NCAB Ad Hoc Subcommittee on Experimental Therapeutics

Rose Aurigemma, PhD
Associate Director, Developmental Therapeutics Program
Division of Cancer Treatment & Diagnosis, NCI

NIH NATIONAL CANCER INSTITUTE

November 29, 2023

AGENDA

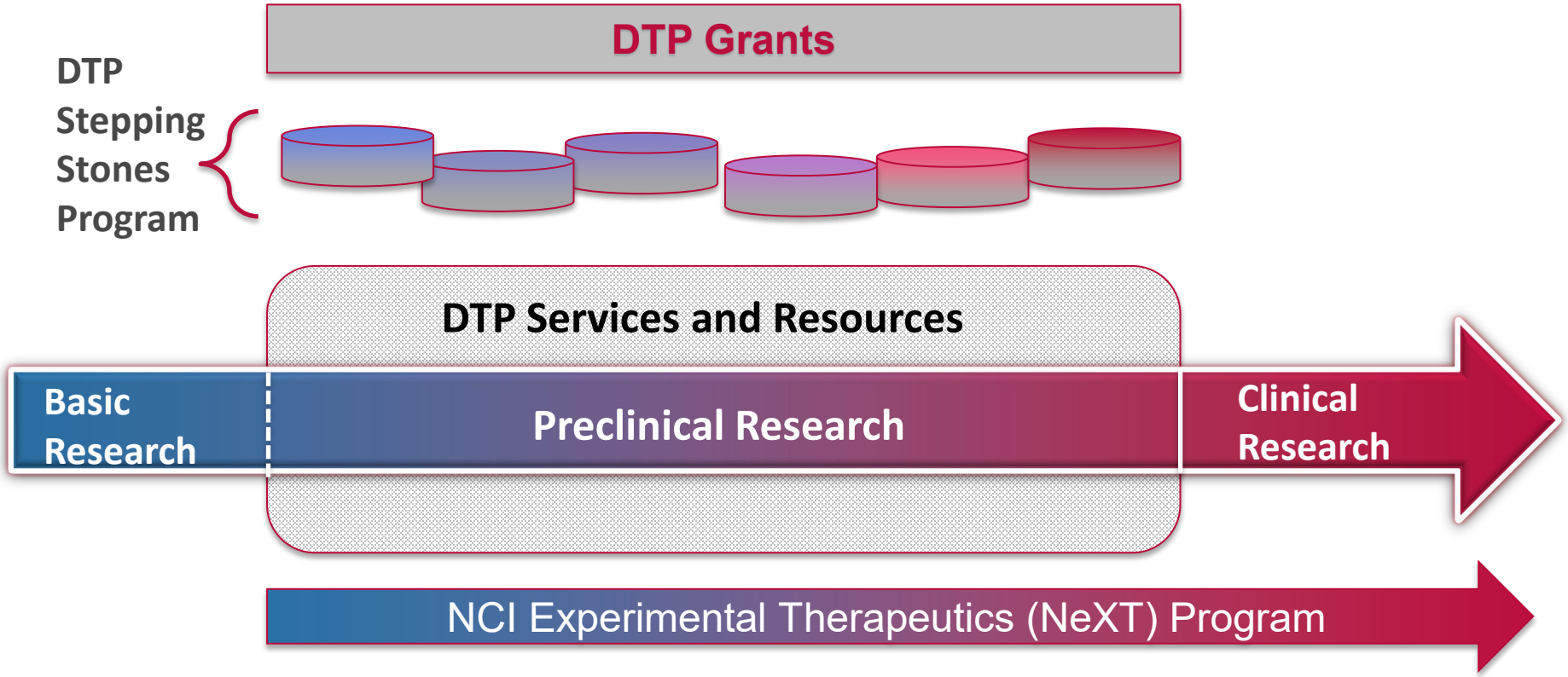
- Welcome and Introduction of Members
- Developmental Therapeutics Program: Mission and Resources
- Overview of Recent Subcommittee Accomplishments
- Discussion of Mission and proposed next steps

Division of Cancer Treatment and Diagnosis (DCTD)

- Biometrics Research Branch (BRB)
- Cancer Diagnosis Program (CDP)
- Cancer Imaging Program (CIP)
- Cancer Therapy Evaluation Program (CTEP)
- **Developmental Therapeutics Program (DTP)**
- Radiation Research Program (RRP)
- Developmental Therapeutics Clinic (DTC)
- Translational Research Program (TRP)
- Office of Cancer Clinical Proteomics Research (OCCPR)
- Office of Cancer Complimentary and Alternative Medicine (OCCAM)

DTP Mission: Support and Assist the Extramural Community to Promote Translation of New Therapeutic Concepts Toward Clinical Use

Overlapping Support for Discovery and Development



DTP Branches: Provide Funding, Repositories and Services

PRECLINICAL THERAPEUTICS GRANTS BRANCH Chief: Sundar Venkatachalam, PhD

- **Grants**: Small molecules, natural products, drug targets, discovery & development of novel therapeutic concepts

IMMUNO-ONCOLOGY BRANCH Chief: Marc Ernstoff, MD

- **Grants**: Immuno-oncology, Immunotherapy, Canine Immunotherapy Network, Pediatric Immunotherapy Network, Cancer Adoptive Cell Therapy Network (CanACT)

BIOLOGICAL RESOURCES BRANCH Chief: Jason Yovandich, PhD, RAC

- **Grants**: Biopharmaceutical discovery & development, novel biotechnology concepts
- **Services:** Development of clinical grade biologics, adoptive cell therapies, analytical testing **(@FNLCR)**
- **Repository:** Biologics (MAbs, cytokines)

DRUG SYNTHESIS & CHEMISTRY BRANCH Acting Chief: Steve White, PhD

- **Repository:** NCI Compound Repository (>200,000 open compounds and associated data)
- **Services:** Synthetic chemistry, route optimization, scale-up **(@FNLCR)**

