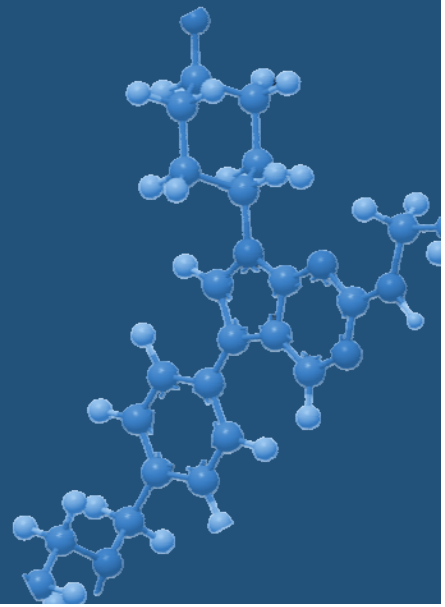
National Cancer Institute

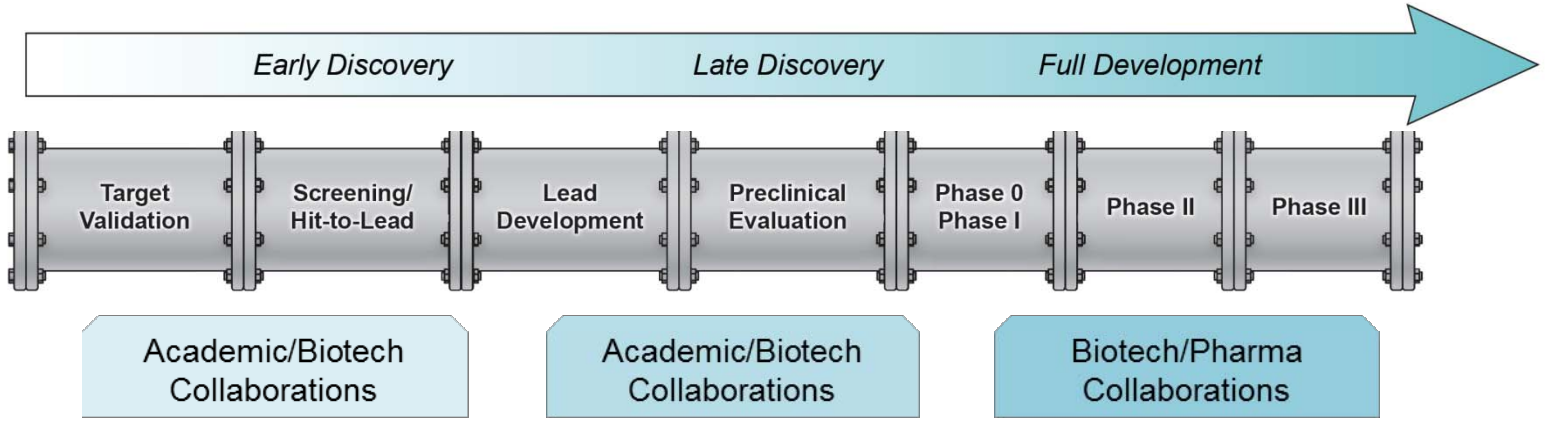
NCI Chemical Biology Consortium

Barbara Mroczkowski
National Cancer Institute



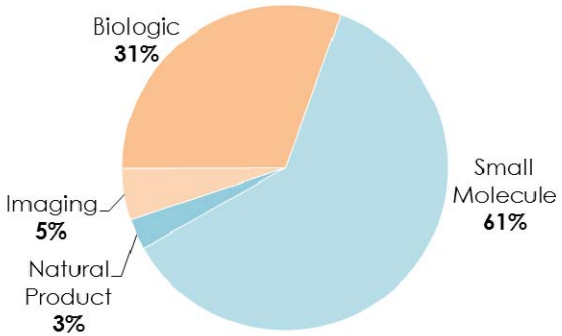
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

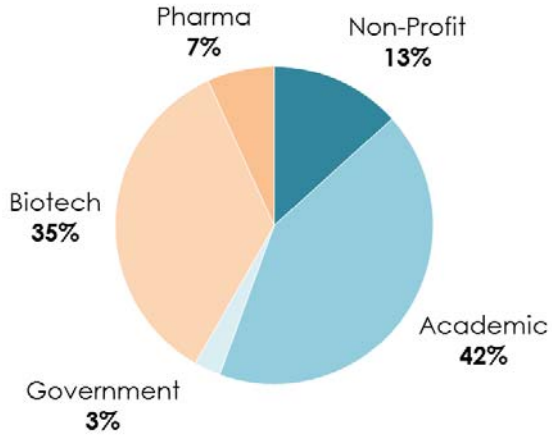
NCI Experimental Therapeutics (NExT) Pipeline



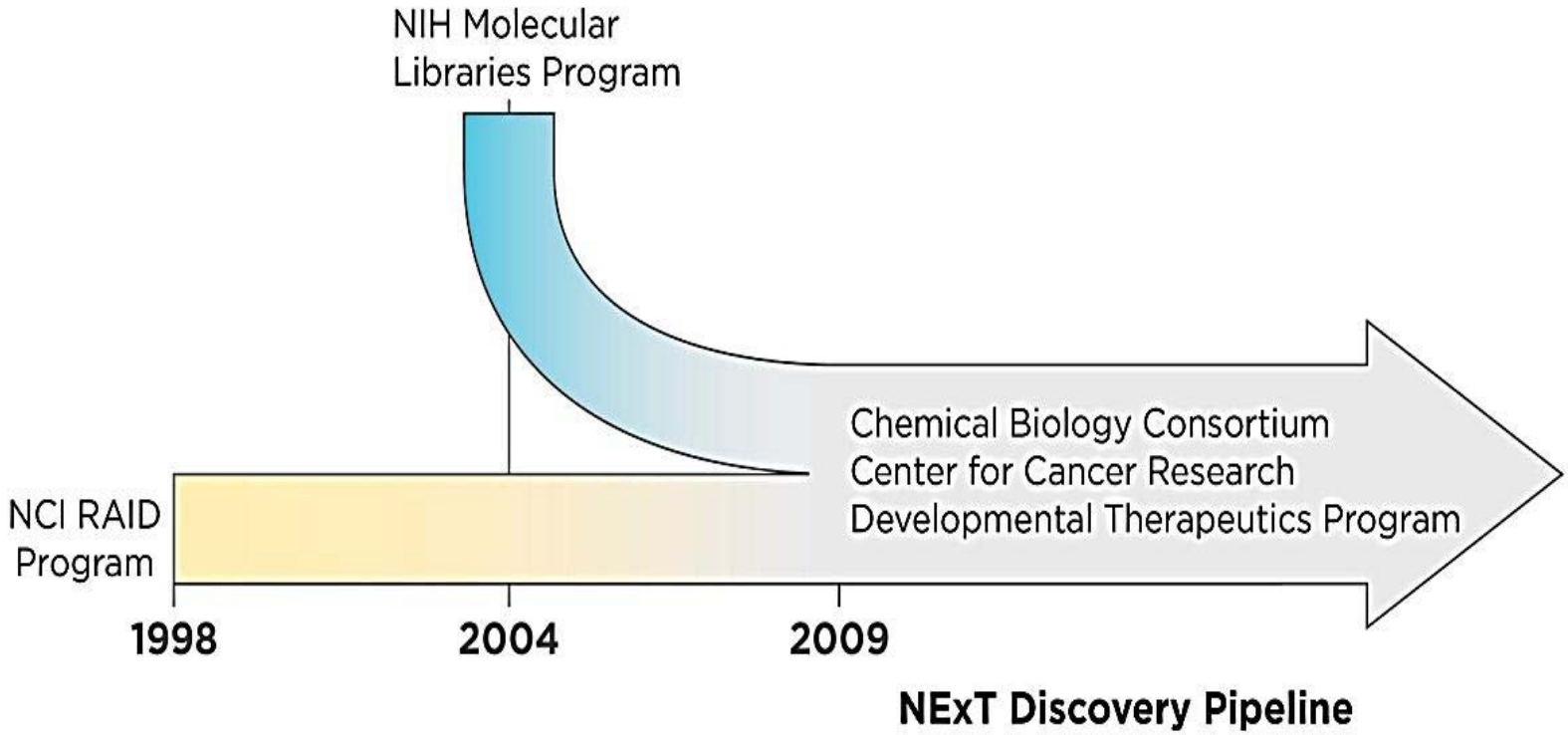
Projects enter the pipeline on a competitive basis

