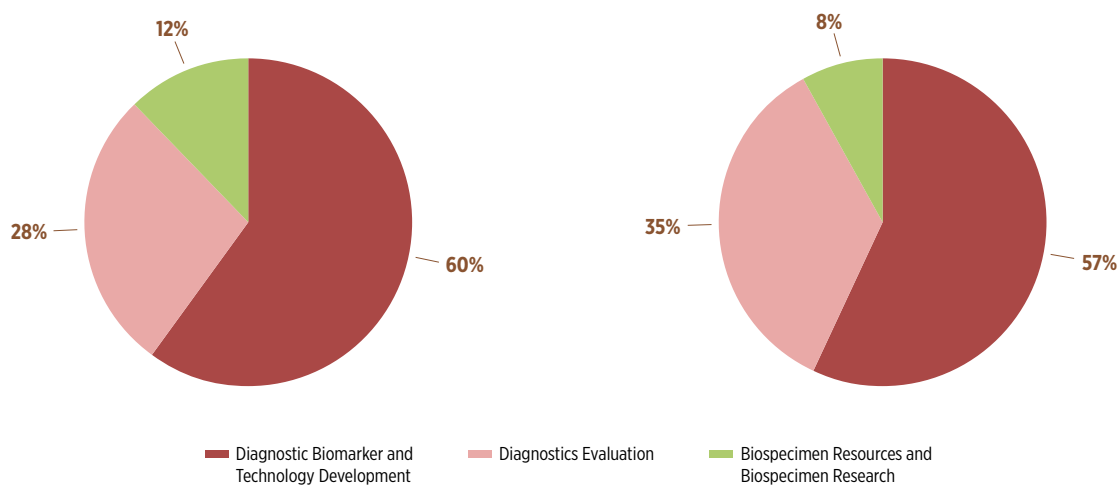
FIGURE 32: DISTRIBUTION OF CDP 2019 GRANT FUNDS (LEFT) AND NUMBERS OF GRANTS (RIGHT) BY RESEARCH AREA.
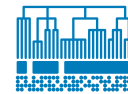
ASSISTANCE TO THE CANCER RESEARCH COMMUNITY

MOLECULAR CHARACTERIZATION LABORATORY (MoCha)

CDP works closely with the MoCha staff at the Frederick National Laboratory for Cancer Research (FNLCR) as it provides instrumental support to DCTD for many initiatives. MoCha provides genomic characterization of biospecimens obtained from patients with cancer in DCTD-supported clinical trials, for example, the NCI-MATCH study, NCI-COG Pediatric MATCH, and ETCTN trials through the National Clinical Laboratory Network (NCLN). In addition, MoCha has provided invaluable support and advice to the CIMAC-CIDC investigators by working with the team on assay harmonization, an area with which it has extensive experience. Furthermore, MoCha will be closely involved with the development of the Molecular Diagnostics Network that will support three large NCI-supported precision medicine clinical trials that are under development.

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, FDA, and NCI, with expertise in clinical oncology, 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 care of people with cancer.

Outcomes include the following:

- Launch of the landmark "Trial Assigning Individualized Options for Treatment" (TAILORx) to evaluate the ability of the Oncotype DX™ assay to predict benefit from chemotherapy.

- Publication of the "Reporting Recommendations for Tumor Marker Prognostic Studies" (REMARK) guidelines for reporting tumor marker studies in biomedical journals

- Development of standards for 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
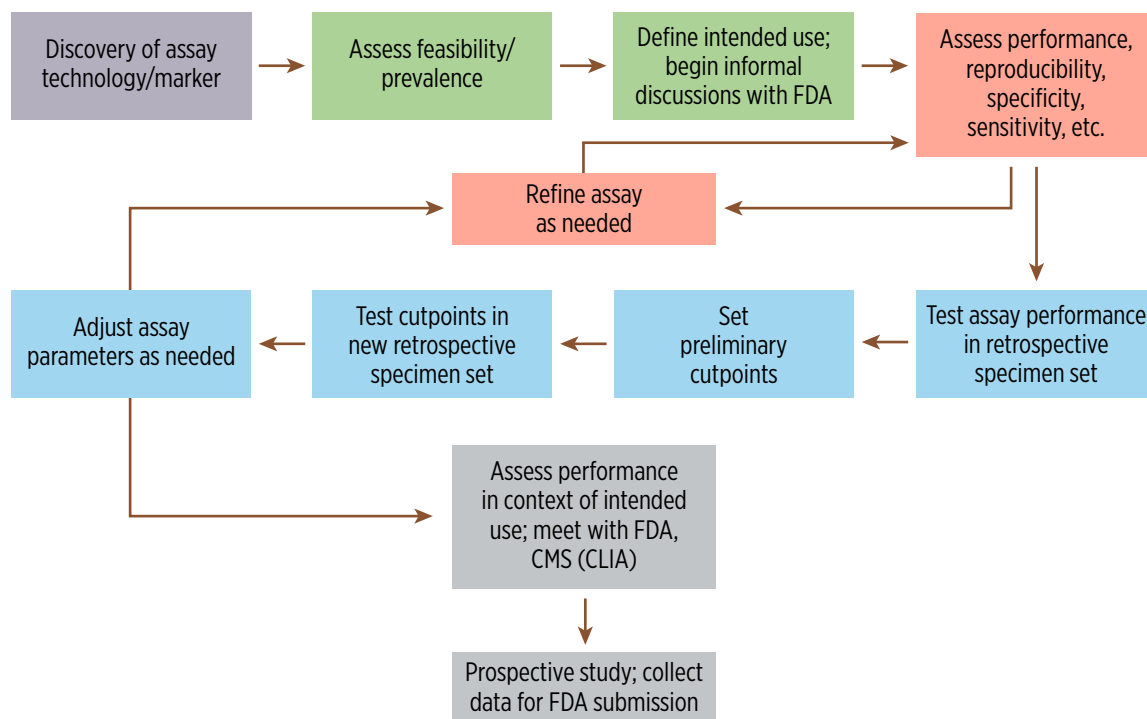
FIGURE 33: THE MARKER DEVELOPMENT PROCESS.

THE TAILORx TRIAL

TAILORx, a trial concept originally developed by CDP, tested 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 women to the most appropriate and effective treatment. The signature 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 has been carried out as a collaboration between CDP, CTEP, and all 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, which 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 was reported in 2018 and clearly showed that chemotherapy was not beneficial for most women in the intermediate risk group (Sparano, 2018). Together with the results reported in 2015, the outcomes in the two arms of TAILORx provided definitive evidence that as many as 70% of women with early-stage breast cancer can safely avoid treatment with chemotherapy. This trial is expected to have a major impact on the treatment of women with breast cancer.
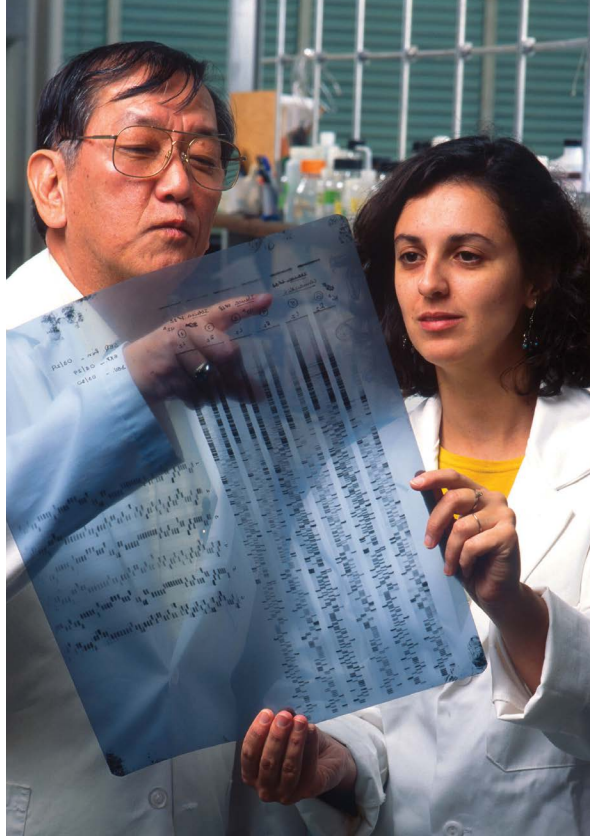
BIOMARKER EVALUATION IN NCI CANCER THERAPY TRIALS

CDP staff review biomarker studies proposed for inclusion in concepts and protocols for CTEP trials, considering both the analytic validity and the clinical utility of novel assays, to 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 (i.e., necessary for the trial to be performed, such as to choose 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. Considering that these trials pose special challenges to the implementation of NCI's operational efficiency initiatives, CDP staff are actively engaged with CTEP and the investigators of its clinical trials consortia to improve both the efficiency and the scientific output of DCTD trials. CDP and CTEP collaborate to foster research on biomarkers of response to new and novel immune therapies, other targeted therapies, and combinations of different therapies. CDP staff also serve as reviewers on the NCTN 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 Organization 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 (Sauerbrei W, 2018).

In 2014, NCI, EORTC, the European Medicines Agency, and AACR started a collaboration to develop a new meeting series with a clearer emphasis on drug development. The first two meetings in this new series, Innovations in Biomarkers and Cancer Drug Development, were held in Brussels, Belgium in 2016 and 2018 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 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.

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 to monitor for the molecular recurrence of chronic myelogenous leukemia after treatment, and efforts in the measurement of minimal residual disease, using various analytes and platforms.

ASSAY VALIDATION OF HIGH-QUALITY MARKERS FOR CLINICAL STUDIES IN CANCER

Since 2015, CDP's Diagnostic Evaluation Branch has led DCTD's participation in this NCI program. Sponsored jointly by DCTD, the Division of Cancer Prevention, and the Division of Cancer Control and Population Sciences, this program has issued a series of funding opportunity announcements to support the analytic and clinical validation of laboratory biomarkers for use in cancer diagnosis, screening, and epidemiology. Most of the grants have used the phased (UH2/UH3) award mechanism to provide support for analytic validation of an assay followed by expedited transition to a clinical validation study after the benchmarks for adequate analytic performance have been achieved. These awards have supported development of assays for a range of analytic platforms and clinical applications:

- Targeted sequencing assays to detect kinase gene fusions and microsatellite instability

- Detection of a prognostic mRNA immune signature in melanoma

- Molecular subtyping of colorectal cancer

- Gene expression signatures for diagnosis and prognosis of peripheral T cell lymphoma and mantle cell lymphoma

- APC and tP53 biomarkers for cetuximab response in colorectal cancer

- Measurement of epidermal growth factor receptor protein complexes for diagnosis in lung cancer
- Blood-based assays to detect the presence of metastatic cells and driver mutations in melanoma

BIOSPECIMEN ACCESS FOR THE CANCER RESEARCH COMMUNITY

Cooperative Human Tissue Network (CHTN)

The CHTN 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 procurement of malignant, benign, and uninvolved (normal adjacent) tissues as requested by an investigator. 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. Board-certified anatomic pathologists conduct quality assurance review on all biospecimens. From 1987-2019, the CHTN has provided over 1,316,200 specimens to more than 3,500 different investigators. Over 4,737 peer-reviewed scientific publications have resulted from the use of CHTN as a resource, reflecting relatively easy access to tissue specimens by many 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 most use the samples for their RO1 grant funded projects. In addition, many 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 patients enrolled in NCI-funded Phase 3 and large Phase 2 clinical treatment trials (see NCTN). These banked specimens are most useful for clinical correlative studies or assay clinical validation studies on uniformly treated populations of patients with cancer. 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 Principal Investigators. The NCTN Group Banking Steering Committee was established with representatives from all the NCTN banks/groups and NCI to lead and implement a harmoniza-

tion of standard operating procedures (SOPs) and a process for fair access to specimens. The NCTN CCSC reviews investigator requests for 'legacy' banked specimens and research proposals for scientific merit. If proposals receive favorable reviews, specimens with clinical, treatment, and outcome data can be made available to researchers through collaborative arrangements. Since its inception in 2017, 'legacy' specimens were distributed to 220 NCTN group investigators and 128 non-group investigators from the scientific community whose research proposals for correlative studies were approved by the NCTN CCSC based on scientific merit.

Experimental Therapeutics Clinical Trials Network (ETCTN) Banks

The ETCTN Biobank collects, processes, and stores high-quality human biospecimens from enrolled patients with cancer. It also provides up-to-date maintenance of specimen inventory and distribution of specimens to qualified, NCI-approved trial investigators and research laboratories. Specimen collections from patients offer several advantages such as:

- uniform information on medical history and treatment

- biospecimen quality assurance/quality control (QA/QC)

- reasonable cost compared to other sources.

These specimen collections are associated with comprehensive clinical data, including detailed drug information, treatment history, and cancer outcome data. PIRB supports this biobank through a U24 grant. The specimens collected are used for:

- validated integral and integrated biomarker assays that can be incorporated as endpoints into ETCTN studies

- demonstration of drug target engagement, mechanism of action, mechanisms of resistance, or to improve patient selection in subsequent studies

- achievement of a long-term goal to accelerate the development of NCI-IND agents

assessment of pharmacokinetics (PK) and pharmacodynamics (PD) of the studied experimental agents

The Cancer Moonshot Biobank

The Cancer Moonshot Biobank aims to support the Cancer Moonshot[SM] goals to accelerate and advance our understanding of cancer and better understand how to intervene in cancer initiation and progression. The Biobank will ask patients with cancer across the United States, who are receiving standard of care cancer treatment, to donate biospecimens and associated health information during cancer treatment. The biospecimens and associated health information will be made available to qualified cancer scientists to help those researchers learn how cancer grows and changes in people, and to find new cancer treatments. To help make sure that patients from all population groups can potentially benefit from the research, people from diverse racial, cultural, ethnic, and socioeconomic groups will be asked to participate in the Biobank.

The Moonshot Biobank will work in collaboration with community hospitals who are part of the NCI Community Oncology Research Program (NCORP) to engage eligible patients and collect biospecimens and extensive biospecimen collection and clinical data. Samples will be stored at a central biorepository that will perform pathology quality control and distribute biospecimens. Clinical laboratories will perform cancer biomarker assays on tumor tissue and return results to the participant and their healthcare provider. The biomarker test results may provide more information for cancer treatment decisions and will help researchers better understand how genes within a tumor can affect cancer progression and treatment. Participant and provider engagement strategies include an External Scientific Panel to provide input to the program, a secure website for return of results and provision of information to participants, local engagement projects, and an embedded Ethical Legal and Social Implications (ELSI) investigation.

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-com-

mercial 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.
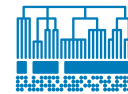
In the event a researcher is unsuccessful in finding the appropriate specimen resource through the SRL, they may contact the NCI Tissue Expediter and speak with a scientist who can further assist them. The NCI Tissue Expediter can also assist researchers to identify potential collaborators. NCI and NCI's 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 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 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 the database of Genotypes and Phenotypes (dbGaP). The GTEx dataset has proven to be one of the most heavily used genomic resources to date, with thousands of scientific studies utilizing the molecular data. 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 Standard Operating Procedures (SOPs)

NCI released to the public a compendium of SOPs that guided the successful collection of normal human biospecimens for the NIH GTEx project. These SOPs provide transparency about the details of this biospecimen collection, which have served as the basis for heavily utilized genomic data, and to enable high quality biospecimen collection by others in the research community.

Biospecimen Research Network (BRN)

The BRN was initiated to systematically address the impact of specific variables in individual specimen types on molecular data from different analysis platforms. Differences in pre-analytic 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

- 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 pre-analytical 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 Cooperative Agreement grants program to integrate biospecimen science studies into clinical assay development for improved reproducibility and utility of clinical biomarker assays utilized in therapeutic clinical trials

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 based on 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 developed a Biorepository Accreditation Program based on the NCI Best Practices.

The revised edition includes:

- recommendations based on the most recent research, guidance, and standards for collecting, processing, and storing specimens

- informatics practices in recognition of the phasing out of the caBIG and caGRID programs

- literature references

The Ethical, Legal and Policy Best Practices was also updated based on more recent guidance concerning:

- informed consent for genomics research

- the return of research results and incidental findings

- genomic data sharing

- community engagement

Updates to the legacy planning recommendations will be published shortly, and a 2020 update to the Ethical, Legal and Policy Best Practices is planned. BBRB also developed and published a Best Practices document for post-mortem biospecimen collection: Best Practices for Postmortem Recovery of Normal Human Tissue for Research.
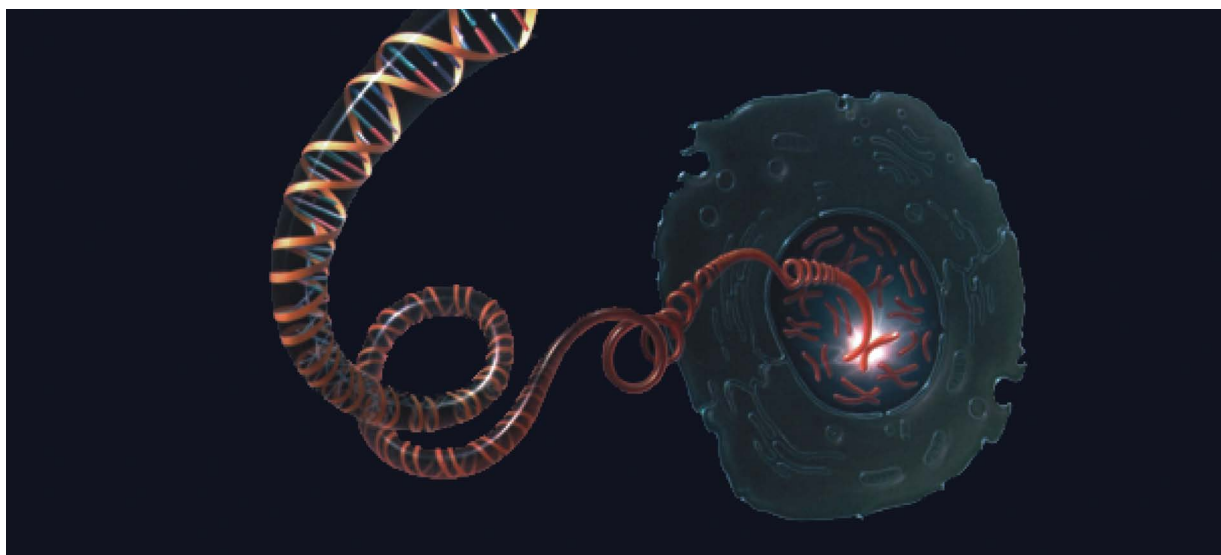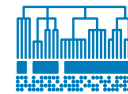
Biospecimen Evidence-Based Practices (BEBPs)

The NCI BEBP series is an expanding collection of procedural guidelines that provides evidence-based and practical information for researchers collecting and utilizing human biospecimens for research. Each document contains:

- step-by-step procedural guidelines

- supportive annotated summaries of literature evidence

- optimal procedures

- acceptable alternatives when the evidence allows, should key reagents be unavailable

The detailed, yet adaptable format, is intended to facilitate the creation of fit-for-purpose SOPs by researchers. Experts from the research community are engaged in review and modification of draft BEBPs so that real world experience is incorporated along with published literature. BEBPs published to date include: Cell-free DNA: Biospecimen Collection and Processing; Nucleic Acid Extraction from Formalin-Fixed, Paraffin-Embedded Tissue; Snap-Freezing of Post-Surgical Tissue Biospecimens.

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 used to collect biospecimen and clinical data on biospecimens donated from patients with cancer and post-mortem donors, for the NCI BPV and NIH GTEx programs. A simplified version known as "CDR Lite" was also 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 (NGS assays, molecular testing, and PD 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 cancer 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.

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

In response to a Cancer Moonshot[SM] directive, CDP has been approaching these recommendations through the Cancer Immune Monitoring Analysis Centers and Cancer Immune Data Commons (CIMAC-CIDC). By applying to the CIMAC Network, investigators who need immune-oncology assays performed as part of their clinical trial can request them. The CIMAC Network consists of a group of academic laboratories that specialize in immuno-oncology research with expertise in the specialized techniques needed to evaluate samples from immunotherapy trials. Thus far, the CIMACs have agreed to support 29 clinical trials from 13 clinical trial networks working with NCI. To assure sample quality, the network developed standardized SOPs for processing based on sample type. This should allow consistency of sample quality that is critical for comparison of assay results within and between trials. In addition, the CIMACs have been challenged to harmonize 'Tier 1' assays that are supposed

to be run in most trials. This, again, will be important for comparing assay results across trials, an important goal for this network. This was achieved for most Tier 1 assays but required multiple rounds of assay exchange between laboratories to achieve agreement of results. The MoCha laboratory and colleagues in the Biometric Research Program provide expertise for study design and data analysis.

The laboratories will begin to run trial samples in a set of retrospective pilot studies for which cohorts are already available. If successful, the CIMAC Network will provide an important set of SOPs for the research community to define the optimal method for immune-oncology assay performance. In addition, the CIDC, supported by the Partnership for Analysis of Cancer Therapy (PACT), will host the data generated by this initiative, which will be an important resource for the scientific community. The PACT initiative represents an important partnership between academia and industry supported through the Foundation for the National Institutes of Health and will also support other immune-oncology pharmaceutical company studies selected by the PACT committee to be run through the CIMACs. Closer relationships with industry partners can only improve our ability to conduct high quality immune-oncology biomarker research.

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 DCTD-supported clinical trials that aim to develop investigational drugs for cancer. These drugs often are of interest because of their activity against biological targets that are aberrant in cancer. The molecular mechanism(s) of action, however, may not be clearly understood, 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, ctDNA analysis, and other molecular characterization of specimens from participants participating in these trials should be informative. 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) have been challenged with producing robust assays that are well characterized and documented by
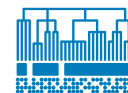
SOPs so that they can be transferred to a clinical laboratory as needed to support drug studies.

In this manner, CDP has already established the NCLN to provide both genomic characterization and PD assays for inclusion in trials conducted in NCI's ETCTN. The broad aim is to accelerate time to drug approval, or to abandon development of unsuccessful drugs, by identifying indicators of drug action, response, and resistance biomarkers in preclinical models and transferring these to robust, well characterized assays for retrospective investigation of specimens from DCTD-sponsored clinical studies. In addition, and where feasible, analytically validated PD and predictive assays will be developed for use as integrated and/or integral assays in a GLP- or CLIA- certified clinical assay laboratory network in NCI-sponsored precision medicine studies. These studies are now under development in a series of MATCH-like trials that are focusing on different populations (MyeloMATCH), technologies (iMATCH), or drug targets (ComboMATCH). These activities will be supported through the Molecular Diagnostic Network run by PADIS and MoCha programs in collaboration with CDP. This Network is charged with providing state-of-the-art assays using genomics, flow cytometry, immunoprofiling, and other novel techniques. Both FNLCR and FNLCR subcontracted laboratories will fulfill the requirements of this diverse set of studies. In addition, careful sample trafficking and processing will be critical due to the number of study sites participating via the NCTN.

CIRCULATING TUMOR NUCLEIC ACIDS

It has been known for several years 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 patients with cancer. These studies have demonstrated the potential of this genetic material to be used as a source of screening through so called "liquid biopsy" for actionable somatic mutations. This approach permits screening of virtually all patients, even those whose tumors cannot be biopsied. It has also been reported that serial assessment of circulating tumor DNA (ctDNA) is useful in determining treatment response and disease progression. Additional applications for circulating nucleic acid assays include monitoring of treatment effect or recurrence, monitoring for the development of action-

able 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 to:

- 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

- develop a full clinical grade assay to identify and/or monitor actionable somatic mutations in patient body fluids. The MoCha laboratory has already developed a novel 500-gene ctDNA assay in collaboration with Illumina™, and is currently working on clinical validation.

Second, CDP will work with outside investigators and the FDA to develop strategies for demonstrating the clinical utility of ctDNA-based diagnostic tests in clinical decision-making for people with cancer. The first step was a workshop in October 2016. BBRB's new best practice document, Cell-free DNA: Biospecimen Collection and Processing, builds upon this foundation.

BIOETHICS AND SCIENCE IN BIOBANKING

Several manuscripts have been published from ongoing BBRB research initiatives in the ethical, legal, and social implications of biobanking. These include the results of studies that were embedded in the GTEx and BPV programs. These studies investigated the attitudes and understandings of biospecimen donors and the families of deceased donors towards research biospecimen donation and engagement in research, including the return of research results. The GTEx study also investigated community attitudes towards biospecimen donation and actively engaged 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. Grants for a new funding opportunity announcement were awarded and together form a growing network of investigators to solve molecular assay challenges when utilizing liquid biopsies and small biopsies, including tissue cores and needle biopsies.

CANCER IMAGING PROGRAM

T1 + gadolinium   rCBF   rCBV

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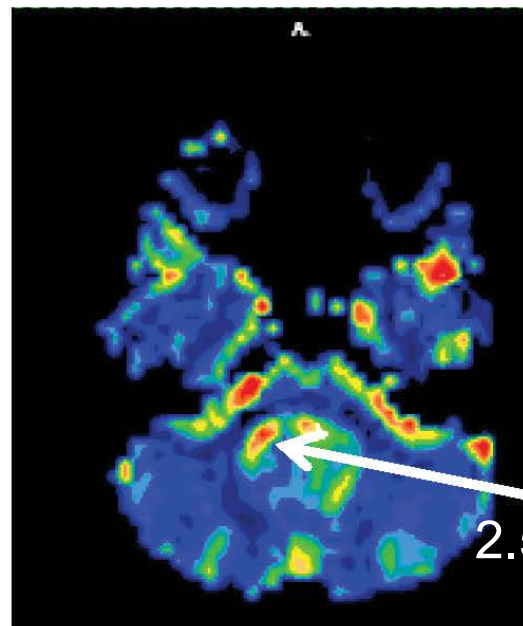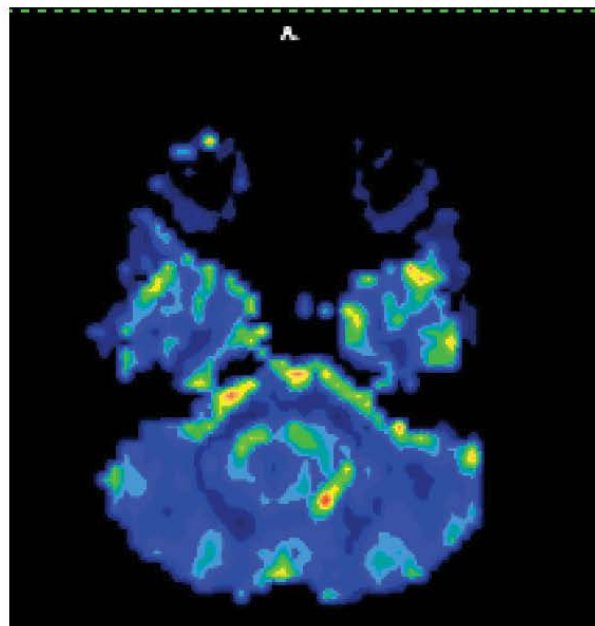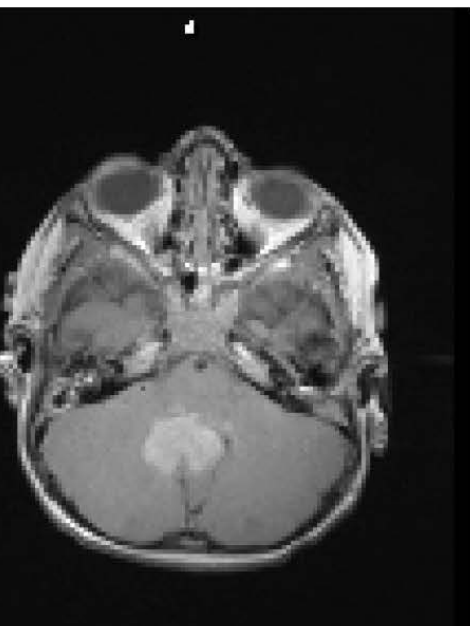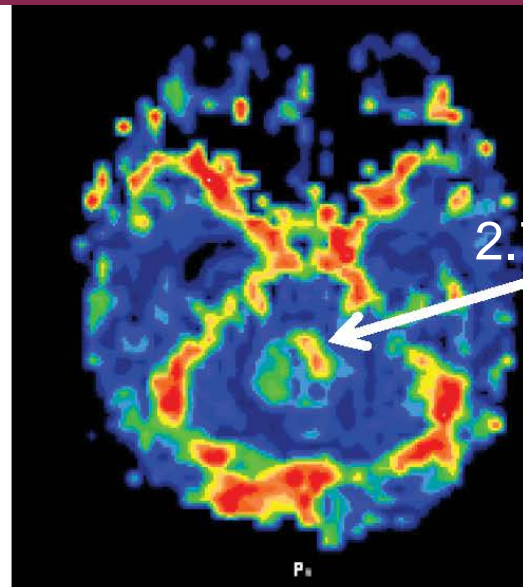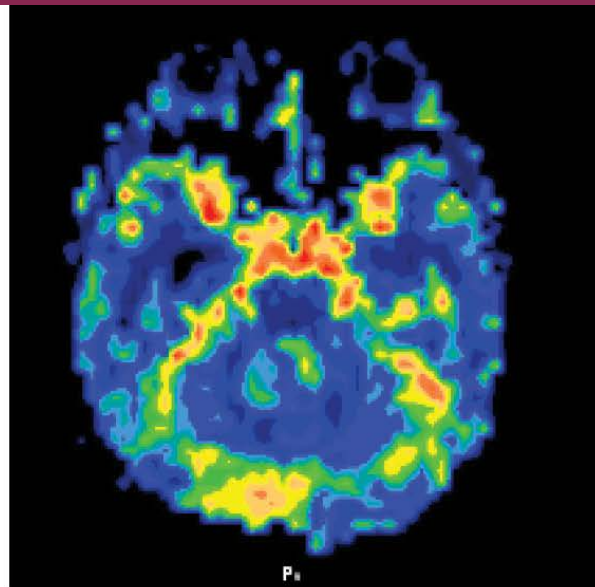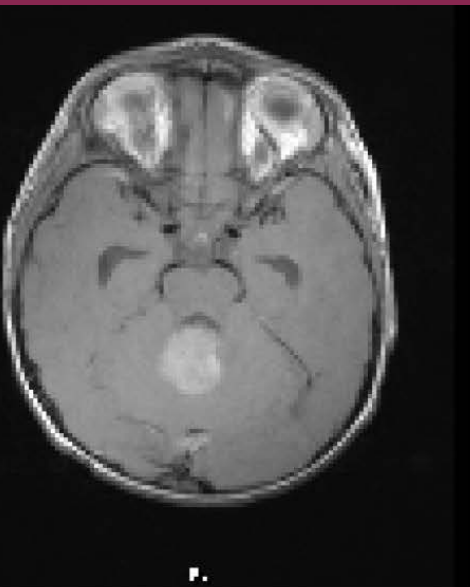
OVERVIEW

The Cancer Imaging Program (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 with cancer.

