NCI Experimental Therapeutics Program (NExT):

A Government, Academic, Industry Partnership for Cancer Drug Discovery

James H. Doroshow, M.D.

Deputy Director for Clinical and Translational Research

National Cancer Institute, NIH

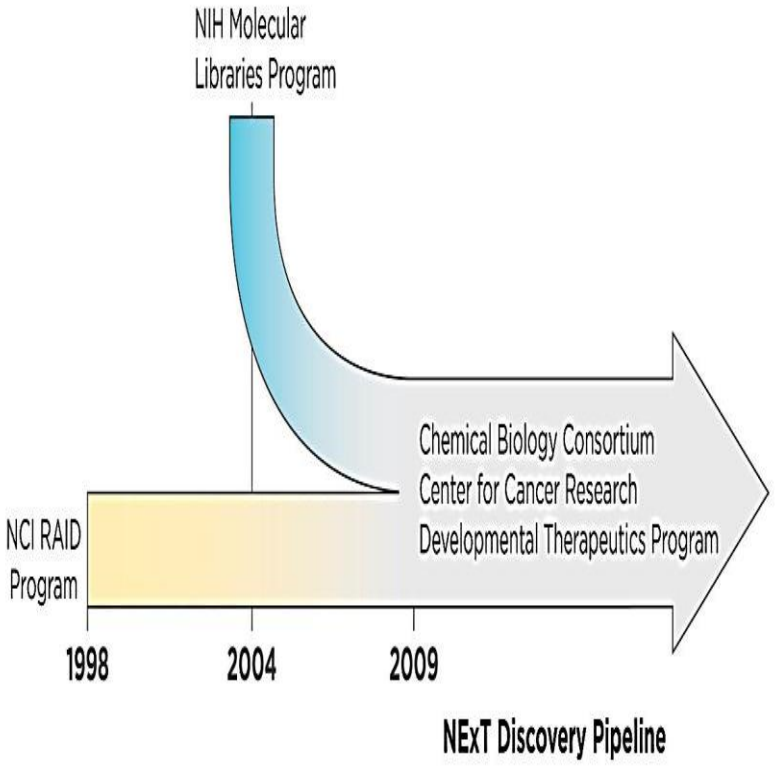
Bethesda, MD USA

NIH NATIONAL CANCER INSTITUTE

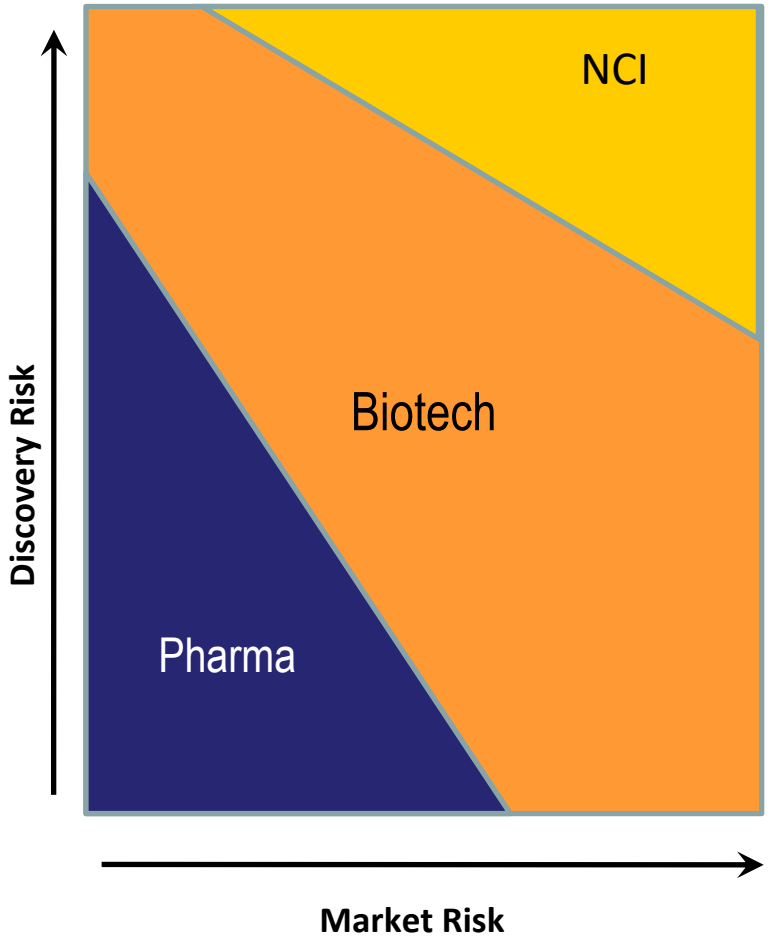
FNLCR Advisory Committee Meeting

June 27, 2022

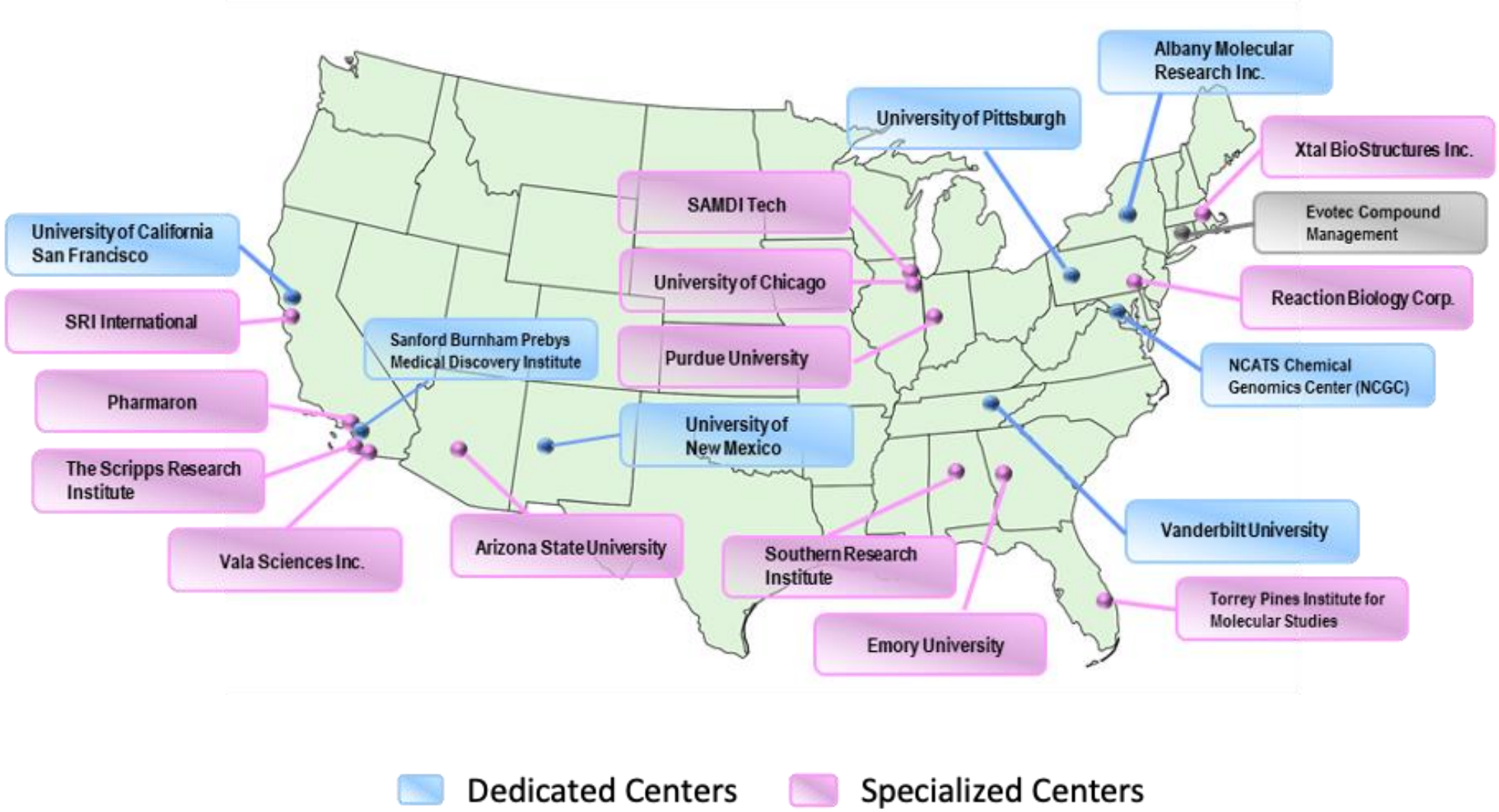
Origin and Goals of the NExT Discovery & Development Pipeline



