

***DCTD Briefing to the
NCAB Ad Hoc Subcommittee on Experimental Therapeutics***

*Rose Aurigemma, PhD, Executive Secretary
Deputy AD, Developmental Therapeutics
Program, DCTD, NCI*

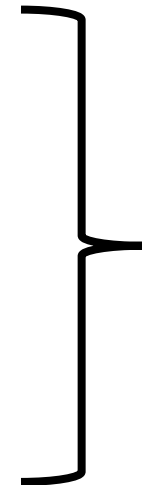
September 1, 2020

Topics

- Overview: NCI Experimental Therapeutics (NExT) program
- Overview: Developmental Therapeutics Program (DTP)
 - Therapeutics discovery and development resources
 - Grants portfolio
- Queries for future committee meetings

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 Complimentary and Alternative Medicine (OCCAM)

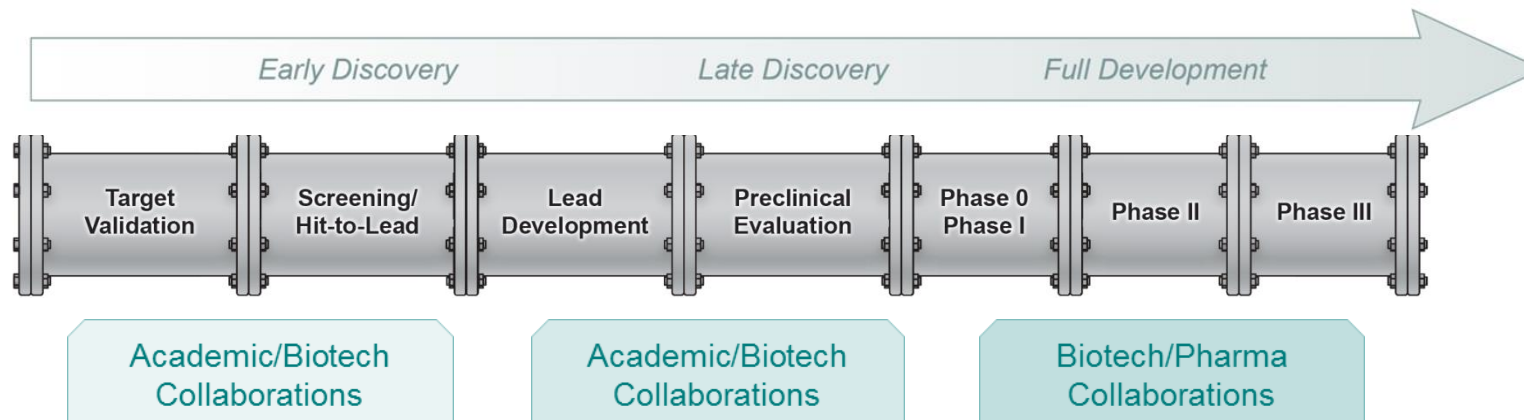


*NExT
support*

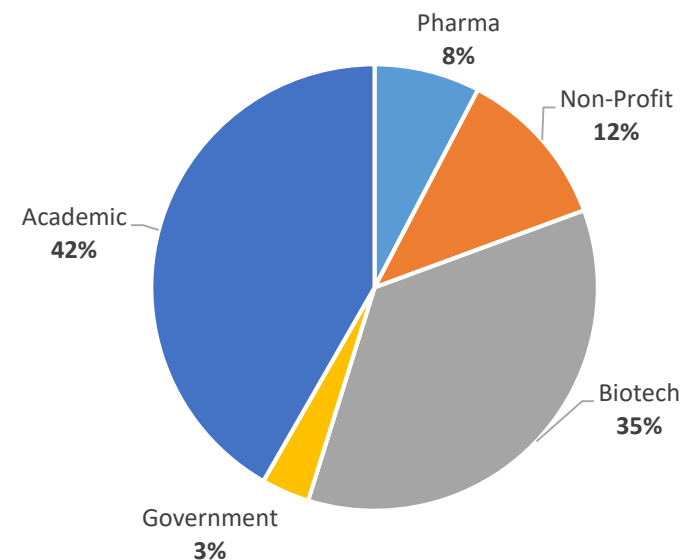
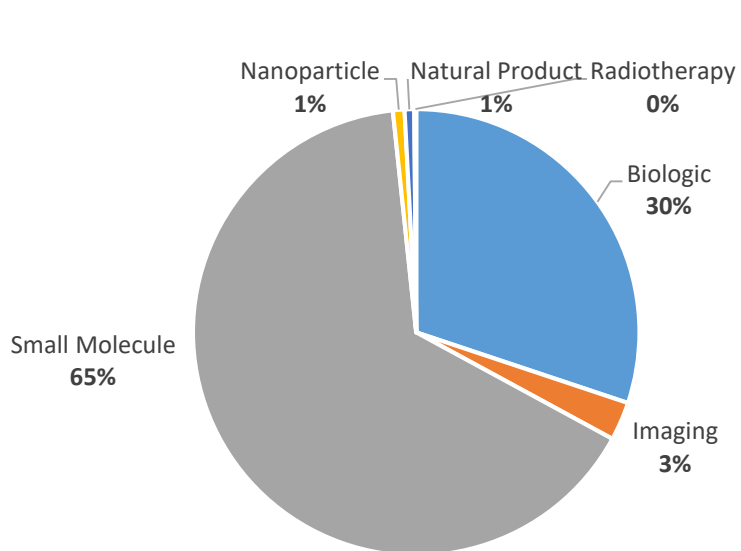
What is NExT?

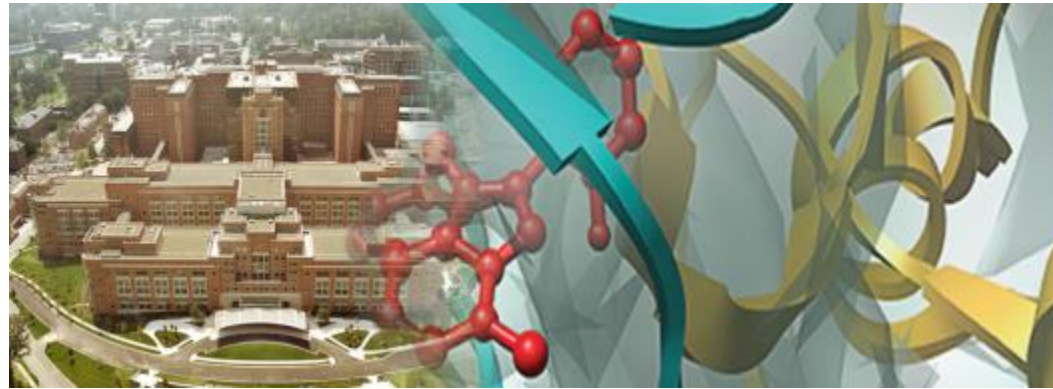
- *NOT a grant mechanism*
- Intended to provide a clear path to clinic/patient benefit
- Provides access to NCI resources and >50 yrs experience in therapeutics development
- Launched in 2009 and integrated a variety of prior decentralized programs (RAID, DDG, etc.)
- Simple application with 3 submission dates/year
- Applicant is a key member of the team: involved in project planning, implementation, and has full access to data

NCI Experimental Therapeutics (NExT) Pipeline

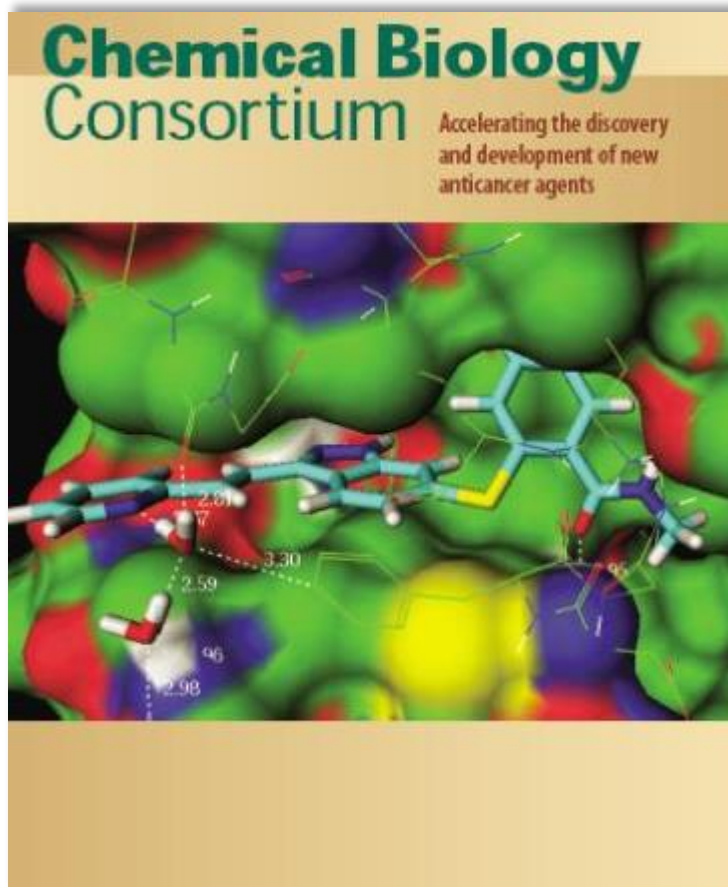


Projects can enter pipeline at any stage of discovery or development
 Since inception in 2009 NExT has received over 650 applications





