

**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*

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

- Increasing the precision of cancer therapy requires increasing the resolution of the assignment of therapy to specific diagnoses
- 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.
- New methods are needed to test novel agents against hundreds of potential tumor subtypes and in multiple combinations to identify the most promising strategies to be tested in the clinic
- 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

- Advancements in technology have created the potential for large-scale PDX collections, comprehensive molecular characterization of each model, and data analysis techniques for integration of complex data.
- These advances provide the opportunity to use PDX models on a large scale to advance Precision Medicine through comprehensive pre-clinical evaluation of novel agent combinations in small, molecularly-defined tumor subgroups
- 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

Portrait of PDX silos from PDX supplement applications

- NCI's initial PDX Precision Medicine effort was pursued through a 1-year administrative supplement for development of PDXs and drug response testing of PDX models
- 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.

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

Both goals will take advantage of the PDTCRNet

- Coordinated development of **large scale PDX collections** that capture disease heterogeneity without duplication
- Coordinated analyses of large datasets, including response data and molecular characterization data, of hundreds of PDX models
- Integrate use of other patient–derived material, such as organoids, for pre-PDX screening of hypotheses
- **Rigorous evaluation** of PDX response to therapeutic intervention
 - Quality control and **harmonized SOP's** to enable cross-validation
 - Demonstrate **reproducibility** of PDX testing prior to clinical testing

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
 - Immediate evaluation of new agents accepted for NCI development by the NExT program to guide project team decision-making.
 - 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

NCI Patient-Derived Models Repository (PDMR) at FNLCR

- The NCI PDMR is a resource that we would leverage in the development of the PDTCRNet
- 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

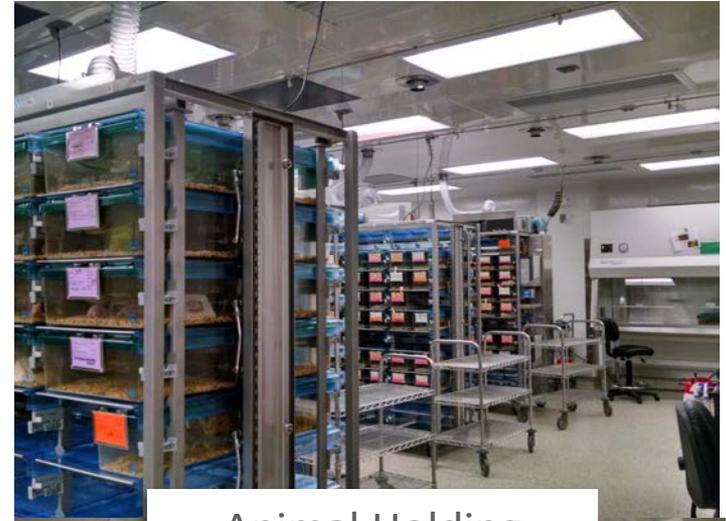


9,500 sq. ft. in 9 buildings

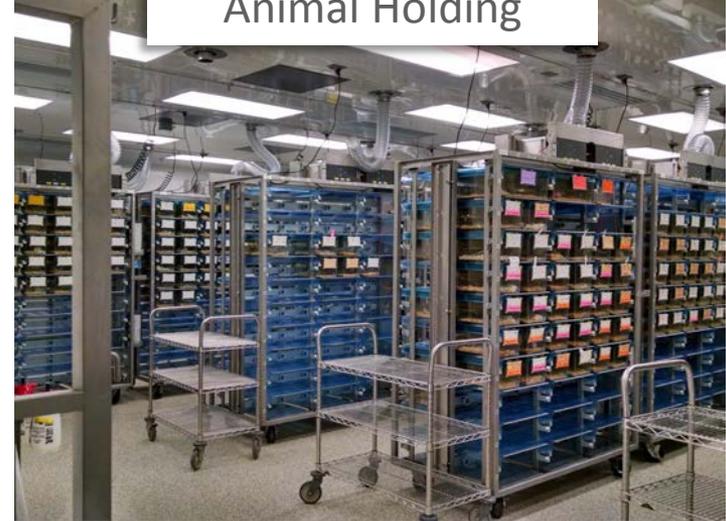
4560 cages [max: 5 mice/ cage = 22,800 mice]

