Re-issue of RFAs for PDXNet: Patient Derived Xenograft (PDX) Development & Trial Centers (PDTCs) (U54) & PDX Data Commons and Coordinating Center for PDXNet (PDCCC) (U24)

Jeffrey A. Moscow, M.D.

Investigational Drug Branch, CTEP, DCTD

Tiffany Wallace, Ph.D.

Center to Reduce Cancer Health Disparities

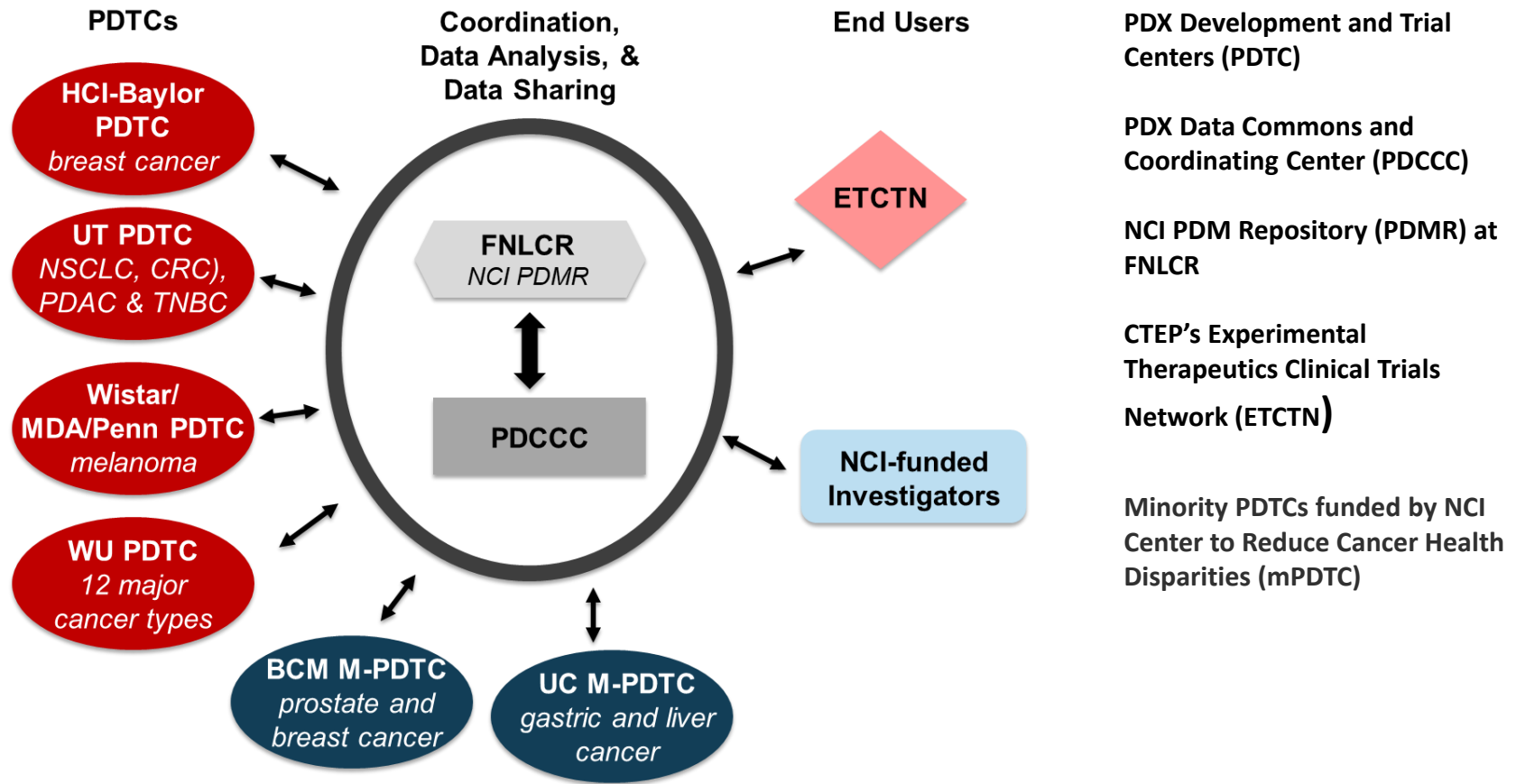**NIH〉NATIONAL CANCER INSTITUTE**

December 13, 2021

Goals of PDXNet

Original DCTD goals in 2017 for PDXNet were to:

- Develop PDX trials that **test original therapeutic strategies** in large scale PDX collections, that could then provide preclinical *in vivo* evidence to support novel early phase clinical trials

- **Address critical scientific issues** related to the use of PDX's as predictive models for clinical benefit through the collaborative network structure of PDXNet

- **Contribute new PDX models** to NCI's Patient Derived Models Repository (PDMR) for distribution to the wider research community

Goals added in addition for CRCHD PDTC's were to:

- **Increase diverse representation and study** of racial/ethnic minority populations in PDXNet and in the PDMR

- **Advance cancer health disparity research**

Structure of PDXNet created by RFAs CA-17-003 (PDTCs), CA-17-004 (PDCCC) and CA-17-032 (mPDTCs)

PDTCs

HCI-Baylor PDTC
breast cancer

UT PDTC
NSCLC, CRC), PDAC & TNBC

Wistar/MDA/Penn PDTC
melanoma

WU PDTC
12 major cancer types

BCM M-PDTC
prostate and breast cancer

UC M-PDTC
gastric and liver cancer

Coordination, Data Analysis, & Data Sharing

FNLCR
NCI PDMR

PDCCC

End Users

ETCTN

NCI-funded Investigators

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)

Minority PDTCs funded by NCI Center to Reduce Cancer Health Disparities (mPDTC)

Collaborative PDXNet accomplishments in first grant cycle (first 4 years)

- Established collaboration with CRCHD to bring in 2 PDTCs focused on disparity research

- Developed a **culture of collaboration** among all grantees with multiple collaborative research projects

  - **Demonstration of multi-center experimental reproducibility** of drug-response studies using PDX models published in Cancer Research

  - **Demonstration of CNV fidelity in successive PDX passages** published in Nature Genetics

  - Demonstration of therapeutic target pathway identification in PDXNet PDX collections published in Nature Communications

  - Ongoing cross-network collaborative study of **drug efficacy evaluation methods in PDX models**, now manuscript in preparation

  - 10 other active intra-network collaborations coordinated by PDCCC

PDXNet accomplishments in first grant cycle (first 4 years)

- **690 unique PDX models** donated to the NCI PDMR

    - Most in the process of expansion and characterization prior to public distribution

- Preclinical evidence developed for **10 CTEP LOI's**

- Website established (**pdxnetwork.org**) for internal network collaboration and public access

    - Development of the PDXNet portal as a platform for data sharing is described in a paper submitted for publication and posted online: https://doi.org/10.1101/2021.10.15.464537

- Collaborative projects necessitated development of workflows to facilitate collaboration; 15 validated workflows publicly shared via PDXNet portal

- In addition, 88 publications from original research projects

External Review of PDXNet

- All 4 external reviewers enthusiastically supported renewal of PDXNet

- Score ranges:
  - Collaborative projects: Median = 2 (1.5 – 3)
  - PDTCs: Median = 2 (1.5 – 4)
  - PDCCC: Median = 1.5 (1 – 2)

- Summary comments:
"There have been **important advances in method harmonization, genomic characterization, and in general developing predictable and well define methods**."

"Overall, the **progress made by the network during the funding period is impressive**, especially considering the impact of the COVID-19 pandemic...."

"...this **initiative deserves continued support**, having the potential to provide an essential resource for preclinical and clinical cancer research."

Discussion focused on

- Tumor Volume Analysis work, supported establishing consensus metrics for drug response

- Support for refocusing supplement program on collaborations with clinician scientists

- IO issues were discussed, but no consensus emerged on incorporating into PDXNet

PDXNet: Request for re-issue for a second grant cycle

Deliverables in the second grant cycle include:

- Development and application of drug response evaluation standards across PDXNet and advocate for adoption across the wider research community

- Provide robust preclinical in vivo data of targeted agent combinations to prioritize at least 20 clinical trials in NCI clinical trials networks (double from first cycle)

- More strategic donations of models to PDMR: Identification of significant gaps in the NCI PDMR PDX repository collection, and orchestrate targeted contributions to fill those gaps

