NCI Experimental Therapeutics Program (NExT):

A Government, Academic, Industry Partnership for Cancer Drug Discovery

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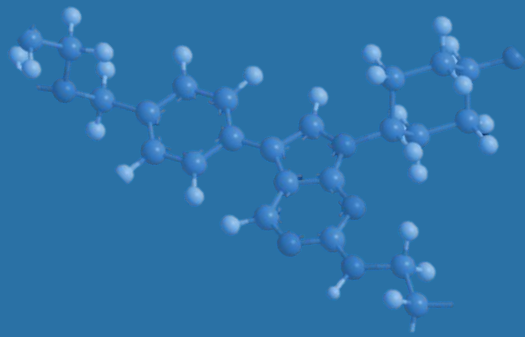
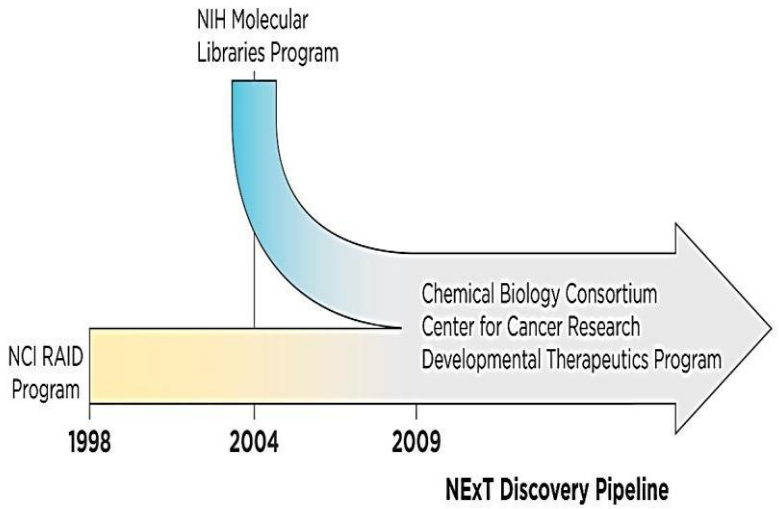


NIH NATIONAL CANCER INSTITUTE

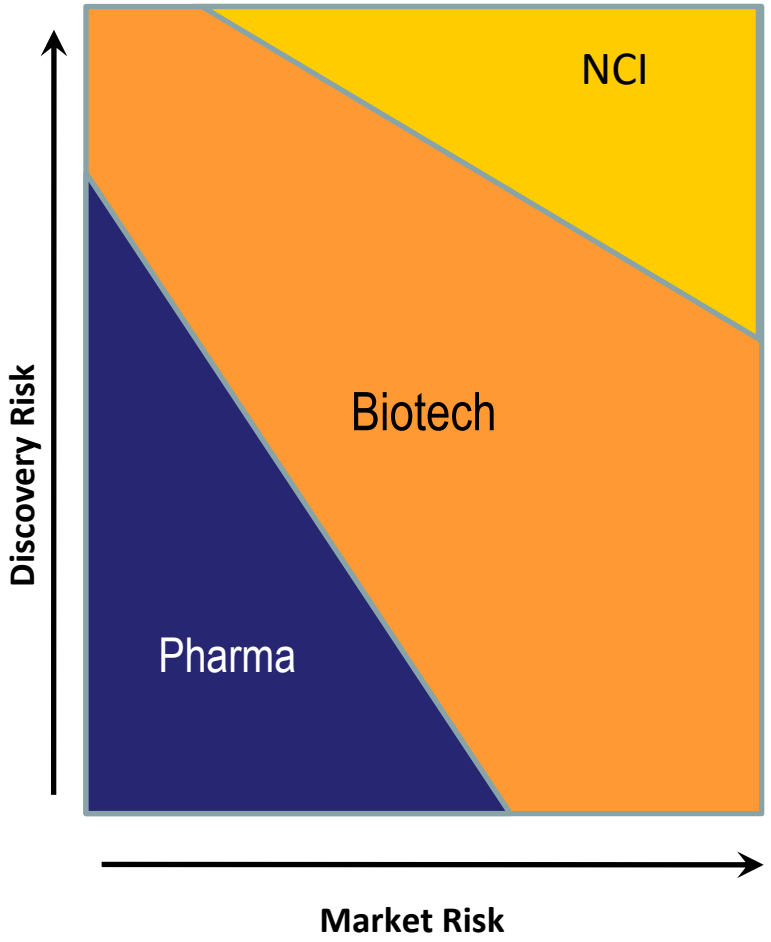
Frederick National Lab Advisory Committee

June 28, 2021

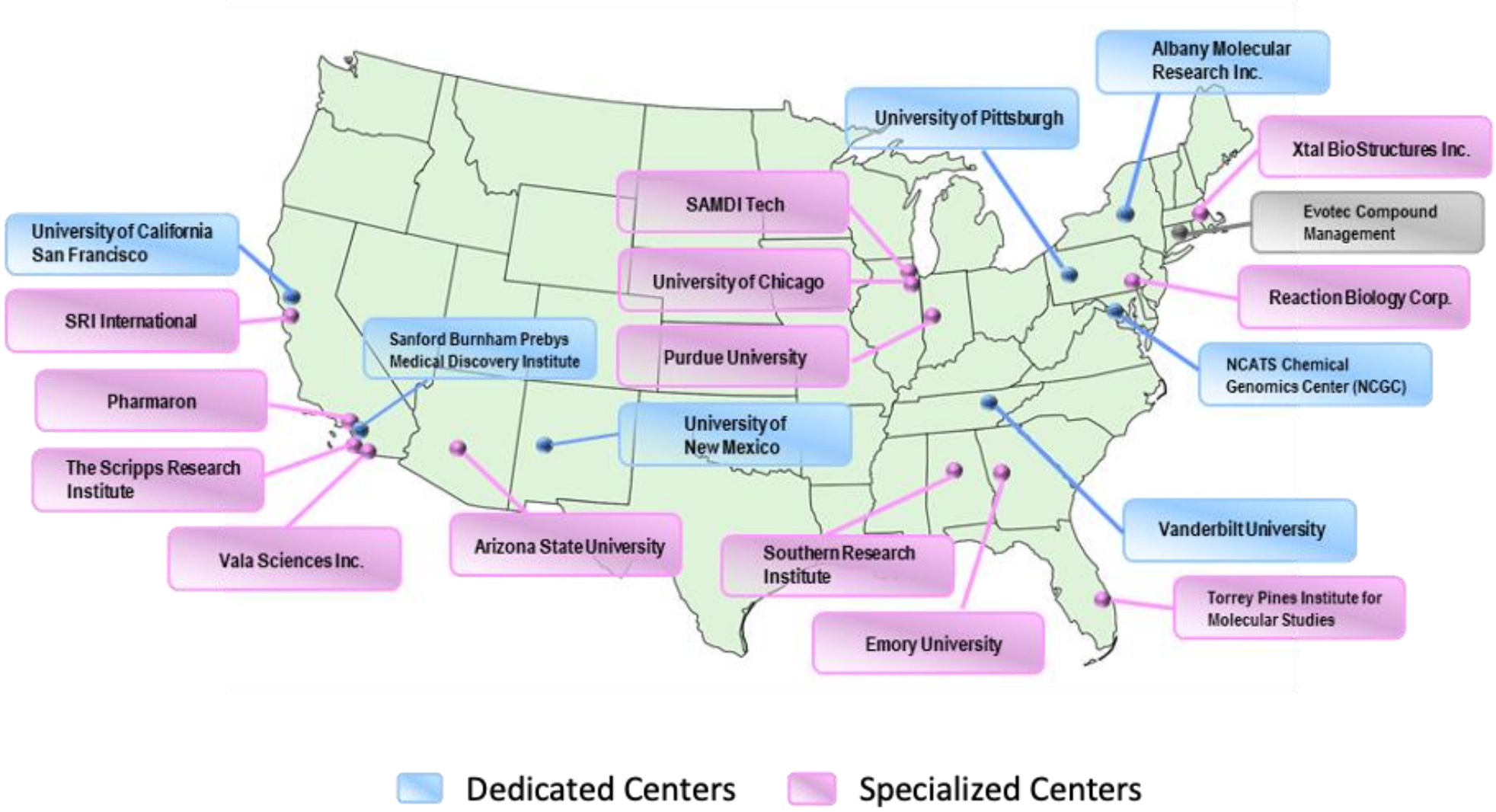
Origin and Goals of the NExT Discovery & Development Pipeline



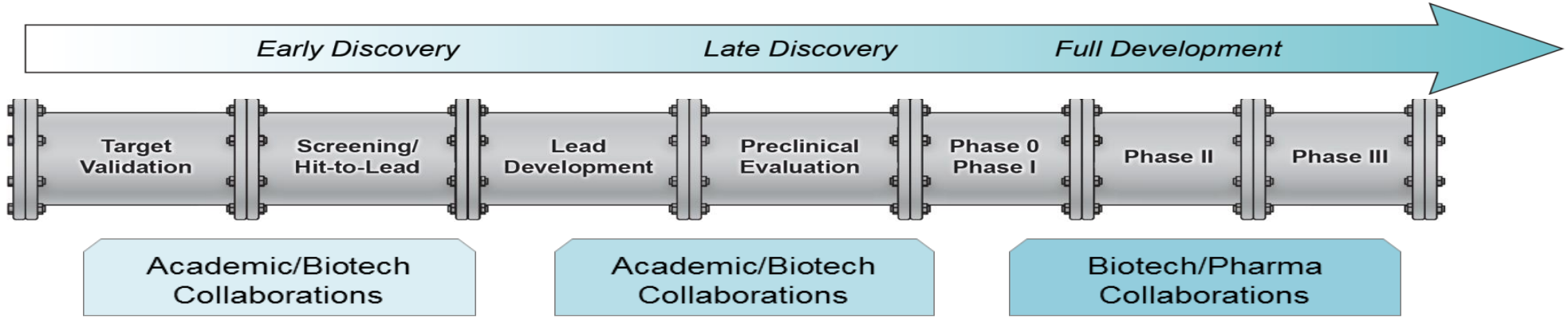
- **Build on >50 yrs of NCI experience in cancer drug development to increase flow of early & late stage candidates from Academia/small biotech to the clinic**
- **Integrated network of chemical biologists, structural biologists, modelers, PK, PD, Tox, imagers & GMP scale up partnering with NCI**
- **Inclusive 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