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

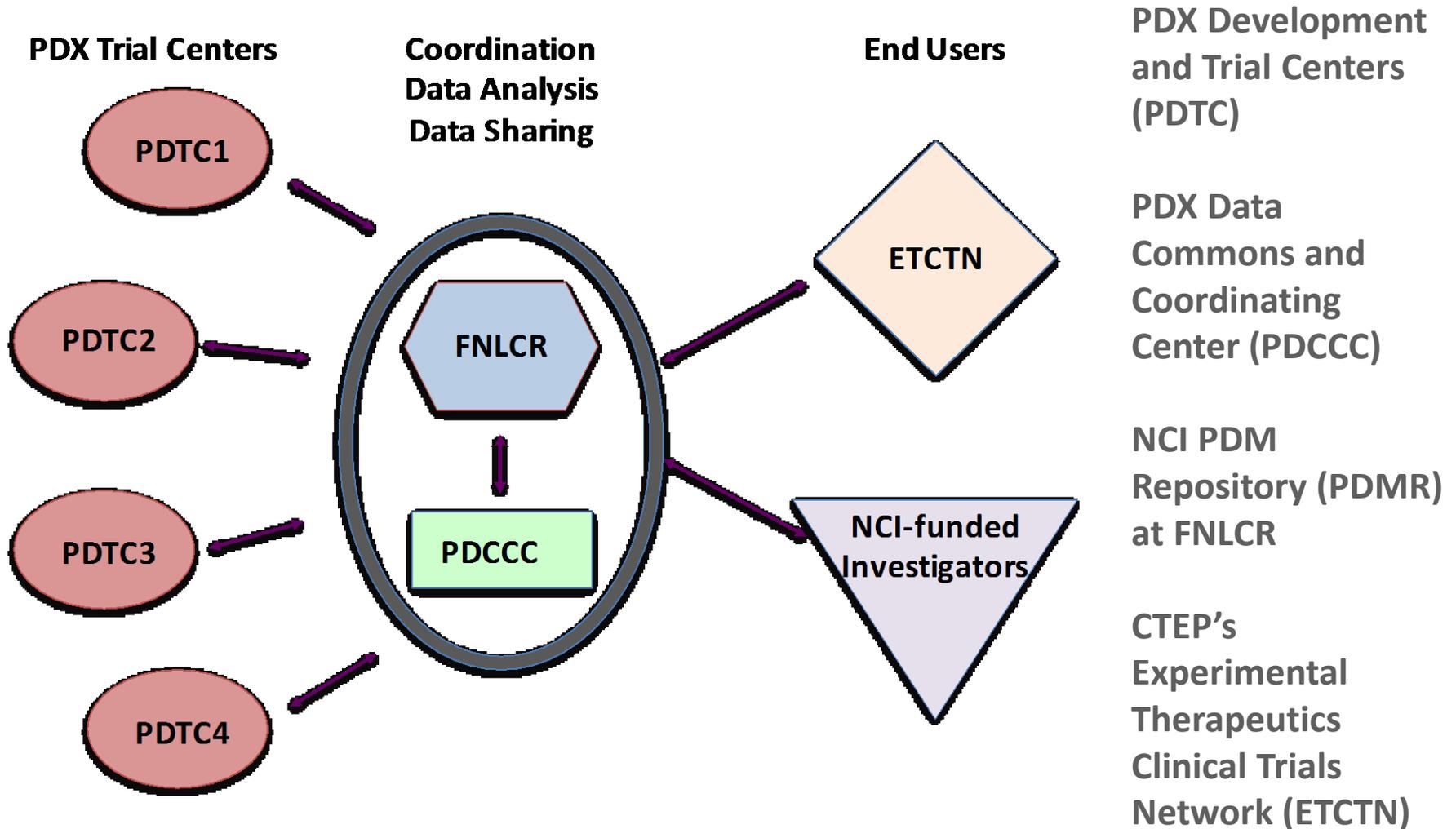
Animal Production facility: 1,300 cages for NSG and nude mice; continuous breeding



