Precision Medicine Initiative: Oncology

FY-16 Supplements & FY- 17 RFAs

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Increase Genomics-Based Clinical and Preclinical Studies of Cancer Treatment

- Expand genomics-based clinical trials
- ✓Understand & overcome resistance to targeted drugs & drug combinations
- ✓Mechanistic understanding of immunotherapy
- ✓Repository of patient-derived pre-clinical models for evaluating targeted therapeutics
- National cancer database to integrate genomic information with clinical response and outcome (GDC)

DCTD Initiatives

Precision Medicine for Oncology: Projects for 2016

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Expand support for development of immunotherapy trials (input from 2 NCI workshops):

- ✓ "Administrative supplements (for CCSG, P50, and U01/U10 grantees) to support biomarker development and correlative studies associated with clinical trials of immunotherapy"—issued April 15, 2016; 23 responses
- ✓ "Administrative supplements (for CCSG, P50, or P01 grantees) to support studies of how the microenvironment of pancreatic ductal adenocarcinoma affects immunotherapy"—issued April 26, 2016; 36 responses
- ✓ "Administrative supplements for P30 CCSGs to support improvement and optimization of T-cell therapies and cGMP manufacturing processes for production of autologous T-cell therapy products targeting solid tumor"—issued May 9, 2016; 15 responses

Precision Medicine for Oncology: Projects for 2016

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Improve pre-clinical models for evaluating targeted therapeutics and immunotherapy (input from NCI workshop)

- ✓ "Adminstrative supplements (for CCSGs) to support research in canine immunotherapy via collaboration of NCI-designated Cancer Centers and Veterinary Medical Colleges"—issued April 12, 2016; 17 responses
- ✓ "Administrative supplements (for CCSGs, SPOREs, NCTN, and UM1 grantees) to support collaborative research efforts to enhance preclinical drug development and preclinical clinical trials utilizing patient derived xenograft (PDX) models"—issued May 2, 2016; 65 responses

Precision Medicine for Oncology: Projects for 2016

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Employ clinical materials from drug resistant patients for molecular analysis, leading to rational studies of targeted combinations

- ✓ "Administrative supplements to CCSGs, SPORES, U10 Cooperative Agreements, and UM1 funded sites in the ETCTN to study mechanisms of cancer sensitivity and resistance to therapy utilizing samples and information from human clinical trials—issued May 31, 2016; 38 responses

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FY '17 RFAs

1. Cancer Immunotherapy Monitoring and Analysis Centers and Cancer Immunological Data Commons – **M. Thurin, H. Chen, N., M. Song,** H. Streicher, E. Sharon, J. Zwiebel, B. Conley, L. McShane, J Abrams

2. Anti-cancer Drug Development using PDX models – **J. Moscow, Y. Evrard,** M Hollingshead, J Zwiebel, K. Witherspoon, J Abrams

3. Mechanisms of Drug Resistance to targeted anti-cancer therapies – **A. Doyle, N. Takebe, B. Teicher**, L. Harris, S Hughes, D Gallahan, J Abrams

4. Canine Immunotherapy Trials and Correlative Studies - **T. Hecht, A. Leblanc**, C. Mazcko

5. Consortium for pancreatic ductal adenocarcinoma translational studies on the tumor microenvironment - **P. Ujhazy, T. Hecht**

Administrative Supplements to Support Biomarker Studies Associated with NCI-Supported Clinical Trials of Immunotherapy

Helen Chen, M.D., CTEP

Magdalena Thurin, Ph.D. CDP

NCI DCTD

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Administrative Supplement for Biomarker Studies Associated with CTEP NETWORK Trials With Immunotherapy

- **Goal of the Supplement**
  - Address *the immediate need of support* for biomarker studies in existing clinical trials for immunotherapy
  - Provide insight for *future* development of a systematic strategy to support immune biomarker studies across NCI trials

- **Specific aims:**
  - *Aim 1:* Perform biomarker assays and analysis in DCTD-sponsored immunotherapy trials, using established, fit-for-purpose methodology
  - *Aim 2:* Demonstrate capacity to integrate and analyze multi-dimensional data within and across trials, using existing or adapted informatics tools.

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Immune Biomarker Supplements

- One-time funding over one year, with one-year no-cost extension
- Eligible parent grants: P30, P50, UM1, U10
- **Eligible clinical trials** for which biomarker projects are proposed:
  - DCTD Network trials (ETCTN, NCTN, CITN, COG, ABTC, PBTC)
  - "Shovel Ready" (trials completed; ongoing; or activation by 10/30/2016)
- 8-10 awards at $750,000 each.
- Applications reviewed
  - Supplement announcement: 4/15/2016; Due date: 6/27/2016
  - 22 applications received;
  - Announcement of award: 9/30/2016

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Review and Selection

Immune Biomarker Supplements

- 21 applications were felt to be responsive
- 13 were awarded, 8 with reduced funding for part of the proposed work

- The awards will support biomarker studies in a variety of clinical trials
  - 2 phase III trials …*Metastatic or adjuvant settings*
  - 9 Phase II trials (randomized or single arm) … *Rare or common tumors (sarcoma, merkel cell, anal cancer, MF …)*
  - 6 Phase I or pilot trials

  Immunotherapy agents involved:
  - Check point inhibitors, vaccines, cytokines, immune adjuvants
  - Novel combinations (with immunotherapy agents or targeted and chemotherapy)

- Scientific objectives to be pursued in the projects
  - Search or validate predictive markers
  - Examine pharmacodynamic effects on the immune system and tumor cells
  - Understand mechanisms of resistance and provide guidance for combination

Biomarker Studies Associated with NCI-supported Clinical Trials of Immunotherapy

Project PI(s)	Parent Grant PI	Institution
Michael B. Atkins, Geoffrey T. Gibney	Louis M. Weiner	Georgetown University
Lisa H. Butterfield	Nancy E. Davidson	University of Pittsburgh
Martin (Mac) Cheever	Gary D. Gilliland	Fred Hutchinson Cancer Research Center
Sandra P. D'Angelo	Monica M. Bertagnolli	Brigham and Women's Hospital, Alliance for Clinical Trials in Oncology
Thomas Gajewski	Michelle M. Le Beau	University of Chicago
David Gerber	Melanie H. Cobb	University of Texas, Southwestern Medical Center
F. Stephen Hodi	Edward J. Benz	Dana-Farber Cancer Institute
Michael Lim	Stuart A. Grossman	Adult Brain Tumor Consortium
Patricia M. LoRusso	Peter G. Schulam	Yale University
Emanuel Maverakis, Joseph Tuscano	Ralph W. de Vere White	University of California, Davis
Kunle Odunsi	Kunle Odunsi	Roswell Park Cancer Institute
Ravi Salgia	Steven T. Rosen	Beckman Research Institute/City of Hope
Ignacio I. Wistuba	Ronald A. DePinho	University of Texas, MD Anderson Cancer Center