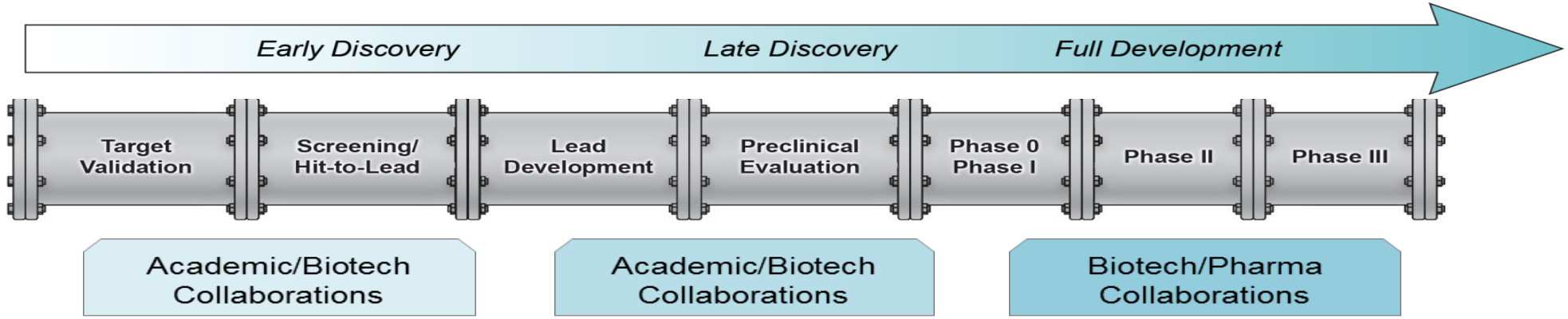
- NExT (NCI Experimental Therapeutics Program) builds on >50 yrs of NCI experience in cancer drug development to increase flow of early & late-stage candidates from Academia/small biotech to the clinic
- CBC (Chemical Biology Consortium) is an integrated network of chemical biologists, structural biologists, modelers, PK, PD, Tox, imagers & GMP scale up partnering with NCI
- CBC is the discovery engine
- Inclusive involvement of CBC members in shared projects developed in parallel across consortium with shared IP
- Not intended to replicate Pharma
- Not a grant program; provides access to drug development services
- CBC members submit own projects and take on those of other investigators
- Focus on developing therapies for underrepresented malignancies & on difficult targets
- Longer time horizon
- 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



NCI Chemical Biology Consortium: Discovery Arm of NExT

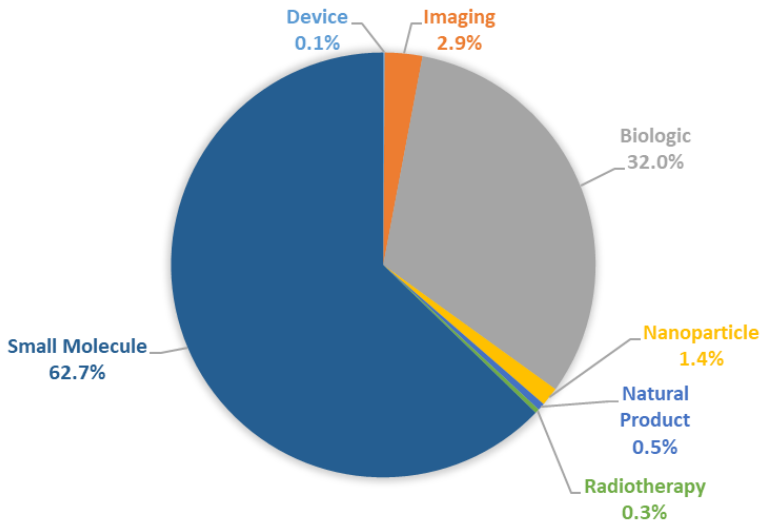


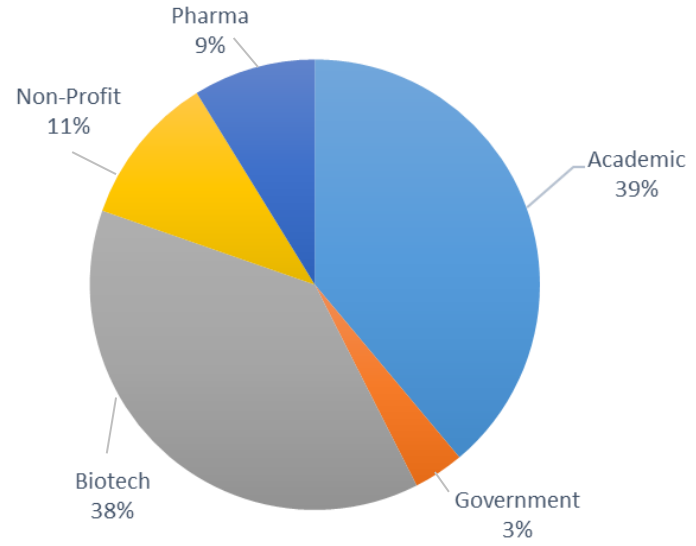
NCI Experimental Therapeutics (NExT) Pipeline