Since inception in late 2009, NExT has received over 600 applications



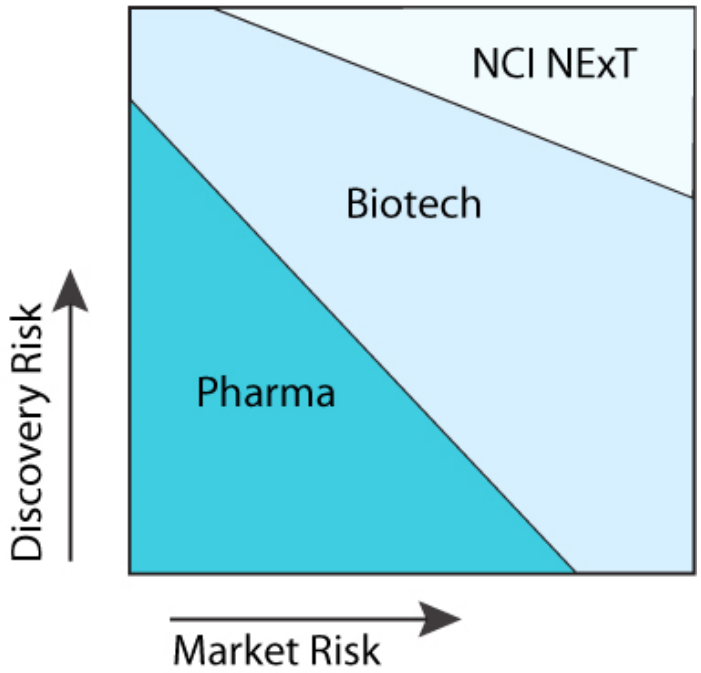


Origin of the Chemical Biology Consortium



Leveraging substantial investment from NIH Common Fund in academic screening centers through the Roadmap Initiative