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Planned follow-up

- Kick-off calls with all awardees October, 2016
- Additional calls with individual sites for more details of the research or modified objectives
- Quarterly calls or updates on progress and challenge
- Face-to-face meeting at the end of the fiscal year
  - Presentations of data; Sharing of experience and expertise
  - Identifying opportunities of collaboration, especially for cross trial data analysis

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DCTD Concept for the Cancer Immunotherapy Monitoring Network

Cancer Immune Monitoring and Analysis Centers (CIMACs) (U24)
&
Cancer Immunologic Data Commons (CIDC) (U24)

Magdalena Thurin, Ph.D., CDP
Helen Chen, M.D., CTEP

Min Song, Ph.D., Howard Streicher, M.D., Elad Sharon, M.D., M.P.H.,
James Zwiebel, M.D., Barbara Conley, M.D., Lisa McShane, Ph.D, and
Jeff Abrams, M.D.

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Cancer Immunotherapy Monitoring Network

Objectives:

- To support high-quality correlative studies in NCI-sponsored early phase (Phase I and Phase II) clinical trials to improve the treatment outcome
- To use the early phase studies as a proving ground for clinically-informative biomarkers which can be validated in late phase clinical trials

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A variety of assays and platforms are required to address the biomarker questions

- However
  - The most potentially informative assays are not always available to all trials
  - Often, in NCI Network trials, there is no designated funding for biomarker studies (need to apply for grant funding which is difficult to coordinate with clinical timelines)
  - Different labs often have different assays, platforms, SOPs, or scoring methods
  - No existing system for data deposit and integrated analysis across trials

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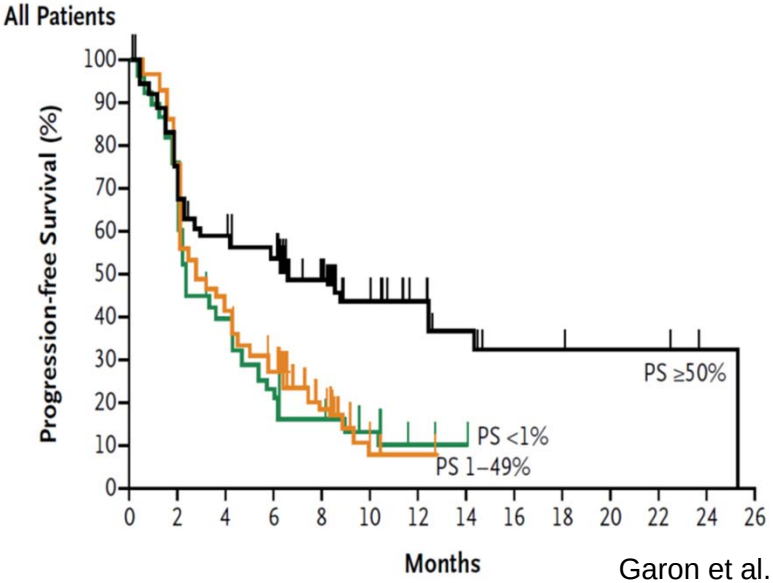
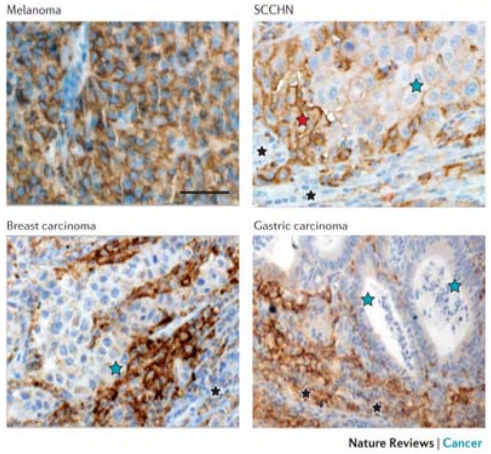
Predictive relevance of PD-L1: Expression level of the PD-L1 is associated with the higher likelihood of clinical benefit in NSCLC patients treated with pembrolizumab