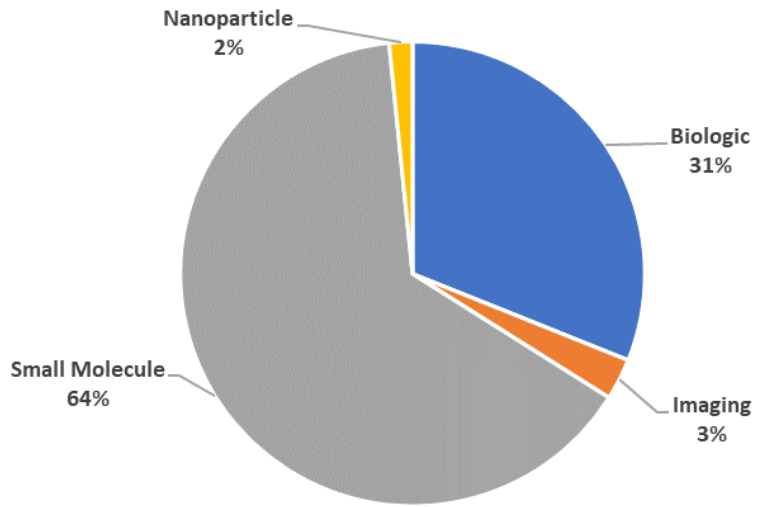


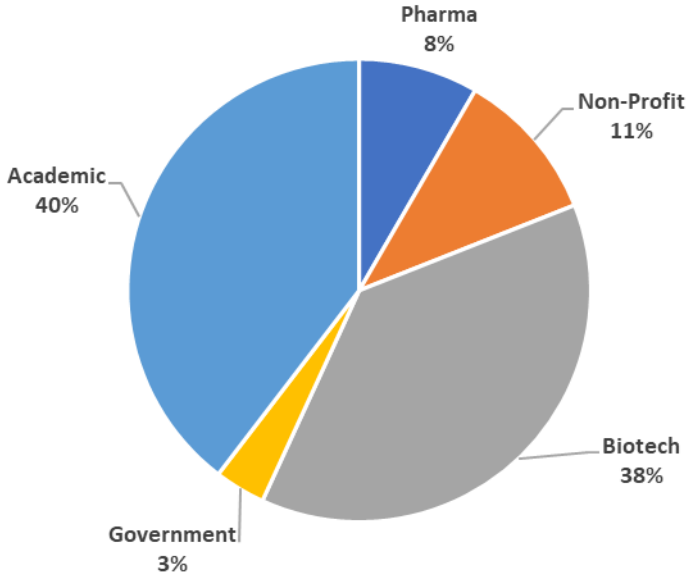
NCI Experimental Therapeutics (NExT) Pipeline



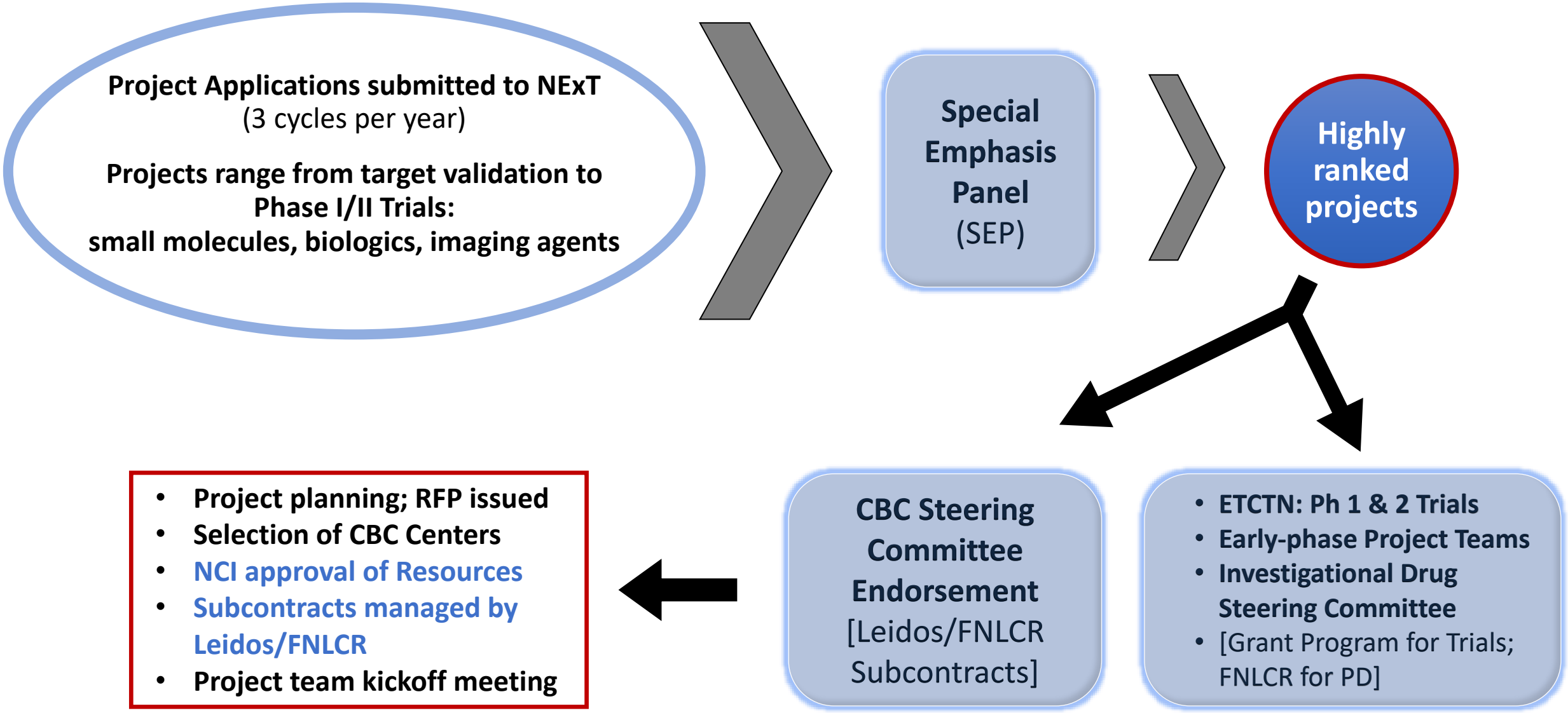
Projects enter the pipeline on a competitive basis at any stage of the pipeline