Animal Holding



Structure of proposed PDTCRNet created by the RFAs



PDTCRNet Roles and Review Criteria: 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
- Three required cores
 - Administrative core
 - PDX core- including PDX maintenance, animal facilities and bioinformatics
 - Pilot projects core- to establish validation and reproducibility between centers, and interact with investigators chosen through administrative supplement program
- Expected that research projects will employ large scale PDX collections, likely greater than 100 models per project

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
 - Develop mechanisms to share consortium data with the larger research community
 - Share PDTCRNet data with NCI GDC

- **Administrative Core**
 - Grant administration of the PDTC and PCC
 - 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: NCI Patient-Derived Model Repository (PDMR) at FNLCR

- Coordinate the development SOPs for PDX model generation, standardized QC of models, drug study set-up standards, and response criteria. Work with consortium members to ensure the SOPs are of the highest standards.
- Receive donated PDX models from consortium members and develop them to share publicly with extramural community
- Share NCI-PDMR PDX models with consortium members
- Molecularly characterize donated PDX models and provide all data to the public through the PDMR public website



PDTCRNet Roles: Experimental Therapeutics Clinical Trials Network (ETCTN)

- Investigational Drug Branch medical officer serves as program director (PD) and science officer (SO) for the PDX consortium
- SO acts as liaison between PDX consortium and ETCTN investigators
- SO is responsible for maintaining a focus of consortium on the development of NCI-IND agents
- SO is responsible for translating promising consortium trial results into ETCTN clinical trials
- SO serves as liaison between PDX consortium and CRADA partners for MTAs and other interactions

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

Benefits of the PDTCRNet FOA's

- Coordinated centers of excellence in PDX model development and testing to **transcend silo structure** of PDX programs
 - **Integrated network of PDX centers** of excellence with a coordinating center
 - **Quality control & harmonized SOPs** with NCI PDMR-FNLCR collaboration
 - Collaboration between centers to create **large-scale PDX libraries** and response data without duplication and which allows cross-validation of studies
 - Coordinated development of preclinical modeling platforms to speed bench-to bedside progress e.g. PDO's and humanized PDX models for immunotherapeutics
- **Purpose-driven** consortium will demonstrate a **practical and focused application of PDX science** by integrating PDX scientists with NCI NExT program (NCI-IND agents) and ETCTN clinical scientists
 - Creates complete model for development of precision cancer medicine – agents, models, molecular characterization, and clinical trials network
 - Directly addresses the challenge of prioritizing targeted agent combinations in molecularly defined tumors for clinical trial development.

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

- **RFA for U54**

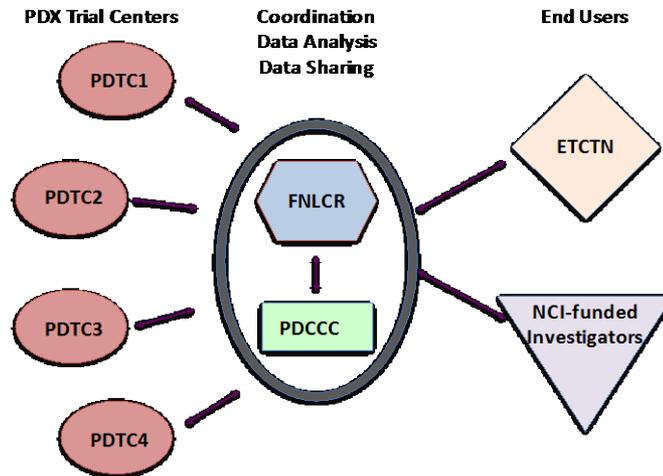
Up to 4 PDX Development and Trials Centers (PDTCs) supported with 5-year U54 cooperative agreements @ \$1.25 M total costs per year = \$5M

- **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



PDX RFA Working Group

- CTEP: Jeff Abrams, Jamie Zwiebel, Kim Witherspoon
- FNLCR: **Yvonne A. Evrard (Leidos)**, Melinda Hollingshead (NCI)



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Future capacities of the PDTCRNet

- Once the network is up and running, additional capacities may be considered
 - Adding additional PTDC's to the consortium to widen the availability of PDX models
 - Including murine hosts with humanized immune systems to test immune therapy agents and agent combinations
 - Testing novel non-NCI-IND agents if it is possible to test the agent in the ETCTN through a Clinical Trials Agreement