NExT Discovery Engine



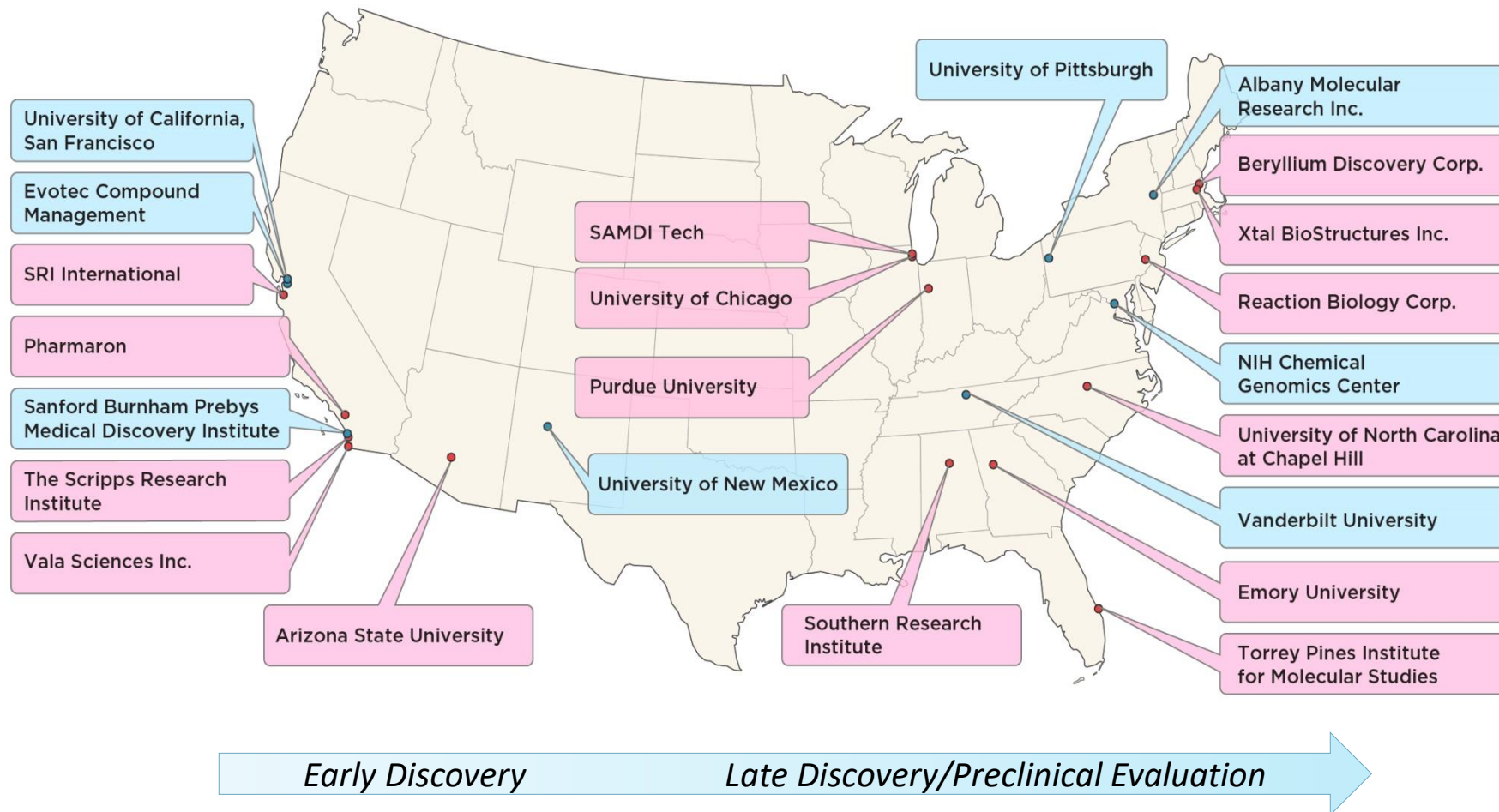
Dramatically increase the flow of early-stage drug candidates into the DCTD therapeutics pipeline by leveraging knowledge from innovative research and discoveries made at leading academic institutions and biotechnology companies

And

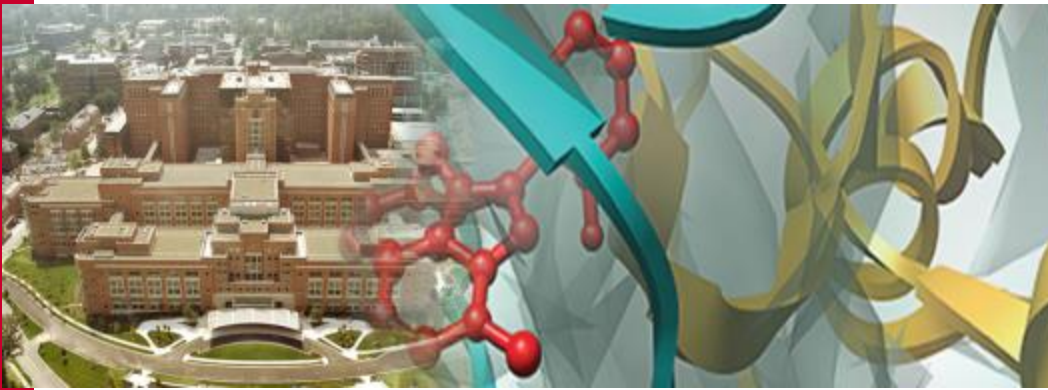
Provide the extramural community the opportunity to participate in a highly collaborative drug discovery partnership with the NCI

Spring 2016: CBC Network Expanded to 23 *Dedicated* and *Specialized* Centers with Expertise and Unique Capabilities to Support Drug Discovery Process

HTS
Bio-informatics
Medicinal Chemistry
Structural Biology



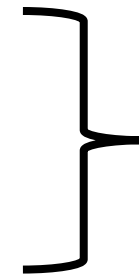
Enable teams to advance differentiated and innovative small molecule therapies to cancer patients in need



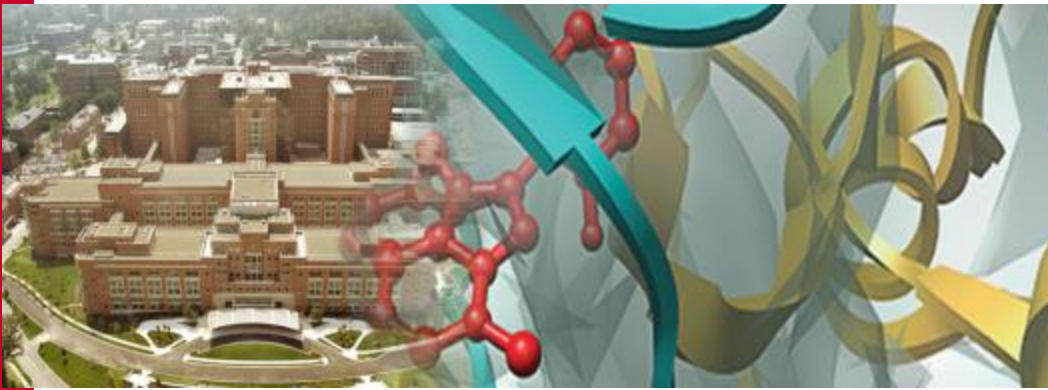
NExT Early Development

Gain access to enabling, leading-edge translational technologies and tools

- Efficacy testing in range of models
- PD Modeling
- Tox/Safety Pharmacology
- GMP Scale-Up
- Imaging supported by Cancer Imaging Program
- Development and validation of PD assays during preclinical stages is supported by the Pharmacodynamics Assay Development & Implementation Section (PADIS) and during clinical stages by the National Clinical Target Validation Laboratory (NCTVL).
- Clinical Assay Development Program (CADP) development and validation of clinical assays (including diagnostic).



*Developmental
Therapeutics
Program (DTP)*



NExT Clinical Development

- DCTD Developmental Therapeutics Clinic, NIH CRC
 - Pharmacokinetic Laboratory
- NCI Experimental Therapeutics Clinical Trials Network (ETCTN) and NCI National Clinical Trials Network (NCTN)
- Approx. 11,000 registered investigators at over 3,300 institutions
- Over 750 active protocols
- 150-250 new protocols/year
- Approx. 30,000 patients accrued/year
- Over 80 collaborative agreements (CRADAs, CTAs, and CSAs) with pharmaceutical companies (Collaborators)

Cancer Therapy Evaluation Program (CTEP)

Extramural innovators access discovery and development resources through the NCI NExT program

About NExT

The mission of the NExT Program is to advance clinical practice and bring improved therapies to patients with cancer by supporting the most promising new drug discovery and development projects.