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

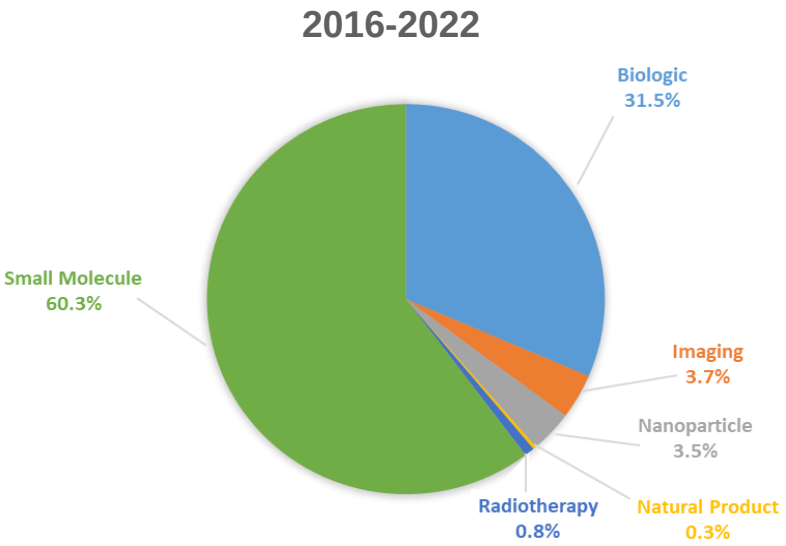
Since inception in 2009 NExT has reviewed over 900 applications: 10-14% success rate; 50% T but V

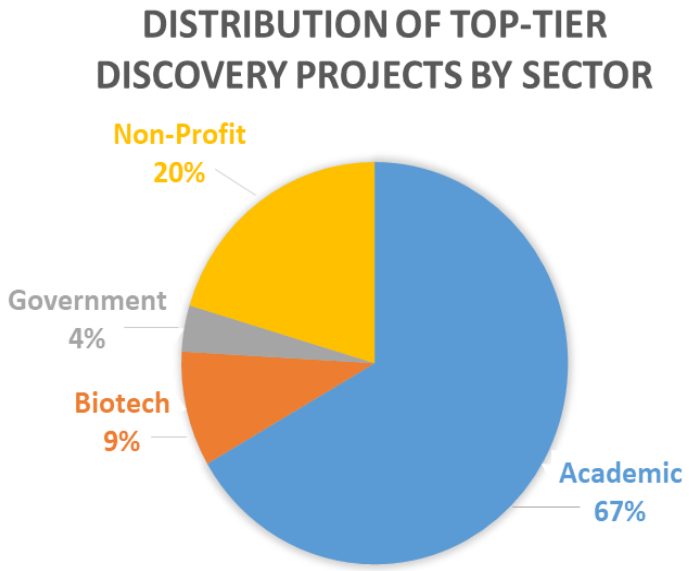


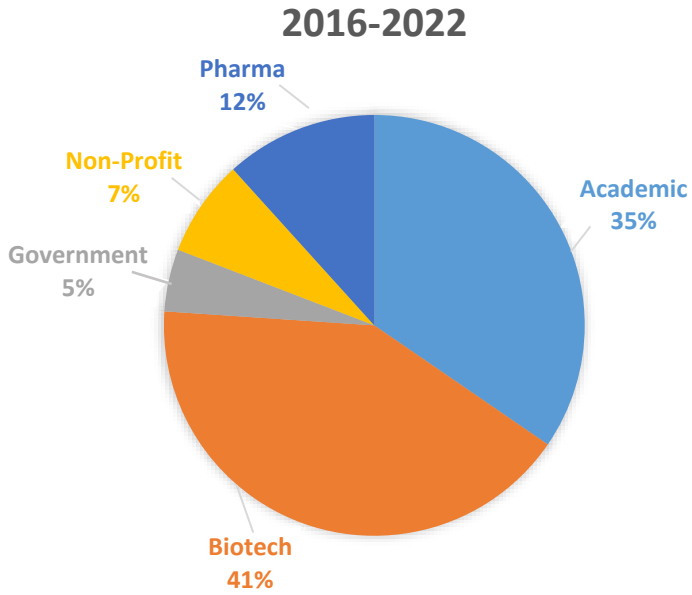


NCI Experimental Therapeutics (NExT) Pipeline

From 2016-2022 NExT reviewed 371 applications

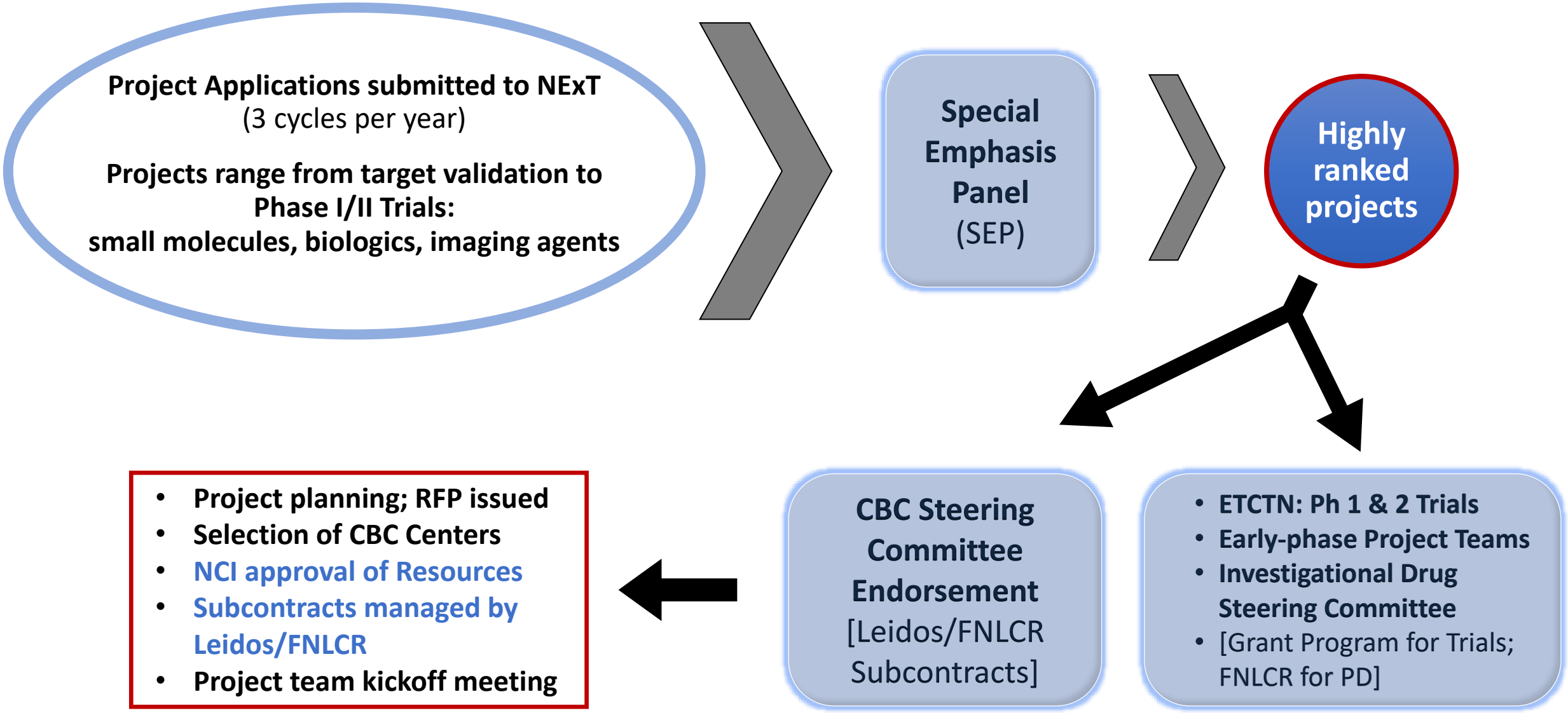






- **24% of top-tier proposals are discovery projects**
- **91% of agents in top-tier discovery proposals are classified as small molecules**