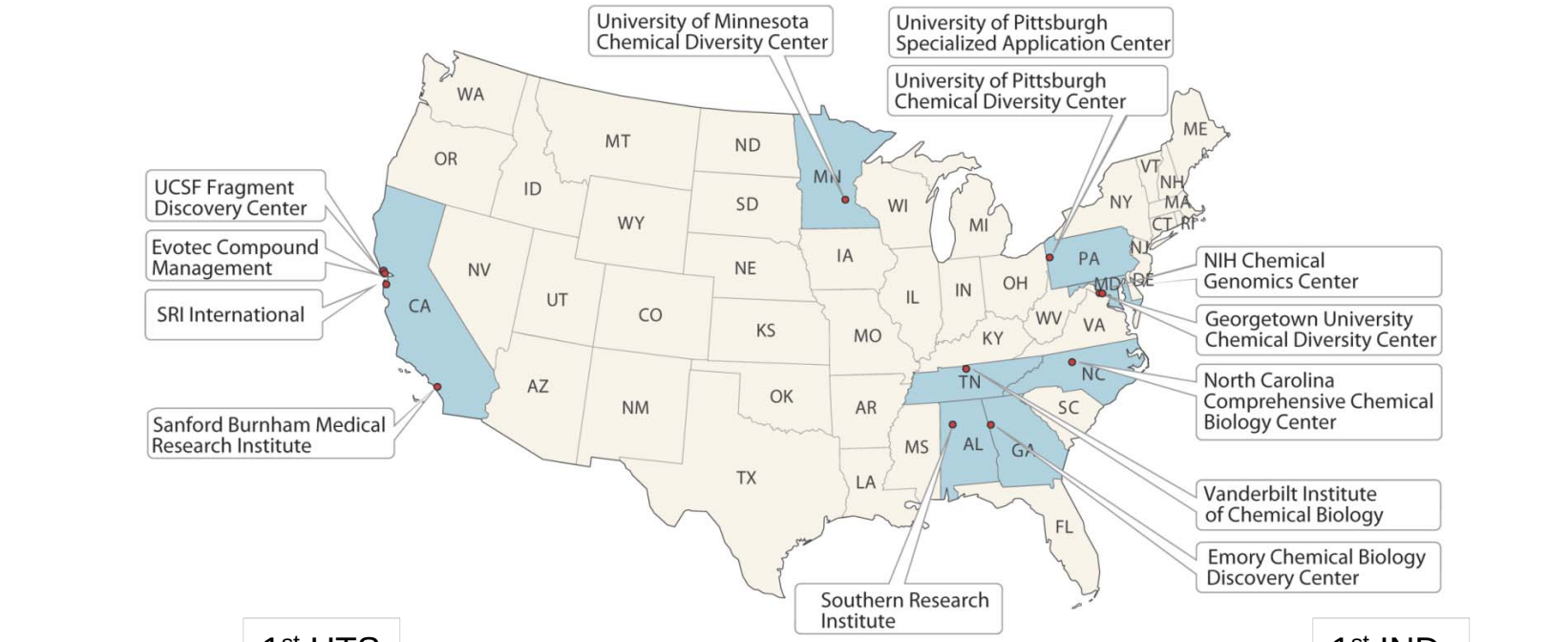
NExT CBC Projects

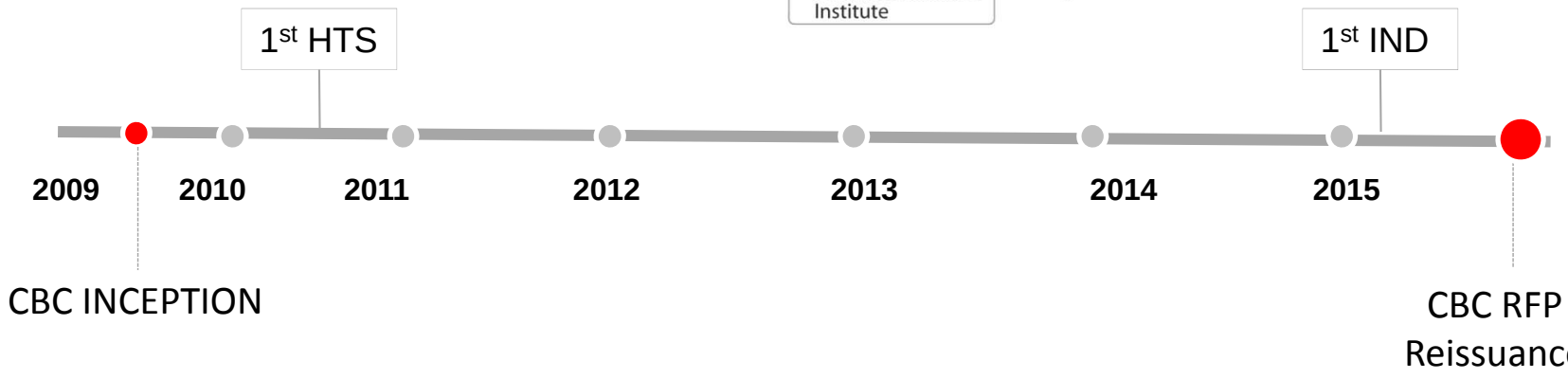


CBC is less risk-averse than Pharma

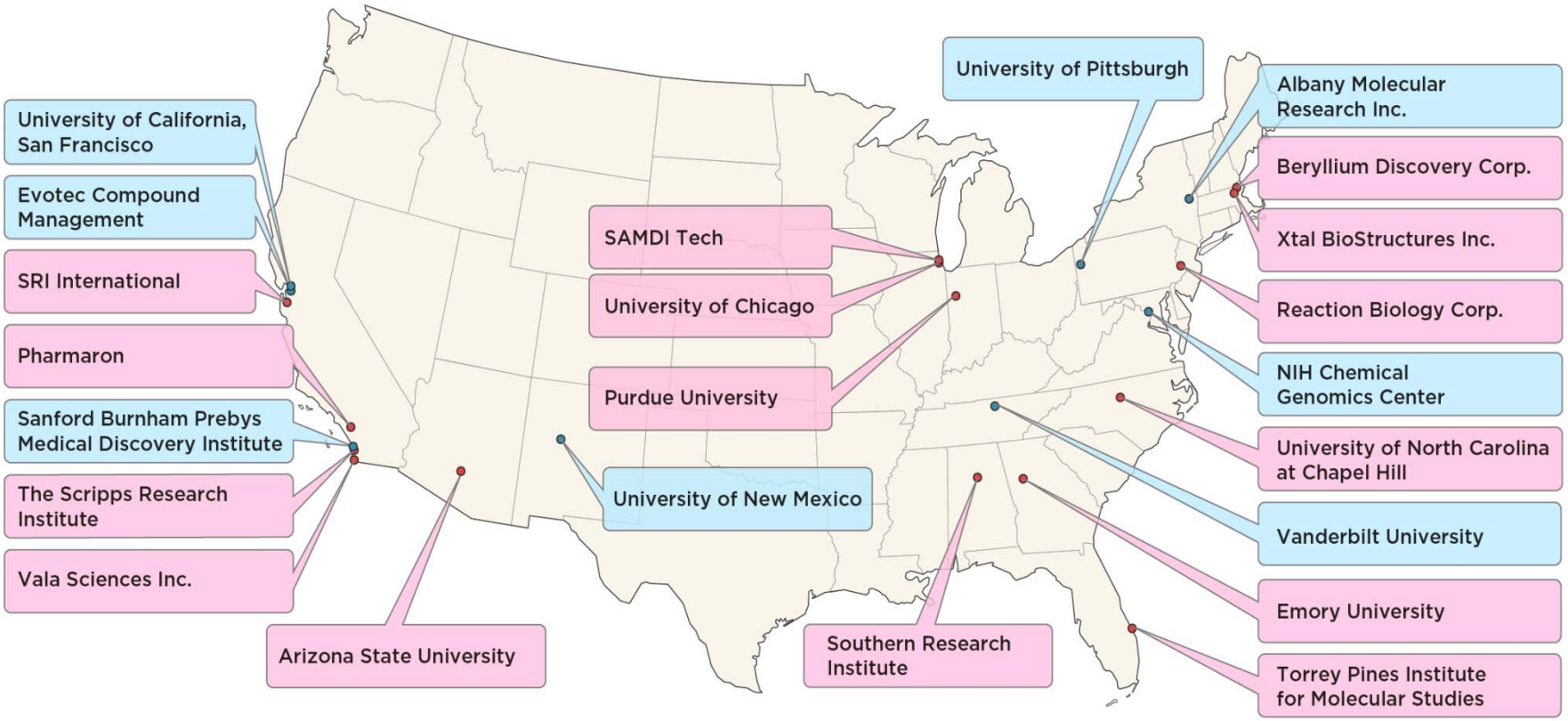
Focus on indications NOT adequately addressed by the pharmaceutical sector.

Pilot Phase of Chemical Biology Consortium





Spring 2016: CBC Network Expanded to 23 Centers



Early Discovery → *Late Discovery/Preclinical Evaluation*

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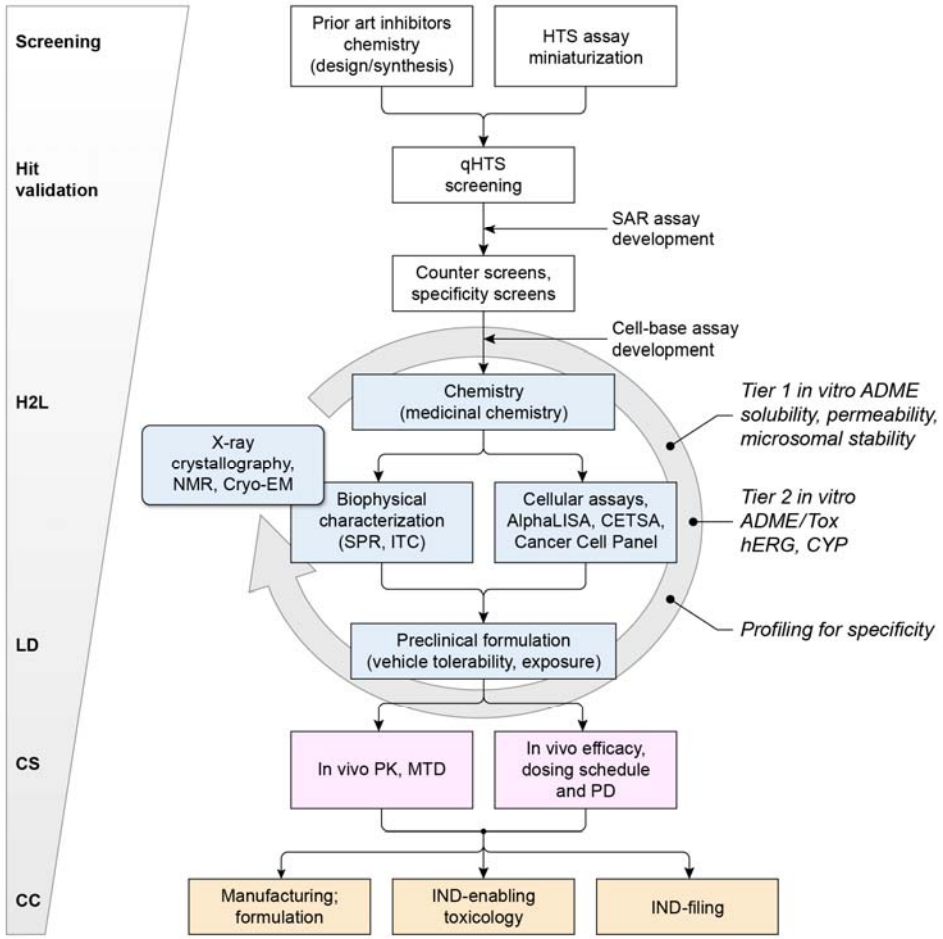
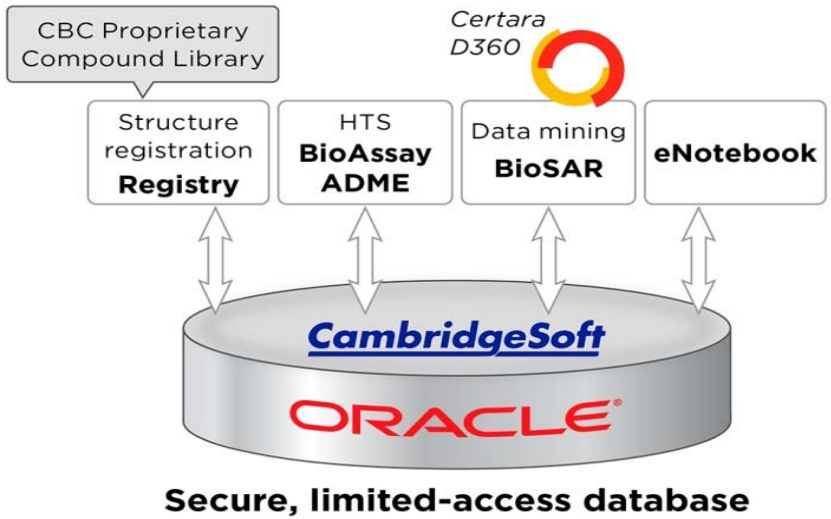
Team Science Approach to Fight Cancer



Breadth and Depth of Scientific Experience in Small Molecule Drug Discovery is Highly valuable Asset in Project Progression to FIH Studies

CBC: New Model for Collaborative Drug Discovery at the NIH

NExT legal framework is structured to support development and commercialization of therapeutic inventions



- ✓ collaborators retain background IP generated prior to initiation of project
- ✓ inventorship of new IP created during collaboration is determined according to U.S. patent law

Seeking partnerships with academic investigators/clinicians who have a passion for translational medicine

Benefits of Partnership with the CBC

- ✓ Significant in-kind support to progress hit and lead molecules to clinical candidates
- ✓ Collaboration with experienced group of industry-seasoned scientists
- ✓ Access to enabling resources, cutting-edge technologies

Participating principal investigators (applicants) are incentivized through broad publishing rights and the ability to use all intellectual property, joint or otherwise, for research purposes.

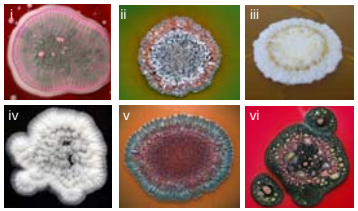
Supplemental funding is available to applicant PI for project related activities.