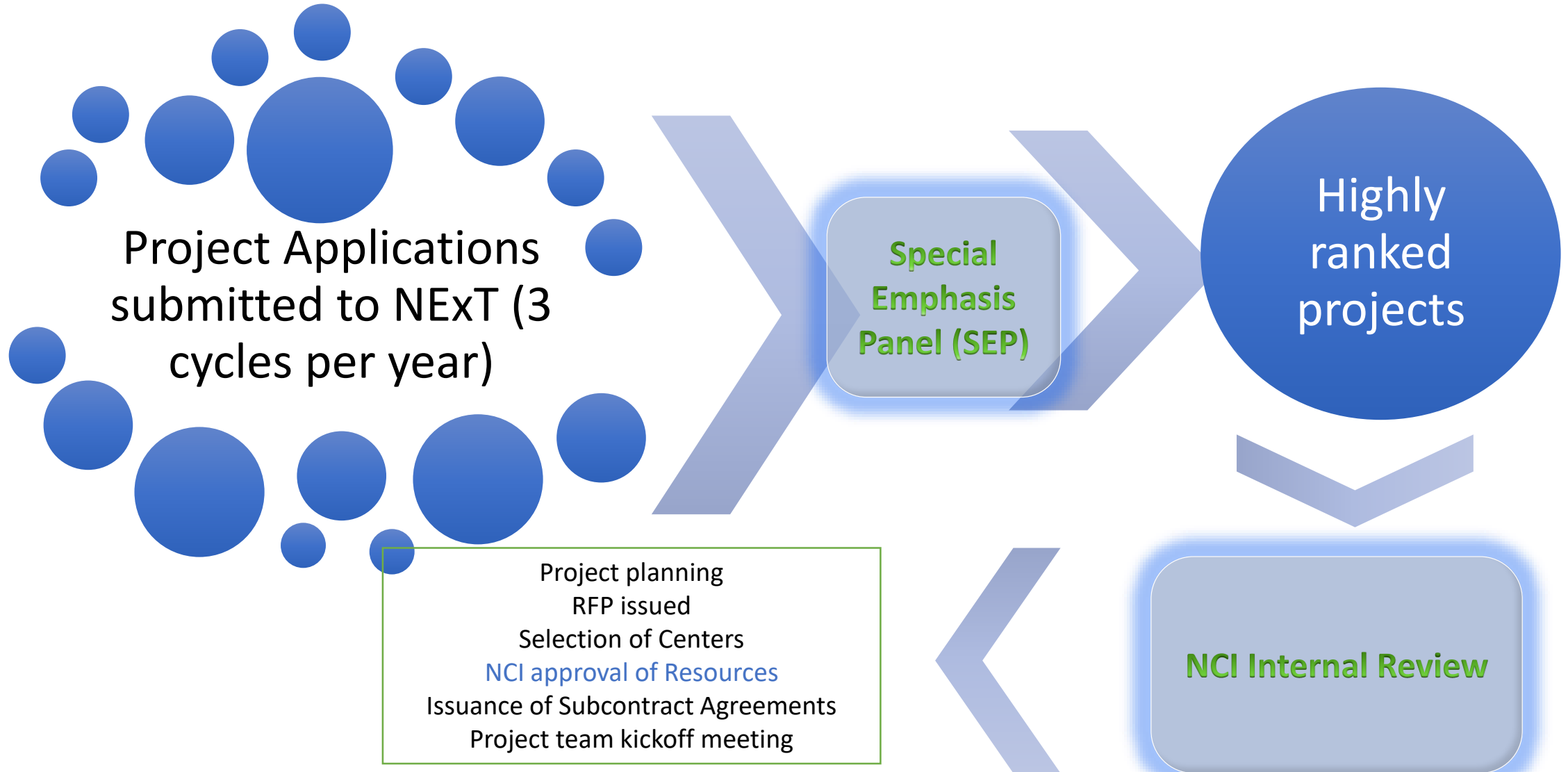
<https://next.cancer.gov>

NExT Pipeline



Services for developing small molecules, biologics and cell therapies

From Application Review to Project Team Kickoff Meeting



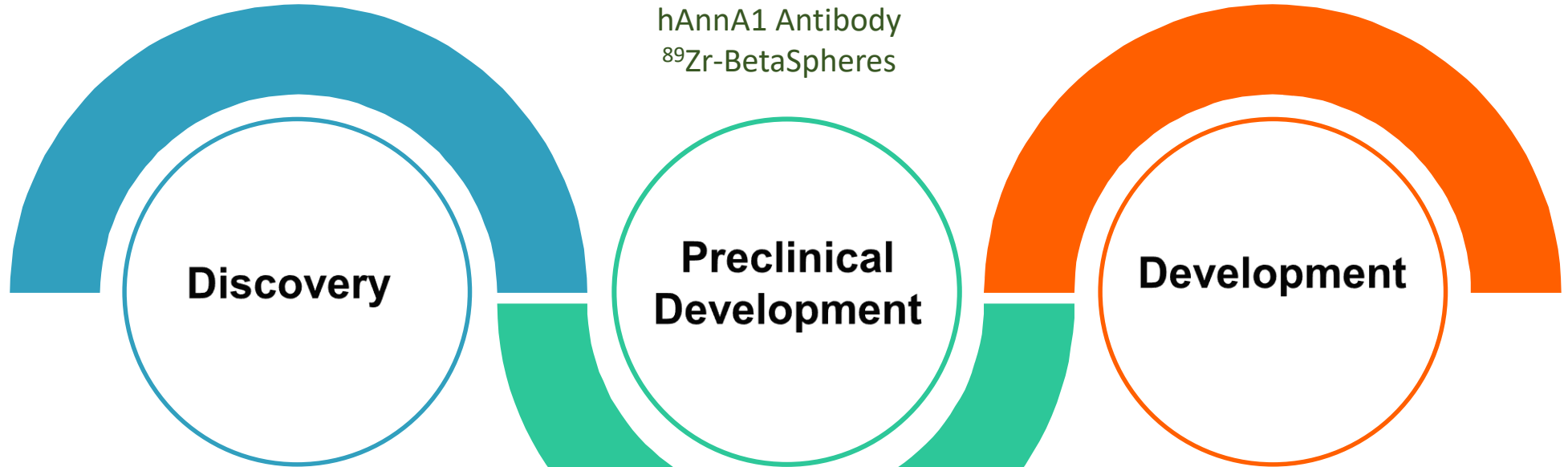
(Participation on discovery projects is approved and funded by NCI and managed through subcontracts administered by Leidos Biomed)

NExT Pipeline (2018)

Artemis Endonuclease inhibitor
Taspase1 Protease inhibitor
WDR5-MLL1 inhibitor
LDHA inhibitor
SHP2 inhibitor
PHGDH inhibitor
MUS81 inhibitor
KDM5 inhibitor

Mutant IDH1 inhibitor
Mcl1 inhibitor
AAA ATPase p97 inhibitor
CFH Antibody
hAnnA1 Antibody
⁸⁹Zr-BetaSpheres

DNMT1 Inhibitors
Mer Kinase Inhibitor
Imaging agents:
NIR Fluorophore
EGFR Panitumumab
LUM015



Discovery

**Preclinical
Development**

Development

Target Validation
Screening/Hit-to-Lead
Lead Development

Candidate
Selection

Clinical Trials

Developmental Therapeutics Program

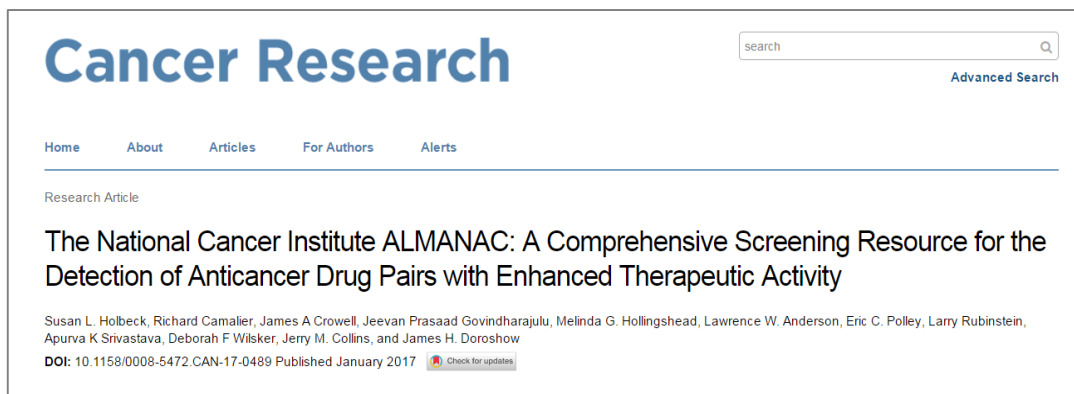
- Supports and Assists the Extramural Community to Advance New Therapeutic Concepts toward Clinical Use
- 10 Branches provide resources spanning discovery to IND-enabling activities along the regulatory critical path
- Oversee largest grants portfolio in DCTD focused on discovery and development of new cancer therapies

Bench-to-Bedside
Product Development



Information Technology Branch

- Create and maintain databases
- **Integrative data:** NCI60 cell molecular characterization, public access to data, allow
- NCI ALMANAC
- **NEWEST:** Development dashboard to integrate databases and allow data analytics



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Research Article

The National Cancer Institute ALMANAC: A Comprehensive Screening Resource for the Detection of Anticancer Drug Pairs with Enhanced Therapeutic Activity

Susan L. Holbeck, Richard Camaler, James A Crowell, Jeevan Prasaad Govindharajulu, Melinda G. Hollingshead, Lawrence W. Anderson, Eric C. Polley, Larry Rubinstein, Apurva K Srivastava, Deborah F Wilsker, Jerry M. Collins, and James H. Doroshow

DOI: 10.1158/0008-5472.CAN-17-0489 Published January 2017 [Check for updates](#)

DTP Bulk Data for Download

- **Compound Inhibition Bulk Data Download**
- **DTP Dose Response Bulk Data Download**
- **NCI-60 Growth Inhibition Data**
- **In Vivo Antitumor Assays**
- **Chemical Data**
- **Compound Sets**
- **Molecular Target Data**
- **Sarcoma Project Data**
- **NCI60 MicroXeno Data**
- **AIDS Antiviral Screen Data**
- **Yeast Anticancer Drug Screen**

Drug Synthesis and Chemistry Branch

*FNLCR resource

NCI Chemical Repository: >200,000 compounds

- Acquire, Synthesize and Distribute Chemical Samples for Research
- Plated sets: Diversity, Mechanistic, Approved Oncology Drug Sets