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



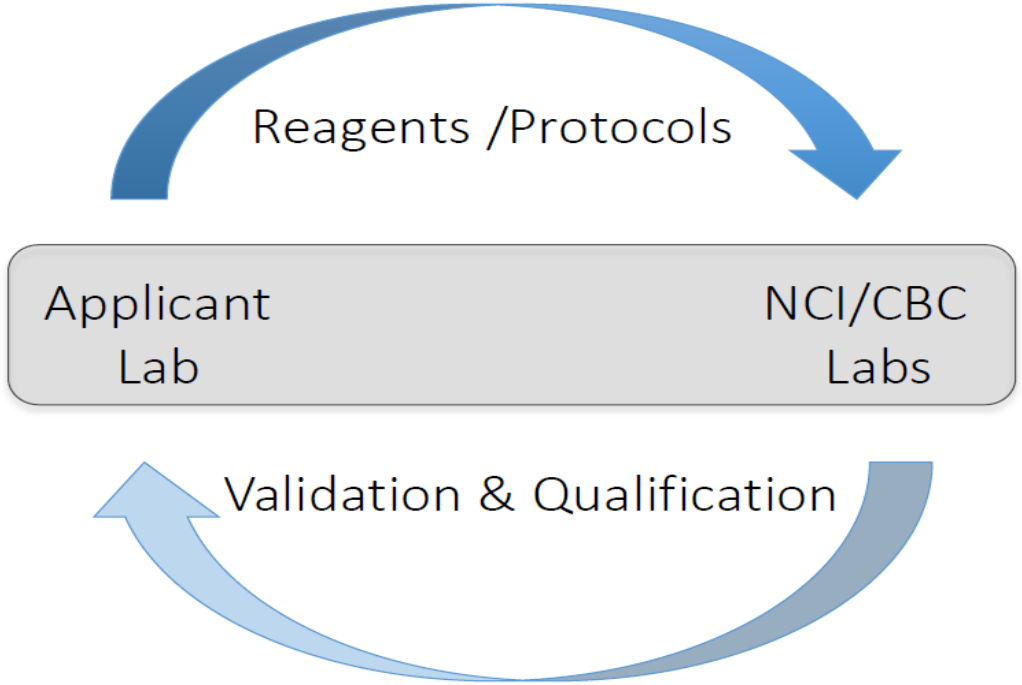


NExT: From Application Review to Project Team Kickoff Meeting



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

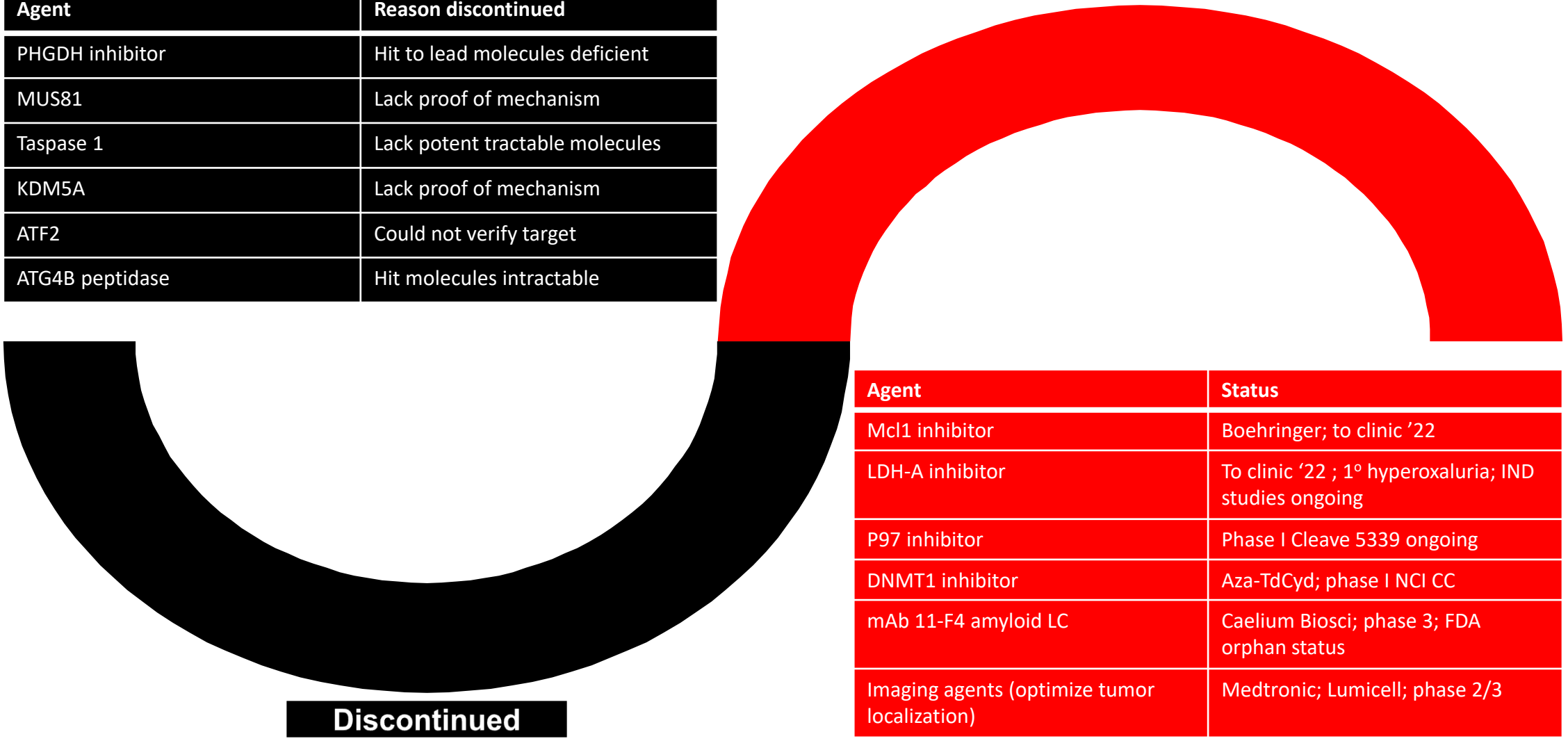
Mcl1 inhibitor**
LDHA inhibitor*
Allosteric p97
WDR5-MLL1 inhibitor
SF1

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#

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

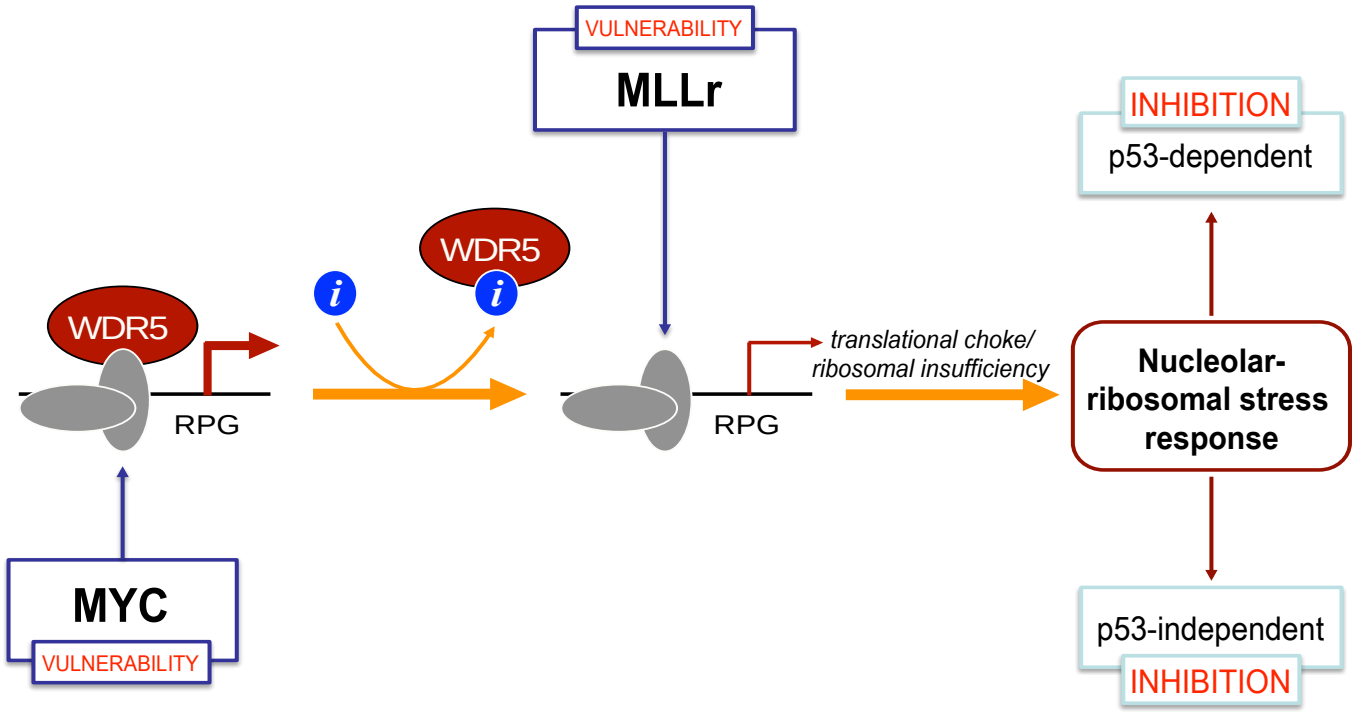
NExT Pipeline: Develop or Discontinue?

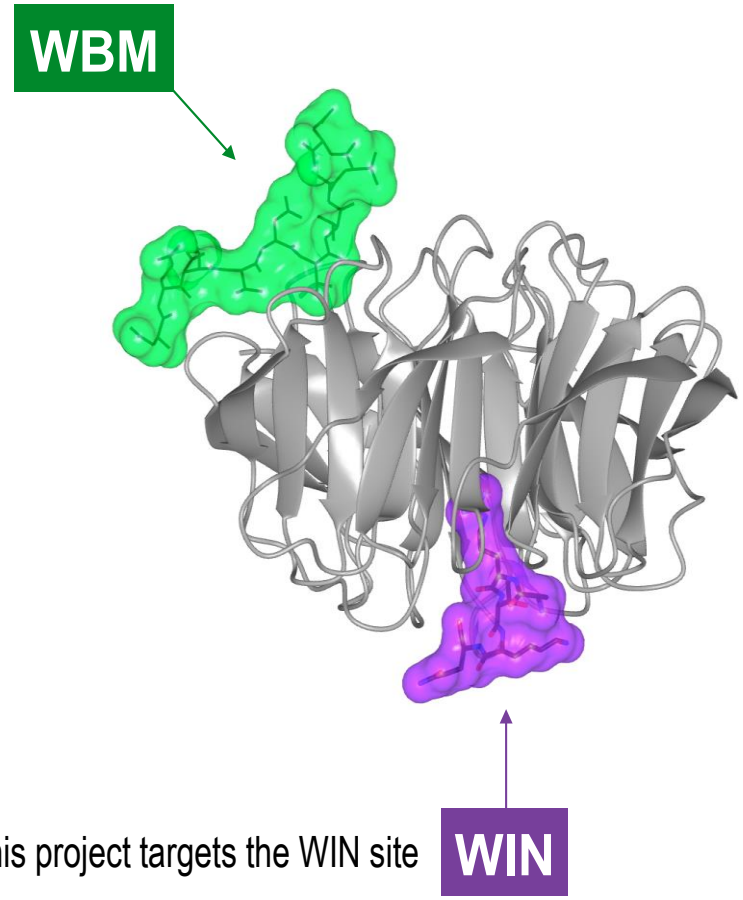
Agent	Reason discontinued
PHGDH inhibitor	Hit to lead molecules deficient
MUS81	Lack proof of mechanism
Taspase 1	Lack potent tractable molecules
KDM5A	Lack proof of mechanism
ATF2	Could not verify target
ATG4B peptidase	Hit molecules intractable



Agent	Status
Mcl1 inhibitor	Boehringer; to clinic ’22
LDH-A inhibitor	To clinic ‘22 ; 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
Imaging agents (optimize tumor localization)	Medtronic; Lumicell; phase 2/3

WDR5: A Novel Cancer Target





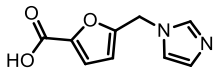
- WDR5 is a novel chromatin binding partner of MYC; WDR5 recruits MYC to sites on chromatin
- Controls many genes involved in protein synthesis
- Interaction with WDR5 critical for tumor maintenance by MYC

BILL TANSEY (Vanderbilt University)

PNAS (2019), 116: 25260-25268

WDR5 Inhibitor Discovery by Fragment-Based Methods & Structure-Based Design

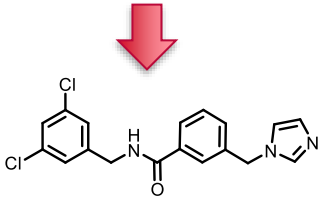
Hit to Lead → **Lead Optimization** → ***In vivo* Optimization**



Fragment hit

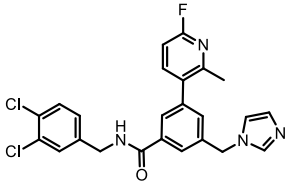
K_i = 140,000 nM

> 14,000,000 x improvement in binding



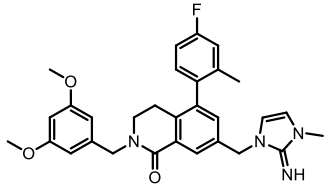
K_i = 42 nM

S_7, S_4 optimization



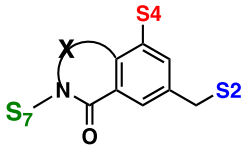
K_i = 2.0 nM

Bicyclic core series



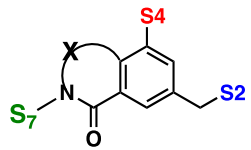
VU0817584
K_d < 0.010 nM
HMT MLL1 IC_{50} = 4 nM
MV4:11 GI_{50} = 32 nM