Garon et al.
NEJM 2015



Topalian, 2016

Keynote - 001

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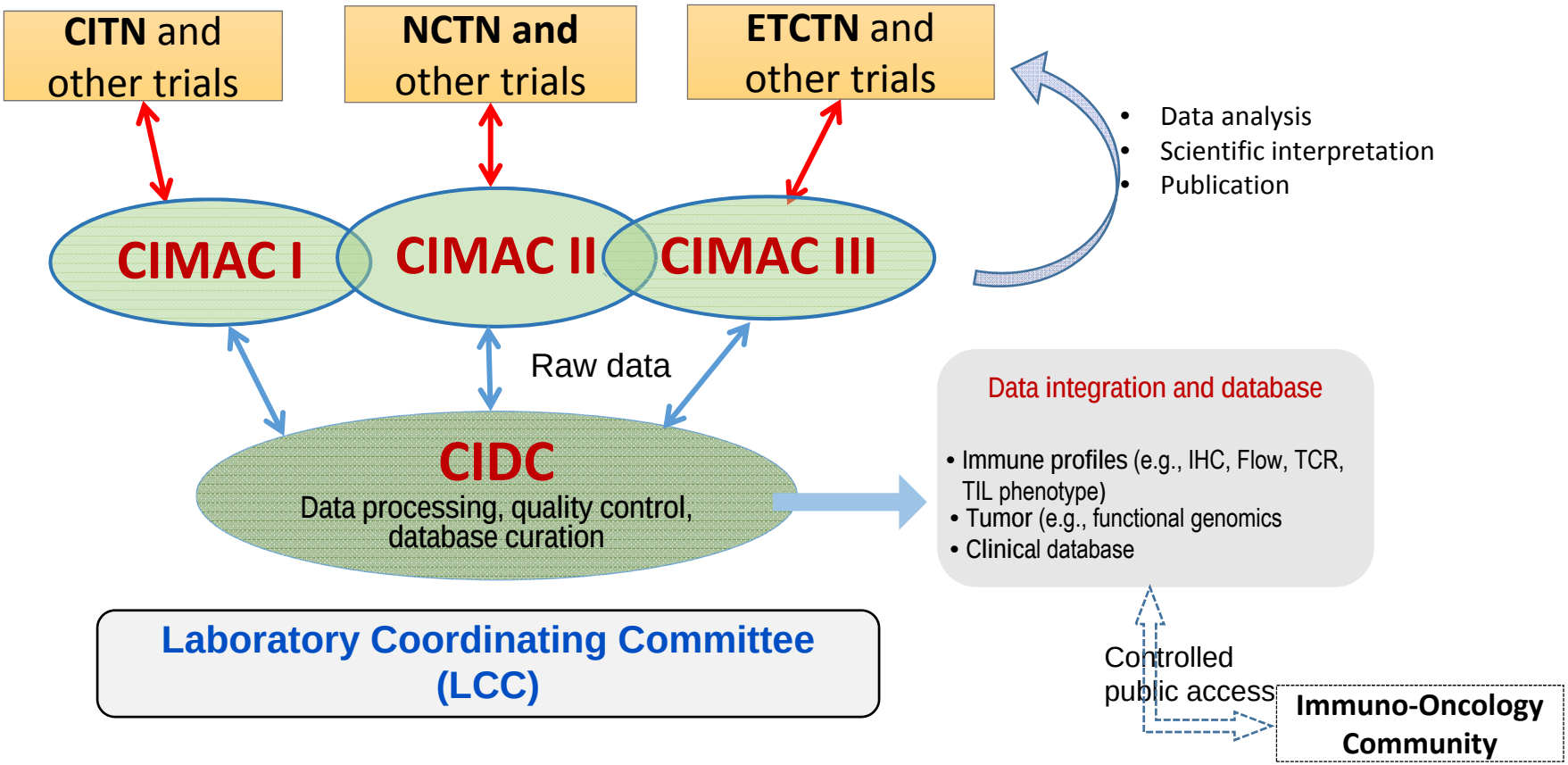
Assays standardized with different methods make it difficult to compare results across studies (and can hinder progress)

- Different PD-L1 specific antibody clones produce different results
- Different staining protocols and platforms
- Different assessment methods (Tumor cells, TILs, or both)
- Different scoring methods (% staining, H-score)
- Cannot compare treatments or easily build upon the results

	5JHU	Merck	BMS	Roche	AZ
mAb	5H1	22-C3 (DAKO pharmDx)	28-8 (DAKO pharmDx)	SP142 (Ventana)	SP263 (Ventana)
Platform	Manual	Link 48 autostainer	Link 48 autostainer	BenchMark ULTRA	BenchMark ULTRA
Scoring criteria	Tumor cells	Tumor cells	Tumor cells	Tumor cells and/or tumor infiltrating immune cells	Tumor cells
Positive cutoff	≥5%	≥50%	≥1%	≥5%	≥25%

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



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Examples of well established assays for monitoring responses to immunotherapy

- Tumor genomics: Whole Exome Sequencing (WES), Targeted gene sequencing, RNA-seq (e.g., mutational load, neoantigen signature)
- Tumor subtyping: nCounter Analysis System for Gene Expression profiling/pathway activation etc., microsatellite instability (MSI),
- T-cell number and function: T-cell receptor (TCR) V region usage, Peptide-MHC Tetramers, Intracellular Cytokines by Multiparameter FACS, Cytokine mRNA Levels by Real-Time Quantitative RT-PCR, nCounter Immune Gene Expression Profiling Panel
- Tumor histopathology: Multicolor IHC, multiplexed immunofluorescence (IF), (e.g., CD3/CD8 Immunoscore, other T cells, MΦ, DC, MDSC, NK, tumor antigens, PD-L1)
- Blood/Serum: Fluorescence activated Cell Sorting (FACS), Mass Cytometry (CyTOF) (e.g., Immunophenotyping, Intracellular cytokines), TCR sequencing for lymphocyte clonality, ELISpot (e.g., T cell functional assay for intracellular IFNγ/granzyme B) , cell free DNA (cfDNA), Multiplex Enzyme-Linked Immunosorbent Assay (ELISA) (e.g., Cytokine panels)

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Network's Annual Budget

CIMACs U24

• Laboratory Centers*	$3,200K
• Scientific Staff	$950K
• Network meetings/travel	$50K
• Direct Costs	$4,200K
• Total Costs	$6,500K

*Expected: 360 patients/year
(at $8,000/patient)

CIDC U24

• Scientific Leadership	$350K
• Bioinformatics Analysis	$150K
• Computers/Data Servers	$120K
• Database Systems Access	$20K
• Network meeting/travel	$10K
• Direct Costs	$650K
• Total Costs	$1,000K

Administrative Supplements to Support Collaborative Research Efforts to Enhance Preclinical Drug Development and Preclinical Clinical Trials Utilizing Patient Derived Xenograft (PDX) Models

Jeffrey A. Moscow, M.D.

Yvonne A. Evrard, Ph.D.

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November 1, 2016

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Administrative supplement for drug development using PDX models

- Aim 1: Develop and characterize new non-hematopoietic PDX models that can be used to test cancer therapies, including drug combinations and NCI-IND agents.
  - Required a minimum of 15 new PDX models
  - Models to be donated to PDMR-FNLCR for characterization, quality assurance
- Aim 2: Demonstration of the capability to test existing PDX models against NCI-IND agents and agent combinations for tumor response; to integrate and analyze PDX molecular characteristics against response to therapeutic regimens; and to collaborate with NCI-funded investigators in the study of mechanisms of drug sensitivity and resistance.
  - Required a minimum study design of 30 existing PDX models in 5 trials with 3 mice per group that tests multiple drug combinations that include NCI-IND agents

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Administrative supplement for drug development using PDX models

- Eligible grants: P30, P50, UM1, U10 (must be US awardee)
- Maximum award $750,000 total costs
- Estimated number of awards: 8
- Total cost of supplement program: $6M

- Supplement application review
  - 65 applications received for review

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Portrait of PDX silos from PDX supplement applications

- 65 applications received provided a portrait of PDX activities in the US
  - 4800 PDX models reported total
  - Median was 42 PDX models per applicant – most PDX collections are not large enough to reflect human tumor diversity
  - Multiple non-collaborative PDX collections: 6 sites focused on ovarian PDX, 8 on CNS PDX, 9 on NSCLC PDX, 5 on breast PDX, etc.