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 a 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 biologic 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, leading to improved standard of care. There is growing interest in combining information gained from imaging methods
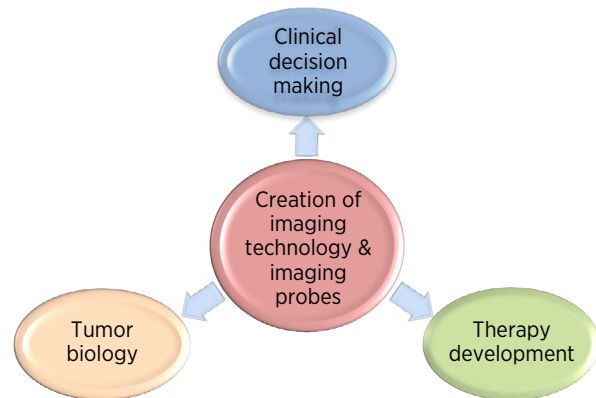
FIGURE 34: ROLE OF IMAGING TECHNOLOGIES.
Importance of imaging in understanding basic tumor biology, therapeutic development, and informing clinical decisions

with information from genomic and proteomic analyses 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 patients with cancer. As NCI continues to guide the discovery of new molecular signatures and cellular pathways of cancer, success can be achieved by understanding how these processes integrate into complex biological systems. With this information, we can contribute to effective therapy development. The challenge in medical imaging research is to continue to deliver sophisticated and integrated imaging methodologies to provide insight into the complex, 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.

JANET F. EARY
ASSOCIATE DIRECTOR
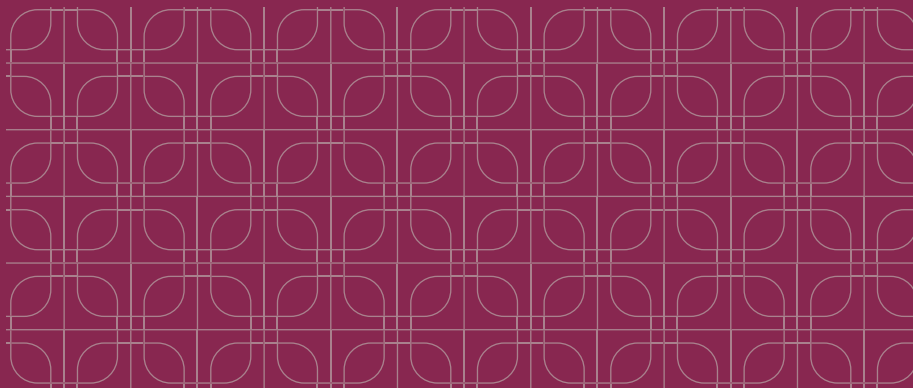
Dr. Eary joined CIP in NCI in 2016. She received her Bachelor of Science degree at the University of Michigan and Doctor of Medicine degree from the Michigan State University College of Human Medicine. She completed postdoctoral training at the University of Washington in Anatomic Pathology, Laboratory Medicine, and Nuclear Medicine, medical specialties in which she holds Medical Specialty Board Certifications. She has also participated as a member of the American Board of Nuclear Medicine. Her academic career began at the University of Washington School of Medicine (UWMC), where she was professor of Radiology, Pathology, and Orthopedics and held a faculty position in the University of Washington Graduate School. While at UWMC, she also served as Director for the Division of Nuclear Medicine and the Molecular Imaging Center and was a full member at the Fred Hutchinson Cancer Research Center where she was the creator and leader of the Cancer Imaging Program in the NCI Comprehensive Cancer Center. She also was the course coordinator of the seminar in Molecular Medicine and served on several institutional committees. Dr. Eary has been a research principal investigator and program leader continuously throughout her career which began in experimental therapy with radiopharmaceuticals and was a pioneer in molecular imaging. She has expertise in molecular imaging, radionuclide therapy, translational studies, clinical trial design, imaging basic science and image analysis, which remain as her researcher interests. Dr. Eary has published over 160 articles in these areas and is also the author of a radionuclide therapy book, numerous book chapters, educational materials, and editorials. From 2014-2016, Dr. Eary was a professor of Radiology and Surgery at the University of Alabama at Birmingham (UAB) School of Medicine and Graduate School, and Radiology Vice Chair of Clinical Research. She was also a member the UAB NCI Comprehensive Cancer Center Experimental Therapeutics Program. Presently, Dr. Eary is a frequent lecturer on advanced imaging topics in the U.S. and internationally. At NCI, Dr. Eary brings her background as a physician scientist and clinician to lead the NCI/CIP to achieve program goals to advance cancer imaging and imaging community contributions to improving outcomes for patients with cancer.

Imaging is essential to increasing our understanding of sub-cellular structural and molecular interactions executed by the proteome-to-cell microenvironment and cell-cell interactions through complex signaling and transfer processes. Imaging provides information across the genotype-to-phenotype continuum and is being applied to evaluate subcellular structure and biology, including protein-protein interactions and compartmentalization within unique intracellular microenvironments. Macro-level imaging is used clinically to evaluate cancer phenotype changes and characterize changes in the cancer microenvironment.

In the next decade, CIP-sponsored research will continue to contribute to the basic understanding of cancer by:

- creating novel methods to enhance the clinical role of imaging in noninvasive diagnosis

- helping identify disease subsets for effective treatment in patients with cancer

- improving disease staging and treatment monitoring

- playing a pivotal role for imaging in development of new therapies

- correlating medical images with genomic and proteomic data in precision medicine, particularly where obtaining tissue samples is difficult, such as in recurrent disease or multiple metastases

As part of its mission, CIP plays a critical role in NCI and NIH activities, 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 with cancer. 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.

Research in extracting information from imaging is a major CIP interest. 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 image data analysis approaches using structured computer-extracted features and AI are yielding increasing disease insights. Similar approaches employing complex cell systems have already revealed unanticipated network connectivity when these systems are perturbed with drugs with the potential to refine 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 development of clinically relevant imaging techniques

- Expand and improve integration of imaging data with clinical, genomic, proteomic data in data science and artificial intelligence goals

- Translate imaging-derived knowledge and techniques to help realize the potential of precision medicine

- Support target identification, imaging agent development, and translation for radionuclide, and optical device-based therapy

- Support development and validation testing for new imaging technology and its applications

STRUCTURE AND FUNCTION

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 (MIB)

MIB supports the goal of *in vivo* cancer molecular imaging by providing 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, PD, 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 by:

- Supporting state-of-the-science workshops and conversations across multi-disciplinary communities

- Collaborating with the Molecular Imaging Program of the Center for Cancer Research and the Molecular Imaging Clinic in the NIH Clinical Center

CLINICAL TRIALS BRANCH (CTB)

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)

- Integrating quantitative imaging tool testing and validation in clinical trials

- Identifying and facilitating clinical trial imaging data archiving to facilitate discovery research

- Developing trial-related informatics

- Promoting the development of radiomics-based clinical support tools

- Integrating imaging data into NCI efforts such as the Cancer Moonshot[SM] Biobank, Clinical Proteomic Tumor Analysis Consortium (CPTAC) and Applied Pro-

teogenomics Organizational Learning and Outcomes (APOLLO) network programs.

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 (IGIB)

IGIB promotes the integration of imaging, informatics, and interventional methods to address diverse clinical challenges such as directed biopsy and surgical resection, image-guided tumor ablation, dimensionality of scale, and targeted drug delivery. IGIB has a programmatic interest in image augmentation probe development, 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, which can be surgery, radiotherapy, cryotherapy, targeted drug therapy, or any of many cancer treatments. Imaging approaches in this process may involve exogenous agents or probes intended to augment the image. Combinations of imaging methods such as optical/MRI or ultrasound/MRI are often applied for image guidance during therapy.

IMAGING TECHNOLOGY DEVELOPMENT BRANCH (ITDB)

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 the current-generation (commercially supported) and 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 branch interest area.

NANODELIVERY SYSTEMS AND DEVICES BRANCH (NSDB)

NSDB develops, funds, and administers initiatives aimed at solving contemporary cancer research and oncology problems with nanotechnology solutions. The NSDB currently provides administrative support for the NCI Alliance for Nanotechnology in Cancer (ANC) program (initially established in NCI Office of the Director in 2005), which has been funding large-scale cooperative research (Centers for Cancer Nanotechnology Excellence – CCNEs). This network initially focused on the development of technology platforms seeking appropriate cancer applications. The program has matured and evolved into defining relevant biological and clinical problems that serve as drivers for implementation of suitable nanotechnologies. Since the beginning of the program, several technologies developed under ANC funding have reached a level warranting the initiation of clinical trials.

NSDB activities extend beyond nano-imaging and include novel in vitro diagnostics and therapeutics benefiting from the incorporation of nanotechnologies. NSDB serves as a focal point for nanotechnology-based grant and contract activities within DCTD and NCI. The NSDB also supports and oversees the Nanotechnology Characterization Laboratory (NCL) in the Frederick National Laboratory for Cancer Research (FNLCR). This laboratory group conducts comprehensive nanomaterials characterization with the aim of supporting translation. The lab also supports the Small Animal Imaging Program (SAIP) activities involving nanomaterials.

CIP RESEARCH GRANTS MANAGEMENT

The CIP research portfolio included 452 funded grants during fiscal year 2019, totaling $221 million. The predominant mechanism is the individual research project grant (R01), followed by cooperative agreements (U series). Because of the specialized nature of imaging research, CIP has developed several funding initiatives that encourage applications in specific areas. Figure 35 shows the distribution of CIP's award mechanisms and research support in 2019.
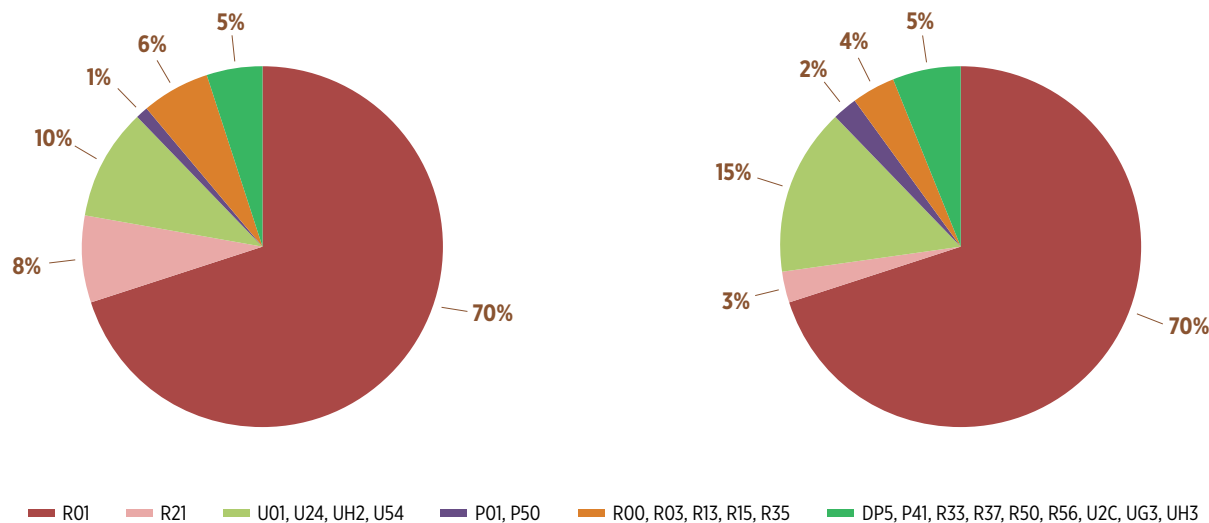
FIGURE 35: DISTRIBUTION OF CIP 2019 GRANTS BY MECHANISM (LEFT) AND BY FUNDS (RIGHT).

ASSISTANCE TO THE CANCER RESEARCH 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 PMSA. This collaboration is bidirectional, forming a novel development pipeline with the extramural imaging community in infrastructure for early clinical trials of imaging probes, and DCTD, which provides expertise in drug development.

NEW IMAGING TECHNOLOGY SUPPORT

uExplorer total body PET/CT. This new technology PET device developed through CIP support is set to revolutionize molecular imaging by allowing a move from traditional whole-body PET/CT imaging to simultaneous whole-body imaging. It accomplishes total body imaging in a single bed position in as few as 20-30 seconds and allows for fast imaging agent tracking throughout the blood and body simultaneously during imaging. The device can yield very high-resolution images at much lower imaging agent radio-activity doses, thereby expanding potential use in pediatric patients who would also benefit from the very fast imaging times. Investigators have generated the first imaging in patients (Figures 36, 37, and 38).[10]

FIGURE 36: UEXPLORER AT UC DAVIS MEDICAL CENTER.

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[10] Badawi RD, et al. *J Nucl Med.* 2019; 60:299–303.
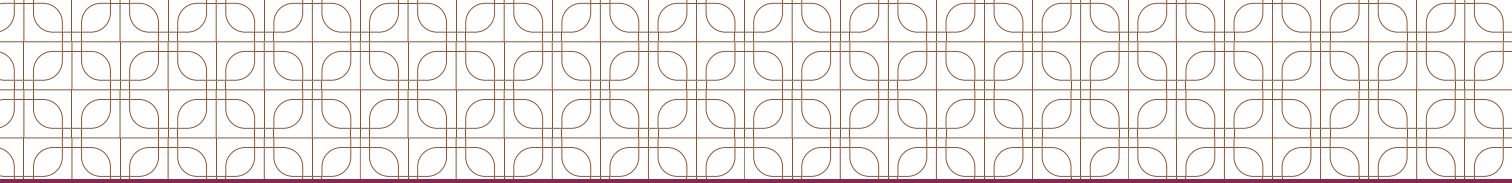
FIGURE 37: UEXPLORER.
1-Minute whole body scan 82 minutes post fdg injection showing high level image quality (left); standard pet/ct fdg 20-minute scan 81 minutes post injection (right).
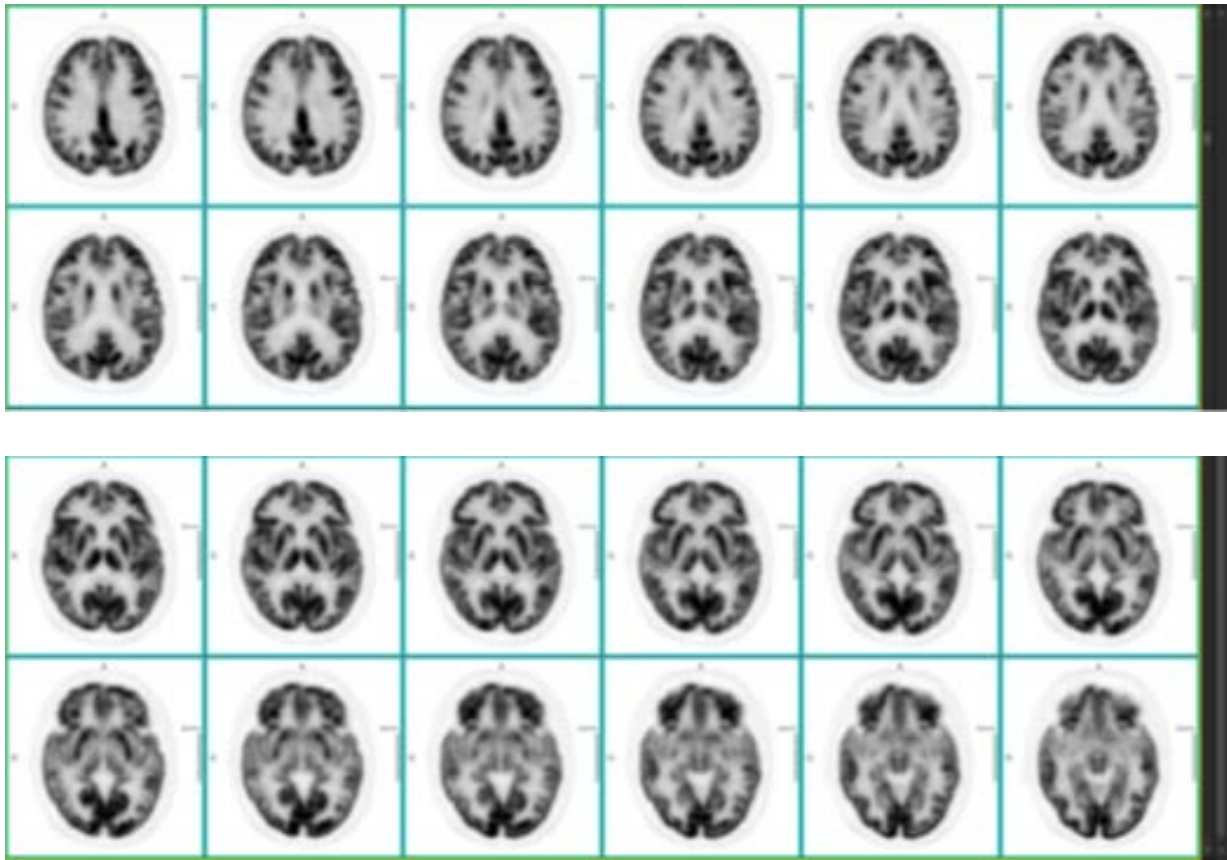
FIGURE 38: UEXPLORER WHOLE BRAIN IMAGES.

SPECIALIZED INITIATIVES

Extramural imaging research funding at NCI includes traditional P01, R01, R21, and other investigator-initiated grants. Several specialized initiatives covering the spectrum of CIP's research efforts, from basic research to clinical trials, have been developed or re-issued during this time to address unmet needs in the field.

In addition to many investigator-initiated basic research efforts, several key program announcements use the R01 and R21 grant mechanisms to foster research in specific areas. 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 goals of this initiative were 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 preliminary evaluations are early in development, this funding opportunity announcement (FOA) provided investigators with support for pilot (Phase 1 and 2) cancer imaging clinical trials, including patient monitoring and laboratory studies. It provided funding for conduct of Phase 0, 1, or small Phase 2 clinical trials designed and developed to facilitate completion within the 3-year funding period. This FOA supported novel uses of known and standard clinical imaging agents and methods as well as 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 National Clinical Trials Network.

- **Quantitative Imaging Network (UG3/UH3).** PAR-18-248: This FOA encouraged research project applications under the cooperative agreement (UG3/UH3) mechanism to address the development, optimization, and validation of quantitative imaging (QI) software tools and methods for prediction and/or measurement of response to cancer therapies or for planning and validating radiation therapy treatment strategies in clinical trials. The scientific scope included development and optimization of QI tools and/or methods for treatment planning, predicting, or measuring response to therapy as open source tools that could translate into clinical trial decision support. The optimized tools would need to be validated in clinical settings to demonstrate their value for decision support in ongoing single-site or multi-site clinical trials. A phased approach emphasizing each of those activities had to be provided in the proposal. Investigators submitted proposals for both the UG3 and UH3 phases together in the application. The UG3 effort was to be for the development and optimization of QI tools and methods chosen for study by the investigating team, while the UH3 phase was for the validation of the tools/methods developed in the UG3 phase. The UG3 phase could be no more than 2 years in duration, and the total project could not exceed 5 years. At completion, UG3 projects would be reviewed by program staff, with those meeting their milestones administratively considered by NCI program staff for transition to the UH3 validation phase.

- **Innovative Research in Cancer Nanotechnology – IRCN (R01).** PAR-17-240: This program enabled mechanistic research focused on understanding processes involved in the *in vivo* delivery of nanoscale systems to tumors, as well as nanomaterial properties that affect the detection of biomarkers using diagnostic devices. The goal was to gain further fundamental knowledge that could provide for more informed translation of nanotechnology to the clinical space.

- **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.

- Integration of Imaging and Fluid-Based Tumor Monitoring in Cancer Therapy (R01 Clinical Trial Optional) (R01). PAR-18-629: The long-term goal of this initiative is to determine the appropriate use of imaging and fluid-based tumor monitoring (liquid biopsy) assays to monitor therapy during active treatment of patients with cancer. The specific combination of assays will likely be dependent on the molecular characteristics of the disease and the assay detection limits. The precise application of a given combination of imaging and liquid biopsy assay should result in the determination of response or emergence of tumor treatment resistance at the earliest, unequivocal time point. Funding will support the integration and analysis of imaging and fluid-based tumor monitoring (liquid biopsy) assays into one or more therapeutic settings.

IMAGING INFORMATICS

CIP's informatics activities address major challenges to the acceleration of cancer imaging research. CIP established and supports The Cancer Imaging Archive (TCIA) to provide readily accessible, large, curated clinical image collections and to overcome the barriers to interinstitutional sharing of image data. CIP is also involved with the design and building of the Imaging Data Commons, a new segment of the Cancer Research Data Commons. Program leaders within CIP have organized an internal oversight committee to integrate program input with CBIIT activities in building the data commons. CIP also provides significant support to other NCI data initiatives such as APOLLO, Cancer Moonshot tasks teams, Cancer Moonshot Biobank, as well as CTEP and Imaging and Radiation Oncology Core (IROC) activities.

MOLECULAR IMAGING RADIOPHARMACEUTICAL RESOURCES

CIP has filed INDs for numerous molecular imaging radiopharmaceuticals to perform multicenter clinical trials and to facilitate access by the wider research community:

- [^{18}F]Fluorothymidine, targeted to areas of increased proliferation

- [^{18}F]Fluoromisonidazole, targeted to hypoxic tissues

- 16α-[^{18}F]Fluoro-17β-estradiol, targeted to estrogen receptors

- [^{18}F]Sodium fluoride, accumulating in areas of increased osteogenic activity

- [^{111}In]Trastuzumab, targeted to HER2-expressing cancers

- [^{89}Zr]Panitumumab, targeted to cancers expressing epidermal growth factor receptor (HER1)

- Ferumoxytol, an iron oxide nanoparticle for magnetic resonance imaging (MRI)

- [^{18}F]Fluorodeoxycytidine, targeted to areas of increased DNA synthesis

- [^{18}F]DCFBC, targeted to prostate specific membrane antigen

- Hyperpolarized [^{13}C]Pyruvate, targeted to areas of increased metabolism

NCI's first IND for an imaging agent, [^{18}F]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 cross-reference letters for 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.

NANOTECHNOLOGY CHARACTERIZATION LABORATORY (NCL)

The NCL was founded in 2005 as part of the Alliance for Nanotechnology in Cancer (ANC) program to provide "pharmaceutical mentorship" to investigators working in cancer nanomedicine. Documented in a memorandum of understanding between the NCI, FDA, and NIST, NCL's mission was to develop an "Assay Cascade" of scientific tests that would help determine the reproducibility, safety, and efficacy of cancer drugs and diagnostics based on nanotechnology and provide investigators with additional tools and information required to meet regulatory requirements to move their technology towards the clinic. NCL's Assay Cascade assays have been used to evaluate nanomaterials submitted to NCL by extramural investigators with the aim of generating data to support future IND or Investigational Device Exemption (IDE) filings to the FDA. The NCL has assisted more than 100 extramural investigators, tested close to 400 nano-formulations in its Assay Cascade, has 14 collaborators with nanomedicine products in clinical trials, and has published more than 200 scientific publications describing important trends in nanomedicine development. The NCL has additionally been developing new drug formulation capabilities designed to reduce drug toxicities and widen their therapeutic windows through administration via nanoparticles. Initial projects in this space involved nanoparticle formulation of natural products from the NCI Natural Products Library.

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 incapable of performing many studies due to several factors, including an absence 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 complementary to those of the Clinical Center 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 ECOG-ACRIN, a group under the NCI NCTN structure that has imaging as one of its foci. Another mechanism for inclusion of imaging in therapy trials is through supplements to trials being funded through other NCTN Groups. These efforts are discussed further below.

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK (ACRIN): 15 YEARS OF PROGRESS IN ONCOLOGIC IMAGING CLINICAL TRIALS

CIP established ACRIN, now a part of ECOG, 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 served on ACRIN's Data Safety and Monitoring Board.

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.

HIGHLIGHTS FROM ECOG-ACRIN IMAGING TRIALS DURING 2018 AND 2019

NCT00983697: Multicenter Trial of FDG-PET/CT Staging of Head and Neck Cancer and Its Impact on the N0 Neck Surgical Treatment in Head and Neck Cancer Patients

Diagnostic procedures, such as fluorodeoxyglucose F 18-PET/CT scan, may help locate head and neck cancer and allow determination of how far the disease has spread. It may also help to plan the best treatment. This study sought to determine the negative predictive value of PET/CT imaging based upon pathologic sampling of the neck lymph nodes in patients with head and neck cancer planning to undergo N0 neck surgery and determine the potential of PET/CT imaging to change treatment. Negative PET/CT scans in N0 necks were truly negative in 87%, and falsely negative in 13% of the patients. About 25% of N0 necks are thought to have occult pathologic LNs present, thus PET/CT showed utility. Nineteen patients had changes in surgical management due to PET scan results. The authors noted that well-designed clinical trials should be performed to test the outcome of omitting neck dissection by using PET/CT.

NCT01564368: Diffusion Weighted MR Imaging Biomarkers for Assessment of Breast Cancer Response to Neoadjuvant Treatment: A Sub-study of the I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And MoLecular Analysis)

Imaging procedures, such as diffusion-weighted magnetic resonance imaging (DWI) and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), may help in evaluating how well patients with breast cancer respond to treatment. This research trial studied DWI and DCE-MRI in assessing treatment response in patients with breast cancer undergoing neoadjuvant chemotherapy by assessing if the change in breast tumor apparent diffusion coefficient (ADC) value measured from each treatment timepoint to baseline is predictive of pathologic complete response (pCR). After 12 weeks of therapy, changes in breast tumor apparent diffusion coefficient at MRI predicted complete pathologic response to neoadjuvant chemotherapy. Midtreatment (12 weeks, between taxane and anthracycline regimens) tumor ADC changes were predictive of pathologic response, with pCR patients demonstrating greater increases in ADC from pre-treatment levels than patients without pCR. Although DW MRI and DCE MRI characterize different and potentially independent prognostic biologic properties related to tumor proliferation and angiogenesis, respectively, preliminary findings of this trial did not confirm them to be complementary in predicting pCR. Further investigation is warranted to assess the potential role of DW MRI as a non-contrast alternative to DCE.

NCT02022579: Multi-Center Study Evaluating the Utility of Diffusion Weighted Imaging for Detection and Diagnosis of Breast Cancer

DWI scans performed in women with breast lesions identified by conventional breast MRI were evaluated. The investigators examined whether an ADC threshold could be defined for distinguishing benign and malignant lesions on DWI, assessed the difference in ADC cutoffs for mass and non-mass lesions, and investigated the potential improvement in accuracy using techniques such as nonzero minimum β–value (to remove perfusion effects in the ADC measures) and normalized ADC measures (to account for variations in water content and other factors). Outcome measurement included if ADC when used systematically in conjunction with conventional Dynamic Contrast Enhanced-Magnetic Resonance Imaging (DCE-MRI), could reduce the biopsy rate by at least 20% while maintaining sensitivity (and decrease MRI false-positives). ADC values averaged about 20% lower in malignant lesions ($p<0.0001$). Application of an ADC threshold (1.53×10^{-3} mm^2/s) lowered the biopsy rate by 20.9% (14/67; 95% CI 11.2–31.2%) without affecting sensitivity. Thus, DWI could re-classify a substantial fraction of suspicious breast MRI findings as benign and thereby decrease unnecessary biopsies, however the ADC thresholds identified in this trial should be validated in future Phase 3 studies.

NCT02352883: Prospective Study of Magnetic Resonance Imaging (MRI) and Multiparameter Gene Expression Assay in Ductal Carcinoma In Situ (DCIS)

In this nonrandomized clinical trial of a pre-specified primary outcome among 339 women with pure ductal carcinoma in situ, after magnetic resonance imaging, 19% of patients eligible for wide local excision converted to mastectomy; 38% of conversions were based on magnetic resonance imaging findings and 62% on other reasons. Wide local excision was the final surgical procedure in 96% of women who received it as the first procedure after magnetic resonance imaging, and adherence to radiotherapy use guided by a 12-gene assay exceeded 90%. Only 171 patients were randomized into 2 groups for final radiotherapy (or not) recommendations. Breast magnetic resonance imaging and a 12-gene assay may be used to tailor primary surgical treatment and radiotherapy, respectively, and inform patient and physician decision-making to support more targeted therapy. This study may provide useful preliminary information required for designing a planned randomized clinical trial to determine the effect of MRI and DCIS score on surgical management, radiotherapy, overall resource use, and clinical outcomes, with the goal of achieving greater therapeutic precision.

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 39).
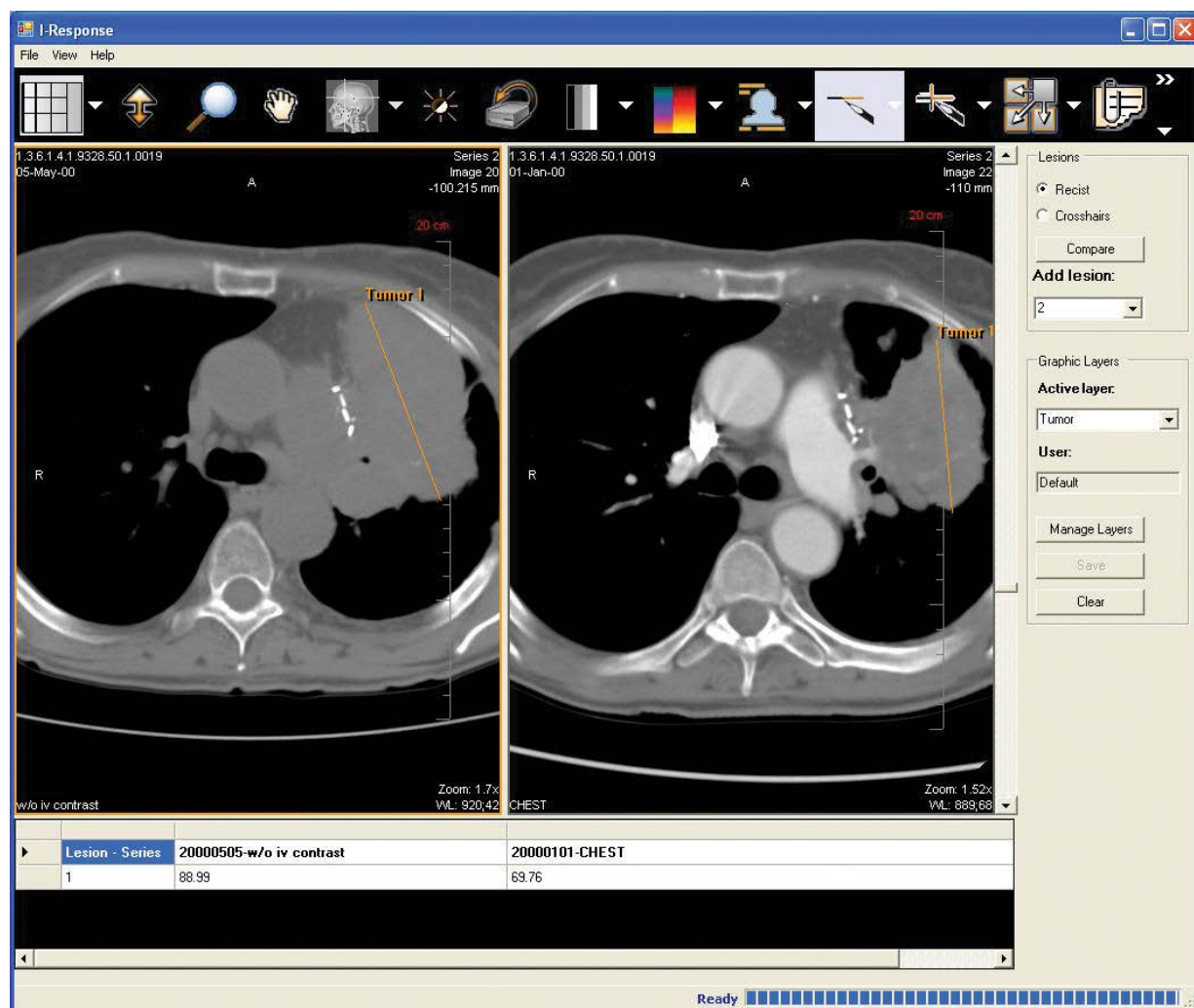
FIGURE 39: RECIST MEASUREMENTS TAKEN ON A LUNG TUMOR AT TWO DIFFERENT TIMES.