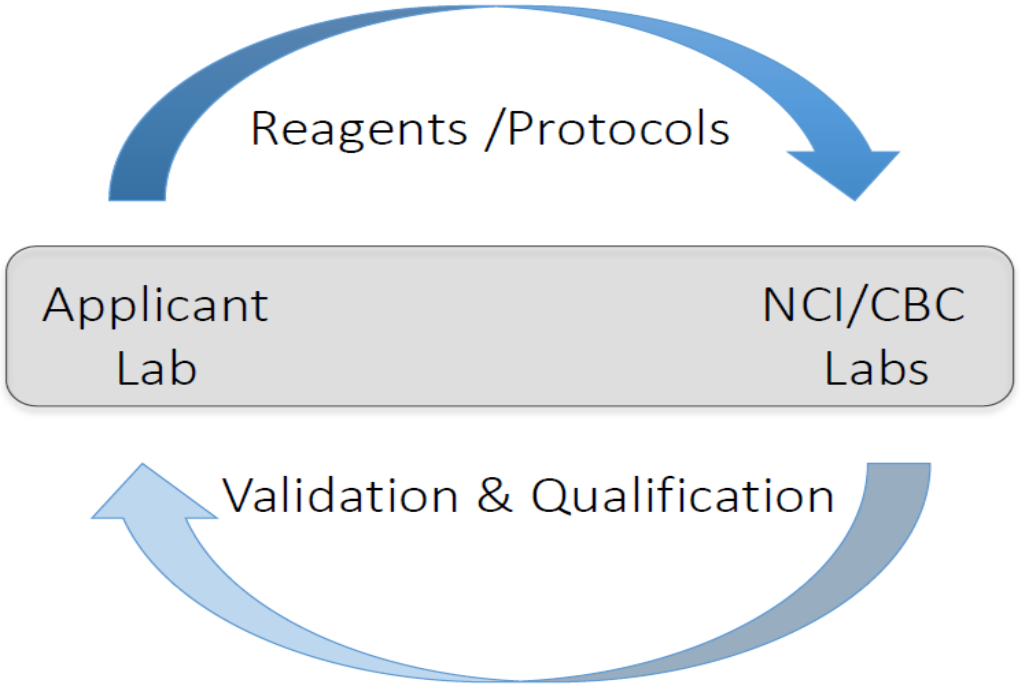
NExT: From Application Review to Project Team Kickoff Meeting



Measures to Increase Reproducibility: Trust but Verify

1/3 of Projects Fail at Trust but Verify Stage

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

CUL4 inhibitor
PI5P4K dual inhibitor
FAK
SHP2 inhibitor
Beta-Catenin inhibitor
Bcl-xl PROTAC

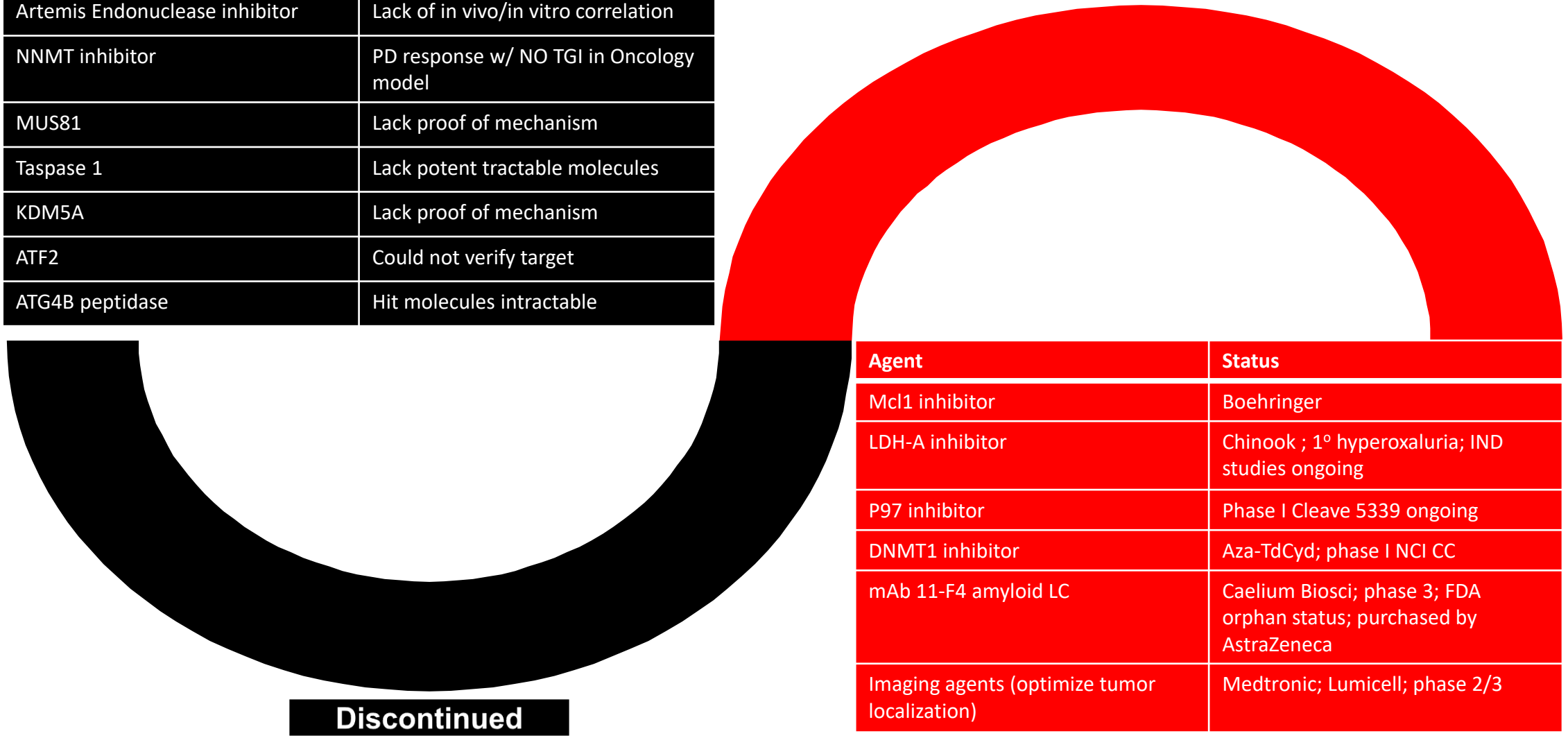
Mcl1 inhibitor**
LDHA inhibitor*
Backup p97 inhibitor
WDR5-MLL1 inhibitor
SF-1

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

*: Licened to Chinook
**: Licensed to Boehringer Ingelheim
***: Licensed to Caelium/AZ
****:Licensing in discussion
#: IN THE CLINIC

NExT Pipeline: Develop or Discontinue?