CBC Enabling Resources: Compound Library Collections

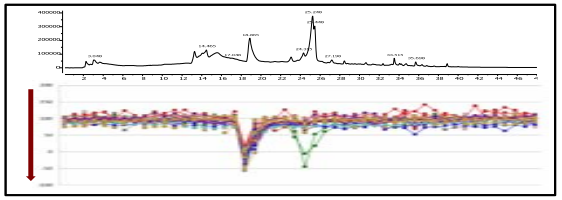
CBC Lead Discovery Library Collection
135,000 Small Molecules
Access to over 5M unique small molecules

Natural Product Screening Collection Unique to the NCI

Repository
- ✓ 230,000 NP crude extracts
- ✓ Pre-fractionated screening samples (~1,000,000)



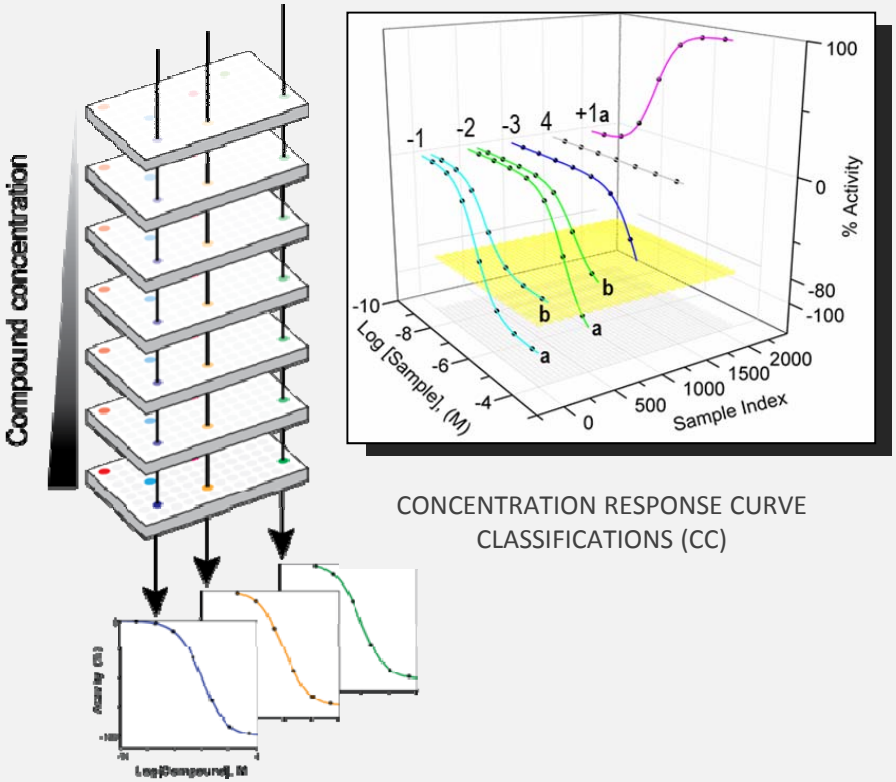
Capabilities
- ✓ Rapid compound identification
- ✓ Isolation and structure elucidation of active compounds



NCI Investigational Oncology Agent Collection: 556 compounds

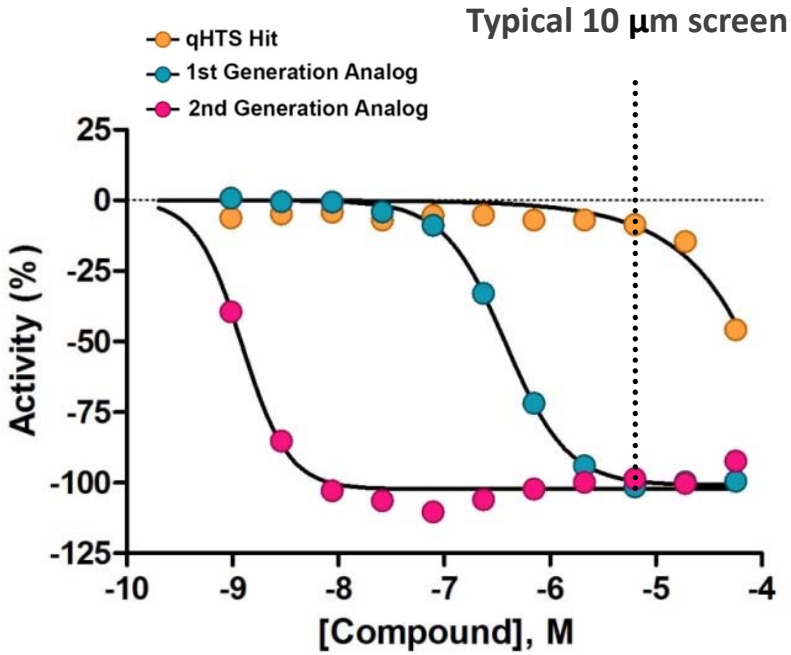
Access to Impactful Technologies

qHTS: Quantitative high-throughput screening
NIH Chemical Genomics Center



CONCENTRATION RESPONSE CURVE CLASSIFICATIONS (CC)

Specialized compound plating + 1536-well miniaturization allows libraries to be screened at 1-15 concentrations



Pictured above: active optimization campaign where single-point screening would have missed hit that launched a successful CBC project

Amenable to Matric Combination Screening to Identify Potential Drug Combinations

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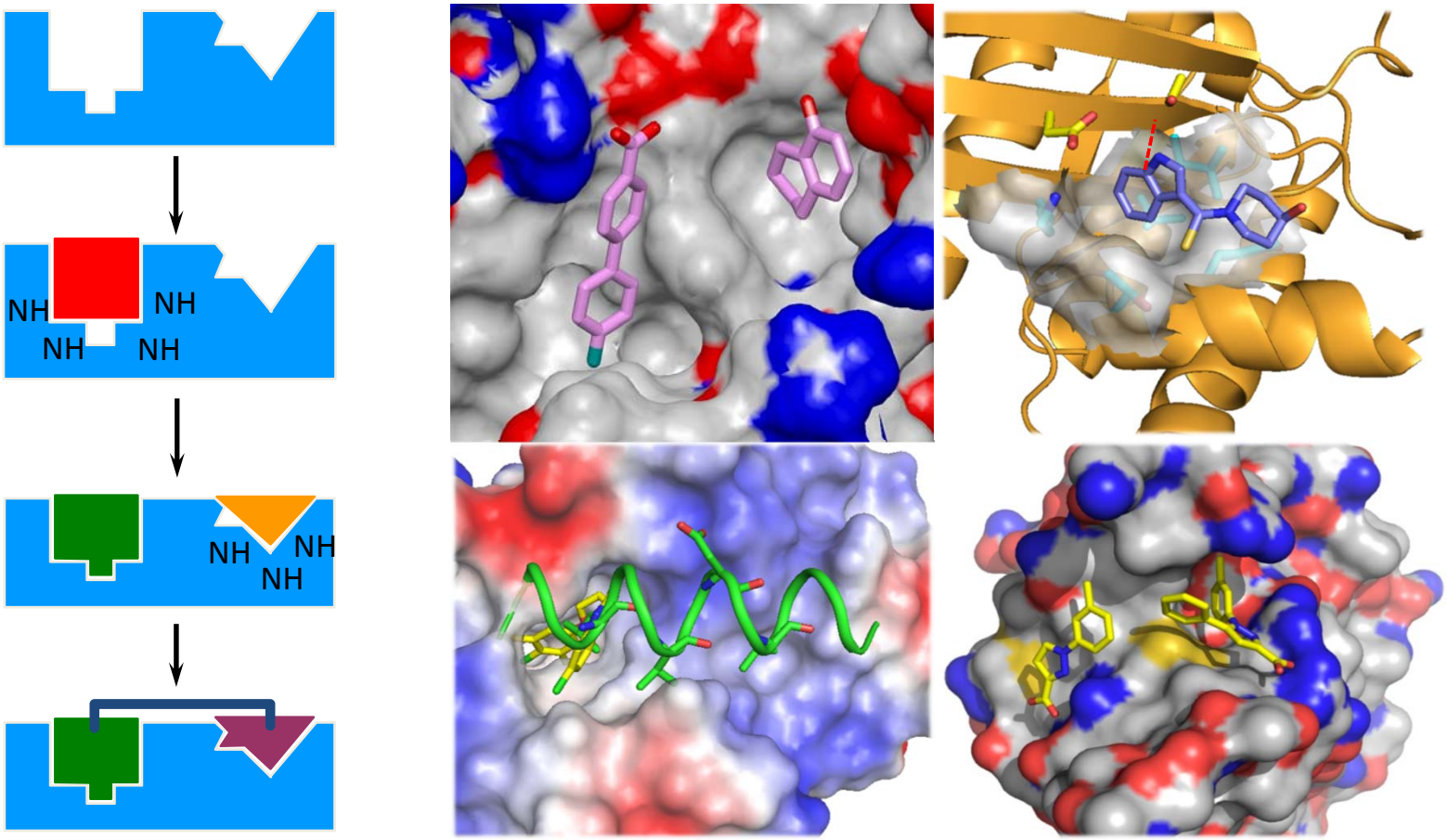
CBC is Heavily Invested in Structure-Based Drug Discovery

