NCI Experimental Therapeutics (NExT) Program

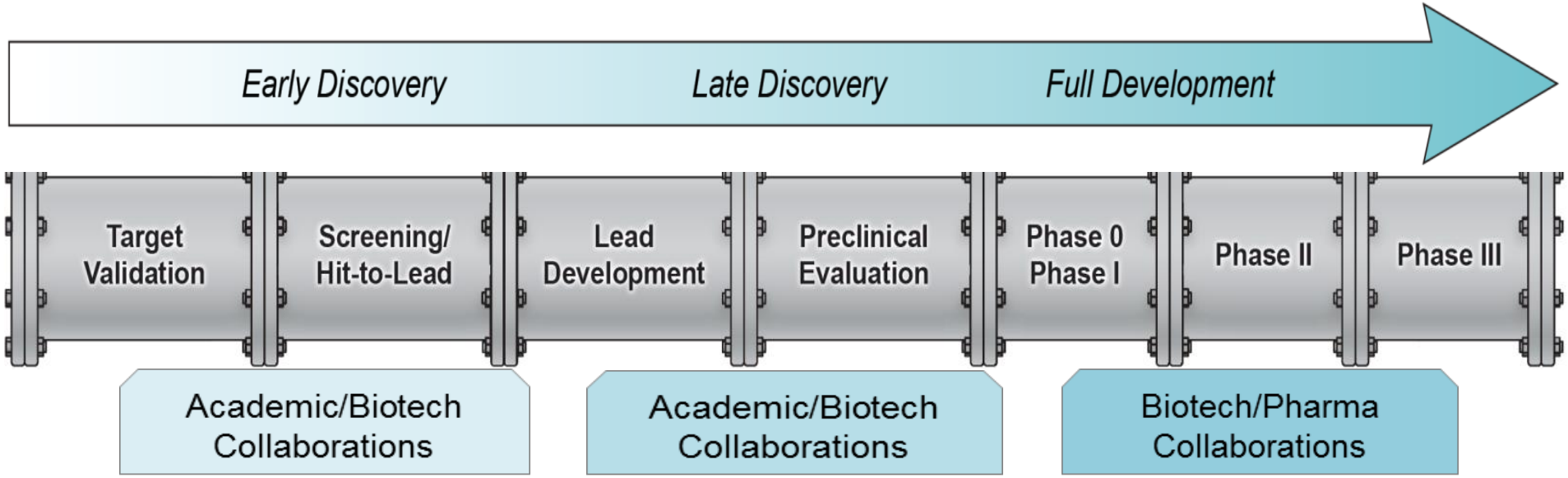
James H. Doroshow, MD
Overview and Drug Discovery

Ralph Parchment, PhD
Pharmacodynamics in Cancer Drug Development

Jeff Moscow, MD
Moving NExT Compounds into the Clinic

FNLAC Meeting
May 8, 2018

NCI Experimental Therapeutics (NExT) Development Pipeline



Today

CBC & Drug Discovery	
Advanced Clinical Projects	**J. Doroshow**
Pharmacodynamics in Drug Discovery, Development, & Phase I Trials	**R. Parchment**
Early Clinical Projects	**J. Moscow**

Next Meeting

Biologics Development Program: Antibodies, Vaccines, Cytokines	**A. Welch**

From Application Review to Project Team Kickoff Meeting

Project Applications submitted to NExT (3 cycles per year)

From Target Validation to Phase I/II

Trials—Small Molecules, Biologics, Imaging Agents

Project planning; RFP issued
Selection of CBC Centers
NCI approval of Resources
Subcontracts managed by Leidos/FNLCR
Project team kickoff meeting