Synthetic and Medicinal Chemistry Resource and Expertise*

- Develop IT Chemistry Solutions



External Synthesis Contracts

- Supports NExT project Initiatives
- Synthesis of benchmark clinical and preclinical candidates

NCI Chemical Repository

- Manages new compounds submitted by extramural researchers
- Distribution of compounds for intramural and extramural research activities

Laboratory of Synthetic Chemistry

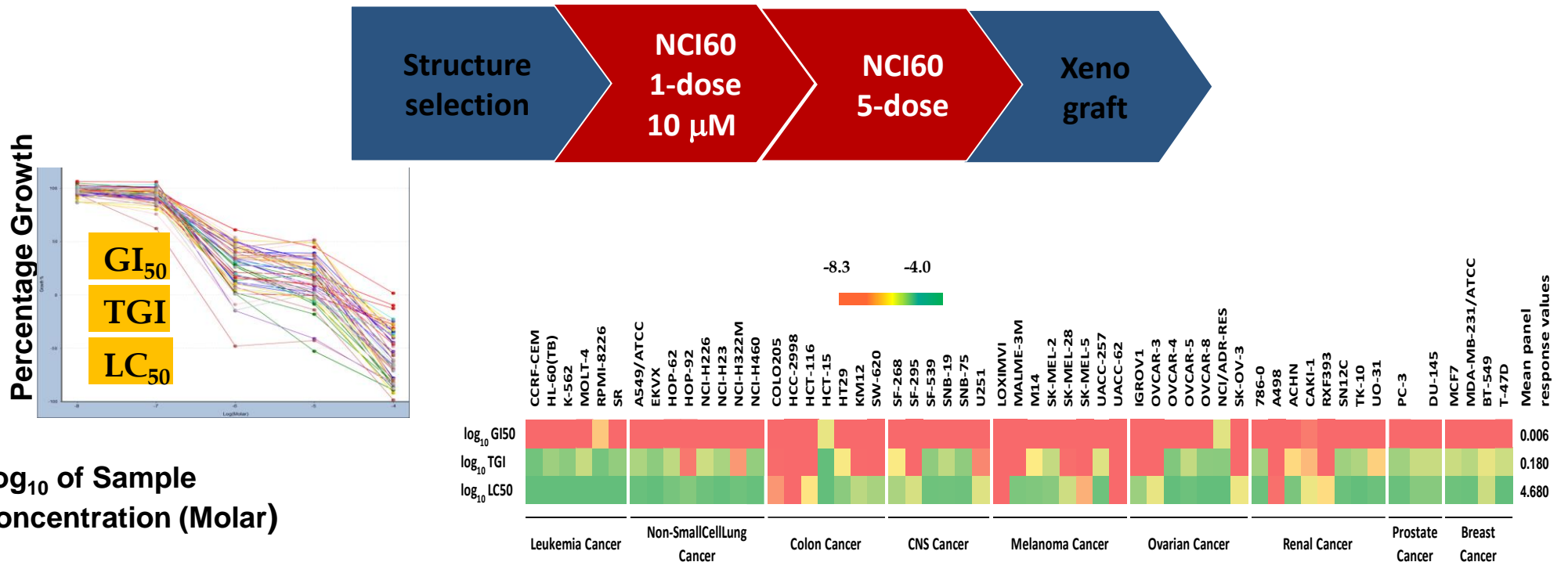
- Supports NExT discovery / development projects
- Provides chemical synthetic enablement expertise and service, across DCTD, including natural products

Pharmaceutical Resources Branch

- **GMP production:** scale-up, purification
- **Formulation:** clinical dosage form, storage conditions, shelf life, compatibility with delivery devices
- **Analytical chemistry:** assay identity, purity, potency, drug stability release specifications



- **NCI60 Cell Screen:** 60 human tumor cell lines representing leukemia, melanoma and cancers of the lung, colon, brain, ovary, breast, prostate, kidney; data can be assessed in pattern recognition algorithms (COMPARE)
- Functional Genomics, Target Validation and Screening
- **NEWEST:** Organoid and spheroid screening, HTS in 384 well platform

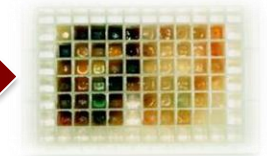
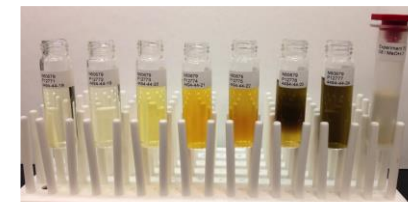


- **Natural Products Repository:** Large, diverse collections of natural product extracts (>230,000 extracts)
- **NEWEST: Pre-fractionated extract libraries,** Automated fractionation and plating for distribution and use in drug discovery

Plant Extract Library



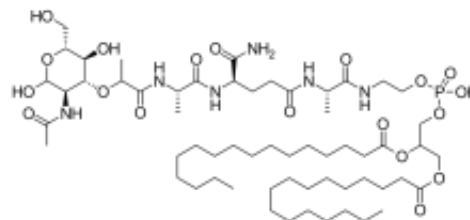
- ▶ ~161,000 extracts (organic + aqueous)
- ▶ ~44,000 plants, including 81,400 raw materials (leaves, roots, fruit, etc.) collected from Africa and Madagascar; North, Central and South America; and Southeast Asia.



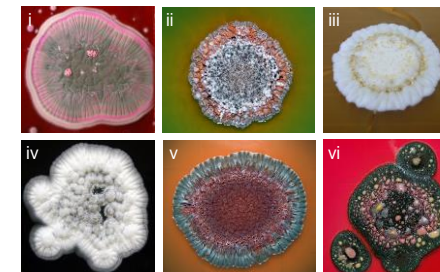
Marine Extract Library



- ▶ ~41,000 extracts (organic + aqueous)
- ▶ ~20,500 organisms collected from the Indo-Pacific region.



Microbial Extract Library



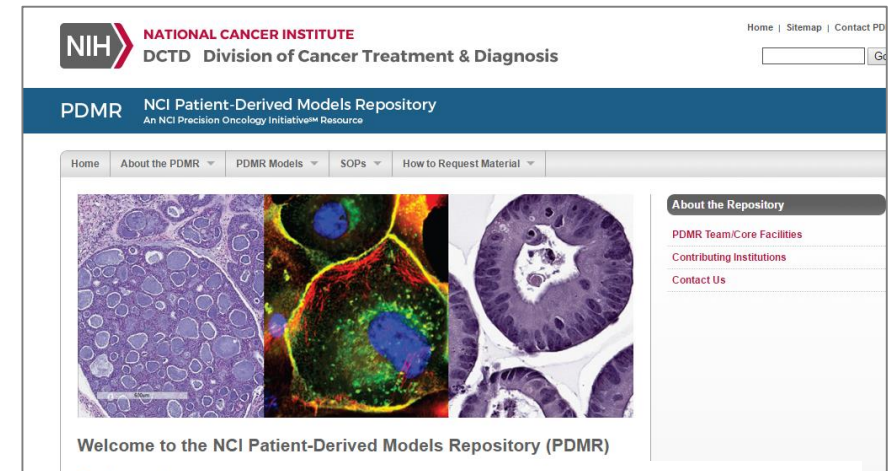
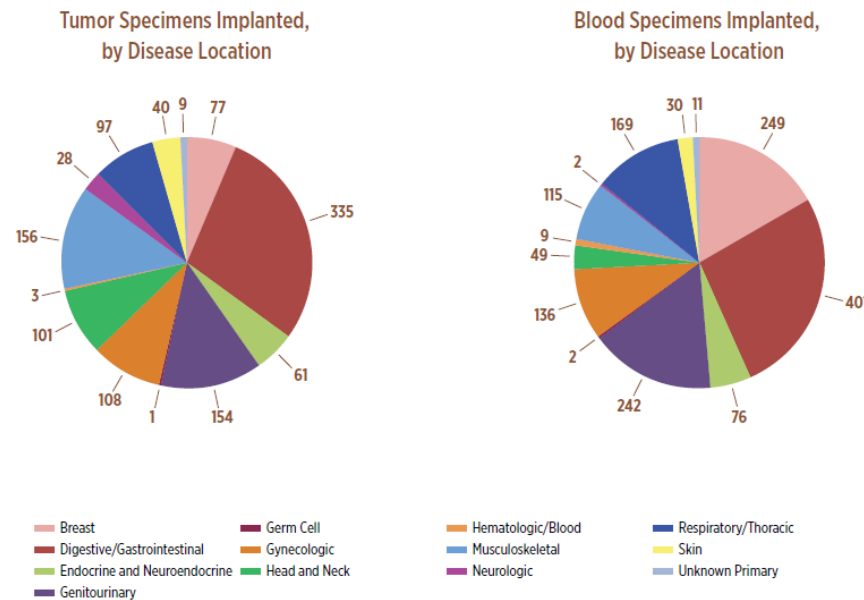
- ▶ ~30,000 extracts (organic + aqueous)
- ▶ ~16,000 organisms:
 - ▶ 4,160 unique genus and species
 - ▶ 7,600 unknown organisms

Biological Testing Branch

*FNLCR resource

- Efficacy Testing of Drugs in Cancer Models
- Pharmacokinetic Profiling, Dosage Testing, MTD
- Extensive Tumor Repository for Distribution
- **NEWEST: Patient Derived Models Repository**
- Collaborates with **Molecular Characterization Laboratory (MoCha)** and **Pharmacodynamic Assay Development and Implementation Section (PADIS)**

