NCI Experimental Therapeutics Program (NExT):

A Government, Academic, Industry Partnership for Cancer Drug Discovery

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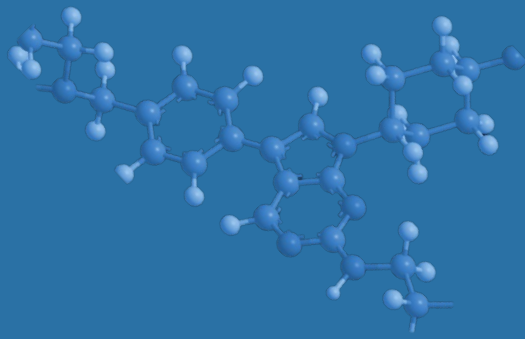

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NCI Drug Development Workshop

Session IX. NCI Translational Resources and Programs

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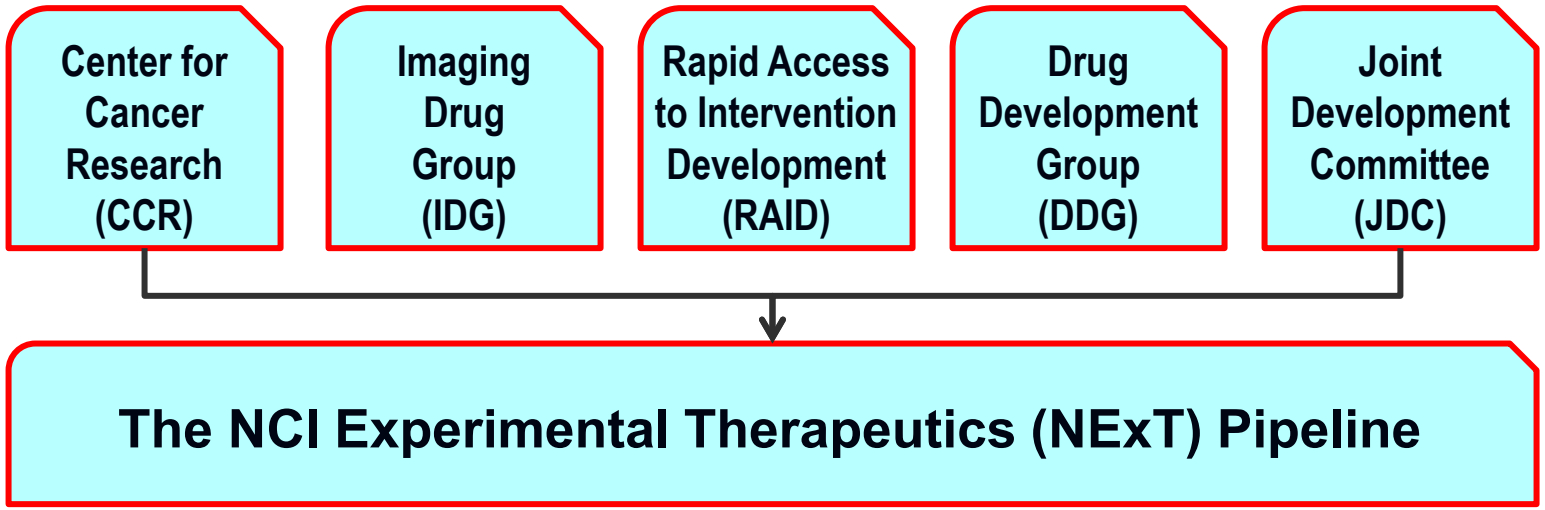
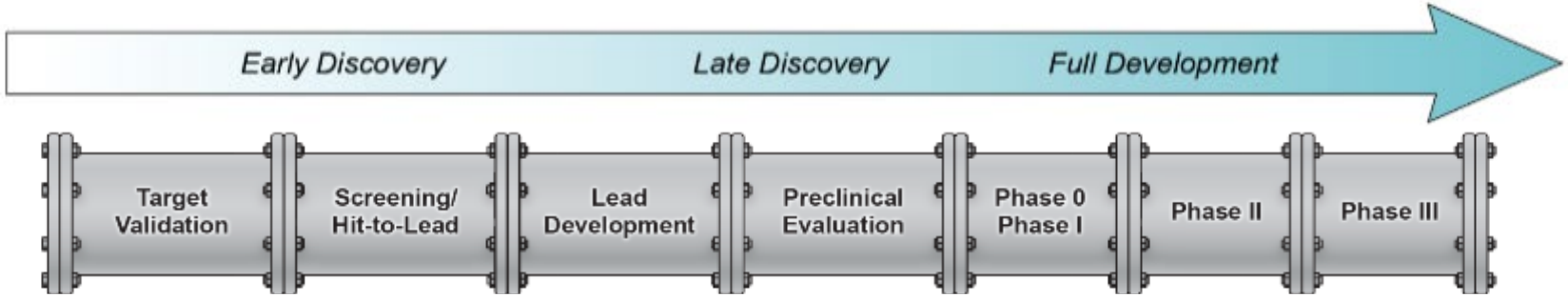
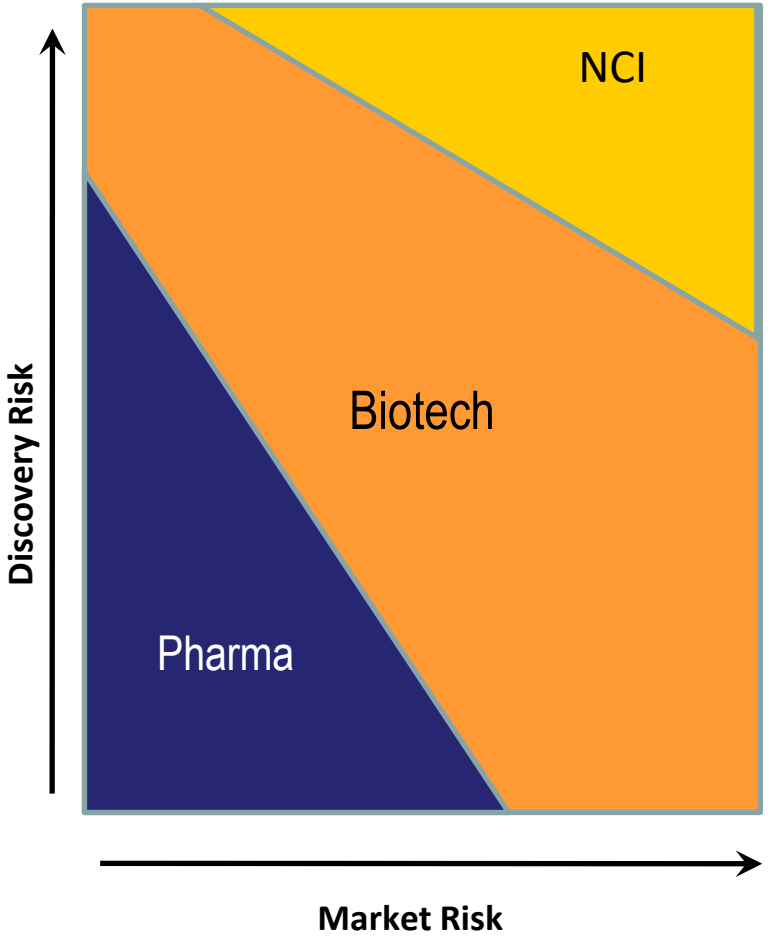
Origins of the NExT Discovery & Development Pipeline