MOLECULAR PHARMACOLOGY BRANCH Chief: Bev Teicher, PhD

- **Services:** NCI-60 tumor cell screen, Patient-derived models screen, target validation, combinatorial screening **(@FNLCR)**

NATURAL PRODUCTS BRANCH Chief: Barry O'Keefe, PhD

Repository: Large pre-fractionated library; collections of extracts (marine, plant, soil, fungi)

- **Services:** Natural product chemistry for novel compounds **(@FNLCR)**

INFORMATION TECHNOLOGY BRANCH Chief: Ron Taylor, PhD

- **Repository/Resources:** Extensive databases for compounds, activity data, computational tools (COMPARE, ALMANAC)

BIOLOGICAL TESTING BRANCH Chief: Melinda Hollingshead, DVM, PhD

- **Repository:** Tumor repositories, Patient Derived Tumor Models repository, immunodeficient & immunocompetent models
- **Services:** Model development, efficacy, dose schedule, MTD **(@FNLCR)**

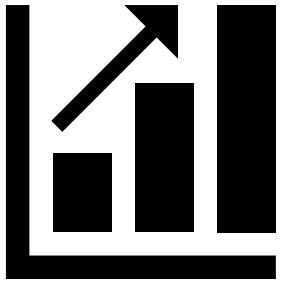
TOXICOLOGY & PHARMACOLOGY BRANCH Chief: Liz Glaze, PhD, DABT

- **Services:** Non-GLP and GLP PK & toxicology, ADME, development of *in vitro* assays for discovery, development

PHARMACEUTICAL RESOURCES BRANCH Chief: vacant

- **Services:** Large scale GMP manufacture bulk API, analytical testing, dose formulation development, Final Drug Product manufacturing, stability program to support clinical use

DTP Grants Portfolio – August 2023



DTP Branch	# Awards	Budget (Millions)
PTGB	734	$322.6
IOB	186	$91.8
BRB	99	$55
	1019*	$469.4

**Does not include NCEs*

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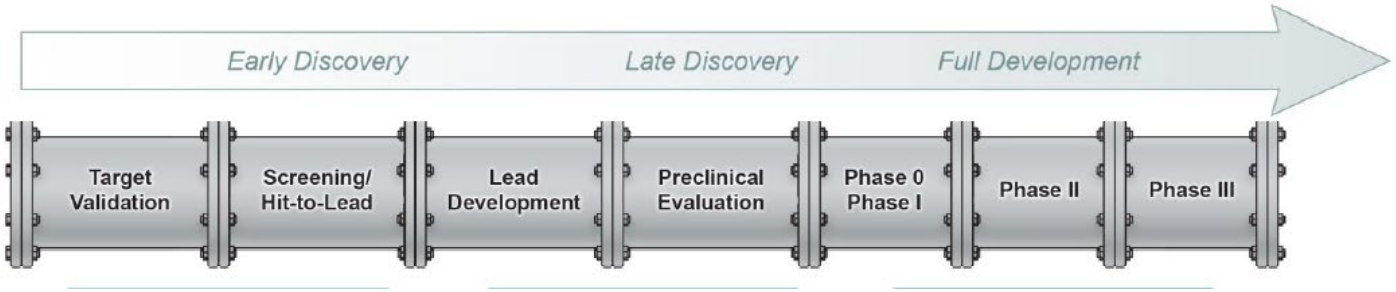
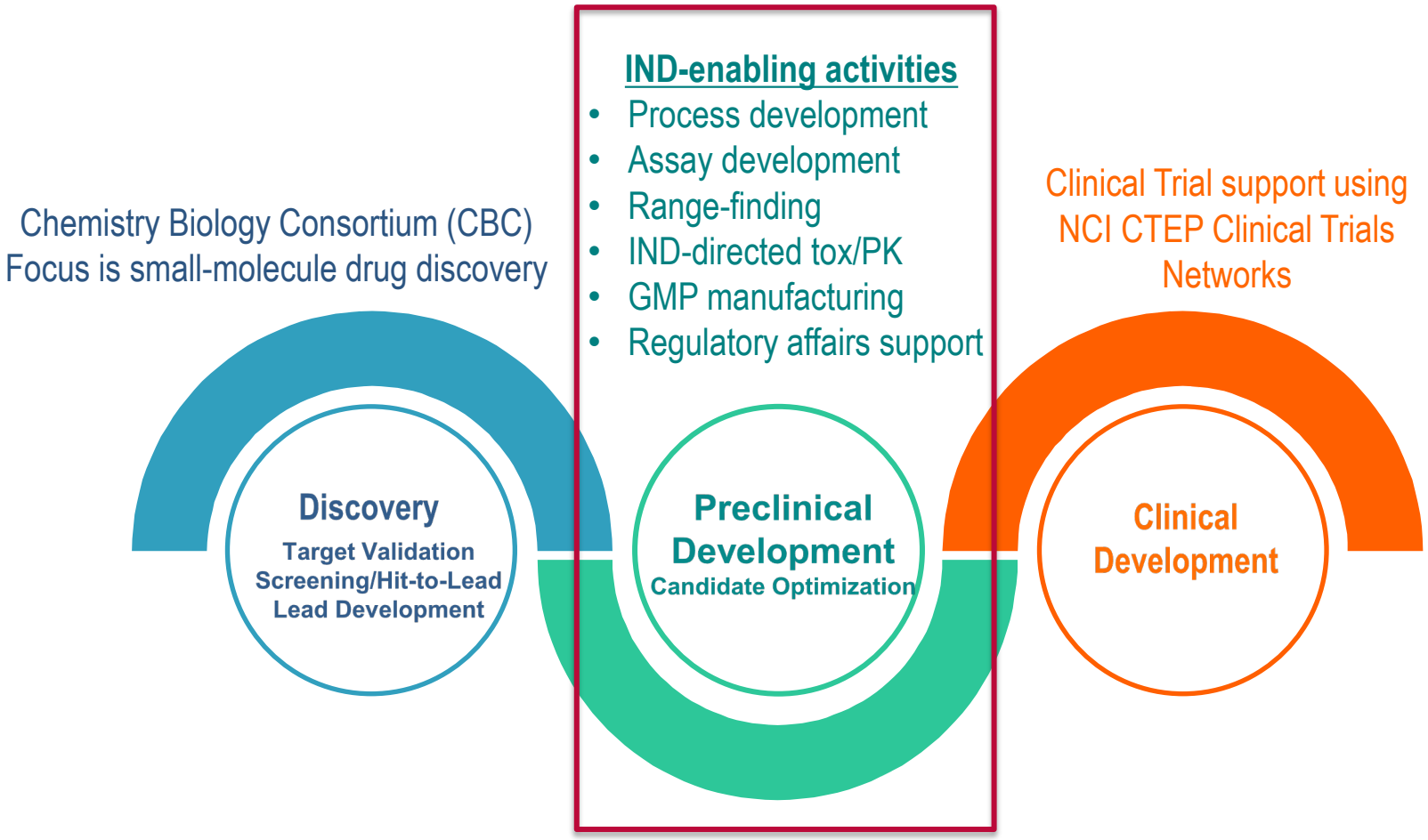
NCI Experimental Therapeutics (NExT) Program