Fragment linking and optimization guided by protein structures has emerged as an effective and powerful alternative to HTS for the identification of lead chemical matter



UCSF and Vanderbilt Institute of Chemical Biology

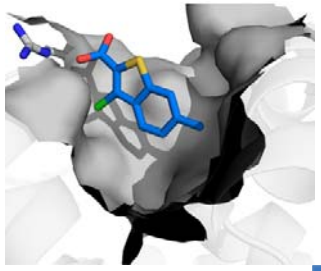
broad and deep expertise in fragment based lead discovery and design

Mcl-1 Inhibitor Discovery by Fragment-Based Methods & Structure-Based Design

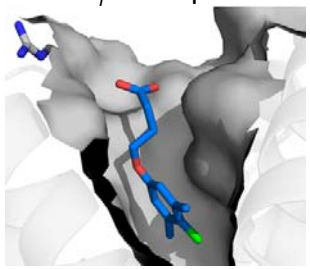
Stephen Fesik, Vanderbilt University

Hit to Lead | **Lead Optimization**

> 200,000x improvement in affinity for target

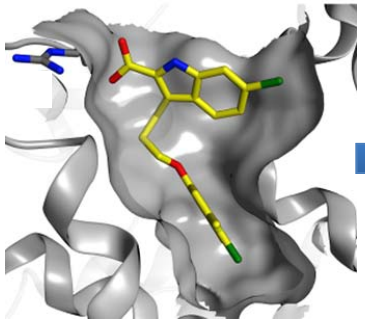


K_i = 131 µM



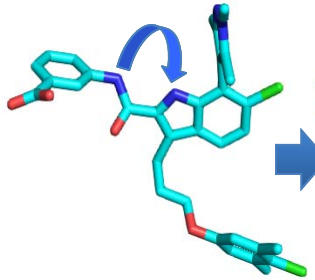
K_i = 60 µM

Fragment hits



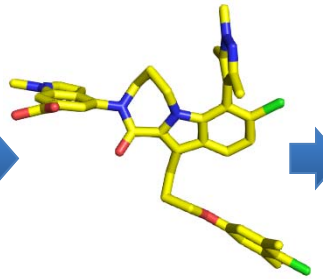
Mcl-1 K_i = 55 nM

Structure-guided fragment merging



Mcl-1 K_i = 23 nM

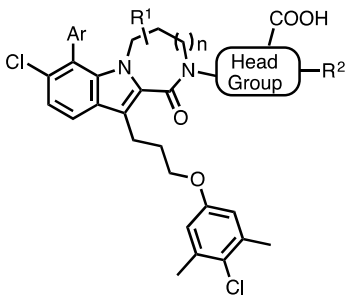
Binding interface Expansion



Mcl-1 K_i = 0.39 nM

H929 GI_{50} = 1.2 µM

Structure-guided Tethering



Mcl-1 K_i = <0.3 nM

H929 GI_{50} = <0.3 µM

Med. Chem. Optimization

- K_i < 0.3 nM Mcl-1
- IC_{50} < 300 nM in multiple cancer cell-lines
- Target-based on-mechanism activity (Caspase activation, JC-1/BH3 profiling, co-IP, multiplex PD apoptosis assays)
- Oral bioavailability, good PK properties
- *In vivo* activity in multiple models (TNBC xenograft model)

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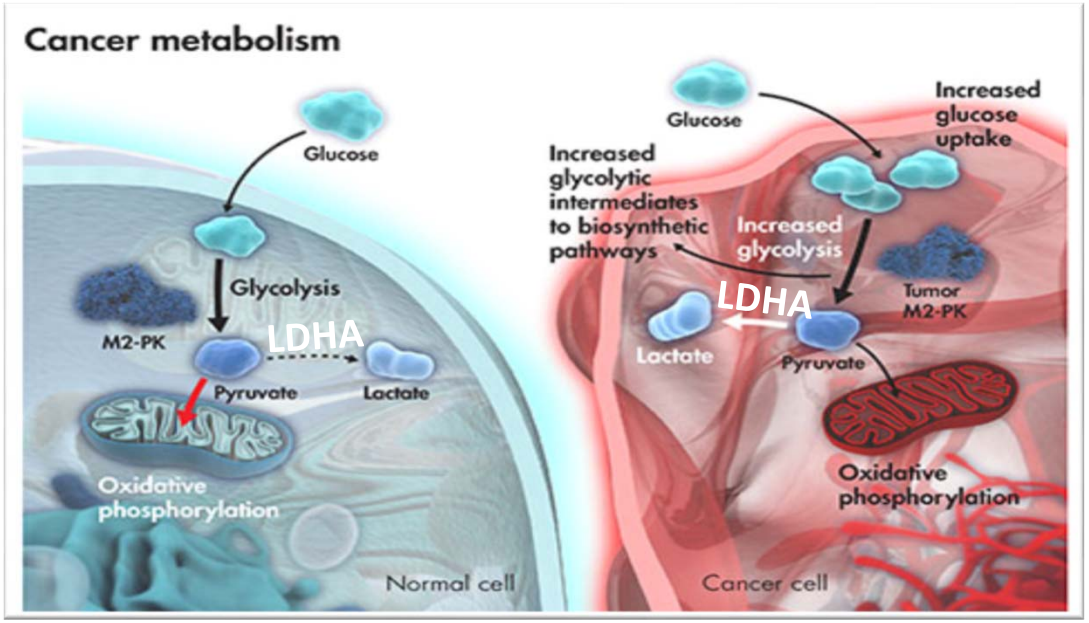
First-in-Class, Orally Bioavailable Inhibitors of Lactate Dehydrogenase A (LDHA/B)

Chi Van Dang, Univ Penn

- No clinical stage inhibitors of LDHA exist; molecules from Astra Zeneca, GSK and Genentech have limited potency and no *in vivo* activity, and have not progressed further
- The NExT Team generated **>700** compounds & 11 crystal structures, identified 2 candidates with optimal *in vivo* properties



National Center for Advancing Translational Scie

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Penn Medicine

NATIONAL CANCER INSTITUTE

BERYLLIUM

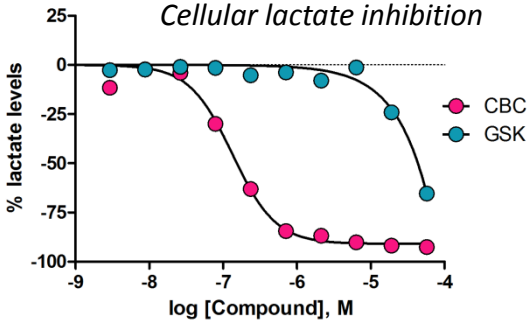
SOUTHERN RESEARCH
Legendary Discoveries. Leading Innovation.