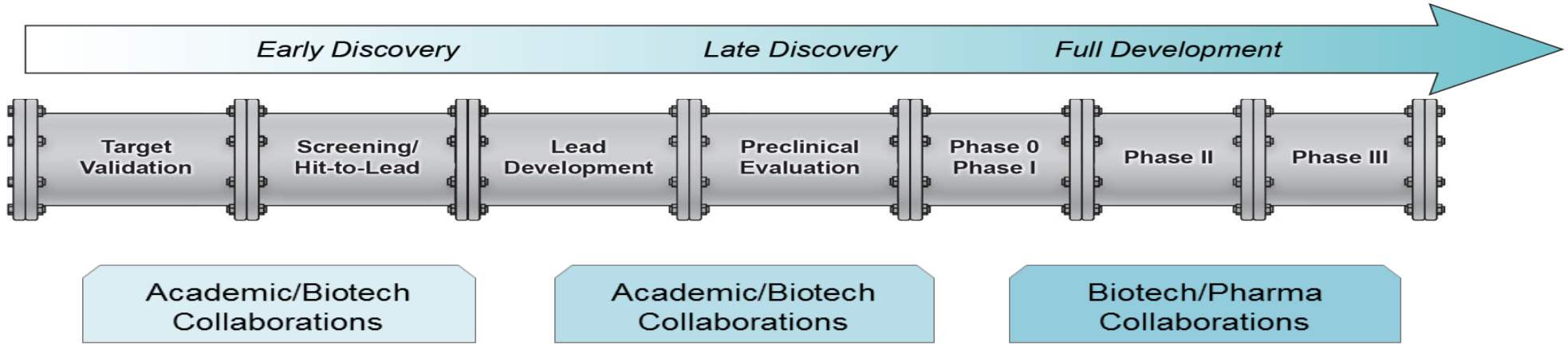
Goals of the NExT Discovery & Development Pipeline