Efficacy optimization

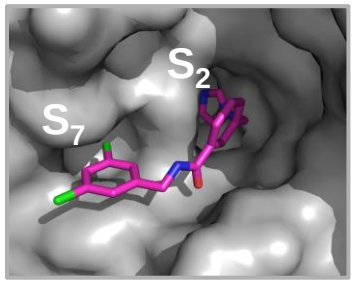


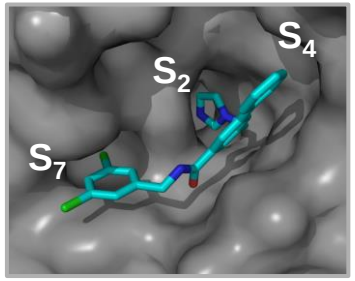
VU0849716
K_d < 0.020 nM
HMT MLL1 IC_{50} = 6 nM
MV4:11 GI_{50} = 27 nM

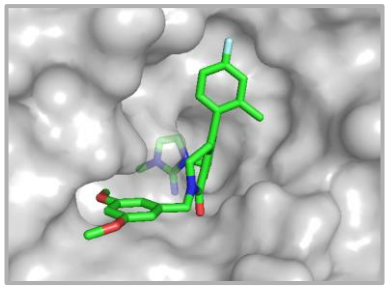
Potential IND candidate



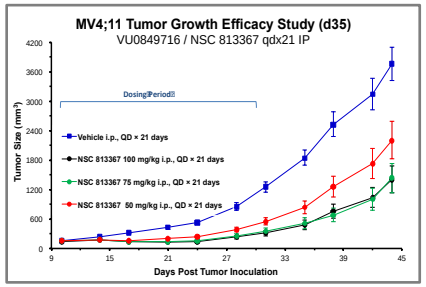
VU0908809
K_d < 0.020 nM
HMT MLL1 IC_{50} = 8 nM
MV4:11 GI_{50} = 14 nM



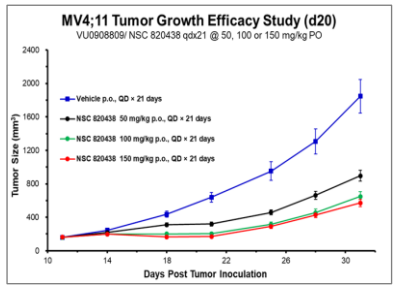




- No oral bioavailability
- *In vivo* efficacy at MTD



- High oral bioavailability
- *In vivo* efficacy by PO dosing



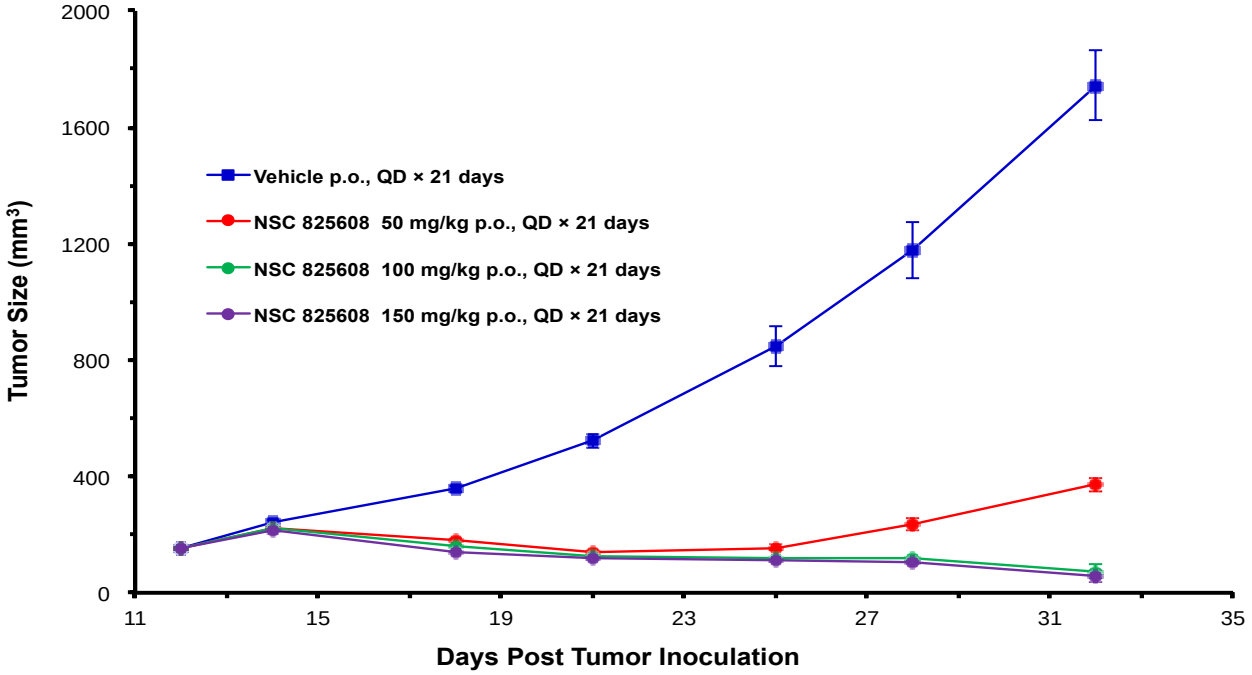
- Good *In vivo* efficacy
- Good PK in all species
- Demonstrated safety in rats
- Limited Aq. Sol (requires formulation optimization)
- Potential hERG liability

STEPHEN FESIK (Vanderbilt University)

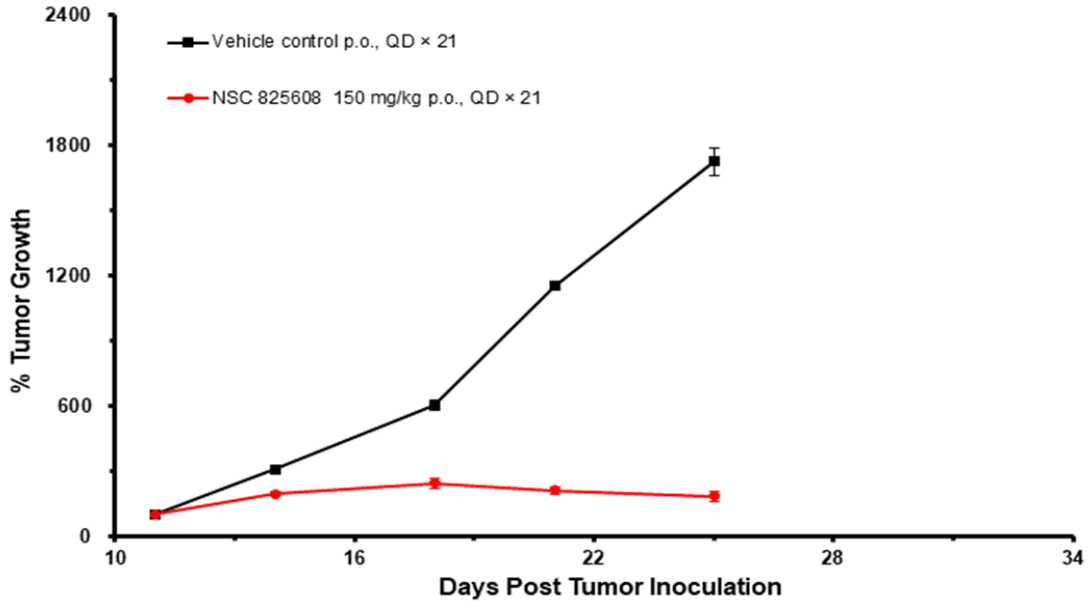
J. Med. Chem. (2020); 63: 656-675

Approaching a Candidate for IND-enabling Studies: First-in-Class VU0914813

MV4;11 Tumor Growth Efficacy Study (d20)
VU0914813 / NSC 825608 qdx21 @ 50, 100 and 150 mg/kg PO



SU-DHL-5 Tumor Growth Efficacy Study (d15)
VU0914813 / NSC 825608 qdx21@150 mg/kg PO



- pM binding to target with nM potency in multiple cancer cell lines
- Good kinetic aqueous solubility at pH 7 (62 μM in PBS)
- Minimal hERG liability (10 μM in patch clamp)
- Desirable PK profiles in all tested species (rat, dog, cyno)
- Scalable synthesis
- Acceptable formulation in 0.5% CMC
- MTD (300 mg/kg) established in 14 d rat DRF study
- No remarkable findings in DRF at efficacious doses

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

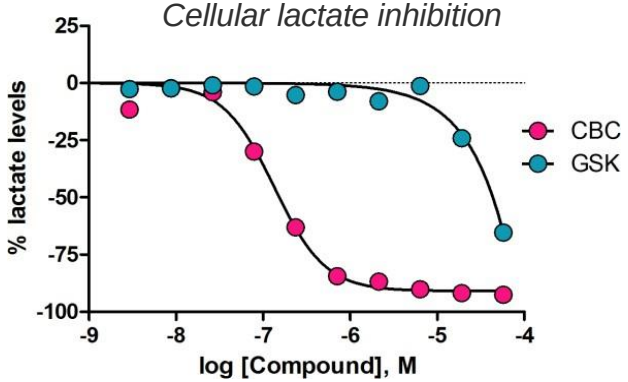
Project team generated >700 compounds & identified candidates with optimal *in vivo* properties

First LDHA inhibitors demonstrating oral bioavailability

LDH inhibitor programs at GSK and Genentech terminated due to lack of *in vivo* efficacy

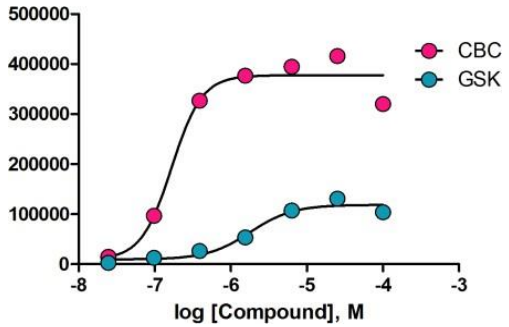
Potent Cellular Activity

Cellular lactate inhibition



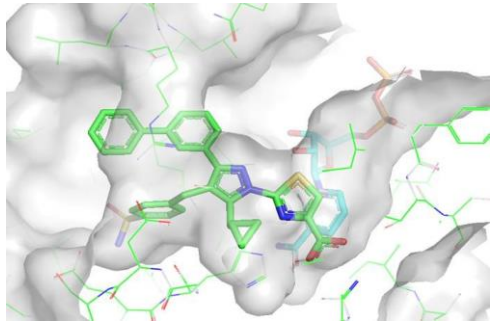
Target Engagement

CETSA demonstrating in-cell binding to LDHA



Structure-Based Design

LDHA co-crystal (1.6 Å) with CBC inhibitor



LDHA Team

NIH National Center for Advancing Translational Sciences

Penn Medicine

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

VANDERBILT UNIVERSITY

leidos Leidos Biomedical Research, Inc.