Collaborative Research Efforts to Enhance Preclinical Drug Development and Preclinical Clinical Trials Utilizing Patient Derived Xenograft (PDX) Models

Project PI(s)	Parent Grant PI	Institution
Carol Bult	Edison Tak-Bun Liu	Jackson Laboratory
Eva Corey	Peter S. Nelson	Fred Hutchinson Cancer Research Center
Bingliang Fang	John D. Minna	University of Texas, Southwestern Medical Center
Barbara Foster	Candace S. Johnson	Roswell Park Cancer Institute
Michael Lewis	C. Kent Osborne	Baylor College of Medicine
Funda Meric-Bernstam	Funda Meric-Bernstam	MD Anderson Cancer Center
Ann Richmond	Jennifer A. Pietenpol	Vanderbilt-Ingram Cancer Center
Jann Sarkaria	Robert Diasio	Mayo Clinic Cancer Center
Alana Welm	Mary C. Beckerle	University of Utah
Agnieszka Witkiewicz	Andrew S. Kraft	University of Arizona

Patient Derived Xenograft (PDX) Development and Trial Centers (PDTCs) Network (PDTCRNet) (U54) & PDX Data Commons and Coordinating Center (PDC) (U24) for the PDTCRNet

Jeffrey A. Moscow, M.D.

Investigational Drug Branch, CTEP

NIH NATIONAL CANCER INSTITUTE

November 1, 2016

Use PDX models on a large scale to address the challenges of cancer precision medicine

- As more targeted agents become available, and as more refined tumor subtypes are defined, the challenge becomes prioritizing the optimal combination of agents to test in increasingly narrow tumor subsets in early phase clinical trials.

- Patient-derived models, such as PDXs and PDOs (organoids), that reflect human tumor biology more closely than established cell lines due to their low passage number**,** offer the potential of more predictive models than traditional cancer cell lines

Develop patient-derived models on a scale and with rigor that can be translated into clinical trial development

- However, the application of PDX's in Precision Medicine thus far has been limited by:
  - **Silo character** of academic PDX programs that limit development of SOPs and prevents cross-validation of results
  - **Lack of standards** for determining quality of PDX models and PDX response to therapeutic intervention
  - No mechanisms to assess **reproducibility** of results between centers
  - **Limited data sharing** between PDX centers

Goals of PDX collaborative network (PDTCRNet)

- **GOAL 1: Apply PDX models for the *specific purpose* of more *efficient and precise* development of NCI-IND agents in the ETCTN**
  - **ETCTN:** UM1-funded network of clinical trial sites devoted to the early clinical development of the 60+ NCI-IND agents
  - By integrating PDTCRNet with ETCTN, the ETCTN will be able to **clinically validate** PDTCRNet research results

- **GOAL 2: Use PDTCRNet resources to test original concepts of extramural investigators**
  - Extramural investigators will have access to the PDTCRNet for rigorous PDX evaluation of therapeutic concepts through competitive administrative supplement awards
  - Studies also could include agents not under NCI IND, studies of drug resistance and sensitivity, biomarkers for patient selection, and other PDX-related research questions

Potential outcomes of RFA

- **Goal 1: Applying PDX science in the proposed network for the ETCTN**
  - ETCTN studies could compare PDX-assigned therapy to SoC therapy based on a database of tumor molecular signatures and PDX response to drug combinations
  - In 3 years, at least **25% of phase 1 studies in ETCTN should originate from PDX program**
  - Development of PDX models obtained from minority/underserved populations, **with a goal of 20% of PDX's from minority/underserved populations,** which will allow ETCTN studies to focus on these populations

- **Goal 2: Facilitate extramural research by providing access to PDX network resources**
  - PDX data that could provide pre-clinical rationale for novel clinical trials where assignment of therapy is based in part on molecular characterization
  - Development of novel biomarkers based on PDX response that are incorporated into clinical trials

Coordination of this RFA with the NCI Patient-Derived Models Repository (PDMR) at FNLCR

- PDMR is a national repository of PDMs that serves as a resource for academic discovery efforts and public-private partnerships for drug discovery
  - Includes clinically-annotated PDXs and patient-derived tumor cell and fibroblast cultures in a publicly available database.
  - Will provide home for >1000 early-passage PDX models developed from tissues and blood from NCI-CC's, NCORP, ETCTN; and donated PDX models

- PDMR infrastructure and expertise
  - PDMR has received > 1200 fresh tumor tissue pieces since 2013 for PDX development in NSG mice, and for in vitro 2D/organoid culture
  - >350 models have grown PDXs, with a take-rate of ~50% across all histologies, including colon, pancreatic, H&N, lung and melanoma
  - Additional 415 implanted models are under assessment for PDX growth

NCI PDM Repository Facilities at FNLCR

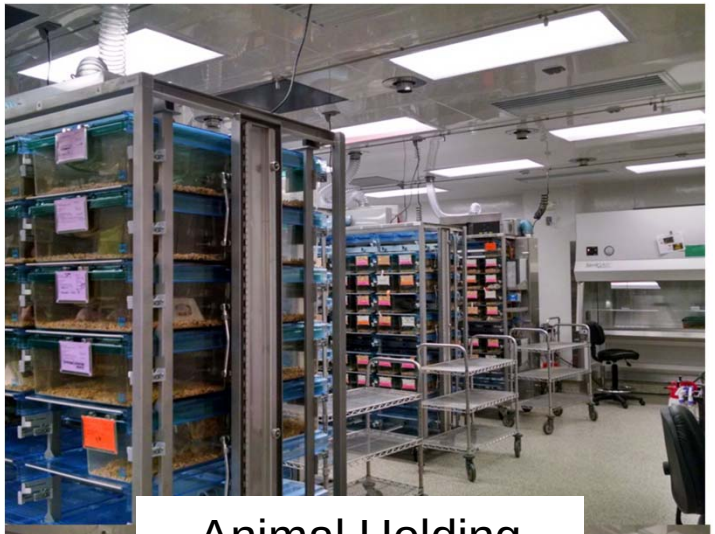
Procedure Rooms

9,500 sq. ft. in 9 buildings

4560 cages [max: 5 mice/ cage = 22,800 mice]