QUANTITATIVE IMAGING NETWORK (QIN)

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. To support this endeavor, CIP established the QIN in 2008 to promote the development and clinical validation of imaging data collection methods and software tools for clinical decision making in oncology. To date, 12 research teams participate as members of the network. This is down from a peak number of 25 teams in 2015 as funding support has been reduced recently. The Network has an active Associate Member program and 29 associate members from the US and abroad are participating. Global participation is shown in Figure 40.

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 team, 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 the NCTN.

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 testing and validation in clinical trials use by IROC.
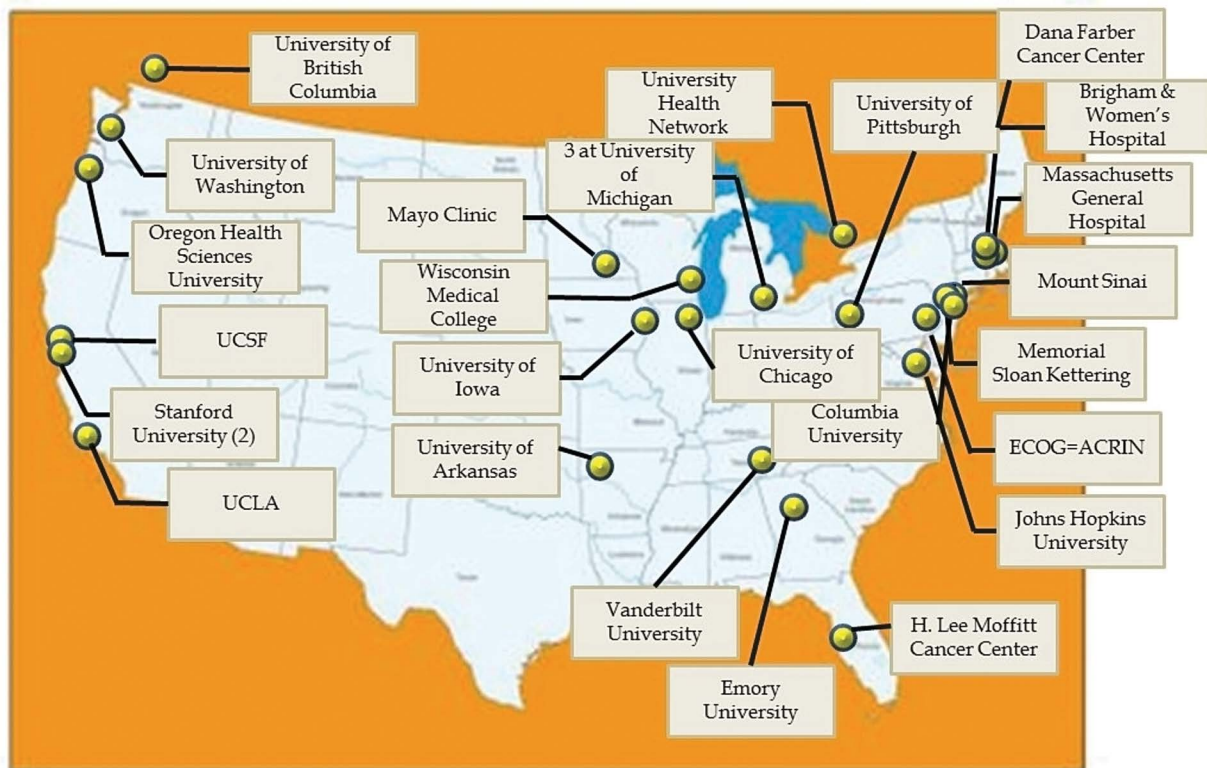
FIGURE 40: GEOGRAPHICAL DISTRIBUTION OF PAST AND PRESENT QIN TEAM MEMBERS.

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 cross-institutional working groups (Table 15).

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 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.

Based on a recent QIN progress and strategy update, the NCI Clinical Trials and Translational Research Advisory Committee (CTAC) and QIN members formed a committee to recommend ways to move the more mature QIN imaging tools into the NCTN for integrated testing in specific trials. The QIN initiated a five-step benchmark procedure to chart the technical progress of tools from early-stage development to clinically ready for validation. This process identified several imaging tools ready for NCTN testing.

Figure 41 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; early clinical research to include clinical testing or validation using retrospective clinical data; and the final stage to include prospective clinical validation demonstrating clinical functionality and useful clinical utility and workflow.

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.

FUTURE DIRECTIONS FOR QIN

QIN is increasing its efforts to bring clinical decision support tools to clinical utility. This involves a close interaction with the NCTN and other organizations focused on clinical trials. The NCI CTAC and QIN are working together to bring imaging quantitation tools into clinical trials for testing. Plans are underway for IROC, the clinical trials coordination program designed to support NCTN efforts in imaging and radiotherapy, to provide avenues for QIN members to begin inserting tools into imaging trials. The next few years will be important for translating QIN and tools and methods designed to predict or measure response to therapy during clinical trials.

Clinical Trial Design and Development	Methods for moving software tools into clinical trials, including those the network develops; 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 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

TABLE 15: QIN WORKING GROUPS AND FOCUS AREAS.

Institution	Concept	Development	Testing & Optimization	Clinical Testing	Commercialization	Clinical Workflow	
Brigham & Women's Hospital 3-D Slicer for Medical Image Visualization							**Open Source**
Brigham & Women's Hospital mpReview: Annotation for multiparamagnetic MRI							**Open Source**
*Brigham & Women's Hospital OncoQuant: DCE-MRI Analysis							**Not yet publicly available**
**Stanford University ePAD Clinical Viewer							**Open Source**

* with GE Global Research
** Active User's Group

Basic Research	Clinical Research	Community

FIGURE 41: PROGRESS OF QIN TEAMS TOWARD CLINICAL WORKFLOW.

ALLIANCE FOR NANOTECHNOLOGY IN CANCER (ANC)

The ANC was established within the NCI Office of the Director in 2005 and has since become a part of CIP. The goal of the ANC was to establish a network of interdisciplinary research teams with the collective expertise to develop and validate nanotechnologies applicable to cancer, up to and including preclinical testing. ANC investigators conduct research in three broad areas:

- early diagnosis using in vitro assays and devices or in vivo imaging techniques

- multifunctional nanotherapeutics, including nanoparticle-driven immunotherapies (introduced in 2005)

- devices and techniques for cancer prevention and control

The ANC Network was initially funded through a set of Requests for Application funding opportunity announcements. Internal and external evaluations of the program, as well as input from the extramural community, guided subsequent development of the ANC through renewal in 2010 and 2015. ANC consists of multiple synergistic funding initiatives for large research centers, smaller research projects under the umbrella of the Innovative Research in Cancer Nanotechnology (IRCN) initiative, support of the NCL, and Multidisciplinary Research Training and Team Development initiatives to foster cross-disciplinary training of graduate students and postdoctoral fellows in nanotechnology and cancer biology (Figure 42).

Another component, the Centers of Cancer Nanotechnology Excellence (CCNEs), are focused on integrating nanotechnology and cancer research to develop solutions that are clinically relevant. CCNEs, which had a tremendous scientific and commercial impact on the cancer nanotechnology community, will close in summer 2020 after 15 years of successful operation. They contributed to a significant increase in overall inter-
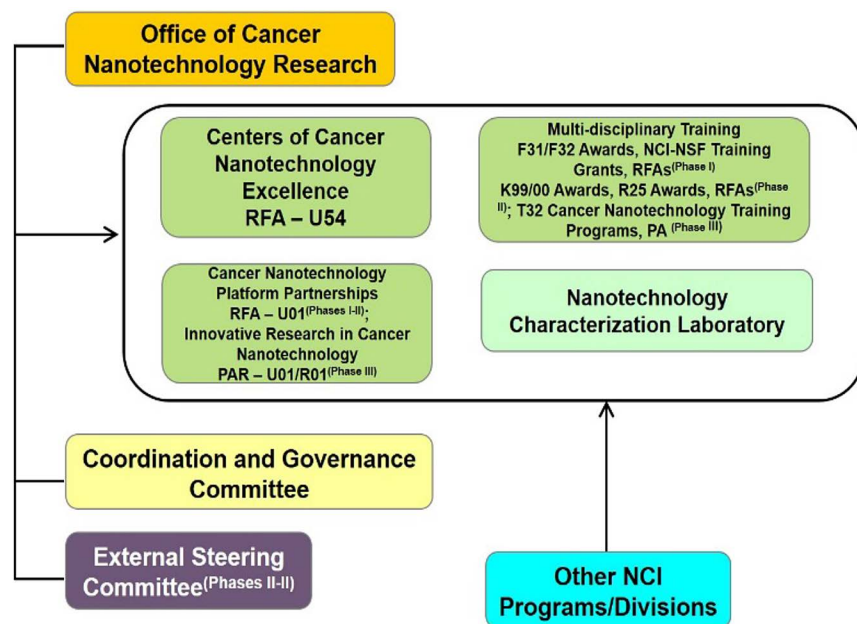
FIGURE 42: ANC PROGRAM ORGANIZATION AND OVERSIGHT.

est in nanotechnology for cancer. CCNEs produced close to 3,000 published manuscripts, but more importantly, the technologies that the CCNEs were developing resulted in the formation of more than 100 start-up companies and initiated more than 30 clinical trials (Phase I and Phase 2) by the end of 2019. These accomplishments went well beyond what NCI funding could support and were possible due to significant leveraging of NCI investment with additional funds from the government, philanthropy, and corporate investment. Nanotechnology has integrated well into the NCI funding portfolio and will continue to be supported through multiple NCI funding opportunities.

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

The CTB is engaged in the following activity 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 defines and develops avenues leading to the discovery of the next scientific breakthroughs and fosters the transfer of new technologies into the product development pipeline while focusing on key societal needs and priorities.

NATIONAL NANOTECHNOLOGY INITIATIVE (NNI) 2.0

The NNI is a collaboration of 20 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.

CIP staff participate in the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of NNI and work 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 the future development of 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.

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

- Workshops with the SNMMI on state of the science in radionuclide therapy and dosimetry

- Giving presentations on relevant medical imaging and regulatory issues at plenary and other scientific sessions at imaging society annual meetings

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

- RSNA Crowds Cure Cancer image annotation crowd source experience

- RSNA annual state of research using TCIA data sets

IMMUNE MODULATION THERAPY AND IMAGING

Immunotherapy is rapidly becoming a successful strategy in treating malignancies. NCI is investing 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 limitations in patients receiving immunotherapy. CIP researchers are pursuing alternative methods of tumor response assessment in this setting.

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 most 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. CIP Medical Officers participated as committee members in this international collaboration, have been co-chairs on the RECIST FDG PET Working Group since 2007, and are leading the next revision of the RECIST criteria.

IMAGING INFLAMMATION IN CANCER WORKSHOP AND CONSORTIUM

In 2019, CIP hosted a trans-NIH workshop bringing investigators together to discuss new approaches, insights, and findings from imaging in inflammatory diseases. This workshop led to publication of a white paper outlining future directions and funding concept opportunities for cross-fertilization of knowledge in this field. An imaging cancer inflammation funding concept and initiative is being developed from this interaction.

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 locations before surgery begins. Imaging probes that remain undetectable in the bloodstream will suddenly activate upon reaching the tumor to reveal the tumor's location. Functional imaging methods will reveal the activity of natural immune responses 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 the initiation of disease. Implanted devices will be capable of detecting and eliminating circulating tumor cells before metastasis can occur. Such feats will be possible if imaging is coupled with 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; however, they are essential to advancing our understanding of human cancer and improving outcomes.

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

CANCER THERAPY EVALUATION PROGRAM
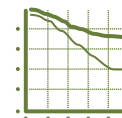
OVERVIEW

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 directly supports and oversees greater than 270 actively accruing cancer treatment clinical trials conducted throughout the nation annually. These trials are funded by more than 75 cooperative agreements and contracts and involve about 20,000 patients annually. This level of activity makes CTEP one of 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 Figure 43.
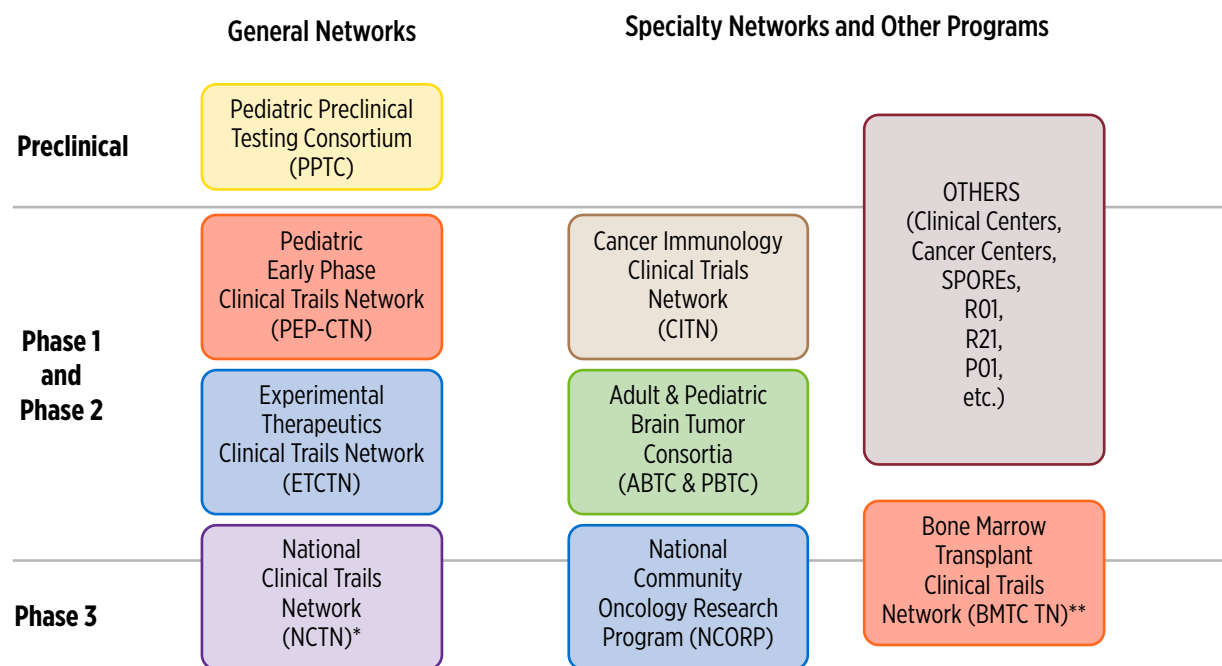
FIGURE 43: NCI CLINICAL TRIALS NETWORK AND PROGRAMS.

SPOREs = Specialized Programs of Research Excellence; R01, R21, P01 are research project, exploratory & developmental research, and program project grants.
CTEP-funded Clinical Trials Networks include the PPTC, PEP-CTN, ETCN, NCTN, CITN, ABTC, PBTC and BMTCTN.

MEG MOONEY
ACTING ASSOCIATE DIRECTOR

Meg Mooney, MD, MS, is the Acting Associate Director of the Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis, at the National Cancer Institute (NCI), and she is also the Chief of the Clinical Investigations Branch (CIB) in CTEP.

She received her medical degree from the University of Chicago Pritzker School of Medicine in Chicago and her general surgical training at the Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire. She completed her Surgical Oncology fellowship training at the Roswell Park Cancer Institute in Buffalo, New York, and holds a Master of Science degree in Management from the Massachusetts Institute of Technology in Cambridge, Massachusetts.

Dr. Mooney joined NCI in 2002 as Head of Gastrointestinal and Neuroendocrine Cancer Therapeutics in CIB. She was appointed Chief of the branch in May 2009. She is responsible for the direction of the NCI National Clinical Trials Network (NCTN) Program. The NCTN performs large, definitive, practice-changing phase 2 and 3 cancer treatment and advanced imaging trials. In April 2014, she was named the Deputy Associate Director of CTEP. Dr. Mooney became the Acting Associate Director of CTEP in December 2018.
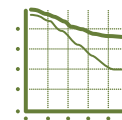
CTEP STRATEGIC GOALS

- 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

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. At the end of 2019, CTEP held 187 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 Figure 43) 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 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.

Twenty-two novel combinations of targeted investigational agents have entered 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 (IDB)

IDB is responsible for the clinical development of anticancer agents that are being developed under NCI sponsorship. NCI develops research collaborations with pharmaceutical partners to develop anticancer agents in the public interest. Pharmaceutical companies seek NCI collaboration in areas such as the development of therapies for rare cancers, and for the development of combination therapies with drugs under development by other companies. In these collaborations, NCI assumes the role of IND sponsor, and is responsible for the design, conduct and safety of trials conducted under NCI-IND. NCI also provides a haven for intellectual property concerns, thereby permitting different companies to overcome industry barriers to co-development of agents. To facilitate the development of NCI-IND agents, IDB coordinates a clinical research network, the Experimental Therapeutics Clinical Trials Network (ETCTN), a UM1 grant-funded network of over 40 clinical trial sites with expertise in early phase cancer clinical trials. IDB provides oversight of clinical trials of NCI-IND agents, and IDB physicians are the medically responsible physicians for all clinical trials of NCI-IND agents. IDB oversees a portfolio of over 100 NCI-IND agents. In addition to their pharmacovigilance role, IDB staff evaluate new 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 NCI-INDs. IDB physicians 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.

CLINICAL INVESTIGATIONS BRANCH (CIB)

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 immunotherapies, 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 Early Phase Clinical Trials Network (PEP-CTN)
- 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 CTEP and Division of Cancer Prevention (DCP) clinical network and consortia 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

OTHER CLINICAL GRANTS AND CONTRACTS FUNCTIONS

CTEP also supports non-network clinical grants and contracts that represent a multidisciplinary clinical research portfolio 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. IDB and CIB provide support for oversight of these investigator-initiated therapeutic research projects.
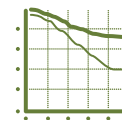
In 2019, CTEP managed 284 active grants totaling $303,746,510 (including$34,072,592 Research Project grants [R01], $37,568,290 Program Project grants [P01], and $224,263,092 cooperative agreements [U grants]).

Program Officers (POs) from IDB and CIB 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:

- Ensure that research project grants and cooperative agreements are scientifically and programmatically sound, and technically appropriate

- Identify areas of scientific gaps and/or overlap

- Discover new areas of scientific investigation

- Develop plans to exploit promising new therapeutic agents, modalities, and treatment strategies

- Provide assistance, information, guidance, and advice to the scientific community

- Ensure regulatory compliance

- Ensure that research project progress is adequate to meet project goals/objectives

- Stimulate interest in scientific areas relevant to clinical and surgical oncology

- Evaluate merit and mission relevance of research proposals

REGULATORY AFFAIRS BRANCH (RAB)

RAB comprises 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. Other types of agreements put in place to support our IND studies include Material Transfer Agreements (for preclinical studies), Clinical Trial Agreements (e.g., NCI-MATCH study), International Agreements, Memoranda of Understanding, and Data Use Agreements.

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 comply with FDA regulations.

As of December 2019, there are 187 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 (PMB)

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 approximately 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 (CTMB)

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 establishes 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 (01/01/2018 – 12/31/19)

- 2,098 NCTN Group audits reviewed

- 47 Non-Network Group audits reviewed

- 64 Cancer Center Site Visits coordinated and performed

- 37 Pediatric Early Phase - Clinical Trials Network (PEP-CTN) Phase 1 Consortium monitoring conducted by the clinical trial management service (CTMS) and reviewed by CTMB staff

- 263 Phase 1 and Phase 2 Protocols assigned for CTMS monitoring involving 2,151 patients audited

- 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

CTEP GRANTS OVERVIEW

The CTEP research portfolio includes 282 active grants and cooperative agreements totaling approximately $358 million during fiscal year 2019. The award mechanisms used by CTEP and their distribution in terms of number of awards and funding in 2019 are shown in Figure 44. 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.
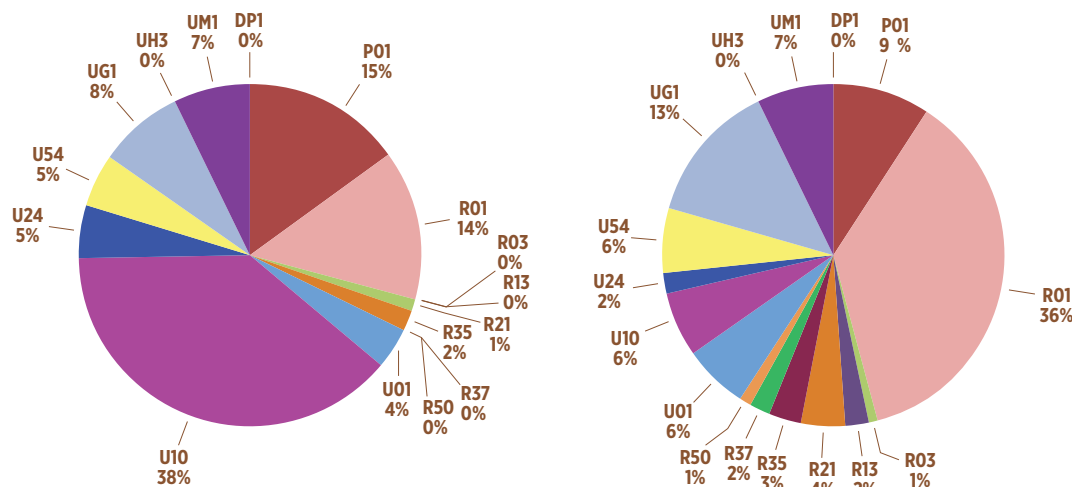
FIGURE 44: DISTRIBUTION OF CTEP 2019 GRANT FUNDS (LEFT) AND NUMBERS OF GRANTS (RIGHT) BY MECHANISM.
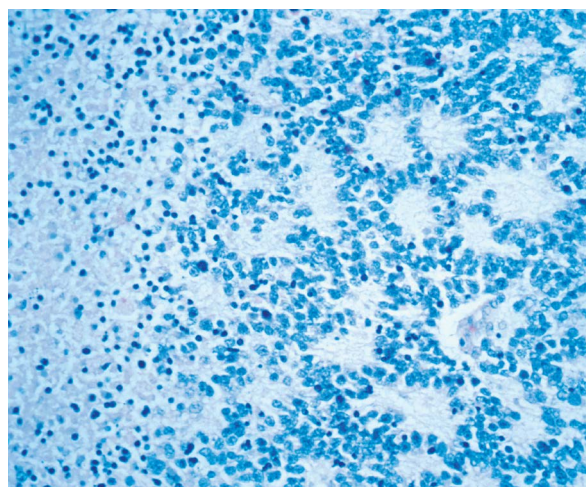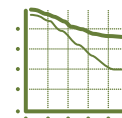
FOSTERING CAREER DEVELOPMENT OF JUNIOR CLINICAL INVESTIGATORS

The Early Stage Investigator (ESI) LOI 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 more than 600 ESI LOIs submitted through the end of 2019, approximately 38% have been approved. Moreover, virtually all members of CTEP Drug Development Project Teams are junior faculty/mentor pairs. ESIs have been submitted through all funding mechanisms, reflecting broad acceptance of the ESI process.

Ten to twenty U.S. and international fellows and junior faculty rotate at CTEP each year, during which they participate in:

- CTEP scientific review of LOIs and protocols
- Scientific presentations by biotechnology and pharmaceutical companies seeking CTEP collaboration
- Mentoring subprojects from CTEP early phase trial data

CTEP also sponsored its first LOI writing workshop for ESI's in September 2019 on the NCI Shady Grove campus. Twenty ESI's attended the 2 and 1/2-day workshop that was staffed by both CTEP staff and extramural mentors. Didactic session topics included preclinical data, trial design, biomarker considerations, and statistical plans. Each participant developed an LOI during the workshop. The feedback from the participants was very positive, and a second LOI workshop has been planned for fall 2020.

CLINICAL TRIALS PROGRAM

NCI NATIONAL CLINICAL TRIALS NETWORK (NCTN)

See the NCTN chapter in Major Initiatives.

The NCTN grant awards were issued in March of 2019. Changes to the Grant packages required the capability of transferring organizations between ETCTN grant holders. Enhancements previously made across the Clinical Oncology Research Enterprise (CORE) (see CORE, below) systems allowed organizations to continue enrolling, treating, and following patients in NCTN studies following the new awards. Enrollment was neither stopped nor suspended while updates were made to the institution and person rosters and the study participant list.

COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENTS (CRADAS)

Following are the numbers and types of agreements for 2018–2019:

- CRADAs Executed: 18
- Total Active CRADAs: 98
- CTAs Executed: 1
- Total CTAs: 28
- International Agreements Executed: 9
- Total International Agreements: 17
- INDs Filed: 43
- Total Active IND Portfolio: 186
- IND Amendments (per year):
  - 1355 Protocol Amendments
  - 58 New Protocols
  - 1209 Expedited Safety Reports
  - 350 Annual Reports

IP AND BIOMARKER DEVELOPMENT

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 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 and approved for the development of collaborative research agreements with NCI may 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). 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 prioritization of Early Stage Investigators (ESIs) in other CTEP and NCI initiatives.

- **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 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 an 8-10-week period to finalize the drug development plan for presentation to the Investigational
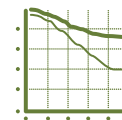
Drug Steering Committee (IDSC). Upon approval of the project development plan and the requisite funding by the NExT Program Senior Advisory Committee (SAC), the clinician and translational scientists on the Project Team submit LOIs to CTEP. CTEP subsequently makes the agent available to qualified investigators, 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 preclinical studies (Figure 45).

New Development Cycle for NCI Experimental Therapeutics
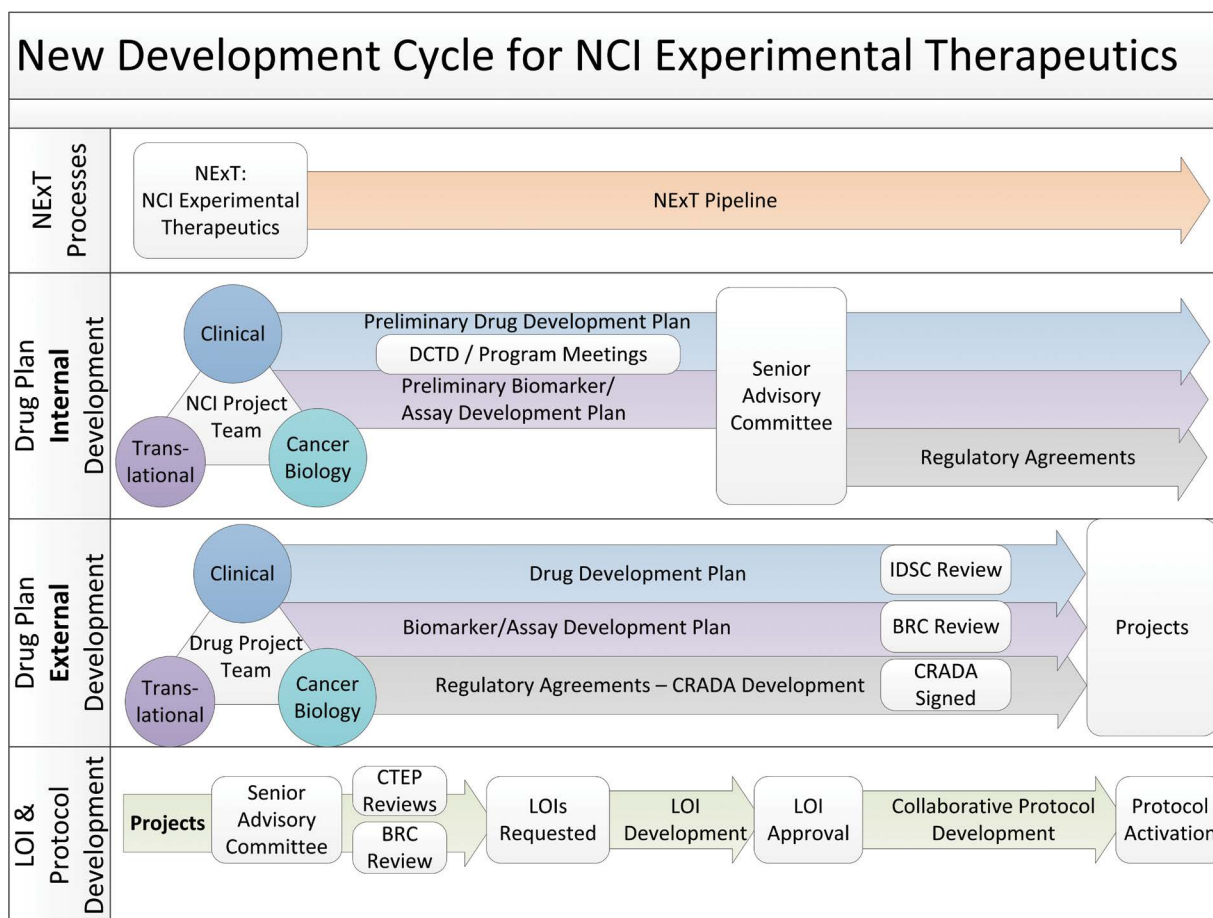
CRADA: Cooperative Research and Development Agreement   **IDSC**: Investigational Drug Steering Committee   **BRC**: Biomarker Review Committee

FIGURE 45: WORKFLOW FOR THE PROJECT TEAM-DRIVEN APPROACH TO NCI CLINICAL TRIALS.