NATIONAL CANCER INSTITUTE

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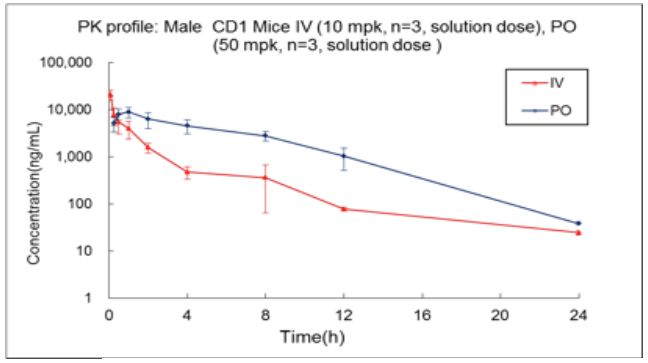
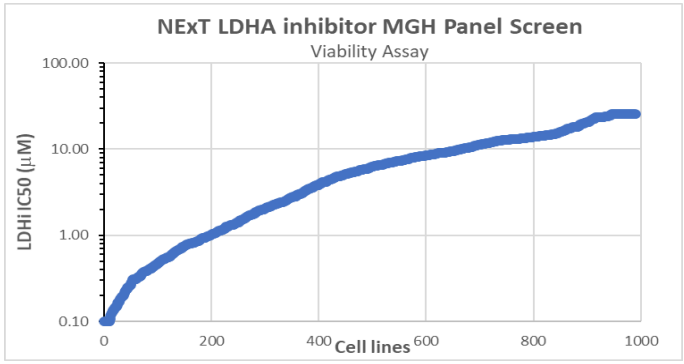


Orally Bioavailable



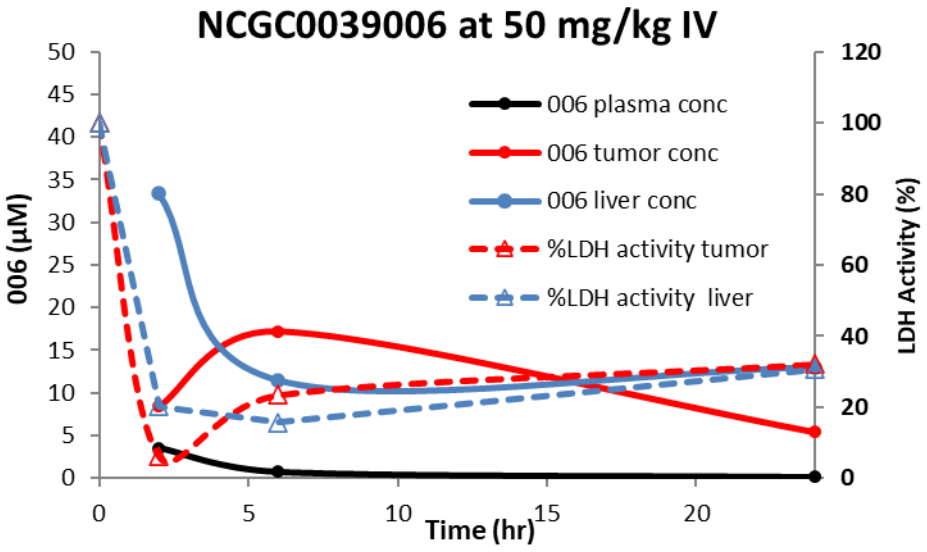
Sub 1μM activity in ~200 cell lines

Jan-11 Jan-12 Jan-13 Jan-14 Jan-15 Jan-16 Jan-17 Jan-18 Jan-19

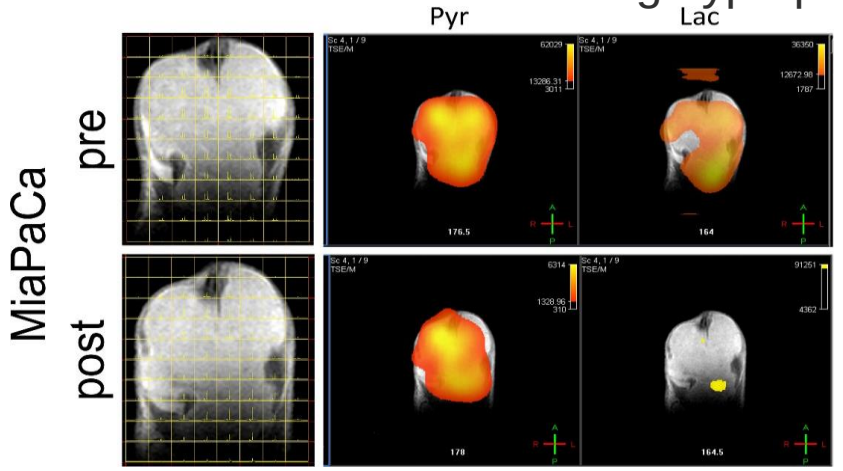
HTS | Hit to Lead | Lead Optimization

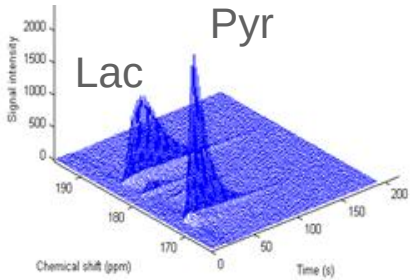
First In Vivo LDH inhibition &Tumor Growth Suppression

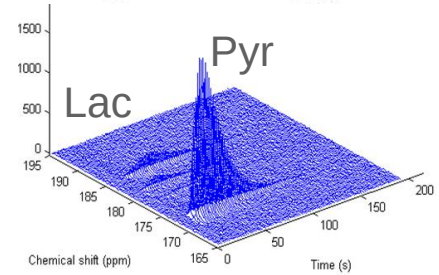
Drug Concentration vs LDH inhibition in vivo



Target Engagement *in vivo* with Pyruvate to Lactate flux measurements using hyperpolarized ^{13}C-pyruvate

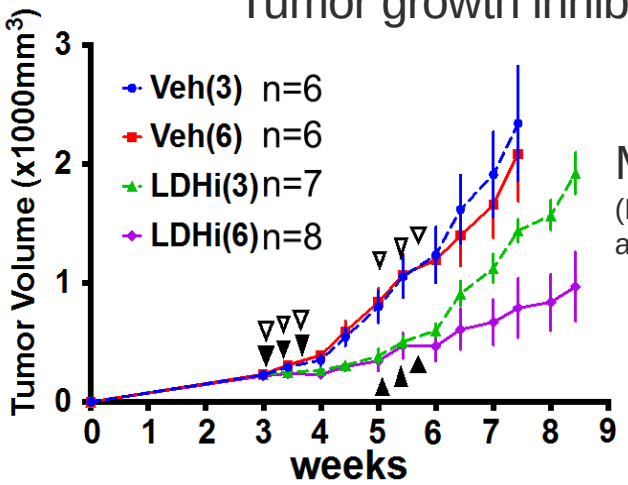




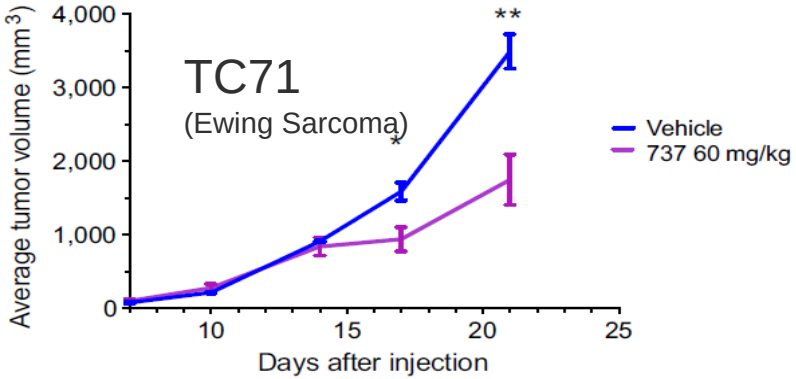


Post = 30 min post single i.v dose of 50 mg/kg inhibitor

Tumor growth inhibition *in vivo* in MiaPaCa and TC71 xenografts



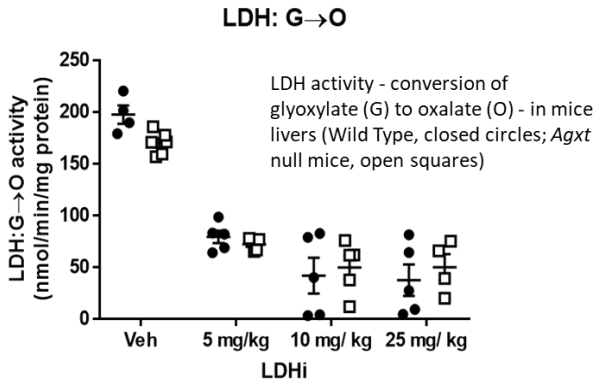
MiaPaCa
(Pancreatic adenocarcinoma)