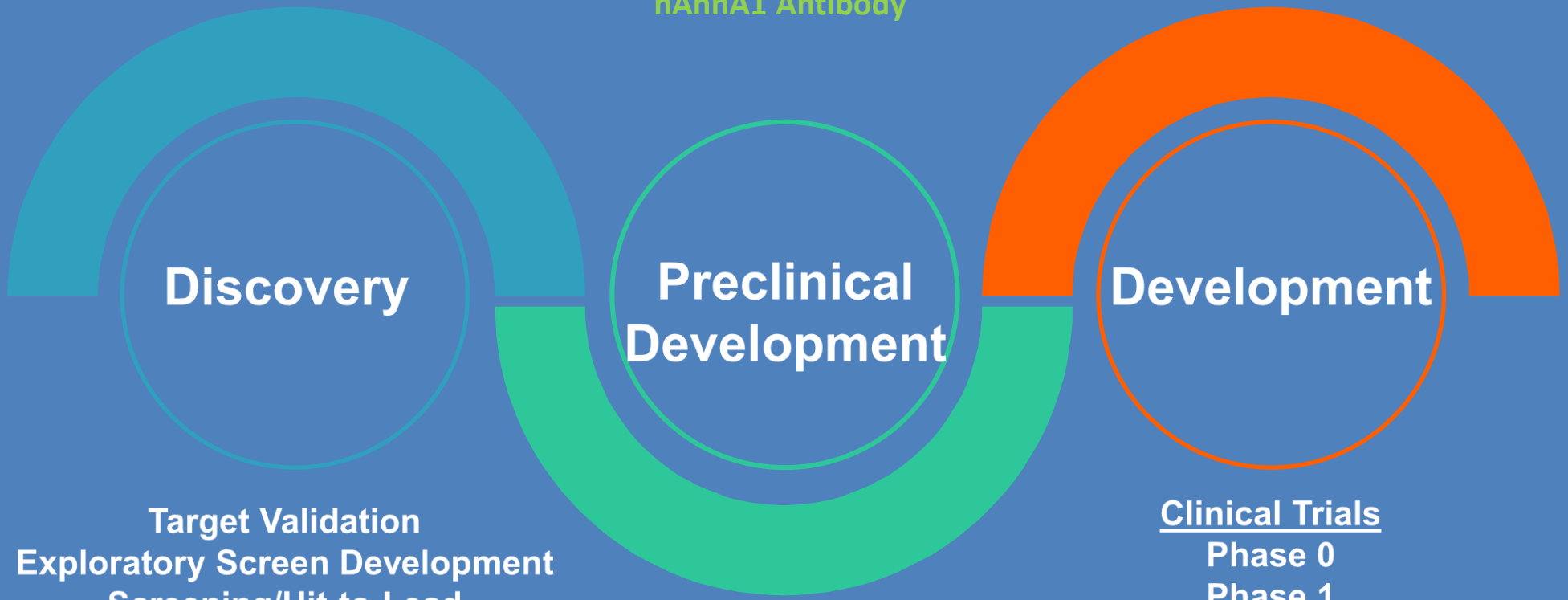
CBC Steering Committee Endorsement [Leidos/FNLCR Subcontracts]

Special Emphasis Panel (SEP)

Highly ranked projects

ETCTN: Performs Ph 1 & 2 Trials
Early Phase Project Teams Investigational Drug Steering Cmte.
[Grant Program for Trials; FNLCR for PD]

NExT Pipeline



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

Target Validation
Exploratory Screen Development
Screening/Hit-to-Lead
Lead Development