Table 16 shows the Drug Development Project Teams assembled since implementation of this concept in 2014 through 2019.

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
2018	DS-8201a	HER 2-targeted antibody-drug conjugate – inhibits topoisomerase I whichleads to apoptosis of the target cells	Human Epidermal Growth Factor Receptor 2 (HER 2)
	Rogaratinib (preclinical)	Inhibits signaling of Fibroblast Growth Factor Receptor (FGFR) Subtypes 1-4	FGFR
	Radium-223	α-emitting radionuclide that, like calcium, is incorporated in the bone matrix at sites of active mineralization via osteoblasts	radiopharmaceutical
2019	Hu5F9-G4	Anti-CD47 Antibody which enhances prophagocytic signals on tumor cells (immune check point inhibitor)	CD47 Receptor
	GMI-1271 (preclinical)	A specific E-selectin inhibitor (antagonist), putatively disrupting leukemia cell survival pathways and enhancing chemotherapy response	E-selectin
	BAY 1895344	An active ataxia telangiectasia mutated and rad3-related (ATR) kinase inhibitor that exhibited an IC50 of of 7nM in a biochemical assay. It is thought to work by preventing DNA repair, resulting in tumor cell death	ATR
	Abemaciclib	An orally available cyclin-dependent kinase (CDK) inhibitor that targets the CDK4 (cyclin D1) and CDK6 (cyclin D3) cell cycle pathway, with potential antineoplastic activity	CDK4/6
	Lutetium-177 Dotatate	Binds to somatostatin receptors with highest affinity for subtype 2 receptors (SSRT2). Upon binding to somatostatin receptor expressing cells, including malignant somatostatin receptor-positive tumors, the compound is internalized	radiopharmaceutical

TABLE 16: NCI DRUG DEVELOPMENT PROJECT TEAMS (2014-2019).
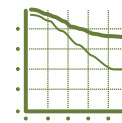
CTEP has also acquired agents that, due to a very limited drug development plan, have not required a Drug Development Project Team. Those agents are listed in Table 17.

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
2018	Thorium-227	An orally available, tropomyosin receptor kinase (Trk) inhibitor, with potential antineoplastic activity	radiopharmaceutical
	Venetoclax	Bcl-2-selective inhibitor that disrupts Bcl-2 signaling in cells and rapidly induces multiple hallmarks of apoptotic cell death in Bcl-2-dependent	Bcl-2
	CB-5339	P97 is a protein "machine" that uses the energy from ATP to attach and process misfolded protein	p97
2019	117m-Sn-Tin-DTPA	Excellent agent for the palliation of pain from bony metastases	radiopharmaceutical
	Erdafitinib	A targerted kinase inhibitor that exerts its action by binding to and blocking the enzymatic activity of several cell proteins, including FGFR1, FGFR2, FGFR3, and FGFR4	FGFR

TABLE 17: NCI AGENTS WITH LIMITED DRUG DEVELOPMENT (2014-2019)

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 54,300 trial-associated health care professionals are registered with NCI. The help desk manages more than 63,000 inquiries and communications annually in support of the registry. Registration is accomplished via the 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 2,000 annually (for 12 blinded, placebo-controlled and patient-specific supply clinical trials accruing patients)

- Open-label study standard order shipments: 23,000 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 12 blinded trials eligible to accrue patients and 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 13,000 e-mails in addition to more than 4,000 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.

- 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.

- Enhancement of investigator and sub-investigator registration website and resources to support the NCI Registration and Credential Repository.

- Facilitated development and maintenance of website in support of the NCI Formulary.

- Meet regulatory requirements to support agent distribution processes for IND Exempt clinical investigations.

CLINICAL TRIALS OPERATIONS AND INFORMATICS BRANCH (CTOIB)

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), Clinical Oncology Research Enterprise (CORE), the CTEP Enterprise System (ESYS), the Cancer Trials Support Unit (CTSU), the NCI Central Institutional Review Board (CIRB), the standard Clinical Data Management System (CDMS), and the Protocol Tracking System (PTS). 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.

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	2018	2019
LOIs	114	126
Concepts	97	65
New protocols	141	120
Protocol revisions	311	314
Protocol amendments	959	888

TABLE 18: ITEMS PROCESSED BY THE PROTOCOL AND INFORMATION OFFICE (2018–2019).

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. The CTEP-CORE is composed of integrated applications from the CTEP Enterprise System (CTEP ESYS), the CTSU Enterprise System (CTSU ESYS), and applications (e.g., MediData RAVE) that work together to support NCI clinical trial conduct and reporting.
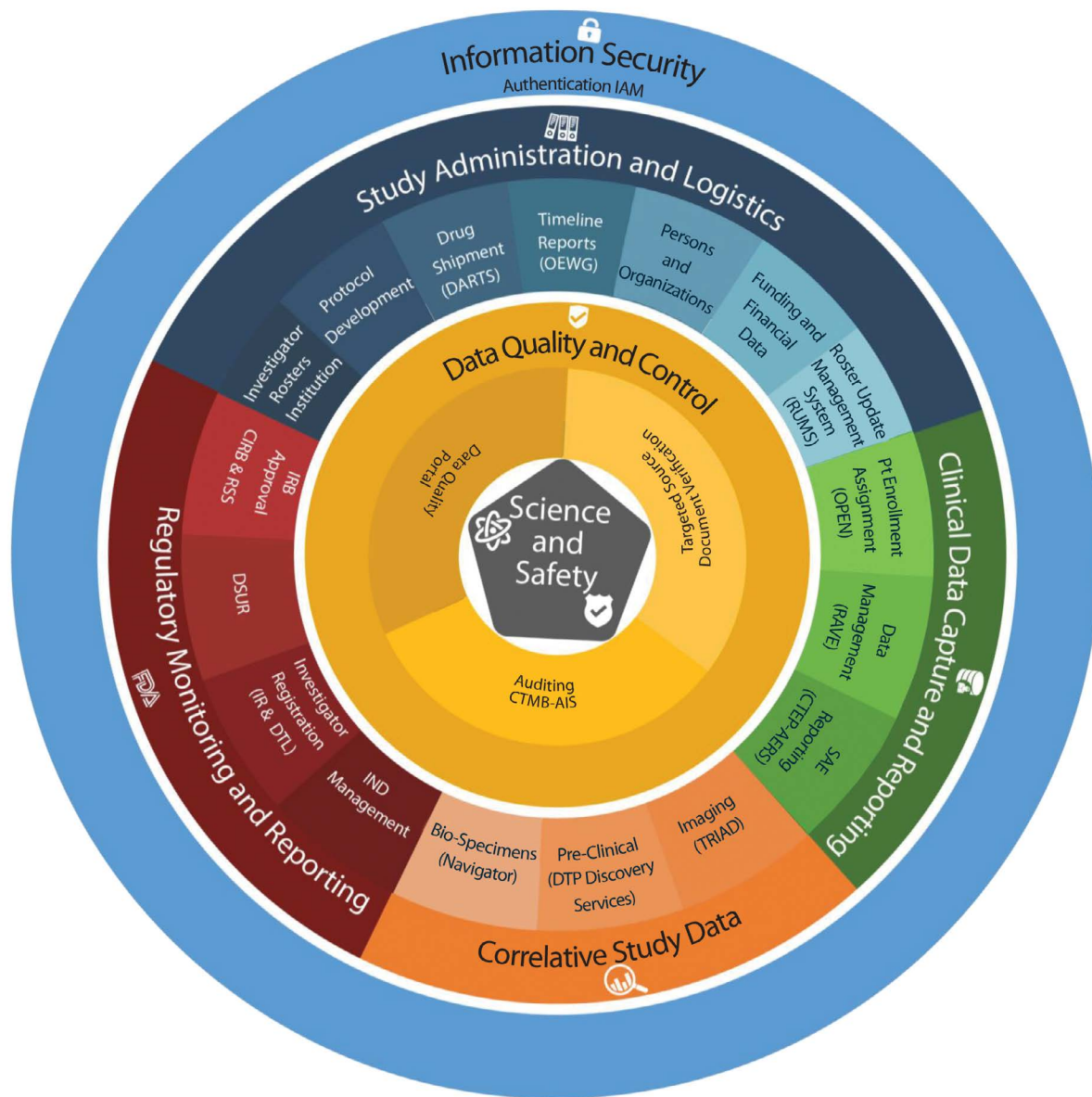
FIGURE 46: CTEP CLINICAL ONCOLOGY RESEARCH ENTERPRISE (CORE).
Provides secure, flexible, and scalable operational infrastructure to a robust clinical trials program.

CTEP Enterprise System (CTEP ESYS)

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

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

The CTEP ESYS applications continue to undergo 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. In addition, with the release of the International Council for Harmonisation (ICH) E6 R2 addendum, regulatory enhancements were added. On February 28, 2018, the FDA released E6 R2 Good Clinical Practice: Integrated Addendum to ICH E6 R1: Guidance for Industry. The guidance was based entirely on the ICH E6 R2 addendum (with a few minor wording differences). Per the FDA, the objective of this ICH GCP guidance is to provide a unified standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. The documents recognize that clinical trials are no longer a largely paper-based process. Advances in the use of electronic data recording and reporting facilitate implementation of other approaches. Per the FDA, their guidance has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording, and reporting while continuing to ensure human subject protection and reliability of trial results. Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency were also updated.

The CTEP ESYS continued to make updates to several systems (new and enhanced) used for submitting and tracking clinical trial information to CTEP. Several updates are shown below:

1. **Drug Authorization and Review Tracking System (DARTS) / AURORA**—As a sponsor for CTEP clinical trials, CTEP is responsible for maintaining adequate records showing the receipt, distribution/shipment, use, and final disposition of investigational agents. The re-engineering of DARTS resulted in AURORA, a new application to consolidate PMB's inventory management system and inventory management activities with clinical trial sites' inventory management activities in one centralized system. AURORA integrates agent ordering, accountability, and enhanced communication tools for CTEP-sponsored studies. The key benefits of the updated technology through AURORA are integration with other CTEP CORE clinical trial management system applications and improvements in data access, inventory management, record retention, system efficiency, and compliance with regulatory requirements.

The first step in the re-engineering effort (late 2017) included structuring an integrated electronic Drug Accountability system. Its intent is to assure that NCI-supplied agents are administered only to patients enrolled on approved NCI trials and to track complete disposition of the agent (as required by the FDA). Accountability for these agents will be tracked via an electronic Drug Accountability Record Form (eDARF) module within AURORA and will include a mechanism to allow agent ordering, receipt, dispensing, transfers, returns, and local destruction to be initiated and documented via the eDARF module. An Inventory Management area was constructed within AURORA such that information concerning agents, components, and kits used for clinical trials and received by, stored in, and distributed by the CTEP clinical repository can be reviewed and managed.

2. **CTEP Adverse Event Reporting System (CTEP-AERS)**— Following the new requirements put forth by the FDA (in line with the ICH guidance), the CTEP-AERS system required significant enhancements (in concert with the Identity and Access Management (IAM) system). Members of the external community (clinical trials staff at sites) are no longer permitted to enter adverse event information into a system without verification of their identity. Access to CTEP-AERS is required prior to having an approved IAM account and entering data. The CTEP-AERS developers provided new data collection screens to pull data from within CTEP-ESYS so that the reporting is tied to specific information for that clinical organization. In addition, the CTEP-AERS and the CTEP-IAM teams created a provisional IAM account, which allows a clinician to create a temporary account to enter adverse events; the contractor can review the clinician's identity during normal business hours, thus not impeding data entry. The CTEP-AERS team participated in a pilot of their AS2 gateway infrastructure to expedite adverse event reporting. In addition, CTEP completed ongoing enhancements to meet evolving regulatory requirements and integration needs with CTSUs Oncology Patient Enrollment Network (OPEN) and Medidata Rave.

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. Due to new security requirements, the IAM system was enhanced to inactive any users who did not access any CTEP-ESYS or other CTEP CORE systems within the 120-day timeframe following email reminders at 90 days and 115 days. A waiver was requested and approved for the external community to continue to submit adverse event reports and access their registration information in the Registration and Credentialing Repository (RCR) for up to 15 months (following reminders at 12, 13, and 14 months). If no attempt to access those systems during that time frame was made, their IAM accounts were inactivated.

4. **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. While re-engineering was completed towards the end of 2017, program decisions to shorten the OEWG timeline to 400 days for LOIs led to the need to reprogram this workflow in START and all downstream reporting systems. In addition, several new study descriptor fields (with access limited to certain roles) were added allowing CIB to capture additional NCTN trial information in START. Enhancements needed for the Clinical Trials Reporting Program (CTRP), Cancer Diagnosis Program (CDP), Cancer Immune Monitoring and Analysis Centers (CIMAC), and Data Mapping Utility (DMU) monitoring methods were also completed.

5. **CTMB Audit Information System (AIS)**—CTMB-AIS is the audit information system used to schedule and perform audits at sites conducting CTEP sponsored studies. Several enhancements were made to the audit reports, and details regarding Multigroup Audits and collection of data from International Audits can be captured. Working in collaboration with the CLASS Learning management system (CTSU contract), the CTMB-AIS restricted access for auditors who had not yet completed the required auditor trainings.

6. **Multiple Systems**—Multiple integration support needs to accommodate Targeted Radiopharmaceutical Facilities (TRFs) and Imaging and Radiation Treatment Facilities (IRTFs) included organization licenses and agent attributes in various systems within the CTEP ESYS structure.

Cancer Trials Support Unit (CTSU)

The 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 operational processes and informatics solutions, including trial data collection and reporting. The CTSU works in tandem with CTEP ESYS to simplify admittance to NCI-funded clinical trials for qualified clinical sites and support the conduct of those clinical trials. There are more than 30,000 registered CTSU members provided access to a wide range of information and support services, such as:

- The Oncology Patient Enrollment Network (OPEN), a web-based patient enrollment system with the ability to enroll patients 24/7. OPEN contains enrollment information from more than 542,000 patients and enrolls approximately 60,000 patients annually. OPEN also supports data collection to facilitate trial funding, a patient registry, and Cancer Care Delivery Research (CCDR) trials.
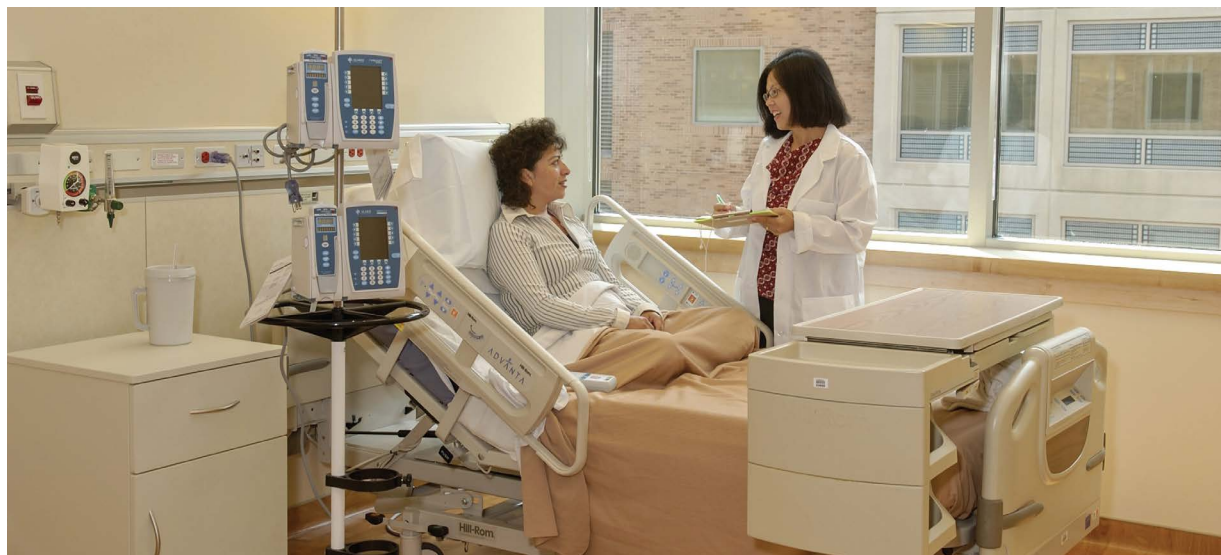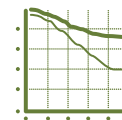
- The Regulatory Support System (RSS) serves as a centralized repository for regulatory documents for NCI-supported clinical trials, providing a streamlined and comprehensive approach to the review and maintenance of site registration, person, and institution documentation essential to the management of clinical trials. The CTSU processes approximately 24,000 IRB approvals per month, with more than 288,000 IRB approvals in 2019.

- The CTSU website is a robust repository containing all components necessary to successfully run an NCI clinical trial. Thousands of registered users visit the site monthly to perform a wide range of tasks, including:

  - Obtaining protocols or related documentation for more than 1,000 trials and funding information for more than 500 trials.

  - Submitting regulatory documentation by direct website upload using the Regulatory Submission Portal.

  - Integration with Medidata Rave, the clinical data management system used for the entry and management of clinical data. An integrated Data Quality Portal assists sites in tracking delinquent forms and outstanding queries for protocols.

  - The Source Document Portal allows sites to directly upload source documents for activities related to central monitoring, AE reporting, and eligibility review.

  - A Roster Update Management system allows sites and lead protocol organizations to streamline and implement uniform rostering practices when managing rosters and personnel roles for communication and system access.

- The Delegation of Tasks Log (DTL) application provides an online system to track site-level DTLs to fulfill protocol requirements.

- Quantifying site performance using metrics to standardize and calculate an official Performance Assessment Score for Sites (PASS).

NCI CENTRAL INSTITUTIONAL REVIEW BOARD (NCI CIRB)

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 clinical trials conducted via the NCTN, ETCTN, NCORP and 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. From 2014-2019 (Table 19), the CIRB maintained the established review timelines while needing to review an increasing number of studies.

As of December 31, 2019, 615 signatory institutions representing 2,476 sites were enrolled in the CIRB. This includes

94% of the NCTN, 100% of the ETCTN, and 99% of the NCORP institutions. The CIRB opened more than 32,000 protocols since its inception in 2001.

Year	Number of New Studies Approved
2014	39
2015	69*
2016	68
2017	96
2018	89
2019	102

*NCI-MATCH reviewed as one study

TABLE 19: NUMBER OF NEW STUDIES REVIEWED BY CIRB (2014-2019).

COMMON NETWORK-WIDE CLINICAL DATA MANAGEMENT SYSTEM (CDMS)

NCI deployed Medidata Rave, which is a standard CDMS, in the spring of 2012 across its clinical trial networks to improve operational efficiency, participant 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.

Rave Inegration
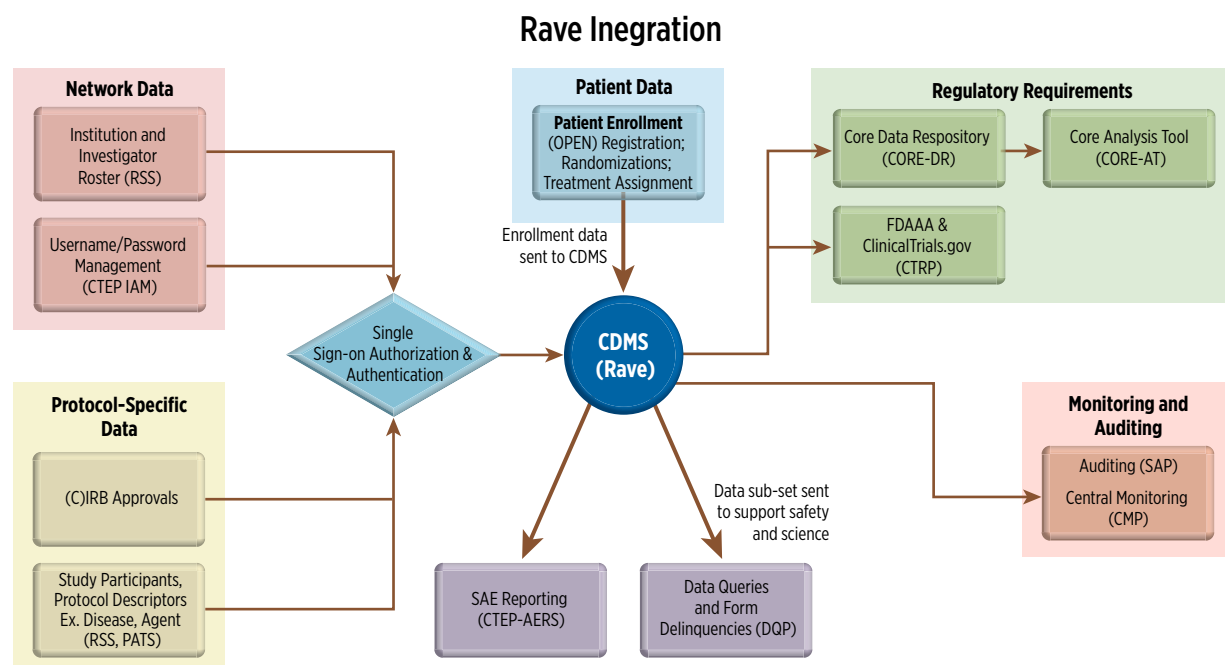
FIGURE 47: INTEGRATION OF THE METADATA RAVE CLINICAL DATA MANAGEMENT SYSTEM (CDM) INTO THE NCI CLINICAL TRIALS IT INFRASTRUCTURE.
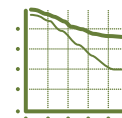
Protocol Tracking System

To support recommendations from the Operational Efficiency Working Group to improve timelines for protocol development, CTOIB provides services for extramural investigators. The website provides a centralized protocol tracking service so that all investigators have 24/7 online access to information about the status of their protocols in the development and approval process (Figure 48). This has helped CTEP and its investigators to reduce protocol development timelines by more than 75% in some cases.
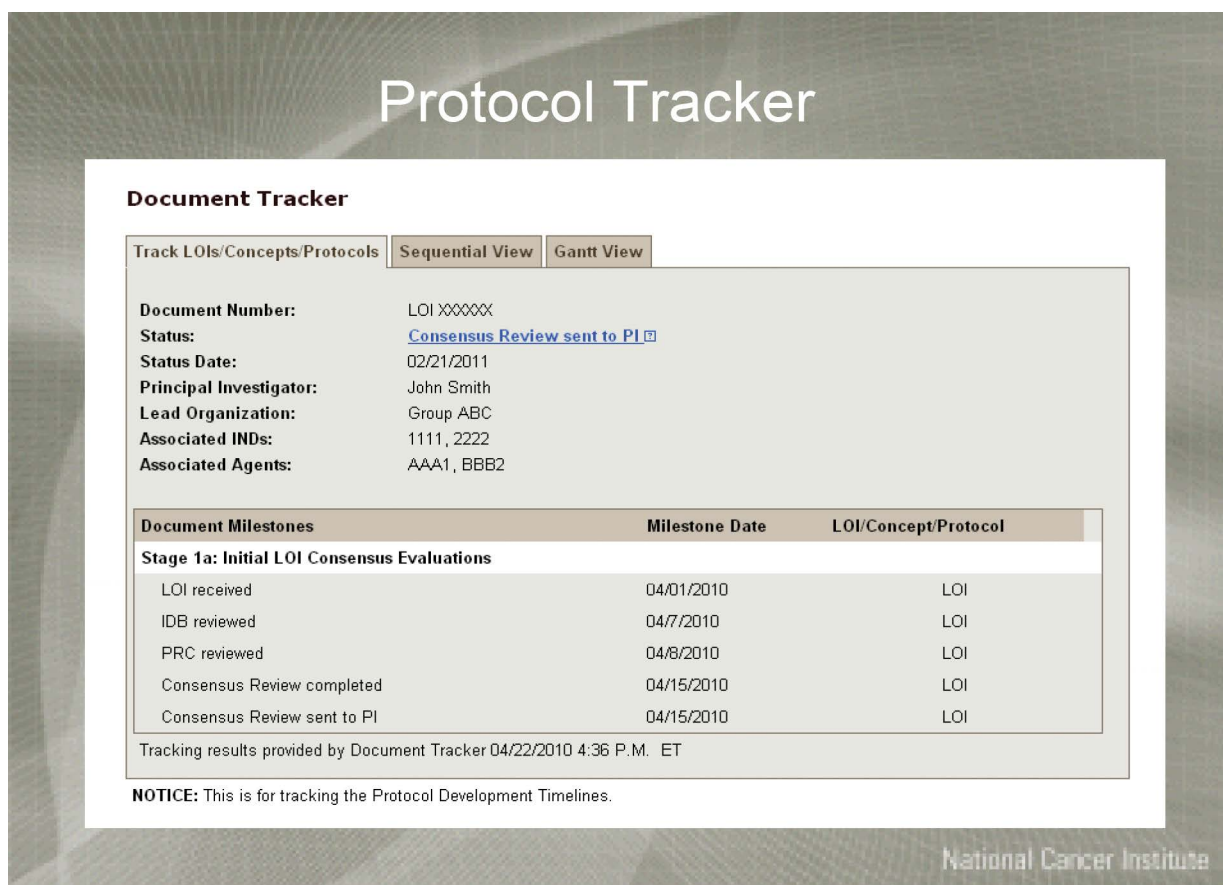
FIGURE 48: CTOIB'S PROTOCOL TRACKER.
Pediatric Translational and Clinical Research Programs

PEDIATRIC CLINICAL TRIALS

CTEP staff members 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 Pediatric Early Phase Clinical Trials Network (PEP-CTN) , 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 Pre-clinical 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. 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 (MD Anderson Cancer Center; Houston, TX)

- 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 (Lurie Children's Hospital; Chicago, IL)

- 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)

Recent accomplishments include:

- Genomic profiling of over 250 PDX models from 37 unique pediatric cancer types, which will allow the PPTC to select models for testing that map the target profile of experimental agents under evaluation. Characterization included whole exome sequencing, RNA-seq, and DNA copy number array analysis (Rokita, 2019).

- Identification of OBI-3424, a novel AKR1C3-activated prodrug as a highly active agent for T-ALL. Activity of OBI-3424 was found to correlate with level of AKR1C3 expression (Evans, 2019).

- An evaluation of entinostat, a potent HDAC inhibitor, that was found to have limited activity as a single agent and to provide limited benefit when added to standard-of-care cytotoxic agents (Kurmasheva, 2019).

- An evaluation of the ATR inhibitor M6620 (VX-970) that was found to have limited single agent in vivo activity against solid tumor PDX models, but that did show modest in vitro potentiation of cisplatin and melphalan for some cell lines and that was able to prolong time to event for a minority of PDX models when tested in vivo in combination with cisplatin (Kurmasheva, 2018).

- Identification of the menin inhibitor VTP50469 as highly active against infant ALL PDX models that have MLL gene rearrangement (Krivtsov, 2019).

Pediatric Early Phase Clinical Trials Network (PEP-CTN)

The PEP-CTN was established in 2019 to continue the work of the Children's Oncology Group Phase 1 Consortium. Its overarching goal is to identify and develop effective new agents for children and adolescents with cancer, through rational and efficient clinical and laboratory research. The PEP-CTN designs and conducts pediatric early phase trials including phase 1 trials that often include phase 2 expansion cohorts. In addition, the PEP-CTN conducts pilot studies of novel agents/regimens to determine their tolerability so that promising agents/regimens can proceed to definitive testing in phase 3 clinical trials (Krivtsov, 2019).
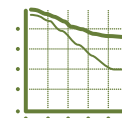
Important characteristics of the PEP-CTN include:

- Ability to conduct trials with seamless transitions from phase 1 to phase 2 testing

- Utilization of the Pediatric Early Phase Agent Prioritization Committee (APC) to prioritize agents for evaluation by the PEP-CTN and to expedite the pace at which novel investigational agents enter clinical testing in children with cancer

- Central monitoring for all PEP-CTN clinical trials

- Incorporation of relevant biological/genomic evaluations to establish eligibility for PEP-CTN clinical trials and/or to facilitate factors determining the activity of agents studied by the PEP-CTN.

Recent accomplishments include:

- ADVL1312 – Phase 1 study of the Wee1 inhibitor adavosertib (AZD1775) with irinotecan in children with relapsed solid tumors. Recommended phase 2 doses for each agent were identified and pharmacokinetics of adavosertib in children was described.[11]

- ADVL1315 – Phase 1 study of axitinib, an inhibitor of VEGF receptors 1-3.

- ADVL1411 – Phase 1 study of the PARP inhibitor talazoparib in combination with temozolomide. Recommended phase 2 doses for each agent were identified.[12] An

expansion cohort for Ewing sarcoma was performed, but no responses were observed in 10 participants.

- In children with refractory solid tumors, the maximum tolerated and recommended 2 dose of axitinib was 2.4 mg/m^2/dose, which provides pharmacokinetic exposures similar to adults.[13]

- ADVL1412 – Phase 1-2 study of nivolumab and nivolumab + ipilimumab for pediatric cancers. Findings to date include that nivolumab is safe and well-tolerated in children. It shows clinical activity in pediatric Hodgkin lymphoma, but has no significant single agent activity in common pediatric solid tumors.[14]

Pediatric Brain Tumor Consortium (PBTC)

The primary objective of the 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-029: Phase 1 and 2 studies of the MEK inhibitor selumetinib (AZD6244) in children with recurrent or progressive pilocytic astrocytoma. The phase 1 portion of the study determined that the pediatric recommended phase 2 dose is less than that tolerated by adults, but despite this

[11] Cole KA, et al. Clin Cancer Res 2019 (Epub ahead of print]
[12] Schafer ES, et al. Pediatr Blood Cancer 2020: 67(2):e28073
[13] Geller JI, et al. Cancer 2018: 124(23):4548-4555
[14] Davis KL, et al. Lancet Oncology 2020: In press

lower dose, activity signals were observed.[15] The Phase 2 expansion determined that selumetinib was active both for participants with NF1-associated low grade gliomas and for participants with genomic alterations leading to BRAF activation.[16] COG has developed phase 3 studies building on the PBTC-029 results.

- PBTC-045: Phase 1-2 study of pembrolizumab in children with diffuse intrinsic pontine glioma (DIPG), non-brain-stem high-grade glioma, ependymoma, medulloblastoma, and hypermutated brain tumors. This study is one of the first to evaluate checkpoint inhibition in pediatric brain tumors, with early results highlighting challenges in applying immunotherapy for patients with DIPG.[17]

- PBTC-047: Phase 1 study of panobinostat for children with recurrent or refractory DIPG. Accrual to the recurrent DIPG stratum has been completed on a 3 weeks on/1 week off schedule.[18] The study is now determining whether a higher dose can be achieved with a 1 week on/1 week off schedule in children with non-progressive DIPG.