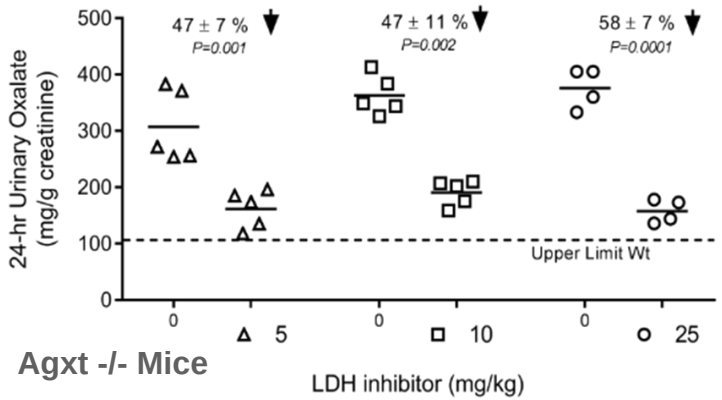
Modest tumor growth inhibition in highly glycolytic tumor models despite high levels of LDH inhibition in vivo, possibly due to very high levels of LDHA in tumors (30-50 µM)

NCI NExT LDH Inhibitor: In Vivo Activity in Lethal Metabolic Disease Model

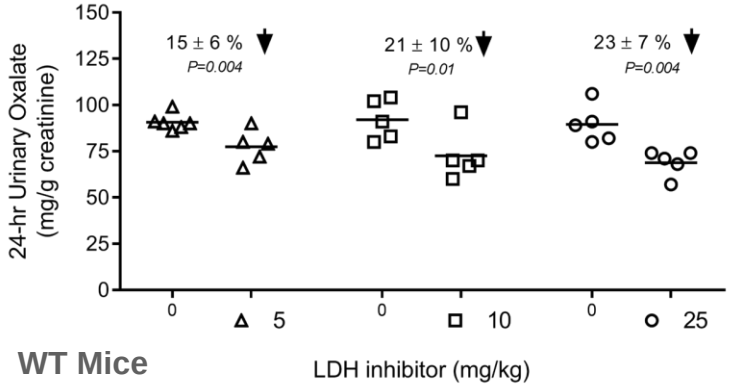
- Accumulation of LDH inhibitors and suppression of LDH activity in liver following oral administration suggested a potential role in metabolic disease models involving LDHA
- Primary hyperoxaluria (PH1) is a rare autosomal recessive disorder (*Agxt* mutation-AGTX gene that codes for enzyme that converts glyoxylate to glycine) characterized by increased endogenous oxalate synthesis in liver resulting in deposits of calcium oxalate, damaging tissues throughout the body and eventually resulting in end stage renal failure
  - ✓ Oxalate formation from glyoxylate in liver is primarily dependent on liver LDH activity
  - ✓ Diminishing hepatic LDHA activity (key enzyme responsible for converting glyoxalate to oxalate) prevents accumulation of oxalate in AGXT null mouse models as measured by oxalate levels in urine



Maximal suppression of oxalate production in livers of mice at only 5-10 mg/kg PO LDH inhibitor



Restoration to approximately WT levels of urinary oxalate in Agxt mutant mice following low levels of oral LDH inhibitor treatment



Modest reduction in levels of urinary oxalate in WT mice following low levels of oral LDH inhibitor treatment

LDHi portfolio recently out-licensed--expect to have a candidate enter clinical trials in late 2021/early 2022

Development of First-in-Class Therapy for Adrenocortical Carcinoma

Adrenocortical Carcinoma (ACC)

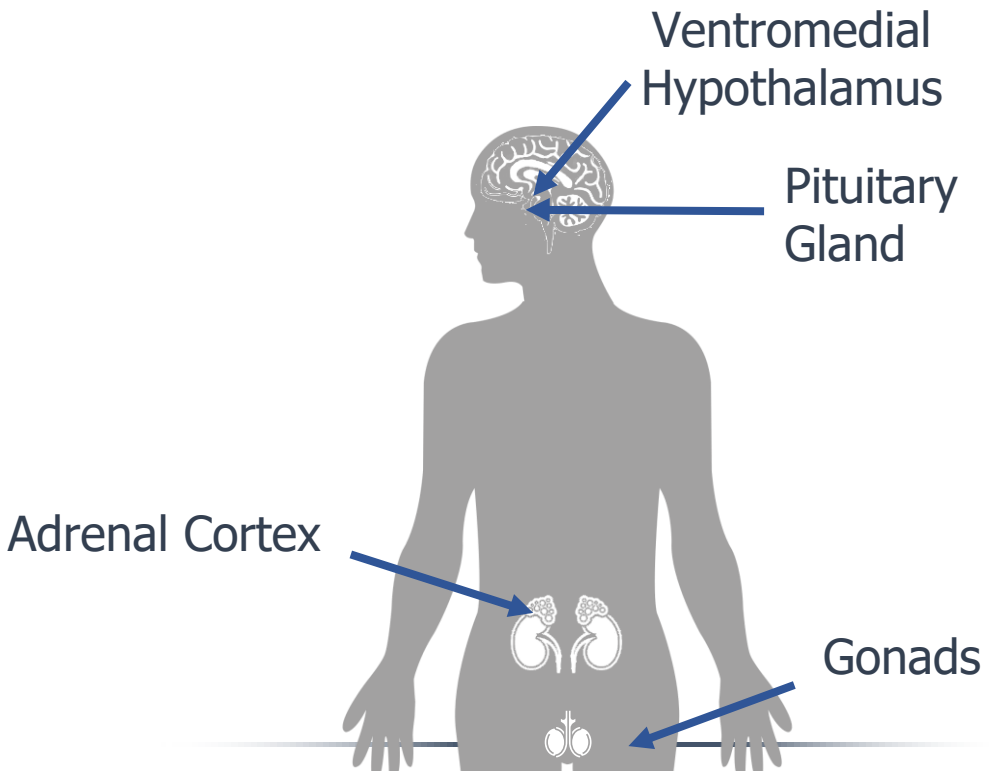
- Estimated prevalence: 600 cases in U.S. & 1,400 in Europe
- Majority locally advanced or metastatic
  - ✓ Five-year survival of metastatic (Stage 4) patients is <15%
- Few options after surgery
  - ✓ Sole medical therapy, mitotane (Lysodren®), was approved in 1970
  - ✓ Mitotane is minimally effective, difficult to dose, and highly toxic
- Limited benefit with PD-1/PD-L1 therapy; no targeted therapies

SF1 Gene Product: New target

- Highly expressed in the adrenal cortex; found only in adrenal, gonads, pituitary, spleen, and hypothalamus
- SF-1 knockout blocks normal adrenal gland development
- Major transcription factor in adult ACC; amplified in >90% pediatric ACC
- Prognostic marker in adult ACC: high SF-1 expression correlates with poor survival

NExT project from small biotech: Orphagen Pharmaceuticals: OR-449

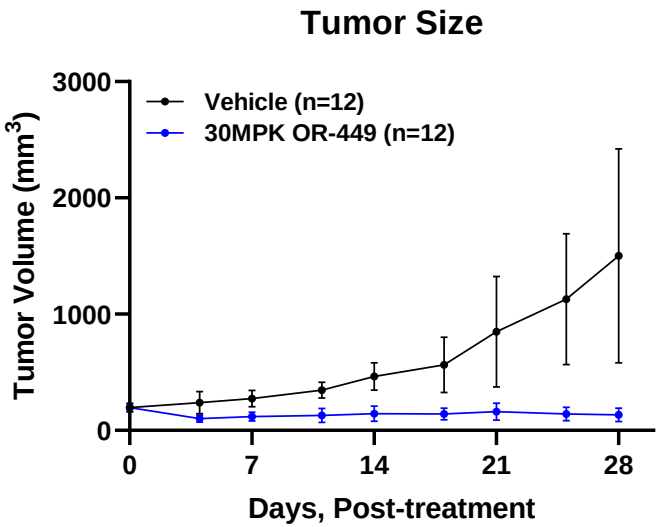
- Requested help in developing/testing in vivo models of ACC with OR-449
- If target validated, move project into development pipeline

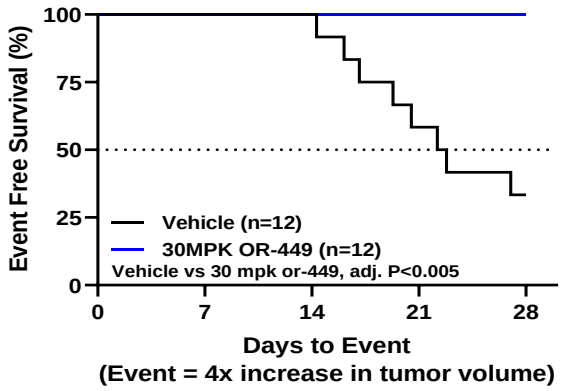


SF-1 Regulates Adrenal and Gonadal Development

OR-449 Is Active in Pediatric ACC Xenograft Models

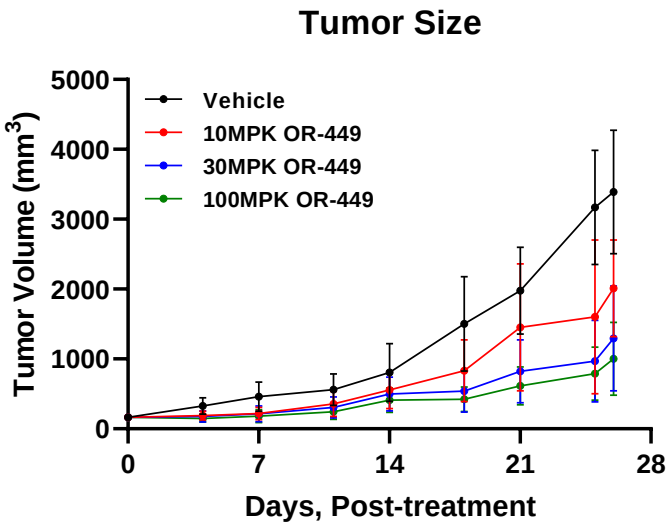
Pediatric ACC PDX #1 (SJ-ACC3)