VANDERBILT UNIVERSITY

CBC LDHA Inhibitor Milestones

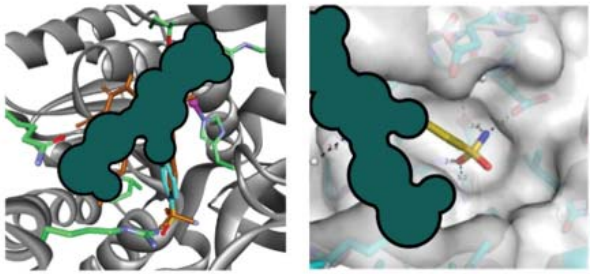
1 Potent cellular activity

Cellular lactate inhibition



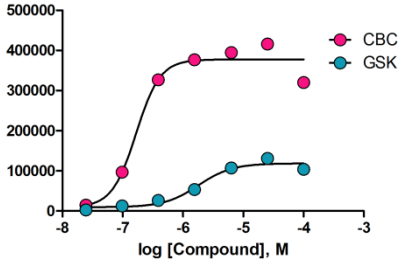
2 Structure-based design

LDHA co-crystal (1.6 Å) with CBC inhibitor

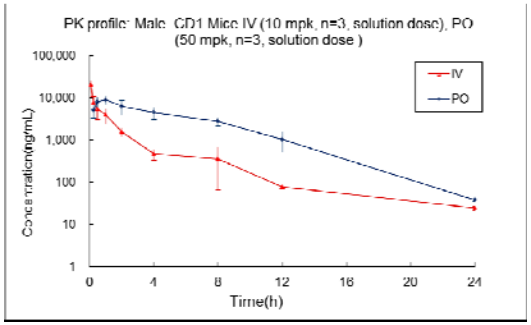


3 Target engagement

CETSA demonstrating in-cell binding to LDHA

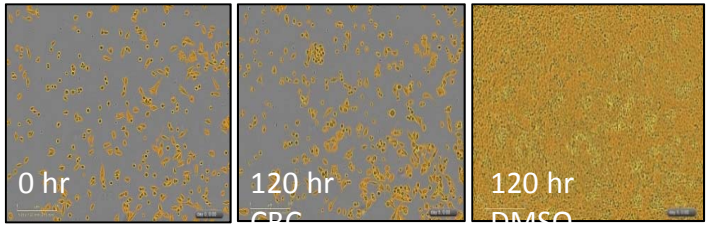


4 Orally bioavailable



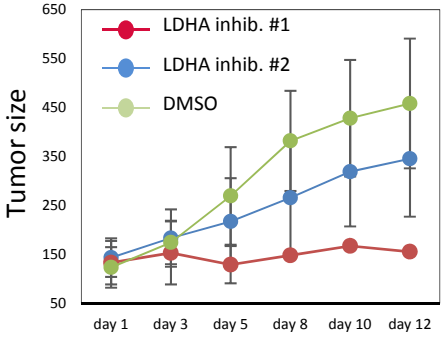
5 Inhibits cell proliferation

5 day incubation w/ LDHA inhibitor



6 Current efforts

- PK Optimization
- Validation of PD Endpoints
- Tolerability
- Efficacy
- Combination Therapy



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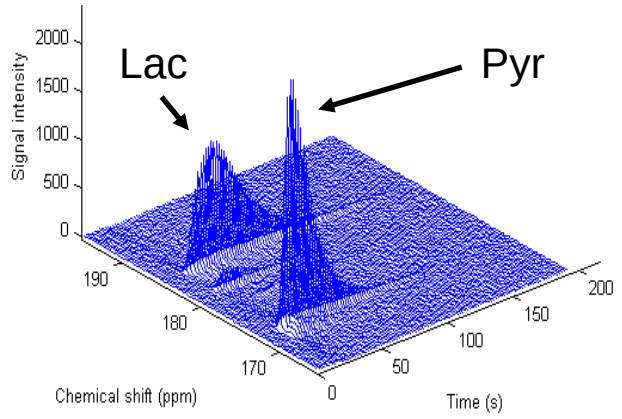
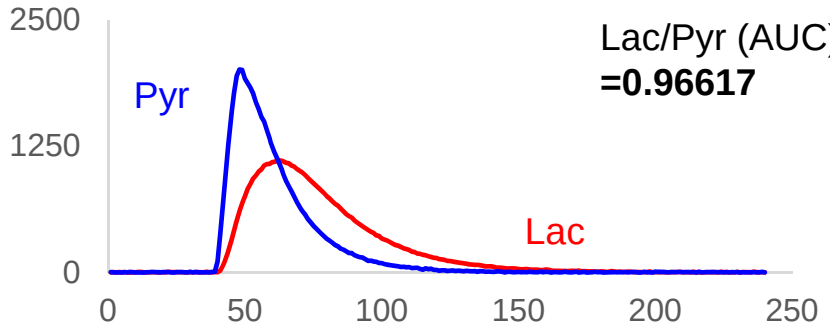
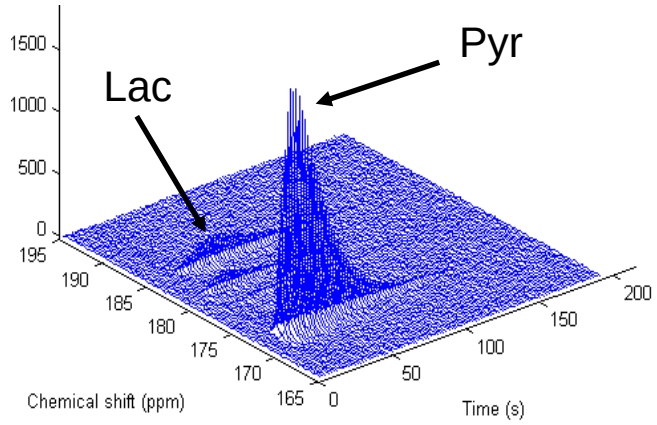
Validation of LDHA Inhibitor PD Endpoint: Hyperpolarized ^{13}C-pyruvate flux to ^{13}C-lactate

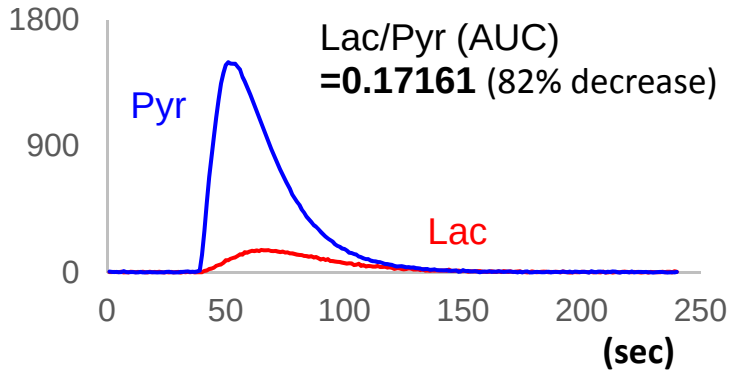
pre





post



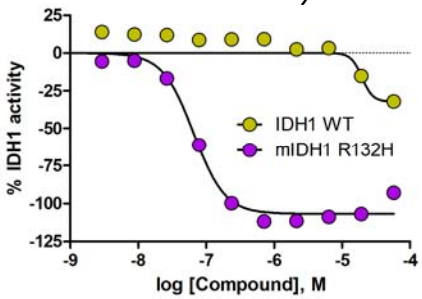


NCI has integral role in preclinical and clinical validation of PD Endpoints

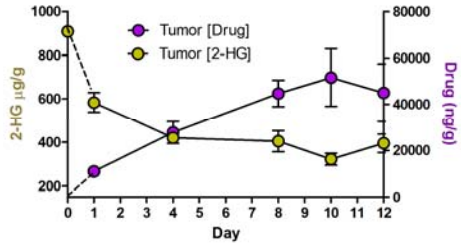
CBC mutant IDH1 inhibitors: Discovery to IND

- **2010** Proposal
- **2011** Launch, assemble team, assay development
- **2012** HTS, hit validation
- **2013** CBC Discovery Resources Triggered
- **2014** Lead development
- **2015** in vivo PK/PD established
- **2016** In vivo models, tolerability & efficacy
- **2016** IND enabling studies

IDH1 selectivity



PK/PD in Tumor Xenografts



Timeline for Identification of Second-Generation mIDH1 Inhibitor Competitive with Industry Standards for Compound Progression

