

Briefing: NCAB Ad Hoc Subcommittee on Experimental Therapeutics

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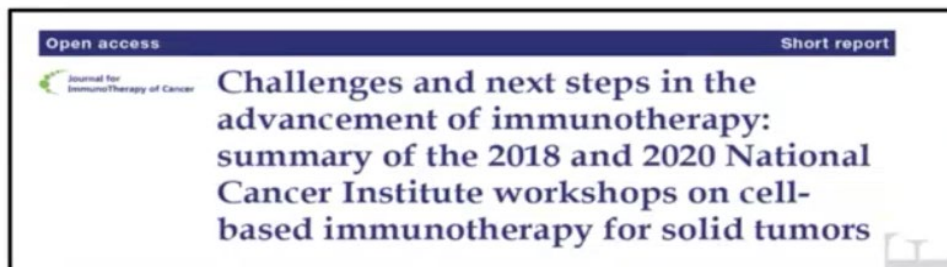
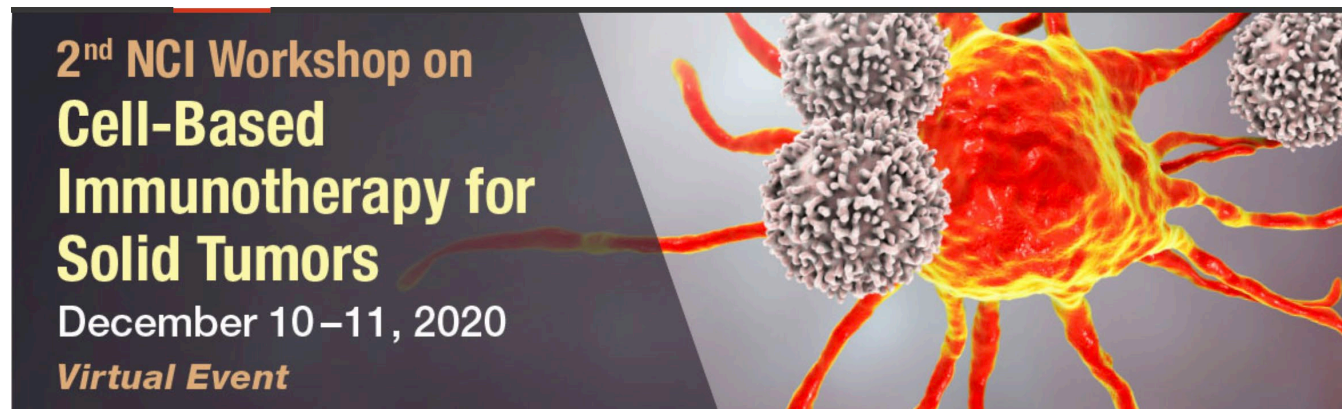
Agenda

- Brief update on Priority Topic 1: Cell therapy
- Progress on Priority Topic 2: *Intelligent drug discovery based on biochemistry, structure, and mechanisms, including artificial intelligence-driven drug discovery*
 - Rational Drug Discovery Workshop Report
 - Current Discovery Resources from NCI
- Proposed next steps

Priority Topic 1: Cell therapy



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



Workshop Recommendations for Supporting Advancement of Cell-Based Immunotherapy for Solid Tumors