Agent	Reason discontinued
PHGDH inhibitor	Hit to lead molecules deficient
Artemis Endonuclease inhibitor	Lack of in vivo/in vitro correlation
NNMT inhibitor	PD response w/ NO TGI in Oncology model
MUS81	Lack proof of mechanism
Taspase 1	Lack potent tractable molecules
KDM5A	Lack proof of mechanism
ATF2	Could not verify target
ATG4B peptidase	Hit molecules intractable

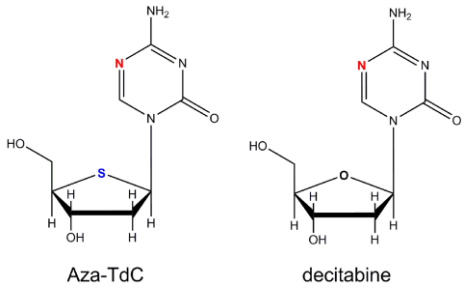


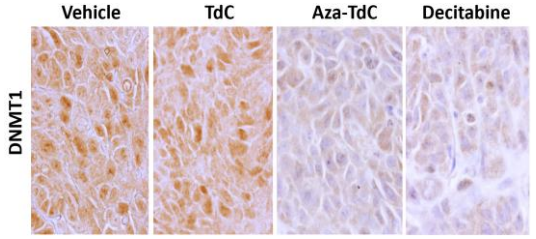
Agent	Status
Mcl1 inhibitor	Boehringer
LDH-A inhibitor	Chinook ; 1º hyperoxaluria; IND studies ongoing
P97 inhibitor	Phase I Cleave 5339 ongoing
DNMT1 inhibitor	Aza-TdCyd; phase I NCI CC
mAb 11-F4 amyloid LC	Caelium Biosci; phase 3; FDA orphan status; purchased by AstraZeneca
Imaging agents (optimize tumor localization)	Medtronic; Lumicell; phase 2/3

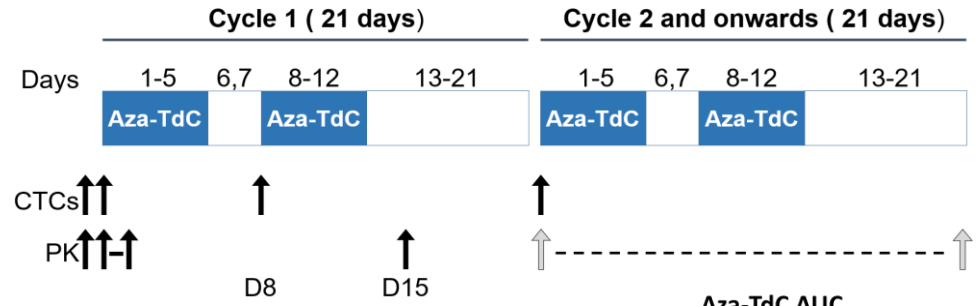
5-aza-4’-thio-2’-deoxycytidine (Aza-TdC)

Southern Research

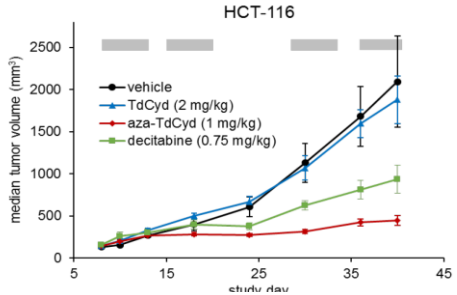
- Inhibits DNA methyltransferase 1 (DNMT1); **no IP**
- Excellent oral bioavailability; higher incorporation rate into DNA at lower levels of toxicity than decitabine
- Improved preclinical antitumor activity compared to other hypomethylating agents in solid tumor xenograft models, including TNBC, and in MEN GEMM; developed new enhanced synthesis; IND filed 2019

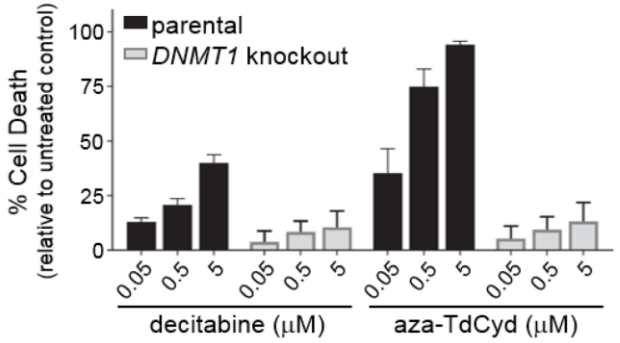


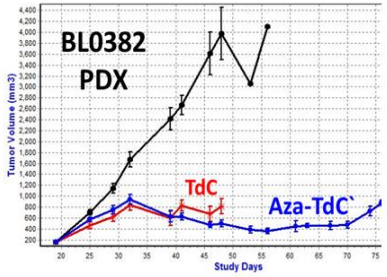




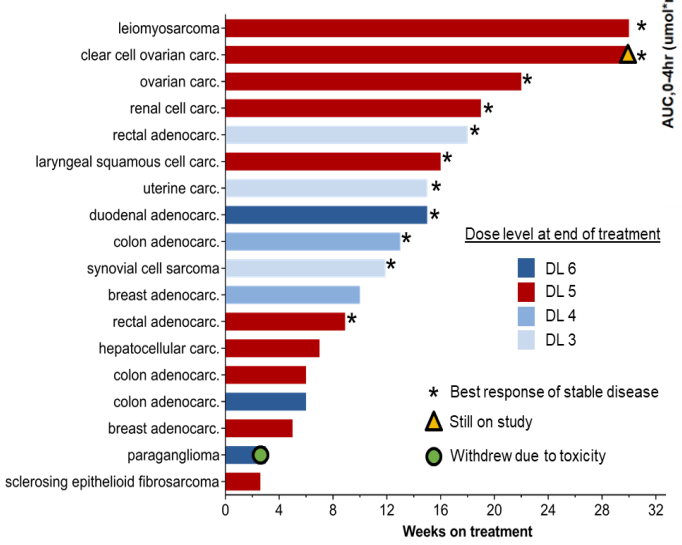
Dose Level (DL)	Aza-TdC (mg)
-1	1
1	2
2	4
3	8
4	16
5*^	32
6	48