- Not a grant program - Provides access to NCI discovery & development resources (i.e., contracts)
- Applicant is a key member of the project team - Involved in project planning, implementation, and has access to data
- Not intended to replicate Pharma - Focuses on developing therapies for under-represented malignancies & difficult targets
- Builds on >50 yrs of NCI experience in cancer drug development to increase flow of early & late-stage candidates from Academia/small biotech/Pharma to the clinic
- Integrated network of chemical biologists, structural biologists, modelers, PK, PD, Tox, imagers, GMP manufacturers and clinicians partnering with NCI
- Longer time horizon & clear path to clinic/patient benefit



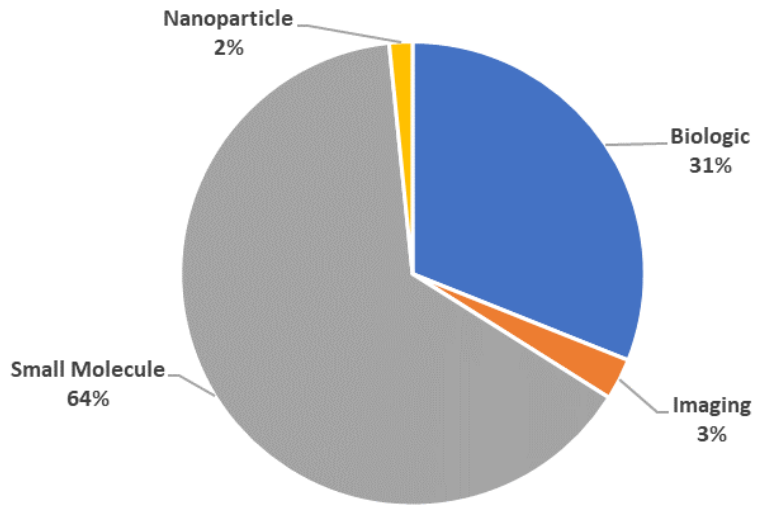
- NCI committed to supporting Discovery and later Development projects from inception through proof-of-concept, PD-driven clinical trials if milestones achieved: NCI positioned to do this