7 Research areas of unmet needs/services identified:

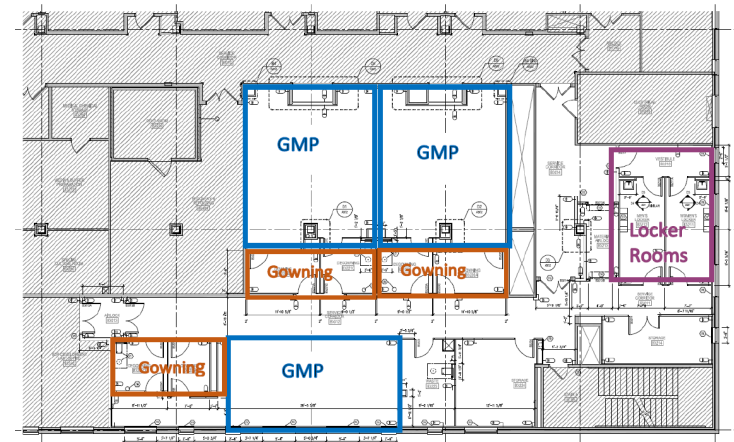
- **Preclinical and translational research** to advance cell therapy for solid tumors (tumor targets, immune cell fitness and persistence, cell trafficking, the immunosuppressive tumor microenvironment, development of preclinical models, and others) in both adult and pediatric patients
- **Small proof of concept studies** to rapidly gain knowledge of promising new treatment approaches
- **Enhancement of cell manufacturing technologies** (new cell expansion methods, genetic engineering including multigene engineering, alternatives to retroviral-based gene delivery, optimization of closed system manufacturing, new strategies for cell product screening, and others)
- **Identification of biomarkers and imaging-based detection** of response to therapy
- **Standardization of cell product characterization** through a Core Laboratory
- **QC testing for cell therapy-related reagents** (e.g., GMP vectors) needed for manufacturing
- **Guidance for investigators on preparing IND** submissions.

Cell Therapy-related Resources at FNLCR

CURRENT TECHNOLOGY	CURRENT FACILITY	CURRENT CAPACITY
<ul style="list-style-type: none"> Genetically-modified autologous cells (closed-system Prodigy platform-based) Lentivirus & Gamma Retrovirus vectors 	2 GMP suites	4 cell therapy products/month 4 virus vector campaigns/year
FUTURE ADDED TECHNOLOGY	ADDED FACILITY	ADDED CAPACITY
<ul style="list-style-type: none"> G-Rex (disposable flask) manufacturing platform CRISPR-based gene editing: FY2023 	3 new GMP suites: Q3 2022	~ 12 cell therapy products/month ~ 8 virus vector campaigns/year

In Development: Cell Therapy Core Services

- Quality Systems and Regulatory Affairs Guidance
 - Assays for product critical quality attributes
 - Provide reagents and SOPs
 - Provide regulatory guidance
- Multi-site Trial cGMP Production Support
 - Provide viral vectors and cell products
 - Novel production technologies
- Clinical Trials Coordination
- Data Coordination



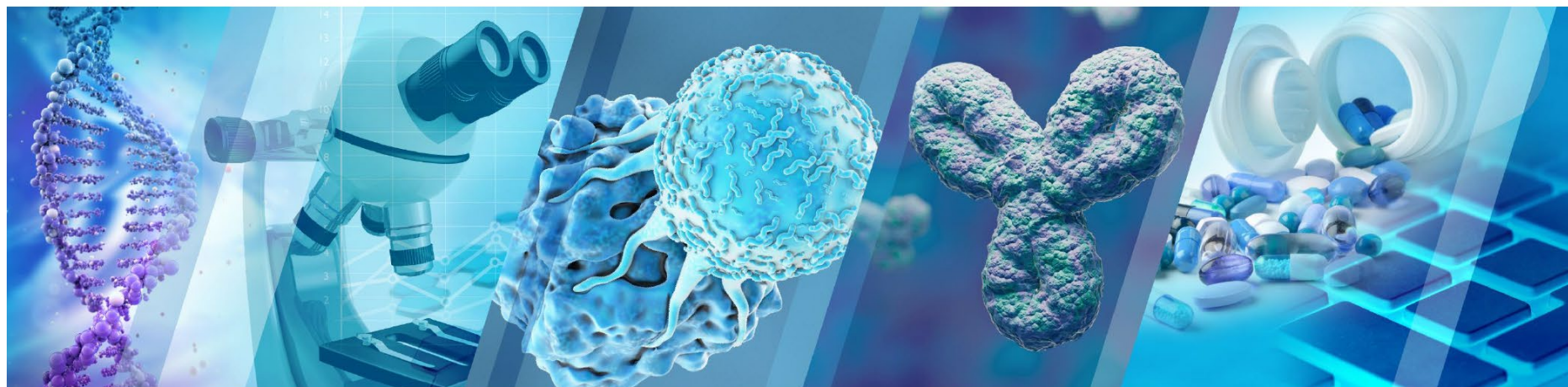
The access path to Core Services is under consideration

Subcommittee Priority Topic 2: Rational Drug Discovery

Ad Hoc Subcommittee identified topic of interest: *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