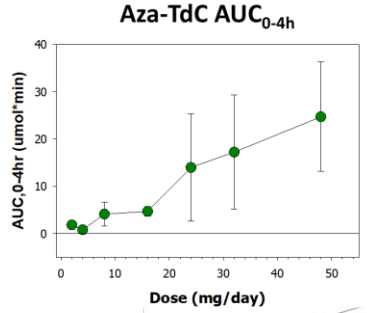




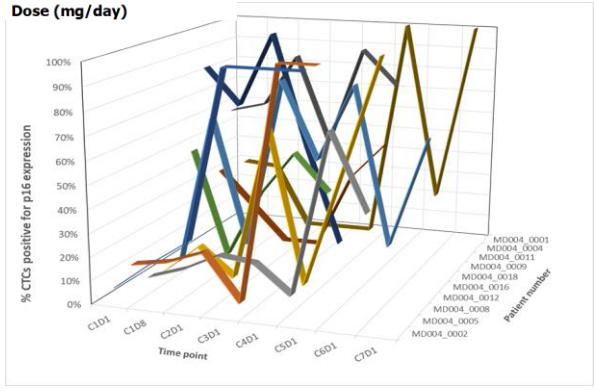


Broadly active in tumor Xgs:
Ovcar-3, H522 NSCLC, HL-60



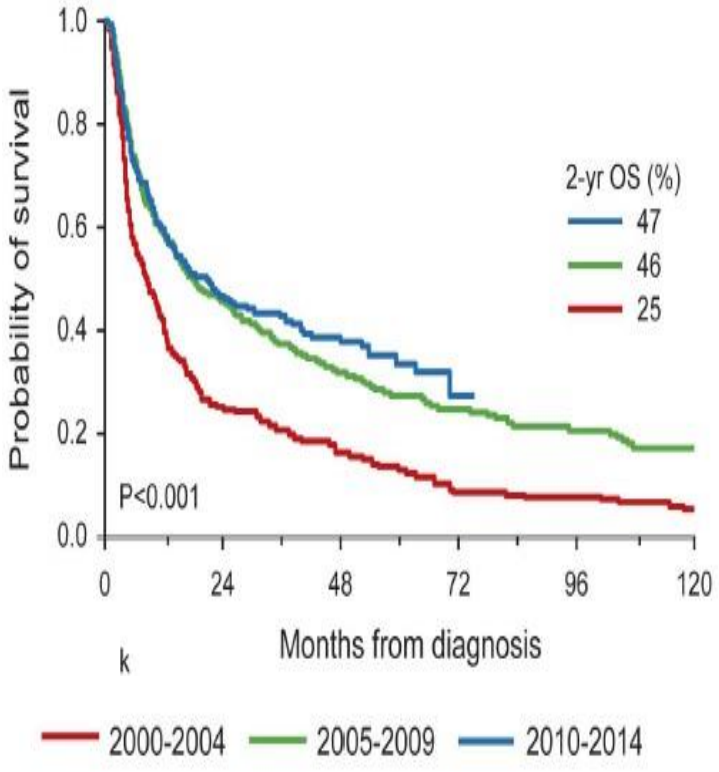


N=18
DLT: Rash; myelo-suppression
Expansion phase
24 mg

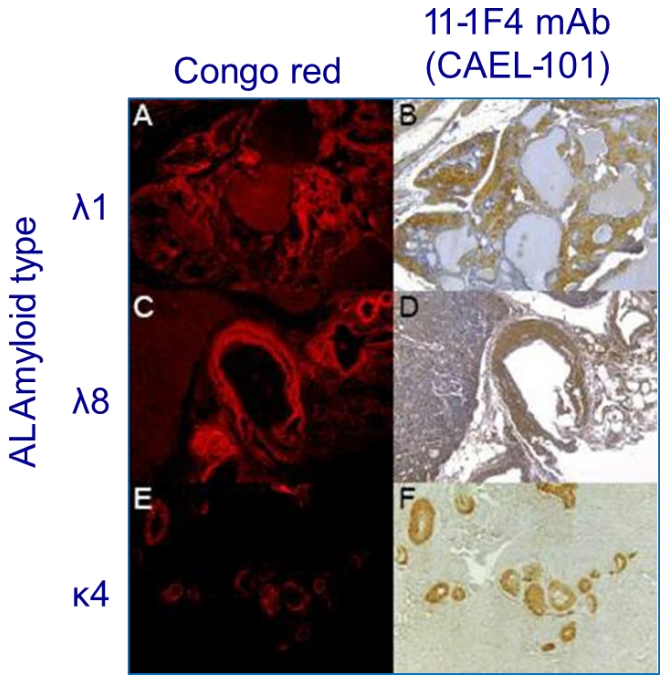


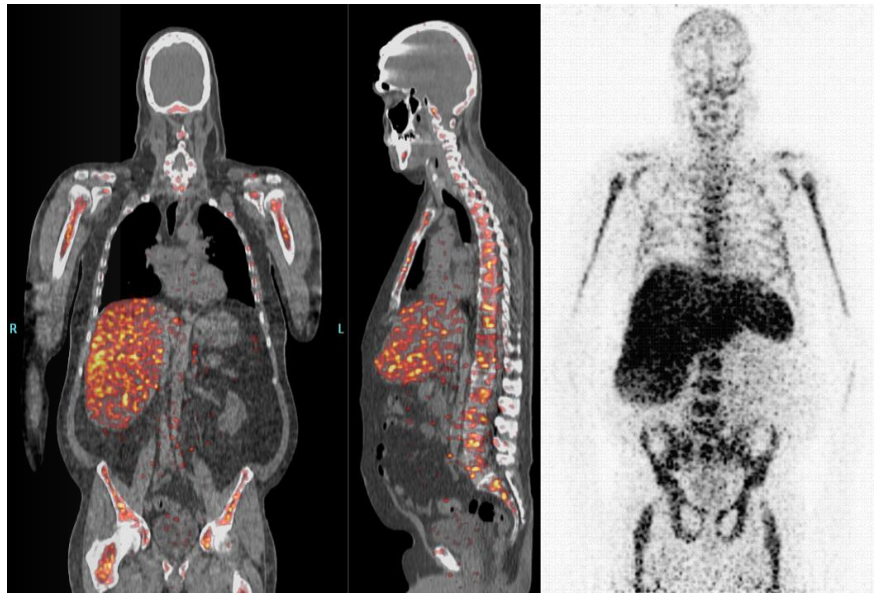
Monoclonal Antibody 11-1 F4 for Patients with Amyloid Light Chain Amyloidosis
Univ. of Tennessee & Columbia & NCI

Amyloid lignt chain disease: rare, fatal illness;
<2000 pts/yr; up to 80% ineligible for ASCT;
40% die in 1 yr