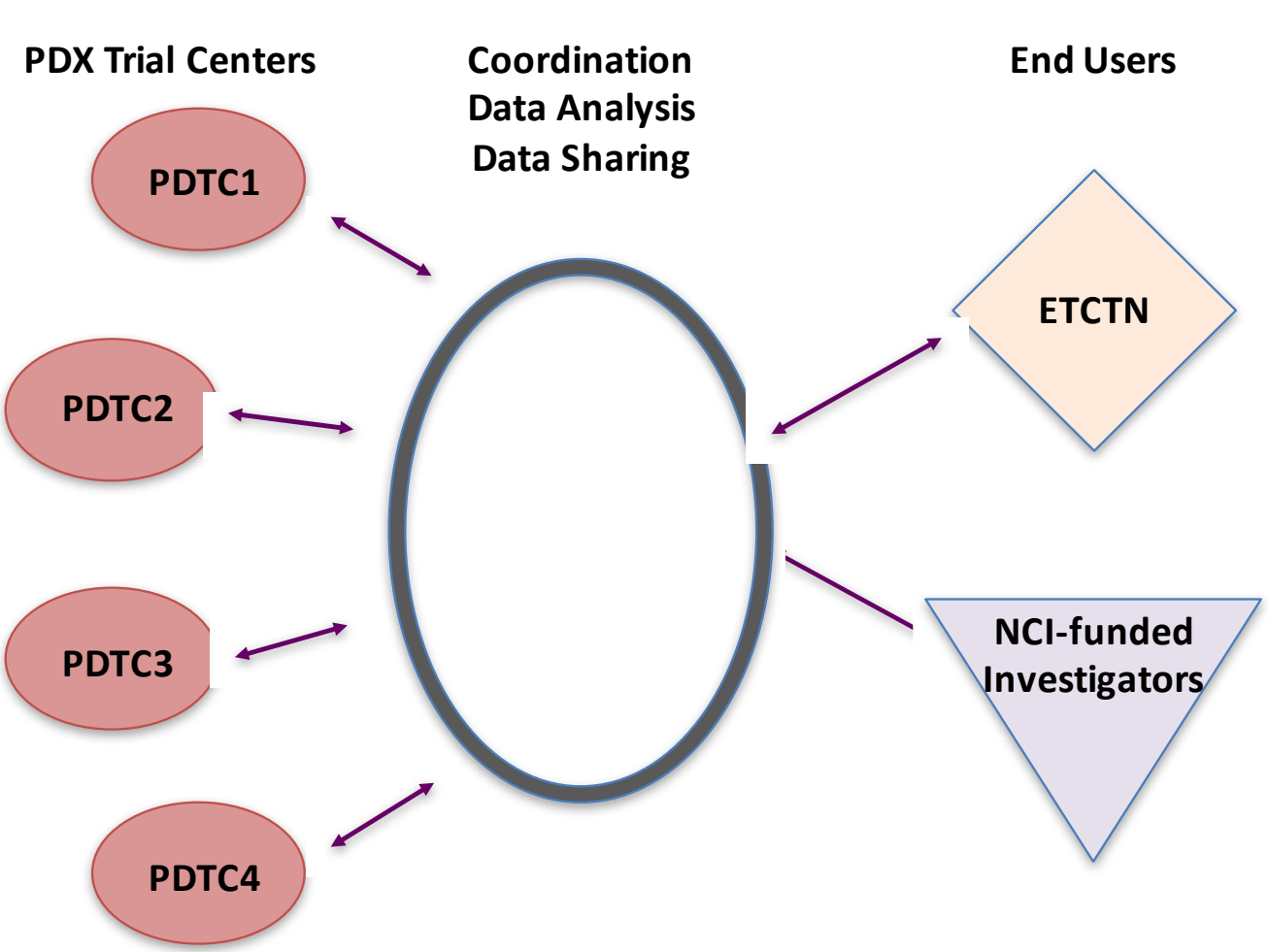
~12,000 mice plus additional 6,000 mice for other projects

Animal Production facility: 1,300 cages for NSG and nude mice; continuous breeding



Animal Holding

Structure of proposed PDTCRNet created by the RFAs



PDX Development and Trial Centers (PDTC)

PDX Data Commons and Coordinating Center (PDCCC)

NCI PDM Repository (PDMR) at FNLCR

CTEP's Experimental Therapeutics Clinical Trials Network (ETCTN)

PDTCRNet Roles and Review Criteria: PDX Development and Trial Centers (PDTCs) (U54)

- Up to 4 awards anticipated
- Review criteria will include:
  - Strength of research plan
  - PDX experience, size of existing PDX collections, PDX drug response experience
  - Commitment to sharing – models and data
  - Mix of PDX model diagnoses and demographics in consortium to maximize impact on ETCTN studies
  - Development of new models or techniques that will expand PDX technology into new areas, such as PDM methods to prescreen drug combinations

PDTCRNet Roles:
PDTCRNet Data Commons and Coordinating Center (PDCCC) (U24)

- Bioinformatics Core
  - Lead development and implementation of data collection standards and data integration across different PDTC's
  - Centralized center for analysis of PDX response to agents across PDTCs
  - Establish a PDCCC website and database structure where each PDTC can deposit molecular profiling data for cross-trial projects across different PDTCs
  - Share PDTCRNet data with NCI GDC

- Administrative Core
  - Logistical and administrative assistance in arranging network-wide meetings, workshops and PDX Network Coordinating Committee (PNCC)
  - Coordinate with NCI evaluation of administrative supplement applications from extramural investigators for access to PDTCRNet resources; establish collaborations with selected investigators