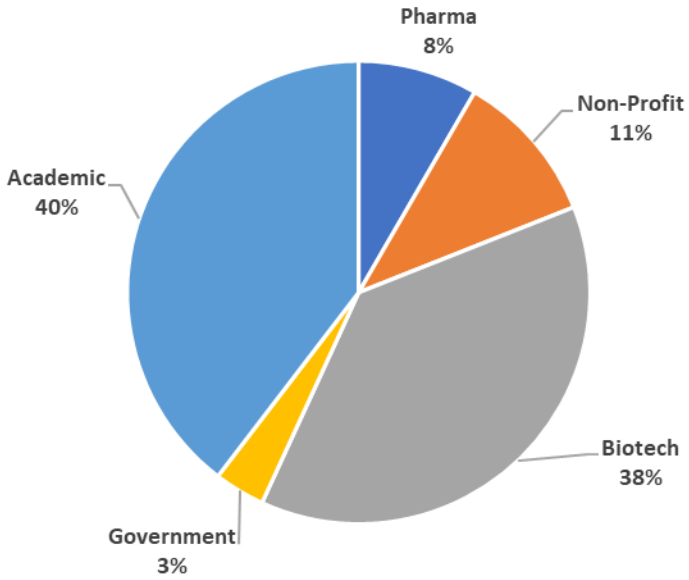
Applicants to the NExT Program



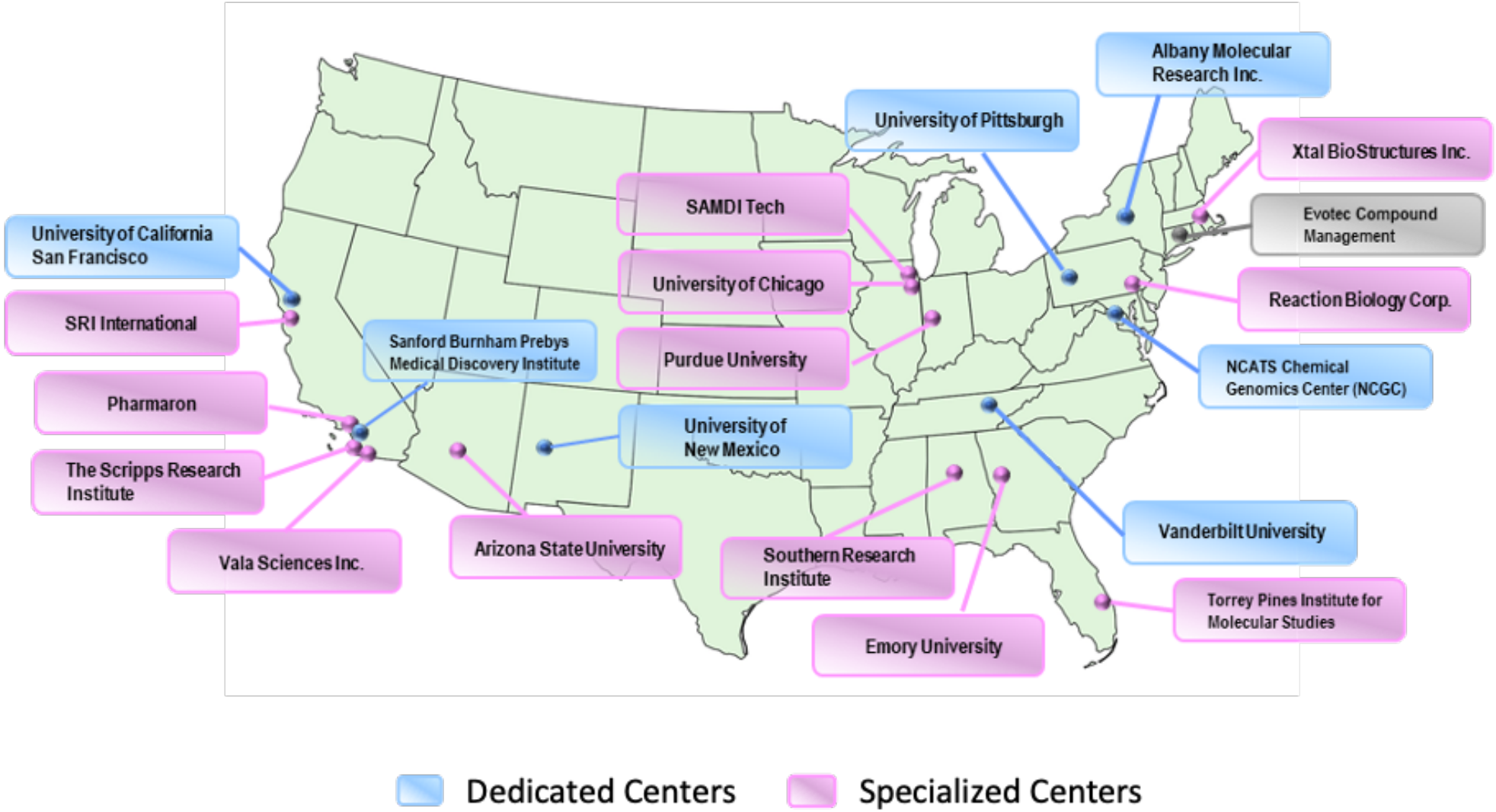
Projects enter the pipeline on a competitive basis at any stage of the pipeline

Since inception in 2009 NExT has received over 900 applications: 10-14% success rate; 50% T but V