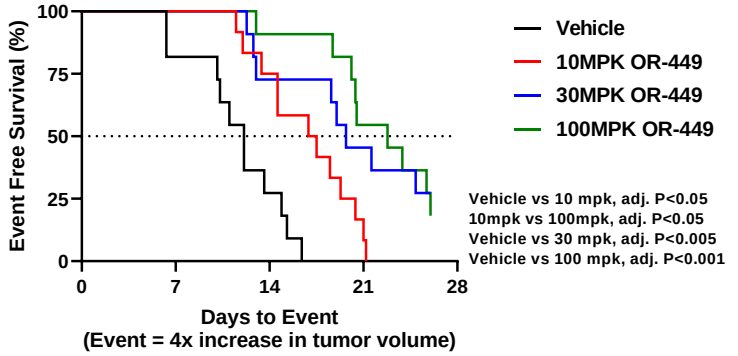




N = 12/group

Pediatric ACC PDX #2 (SW1939)

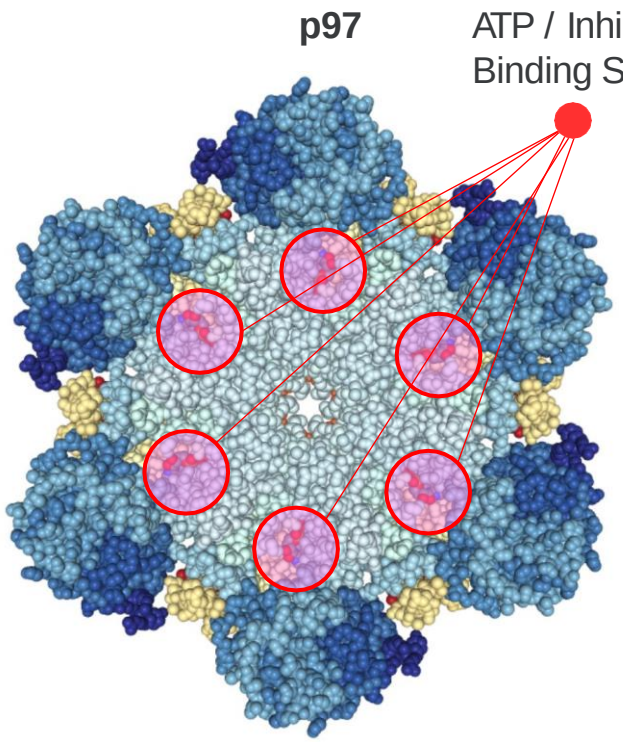




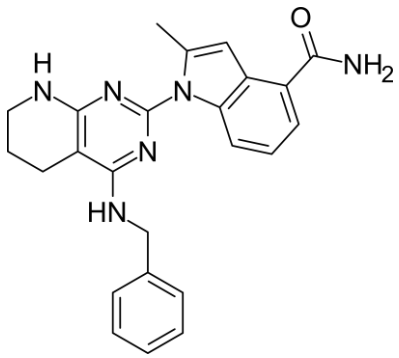
14 day exploratory oral toxicity study in mice: OR-449 is well-tolerated in mice at exposures >3-fold above the efficacious exposure

Discovery/Clinical Evaluation of Novel Protein Homeostasis Pathway Inhibitor

CB-5339, First-in-Class p97 Inhibitor



Novel target



CB-5339

- p97 is an AAA ATPase enzyme that extracts and unfolds proteins & critical for ubiquitin proteasome system—a validated target
- CB-5339 is a 2nd generation small molecule, ATP-competitive inhibitor of p97
- CB-5339 is highly selective for p97
- CB-5339 has a biochemical potency of 9 nM
- NCI collaborated with Cleave Therapeutics to perform IND-enabling studies & produce clinical product for first-in-human trials after ocular toxicity led to failure of 1st generation molecule; CB-5339 demonstrated excellent safety profile

Phase 1 AML/MDS Trial of CB 5339 Fast Moving

Open to R/R AML/MDS and Myeloid Malignancies

Completed - Cohorts 1-4

Accelerated Titration

In Progress - cohorts 5+

3 + 3 Escalation

Monotherapy Dose Expansion
R/R AML at RP2D

Combination
R/R AML at RP2D

Monotherapy Dose Expansion
Int./Higher Risk MDS

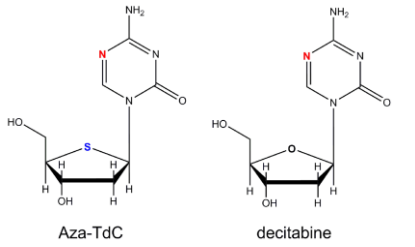
Combination
Int./Higher Risk MDS

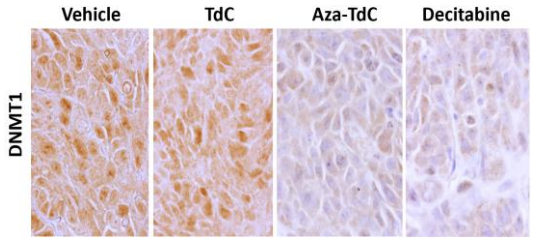
- CB-5339 dosed orally QD on days 1-4 each week
- 28-day cycles and DLT window
- Study open at nine sites in the US and Australia

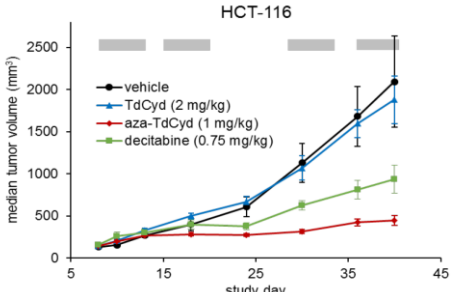
- Favorable safety profile to date through multiple dose escalation
- First seven patients enrolled; data to date supports achieving therapeutic exposure without the off target visual toxicity that halted development of Cleave's first-generation p97 inhibitor (CB-5083)
- Signs of Activity will be gauged using several readouts:
  - ✓ Circulating and bone marrow blast counts allow for rapid and direct measurement of disease burden
  - ✓ PD biomarkers (K-48/Caspase-3) provide indication of pathway engagement
  - ✓ Exploratory biomarkers in DNA damage response (gH2Ax/mRNA) provide mechanistic information

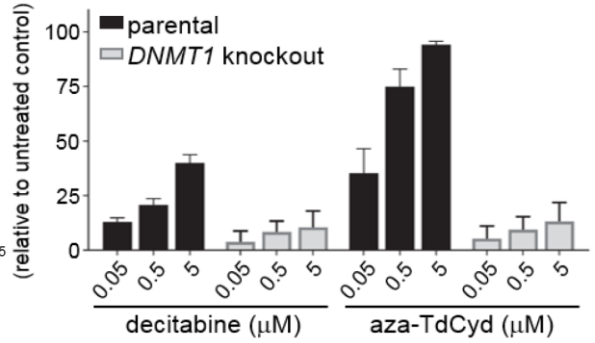
5-aza-4’-thio-2’-deoxycytidine (Aza-TdC)
Southern Research

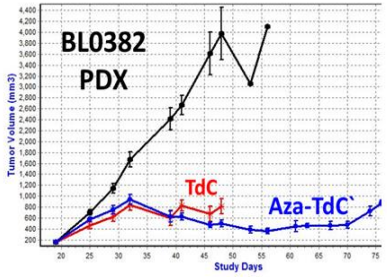
- Inhibits DNA methyltransferase 1 (DNMT1); **no IP**
- Excellent oral bioavailability; higher incorporation rate into DNA at lower levels of toxicity than decitabine
- Improved preclinical antitumor activity compared to other hypomethylating agents in solid tumor xenograft models, including TNBC, and in MEN GEMM; developed new enhanced synthesis; IND filed late 2018