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

General Challenges

Data sharing

- Accessibility to data at early stages is lacking, open data sharing portals in specific areas with associated metadata would be beneficial

Data reproducibility

- Too many studies are irreproducible; this is a critical challenge

Unifying the research community

- There is a need to foster a community that enhances knowledge sharing, catalyzes interactions, and creates initiatives with shared connection across researchers

Taking an idea to a product

- The transition from 'idea to product' is referred to as the 'valley of death' as many discovery projects fail to traverse this gap – academics need help in translating their lab discoveries and ideas to a product for clinical use

Gaps and Opportunities

Leveraging Structural Biology and enabling tools

- Integration of cryo-EM into standard practice for structure-based discovery
- Greater support for computational resources and data management
- Expanded use of *in situ*/in cell structures in various functional states with correlative microscopy

Small molecule chemistry and novel modalities

- Support for exploring ‘undrugged’ and ‘undruggable’ targets and methods to identify novel chemical starting points for such targets
- Support for investigation of emerging small molecule discovery modalities
- Access to medicinal chemistry resource
- Earlier integration of screening with AI/ML (design vs. screening) Greater access to advanced discovery resources (e.g. fragment-based drug discovery, DNA encoded libraries)

Gaps and Opportunities

Enhancing target evaluation

- Support for 3D in vitro models and screening complex mixtures with integration into therapeutic development pipelines
- Support for genome technologies to identify possible targets for cancer immunotherapy
- Need enhanced access to medicinal chemistry with efficient follow up to target validation and lead optimization
- Target interrogation technologies and data are widespread and not harmonized

AI/ML challenges in discovery

- Overcoming conventional thinking - are we discovering ligands or drugs?
- Need experts in cancer biology and computational methods
- Data quality, data completeness, differences in terminology, source datasets, training sets (size, scope)
- Access to wet lab researchers to explain and annotate resulting data from AI/ML; models outnumber experiments that can be performed in real time

Opportunities for NCI

Support innovation

- Funding high risk/novel approaches at the earlier/vulnerable stages (R21 awards)
- Funding research on all types of cancer targets (not just druggable ones), assays and tools
- Investment in modalities beyond reversible inhibitors and occupancy-driven pharmacology

Access to resources

- Centralized medicinal chemistry core
- Increasing access to translational resources
- Sample and grid optimization process for cryoEM; provide access to other technologies such as fragment-based drug design, DNA encoded libraries

Opportunities for NCI

Technology and training support

- Improving cell models, and organoid screening capability
- Computational resources for protein prediction and design
- Support for new modalities and platforms in AI/ML
- Funding for training in specific disciplines

Fostering collaboration and quality

- Enhanced role in leading workshops, colloquia, and meetings, catalyzing interactions
- For promoting open data sharing and knowledge sharing
- Incentivizing quality and coordinating confirmatory studies

Extramural Support: Grant Funding

- Therapeutics discovery and preclinical development portfolio has ~ 850 active awards (R01, R21, P01, U01; no SBIR/STTR)
- Continually adding new funding opportunities and interests:

Assay development and screening for discovery of chemical probes, drugs or immunomodulators (R01 Clinical Trial Not Allowed)

<https://grants.nih.gov/grants/guide/pa-files/PAR-20-271.html>

Notice of Special Interest (NOSI): Advancing the development of tumor site-activated small molecules

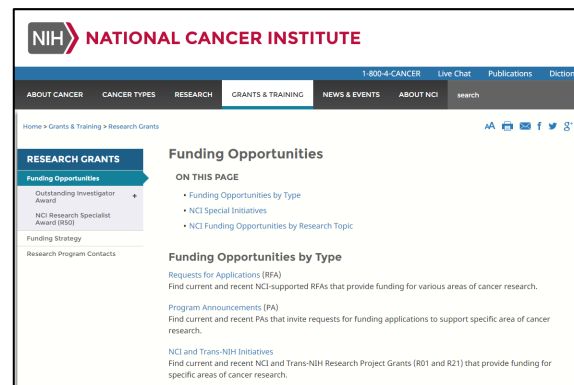
<https://grants.nih.gov/grants/guide/notice-files/NOT-CA-21-101.html>

NCI Clinical and Translational Exploratory/Developmental Studies (R21 Clinical Trial Optional)