- PBTC-033: Phase 1-2 study of veliparib with concurrent radiation therapy followed by veliparib and temozolomide in children with newly diagnosed DIPG. The study showed a lack of survival benefit compared to PBTC historical controls,[19] but it set the stage for a COG study of this regimen in non-brainstem high-grade gliomas.

Childhood Cancer Survivor Study (CCSS)

The 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 38,036 childhood cancer survivors and approximately 5,000 of their siblings.

Major accomplishments of the CCSS are:

- Extensive use by the research community resulting in 350 published or in press manuscripts now cited over 26,500 times, 327 abstracts accepted or presented, 56 investigator-initiated grants totaling $55 million, and five ongoing 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. With expansion of the cohort to include survivors diagnosed across three decades (1970-1999), reduction in the incidence of chronic health conditions in more recent eras was observed and attributable to temporal reductions in treatment intensity.

- 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 BRCA1 mutation carriers and much higher than the general population (4%).

- In addition to the previously mentioned reductions in chronic health conditions, CCSS identified that risk for subsequent malignant neoplasms was reduced in survivors diagnosed in the 1990s compared to those from the 1970s, attributable to reduction in radiation exposure. Within specific survivor populations results varied.

- Evidence for a novel association between anthracycline exposure in childhood and increased risk for subsequent breast cancer was strengthened by identification of a dose response effect between anthracycline exposure and breast cancer risk and discovery of an additive effect between anthracyclines and chest irradiation. Additionally, radiation to the chest given within one year of menarche was identified to be associated with an increased risk for breast cancer. Finally, the outcomes after diagnosis with a

[15] Banerjee A, et al. Neuro Oncol. 2017;19(8):1135-44
[16] Fangusaro J, et al. Lancet Oncol. 2019;20(7):1011-22
[17] Hwang E, et al. Neuro Oncol. 2018;20(Suppl 2):i27-i213
[18] Cooney T, et al. Neuro Oncol. 2018;20(Suppl 2):i27-i213
[19] Baxter PA, et al. Neuro Oncol. 2020: In press
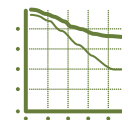
subsequent breast cancer were previously unknown. CCSS investigators defined that female survivors of childhood cancer who develop a subsequent breast cancer have lower breast cancer survival rates than the general population, attributable to the burden of other chronic health conditions including cardiac disease.

- 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 children with cancer/families that cure of their child's cancer is not accompanied, in most cases, by a diminished quality of life.

- Vigorous exercise in early adulthood was associated with lower risk of mortality in adult survivors of childhood cancer and an increase in exercise over time was shown to reduce all-cause mortality by 40% providing important evidence for future behavioral and exercise interventions in survivors.

- CCSS collaboration with other large cohorts identified that the dose equivalence of mitoxantrone to doxorubicin to be 10.5:1. Thus, the previous hematologic-based doxorubicin dose equivalency of mitoxantrone (4:1) appeared to significantly underestimate the association of mitoxantrone with long-term cardiomyopathy risk. This finding provides important guidance for the use of mitoxantrone in clinical trials.

MAJOR NCI-SUPPORTED MULTISITE INITIATIVES

MYELOPROLIFERATIVE NEOPLASM RESEARCH CONSORTIUM (MPN-RC)

The MPN-RC, formerly known as the Myeloproliferative Disorders-Research Consortium (MPD-RC), was funded in 2006 through a P01 grant to support an international consortium dedicated to advancing MPN research and improving MPN outcomes. Currently, the MPN-RC comprises 11 clinical member sites located in the US and Canada and a central tissue bank located in New York. The P01 was renewed in 2018 with an emphasis on identifying therapeutic targets for primary myelofibrosis (MF) and translating them into clinical trials. Three of the four projects study the molecular pathogenesis of MR, the role of megakaryocytes in MF, and the depletion of MF stem cells. The MPN research also includes polycythemia vera and essential thrombocythemia.

Recently published studies provided insight into:

- the unexpected role of $JAK2^{V617F}$-mutant megakaryocytes in the establishment and maintenance of MPN in vivo[20]

- the events that lead to the dysfunction of the TP53 pathway (i.e., the deletion and mutations of TP53, the upregulation of MDM2/4) and are associated with *advanced forms of MPNs*.[21]

[20] Woods B, et al. *Clin Cancer Res*. 2019 Oct 1;25(19):5901-5912
[21] Marcellino BK, et al. *Blood Adv*. 2018 Dec 26;2(24):3581-3589

Since then, the consortium, has developed six protocols and activated two MF-related trials: one testing the combination of ruxolitinib with enasidenib (NCT04281498), and the second evaluating the *TGF-β* inhibitor, AVID200 (NCT03895112). Recently completed trials demonstrated favorable safety profiles for the combination of decitabine and ruxolitinib to treat patients with accelerated and blast-phase MPNs,[22] and idasanutlin, antagonist of MDM2, for treating patients with high-risk polycythemia vera and essential thrombocythemia.[23] Both studies have advanced to Phase 2 efficacy trials.

MAJOR CO-FUNDED NETWORKS

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK (BMT CTN)

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 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 53 trials either alone or in collaboration with NCTN and conducted 56 ancillary and correlative studies. It has completed accrual to 40 of these trials, enrolling 11,300 participants from more than 100 transplant centers across the U.S. The BMT CTN has also established a research repository containing more than 416,000 biospecimens.

Recent completion of BMT CTN clinical trials have provided the following important insights:

- **NCT01109004 (BMT CTN 0702)**: This Phase 3 trial contributed to the abandonment of tandem autologous hematopoietic cell transplant approaches for treating multiple myeloma. Thirty-eight-month progression free survival (PFS) and overall survival (OS) rates did not

improve for participants receiving a second autologous PBSC transplant with the same conditioning regimen as the first, or combined with RVD consolidation therapy, or maintenance with lenalidomide. Single AHCT followed by lenalidomide maintenance should remain as the standard approach for this population.[24]

- **NCT02806947 (BMT CTN 1501)**: This trial demonstrated comparable efficacy using sirolimus, a steroid-free alternative, to the standard prednisone treatment as a first-line therapy in treating patients with standard risk acute GVHD. No differences were detected in steroid refractory acute GVHD, disease-free survival, relapse, non-relapse mortality, or overall survival for low-risk participants stratified according to the Minnesota GVHD clinical risk score and the Ann Arbor Biomarker score. This intervention was accepted into the Hematopoietic Cell Transplantation National Comprehensive Cancer Network (NCCN) guidelines, Version 2.2020, as an appropriate alternative to systemic corticosteroids.[25]

- **NCT02208037 (BMT CTN 1203)**: This trial demonstrated a higher rate of GVHD-free, relapse free survival at one year after transplant using tacrolimus, mycophenolate mofetil, and post-transplant cyclophosphamide in the HLA-matched setting, which is now being tested in a Phase 3 trial. This has rapidly become one of the standards of care GVHD prophylaxis regimens.[26]

- **NCT01339910 (Ancillary Study to BMT CTN 0901)**: This study provided evidence that modulating the intensity of the alloHCT conditioning regimen in patients with AML who tested positive for MRD can impact survival. Results show that myeloablative conditioning rather than reduced intensity conditioning in these participants improved survival with OS rate of 61% vs. 43%, respectively.[27]

CENTER FOR INTERNATIONAL BLOOD AND MARROW TRANSPLANT RESEARCH (CIBMTR)

The 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

[22] Rampal RK, et al. *Blood Adv*. 2018 Dec 26;2(24):3572-3580
[23] Mascarenhas J, et al. *Blood*. 2019 Aug 8;134(6):525-533
[24] Stadtmauer EA, et al. *J Clin Onc*. 2019 Mar 1; 37(7):589-597
[25] Pidalla J, et al. *Blood*. 2020 Jan 1; 135(2):97-107
[26] Bolanos-Meade J, et al. *The Lancet Haematology*. 2019 Mar 6; 6(3):PE132-E142. 5
[27] Hourigan CS, et al. *J Clin Oncol*. 2020 Apr 20;38(12):1273-1283
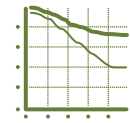
NHLBI and NIAID. The CIBMTR primarily collects baseline and outcomes data from consecutive patients transplanted at centers throughout the world to advance hematopoietic stem cell transplant therapy.

The CIBMTR was also awarded a U24 grant in 2018 through the Immuno-Oncology Translational Network (IOTN) Cancer MoonshotSM to develop and operate a Cellular Immunotherapy Data Resource (CIDR). This data registry collects outcomes of patients receiving cellular immunotherapies to support observational studies and inform subsequent studies and clinical trials. The CIDR is also running two post-market studies on the commercial CAR T-cells, Yescarta and Kymriah.

As of 2019, the CIBMTR-CIDR registry includes:

- 540,000 HCT recipients from more than 380 transplant centers worldwide (over 35 countries)

- Information for 100% of the allogeneic transplants done in the US (mandated by law) and 85% of US auto-transplants

- 2,908 non-transplant cellular therapy participants from 155 participating centers, of which 1,811 received CAR T-cell therapy

- Patient-reported outcomes data defined by disease, ethnicity, and other demographics

The CIBMTR has a proven system (>1,400 publications, 240 studies) for facilitating the utilization of its database for research projects via 15 scientific/research working committees with more than 2,700 researchers participating, as well as collaborations with government agencies, professional groups, international partners, and patient organizations.

CANCER IMMUNOTHERAPY TRIALS NETWORK (CITN)

The CITN was established in the fall of 2010 through a cooperative agreement award to the Fred Hutchinson Cancer Research Center. This award created a consortium of the leading investigators and institutions with expertise in tumor immunology and cancer immunotherapy to develop and implement early phase clinical trials in this field. The CITN consists of a Central Operations and Statistical Office, 43 clinical member sites, and a central immune oncology laboratory to support other laboratories with standardize assays and correlative studies. The CITN also established a pediatric consortium (Ped-CITN) in 2017 to conduct multicenter immunotherapy trials focused on childhood and young adult cancers.

The current CITN is tasked to recognize the research opportunities and expeditiously translate them into clinical testing with the requisite laboratory correlates to obtain optimum information on the effects of the treatment. The network has activated 12 clinical trials with pediatric trials expected to open in 2021 or early 2022. Of the four open trials, two have completed accrual and are in follow up or evaluating immune response data, and two are actively accruing participants:

- **NCT02267603:** This randomized Phase 2 trial studies how well pembrolizumab, a PD1 checkpoint blockade inhibitor, works in treating patients with Merkel cell cancer (MCC).

- **NCT03063632:** This Phase 2 trial tests the combination of two drugs, pembrolizumab and interferon-γ, in treating patients with stage IB-IVB mycosis fungoides, Sezary syndrome (MF/SS), and advanced synovial sarcoma.

- **NCT03513952:** This Phase 2 trial is recruiting participants to determine the efficacy in combining atezolizumab and CYT107, glycosylated recombinant human interleukin 7, in treating participants with locally advanced, inoperable, or metastatic urothelial carcinoma.

- **NCT02595866:** This Phase 1 trial is recruiting participants to study the side effects of pembrolizumab in treating patients with HIV with relapsed, refractory, or disseminated malignant neoplasms.

Highlights of recently completed CITN trials include a study showing that it is safe to use pembrolizumab (Keytruda) to treat HIV-positive people with cancer (Uldrick, 2019) and a trial of the same drug that provided a much-needed new treatment option for people with a deadly skin cancer called Merkel cell carcinoma (MCC) (Nghiem, 2019). The U.S. Food and Drug Administration approved pembrolizumab for MCC in December 2018 based on the strength of these results. Pembrolizumab also demonstrated significant antitumor activity with durable responses and a favorable safety profile in patients with advanced MF/SS (Khodadoust, 2019).

NCI CLINICAL TRIALS QUALITY ASSURANCE PROGRAM

The Clinical Trials Monitoring Branch is responsible for managing quality assurance and quality control of the ETCTN Phase 1 and 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

- 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 ETCTN 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	263	139	2,151
NCTN Groups & Other Consortia (AMC, PBTC)	2,098	810	11,180
Cancer Centers and Single Institutions	64	82	778
PEP-CTN	37	19	180

TABLE 20: NCI QAP AUDIT STATISTICS (2018-2019).

NEW INITIATIVES AND RECENT ACCOMPLISHMENTS (1/1/2018-12/31/2019)

- Development and implementation of seven Standard Operational Procedures (SOPs)

- Development and implementation of the 'NCI Guidelines for Monitoring the Experimental Therapeutics Clinical Trials Network (ETCTN) and Other Early Phase CTMS-Monitored Studies,' commonly referred to as Monitoring Guidelines

- Development of a Central Monitoring tool (Source Document Portal) that includes a tool for redaction of PII (Personally Identifiable Information) and enables the site to upload documents for review by the Lead Protocol Organization (LPO) for source document verification

- Establishment of a DSMB (Data Safety Monitoring Board) for ETCTN randomized Phase 2 clinical trials

- Implementation of a Specimen Tracking System for the ETCTN for shipment of specimens from participating sites to the ETCTN Biobank

- Deployment of an Auditor Training Module to provide standardized training to conduct reviews per the monitoring and auditing guidelines
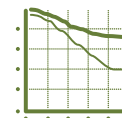
FUTURE DIRECTIONS

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

1. Expand efforts in biomarker-driven, targeted therapeutics, immunotherapy, and combination therapy 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 and combination therapy, including umbrella/basket trials requiring screening of large number of participants

3. Implement a strategic vision for more flexible, faster, simpler, less expensive, high impact trials that seamlessly integrate with clinical practice by focusing on:

   • reducing the complexity of clinical trial procedures and data collection (including electronic extraction from existing data sources)

   • shifting the performance of appropriate trial procedures/assessments remotely or via telehealth

   • improving accrual and access to NCI clinical trials, especially for minority and underserved participants

   • enhancing the efficiency of statistical design and analysis

   • continuing to improve the timelines for trial development and accrual

4. Increase contributions to the mentoring of the next generation of clinical investigators

DEVELOPMENTAL THERAPEUTICS PROGRAM
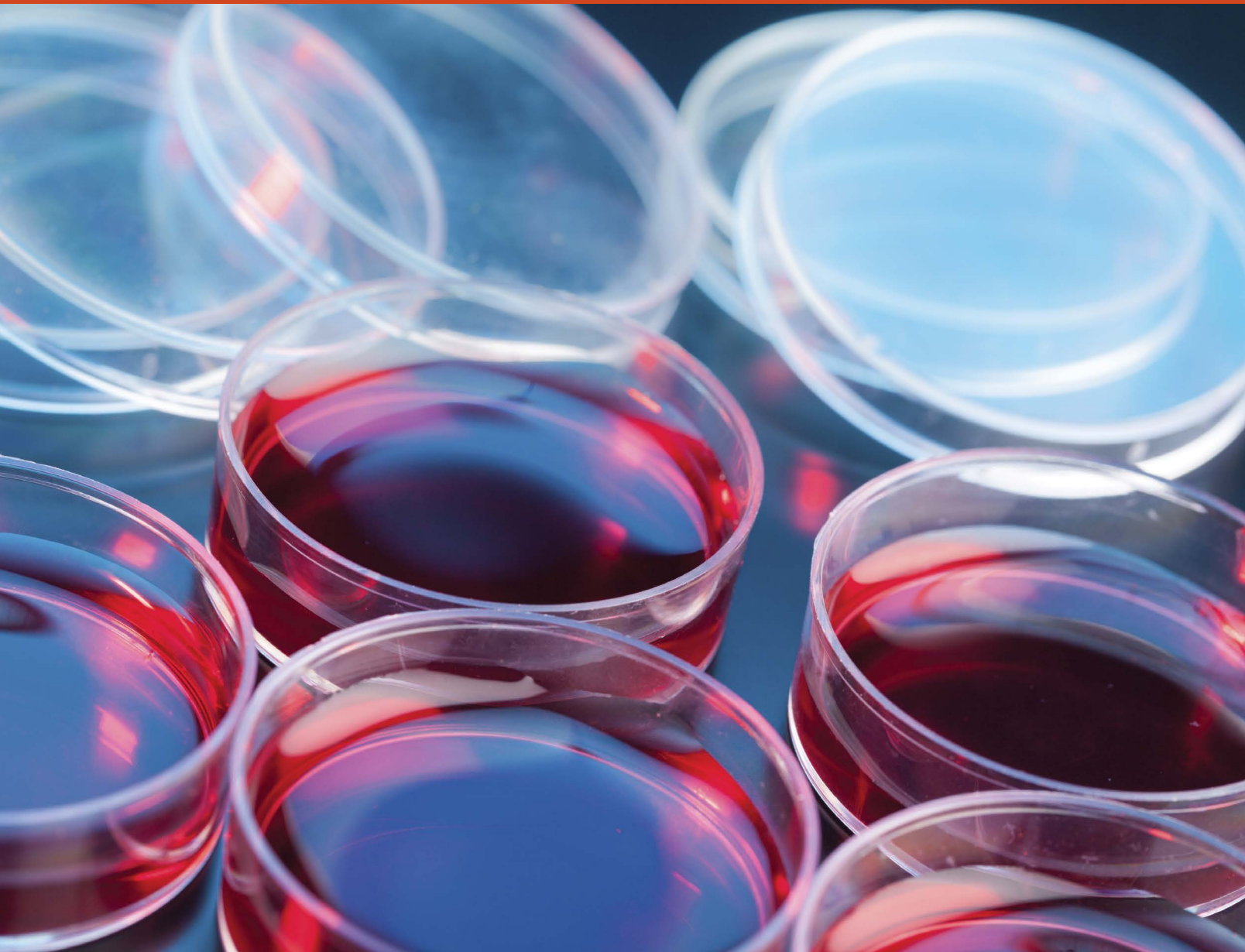
OVERVIEW

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. DTP is also a resource for the generation of preclinical information and research materials, including vialed 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 145, DTP has 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
    - More than 790 active grants managed in 2019
- Resources for a robust discovery and development infrastructure
    - Compound libraries, chemical synthesis, and structure-activity modeling
    - Models for measuring *in vitro* anti-cancer activity
    - Models for testing *in vivo* efficacy
    - Preclinical testing for *in vitro* anti-cancer activity and in vivo efficacy
    - 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. In 2018, DTP launched a new program to assist extramural investigators within the grants portfolio with drug candidate characterization. By performing small studies, such as early PK or chemical synthesis optimization, DTP augments drug development efforts that are not otherwise covered under grant support. The aim is to propel novel drug candidates in the grants portfolio toward the IND-enabling stage of development.

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 DTP in September 2005.

Dr. Collins's areas of expertise are clinical pharmacology, the application of pharmacokinetic (PK) and pharmacodynamic (PD) 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 PK and PD principles in the field of cancer. His current work also includes extending these principles with PET imaging.

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 (OAD)

The OAD organizes and coordinates activities across DTP to expedite the discovery and preclinical 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 an ongoing seminar series that highlights drug discovery and development projects from DTP's extramural grant portfolio. The purpose of this quarterly seminar series is to share the diverse array of DTP-supported translational research activities with NCI extramural grant program staff through presentations by DTP grantees.

PRECLINICAL THERAPEUTICS GRANTS BRANCH (PTGB)

The 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, nanomedicines, and the co-development of drugs and biomarkers to support the new era of precision medicine. The portfolio emphasizes 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. PTGB is also actively involved in the Provocative Question (PQ) Initiative; PTGB staff lead PQ topics related to adverse effects of cancer therapy and treatment-induced cell lineage plasticity.

MOLECULAR PHARMACOLOGY BRANCH (MPB)

The 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
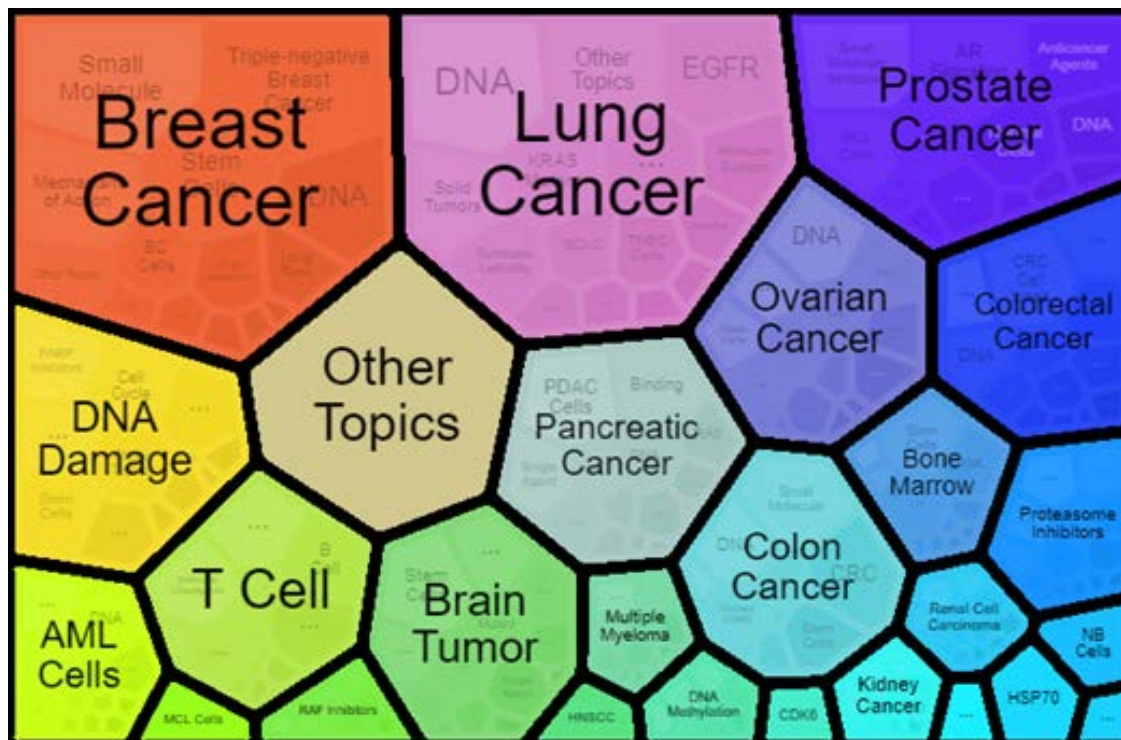
FIGURE 49: FOCUS AREAS OF ACTIVE AWARDS MANAGED BY PTGB (FY 2019).

research community and other NCI laboratories. In support of this mission, MPB oversees the work of several laboratories at the Frederick National Laboratory for Cancer Research (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 (TVSL)

The TVSL is dedicated to screening targets and cell lines to identify new drugs and disease sensitivity to investigational agents. The 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 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 that the NExT Program's Chemical Biology Consortium developed, and in studies of novel, investigational-investigational agent combinations in advance of CTEP's early phase clinical trials.

Translational Support Laboratory (TSL)

The 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 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.

Compounds mixed to give 6 x 5 concentration matrix

Tumor cells (60%) Endothelial cells (25%) Mesenchymal stem cells (15%)

ULA Plate well

Incubate 37^{0}C/5% CO_2

Day 0

Compounds added to spheroids

Incubate 37^{0}C/5% CO_2

Day 3

Add Cell Titer Glo 3D

Day 10

Luminescent signal read in plate reader
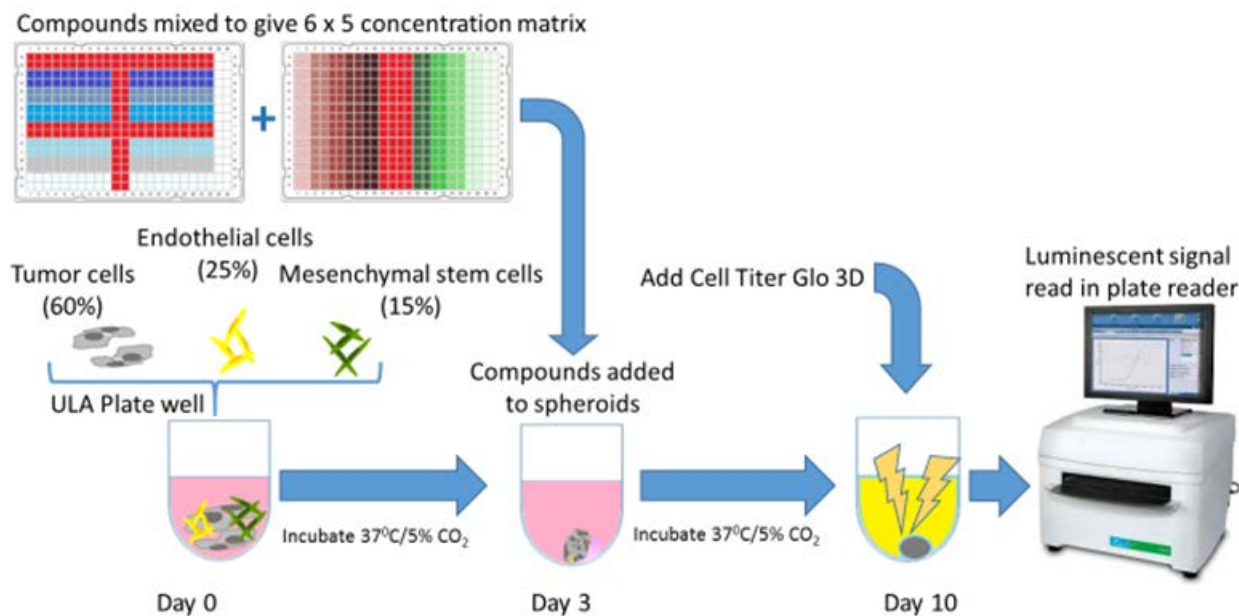
FIGURE 50: EXAMPLE WORKFLOW FOR MIXED CULTURE SPHEROID ASSAYS.

BIOLOGICAL TESTING BRANCH (BTB)

The 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 vivo* screening models

- Providing support for preclinical *in vivo* PK and PD 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, established methodologies for collecting and stabilizing tumor biopsies for subsequent analysis. These assays and projects included:

- inhibition of DNA methylation
- γ-H2AX assay
- c-Met assay
- HIF1α assay
- Mer kinase assay
- EMT immunofluorescence assay
- preclinical development of T-dCyd
- PARP inhibitors project
- development of multiplex immunofluorescence assays
- calf intestinal alkaline phosphatase assay
- topoisomerase 1 complex assay
- apoptosis 15-plex panel

APPROVED CANCER TREATMENT DRUGS DEVELOPED WITH DTP INVOLVEMENT

2018   Moxetumomab pasudotox-tdfk

2015   Dinutuximab (Unituxin, NSC 764038)

2012   Omacetaxine (homoharringtonine, NSC 141633)

2010   Eribulin (NSC 707389)

       Sipuleucel-T (NSC 720270)

2009   Romidepsin (NSC 630176)

       Pralatrexate (NSC 713204)

2004   Cetuximab (NSC 632307)

2003   Bortezomib (NSC 681239)

1998   Denileukin diftitox (NSC 697979)

1996   Polifeprosan 20 with carmustine implant (NSC 714372)

       Topotecan (NSC 609699)

1995   All-trans retinoic acid (NSC 122758)

1992   2-Chlorodeoxyadenosine (NSC 105014)

       Paclitaxel (NSC 125973)

       Teniposide (NSC 122819)

1991   Fludarabine phosphate (NSC 312887)

       Pentostatin (NSC 218321)

1990   Hexamethylmelamine (NSC 13875)

       Levamisole (NSC 177023)

1989   Carboplatin (NSC 241240)

1988   Ifosfamide (NSC 109724)

1987   Mitoxantrone (NSC 301739)

1983   Etoposide (NSC 141540)

1982   Streptozotocin (NSC 85998)

1979   Daunorubicin (NSC 82151)

1978   Cisplatin (cis-platinum) (NSC 119875)

1977   Carmustine (BCNU) (NSC 409962)

1976   1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosurea (CCNU) (NSC 9037)

1975   Dacarbazine (NSC 45388)

1974   Doxorubicin (NSC 123127)

       Mitomycin C (NSC 26980)

1973   Bleomycin (NSC 125066)

1970   Floxuridine (FUDR) (NSC 27640)

       Mithramycin (NSC 24559)

       Mitotane (o-p'-DDD) (NSC 38721)

1969   Cytarabine (ARA-C) (NSC 63878)

       Procarbazine (NSC 77213)

1967   Hydroxyurea (NSC 32065)

1966   Pipobroman (NSC 25154)

       Thioguanine (NSC 752)

1964   Melphalan (NSC 8806)

       Actinomycin D (NSC 3053)

1963   Vincristine (NSC 67574)

1962   Fluorouracil (NSC 19893)

1961   Vinblastine (NSC 49842)

1959   Cyclophosphamide (NSC 26271)

       Thiotepa (NSC 6396)

1957   Chlorambucil (NSC 30

DRUG SYNTHESIS AND CHEMISTRY BRANCH (DSCB)

The DSCB is responsible for the following activities in support of the discovery and development of novel anti-cancer agents (Figure 51):

- Worldwide scientific liaising with universities and industries to stimulate the submission of a 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 preclinical 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 Program development and discovery projects

- Collaboration with DTP's Natural Products Branch to identify novel chemical scaffolds, as well as develop synthetic methods to generate further supplies for active compounds that have been isolated from natural product extracts

External Synthesis Contracts	• Supports NExT project Initiatives • Synthesis of benchmark clinical and preclinical candidates
NCI Chemical Repository	• Manages new compounds submitted by extramural researchers • Distribution of compounds for intramural and extramural research activities
Laboratory of Synthetic Chemistry	• Supports NExT discovery / development projects • Provides chemical synthetic enablement expertise and service, across DCTD, including natural products

FIGURE 51: CHEMISTRY SUPPORT FOR DCTD.

NATURAL PRODUCTS BRANCH (NPB)

The primary responsibility of the NPB is to obtain crude natural product materials from terrestrial and marine environments and prepare crude extracts for screening in various intramural and extramural screening programs, including the NCI-60 Human Tumor Cell Lines Screen. For example, NExT Program has provided extracts to extramural investigators for screening in biologic HTS assays. In addition to maintaining a repository of crude extracts, NPB has established the NCI Program for Natural Products Discovery (NPNPD) to create an enhanced pre-fractionated library more suitable for high-throughput targeted screens, increasing the scope and efficiency of natural product drug discovery efforts.

NPB also oversees the operations of the Natural Products Support Group at FNLCR, 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 preclinical and early clinical evaluation.