Co-localization of ^{124}I-m11-1F4 with Hepatosplenic and Bone AL Amyloid





Alan Solomon, Univ. of TN, NCI grantee

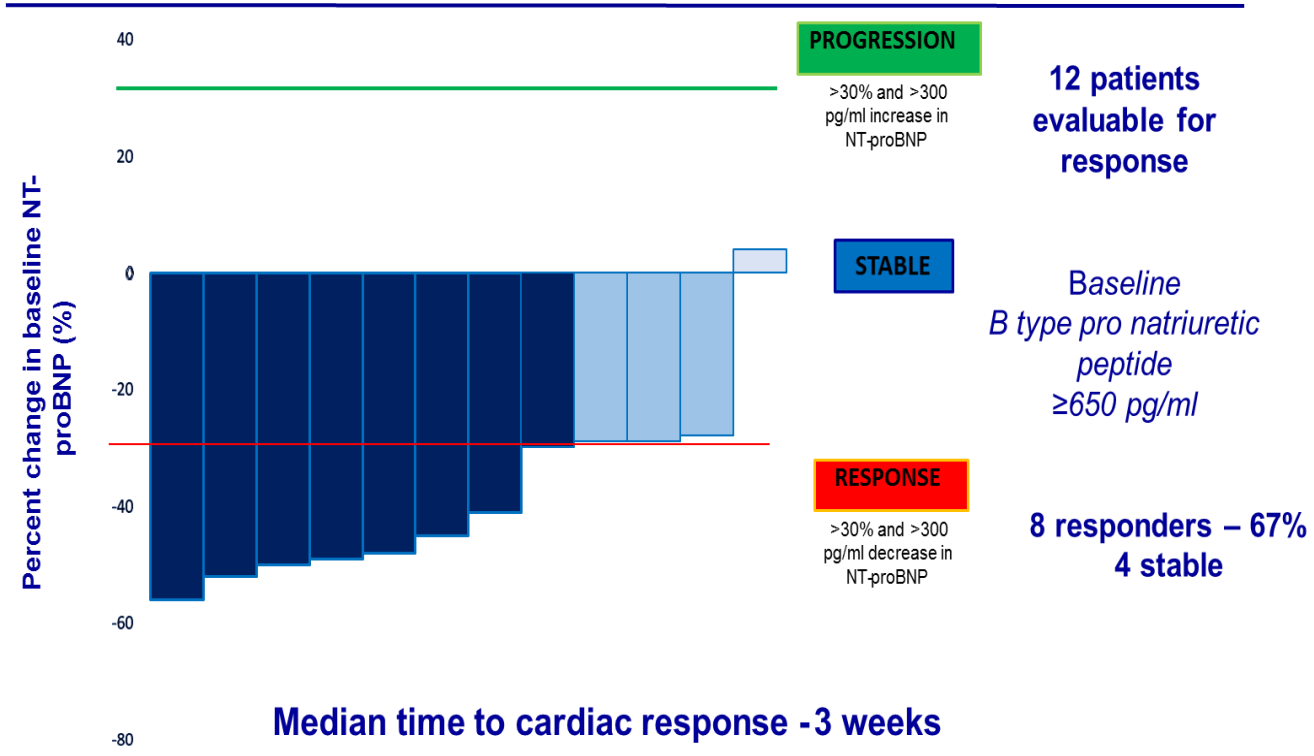
- **Used Bence Jones protein to develop human monoclonal Ab vs light chain in Amyloid fibrils not reactive with circulating light chains**
- **Reacts with Amyloid deposits in tissues**

- **GMP-grade Amyloid fibril-reactive IgG1 11-1F4 mAb (CAEL 101) produced by NCI Biological Resources Branch for imaging and Phase I/II trials**

Monoclonal Antibody 11-1 F4 for Patients with Amyloid Light Chain Amyloidosis

- NCI-supported Phase I trial of 11-1F4 mAb for pts with refractory/relapsed amyloidosis based on remarkable dissolution of amyloid deposits in mouse models
- Goal: MTD and define any possible decrease in amyloid burden and/or improvement in organ function (heart, liver, kidneys)
- Enrolled 27 pts: 60% heart, K, soft tissue, gi
- All had progressed after median of 2 prior plasma cell directed therapies
- NO grade 3 or 4 toxicities
- 15 of 24 evaluable pts had organ responses in heart, K, gi, skin, soft tissues; most in less than 3 weeks of weekly iv ab infusions; no organ progressions
- 93% OS at 19 months; 78% OS at 37 months
- Orphan drug designation by FDA

Current: Outlicensed to CAELUM Biosciences; currently 2 ongoing Phase III trials for cardiac amyloid light chain disease; CAELUM acquired by AstraZeneca in October 2021.



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 80 publications to date
- Over 18 patents filed

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.

Out-licensed Projects:

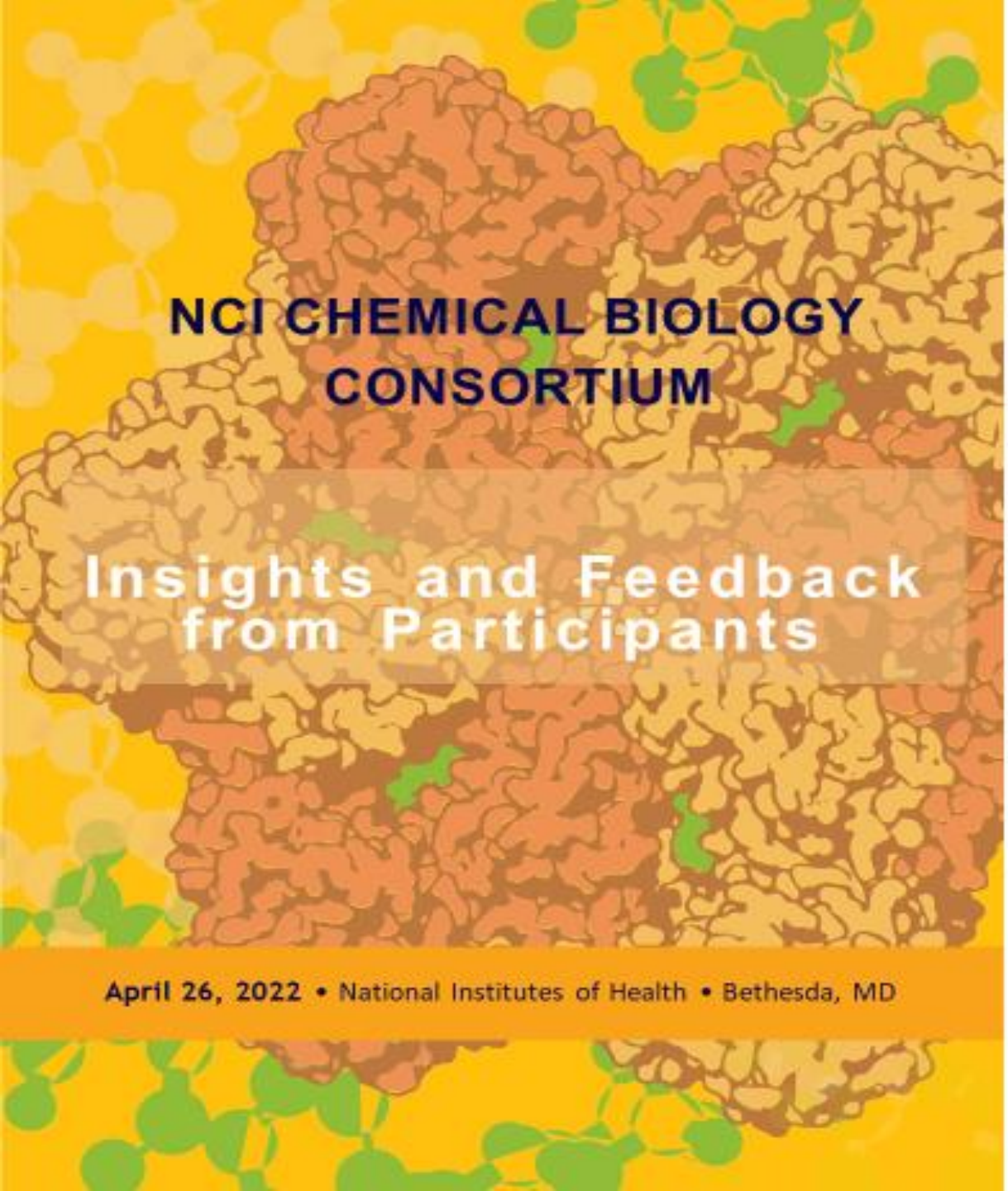
- First-in-class orally bioavailable LDHA inhibitor, Chi Dang, P.I. Licensed to Chinook Therapeutics for primary hyperoxaluria
- High affinity inhibitor of Mcl-1 dependent protein-protein interactions, Stephen Fesik, P.I. (licensed to Boehringer Ingelheim)

Therapeutic Agents Originating from CBC Pipeline Entered the Clinic:

- First-in-class oral Mer TK inhibitor, E. Shelton Earp, P.I. (phase 1)
- First-in-class oral ATPase inhibitor targeting proteotoxic stress, Ray Deshaies, P.I. Caltech, collaboration with Cleave (phase 1)
- 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 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, purchased by AstraZeneca 10/2021
- First-in-human trial: oral endoxifen for tamoxifen resistant ER+ tumors; active in Tam-resistant breast cancer; licensing discussion ongoing

Partnership with NCI Comparative Oncology Program:

- Canine trials used to assess tolerability, efficacy and validate PD endpoints.
- Validation of **PD biomarker** for p97 inhibitor human clinical trials



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CHEMICAL BIOLOGY CONSORTIUM AGENDA

APRIL 26, 2022
10:00 AM – 2:00 PM EDT

Chair: Larry Marnett, PhD

Participants: Christopher Austin, MD; Howard A. Fine, MD; Nathanael Gray, PhD; Julian Levell, PhD; Craig W. Lindsley, PhD, FRSC; Frank McCormick, PhD, FRS, DSc (Hon); Kevan Shokat, PhD; Shaomeng Wang, PhD

10:00 AM	Larry Marnett, PhD, *Vanderbilt University*
10:10	James H. Doroshow, MD, *National Cancer Institute* *NCI Experimental Therapeutics Program*
10:25	Stephen W. Fesik, PhD, *Vanderbilt University* *Highlight of Vanderbilt's scientific contributions*
10:45	Alex G. Waterson, PhD, *Vanderbilt University* *Degradation Approaches for the Wnt pathway and Bcl-xL*
11:05	Stephen Frye, PhD, *University of North Carolina, Chapel Hill* *Targeting MerTK in tumors and the immune system*
11:25	Q&A
11:40	Break
11:50 PM	Matthew D. Hall, PhD, *National Center for Advancing Translational Sciences* *LDH and IDH inhibitor programs*
12:15	Stephen W. Fesik, PhD, and William P. Tansey, PhD, *Vanderbilt University* *WDR5 project*
12:35	*AAA ATPase p97/VCP as a Cancer Therapeutic Target* Scott Harris, MS, *Cleave Therapeutics, Inc.* *Update on the clinical status of first-in-class p97 inhibitor CB-5339* Mark Wolf, PhD, *Curia Global, Inc.* *Overview and update on p97 allosteric inhibitor backup effort*
1:15	Q&A
1:25	Brooke Emerling, PhD, *Sanford Burnham Prebys* *The promise and progress of targeting PI5P4Ks for cancer therapy*
1:40	Shared Insights and Feedback from Participants Larry Marnett, PhD, *Vanderbilt University*
2:00 PM	Adjourn

NCI Experimental Therapeutics Program: Chemical Biology Consortium Review
Shared Insights and Feedback from Participants
April 26, 2022

Closing Statement from Chair
Larry Marnett, PhD, Vanderbilt University

"This has been a very impressive day. When the CBC first began, it was unclear whether such a program would succeed, but we've seen based on the presentations today that it has. The CBC is supporting rigorous science, in part by maintaining a tolerance for temporal flexibility and the changing nature of these projects—a tolerance that the private sector often does not have. Since the termination of the NIH Molecular Libraries program, the CBC has become the standard and perhaps the only organized program to do this type of work in any disease."

Shared Insights and Feedback from Participants

- I would echo the prior statement—the level of risk tolerance, the scientific rigor—all of that came through in spades.

- I would also like to echo the previous comments; being on the entry side of the NExT Program, it's exciting to see the incredible science and drug discovery coming out on the other end. This is what the NIH and the NCI are for.

- The teams in place have a great amount of experience, and it would be wonderful to see the transfer of some of this expertise (for example, the fragment screening capabilities at Vanderbilt) to other projects as well.

- You have created and showcased a prototypic and exemplary program of what the NCI/NIH can accomplish, with the correct vision and leadership, that cannot be done in any other venue. I believe this is exactly what the NCI should and needs to be doing, and both of you should take great pride in creating something that I suspect many would have doubted was possible at the NIH.

- I thought it was great that some projects were discontinued because it shows a rigor and critical thought about resources that is very important in drug discovery. I was also impressed with the number of true collaborations between the NCI/academic labs/industry partners. The projects which span these three stakeholders really have the chance to be impactful and lead to transformative medicines. I was trying to think of the "secret sauce" in the program. One element I think is the participation of experienced drug discoverers like Stephen Frye and Steve Fesik who not only bring their experience but also their ambition to go after targets/biology that would not be pursued by pharma or academic scientists alone. I hope the NCI continues the program because I think it fills an incredibly important role in the landscape of drug development here in the US.

- I am a fan of this program and think a lot of very impressive science has been done. However, it's clear that the people that have been successful navigating the system are industry-experienced drug discovery 'black-belt' experts like Stephen Frye and Steve Fesik. There is nothing 'wrong' with this, but one hope for the program would be for motivated academic PIs who don't have this expertise to be able to do early-stage drug discovery. Maybe this was an unrealistic expectation. I think these two have been very successful for these reasons:

    - They have figured out ways to bring significant additional resources to support their programs (industry partnerships, school funds, philanthropy etc., especially Fesik)
    - They have experience managing up and down in a matrix fashion (traditional academic PIs are often not good at this).
    - They have prior experience to know how to solve technical challenges and what is operator error versus genuinely difficult.

- You always need a project champion who can keep people motivated; there are so many reasons to give up at various stages, and the competitive position is always vexing and especially so with government funding when there are competing private efforts. It's

Outreach Suggestions in Response to "We would appreciate any ideas that you might have to encourage more people to send in applications. We are really interested in high-quality science and things that are largely not being done by pharma"

Suggested mechanisms to make the industry and academic population more aware and get more and better-quality proposals

- Leverage social media
- Publications
- Conference sessions like ACS sessions in 2019
- Review cutting-edge science at biotechs and academia and solicit applications from them
- Sabbatical exchanges from industry into CBC and vice-versa
- VC collaborations. Big VC firms are looking for seed ideas to start new biotech
- Lecture tours. Present overview of the program and a case study at various conferences, universities, and companies around the US
- You might look at this paper https://pubmed.ncbi.nlm.nih.gov/26046436/ which we published about the ML network and its remarkable productivity. Unfortunately, it served as an epitaph of the program, but you could publish an analogous paper while the CBC is still living, to draw more applicants.

Project-Related Insights

- Are the results from failed projects published so that we can learn from them?

    - All the chemical structures are published, and we maintain a repository of NExT compounds that lack activity that we can distribute. PIs can keep their agents for further R01-supported research into mechanisms. It is hard to say whether smarter chemists would have done better, but we took many projects far enough to show that the biology *in vivo* just didn't translate to efficacy.

REVIEW OF CHEMICAL BIOLOGY CONSORTIUM: LESSONS LEARNED

- Critical role of integrating academic expertise in cancer biology with drug development and sufficient time commitment to bring agents to the clinic
- Maintain focus on difficult targets too risky for Pharma/Biotech
- Continue strong emphasis on ‘trust but verify’ to discontinue projects that are not productive
- Broaden visibility to enhance engagement with academic investigators and small biotechs
- Consider new focus on combination therapy