<https://grants.nih.gov/grants/guide/pa-files/PAR-20-292.html>

Grant Program Officials:

<https://dtp.cancer.gov>



Examples: Current Discovery Resources from NCI

Cryo-Electron Microscopy at the Frederick National Laboratory

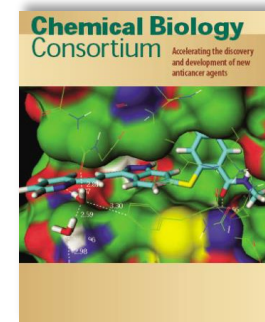
<https://www.cancer.gov/research/resources/cryoem/access>

NCI Experimental Therapeutics Program (NExT)

Chemical Biology Consortium:

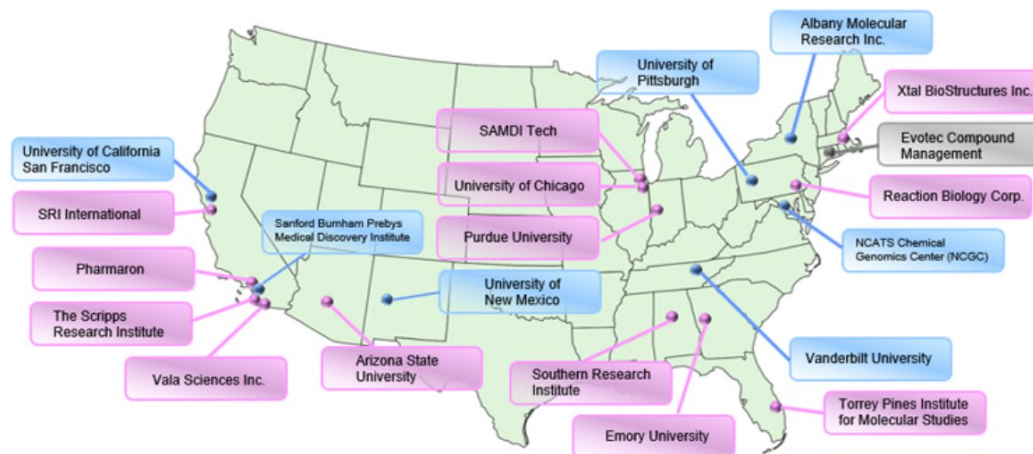
Target validation to lead optimization

<https://next.cancer.gov/discoveryResources/cbc.htm>



- In vitro and in vivo target validation
- High-throughput screening (HTS)
 - Assay design, development, validation
 - Compound library screening, hit conformation & validation
- Secondary Screening Assays
- Medicinal Chemistry
- Biophysical Characterization
 - SPR microscopy, co-crystallization
- In vitro in vivo toxicology, pharmacokinetics, pharmacodynamic marker modulation, efficacy

Map of the CBC Network



Extramural Support: Drug Synthesis & Chemistry Branch

- **NCI Chemical Repository:** >200,000 open compounds
- Synthetic and Medicinal Chemistry Resource and Expertise
- Continued acquisition of clinical and pre-clinical investigational oncology agents, bringing the total collection to 935 drugs, representing more than 60 target mechanisms

NCI 60 *in vitro* screening submission URL:

<https://ntp.cancer.gov/organization/dscb/compoundSubmission/default.htm>

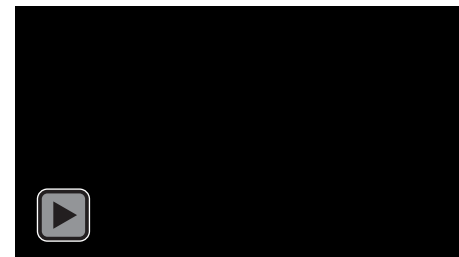


Extramural Support: Natural Products Branch

- Prefractionated natural product extracts
 - >485,000 natural product fractions have been produced so far
 - First 326,000 fractions released to the public
- Acquisition to expand breadth of libraries available to community
 - >21,000 U.S. soil fungi/~6700 Australian marine microbes obtained
 - >70 requests from screening centers for NPNDP fractions
 - 32 MTAs completed for fraction library, 52 additional MTAs for extracts
 - ~4,800,000 samples total shipped to screening centers worldwide.
- Collaborations yielded >1,900 bioactive hit fractions processed in FY2020