NCI Chemical Biology Consortium: Discovery Arm of NExT



NCI Chemical Biology Consortium

From Target Validation to Lead Optimization

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

NExT Early Development

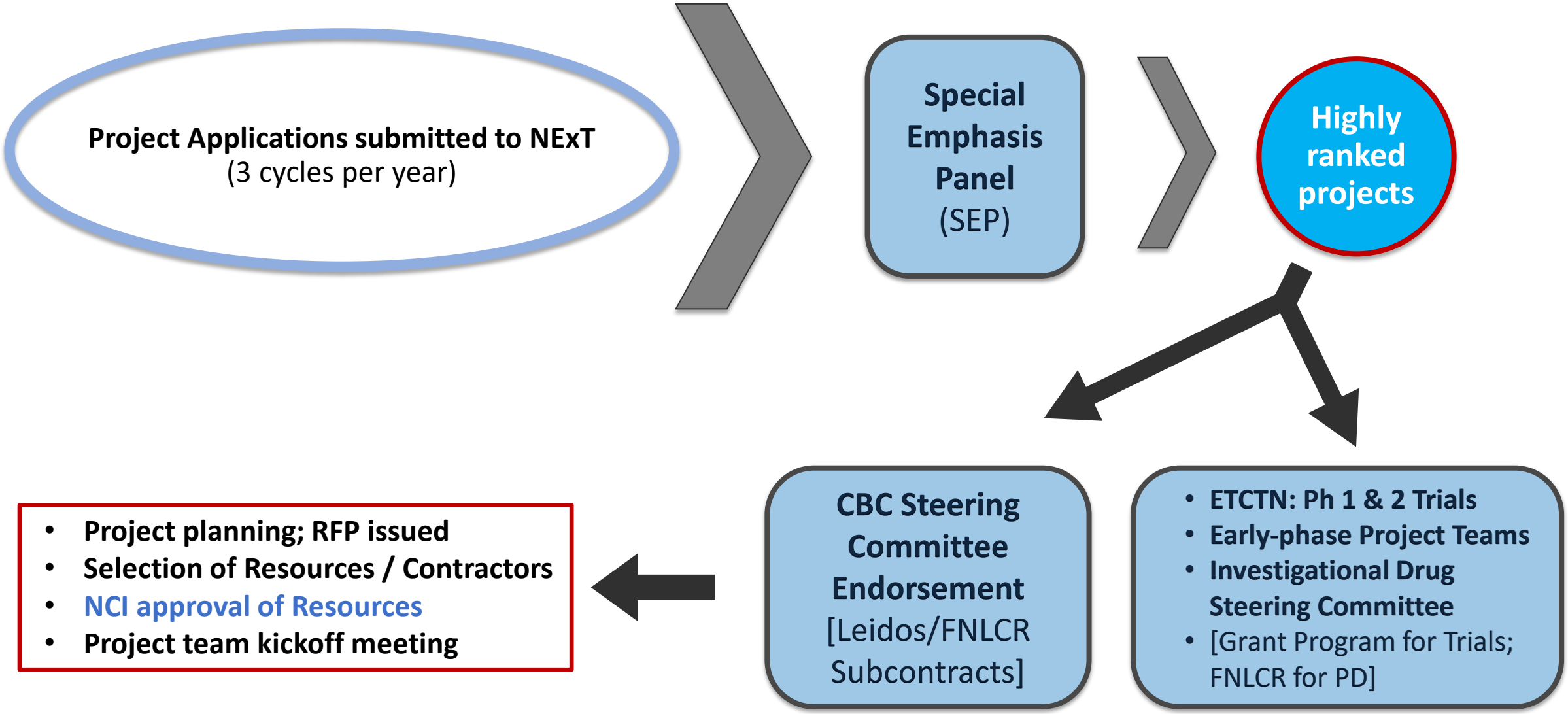
Access to enabling, leading-edge translational technologies and tools

- PK/PD Modeling
- Tox/Safety Pharmacology
- Good Manufacturing Practices (GMP) Scale-Up
- Imaging Studies
- Development and validation of PD assays during preclinical and transfer to clinical stages
- Development and validation of clinical assays (including diagnostic).