- Projects can enter at any stage of discovery or development
- Applications are peer reviewed by NExT Special Emphasis Panels
- Submission deadlines: February 15, June 15 and October 15
- NExT program provides resource, not funding or money, for approved studies
- Applicants retain ownership of intellectual property that they bring to the program

Significance: clinical hypothesis directed at unmet medical need
Innovation: novelty of proposed target and/or mechanism of action
Readiness: strong preclinical data (for clinical candidate)
Typical shortcomings:
No or little data in preclinical models of the target disease
Issues with 'druggability'
No or little data with the actual clinical candidate

NCI NExT Resources: DTP Supports Clinical Candidate Readiness



Additional Development Resource: Stepping Stones

Assist academic innovators with critical data gaps

- Limited access to full range of development resources
- Academic funding may not cover iterative/routine development tasks
- Unavailable expertise in full range of regulatory critical path steps toward IND

Support NCI investment in the grant portfolio

- Limited to grantees
- Small investment (<$100K) to advance promising lead **candidates**
- **Provide critical data** a PI can't easily obtain and isn't covered by grant (e.g. formulation work, synthesis optimization, discrete DMPK/ADME studies, etc.)
- **Improves chances for gaining other resources** (NExT, VC, SBIR/STTR)
- Special emphasis on area of unmet need and institutions with fewer resources

Examples of Stepping-Stones Project Support

Formulation Development

- Produced an orally available drug formulation, enabled STTR Ph I and II funding

Synthesis and PK studies

- Synthesis improvements, multi-gram quantities of non-GMP API, and salt-forms
- PK studies (mouse, rat) to characterize bioavailability

Biomarker studies

- Connected to resources for pilot PD studies

***In Vitro* ADME and safety studies**

- De-risking and ID of liabilities early (CYP, UGT, metabolic stability, hERG, etc)

Indications supported:

- Uveal Melanoma
- Pancreatic Cancer
- Melanoma
- K-Ras (G12D) mutant cancers
- Glioblastoma multiforme (GBM)
- Castration Resistant Prostate Cancer (CRPC)
- Acute Myeloid Leukemia (AML)
- Triple Negative Breast Cancer (TNBC)
- Chemotherapy Induced Peripheral Neuropathy (CIPN)

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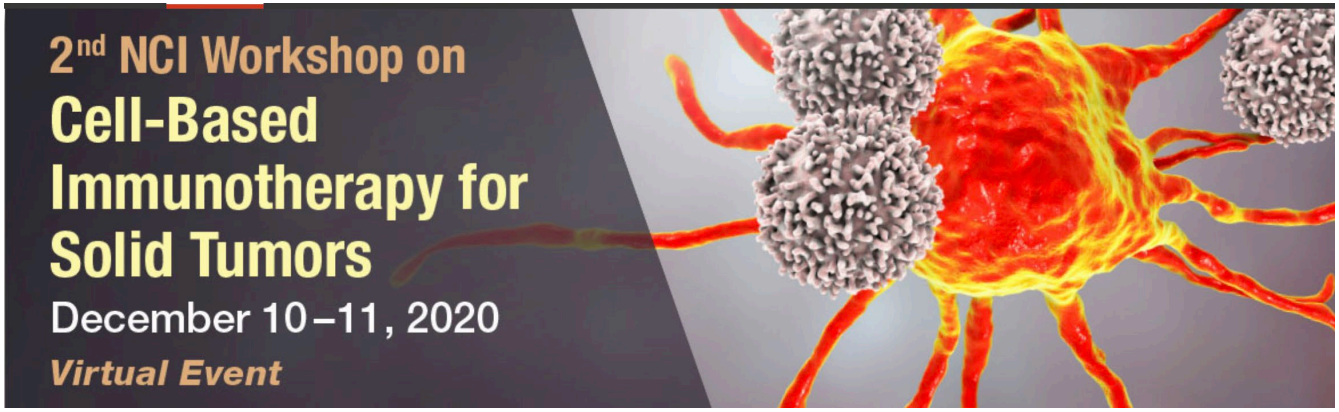
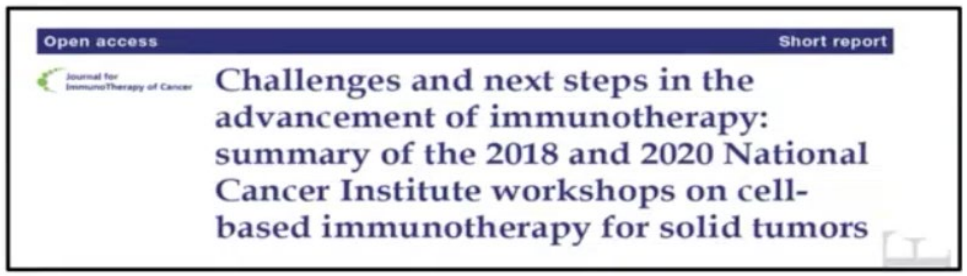
2020-2021 Priority Topic 1: Cell therapy