DTP, DCTD TUMOR REPOSITORY
 A CATALOG OF *IN VITRO* CELL LINES, TRANSPLANTABLE ANIMAL AND HUMAN TUMORS AND YEAST

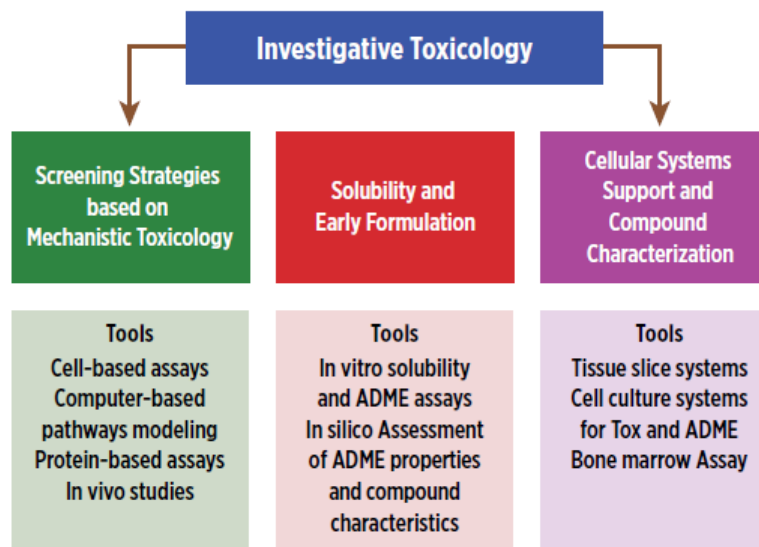
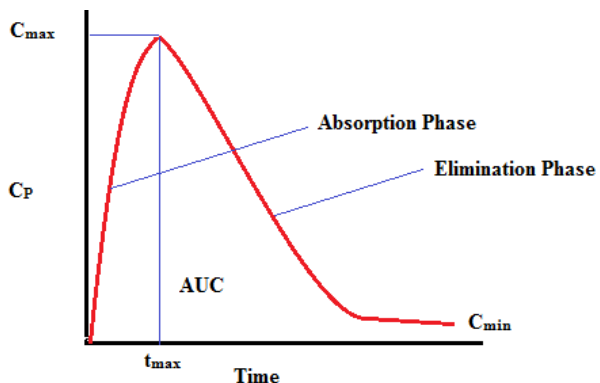


Toxicology and Pharmacology Branch

- Pharmacokinetic and toxicological profile; MTD and clinical dose setting
- **Investigational Toxicology Laboratory:** Development of special target organ toxicity assays (e.g. screening CIPN protectants)
- IND-directed toxicology studies including toxicokinetics
- Documentation for IND filing



*FNLCR resource



Biological Resources Branch

*FNLCR resource

Grants portfolio focused on development of novel biologics for clinical use Biopharmaceutical Development Program

- Cell banking: MCB and WCB production, testing and release
- Process development: optimize expression and purification
- GMP manufacturing: mammalian and fermentation using variety of platforms
- Analytical methods: development for product release and stability program
- **NEWEST**: Adoptive cell therapy and virus vector manufacturing, CRISPR editing of cell therapies



Repository of Biological Reagents:

- Monoclonal Abs
- Murine & Human Cytokines, Growth Factors
- Interferons & Interleukins



Cell therapy and virus vector manufacturing

ATRF B2300/B2310 renovation completed

Ready for cGMP manufacturing Q4 2020



FNLCR Cell Therapy & Virus Manufacturing Capacity

Product Type	Suite	Status/Capacity
Autologous cell therapy	<i>B2310 Cell Therapy Suite</i>	<ul style="list-style-type: none"> • Prodigy-based only • 2 Prodigy units produce 4/month
Lentivirus vectors	<i>Virus Production Facility (VPF)</i>	<ul style="list-style-type: none"> • 1st cGMP production in Q1 2021 • 4 campaigns per year (lenti or retro)
Gamma retrovirus vectors	<i>Virus Production Facility (VPF)</i>	<ul style="list-style-type: none"> • Process development ongoing • cGMP capability by Q2 2021 • 4 campaigns per year (lenti or retro)
Cell therapy or virus vectors	<i>New construction 3rd floor ATRF</i>	<ul style="list-style-type: none"> • 3 new suites expected on-line 2022 • 12 virus campaigns/year • Capacity for cell therapy production is product-type dependent (i.e. autologous or allogeneic, manufacturing platform)

DTP Grants Portfolio

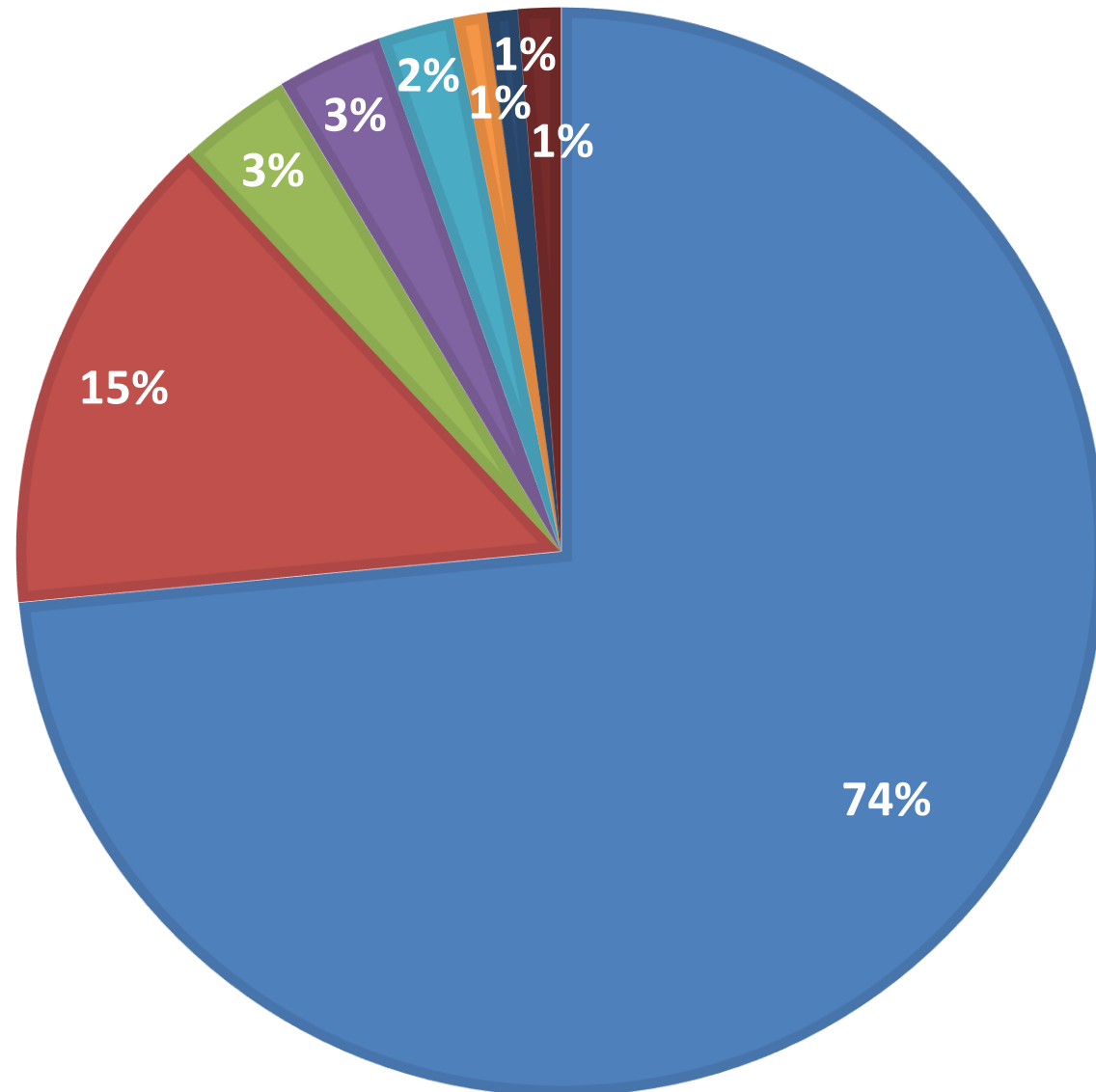
Three DTP Branches oversee grant portfolios:

- **Preclinical Therapeutics Grants Branch:** small molecule therapeutics and natural products discovery & development
- **Biological Resources Branch:** Biologics/Biopharmaceutical development
- **Immuno-oncology Branch:** immunotherapy, comparative oncology, immune modulators

The screenshot displays the NIH National Cancer Institute website. The top navigation bar includes links for '1-800-4-CANCER', 'Live Chat', 'Publications', and 'Dictionary'. The main navigation menu features 'ABOUT CANCER', 'CANCER TYPES', 'RESEARCH', 'GRANTS & TRAINING' (which is highlighted), 'NEWS & EVENTS', and 'ABOUT NCI'. A search bar is located on the right side of the navigation menu. Below the navigation, the breadcrumb trail reads 'Home > Grants & Training > Research Grants'. The page content is divided into two main columns. The left column, titled 'RESEARCH GRANTS', contains a sub-section 'Funding Opportunities' with a plus sign icon, and a list of links: 'Outstanding Investigator Award', 'NCI Research Specialist Award (RSO)', 'Funding Strategy', and 'Research Program Contacts'. The right column, titled 'Funding Opportunities', has a sub-section 'ON THIS PAGE' with links to 'Funding Opportunities by Type', 'NCI Special Initiatives', and 'NCI Funding Opportunities by Research Topic'. Below this, there are three sections: 'Funding Opportunities by Type', 'Requests for Applications (RFA)' (describing current and recent NCI-supported RFAs), 'Program Announcements (PA)' (describing current and recent PAs), and 'NCI and Trans-NIH Initiatives' (describing current and recent NCI and Trans-NIH Research Project Grants).