- One award anticipated

PDTCRNet Roles:
Administrative supplements for non-U54 investigators

- Non-U54 investigators may apply to use PDTCRNet resources through an administrative supplemental award application process
- Applications will be evaluated and prioritized by an external Special Emphasis Panel
- Facilitate investigator-initiated clinical trials by providing access to the PDTCRNet for pre-clinical evaluation of the proposed therapy
- Proposals may also include development of novel agents, development of biomarkers, investigation of mechanisms of resistance, comparing other preclinical model predictive capabilities with PDXs, and other PDX-related research questions
- $1M will be set aside annually to support administrative supplement research projects

Budget request - Total of $7M per year for PDTCRNet

- **RFA for U54**

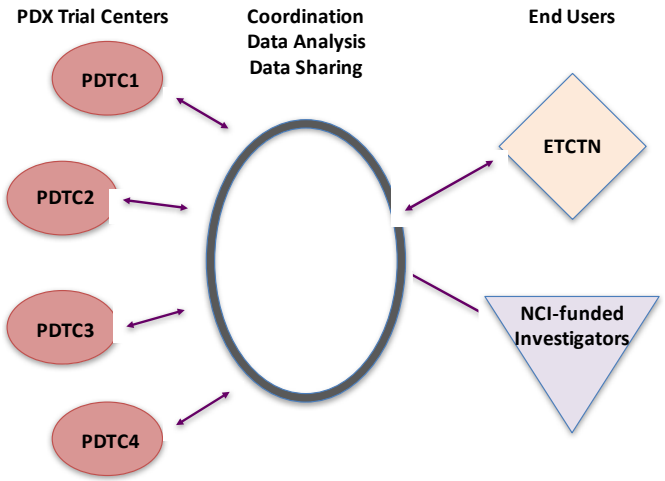
  Up to 4 PDX Development and Trials Centers (PDTCs) supported with 5-year U54 cooperative agreements @ $1.25 M total costs per year = $5M

- **RFA for U24**

  One PDCCC with bioinformatics and administrative cores supported for 5-year U24 cooperative agreement @ $1M total costs per year

- **Administrative supplements for collaboration with PDTCRNet**

  7 supplements @ $150k total costs per supplement = $1.05M



Administrative Supplement to Study Mechanisms of Cancer Sensitivity and Resistance to Therapy Utilizing Samples and Information from Human Clinical Trials

Austin Doyle, Naoko Takebe, Beverly Teicher

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Topics for the supplement responses

Studies may address either or both of the following Topics:

Topic 1: To investigate mechanisms of intrinsic and acquired drug resistance in tumor biopsies, blood samples, or other biologic material from patients on trials with targeted anticancer agents.

Topic 2: To understand the genetic and cellular basis for increased sensitivity of cancers to treatment with agents targeting the DNA damage response, apoptosis and epigenetic pathways, and to corroborate these findings with the analysis of tumor specimens and clinical outcomes from cancer trials.

Eligibility and funding for drug resistance supplements

- Up to $750,000 was awarded for total (direct + indirect) costs for each supplement.
- Supplemental funding was available for active grants using the following grant mechanisms:
  - P30 Cancer Center Support Grants (CCSG)
  - P50 Specialized Program of Research Excellence (SPORE) Grants
  - U10 Cooperative Clinical Research – Cooperative Agreements for the 5 US NCTN groups (both Operations and Statistical Grants)
  - Adult Brain Tumor Consortium (ABTC)
  - Pediatric Brain Tumor Consortium (PBTC)
  - UM1 Research Project with Complex Structure Cooperative Agreement – Cooperative Agreements for the 11 US sites from NCI Experimental Therapeutics Clinical Trials Network (ETCTN).

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Eligible clinical trials

- Specimen collection completed by Sept 2016.
- Clinical trials used a targeted anti-cancer agent.
- Clinical outcome data exist for clinical trial participants from whom specimens are derived.
- Sequential samples preferred. Archival acceptable.
- Agents have Level of Evidence 1 or 2 in setting of trial.
  - LOE1: FDA approved agents
  - LOE2: Agent met a clinical endpoint with evidence of target inhibition.

Note: Supplement scope does not include studies of cytotoxic agents alone, radiosensitizers, or immunotherapy.

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Outcomes of analysis

- An expected outcome is demonstration of association of results of the specimen analysis with a clinical endpoint (e.g., survival, response, disease presence or absence).
- The objectives of the analysis may include readout of drug mechanism, or identification or cross-validation of predictors of clinical outcomes.

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Awardees and associated clinical trials

Awardee, Project PI(s)	Agents & Diseases	Associated clinical trials
Alliance Himisha Beltran, MD Susan Halabi, PhD Alexander Wyatt, PhD Martin Gleave, MD	ADT + docetaxel in prostate cancer	CALGB-90203: Immediate prostatectomy versus neoadjuvant docetaxel and androgen deprivation therapy for men with high risk, localized prostate cancer
Mayo Clinic Thomas E. Witzig, MD	Lenalidomide/RCHOP (R2CHOP) in lymphoma (DLBCL)	MC078E: Lenalidomide, Rituximab, and Combination Chemotherapy in Treating Patients With Newly Diagnosed Stage II, Stage III, or Stage IV Diffuse Large Cell or Follicular B-Cell Lymphoma
MIT Forest M. White, PhD Jann N. Sakaria, MD Nathalie Agar, PhD	AZD1775 in glioblastoma	ABTC1202: A Phase I Study of MK-1775 [now AZD1775] with Radiation and Temozolomide in Patients with Newly Diagnosed Glioblastoma and Evaluation of Intratumoral Drug Distribution in Patients with Recurrent Glioblastoma
MSKCC Ross L. Levine, MD, PhD	IDH1/2 inhibitors in AML mTORC1 inhibitor, everolimus, in breast cancer BRAF inhibitors in colorectal cancer	AG221/AG120 phase I/II clinical trials in AML BOLERO-2: Everolimus in Combination With Exemestane in the Treatment of Postmenopausal Women With Estrogen Receptor Positive Locally Advanced or Metastatic Breast Cancer Who Are Refractory to Letrozole or Anastrozole Two clinical trials in triplet therapy with RAF, MEK, and EGFR inhibitors: (1) RAF inhibitor dabrafenib, MEK inhibitor trametinib, plus EGFR antibody panitumumab and (2) RAF inhibitor encorafenib, MEK inhibitor binimetinib, and EGFR antibody cetuximab in colorectal cancer
NRG Oncology Katherine Pogue-Geile, PhD	anti-HER2 and anti-estrogen therapies in breast cancer	NSABP B-52: A Randomized Phase III Trial Evaluating Pathologic Complete Response Rates in Patients with Hormone Receptor-Positive, HER2-Positive, Large Operable and Locally Advanced Breast Cancer Treated with Neoadjuvant Therapy of Docetaxel, Carboplatin, Trastuzumab, and Pertuzumab (TCHP) With or Without Estrogen Deprivation