- 2 workshops
- Summary publication in *Journal for Immunotherapy of Cancer*, July 2021




Open access Short report

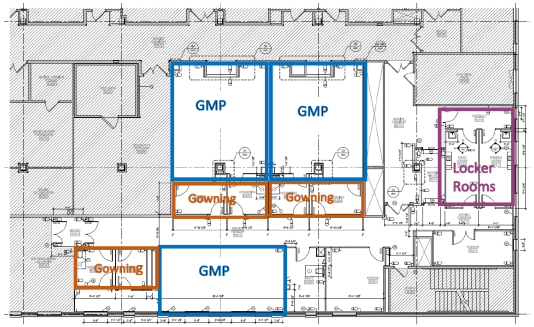
Journal for ImmunoTherapy of Cancer

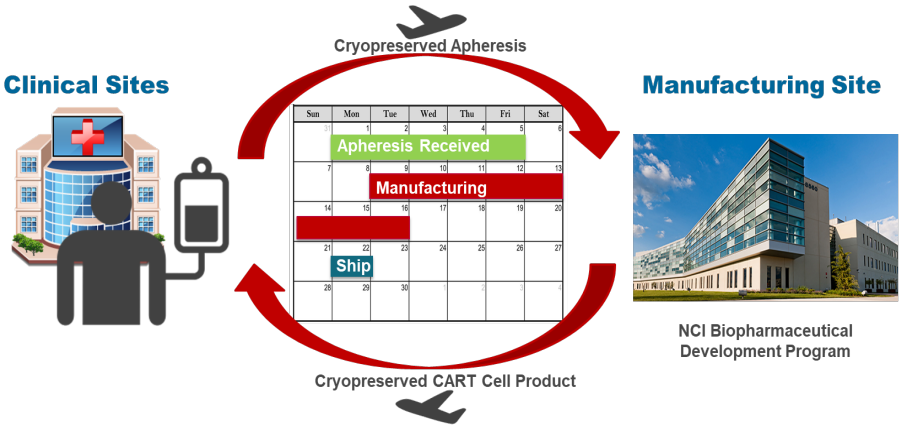
Challenges and next steps in the advancement of immunotherapy: summary of the 2018 and 2020 National Cancer Institute workshops on cell-based immunotherapy for solid tumors

Biological Resources Branch: Expanded Cell Therapy Resources

TECHNOLOGY	CURRENT FACILITY	CURRENT CAPACITY
• Genetically-modified autologous cells (closed-system Prodigy platform-based) • Lentivirus & Gamma Retrovirus vectors • G-Rex (disposable) manufacturing platform • CRISPR-based gene editing: FY2023	5 GMP suites	• 12 cell therapy products/ month • 8 virus vector campaigns/year • Controlled storage for cell and virus products

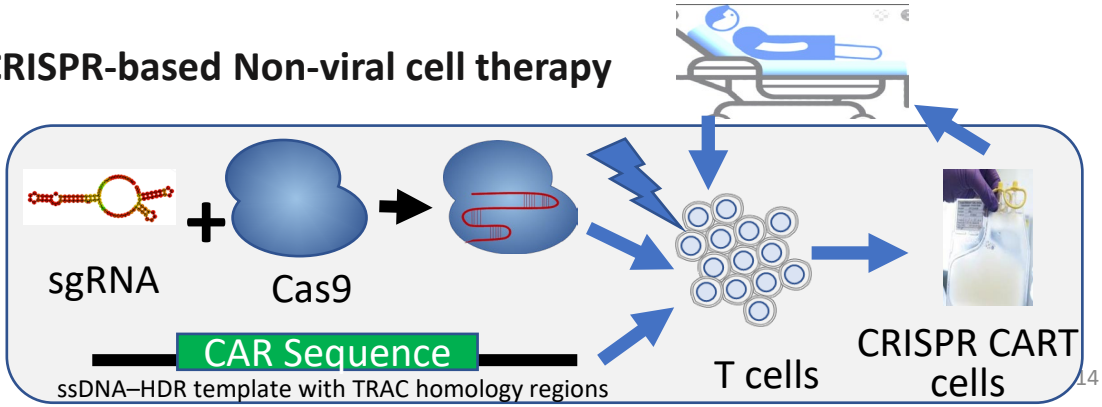
New GMP Suites





Biobubble with Wave bioreactor

CRISPR-based Non-viral cell therapy



RFA: Cancer Adoptive Cellular Therapy Network (Can-ACT) Awards managed via collaboration between DTP, CTEP, CIP, CDP, TRP

Goals

- Develop and enhance immune cellular products modified genetically or through other manipulations for the treatment of **adult and pediatric patients with solid tumors**
- Support **early phase clinical trials** through **UG3/UH3** mechanism
- Explore **imaging and biomarker** development
- Expand our understanding of the mechanism of action as well as natural and acquired resistance
- Evaluate strategies to modulate the immunosuppressive tumor microenvironment