  - Examples: racial/ethnic underserved and clinical relapsed/resistant models

- Create methods and workflows to integrate complex omic and imaging data from multiple sites into a searchable PDX database for model selection, and make these tools available

- Create productive collaborations between PDXNet scientists and early phase clinical trialists

PDX Development and Trial Centers (PDTCs) (U54)

- Research projects (at least 2) in mechanism-based drug combinations in genetically or histologically defined tumor subgroups that explore the relation of the tumor characteristics to tumor drug response

  - Primary goal is preclinical evidence generation to support early phase studies of NCI-IND agents in NCI-funded clinical trial networks

  - Focus on new NCI-IND agents coming into portfolio to accelerate trials

  - CRCHD track: Focus on models relevant to cancer heath disparities

- Four required cores

  - Administrative core

  - Bioinformatics core – to facilitate data sharing and to interact with PDCCC data commons

  - PDX core- including PDX maintenance and animal facilities

  - Pilot projects core- for PDXNet intra-network collaboration and to interact with investigators chosen through administrative supplement program

- Expected that research projects will employ large scale PDX collections

PDXNet Data Commons and Coordinating Center (PDCCC) (U24)

- Bioinformatics Core
  - Lead development and implementation of data collection standards, workflows, and SOPs for harmonization and data integration across different PDTC's
  - Centralized center for analysis of PDX response to agents across PDTCs
  - Maintain the PDXNet website and database
  - Share PDXNet data with NCI GDC and the larger research community

- Administrative Core
  - Grant administration of the PDTC and PDCCC
  - Scientifically-informed project management of PDXNet collaborative projects
  - Logistical and administrative assistance in arranging network-wide meetings, workshops and PDXNet Executive Committee (PEC)

Administrative supplements for non-U54 investigators

- Non-U54 investigators may apply to for PDXNet collaboration through an administrative supplemental award application process

- Current RFA: Laboratory scientists apply to collaborate with PDXNet scientists

  - Overall productivity of supplement program was modest

- Proposed RFA: Clinician scientists apply to collaborate with PDXNet scientists

  - New structure to facilitate investigator-initiated clinical trials by providing clinician scientists access to the PDXNet for pre-clinical evaluation of proposed therapies

  - Proposals may also include biomarker development, investigation of mechanisms of resistance or other PDX-related research questions

Benefits of the PDXNet FOA's

- Coordinated centers of excellence in PDX model development and testing to **transcend silo structure** of PDX programs

  - **Integrated, coordinated and collaborative network of PDX centers of excellence** to address multiple scientific issues

  - **Focused development of preclinical *in vivo* evidence for rapid translation** through integration with NCI clinical networks

  - **Harmonization** of SOPs and workflows facilitating collaboration and shared

  - **Multicenter donation of PDX models to PDMR to fill resource gaps**

    - Models from racial/ethnic minority populations and from clinical resistance

- **Purpose-driven** consortium for a **practical application of PDX science** by integrating PDX scientists with NCI NExT program (NCI-IND agents) and clinical scientists (NCI clinical trials networks) creating a complete enterprise for development of precision cancer medicine

  - Addresses our need for *in vivo* evidence to **prioritize targeted agent combinations** in molecularly defined tumors for NCI clinical trial development

  - Complements DCB's Patient Derived Models of Cancer (PDMC) program focused on biology of PDM's

PDXNet: Request for re-issue for a second grant cycle

- **Current** CM annual total cost funding level is **$10.5M**
  - DCTD U54 PDTCs (4) @ $1.25M TC per PDTC
  - CRCHD U54 PDTCs (2) @ $1.25M TC per PDTC
  - PDXNet U24 PDCCC (1) @ $1.5M TC per year
  - Supplement program @ $1.5M TC per year
- **Proposed** annual total cost request for second cycle is **$8M** per year
  - Decrease from 6 U54 PDTCs to 5 U54 PDTCs (3 or 4 from DCTD and 1 or 2 from CRCHD based on priority score) @ $6.25M (decrease of $1.25M)
  - PDXNet U24 PDCCC @ $1M per year (decrease of $0.5M)
  - Supplement program @ $0.8M per year (decrease of $0.7M)
- Open competition RFA requested

*The estimated total costs for the <u>full project period</u> is **$40M TC** (FY23 – FY 27)*

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