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Awardees and associated clinical trials, continued

Awardee, Project PI(s)	Agents & Diseases	Associated clinical trials
Oregon Health and Science University Brian Druker, MD	FLT3 kinase inhibitors (crenolanib, quizartinib, sorafenib) in FLT3-mutated AML JAK inhibitor (ruxolitinib) in Philadelphia-negative neutrophilic Leukemia (CNL and aCML)	AROG phase 2 trial of crenolinib in FLT3-mutated AML 7195 phase 2 trial of sorafenib in FLT3-mutated AML AC220 phase 2 trial of quizartinib in FLT3-mutated AML Incyte phase 2 trial of ruxolitinib in CNL/aCML
UCSF Felix Feng, MD, PhD	PARP1 inihibition and androgen-directed therapy in prostate cancer (veliparib, abiraterone)	NCI 9012: A Randomized Gene Fusion Stratified Phase 2 Trial Of Abiraterone With Or Without ABT-888 For Patients With Metastatic Castration-Resistant Prostate Cancer
Vanderbilt School of Medicine Carlos L. Arteaga, MD	FGFR inihibitor, anti-estrogen, CDK4/6 inhibitors in breast cancer	NCT00651976: Letrozole in Treating Postmenopausal Women With Stage I, II or III Breast Cancer That Can Be Removed by Surgery Preoperative Palbociclib (POP) randomized trial in early breast cancer MONARCH 2 trial: A Study of Abemaciclib (LY2835219) Combined With Fulvestrant in Women With Hormone Receptor Positive HER2 Negative Breast Cancer
Yale (Lung cancer SPORE) Katerina Politi, PhD Don Nguyen, PhD Narendra Wajapeyee, PhD	TKIs in EGFR mutant and ALK-rearranged lung cancer	The Yale Lung Rebiopsy Program
Yale Cancer Center Lajos Pusztai, MD, DPhil Christos Hatzis, PhD	Anti-HER2 plus paclitaxel in breast cancer	Neo ALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) Study: A Randomised, Multicenter Open-label Phase III Study of Neoadjuvant Lapatinib, Trastuzumab and Their Combination Plus Paclitaxel in Women With HER2/ErbB2 Positive Primary Breast Cancer

Drug Resistance and Sensitivity RFA Concept Presentation to Board of Scientific Advisors

Austin Doyle, M.D

IDB/CTEP/DCTD

For the NCI Drug Resistance Working Group: Naoko Takebe, William Timmer, Beverly Teicher, Lyndsay Harris, Shannon Hughes, and Daniel Gallahan

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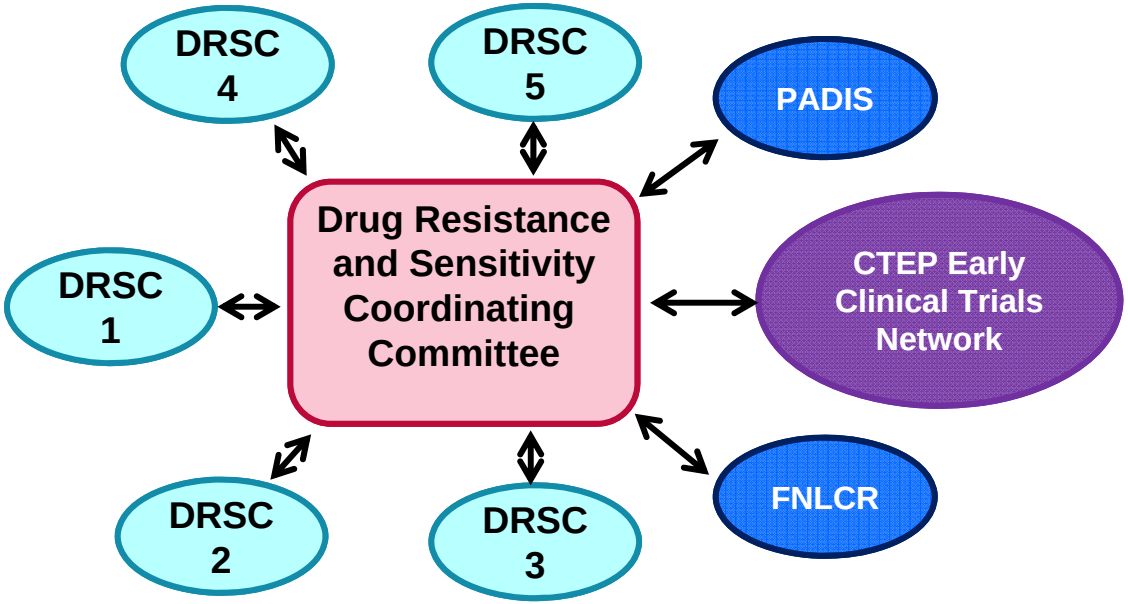
October 31, 2016

Intent of RFA for Studies of Mechanisms of Cancer Resistance or Sensitivity to Therapy

- Create a specialized Drug Resistance/Sensitivity Network (DRSN) formed by up to 5 sites. Each U54 project team will be asked to focus on a unique broad area of drug resistance/sensitivity research and to provide NCI with expertise in new drug development.



- Each U54 response will include several linked projects in that area of drug resistance/sensitivity.