BIOLOGICAL RESOURCES BRANCH (BRB)

The 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 include recombinant proteins, monoclonal antibodies, genetically modified viruses, bacteria and mammalian cells, peptides, and oligo- nucleotides. These entities may function as cytokines, growth factors, vaccines, adjuvants, or other immune-modifying agents. BRB manages a coordinated portfolio of research grants and contracts that represent the flexible utilization of all three legs of the discovery, development, and translational process.

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

The active BRB-managed grant portfolio consists of over 160 grant awards (R01, R03, R15, R21, and P01) focusing on the discovery, testing, and development of biotechnology- and synthetic biology-based products 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 the NExT Program.

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 the BRB Preclinical Biologics Repository.

Preclinical product development, cGMP manufacturing, testing, and release of biologic material and autologous cell therapies for IND-directed preclinical studies through Phase 3 clinical trials

BRB provides oversight of the BDP at the Advanced Technology and Research Facility (ATRF), part of FNLCR. BDP provides development and manufacturing capabilities for the following types of investigational products: monoclonal antibodies, recombinant proteins, viral and DNA vaccines, peptides, gene therapy vectors, and whole cell-based products.

TOXICOLOGY AND PHARMACOLOGY BRANCH (TPB)

The 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 PK and 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. This includes organ-specific toxicology studies, such as cardiovascular monitoring and assessment of chemotherapy-induced peripheral neuropathy (CIPN). 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 (PRB)

The 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.

PRB staff manage these major contract areas:

- 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 (ITB)

The ITB manages the wide array of systems and computer infrastructure that captures, stores, analyzes, and reports the vast amount of data that DTP generates. On the IT engineering side, ITB staff focus on four priorities:

- data sharing
- modernization of all systems and subsystems running DTP IT infrastructure on a 24/7 basis
- implementation of security measures to protect user data and IP
- the addition of new applications to address the demands of the dynamic DTP research environment

ITB engineering staff also team with the Computational Drug Development Group (CDDG) on integrated project teams to support DTP and DCTD objectives, utilizing the analytical power of artificial intelligence, deep learning, structure-based modeling, and quantum chemistry. In

project teams, scientists and software engineers partner to develop informatic toolkits to parse "big data" into manageable scientific insights. One example is the COMPARE program, which analyzes the results from the NCI-60 Human Tumor Cell Lines Screen and provides therapeutic profiles for compounds that are active in cancer cell lines. Via web access, COMPARE is used by the extramural research community as a discovery tool and by DTP/DCTD internally as a drug evaluation tool for decision-making. The Drug Synthesis and Chemistry Branch (DSCB) recently released a new version of COMPARE, which offers new ways of analyzing and viewing both public and confidential NCI data.

Integrating with the new COMPARE, ITB/CDDG will soon release a new toolkit called PRISM (Pattern Recognition Integrated with Structural Medicinal-Chemistry) that combines the biological activity patterns from COMPARE with 3D pharmacophoric overlaps of the molecular structures responsible for activity (Figure 52). PRISM extends the research scope of COMPARE by providing insights into drug target interactions as well as a starting point for new medicinal chemistry campaigns. Additional functionality may allow for pattern recognition in other data, such as high-content imaging or proteomics. An evolving technology, PRISM has the potential to become a platform for precision medicine discovery.

Patterns   **Structures**   **Pharmacophore**
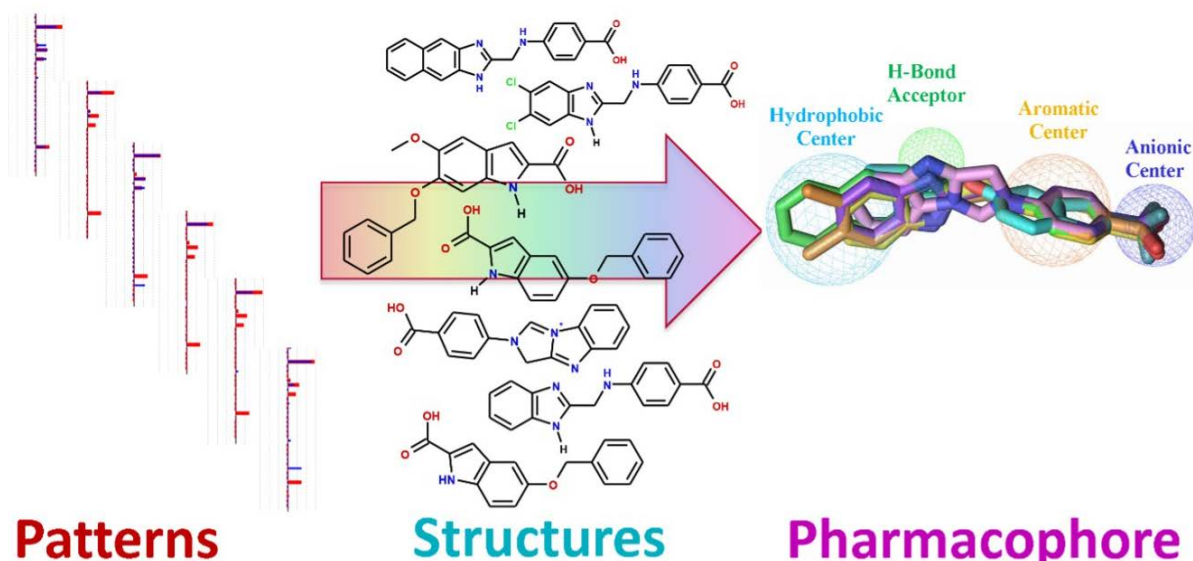
FIGURE 52: PATTERN RECOGNITION AND MOLECULAR STRUCTURE ALIGNMENT BY THE PRISM PLATFORM.
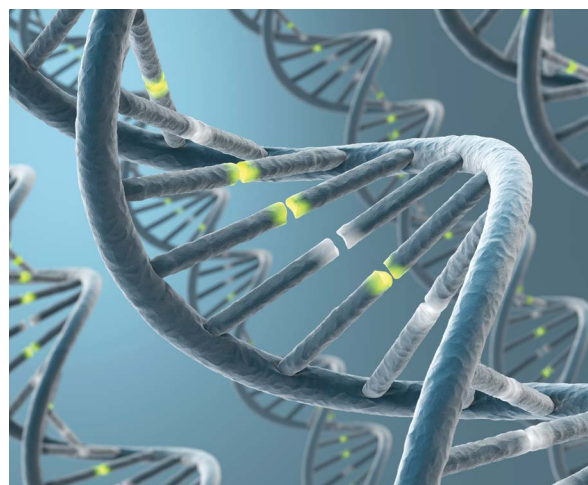
ITB (in tandem with the CDDG) uses cutting-edge industry software in protein modeling, quantum mechanics, drug design, and systems biology to solve scientific questions in drug development for DTP groups, other programs in DCTD, and the extramural research community.

IMMUNO-ONCOLOGY BRANCH (IOB)

The IOB supports immunotherapy-related projects within NCI and in the extramural research community. The branch manages an immuno-oncology grants portfolio consisting of preclinical and early-phase clinical studies that focus on utilizing or exploiting the immune system for the treatment of cancer. A wide range of research aims are supported, including enhancement of T cell activity by checkpoint inhibition or other mechanisms, assessment of CAR-T cell therapy and other cell-based immunotherapies, modulation of the immunosuppressive tumor microenvironment, and reduction of immunotherapy-associated toxicities. IOB also provides the biomedical research community with guidance on the processes required to develop new immunotherapeutic agents, including preclinical and clinical PK, toxicology and pharmacology, drug formulation and production, PD, and IND-directed regulatory requirements.

In addition to administering grants, IOB develops various immunotherapy resources and funding initiatives to advance immunotherapy-related projects in key areas of scientific investigation. The branch is involved in coordinating the NCI-funded PRECINCT network of canine cancer immu-

notherapy trials, as well as tools for canine data analysis, to promote comparative oncology research. IOB has fostered partnerships with other programs across DCTD to support a multidisciplinary approach to immunotherapy. Areas ripe for collaboration include development of monoclonal antibody imaging agents with the Cancer Imaging Program, immune biomarker development with the Cancer Diagnosis Program, exploration of immunotherapy/radiation therapy combinations with the Radiation Research Program, and analysis of complex immune responses with the Biometric Research Program.

The branch has also coordinated several conferences and workshops to facilitate collaboration and data sharing among extramural investigators in the immunotherapy field, including the Workshop on Cell-based Immunotherapy for Solid Tumors held in December 2018 and the NIH-AACR Cancer, Autoimmunity, and Immunology Conference held in April 2019 (co-organized by NIAID and NIAMS). IOB is currently planning similar meetings for the immunotherapy research community in 2020 and beyond.

DTP GRANTS OVERVIEW

The DTP research portfolio included 794 funded grants with a total budget of ~$309 million during fiscal year 2019. DTP's grants portfolio covers various aspects of the discovery and preclinical development of small molecule and biological therapeutic agents, such as drug discovery screen assays and models, medicinal chemistry, mechanism of actions,

biomarkers, cGMP production, and immunotherapy. DTP's grant award mechanisms and their distribution in terms of research support in 2019 are shown in the accompanying graphs and charts. The predominant mechanism is the individual research project grant (R01), followed by exploratory phase grants (R21).
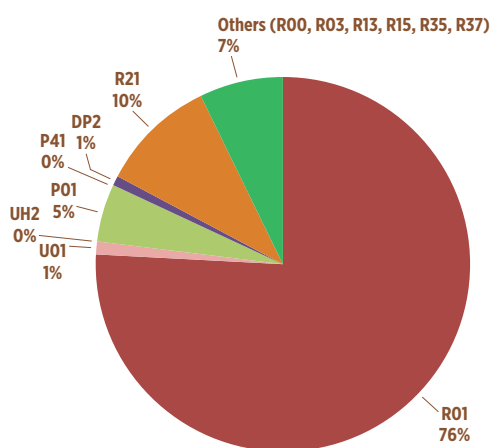
FIGURE 53: DISTRIBUTION OF DTP 2019 GRANT FUNDING BY MECHANISM.

Funding Mechanism	Number of Grants	Total Cost
R01	466	$ 186,051,196
U01	11	$ 6,252,572
P01	6	$ 10,634,432
R21	85	$ 15,748,312
R00	3	$ 757,106
R03	12	$ 954,527
R15	6	$ 2,250,909
R35	13	$ 11,162,318
R37	8	$ 2,979,890
R50	8	$ 1,260,832
R56	1	$ 204,188
U54	1	$ 5,000,000
UH2	1	$ 168,779
Total	**621**	**$ 243,425,061**

TABLE 21: FY19 SMALL MOLECULE GRANTS PORTFOLIO.

In 2019, DTP's PTGB grants portfolio contained 621 grants with a total budget of ~$243 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, and understanding, preventing, and overcoming drug resistance. Meanwhile, BRB's biologicals grant portfolio contains 173 grants with a total budget of ~$66 million that supports concept discovery and development for biologic agents and cell-based therapies in preclinical models, conducted in parallel with ongoing clinical trials.

FIGURE 54: DISTRIBUTION OF DTP 2019 FUNDED GRANTS BY THERAPEUTIC AGENT CLASS.
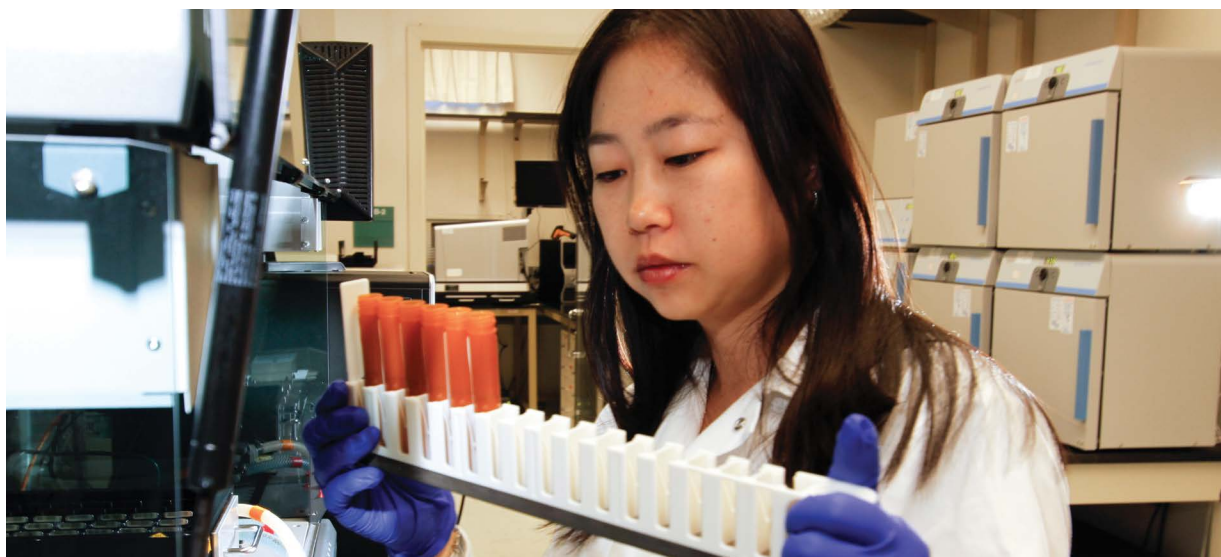
Funding Mechanism	Number of Grants	Total Cost
R01	119	$ 44,724,300
R21	31	$ 5,801,200
R15	1	$ 440,220
R03	9	$ 716,373
P01	1	$ 1,786,322
U54	1	$ 7,174,211
R13	3	$ 38,500
R35	4	$ 3,818,657
R37	2	$ 996,289
R50	1	$ 103,639
R56	1	$ 233,250
Total	**173**	**$ 65,832,961**

TABLE 22: FY19 BIOLOGICAL GRANTS PORTFOLIO.

ASSISTANCE TO THE CANCER RESEARCH COMMUNITY

NCI-60 HUMAN TUMOR CELL LINES SCREEN

The NCI-60 Human Tumor Cell Lines 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 tumor cell lines.

The NCI-60 cell lines have been thoroughly characterized biologically and molecularly through the Molecular Targets Program. 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 Human Tumor Cell Lines 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 FY2019 the NCI-60 Cell Line Screen laboratory:

- Performed single-concentration testing on more than 5,250 new synthetic compounds and 2,700 natural product extracts

- Performed five-concentration testing on 1,023 new synthetic compounds and 225 natural product extracts

As an additional service to the extramural research community, Molecular Targets Program investigators received access to and provided molecular characterization for vials of frozen cell pellets, DNA, RNA, or frozen live cells prepared from each of the 60 cells.

IN VIVO MODEL DEVELOPMENT AND TESTING

Over the past two [2018-2019] years, BTB has assessed more than 257 synthetic molecules, 3 natural product extracts, and 11 unique vehicle formulations for determination of maximum tolerated dose in preparation for in vivo efficacy studies. BTB conducted 91 xenograft studies assessing the antitumor activity of small molecules and natural product extracts, as well as of agent combinations. These represent more than 70 unique human tumor xenograft models.

The branch has conducted 188 drug studies using patient-derived xenograft (PDX) models to assess efficacy (single agent and/or combination) and/or to collect samples for PD endpoint determinations. The branch performed 51 additional mouse studies including general growth assays, assessment of the impact of castration/ovariohysterectomy on estradiol sensitivity and tumor growth, assessment of cloned cell line growth compared to parental cells, and tumor target studies. BTB also conducted 25 studies evaluating the growth of PDX tumor lines in athymic nude rats to assess the utility of using PDX tumors in rats for pharmacological or other studies where a larger experimental animal may afford scientific advantages.
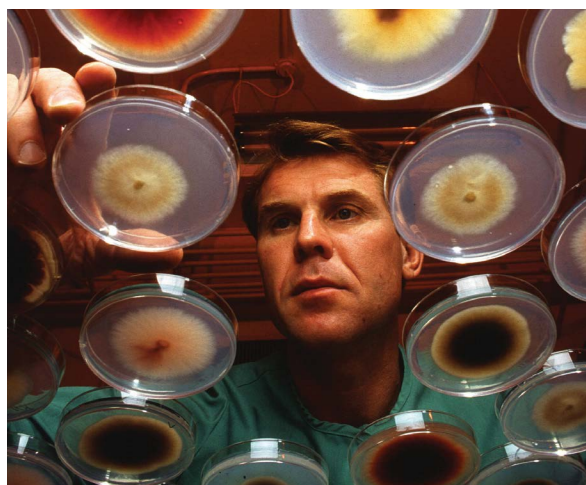
As of the end of 2019, the branch received more than 9,000 patient samples (blood or tumor) for implantation into mice to generate PDXs. Almost 700 PDX models have been created and cryopreserved (>120 vials/model) for distribution through the NCI Patient-Derived Models Repository (PDMR). At the end of 2019, 411 PDX models, 88 organoid models, 95 tumor cell lines, and 200 cancer-associated fibroblast cell lines are available to the research community through the PDMR.

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 preclinical research purposes (Table 23). The repository collection is a uniquely diverse set of more than 200,000 compounds that have been either submitted to DTP for biological evaluation 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
2018	8,870	19,156	1,624
2019	10,473	18,926	1,786

TABLE 23: COMPOUND REPOSITORY DISTRIBUTION AND PROCUREMENT SUMMARIES (2018-2019).

* As of 11/30/2017
** Plates include approved oncology drugs set, structural diversity set, mechanistic diversity set, and natural products set.

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 anti-cancer studies. These compounds are provided for evaluation in the NCI-60 Human Tumor Cell Lines Screen, as well as to other DCTD programs, such as PADIS and the Molecular Pharmacology Lab in MPB, and to investigators in NCI's Center for Cancer Research. 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.

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 Program development and discovery projects, the DTP Stepping Stones Program, and the DCTD Acquisition of Oncology Agents initiative. DSCB resources and expertise include iterative drug design and synthesis, synthetic method development, and process synthesis development. One such NExT Program project utilizing DSCB resources involved the preclinical synthesis of two DNMT1 inhibitors, currently in clinical development (Phase I trials) at NCI. The Laboratory of Synthetic Chemistry (LSC) was responsible for the development of much of the synthetic chemistry enablement that allowed for the preparation of kilogram quantities of these potential chemotherapeutics. The large-scale synthesis of both agents to support future canine trials was also accomplished with LSC resources.

The LSC also provides support to the DTP Stepping Stones Program, which provides critical resources for the advancement of innovative anti-cancer therapeutics toward clinical development. These resources have included synthetic chemical enablement of key lead compounds, preparation of target agents for efficacy and PK studies, and evaluation of alternative salt forms. Finally, DSCB has played a key role in DCTD's oncology drug acquisition initiative that acquires gram quantities of both FDA-approved oncology drugs and promising anti-cancer investigational agents in clinical and preclinical development. The LSC has provided key synthetic chemistry resources for the preparation of several complex investigational agents that are difficult to obtain through external vendors.

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. NPB initiated the Natural Products Repository Program 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 preclinical 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 (Table 24).

Year	Vials	Extract Plates	Fraction Plates	Total Samples	Cultures
2013	4667	131	NA	16,195	0
2014	3637	439	NA	42,269	0
2015	630	2025	NA	178,885	25
2016	788	667	NA	59,531	0
2017	531	493	NA	43,919	1
2018	394	293	428	176,834	1
2019	390	135	5592	1,980,654	29

TABLE 24: SHIPMENTS MADE BY NPB TO NON-DCTD INVESTIGATORS AND COLLABORATORS (2013-2019).

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 >300 material transfer agreements with extramural researchers to investigate various aspects of the bioactivity and chemical diversity of DCTD's Natural Products Repository extracts enacted since 1990.

Marine Collections

NPB successfully arranged the international transfer of marine samples from the Australian Institute of Marine Sciences in Townsville Australia to FNLCR obtaining more than 4,000 individual marine invertebrate specimens and more than 6,000 marine microbe cultures for NCI's use.

Plant Collections of Opportunity

Although NCI has not funded contracts for collections of plants since 2004, NPB has been successful in continuing the acquisition of these materials through collaborations and donations. One such collection is of plants used in traditional Chinese medicine (TCM). A library of TCM extracts has been produced, plated, and made available to the research community.

Microbial Collections

In 2016 NPB gained access to a new fungal library through an FNLCR subcontract to 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. The University of Oklahoma sponsors a citizen science collection program that collects these fungi. The contract has supplied >10,000, taxonomically typed, non-duplicative fungi to NPB/NCI so far. NPB has cultured, photographed, and prepared cryovials of the soil fungi. Liquid culture of the fungi, and extraction of the cultures has begun. The soil microbe library extracts will be pre-fractionated and supplied to researchers worldwide.

Natural Products Support Group (NPSG)

The NPSG extracts samples of natural products for testing in the NCI-60 Human Tumor Cell Lines 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 Human Tumor Cell Lines Screens and the *in vivo* hollow-fiber and xenograft tests run by BTB. The lab prepared 9,050 synthetic compounds and 7,560 natural product fractions one-dose samples in support of the NCI-60 primary

anticancer screen. In addition, 1,720 synthetic compounds and 279 natural products, extracts, and fraction five-dose samples were prepared. In support of DTP *in vivo* anticancer testing, there were 38 experiments (124 drugs tested in 1146 dosing vials) prepared.

- 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 Human Tumor Cell Lines Screen.

- Purification and identification of active materials (both natural and synthetic) from within DCTD whose chemical structures require independent confirmation. The Chemistry Laboratory has developed and implemented new isolation and rapid compound identification procedures that has enabled fast project turnaround times. The laboratory investigated 188 natural product extracts for the isolation and identification of anticancer active natural products and identified 54 pure natural products that have anti-proliferative activity. In addition, four large-scale isolations of plant and marine biota were completed, and fractions and pure compounds were supplied for further *in vivo* biological evaluations.

- Isolation, curation, and subsequent growth of microbes isolated under contract with the University of Oklahoma Citizen Science Soil Collection Program. More than 5,600

fungal isolates have been processed and determined to be pure and viable, resulting in more than 33,600 cryovial stocks for future fermentations.

- 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 more amenable to use in modern screening programs and is expected to contain approximately 1,000,000 samples. To date, the laboratory has pre-fractionated 41,100 extracts and generated more than 288,000 fractions.

- NPSG has continued the isolation and structure elucidation of active compounds from extracts identified through bioinformatic methods. 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, the laboratory investigated 188 individual chemical characterization projects. NPSG pursued and brought these projects to completion by identification of the compound or class of compounds responsible for the cytotoxicity of the extract. In addition, four large-scale isolations of plant and marine biota were completed, and fractions and pure compounds were supplied for further *in vivo* biological evaluations.

cGMP MANUFACTURING AND FORMULATION

PRB produces clinical supplies and chemistry, manufacturing, and control (CMC) data to support DCTD-sponsored INDs. 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 did the following:

- prepared parenteral dosage forms, including freeze-dried and liquid-filled products

- prepared oral dosage forms (mostly capsules) of several compounds in multiple batches and strengths to accommodate dosing needs in ongoing clinical trial

- conducted shelf-life studies of these preparations at several points each year

- performed pre-formulation and formulation to identify the conditions required for preparing suitable and stable formulations, with the results transferred to the manufacturers of the clinical supplies

- synthesized several lots of GMP bulk drugs, requiring quality-control release testing of each batch

- developed formulations and/or new size configurations

- manufactured sterile injectable and capsule dosage forms as appropriate for each drug

INVESTIGATIVE TOXICOLOGY LABORATORY

The Investigative Toxicology Laboratory, overseen by TPB, generates insights about the cellular toxicity of compounds. Toxicology evaluations performed include ADME (absorption, distribution, metabolism, and excretion) studies, dose range-finding studies, and studies of organ-specific toxicity, such as *in vitro* assessments of potential cardiac toxicity and neurotoxicity (Figures 55 and 56). Better characterization of mechanisms of toxicity aids in the selection of drug

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
- O6BG
- FAU
- SJG136
- AFP464
- Triapine

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.

Exploratory Screen Development	Hit (SDS) to Lead ID	Lead Development	Candidate seeking and qualification	Clinical Candidate

Discovery and Early Development

- Cellular and tissue slice systems
- CD34+ progenitor cell culture assay (Bone marrow toxicity)
- Assessment of Cardiac toxicity risk using cardiac myocytes in culture
  – Cardiac injury biomarkers and arrhythmia
- Dorsal Root Ganglion for peripheral Neuropathy
- ADME characterization, solubility testing
- Issue resolution for Project teams

Full Development

- Toxicology biomarkers
- Issue resolution for Project teams
- Application of tailored screens for investigations of organ specific toxicity

FIGURE 55: INVESTIGATIVE TOXICOLOGY ACTIVITIES IN SUPPORT OF DRUG DEVELOPMENT.
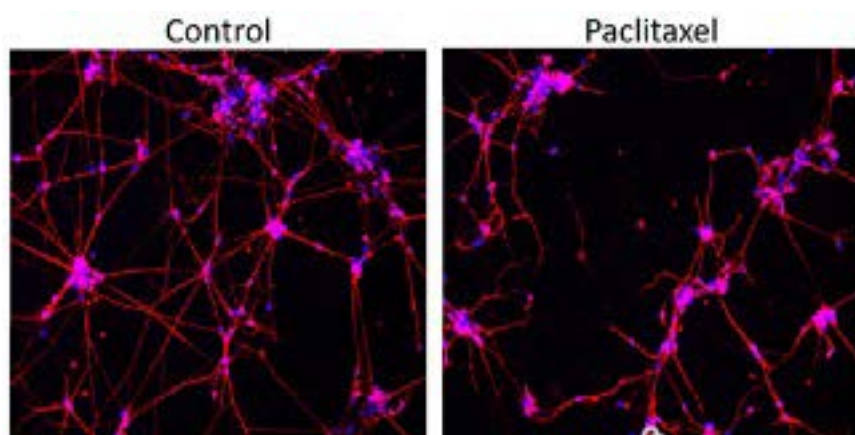
FIGURE 56: IN VITRO STUDY OF NEUROTOXICITY

Dorsal root ganglion neuronal cultures. Neurons with axons extended for the transmission of sensory information are seen in the control panel. Treatment with the chemotherapy drug paclitaxel results in axonal loss and degeneration, features of peripheral neuropathy. Chemotherapy-induced peripheral neuropathy can manifest in patients as weakness, pain, and loss of sensation.

THE BIOPHARMACEUTICAL DEVELOPMENT PROGRAM (BDP)

The BDP manufactures cGMP material for IND-directed toxicology and clinical use in Phase I, early Phase II, and selected Phase III clinical trials. Established in 1993, the BDP mission is to advance the development of novel therapeutics for treatment of cancer and other diseases by providing manufacturing, process development, process analytics, quality assurance, and regulatory affairs capabilities and expertise. The Biological Resources Branch (BRB) provides programmatic, contractual, technical, and budgetary oversight of the BDP.

Facility

The BDP is located at the Advanced Technologies Research Facility (ATRF), a state-of-the-art research facility at FNLCR with 55,000 ft^2 occupied by a process development laboratory, cGMP manufacturing, and fill-finish suites (Figures 57 and 58). The cGMP facility contains distinct upstream bioprocessing and purification trains for mammalian and bacterial products, plus separate isolated suites for viral vector production and cell therapy manufacturing. The BDP facility often serves as a site for the FDA's biologics inspectors

training program and maintains cGMP compliance through audits by qualified independent contractors.

Capabilities

- cGMP manufacturing, filling, testing, and release
- Process development and feasibility studies
- Process Analytics/QC testing
- Quality Assurance oversight
- Regulatory Affairs support
- Development and manufacturing capabilities for biologics, including monoclonal antibodies, recombinant proteins, viral and DNA vaccines, peptides, gene therapy products, and other protein, nucleic acid, and cell-based products

Activities

Since 2017, 18 different BDP products have been used in IND-supported clinical trials. In that interval, BDP released 21 new product lots including GMP lots, master cell banks, toxicology/engineering lots, diluents/placebos, and other associated products. BDP provides quality control, quality assurance, and regulatory support for its products, including technical packages for pre-IND meetings with FDA; CMC documents for IND applications; post-filing technical and regulatory assistance, as well as ongoing stability studies for the duration of their use in clinical trials. The following are some significant milestones for BDP products in recent years:

- Two novel oncolytic herpesviruses produced at the BDP entered clinical trials for glioblastoma at University of Alabama Birmingham: M032 and C134
- Technology transfer of the recombinant poliovirus (PVS-RIPO) manufacturing and testing from BDP to Istari Oncology for commercial development to treat glioblastoma and other solid tumors
- CD33 Chimeric Antigen Receptor (CAR) autologous T-cell therapy for a pediatric and young adult AML

multi-center clinical trial was approved in July 2019, with manufacturing by the BDP planned for 2020 (clinical trial number: NCT03971799)

- Successful cGMP production of a novel recombinant FGF-1 molecule, TTHX114, to be evaluated in clinical trials for treatment of Fuchs Dystrophy
- Development and cGMP production of two Epstein-Barr virus (EBV) virus-like particle (VLP) vaccines, EBV-gp350-FN and EBV-gHgLgp42-FN, for upcoming clinical trials
- Development and generation of a chimeric monoclonal antibody that targets canine CTLA-4 to be used in clinical trial in pet dogs through the NCI Comparative Oncology Program. This agent is designed to be a canine version of the human drug ipilimumab and a tool in the establishment of the dog as a model for human immunotherapy development and study.

Training

The BDP provides training on GMP regulations (21 CFR 210, 211). Beside BDP employees, participants in this training have included scientists involved in cGMP manufacturing, quality control, and supporting operations at the NIH and FDA. In addition, the BDP was selected to train reviewers and inspectors from the Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) at the FDA.

Partnerships and Service

Technical and regulatory expertise and specialized capabilities in BRB and BDP primarily support the production of biologic agents for DCTD initiatives; however, the BDP is frequently engaged in collaborations within NCI as well as outside of NCI with the following other government programs:

- Center for Cancer Research (CCR) for cancer and AIDS vaccines, and autologous cell therapies

- NCI Division of Cancer Prevention for novel cancer vaccines supported by the PREVENT program

- National Institute of Allergy and Infectious Diseases (NIAID) and the U.S. Army Medical 1Research Institute for Infectious Diseases (USAMRIID) for vaccine development to treat or prevent infectious diseases

- National Center for Advancing Translational Sciences (NCATS) for rare and neglected disease treatments and gene therapies

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

FIGURE 57: ADVANCED TECHNOLOGIES RESEARCH FACILITY (ATRF) IN FREDERICK, MD.

FIGURE 58: CGMP FILL/FINISH ACTIVITY AT THE BDP, FNLCR.

BRB PRECLINICAL REPOSITORY

This NCI-sponsored facility stores cytokines, monoclonal antibodies, and other biologic reagents under carefully controlled conditions. The repository provides a uniform, high-quality supply of these reagents to qualified research investigators at academic and non-profit institutions at no charge.