NExT Clinical Development

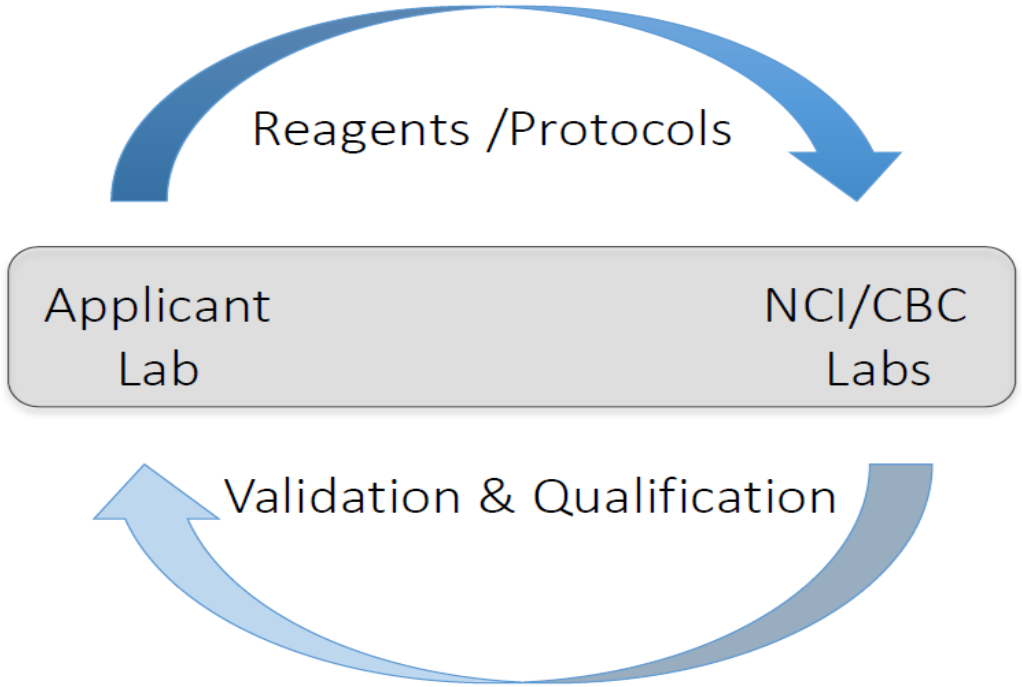
- DCTD is the largest sponsor of Cancer Clinical studies in the world
  - Currently sponsors over 100 INDs
  - Approx. 11,000 registered investigators at over 3,300 institutions
  - Over 750 active protocols
  - 150-250 new protocols/year
  - Approx. 30,000 patients accrued/year
  - **Over 80 collaborative agreements (CRADAs, CTAs, and CSAs) with pharmaceutical companies (Collaborators)**
- Over 30 years of experience, we have partnered with almost every major pharmaceutical company in the cancer development space.

NExT: From Application to Project Team Kickoff



Measures to Increase Reproducibility: Trust but Verify

Reproducing key data is initial milestone of project plan



Factors to consider

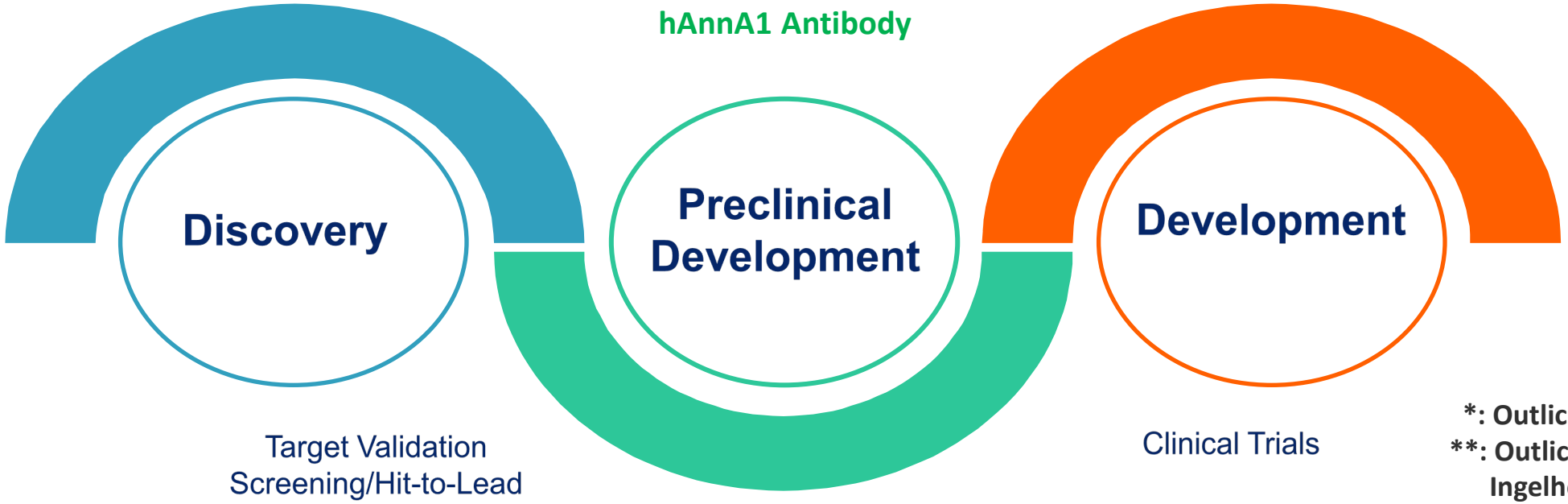
- Qualification of reagents
  - antibodies
  - cell lines
  - compound purity
- Animal models
- Assay conditions
- Protocols