Can-ACT Network Structure FY23 & FY24

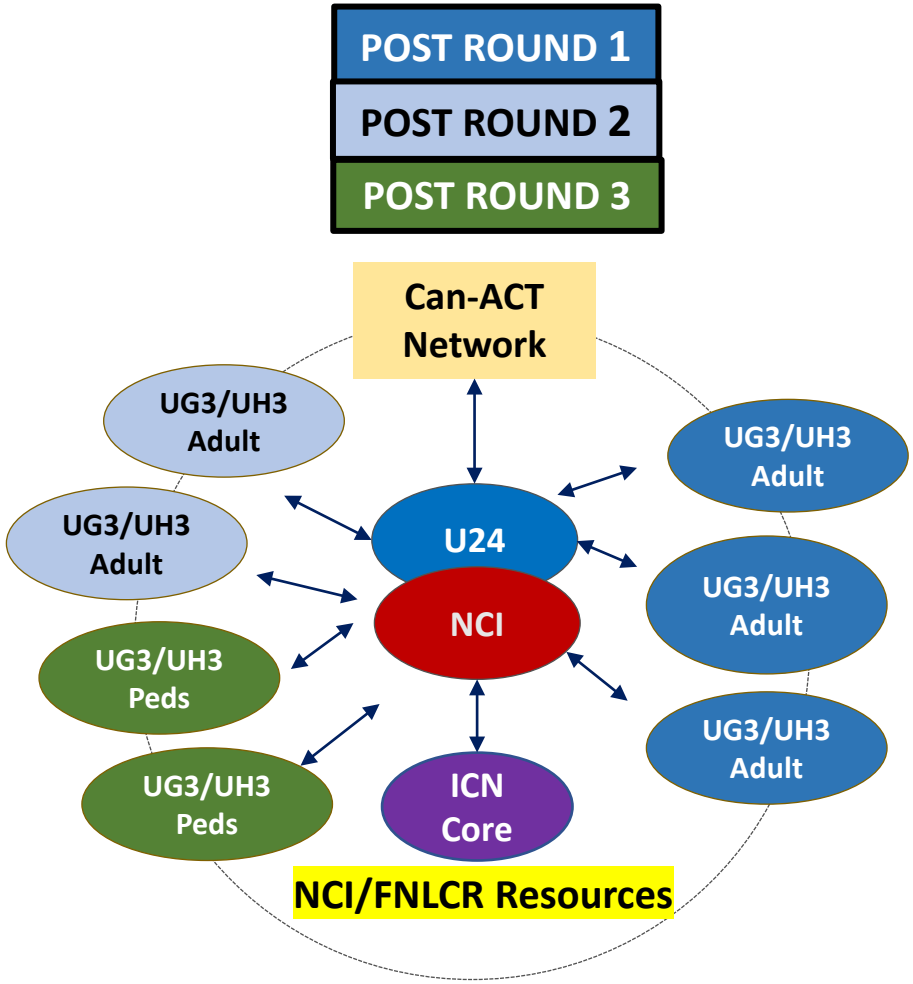
The goal of Can-ACT RFAs is to foster innovation and promote **early-stage clinical testing** of novel **cell-based immunotherapies for solid tumors** in adult and pediatric patients and leverage NCI resources to support the cell therapy community.

- Can-ACT for **Adult** Cancers (UG3/UH3)
- Can-ACT for **Pediatric** Cancers (UG3/UH3)
- Can-ACT **Coordinating** Center (U24)
- Immune Cell Network (ICN) **Core** (FNLCR)

Round 1 (3 adult):
UG3 Carreno; U Penn (Kras solid tumors)
UG3 Yee; MDACC (GE cancer)
UG3 Maus; MGH (Pancreatic cancer)
U24 Geyer; Mayo

Round 2 (2 adult) – FY24

Round 3 (pediatric only) – FY24



2020 Subcommittee Priority Topic 2: Rational Drug Discovery -

Intelligent drug discovery based on biochemistry, structure, and mechanisms, including artificial intelligence-driven drug discovery

- NCI organized a workshop inviting subject-matter experts from academia, industry, and federal agencies
- 18 presentations and 4 facilitated discussions in an interactive format
- Nearly 700 virtual attendees
- Reviewed drug discovery research with respect to structural biology, novel therapeutic modalities, target interrogation, and artificial intelligence (AI) in drug discovery for an understanding of the 'state of the field'
- Identified gaps in knowledge, resources, technologies as well as critical barriers to advancing rational drug discovery
- Gained insight on opportunities for NCI to augment support for the extramural community to accelerate discovery of new cancer treatments

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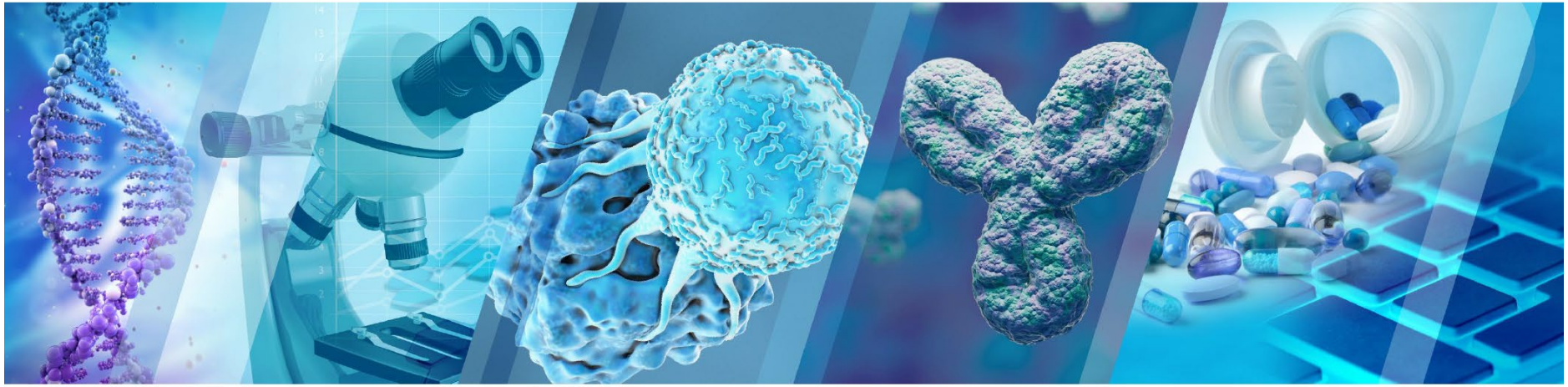
RATIONAL DRUG DISCOVERY