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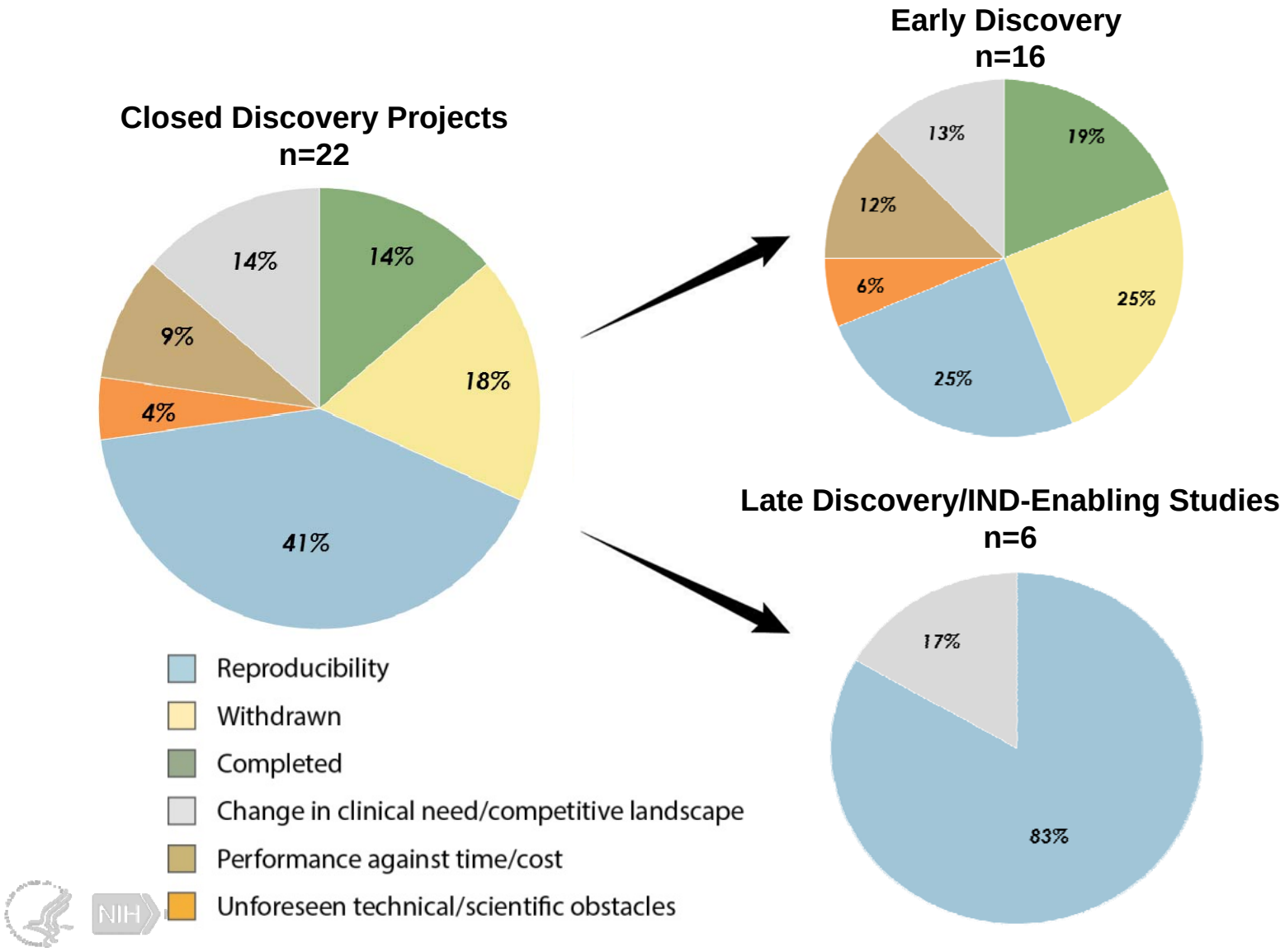
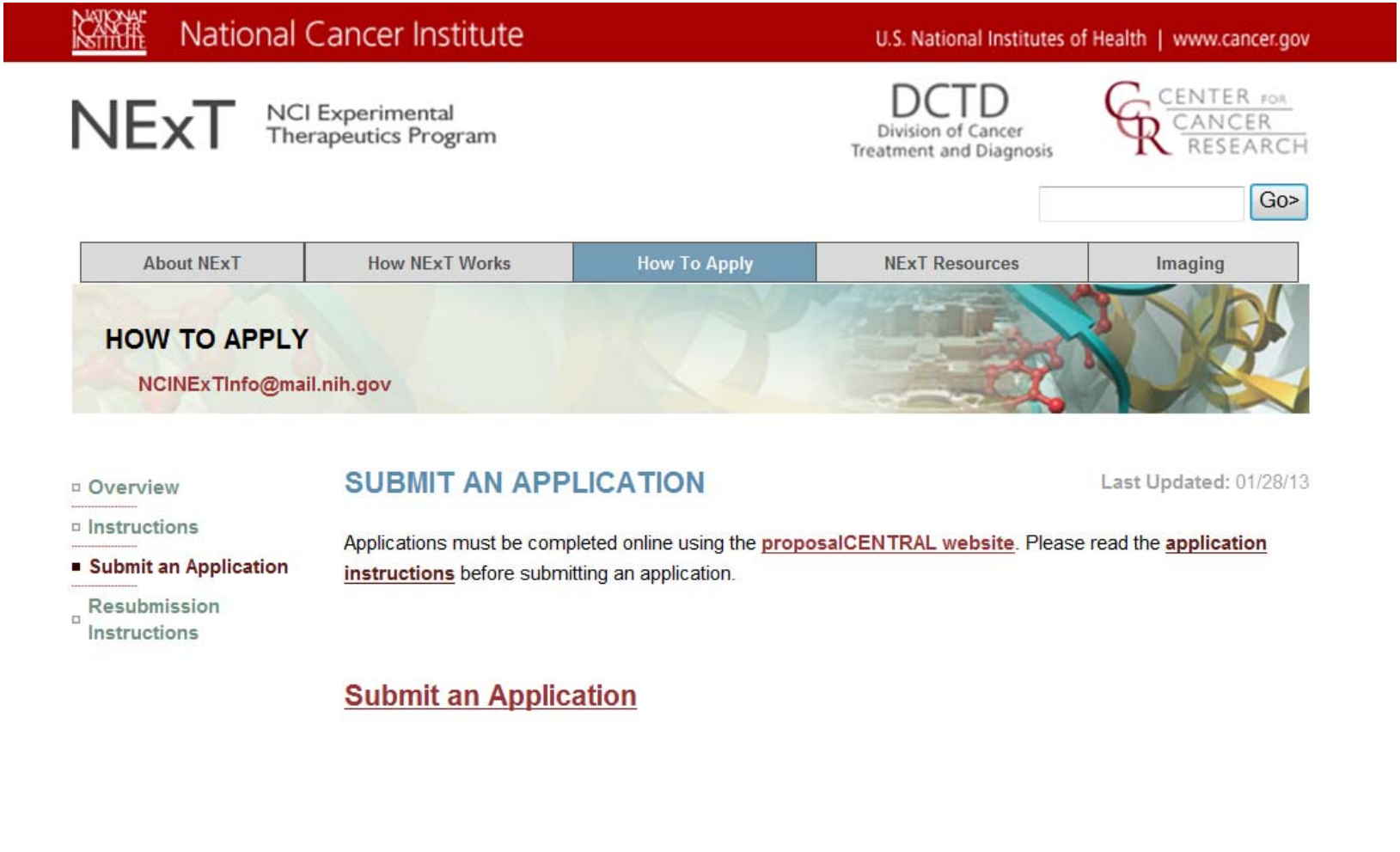
Factors Contributing to Project Closure

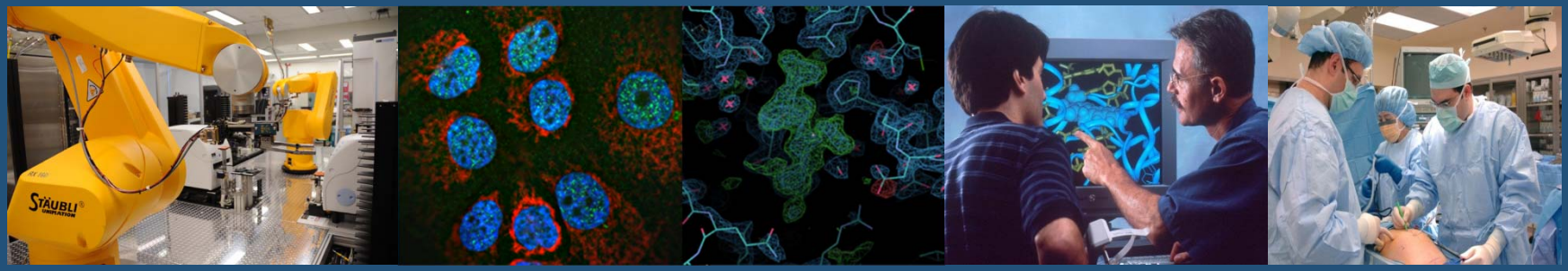


Please Visit our Website
NEXT.CANCER.GOV



NCI Experimental Therapeutics (NExT) Program

http://next.cancer.gov



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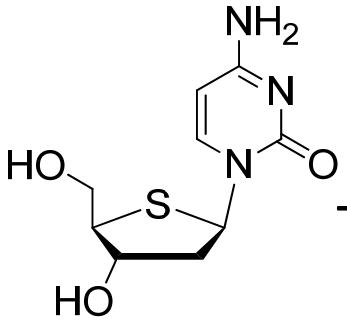
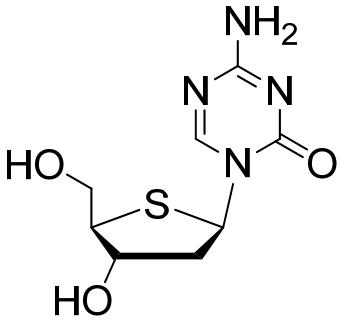
Inhibitors of DNA Methyltransferase (DNMT1)
Southern Research