OVERALL DTP PORTFOLIO BY ACTIVITY CODE

R01 R21 R03 R15 R37 R35 U01 Other

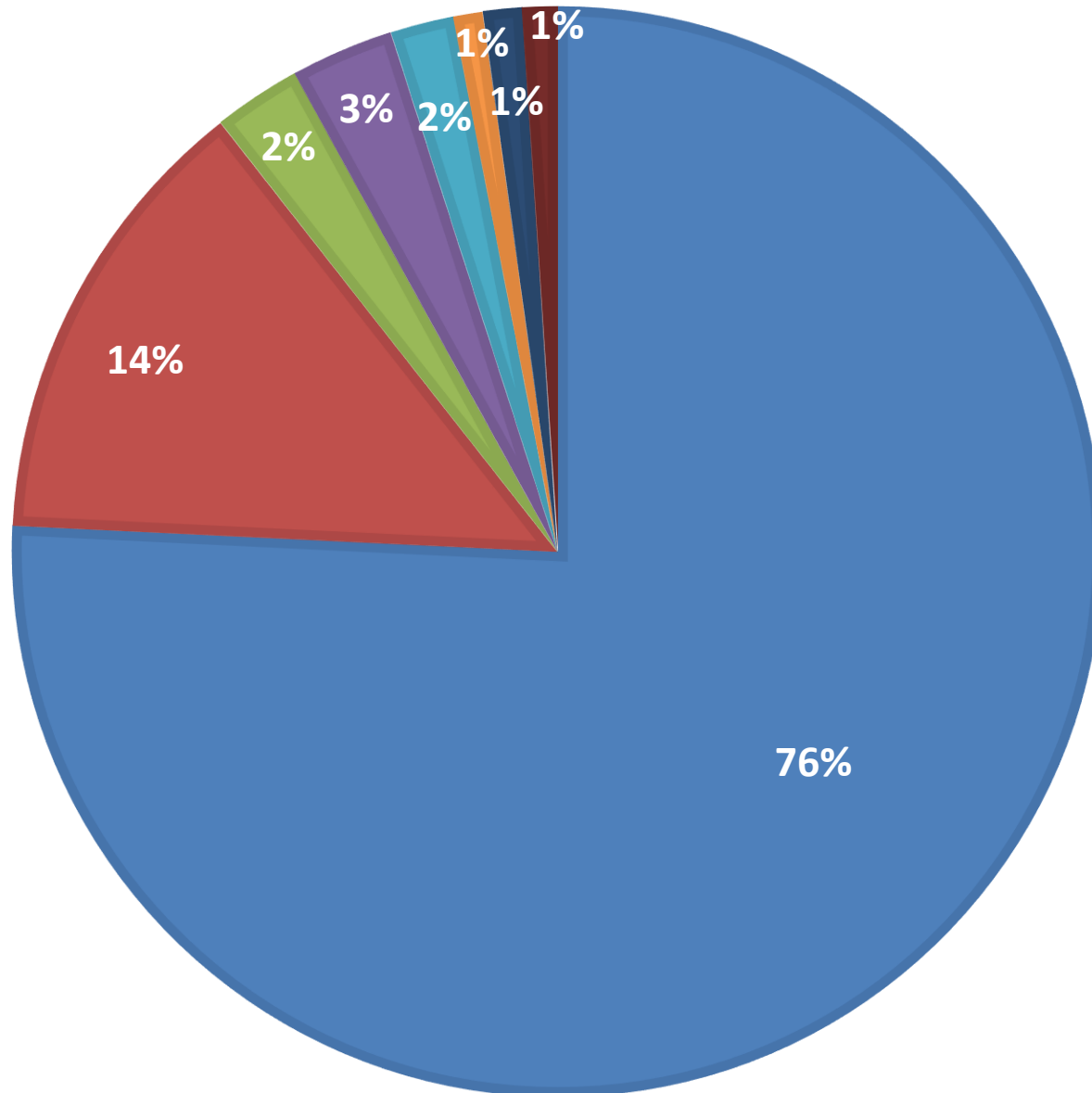


886 Active Awards
(8/31/2020)

*Other: R00, R13,
R56, U54, UH2

PTGB PORTFOLIO BY ACTIVITY CODE

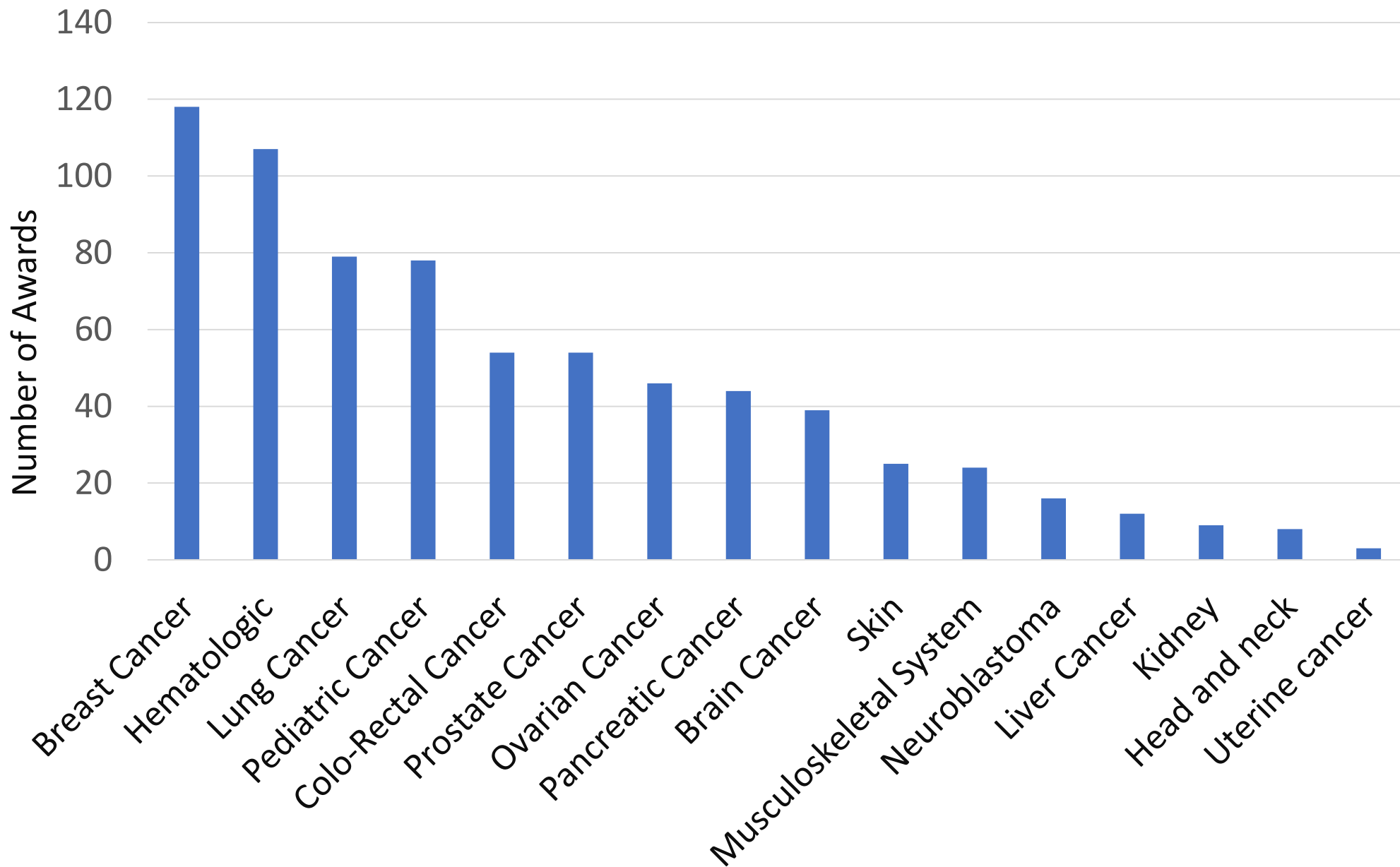
■ R01 ■ R21 ■ R03 ■ R15 ■ R37 ■ R35 ■ U01 ■ Other