NExT Pipeline

Artemis Endonuclease inhibitor
FAK
SHP2 inhibitor
NNMT inhibitor
Beta-Catenin inhibitor
Bcl-xl PROTAC

Mcl1 inhibitor**
LDHA inhibitor*
Allosteric p97
WDR5-MLL1 inhibitor
SF1
hJAA-F11 Antibody
hAnnA1 Antibody

DNMT1 Inhibitor#
Mer Kinase Inhibitor#
11-1 F4 Anti-amyloid light chain antibody**
AAA ATPase p97 inhibitor***
Endoxifen***,#**
Imaging agents:
Near Infrared Fluorophore#
Cathepsin-activatable fluorescent probe#
EGFR-Panitumumab Infrared Dye#



Target Validation
Screening/Hit-to-Lead
Lead Development

Candidate Selection

Clinical Trials

*: Outlicened
**: Outlicensed to Boehringer Ingelheim
***: Licensed to Cleave
****: Licensed to Caelium
*****: Licensing in discussion

NExT Output

Noteworthy Scientific Accomplishments:

- First high-resolution structures of targets in portfolio (both apo and complex):
  - ✓ Artemis endonuclease
  - ✓ Beta-catenin
  - ✓ Taspase1
  - ✓ Cryo-EM p97 ATPase demonstrating conformational changes accompanying ATP hydrolysis (published in Science)

Publications and Patents:

- Over 50 publications to date
- Over 10 patents filed
- 10 US / International patents awarded

Active out-licensing efforts:

- Mutant IDH1/2 oral inhibitor differentiated from first in class inhibitors. Joint collaboration between NIH NCATS and Stephen Frye, P.I., UNC.
- First-in-class orally bioavailable WDR5 inhibitor, Stephen Fesik, P.I., Vanderbilt

Partnership with NCI Comparative Oncology Program:

canine trials used to assess tolerability, efficacy and validate PD endpoints.

Therapeutic Agents Originating from CBC Pipeline Entered the Clinic:

- First-in-class oral Mer TK inhibitor, E. Shelton Earp, P.I. (phase 1)
- First **orally bioavailable novel** cytidine analog (Aza-TdCyd) demonstrated to inhibit DNMT1 in vivo; currently in Phase I dose escalation at the NCI (collaboration with Southern Research)
- First-in-class oral ATPase inhibitor targeting proteotoxic stress, Ray Deshaies, P.I. Caltech, collaboration with Cleave (phase 1)
- First-in-class targeted therapy for Light Chain Amyloidosis (chimerization of murine monoclonal antibody and GMP production to support Phase 1 trial). Technology licensed to Caelum Bioscience, currently being developed under two FDA Orphan Drug Designations
- First-in-human trial: oral endoxifen for tamoxifen resistant ER+ tumors

Therapeutic projects anticipating IND filing in 2021:

- High affinity inhibitor of Mcl-1 dependent protein-protein interactions, Stephen Fesik, P.I. (licensed to Boehringer Ingelheim)
- First-in-class orally bioavailable LDHA inhibitor, Chi Dang, P.I. (licensed to Biotech)

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