October 18-19, 2021

Virtual Workshop

Co-chairs:

Tudor Oprea, MD, PhD
University of New Mexico

Rommie Amaro, PhD
University of California, San Diego

Video Archive: https://events.cancer.gov/dctd/drugdiscovery/meeting-recordings

DTP Planning Committee: Sharad Verma, Paul Grothaus, Brian Peyser, Tam Nguyen, Anju Singh, Kasia Bourcier, Rick Gussio, Monica Cooper

Home Agenda Registration Participant Bios Recordings Summary

The Quest for Innovative Molecular Treatment Modalities for Intractable Disease Targets

November 17-18, 2022 | 11:00am-4:00pm EST

Virtual Workshop

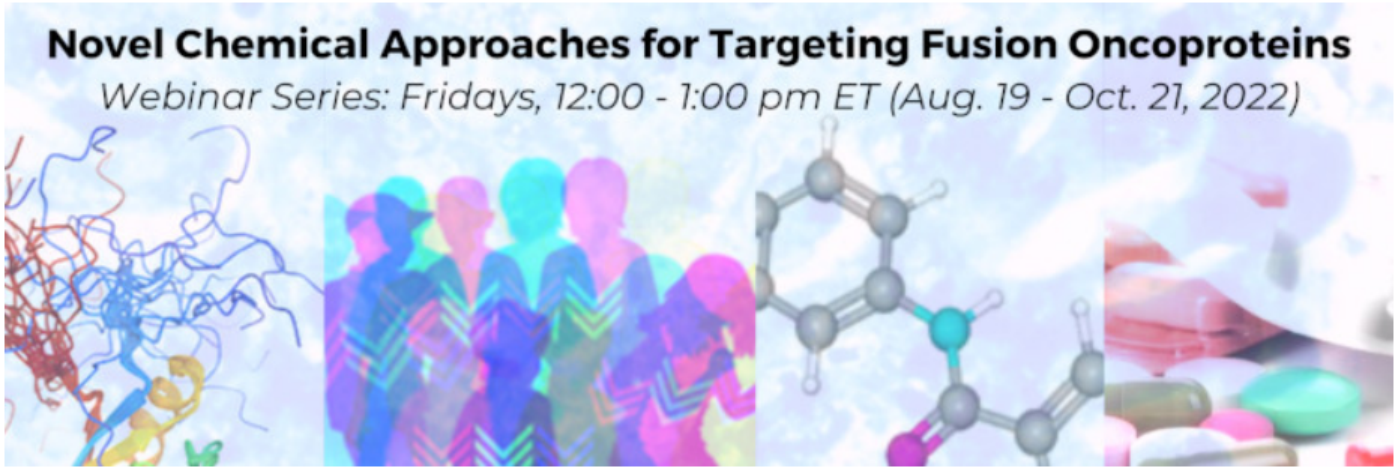
Register

Photo of The Rod of Asclepius Medical Symbol

Significant numbers of human diseases are caused by proteins or mechanisms that cannot be treated via traditional drugs or gene therapy. Many of these conditions are considered untreatable as they are caused by pathologies for which we lack drug development options, such as protein misfolding, proteins with hidden active sites, defective protein-protein interactions or where the targets are “other cellular entities” (e.g., RNAs and small molecules). With the recent development of novel emerging therapies to overcome many of these druggability challenges, the field is primed to open up new classes of molecular entities and explore expanded horizons outside of the traditional small molecule discovery tract.

‘Proceedings’ white paper is in preparation for publication.

The recordings of the individual webinars are posted below.



Overview

A joint effort between DCTD's Developmental Therapeutics Program and NCI's Division of Cancer Biology, this webinar series enhanced understanding within the NCI and the research community of opportunities for targeting fusion oncoproteins through emerging chemoproteomic methods.

Background and Research Challenge

Research has advanced our understanding of the biology underpinning pediatric fusion oncoproteins. For example, menin inhibitors for KMT2A-rearranged leukemias achieved proof-of-concept for the blockade of transcription factor fusion oncoprotein action, and agents targeting the menin-MLL protein-protein interaction are in clinical testing. However, current progress towards targeting additional transcriptional factor fusion oncoproteins has been limited. Consequently, the absence of small molecule therapeutics targeting fusion oncoproteins limits improvement in outcomes for pediatric patients with cancer.

Webinar series organized by CTEP and DTP, in collaboration with DCB

Workshop Led to New Initiative: Awards Pending Q3 2024

Notice of Intent to Publish a Funding Opportunity Announcement for Mechanisms of Fusion-Driven Oncogenesis in Childhood Cancers (U01 Clinical Trial Not Allowed)

Notice Number: NOT-CA-23-057

Key Dates

Release Date: April 05, 2023

Estimated Publication Date of Notice of Funding Opportunity : June 29, 2023

First Estimated Application Due Date: November 17, 2023

Notice of Intent to Publish a Funding Opportunity Announcement for Next Generation Chemistry Centers for Fusion Oncoproteins (UM1 Clinical Trial Not Allowed)

Notice Number: NOT-CA-23-058

Key Dates

Release Date: April 05, 2023

Estimated Publication Date of Notice of Funding Opportunity : June 29, 2023

First Estimated Application Due Date: November 17, 2023

2022 Subcommittee Priority Topic: Support for Translational Research Training

NCI serves at the key hub for basic translation training via an Electronic Format

- Archive library of topics for rapid access
- Harmonization of training
- Reduces redundancy of developing curriculum nation-wide
- Instruction by the leaders in the field

Cancer Centers with unique expertise instruct in a given domain and become part of the lecture series

Certification?