T-dCyd



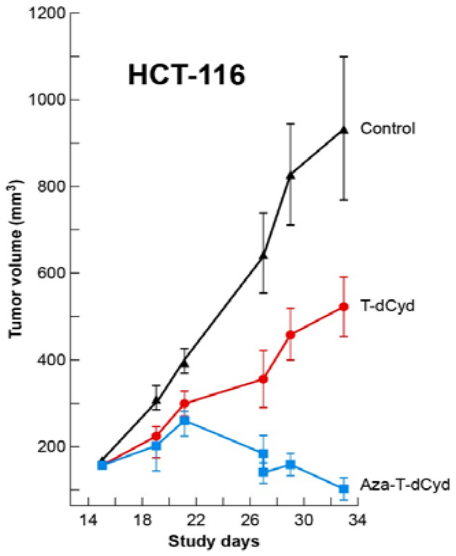
Aza-T-dCyd

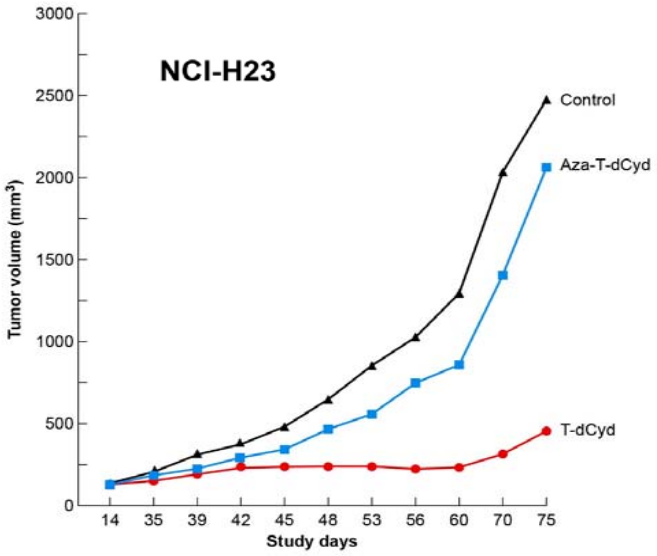
Phase I Trial Initiated at NCI Clinical Center in Spring 2015

1st IND

2009 **2010** **2011** **2012** **2013** **2014** **2015**

CBC INCEPTION





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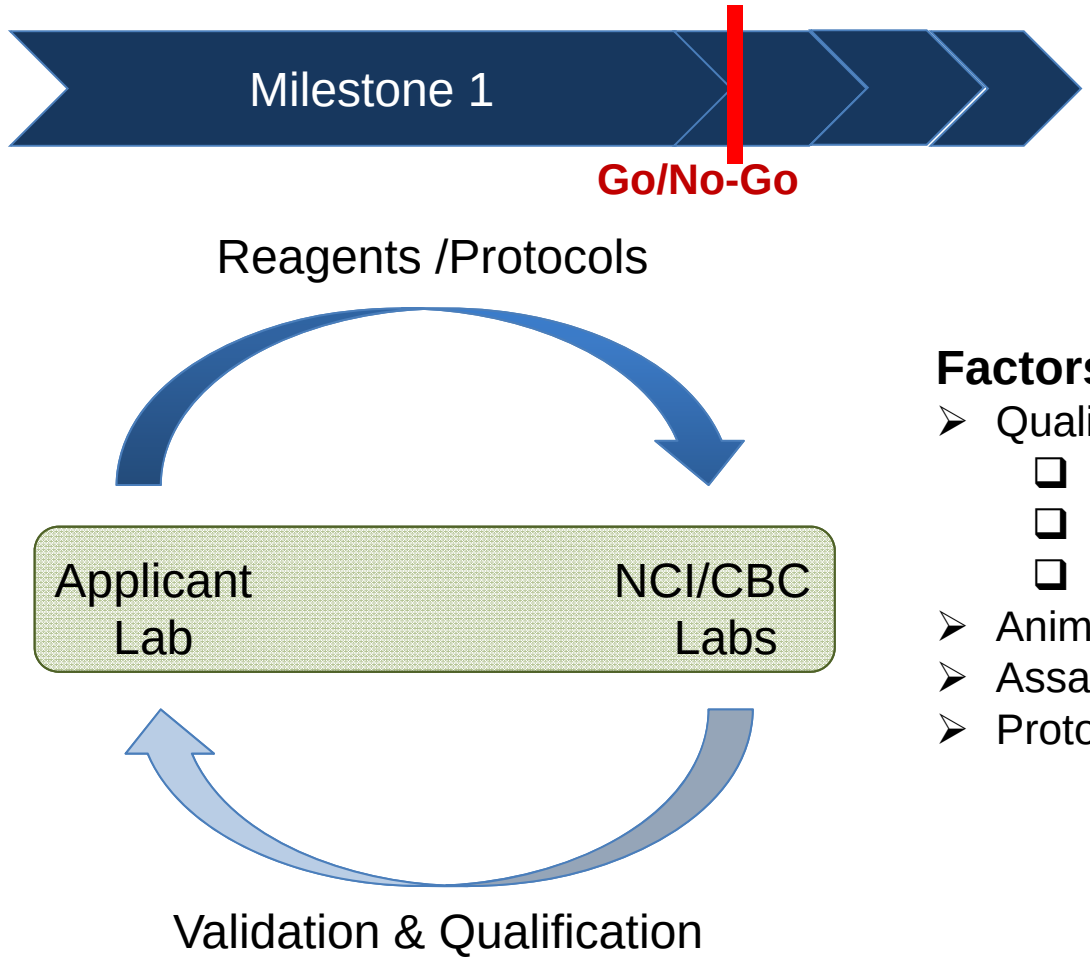
Measures to Increase Reproducibility: Trust but Verify

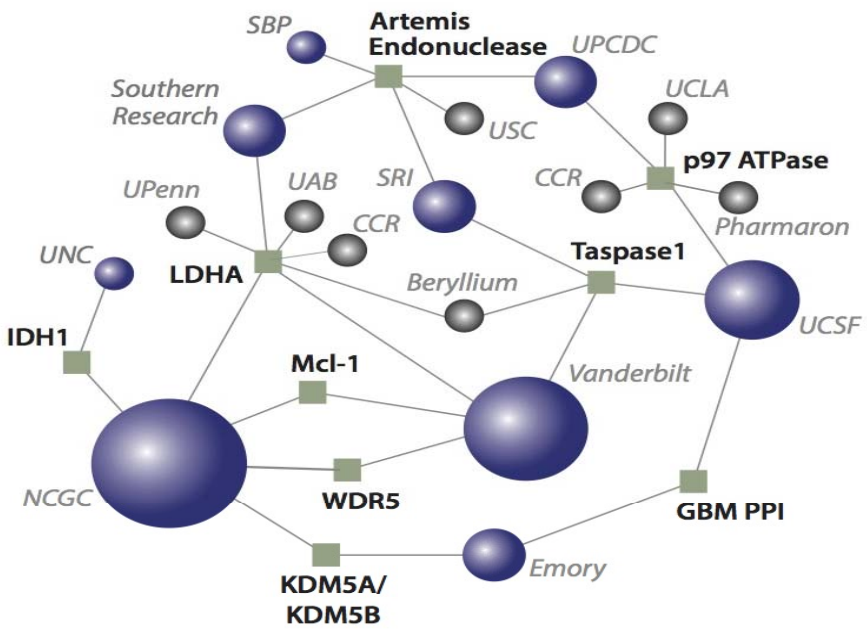
Reproducing key data is initial milestone of project plan



Factors to consider

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

CBC Network Interactions



CBC Center | Non-CBC Center providng critical scientific support | CBC Project

The size of the sphere representing the CBC Center is proportional to the number of projects being worked on.

Emory: Emory Chemical Biology Discovery Center
NCGC: NCATS Chemical Genomics Center
SBP: Sanford Burnham Prebys Medical Discovery Institute
SRI: SRI International

Beryllium: Beryllium Corperation
CCR: Center for Cancer Research, National Cancer Institute
Pharmaron: Pharmaron, Inc.
UAB: University of Alabama at Birmingham

UCSF: The Small Molecule Discovery Center, UCSF
UNC: North Carolina Comprehensive Chemical Biology Center
UPCDC: University of Pittsburgh Chemical Diversity Center
Vanderbilt: Vanderbilt Center for Cancer Drug Discovery

UCLA: University of California, Los Angeles
USC: University of Southern California
UPenn: University of Pennsylvania