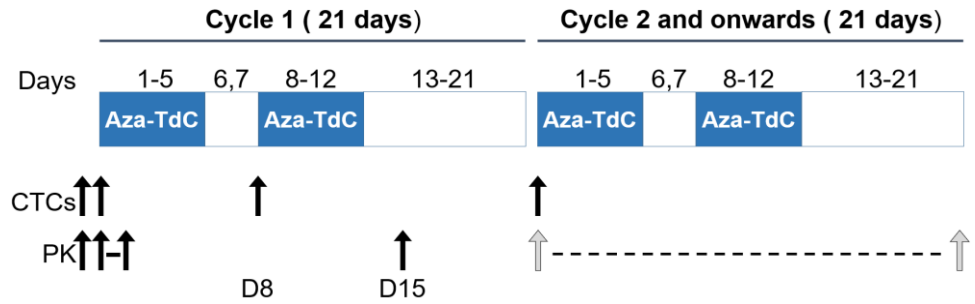




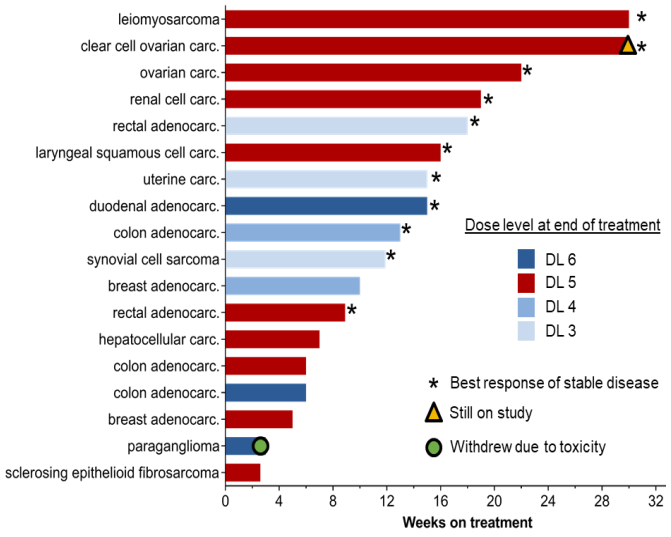


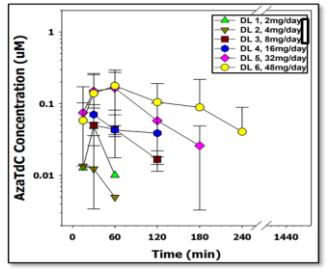


Broadly active in tumor Xgs:
Ovcar-3, H522 NSCLC, HL-60

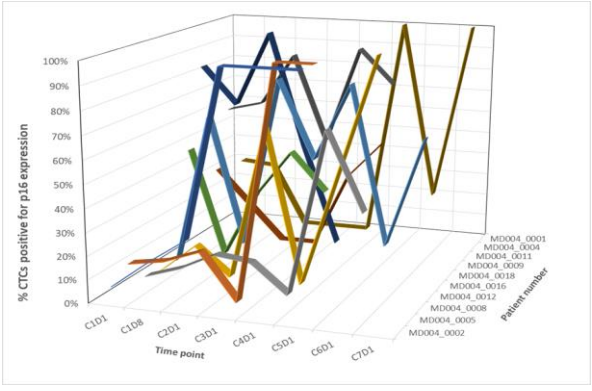


Dose Level (DL)	Aza-TdC (mg)
-1	1
1	2
2	4
3	8
4	16
5*^	32
6	48



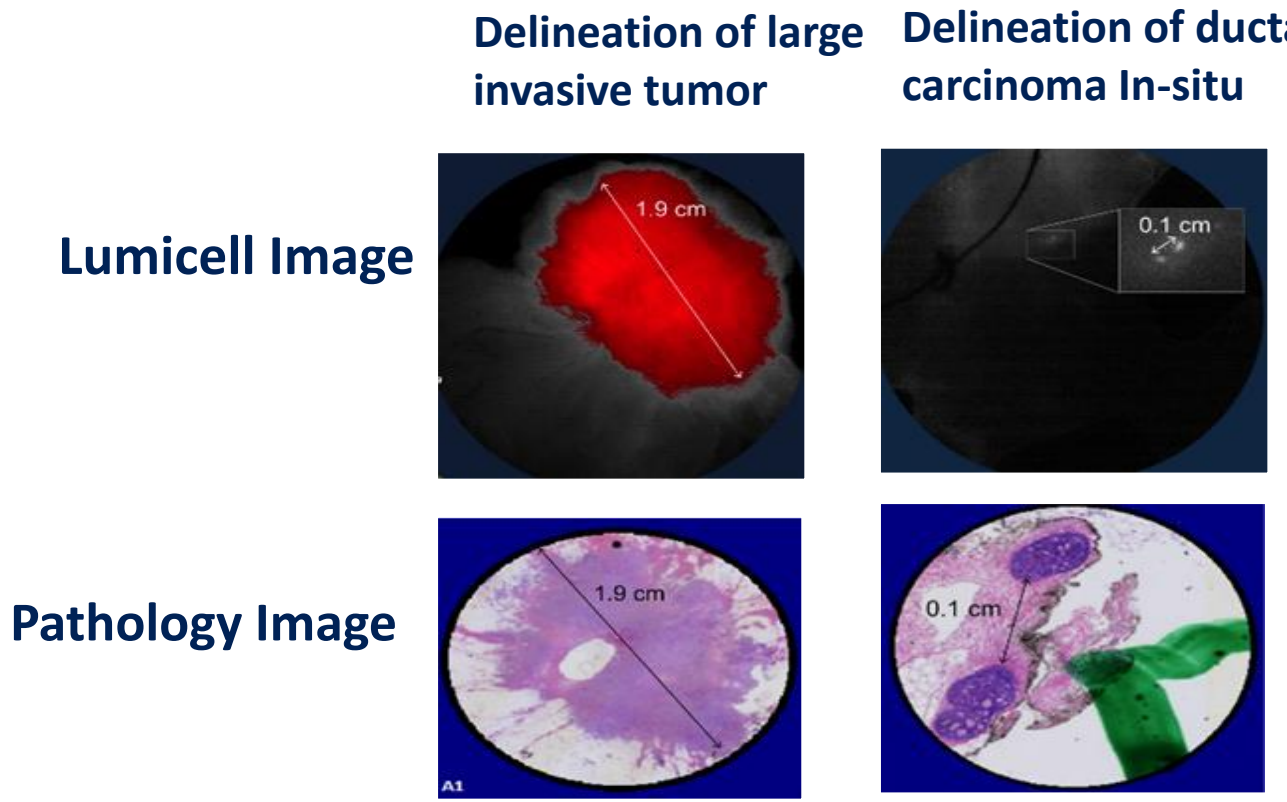


N=18
DLT: Rash; myelo-suppression
Expansion phase



Imaging Agent Development (1)

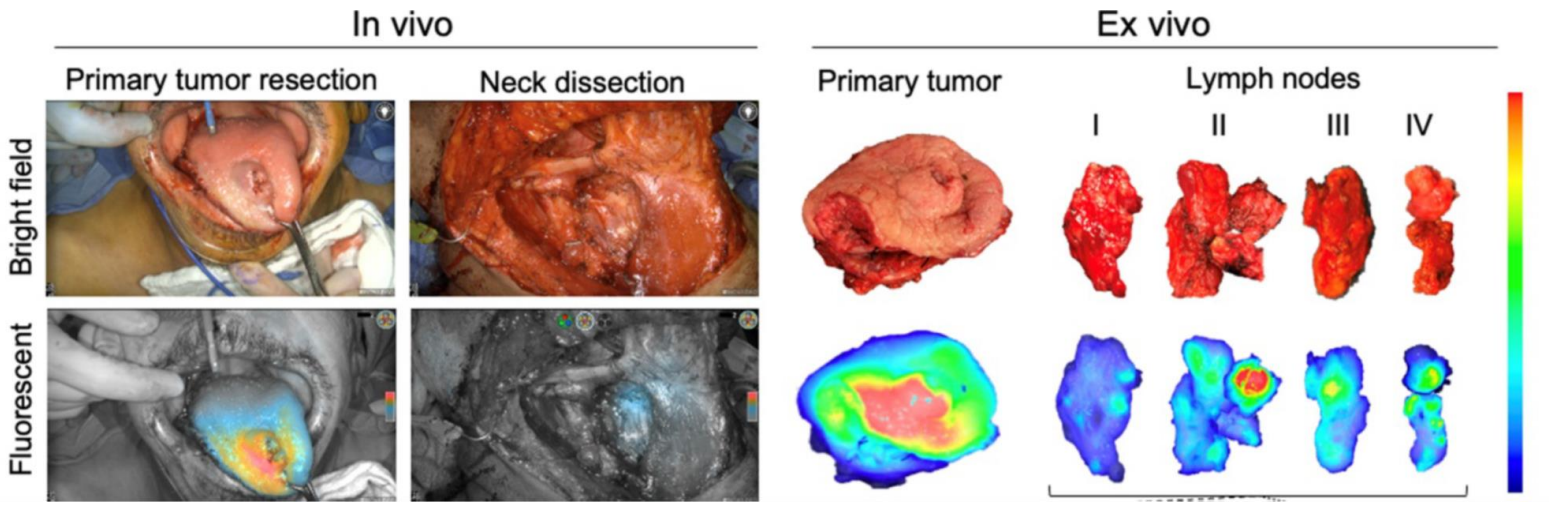
- **LUM015: David Kirsch; Duke University; Licensed to Lumicell**
  - ✓ New tumor specific imaging agent (VM249) activated by cathepsins to aid in detection of positive margins, particularly in sarcomas, breast cancer.
  - ✓ NCI provided pre-IND toxicity studies
  - ✓ Fluorescent optical contrast agent with hand-held imaging device
  - ✓ Current status: Venture funding >$40M
  - ✓ Phase III registration trial in breast cancer (NCT03321929); FDA Fast Track designation
  - ✓ Resected tumor mass imaged ex vivo to evaluate margins
  - ✓ Demonstrate concordance of imaging and pathology



Breast Cancer Research and Treatment 187: 145-153, 2021
Ann Surg Oncol 27: 1854-1861, 2020

Imaging Agent Development (2)

- **IRDye800CW-Panitumumab: Eben Rosenthal, Stanford**
  - ✓ Overexpression of EGFR in HNSCC exploited to detect tumors intraoperatively by optical imaging
  - ✓ Systemic administration of fluorescently labeled anti-EGFR antibodies in preclinical models were sensitive and specific for detection of subclinical disease
  - ✓ Phase I trials for head and neck squamous cell carcinoma (HNSCC) complete and published
  - ✓ Phase II trial for nodal detection in HNSCC is complete and published
  - ✓ Investigators evaluating analog agent labeled with In-111
  - ✓ NCI provided GMP material for trials



Representative case demonstrating intraoperative fluorescence imaging during resection of an anterior tongue tumor and elective level I – IV neck dissection. The signal intensity in resected nodes matched the pathology findings

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.

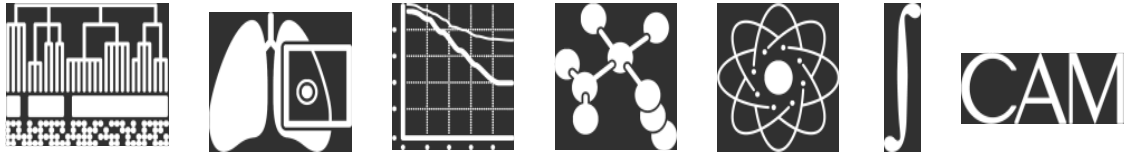
Therapeutic Agents Originating from CBC Pipeline Entered the Clinic:

- 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)

DCTD **Division of Cancer Treatment and Diagnosis**



Accelerating Cancer Diagnosis and Drug Development

- **Developmental Therapeutics Program & FNLCR**

Melinda Hollingshead

Ralph Parchment

Robert Kinders

Bev Teicher

Deborah Wilsker

Apurva Srivastava

Alice Chen

Naoko Takebe

Geraldine O'Sullivan-Coyne

Rose Aurigemma

Anthony Welch

- **Center for Cancer Research**

Yves Pommier

Bill Dahut

Peter Choyke

- **DCTD OD**

Toby Hecht

Jason Cristofaro

Barbara Mroczkowski

Michael Difilippantonio

Yvonne Evrard

- **CTEP, Biometrics, & Cancer Imaging Programs & DCP**

Jeff Moscow | Meg Mooney | Howard Streicher

Paula Jacobs | Elad Sharon

Larry Rubinstein | Helen Chen | Lisa McShane

Percy Ivy | Worta McCaskill-Stevens

- **Cancer Diagnosis Program & CBIIT**

Lyndsay Harris | Tracy Lively

Mickey Williams | Kris Karlovich

Magdalena Thurin | David Patton

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