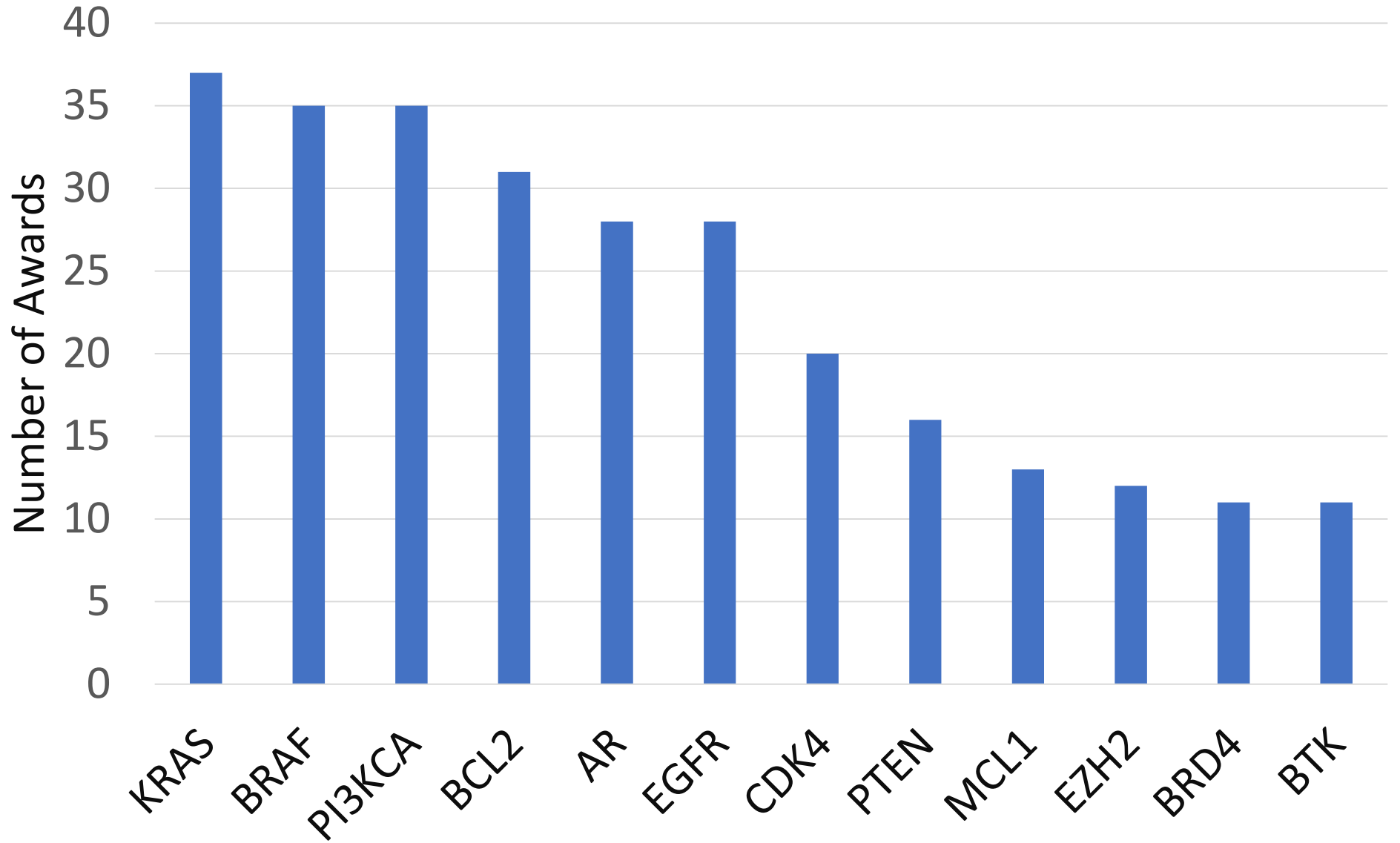
688 Active Awards
(8/31/2020)

*Other: P01, R00,
R13, R56, U54, UH2

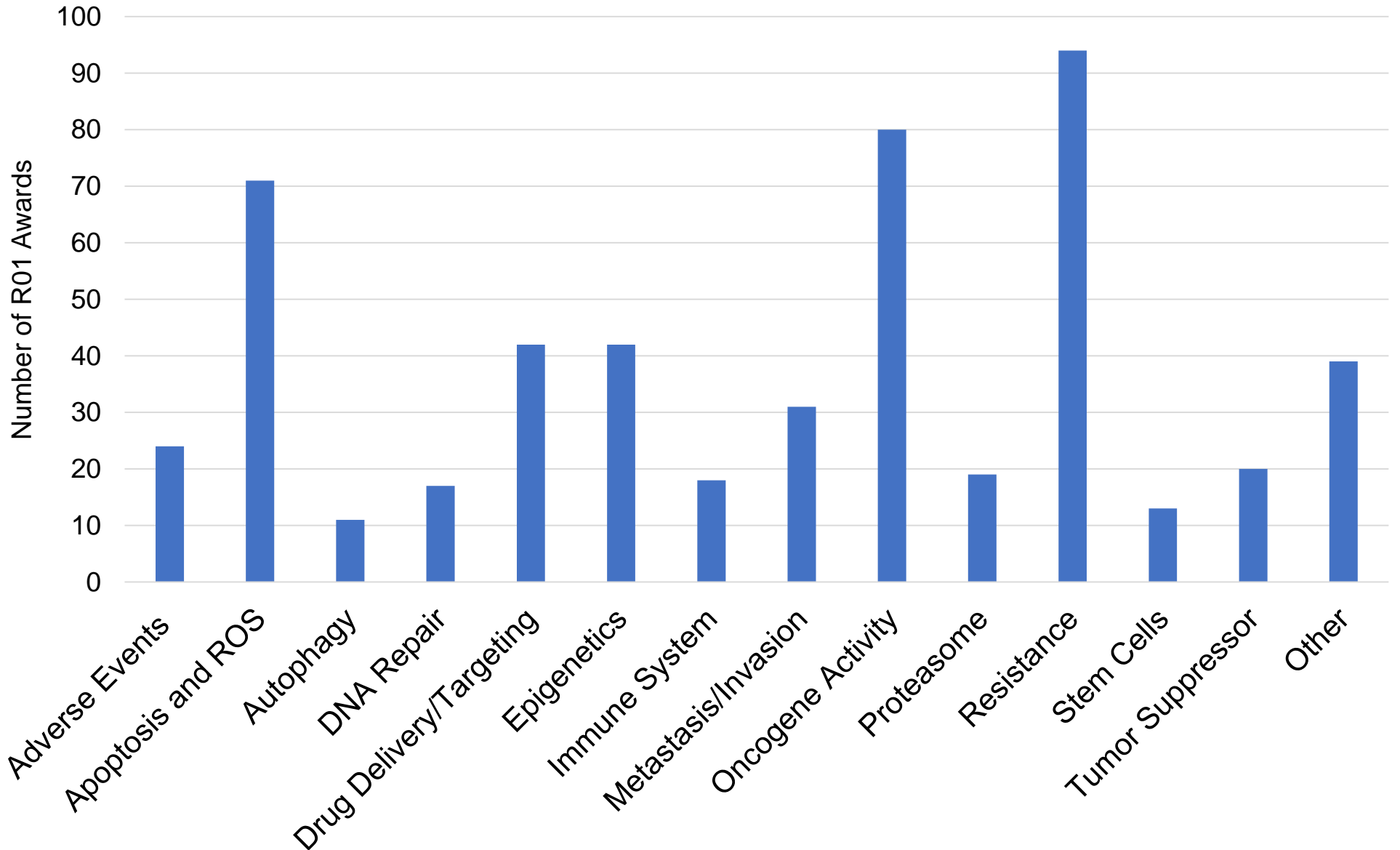
PTGB Awards by Organ/System



PTGB Top Targets (based on iSearch)

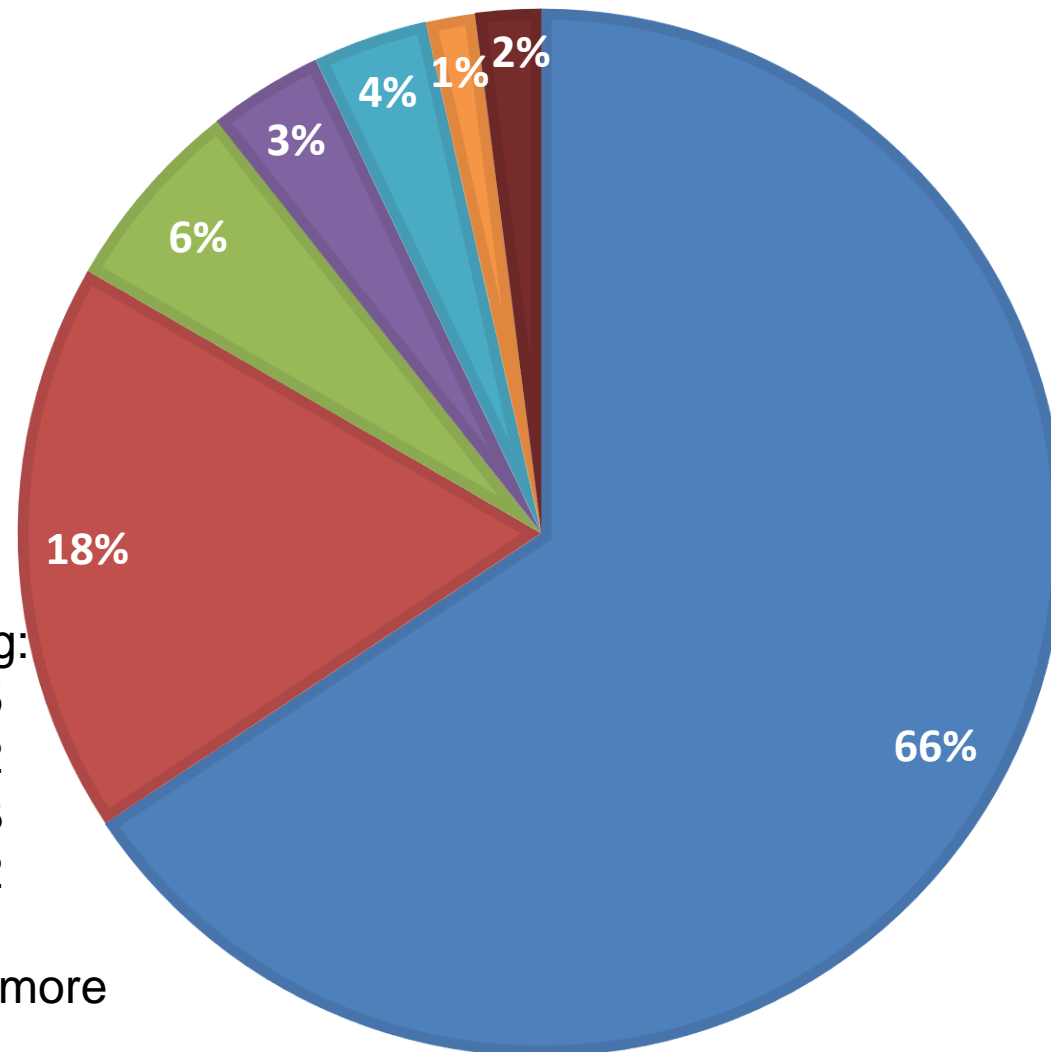


Primary Topic Areas (R01s)