Can we use the current curriculum offered by the NCI as a starting point for this initiative

DCTD Support for Translational Research Training

NCI Drug Development Workshop:
How to Advance A Therapeutic Candidate from Bench to Bedside

Session I.
Grand Overview

Session II.
Pre-clinical Proof of Concept: Establishing Activity, Bioavailability, and Associated Effect, in Cancer Relevant Models

Session III.
Non-clinical Toxicology

Session IV.
Chemistry Manufacturing and Controls (CMC) for Small Molecules

Session V.
Development of Biological Products

Session VI.
Regulatory Considerations

Session VII.
Clinical Translation

Session VIII.
Entrepreneurship: Partnering and Advancing

Session IX.
NCI Translational Resources and Programs

Session X.
Case Studies

DCTD Support for Translational Research Training

NCI Drug Development Workshop II:

Specialized Topics in Preclinical Development of Small Molecule Cancer Drugs

Purpose: To help investigators reduce the translational risk of selected candidates during later stages of product development and increase the chances of entering clinical evaluation.

Workshop content: Six webinar sessions addressing specialized topics important for preclinical development of small molecule cancer drugs. Lectures will be 60 - 90 minutes, followed by 15-minute Q&A.

Session I. Considerations for Lead Optimization of Small Molecules (Thursday, June 22, 1 pm – 2:45 pm, ET)
Session II. Considerations for Advancing to Late Preclinical Development (Friday, June 23, 1 pm – 2:45 pm, ET)
Session III. Safety and Toxicity Studies for Small Molecules (Thursday, July 13, 1 pm – 2:15 pm, ET)
Session IV. Formulation of Small Molecules (Friday, July 14, 1 pm – 2:45 pm, ET)
Session V. Nanoparticle Delivery of Cancer Drugs (Thursday, July 27, 1 pm – 2:45 pm, ET)
Session VI. Good-to-know IP Knowledge (Friday, July 28, 1 pm – 2:15 pm, ET)

Target Audience: Scientists who are interested in preclinical drug development for cancer

Registration is **free** and open to the public: www.events.cancer.gov/dctd/drugdevelopment
(scan QR code to register)

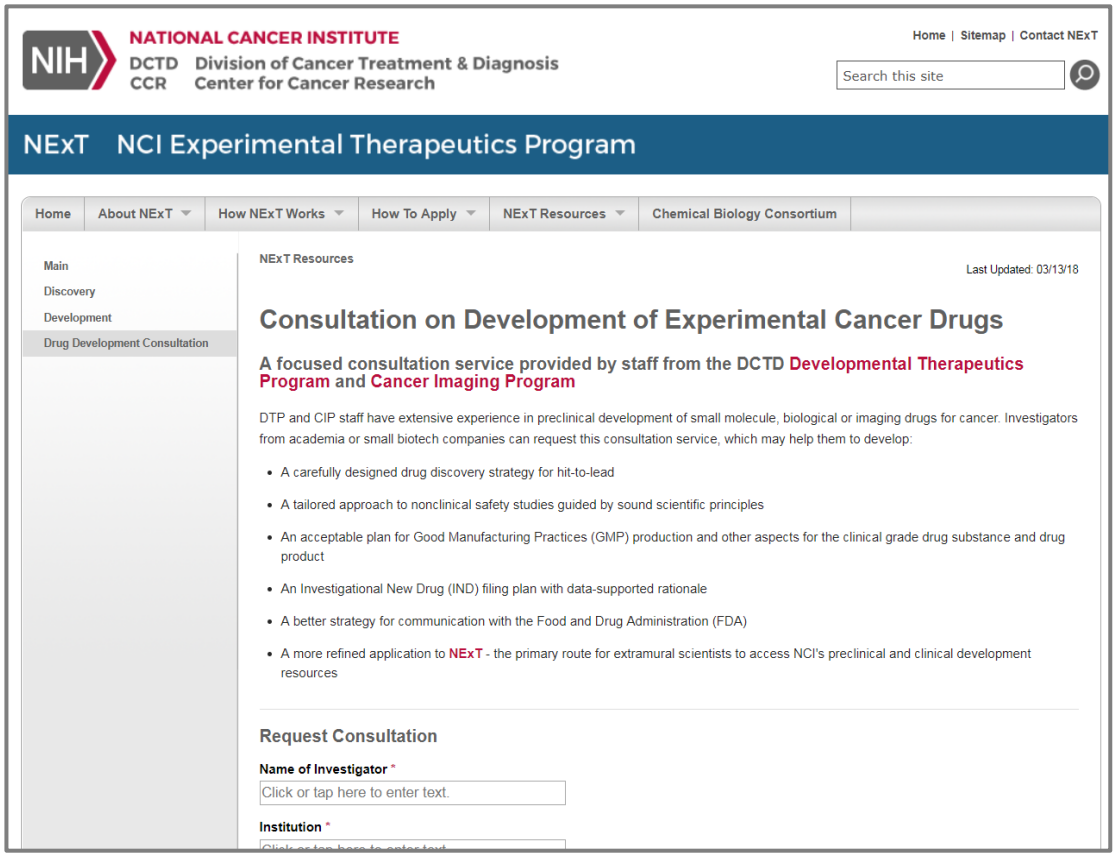
Contact: Weiwei.Chen@nih.gov; Sundar.Venkatachalam@nih.gov; or, Jason.Yovandich@nih.gov

DTP/DCTD Preclinical Development Consultation Service

https://next.cancer.gov/experimentalTherapeutics/form.htm

- Confidential
- Provides broad product development
- Small molecules, biologics, cell therapies, imaging agents and nanotechnology products