Focus of a Drug Resistance/Sensitivity Network (DRSN)

- The DRSN will focus on new models and diagnostic techniques, and use human tumor samples whenever possible
- Applicants should have components of their proposed research involve druggable targets, and use an iterative approach between bench and bedside
- While studies involving NCI IND agents* (or other agents that target the same pathway as NCI IND agents) are preferred, applications that propose strategies for understanding resistance/sensitivity to other agents are permitted

**Note: The NCI-IND agents (>60) include a wide variety of small molecule and antibody inhibitors impacting cancer growth and survival, and modulating DNA repair, epigenetic regulation of gene expression, control of immune checkpoints, tumor angiogenesis and hypoxia (https://ctep.cancer.gov)*

Review Considerations for Drug Resistance and Sensitivity Applicants

- Demonstrate preliminary data with potential for making clinical advances to overcome cancer resistance.
- Expertise in patient-derived models for in vivo studies of drug resistance/sensitivity.
- Ability of laboratory to confirm presence of putative resistance mechanisms in cancer patient biospecimens.
- Access to patient specimens appropriate for the mechanism or drug target being proposed.
- Ability to conduct pharmacodynamic and pharmacokinetic studies in animal models to demonstrate inhibition of cancer targets *in vivo*.
- Multidisciplinary expertise of team for proposed studies in cancer drug resistance or sensitivity to therapy.

Development of a Drug Resistance and Sensitivity Coordinating Committee (DRSCC)

- The DRSCC will facilitate the network activities to encourage interaction and utilization of resources.
- The DRSCC will be composed of
  - The Principal Investigators of each U54
  - NCI members from DCTD and DCB program staff
  - Ad hoc participants from other NCI Divisions and extramural experts.
- DRSCC will promote exchange of scientific findings and facilitate potential collaborations between the investigator teams and the NCI.
- Formal meetings of the DRSCC will be held twice each year
  - To engage the greater community, one DRSCC meeting each year will invite non-U54 holders to have the opportunity to present new proposals in cancer drug resistance or sensitivity.

Available NCI Resources in Support of Drug Resistance and Sensitivity Center Projects

- Access to patient-derived specimens (tumor biopsies or blood samples) from NCI-sponsored trial networks.
- Collaboration with Frederick National Laboratory for Cancer Research (FNLCR) staff for pre-clinical combination studies of targeted anticancer agents.
- Access to the Patient-Derived Models Repository (PDMR) - national repository of PDMs.
- Potential collaboration with the Pharmacodynamic Assay Development & Implementation Section (PADIS) Laboratory - validated PD assays for critical tumor pathways.
- Facilitated entry of genomic and clinical data into the Genomic Data Commons repository, to utilize databases and analytic tools within the GDC.

Requested Funding

Number of awards:	five U54 awards
Funding:	$1.25 M / year total costs per award
Project period:	five years; each award
Estimated total cost:	$31.25 M

- From review of the recent drug resistance supplement requests, a likely breakdown of yearly costs per award would be expected:
  - Personnel $280K
  - Animals and supplies $130K
  - Sequencing and core facilities $415K
  - Indirect costs $425K

Additional supplement awards over course of U54 awards

- As part of DCTD's precision medicine initiative, the division will fund additional supplement awards for proposals over years 1 through 5 of the award period.
- These supplement awards will be given to non-U54 awardees, to support new breaking discoveries in drug resistance/sensitivity.
- The awards would be given out after evaluation and prioritization of proposals by a Special Emphasis Panel, created by NCI for this purpose.
- Recipients could receive funding for either 1 or 2 years by this mechanism, with the second year contingent on a successful review of progress by the SEP.
- Two awards/year for 5 years at up to $780,000 per award per supplement would come to a total of $7.8 million dollars for supplements.
- The $7.8 million for supplements, plus the $31.25 million for the five awarded U54 grants totals approximately $39 million.
- These supplements will allow additional investigators studying drug resistance/sensitivity to engage with NCI's drug development program.

Optimization of T-cell therapies and cGMP manufacturing processes for production of autologous T-cell therapy products targeting solid cancers

Anthony Welch, Stephen Creekmore, Howard Streicher, Elad Sharon, Helen Chen, Toby Hecht, Jeff Abrams

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Optimization of T-cell therapies and cGMP manufacturing processes for production of autologous T-cell therapy products targeting solid cancers

Aim 1:

- Optimization or improvement of TIL selection, expansion and antigen characterization
- Optimization of neo-epitope discovery, TCR selection and transduction of T-cells
- CAR engineering of autologous T-cells
- TCR engineering of autologous T-cells

Aim 2:

- Demonstrate that the TIL, CAR or TCR-engineered T-cell product selected in Aim 1 can be prepared according to cGMP specifications such that it could be utilized in a multi-center trial. Specific requirements that are necessary to support this aim include:
- Improved cGMP manufacturing capacity for autologous T-cell therapies.
- Validation of patient-specific raw material and T-cell product shipping and receiving.
- Demonstration of manufacturing consistency by evaluation of lot-to-lot variation

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Optimization of T-cell therapies and cGMP manufacturing processes for production of autologous T-cell therapy products targeting solid cancers

- **Eligibility Information**
- Supplemental funding will be available for active grants using the following grant mechanism:
- P30 Cancer Center Support Grants (CCSG)

- **Number of Applications:** Only one application per NCI award is allowed. Each application must include a cover letter from the grantee Principal Investigator (PI) or contact PI, with concurrence from the Authorized Organization Official (AOR).

- Up to 3 awards – total cost $1M

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Awardees

Institution & PIs	T-cell product	Solid tumor targeted	Aim 2 cGMP manufacturing improvements	Overall Strengths
MD Anderson C. Bernatchez E. Schpall	TIL	PDAC	Extensive in-process TIL characterization, 4-1BBL, G-Rex closed system, cryopreserve	Targeting PDAC; proposed closed and scalable system for TIL identification and expansion; extensive TIL characterization
Moffitt L. Kelly J. Mule	TIL	PDAC, bladder, Head/Neck, GI sarcoma, cervical	4-1BBL, K562, serum source, G-Rex closed system, cryopreserve	Proposed closed, scalable system; novel improvements in screening and expanding TILs; multiple solid tumors to be evaluated
MSKCC I. Riviere M. Sadelain	CAR targeting PSMA (3^{rd} gen, Pd28z/4-1BBL and EGFRt for safety)	Prostate	TransAct beads, CliniMACS Prodigy closed system vs current WAVE/Xuri platform.	Improved CAR design; extensive manufacturing experience; Prodigy closed system

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- Individual meetings with investigators have occurred or will soon.
- A kickoff meeting of all awardees is planned for late November
- Institutional site visits by NCI staff will be part of this initiative