One of the more 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. Other popular agents developed and manufactured under NCI-sponsored

programs that are available through the repository include anti-GD2 ch14.18 and 1A7 monoclonal antibodies, and IL-7, IL-12, and IL-15 cytokines.

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-vialed by BDP to enable distribution of high-quality reagents for research and development use only. On-line ordering and standard material transfer agreements provide agents to the research community. Since 1996, just fewer than 80,000 vials of different reagents have been shipped domestically and internationally to over 4,000 scientists. In recent years, the repository has been providing an increasing number of vials each year through an increasing number of shipments (Figure 59).
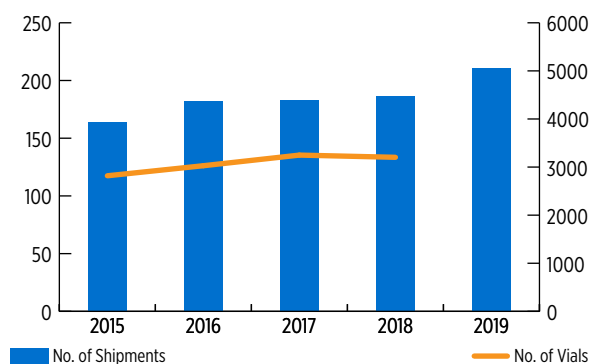
FIGURE 59: NUMBER OF VIALS SHIPPED FROM THE BRB PRECLINICAL REPOSITORY.

FUTURE DIRECTIONS

DTP will continue to provide services and resources to the academic and private sectors 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 immuno-therapy 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.

RADIATION RESEARCH PROGRAM
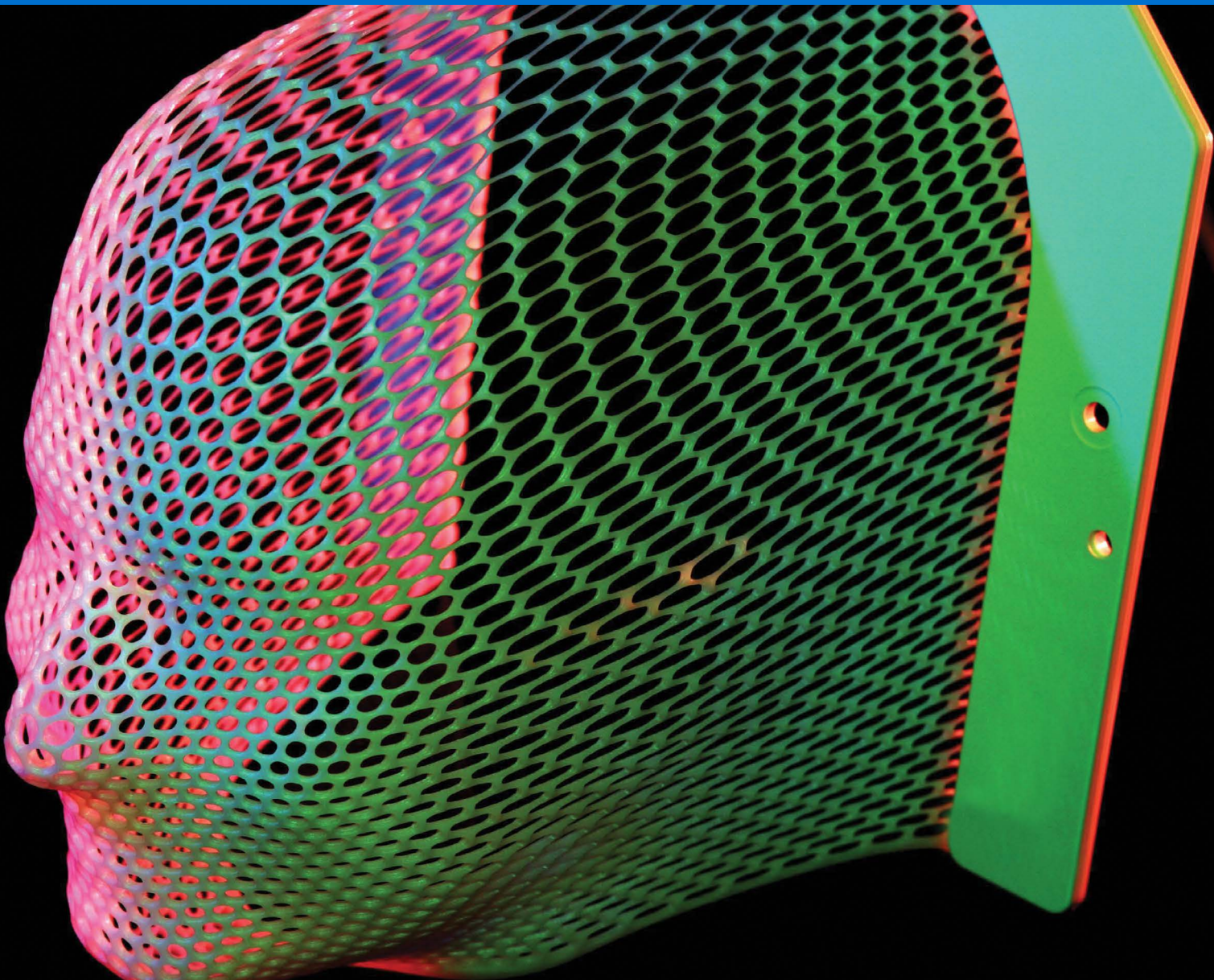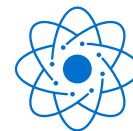
OVERVIEW

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
- 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. More than half of people with cancer receive radiation therapy during their cancer treatment, which 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 support 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.

C. NORMAN COLEMAN
ASSOCIATE DIRECTOR
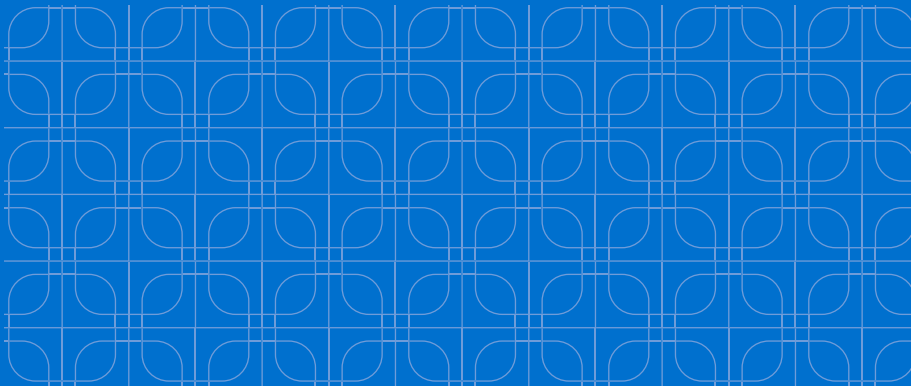
C. Norman Coleman, MD, is Associate Director of RRP, Senior Investigator in the Center for Cancer Research's (CCR) Radiation Oncology Branch (ROB), and a Special Advisor to the NCI Director. He received his medical training at the Yale University School of Medicine. Dr. Coleman completed his internship 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 Director of NCI's Radiation Oncology Sciences Program, and in addition to RRP, he served as Chief of CCR's ROB from 1999 until 2004. He maintains an active laboratory program in molecular radiation oncology.

He has written extensively in his field, has fellowships in a number of medical and radiation professional societies, and has won numerous awards, including the Gold Medal Award from American Society for Therapeutic Radiation Oncology (ASTRO) for his many scientific and professional contributions to the fields of radiation oncology and radiation biology (2005), Service to America Homeland Security Medal (2011), Failla Award from the Radiation Research Society (2016), Doctor of Science, honoris causa (2015), Ellen Lewis Stovall, Patient Centered Cancer Care Award from the National Coalition for Cancer Survivorship (2018), and Warren Sinclair Medal from the National Council of Radiation Protection and Measurements (2019).

Since 2004, Dr. Coleman has been a Senior Medical Advisor and Team Leader/member of the Chemical, Biological, Radiological, Nuclear and Explosive (CBRNE) Team in the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services.
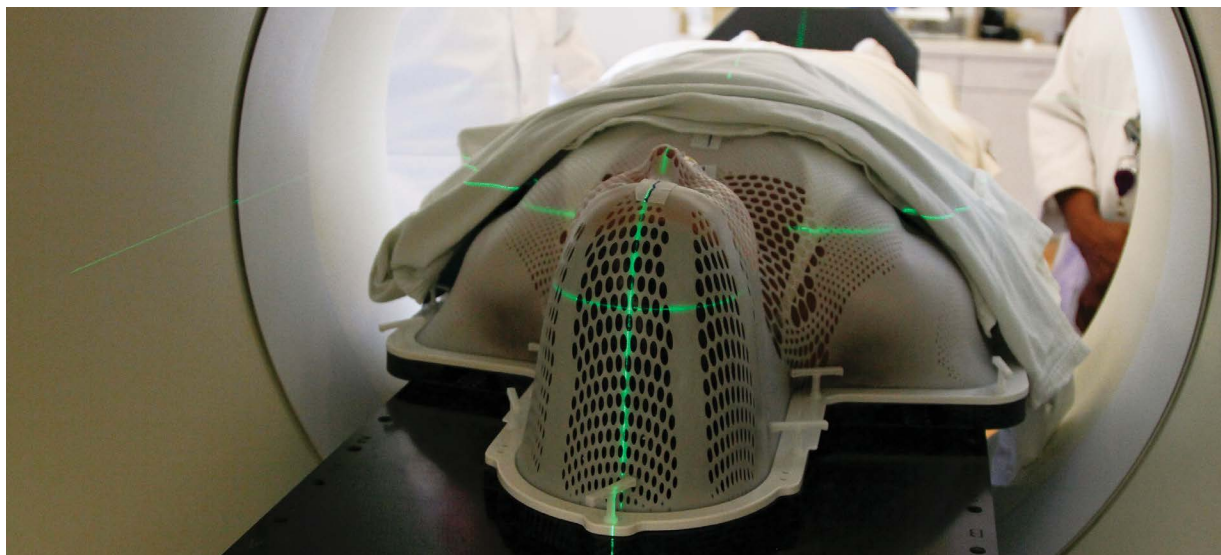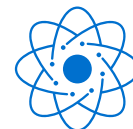
STRUCTURE AND FUNCTION

RRP is divided into two branches:

- Radiotherapy Development Branch (RDB)
- Clinical Radiation Oncology Branch (CROB)

The primary responsibility of RRP is to the grantees and contractors of NCI and NIH. In fiscal year 2019 (FY19), RRP administered more than 256 grant applications. 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).

RADIOTHERAPY DEVELOPMENT BRANCH (RDB)

RDB is responsible for the overall coordination of RRP's research portfolio, which encompasses a broad range of topics that include:

- Mechanistic understanding of RT in the context of molecular and cellular processes to identify therapeutic targets and improve treatment strategies
- Combining the full range of RT approaches with standard and emerging-targeted treatments to create new treatment paradigms
- Development and implementation of advanced technologies for the production and delivery of radiation (in collaboration with RRP's CROB), as well as sensor modalities to monitor biological changes before, during, and after RT

- Preclinical and clinical development of multi-modality cancer therapy including diagnosis, predictive and prognostic biomarkers, treatment, and long-term outcomes/toxicity
- Examination of how radiation-inducible changes at the physical and molecular scales in both tumor and normal tissues can be exploited to improve outcomes with drugs and 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 radio-immunotherapy
- Non-ionizing radiation–based therapies such as photodynamic therapy and hyperthermia

RDB and CROB collaboratively manage grants that deal with image-guided RT (IGRT), the physics of basic radiation track (beam) structure and radiation chemistry. RDB and CROB facilitate coordination of scientific interest groups in the areas of brain metastases, colorectal cancer, upper gastrointestinal tract cancer, glioblastoma, sarcoma, thoracic lung cancer, radiation-immune system, and imaging. These interest groups interface with extramural radiation oncology researchers to develop radiation modifiers for tumor sensitization and to establish assays for better guidance of clinical trial designs.

RDB staff also organize strategic workshops and symposia both within NCI and at the national and international levels that highlight emerging areas of RT that interface with cancer biology, prevention, diagnosis, and treatment from the

perspective of both tumor and normal tissues. Workshops address 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, the Society of Nuclear Medicine and Molecular Imaging (SNMMI), and the Radiation Research Society (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)

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, including:

- **Colossus Project** – Working on a parallel field-programmable gate array (FPGA)-based high-performance computer and project to port TOPAS/TOPAS-nBIO (NCI grantees) and Geant4 (global project) to FPGA to explore ultrafast computation for biological dose, later focusing on artificial intelligence (AI) research to serve our grantees and other NCI missions and research areas.

- **Hadron Beam Dosimetry Projects** –Assisted the CTEP supported Imaging Radiology Oncology Core (IROC) to develop evaluation methods of the hadron beam quality in the context of possible future clinical trials. Performed a formal analysis of the Brookhaven beamline data.

- **CTEP and CIP** – Assisting with their cooperative clinical trial groups and early-phase trials consortia.

- **The Coordinating Center for Clinical Trials (CCCT)** – Working with steering committees and task forces

- **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 patients with cancer 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 and International Organizations** – Facilitating transition of the most promising, radiation-based, experimental therapies to clinical practice by working with such groups as SNMMI, American Association for Physicists in Medicine (AAPM), American Association for Cancer Research (AACR), Society for
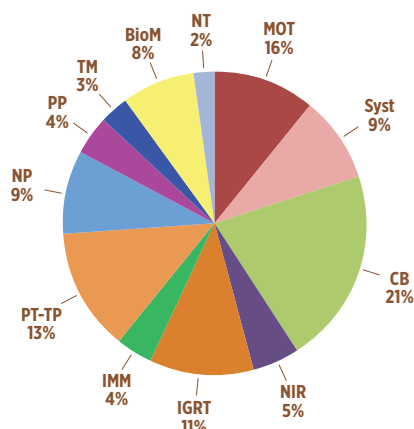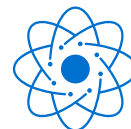
FIGURE 60: DISTRIBUTION OF RRP 2019 GRANTS BY RESEARCH AREAS.
The above graph depicts the distribution of FY19 grants based on the number funded in each of the categories. Molecular targeting of tumor signaling (MOT), Radioimmunotherapy/ systemic radiotherapy (Syst), Cancer Biology and responses to radiation (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).

Immunotherapy of Cancer (SITC), ASTRO, ASCO, 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.

RDB also facilitates interest groups on Neutron Capture Therapies (NCT), Targeted Radionucleotide Therapies (TNT), and quantitative imaging.

RRP GRANTS OVERVIEW

The 2019 RRP research portfolio comprised approximately 158 awarded grants distributed across several areas of radiation research (Figure 60). The grant award mechanisms used by RRP and their distribution in terms of research support in 2019 are shown in Figure 61. The predominant mechanism is the individual research project grant (R01), followed by exploratory phase grants (R21).

Distribution of RRP 2019 Grant Funds
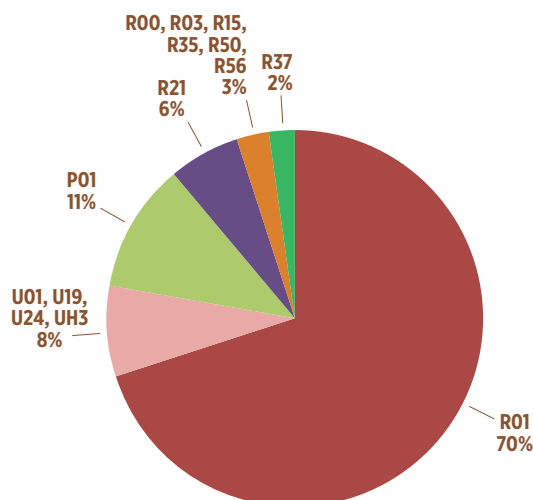
Distribution of RRP 2019 Numbers of Grants
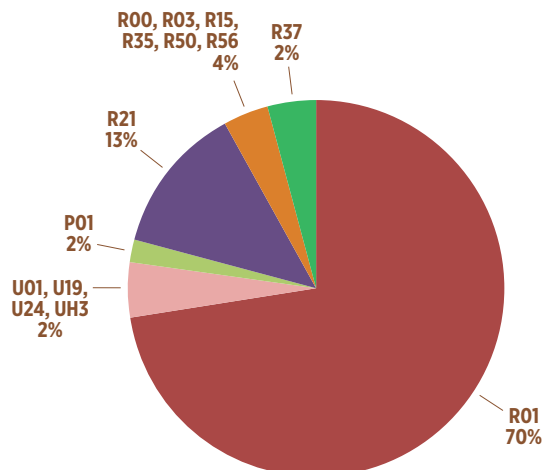
FIGURE 61: DISTRIBUTION OF RRP 2019 GRANT FUNDS (LEFT) AND NUMBERS OF GRANTS (RIGHT) BY MECHANISM.

ASSISTANCE TO THE CANCER RESEARCH COMMUNITY

IMAGING AND RADIATION ONCOLOGY CORE (IROC)

The 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 patients with cancer 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 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.

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. IROC St. Louis QA Center also has experience developing consensus contouring atlases and supporting secondary analyses.
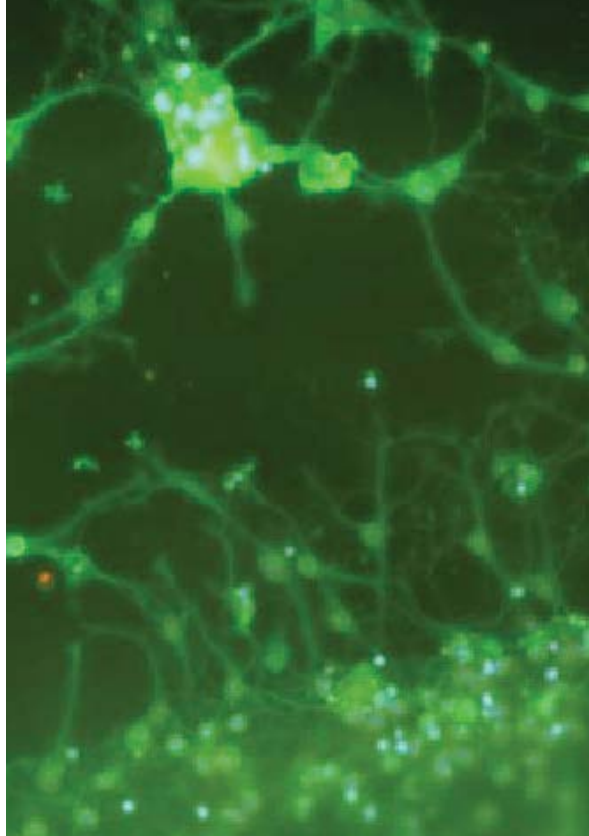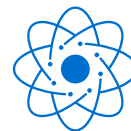
RADIOBIOLOGY BIOTERRORISM RESEARCH AND TRAINING GROUP (RABRAT)

RABRAT is an informal interest group comprising representatives from Federal agencies to discuss opportunities and items of mutual interest on research and training for meeting the challenges of radiation/nuclear terrorism. RABRAT meets three to four times per year.

WORKSHOPS

NCI Workshop on Radiation Dosimetry in Targeted Radionuclide Therapy (TRT), April 19-20, 2018

This joint workshop with NRG on Systemic Radiopharmaceutical Therapy (SRT) and Targeted Radionuclide Therapy (TRT) was convened to address issues and strategies of dosimetry for future clinical trials that NRG Oncology may support. The meeting focused on:

- Current dosimetric approaches for clinical trials
- Dosimetric strategies under development that would provide optimal dose reporting
- Future desired/idealized approaches for the new and novel emerging radioisotopes and carriers in development

Several long- and short-term challenges were addressed at the meeting including:

- The considerable effort required to perform personalized dosimetric measurements and calculations

- Better understanding of radiation toxicity to normal tissue and of therapeutic levels of radiation dose to tumors
- Perceptions that personalized dosimetry is to costly and logistically difficult
- Resolution of the tension between commercial business profit maximization and longer-term assessments of outcome optimization for people with cancer
- Clearly defining next steps in achieving broader consensus and approvals for routine personalized dosimetry in theranostics

2018 Grid Lattice Understanding High-dose, ultra-dose-rate and spatial fractionated radiotherapy Workshop, August 20-21, 2018

In collaboration with RSS, this workshop brought together experimental and clinical experts in high-dose, ultra-high dose rate and spatially fractionated radiotherapy. The overall aims were to understand the biological underpinning of these emerging techniques and the technical/physical parameters that must be further defined to drive clinical practice through innovative biologically based clinical trials.

Liver/Hepatocellular Carcinoma (HCC): New Indications and Future Directions, November 7-8, 2018

This NCI workshop, presented in collaboration with AACR and the American Association for the Study of Liver Diseases, brought together leaders in the field to discuss

preclinical translational research concepts as well as phase I and phase II clinical trial ideas with novel, clinically important endpoints for the management of patients with HCC. The goals of the workshop were to facilitate collaboration among institutions and industry, promote access to CTEP investigational drugs, and expedite the development of clinical trials with a high likelihood of changing outcomes for patients with cancer.

NCI/SNMMI Theranostic Consensus Conference, November 8-9, 2018

Participants included representatives from the FDA and NCI, as well as academicians, clinical physicians, and pharmaceutical company executives. The conference was organized to share perspectives and identify consensus views on:

* a pathway for regulatory approval of targeted radiotherapies and their companion diagnostics

* the data needed by government and private payers to support reimbursement for imaging and therapeutic agents

NCI Workshop on Artificial Intelligence in Radiation Oncology, April 4-5, 2019

Together with Stanford University, this workshop focused on the promising applications of AI to radiation oncology. This recent, cutting-edge technology has the potential to facilitate cancer diagnosis, assess RT response, and data-mine the Big Data emanating from clinical and imaging databases of NCI clinical trials and other publicly accessible archives, such as the Cancer Imaging Archive (TCIA). Using AI may also lead to the correlation of radiomics and genomics with tumor and normal-tissue response and help discover imaging biomarkers that could predict outcomes for people with cancer and improve future therapeutic strategies.

2019 DOE Workshop - Basic Research Needs Workshop on Compact Accelerators for Security and Medicine, May 6-8, 2019

RRP convened a workshop in collaboration with DOE, DOD, and other agencies to evaluate the scientific infrastructure and needs for the near and far future for the linear accelerator in terms of medical and security uses. More than 120 invited participants from around the globe attended. A public document is in the final stages of preparation and will be available on the DOE website.

Third Targeted Radionuclide Therapy (TRT) Conference, December 16, 2019

SNMMI and NCI collaborated to convene this conference that included global representation from the following major stakeholders in theranostics: FDA, NCI, academicians, clinical physicians, and pharmaceutical company executives. The following four comprehensive sessions focused on the central topic "What is the Goal of Radionuclide Therapies: Palliative, Curative, or Adjuvant Treatment?":

* Maximizing dose to tumor while sparing normal tissue

* The current state of the science

* State-of-the-art clinical trial design

* Strategies for achieving response

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, which we call "accurate, precision radiation medicine" (Coleman, 2018), greatly improves 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, including radiation-inducible molecular and immunological targets. 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, radiation oncology has robust data sets that, under the appropriate safeguards, 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 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.
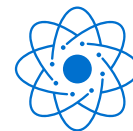
With a staff actively engaged in research planning and conduct, collaboration with CCR, NIAID, and ASPR's BARDA, RRP generates a strong level of enthusiasm, collaboration, and innovation among agencies, investigators, and partners. This leadership helps to sustain a critical mass of talent and enthusiasm within government (RABRAT), and with academic, industrial, and global partners.

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. The term "classical" remains as relevant to laboratory technique and safe clinical application of radiation as it does to systemic therapy where dose, timing, and interactions of agents are important. Working with professional societies, RRP will endeavor to assist in education and training of radiation cancer biologists and physicists to bring "accurate, precision radiation medicine" to the clinic as an effective cancer treatment.

In collaboration with NCI's Center for Cancer Training (CCT) and ASTRO, an effort is being made to enhance current education in the radiation sciences at a national level through the development of supplemental courses that will incorporate radiobiology, radiation physics, and translational and experimental methodology. Support in preparing applications for 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

The importance of radiation oncology to the field of cancer immunotherapy is increasingly being recognized. Radiation is now used in combination with cell-based and immune check-point inhibitor therapies to induce robust presentation of antigens, including neo-antigens, and alter DNA damage and repair to enhance the efficacy of immunotherapy,

including abscopal effects where the immune system in distal tumors becomes activated by irradiation of a single tumor

This cross-discipline interaction between radiation oncology and immuno-oncology requires:

- Mutual in-depth understanding of the disciplines of radiation biology, tumor biology and metabolism, and cancer immunotherapy
- An exchange of research materials, including biomarker assays and immune competent models, for preclinical and clinical studies

One of RRP's missions is to expand opportunities to expose cancer immunotherapists to the science of radiation oncology/biology in order to foster the development of strategic initiatives that translate into successful combined modality trials. RRP's staff worked with others in DCTD and extramural investigators to establish the Radiation and Immune Modulation Working Group, which develops sound multi-center clinical concepts. RRP is highlighting the following critical issues that need to be addressed when combining radiation plus immunotherapy:

- Immunomodulation of tumor microenvironment and tumor cells by radiation
- Effective combinations of radiation and immunotherapy
- Biomarkers of opportune immunogenicity after combined radiation-immunotherapy

TARGETED RADIONUCLIDE THERAPY

TRT involves targeting of radioactive isotopes to cancer-specific targets. The short range of the emitted particles in tissues allows delivery of lethal radiation to tumor cells, while sparing the surrounding normal tissues. FDA has approved TRT for the treatment of several types of cancer. Clinical trials of new radiopharmaceuticals are ongoing and show clinical promise.

TRANSLATIONAL RESEARCH PROGRAM
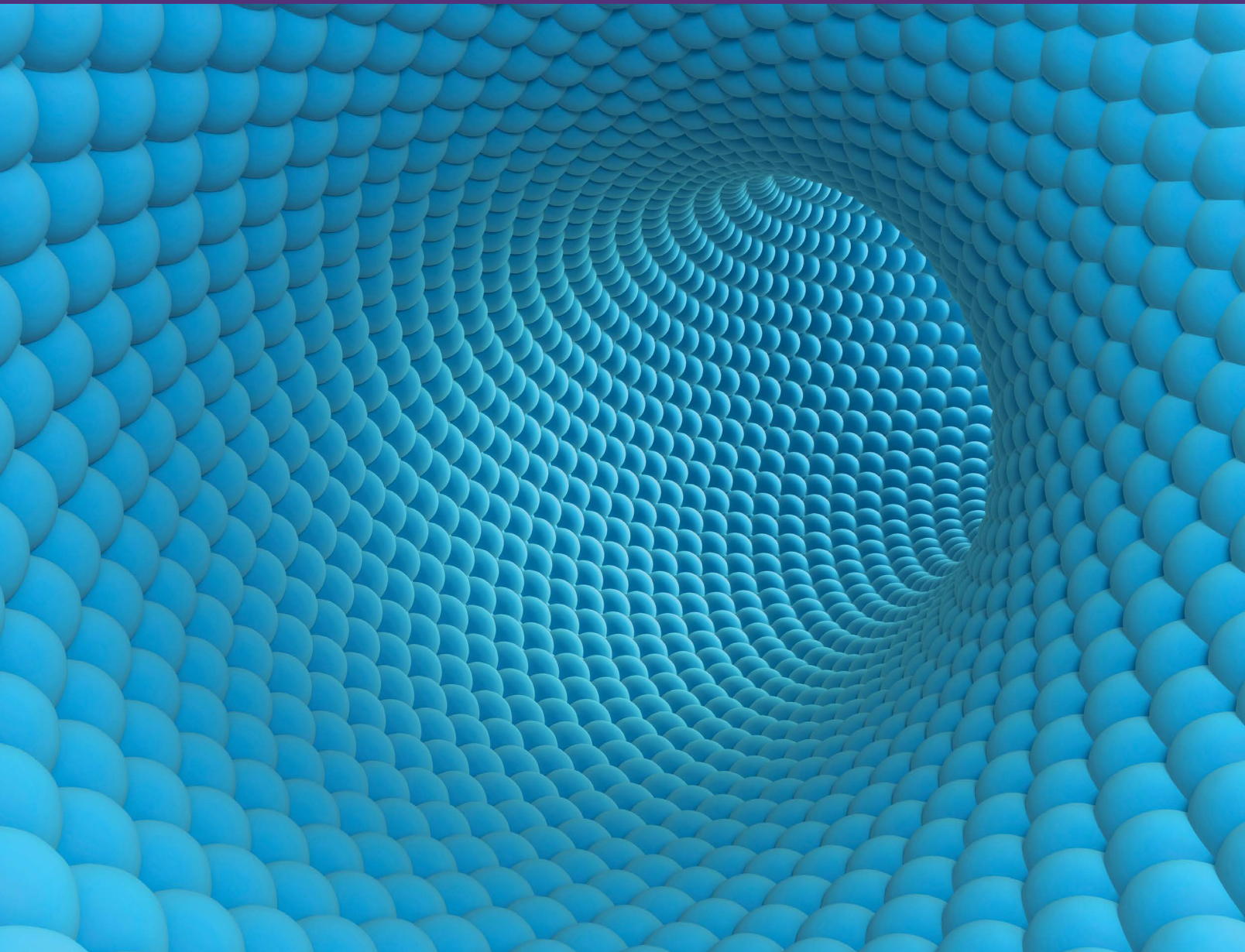
OVERVIEW

The Translational Research Program (TRP) is committed to reducing cancer incidence and mortality and improving survival and quality of life for people with cancer. TRP uses advances in the laboratory to develop new clinical 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 (Figure 62). 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 and population science studies.

- Encouraging a multidisciplinary and bidirectional approach to translational research

- Promoting research in high incidence as well as rare cancers

- Facilitating collaborations for 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
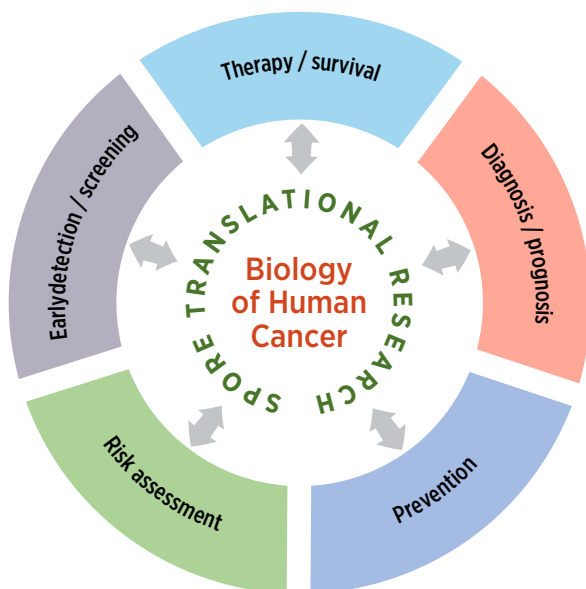
FIGURE 62: MULTIDIRECTIONAL APPROACH TO TRANSLATIONAL RESEARCH.
TRP coordinates interdisciplinary investigations that are based on the biology of human cancer.