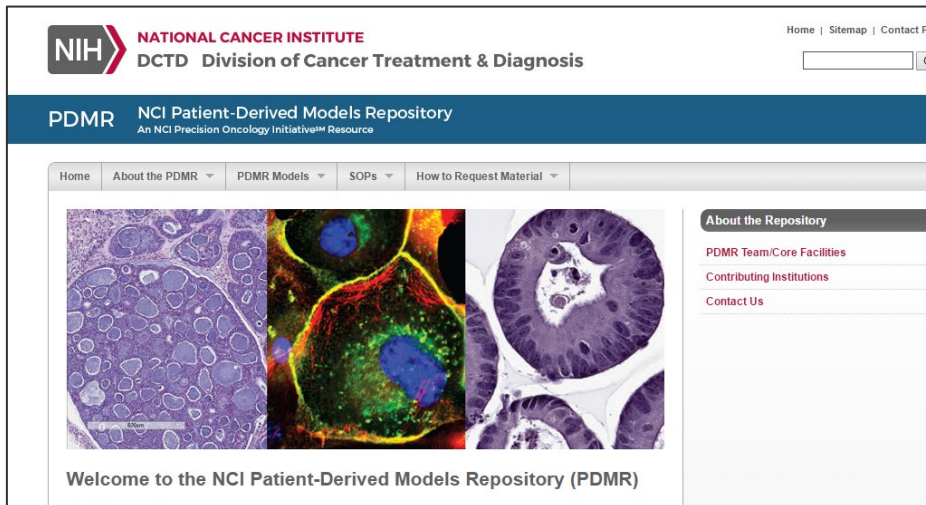
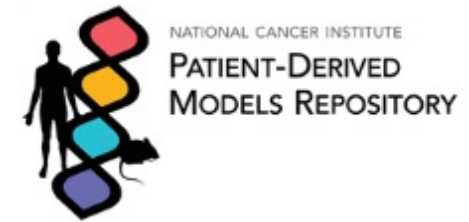
Information on NPB Repositories:

<https://ntp.cancer.gov/organization/npb/introduction.htm>



Extramural Support: Biological Testing Branch

- Efficacy Testing of Drugs in Cancer Models
- Pharmacokinetic Profiling, Dosage Testing, MTD
- Extensive Catalog of human and mouse tumors for Distribution
- **Patient Derived Models Repository (PDMR)**



<https://pdmr.cancer.gov/>



Possible Avenues for Augmented Support

- Expand access to discovery resources (CryoEM, FBDD, libraries)
- Expand access to medicinal chemistry services to collaborate with extramural groups
- Standardize language/terminology for AI/ML and criteria for completeness and source of datasets
- Sponsor training programs in AI/ML specifically for ‘wet lab’ researchers
- Invest in large and accurate publicly available screening datasets like the CRISPR knock-out database DepMap to aid in identifying targets of value
- Coordination of confirmatory studies
- Improved domain expertise and accurate data for AI/ML
- Expanding use of AI/ML in drug discovery
- Coordinated Grants, similar to Common Fund programs under the “U24/U54” umbrella

Fostering Collaboration and Community

- Lead workshops, colloquia, case studies, and special topic lectures in drug discovery to enhance community building
 - Be the 'glue' that connects the community and shares information on accessing resources, catalyze interactions, connect across initiatives, and support training, workshops, meetings, knowledge sharing, and support for aspects of the pipeline
- Increase opportunities to access drug development resources
 - Fast track access to SBIR or STTR grants for moving novel leads into pre-clinical and clinical trials; catalyze interactions with private sector and include clinicians early in the translation process (as awardees on grants)
- Promote data sharing through existing portals and tie to grant funding
 - Not a 'data dump', but curated, harmonized data using common language and having defined criteria and standards, available for viewing.

Next Steps

NCI will assess the challenges and opportunities for each area covered in the Rational Drug Discovery Workshop to:

- Formulate a list of possible actions that will assist the extramural community with RDD research
- Prioritize possible actions for feasibility, cost, strength of impact
- Return with an analysis of potential paths to assist the extramural stakeholders in the rational discovery of new cancer therapeutics



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