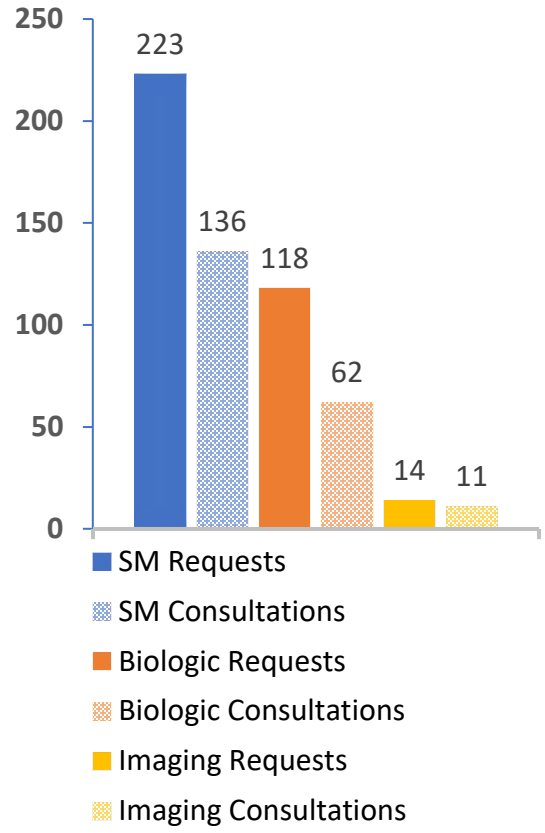
Coordinators:
Morgan O'Hayre– Small Molecules
Rachelle Salomon - Biologics



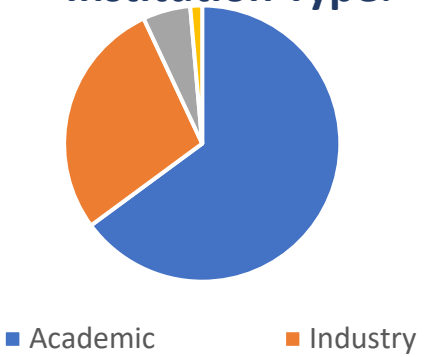
Product Development Consultation Service: Metrics

~ 4.75 years (August 2023): 361 Requests; 209 Consultations (*via WebEx*)

Type of Product:



Institution Type:



Topics Requested:

Communication with FDA	147
Preclinical tox and pharm	223
Efficacy and POC	193
Scale-up synthesis/GMP manufacturing	167
Medchem and small-scale synthesis	95
Immunotherapy	74
Nanotechnology	31
Radiotherapy (*Topic added in 2023)	3

NIH Funding Status:

Active grant = 162

Location:

37 states; 17 other countries

State (number of requests)		
AL (7)	LA (6)	OK (1)
AR (1)	MA (25)	OR (3)
AZ (2)	MD (15)	PA (17)
CA (43)	MI (12)	SC (2)
CO (3)	MN (4)	TN (9)
CT (5)	MO (5)	TX (26)
FL (18)	MS (1)	VA (20)
GA (11)	NC (7)	WA (8)
HI (1)	NE (4)	WI (2)
IA (5)	NH (3)	WV (3)
IL (7)	NJ (6)	*DC (1)
IN (6)	NY (36)	
KY (1)	OH (12)	
International: Australia, Brazil, Canada, China, Chile, Egypt, India, Israel, Italy, Norway, Pakistan, Portugal, Spain, Sri Lanka, Sweden, UK, Ukraine (24 total)		

AACR Handout: Developmental Therapeutics Program (DTP)

Drug Discovery/Development – Anti-cancer activity screening and proof-of-concept studies *in vitro* and *in vivo* and support for product development through all phases of the critical path toward clinical use from medicinal chemistry through safety testing and cGMP manufacturing

NCI-60 Human Tumor Cell Lines Screens – Unique cell killing dose response screens across 60 human tumor cell lines allowing response patterns to be analyzed by algorithms (**COMPARE**)

Stepping Stones Program – Discrete drug development studies for grantees

Consultation Service – Helping innovators to meet standards required for early-phase clinical trials via **NeXT**

Repositories – Tumors, cell lines, patient-derived models, chemicals, natural products, and biological reagents

Grants Funding – FOAs:

RFA-CA-22-028: Can-ACT Adult

RFA-CA-22-29: Can-ACT Pediatric

NOT-CA-21-101: Advancing tumor site-activated small molecules

PAR-22-216: NCI Clinical and Translational Studies

PAR-20-271: Assay development and screening

Databases & Tools – including data search tools, bulk data download, COMPARE analysis, NCI-ALMANAC, and ROADMAPS datasets

dtp.cancer.gov

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Mission: Ad Hoc Experimental Therapeutics Subcommittee

The purpose of this subcommittee is to provide advice and oversight of the NCI Experimental Therapeutics Program (NExT) and to assist the Division of Cancer Treatment and Diagnosis (DCTD) in the translation to the clinic of novel anticancer therapeutic interventions, either synthetic, natural product, or biologic that have been approved for development. In particular, academic institutions need a bridge between discovery and clinical testing, so that efficient translation of promising discoveries may take place even in the absence of development capacity or clinical expertise in the institution where the discovery was made and the NCI's NExT Program helps bridge this gap. This committee should also foster greater interactions with industry, academia, government, etc. to enhance the drug development process.

This subcommittee will also provide advice on policies, procedures and programs that will enhance the pre-clinical discovery and development of small molecules and biologics. Particular emphasis will be to provide oversight of the NCI Chemical Biology Consortium and NExT program. The goal is to optimize the functionality and output of these programs and to explore the potential contribution of current and future drug discovery and development practices to optimize strategies to preempt cancer at various stages.

Established: December 2006

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www.cancer.gov **www.cancer.gov/espanol**