BRB AND IOB PORTFOLIO BY ACTIVITY CODE

■ R01 ■ R21 ■ R03 ■ R15 ■ R37 ■ R35 ■ U01 ■ Other



198 Active Awards
(8/31/2020)

-IOB: 74

-BRB: 124

*Other: P01, R00, R13, R56, U54, UH2

BRB grants involving:

Immunotherapy	85
Oncolytic virus	12
Nanoparticle	13
Gene therapy	32

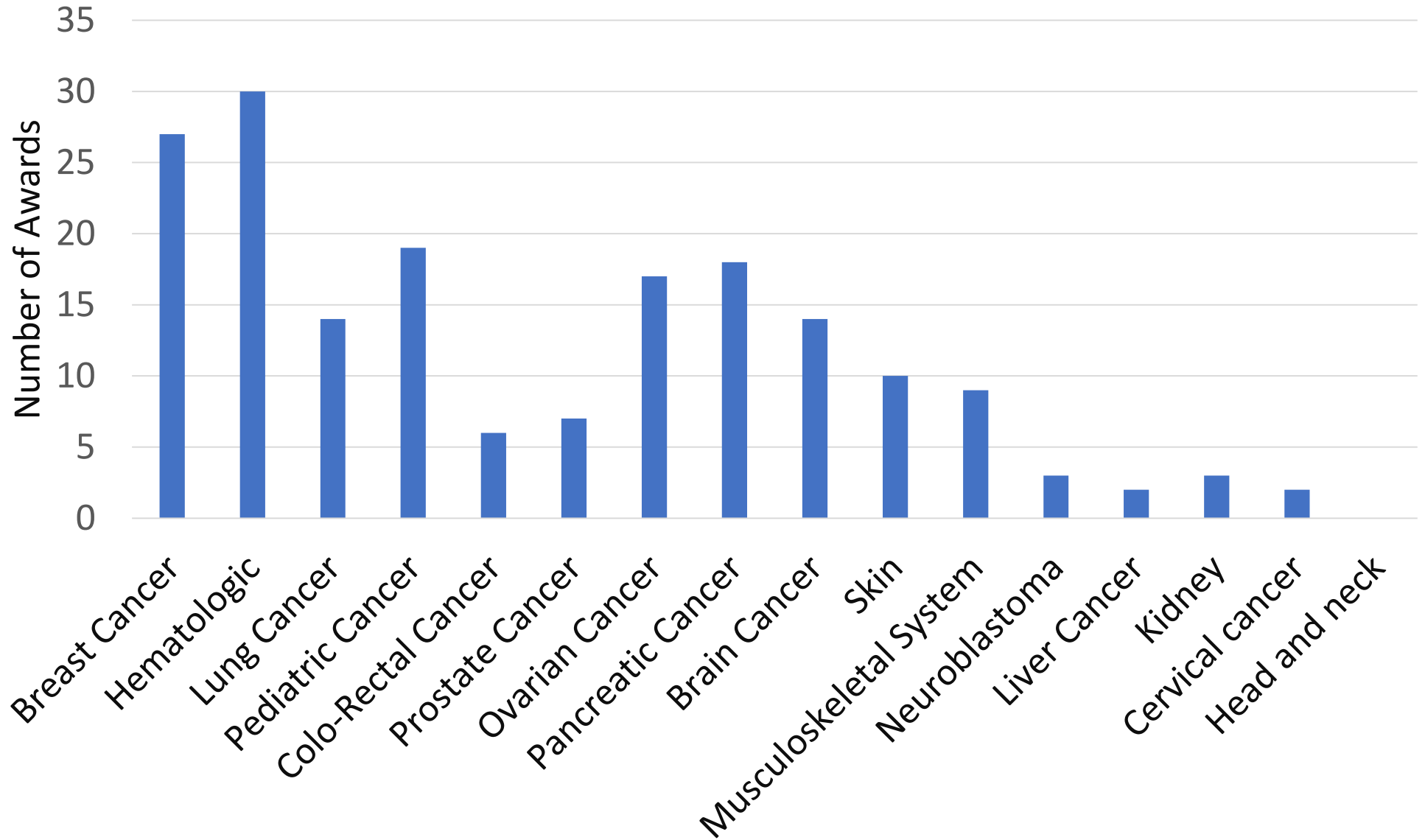
*grants may involve more than one topic

IOB grants involving:

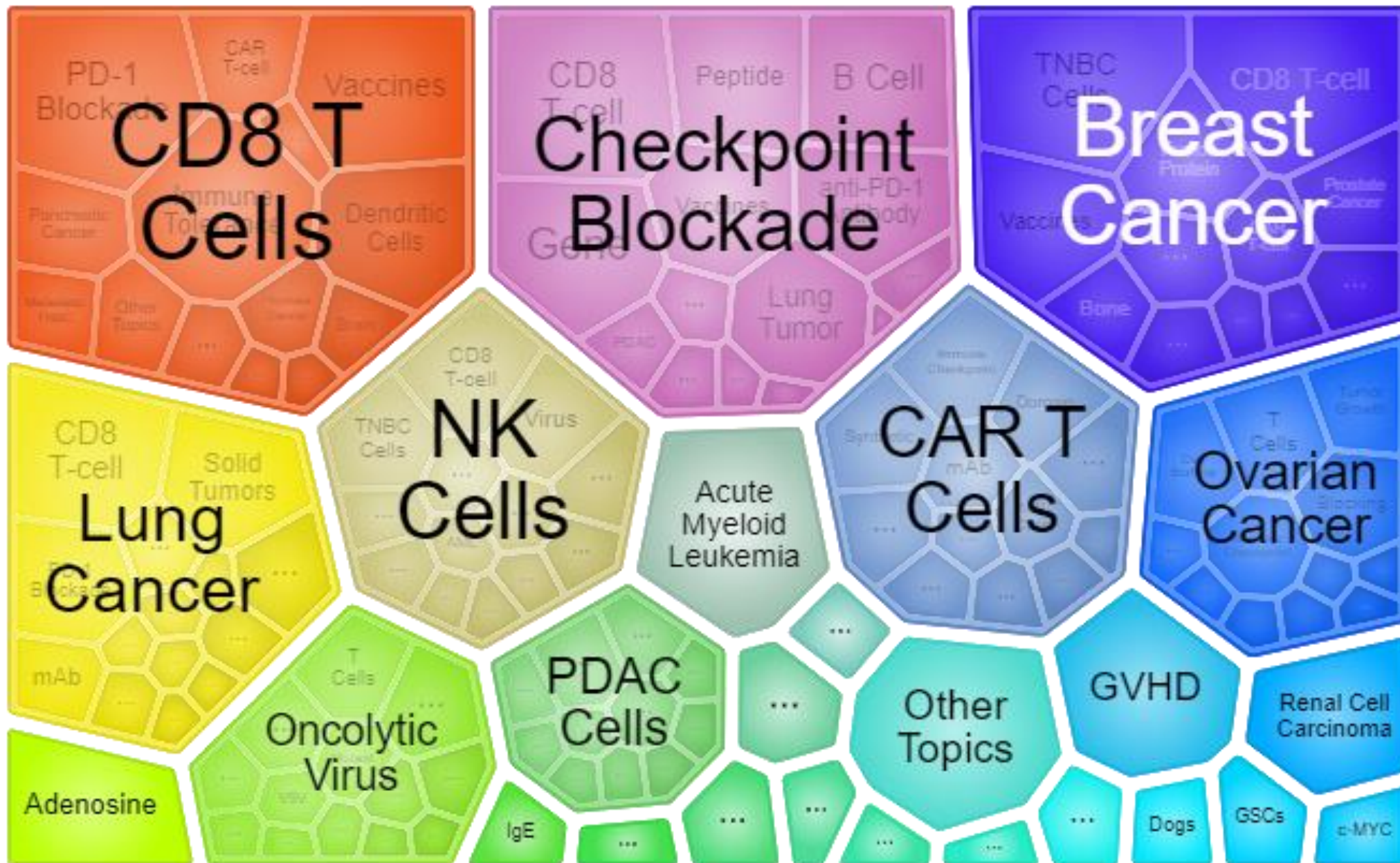
Adoptive cell Rx	13
ICI therapy	10
Canine Rx	6
Other	50

*grants may involve more than one topic

IOB and BRB Awards by Organ/System



IOB and BRB Portfolio Visualization (iSearch)



Q: What information should be provided for future committee meetings?

- Metrics for NExT portfolio
- Status of NExT projects
- Gap analysis on discovery/ developmental resources
- Deeper dive into grants portfolio