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 Research Act of 2012; and R50 Research Specialist Career Awards, where the applicant is integral to the work of a funded SPORE. TRP is also involved in the following activities:

- PRE-medical Cancer Immunotherapy Network of Canine Trials (PRECINCT) and the Integrated Canine Data Commons (ICDC)

- Small Cell Lung Cancer Consortium (SCLC-C)

- Pancreatic Cancer Microenvironment Network (PaCMEN)

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 patients with cancer 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 people with cancer. 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 patients with cancer, to determine the biological basis for clinical observations, and to use specimens from clinical studies to determine correlations between biomarkers and outcomes

- 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 and 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 40 years at NIH, 32 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. During her tenure, the Program grew and is now accepting applications in thematic areas, such as cancer health disparities, pediatric cancers, and signaling pathway alterations. She also integrated the SPORE planning grant (P20) grantees in cancer health disparities into the larger SPORE community to encourage closer collaborations between investigators with common interests. In 2015, she was selected as Deputy Director of DCTD. During the five years of working across DCTD programs, she instituted a network of canine cancer clinical trials as a model for human immunotherapy and began the work to establish an Integrated Canine Data Commons as a functional node in the NCI Cancer Research Data Commons (CRDC) so that investigators can use comparative oncology data and analytical tools to gain better insight into treatment of human disease.

TRP GRANTS OVERVIEW

TRP uses the P50 (and the U54) funding mechanism for the SPORE program. In 2019 there were 54 funded SPOREs, covering 20 organ sites and systems, including one signaling pathway-focused grant (Figure 63). Fifty-three grants used the P50 mechanism, and the remaining grant was funded through a U54. In addition, TRP staff oversee a relatively smaller number of R21, R01, and R50 translational research grants.

Prostate — Ovarian — Endometrial
Brain — Skin/Melanoma — Neuroendocrine
GI — H&N/Thyroid — Pancreatic
Breast — Kidney — Pediatrics/RAS
Lung — Liver — Bladder
Lymphoma — Myeloma — Sarcoma
Leukemia — Cervical
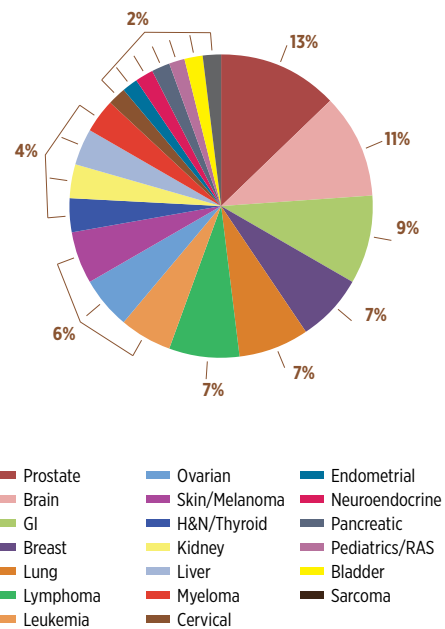
FIGURE 63: DISTRIBUTION OF TRP 2019 SPORE GRANTS ACROSS ORGAN SITES/PATHWAYS.

ORGANIZED SPORE WORKSHOPS

BRAIN SPORE WORKSHOPS (2018-2019)

The Mayo Clinic Brain SPORE hosted the Annual Brain SPORE Workshop in 2018 at Amelia Island, Florida, and the UCLA Brain SPORE hosted in 2019 in Los Angeles, California. The investigators of the Brain SPOREs and the NCI Physical Sciences of Oncology Network collaborated on the 2018 workshop to identify the most provocative and impactful translational research questions in adult and pediatric brain cancer. The investigators compiled a summary of these questions as well as key knowledge gaps in the field for submission to NCI leadership. The report spanned several major areas of research, including biology and omics, mathematic and computational modeling, novel therapeutic development, and clinical trials. The 2019 workshop extended this mission by reconvening the currently funded Brain SPOREs for a series of presentations summarizing recent SPORE advances as well as panel discussions on clinical trials, biomarkers of response, neuroimaging, immune monitoring, big data, and biospecimen procurement.

GASTROINTESTINAL (GI) AND PANCREAS CANCER WORKSHOPS (2018-2019)

SPORE workshops were held in 2018 and 2019 in the areas of GI and pancreas cancer and included participation from GI cancer, Pancreas cancer, Liver cancer, and Neuroendocrine tumor SPOREs. The first workshop, organized by University of Nebraska Pancreatic SPORE staff led by Dr. Tony Hollingsworth and by TRP program staff, was held October 2018 at the University of Nebraska Medical Center in Omaha, NE. The second workshop was held November 2019 at Johns Hopkins University in Baltimore, MD. It was organized by the Johns Hopkins University GI SPORE staff, led by Dr. Alison Klein, and TRP program staff. Both workshops included a session at the beginning that allowed newly funded SPORE groups to present an overview of the activities in each of the components of their SPORE. Subsequent sessions were organized around specific scientific topics of relevance, including:

- metabolism
- immunotherapy
- molecular therapies, tumor progression, and drug resistance
- biomarkers and cancer detection
- tumor microenvironment
- epidemiology, population studies, and early detection
- novel imaging approaches

Each workshop included a brief session on NCI initiatives, a poster session, and a tour of the medical center facilities at each location.

SKIN SPORE WORKSHOPS (2018-2019)

The Skin SPORE Annual Workshop was hosted at Moffitt Cancer Center in 2018 and at Wistar Cancer Institute in 2019. The 2018 workshop included presentations summarizing recent SPORE advances and covered a wide range of topics in both melanoma and non-melanoma skin cancers, such as MAPK signaling, melanoma models for the evaluation of anti-cancer immune responses, reversing metabolic insufficiency in the tumor microenvironment, data sharing, and computational tools for single cell heterogeneity analysis. The 2019 workshop maintained a similar format, providing brief highlights on recent SPORE advances followed by presentations in the areas of immunotherapy, mechanisms of resistance to therapy, early-stage disease, collaborations in big data, patient-derived xenograft (PDX) repositories, and novel therapeutic targets. Breakout sessions were convened in the areas of biomarker evaluation/development, biostatistics/bioinformatics, and clinical trials for rare disease, novel combinations, and personalized medicine.

LUNG CANCER SPORE WORKSHOPS (2018-2019)

The Lung Cancer SPOREs hosted workshops in 2018 and 2019 at the University of Texas Southwestern (UTSW) and the NCI, respectively. David Gerber and Kathryn O'Donnell (UTSW), Don Gibbons (MD Anderson Cancer Center), and Elda Railey (Research Advocacy Network) assembled the agenda for the 2018 workshop, which consisted of ten sessions on the following topics: genomics, molecular targets, response/resistance, immunotherapy, metabolism, early detection, patient advocacy, SCLC, and metastasis. Highlights from the workshop included the immunogenicity of BRAF and c-MET alterations in contrast to the immunosuppressive behavior

of STK1 alterations in non-small cell lung cancer (NSCLC), validation of cell lines and PDX models and their concordance with primary tumors, AXL as a potential therapeutic target, mechanisms of resistance to epidermal growth factor receptor (EGFR) 3rd generation tyrosine kinase inhibitors (TKIs), metabolic considerations in NSCLC, new cell line-derived xenograft (CDX) models of SCLC, inosine-5'-monophosphate dehydrogenase (IMPDH) as a druggable target in SCLC, deeper understanding of the heterogeneity in SCLC, transmembrane protein 106b (TMEM106b) as a metastatic driver of neuroendocrine tumors, and advances in immunotherapy of NSCLC in the neoadjuvant setting.

TRP staff, lung cancer investigators, and advocates organized the 2019 meeting. The following scientific sessions covered an array of topics:

- KRAS, LKB1, and Related Pathways
- Immunotherapy
- EGFR and Other Signaling Pathways
- Therapeutic Resistance
- Premalignancy, Risk Stratification, and Chemoprevention
- Novel Targets
- Molecular Profiling and Biomarkers
- SCLC
- Epidemiology, Pathology and Clinical Trials

Highlights included a keynote address by Dr. Lieping Chen on the new immune checkpoint SIGLEC 15 and the introduction of two newly funded Lung Cancer SPOREs from Fred Hutchinson Cancer Research Center (Dr. McGarry Houghton, Principal Investigator (PI)) and Emory University (Drs. Suresh Ramalingam and Haian Fu, PIs).

BREAST SPORE WORKSHOP (2018)

Ingrid Mayer, MD, Vanderbilt University, Breast Cancer SPORE PI chaired the 2018 Breast SPORE Workshop. The goals of the workshop were to identify preclinical, translational research challenges, highlight advances, define resources and technologies, and foster collaborations among the Breast Cancer SPORE sites, patient advocates, and NCI staff. The Breast Cancer SPORE PIs presented overviews of

their programs in the morning sessions. Some highlights from the afternoon sessions on Resources and Technologies Available to the Breast Cancer Scientific Community and Translational Breast Cancer Research were the following:

- NCI data sharing resources available to the cancer research community via the NCI Office of Data Sharing and the CRDC
- Studying benign breast tissue for signatures, biomarker discoveries, and transcriptomes
- Utilizing immunoPET-assisted, non-invasive immunotherapy targets in the preclinical and clinical settings
- Preclinical challenges and advances in the Breast Cancer SPOREs' Career Enhancement Program and Developmental Research Program projects
- Research opportunities for inter-SPORE collaborations

HEAD & NECK/THYROID CANCER SPORE WORKSHOP (2018)

SPORE Directors, Drs. David Sidransky of Johns Hopkins University (Head & Neck), Paul Harari of the University of Wisconsin (Head & Neck), and James Fagin, Memorial Sloan Kettering Cancer Center (Thyroid), convened a Head & Neck/Thyroid SPORE Workshop at the NCI. The purpose was to define obstacles to success in the field of head & neck/thyroid cancer research and to identify resources needed to overcome these barriers. The topics were translational models and repositories, treatment resistance, premalignancy, novel tumor targets, and immunotherapy and the tumor microenvironment. Special sessions and panel discussions were held to develop and initiate collaboration opportunities among head & neck/thyroid investigators, including:

- Precision medicine: the evolving clinical and regulatory path ahead
- Immunotherapy in head & neck cancer: beyond checkpoint inhibitors
- Translational models: collaboration and discovery opportunities
- Collaboration opportunities in thyroid cancer: a study on active surveillance vs surgery for thyroid lesions
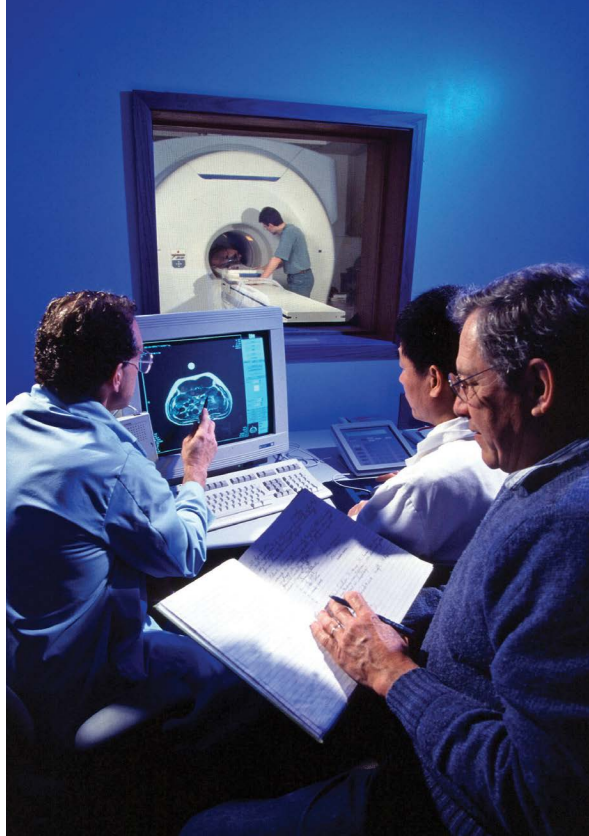
GYNECOLOGIC (GYN) CANCERS WORKSHOPS (2018-2019)

The GYN SPOREs held a workshop in 2018 adjacent to the American Society of Clinical Oncology (ASCO) Annual Meeting and in 2019 adjacent to the American Association for Cancer Research (AACR) Annual Meeting. These workshops attracted a broad audience of scientists, clinicians, NCI staff, and patient advocates. During each of the workshops, funded SPOREs gave an oral presentation.

The 2018 workshop covered a broad array of topics in ovarian, endometrial, and cervical cancers, including PARP inhibitor therapy, novel targeting of SIK2, non-coding RNA therapeutic options, immunotherapy for HPV-associated malignancies, ovarian cancer PDX models, and advances through collaboration. Additionally, the workshop incorporated panel discussions on second-look laparotomy for minimal residual disease, tumor/blood sample resources, and immunotherapy. During the 2019 Workshop, there were two main sessions. The first session entitled "PARP inhibitors: Which Patients, Which Drugs and Which Combinations" had speakers from MD Anderson, University of Pennsylvania, and The Wistar Institute. The second session entitled "Advances in Immunotherapy for Gynecological Malignancies" had speakers from Johns Hopkins University School of Medicine, Mayo Clinic, MD Anderson, and University of Pittsburgh Cancer Center. Discussions from the workshops were agenda items during GYN monthly teleconferences.

TRANS-NCI WORKSHOPS IN TRANSLATIONAL RESEARCH

NCI Workshop on Lineage Plasticity and Androgen Receptor-Independent Prostate Cancer (2018)

NCI-funded investigators with expertise in prostate cancer and neuroendocrine tumors, including the prostate SPOREs, participated in a workshop with NCI intramural and extramural staff in December 2018 to understand the emergence of a treatment-associated small cell, neuroendocrine (t-SCNC) population of prostate cancer cells.

During prolonged androgen deprivation therapies (ADT), tumor cells in 20% of these people become resistant to the treatment and begin to grow as small cell endocrine tumors, a demonstration of plasticity from their luminal cell lineage. The workshop's publication (Beltran, 2018) provides summaries and analyses of the working groups that defined knowledge gaps and suggested addressing the following areas:

- How lineage plasticity occurs

- The timing and cooperation of lineage-derived transcription factors and of emerging drivers

- What preclinical models can recapitulate the biology of disease and the recognized phenotypes

- Identification of therapeutic targets and novel trial designs

The discussion included mechanisms underlying this resistance mechanism and provides a path towards developing biomarkers and trials to support this molecularly unique set of people with cancer.

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. 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 (TM) systems as defined by the World Health Organization

2. Using complementary approaches to improve the therapeutic ratio of standard and investigational anticancer therapies

3. Lifestyle modification research (e.g., diet, exercise, mind–body approaches) for their impact on cancer outcomes (e.g., response to conventional cancer therapy, survival)

Four organizational components accomplish OCCAM's work:

- 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

- International Research Program – Establishes research collaborations with foreign research organizations predominantly in the areas of natural product and TM product evaluation

- Office of the Director – Supports the other programs, provides topic area expertise for internal and external contacts, manages communication and education activities

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

MISSION

The mission of OCCAM is to improve the quality of care for people with cancer, those at risk for cancer, and those recovering from cancer treatment by contributing to advances in 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 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 where he performed laboratory research in immunology and molecular biology and co-ordinated 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 (precursor to the National Center for Complementary and Integrative Health). In October 1998, he was selected 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 2019 are shown in Figure 64 and 65. The predominant mechanism is the exploratory phase grants (R21), followed equally by the individual research project grant (R01) and conference grant (R13).
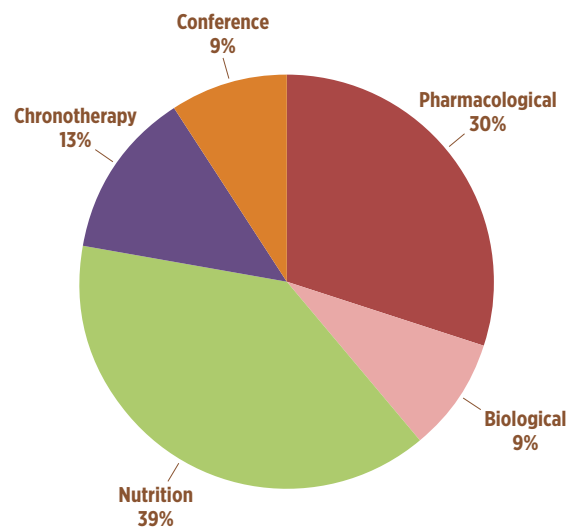
FIGURE 64: PERCENT DISTRIBUTION OF OCCAM FY19 GRANTS BY RESEARCH AREA.
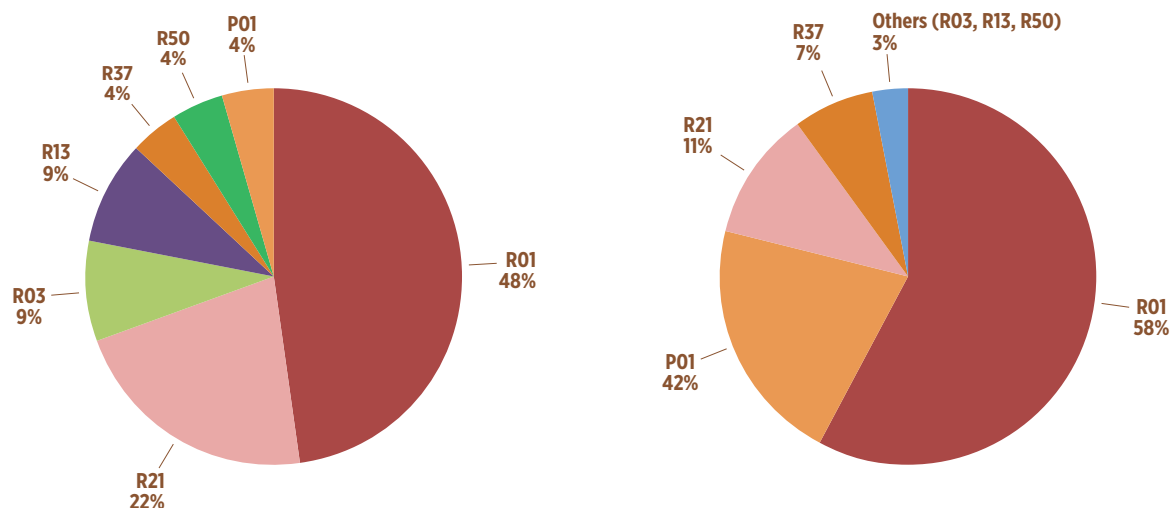
FIGURE 65: DISTRIBUTION OF 2019 GRANT NUMBERS (LEFT) AND FUNDING (RIGHT) BY MECHANISM.

ASSISTANCE TO THE CANCER RESEARCH COMMUNITY

MICROBIAL-BASED CANCER THERAPY RESEARCH PROGRAM

Following a very successful conference in July 2017 that led to a published white paper (Curry, 2018), OCCAM sought to advance research on microbial-based cancer therapy. The aim is to stimulate the development of novel microbial-based cancer therapies, especially for conditions where conventional cancer therapies are inadequate, such as poorly vascularized, hypoxic, solid tumors, dormant or slowly dividing cells resistant to current interventions, and brain tumors.

To stimulate new research in the field, two new funding opportunities were initiated in 2019: PAR-19-194, aimed at promoting early research without preliminary data, and PAR-19-193, to support more advanced research.

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 people 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 in 2010, 220 cases were submitted for review, of which 58 cases met the eligibility criteria. In 2019, one case series met all eligibility criteria and received favorable reviews from the protocol investigators. The submitted solicited further documentation to enable external reviewer evaluation.

CONFERENCES

NCI Strategic Workshop on Rigor and Reproducibility: Precision Fecal Microbiota Transplant and Microbiome Cancer Therapeutics

The microbiome may play an important role in cancer therapeutic outcomes; therefore, NCI convened a workshop in September 2019 with the following goals:

- Assess the current state of clinical research and clinical trials involving fecal microbiota transplants (FMT) and microbiome-based cancer therapeutics

- Discuss the knowledge gaps and future opportunities in the field

- Provide feedback to NCI and NIH regarding future priority areas to enhance precision- and mechanism-based rigor and reproducibility of defined microbiome-based therapeutic clinical research for cancer and other diseases

A few areas of focus were:

- standardization (material manufacture and quality control)
- FMT donor selection
- microbiome measurement
- clinical protocols
- procedures
- trial design
- microbiome composition and function as biomarkers associated with cancer therapy, such as reproducibility, safety, and efficacy

One highlight from the meeting was preliminary human and mouse data showing possible immunotherapy benefits from providing FMT from anti-PD1 responders to some non-responders. In addition, in mice, a fiber-rich diet improved anti-PD-1 immunotherapy, and an association was observed in humans along with improvement in gut microbiome diversity. The workshop summary report and recorded videos are posted on the DCTD website.

Acupuncture for Cancer Symptom Management

As a follow-up to the 2016 conference on acupuncture for cancer symptom management, OCCAM and the National Center for Complementary and Integrative Health jointly organized the "Translating Fundamental Science of Acupuncture into Clinical Practice: for Cancer Symptom Management, Pain and Substance Abuse" workshop held February 11 - 12, 2019 at Lister Hill Center Auditorium on the NIH campus. The meeting focused on:

- Basic and translational research to increase the understanding of mechanisms underlying the effects of acupuncture on specific symptoms, pain, and substance abuse
- Mechanistic studies to inform the type of needle stimulation required and/or dosage that may improve effects on specific symptoms
- Translational research incorporating biological markers (such as genetic polymorphisms) or behavioral measures to identify who may respond best to acupuncture intervention

More than 200 people participated either onsite or virtually. The workshop summary report and recorded videos are posted on the OCCAM website.

CAM and Cancer Surveillance

To explore the real-world outcomes resulting from the integration of Western and traditional Chinese medicine (CM) on cancer, OCCAM and the DCCPS Surveillance Epidemiology and End Results (SEER) program organized a series of training courses on cancer surveillance systems. These were held at NCI from August 26 – September 13, 2019 for 12 CM practitioners and information analysts from Beijing, Shanghai, Tianjin, Guangzhou, Shenzhen and Sichuan. The trainees learned about the cancer registry system components and data collection and validation procedures. They also viewed demonstrations of two US State Cancer Registries (Louisiana and Georgia). The US cancer registry researchers and CM practitioners and information analysts plan to collaborate to establish an Integrative Cancer Surveillance System (ICSS).

NCI Integrative Medicine Course

Resulting from the NCI DCTD CAM strategic workshop and needs assessments of NIH fellows, NIH launched the innovative, original NCI-NIH Integrative Medicine (IM) course. It is complementary to an ongoing flagship training curriculum that the NCI Center for Cancer Training (CCT) offers, the Translational Research in Clinical Oncology (TRACO) course.

The IM course is designed for NIH fellows who want to enhance and broaden their knowledge of evidence-based comprehensive integrative healthcare to improve people's lives, including those with cancer. The NCI CCT implements and the Trans-NIH IM course training committee coordinates the course. The course includes:

- Complementary and integrative medicine topics presented with research evidence, followed by clinical scenarios
- Opportunities to better understand the current state of the science of each subject and introductions to cutting-edge advances in medical research
- Timely topics and FDA regulatory policy

The 2019 topics included acupuncture, sleep, chronomedicine, and dietary supplement and natural product safety. The 2020 spring term topics will include pain and opioid use, cannabis and cancer, microbiome and fecal microbiota transplant, regulatory policy, and exercise.

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 "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 OCPL manages. This board produces evidence-based summaries of the literature about various CAM approaches that people with cancer use.

NCI Center for Cancer Research (CCR)

OCCAM collaborates on several projects with NCI's CCR:

- CCR's Laboratory of Molecular Immunoregulation is studying a CM herbal compound, cryptotanshinone (CT),

against Lewis lung carcinoma (LLC) and liver cancer (HCC) using animal models. The study[28] showed that CT could inhibit the proliferation of mouse LLC cells by upregulating p53, downregulating cyclin B1 Cdc2, and consequently inducing G2/M cell cycle arrest of LLCs cells. CT also promoted maturation of mouse and human dendritic cells (DC) with upregulation of costimulatory and MHC molecules, and stimulated DCs to produce TNFα, IL-12, IL-β in vitro. CT was effective in the treatment of LLC tumors in vivo, inducing complete responses via antiproliferative and immunotherapeutic effects. In the HCC study[29], CT significantly inhibited the growth of syngeneic Hepa1-6 hepatoma tumors, and in combination with anti-PD-L1 cured Hepa1-6 bearing mice through the induction of long-term anti-Hepa1-6 specific immunity.

- The Signal Transduction Section in CCR's Laboratory of Genitourinary Cancer Pathogenesis studies CM compounds (such as Gambogic Acid) and extracts (such as FKI) and their inhibitory effects on prostate cancer stem cell growth and related mechanisms.

Intradivisional and International Collaborations

Lifestyle and Past Medical History Survey of Adult Patients Participating in the NCI's Exceptional Responders Initiative

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[28] S Liu, Z Han, AL Trivett, et al. Cancer Immunology and Immunotherapy. 2019
[29] Z Han, S Liu, H Lin, et al. Cancer Immunol Immunother. 2019

The Exceptional Responders Initiative (ERI) is a pilot study to investigate the underlying molecular factors associated with exceptional treatment responses to drug therapies in people with cancer. People in this study are offered the opportunity to participate in a survey designed to assess any changes in their diet, physical activity, or CAM use before, during, or after their exceptional response. The objectives of the study in this group of people are to:

- Qualitatively assess these aspects of their lives

- Gather information about co-morbid conditions and medication

- Estimate the frequency of CAM use

- Characterize the types of CAM interventions used

CM Herb Library

Together with DTP's Natural Products Branch (NPB), OCCAM has worked to develop a CM herb library containing 332 samples of unfractionated extracts from 132 plant species collected from different locations in China. This library represents the potential therapeutic contents found in the most common TCM herbal prescriptions. A 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 is 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. Natural products in the form of pure compounds (n=357) and plant extracts (N=210) have been collected from five institutes in China (Kunming Institute of Botany; Key Laboratory of Chemistry for Natural Products (KLCNP) in Guizhou Province; Institute of Matera Medica, China Academy of Medical Sciences; Cancer Institute, China Academy of Chinese Medical Sciences; and Hong Kong Baptist University). To date, 74 pure compounds have been screened on the NCI-60 human cancer cell lines; 14 of them in 5-dose response screens. CCR's Molecular Targets Laboratory has screened 26 pure compounds against seven cell targets (GP78, PLK1, NF1, EpCAM, META, SUMO, p38) as well as 152 medicinal herb extracts against eight cell targets (GP78, NF1, EpCAM, MALT1, p38, SUMO, TRAIL and META) and identified hits. Hit extracts or compounds will be further tested on cell target assays.

FELLOWSHIPS AND GUEST RESEARCHERS

OCCAM continues to educate the next generation of researchers in CAM through two Cancer Research Training Award (CRTA) fellow positions. These fellows generally have a Masters degree-level education and are interested in pursuing a higher degree or work in medical research, clinical medicine, or public health.

Additionally, eight international visiting fellows (seven from the Cancer Institute of the China Academy of Chinese Medical Sciences, and one from Changchun University of Chinese Medicine) have consecutively joined investigators from the Laboratory of Molecular Immunoregulation, the Laboratory of Cancer Prevention at NCI's Frederick National Laboratory for Cancer Research, and the 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, CT, FKI). Seven 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 of care to control cancer growth and decrease the side effects of chemotherapy.

FUTURE DIRECTIONS

Because industry and academia are not likely to invest heavily in the robust scientific evaluation and 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:

- Establish a dialog within NCI about diet, physical activity, and stress management after cancer diagnosis. The focus is on interactions of these factors with standard and investigational cancer therapies, and the goal is to understand past and current research activities in this area, the extent to which NCI has supported this work, and to identify areas of potential opportunity for program development and action.

- Further explore 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 through both collaborations with intramural and extramural research laboratories and in the clinical setting.

- Explore the clinical evaluation of various CAM approaches to managing symptoms of cancer, 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.

- Working with radiation oncologists from Johns Hopkins University, OCCAM has facilitated a project exploring the skin protective effects of herbal-based creams (Herb-to-Sooth, Hand-to-Heal) developed by Unitech Medical. Preliminary results showed apparent beneficial effects in people with head and neck cancer on indicators of skin inflammation (e.g., erythema, edema, and alopecia) after radiotherapy. Researchers at other medical centers are considering implementation of similar studies.

- Working with NCI's Center for Global Health (CGH) and the HHS Office of Global Affairs, OCCAM has applied for an Asia Pacific Economical Collaboration (APEC) funding program to form the APEC Traditional Medicine and Cancer Network. 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 TM and cancer; share information on TM and cancer care; establish a TM and Cancer Network website/database; propose standards for TM practice and products; and promote regulations on the safety, quality, and efficacy of TM products.

- Working with NCI's CGH to organize a workshop around successful examples of, and challenges to, the integration of Western biomedical oncology and the approaches of TM systems in low- and middle-income countries.

- To explore the effectiveness and efficacy of integration on conventional medicine and alternative medicine, OCCAM, along with DCCPS plans to work with researchers and practitioners in the US to start developing an Integrative Cancer Surveillance System (ICSS). With more

variables from alternative medicine added to the current cancer surveillance system, it may provide insight into whether the quality of life (QOL) and overall survival time (OT) can be changed/improved when two medical systems are integrated.

- Working 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 complementary and integrative medicine in the priority areas suggested in the May 25-26, 2016 workshop, "The State of the Science: Cancer Complementary and Alternative Medicine Therapeutics Research," 2017 NCI Chronomedicine workshop, and 2019 NCI Strategic Workshop on Fecal Microbiota Transplant and Microbiome Cancer Therapeutics, such as nutrition/diet and cancer immunotherapy, FMT and microbiota-based therapy clinical research, and chronotherapy/chronomedicine 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 information on CAM and cancer for people with cancer has increased, but tailored education is needed. OCCAM will continue working with NCI's OCPL to develop evidence-based education resources.

- The frequency of CAM use is high (approximately 40-50%) among people with cancer, but studies have shown a significant gap in the disclosure of this use to physicians and infrequent and meager conversations between physicians and people with cancer about this topic. OCCAM will work with other programs at NCI and possibly NCCIH to address the following issues:

  - The clinical significance of CAM non-disclosure in the cancer setting

  - The potential value of improving communication between provider and people with cancer on this topic

  - Legal implications of CAM communication

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