AAA ATPase p97 inhibitor
MCL1 Inhibitor
Mutant IDH1 inhibitor
hAnnA1 Antibody

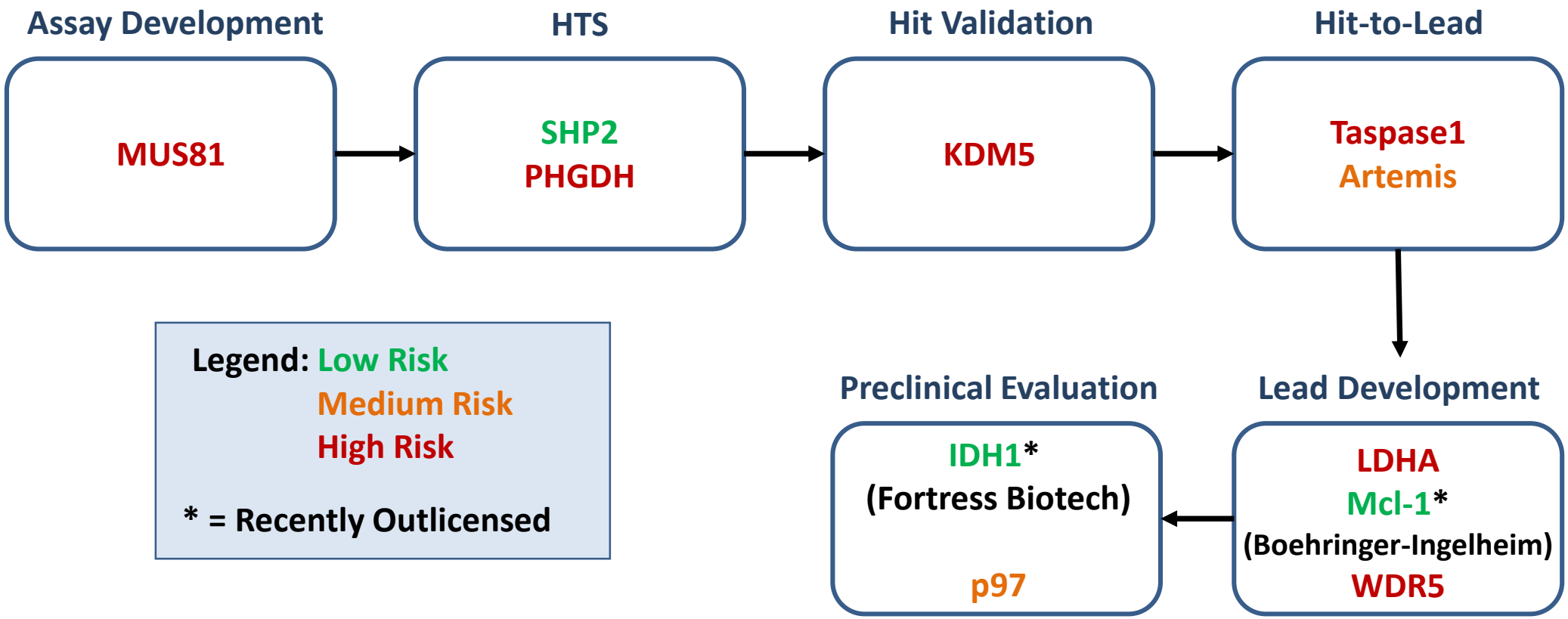
Candidate Selection

DNMT1 Inhibitors (TdCyd)
Endoxifen
>70 IND agents
11-1F4 mAb Amyloidosis
Mer Kinase Inhibitors
NIR Fluorophore
EGFR Panitumumab
LUM015

Imaging agents

Clinical Trials
Phase 0
Phase 1
Phase 2
Phase 3

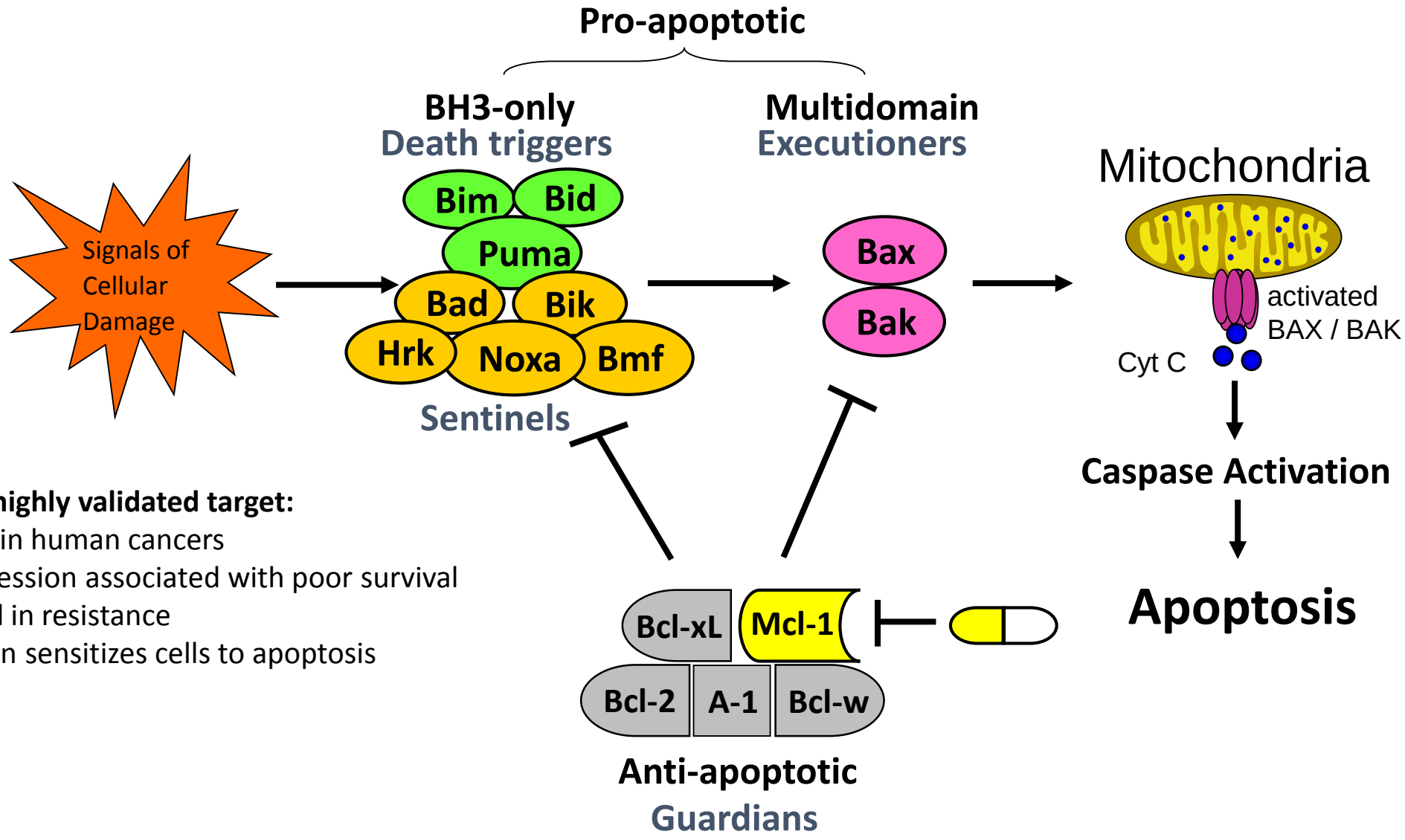
CBC Discovery Portfolio



Risk Assessment Weighted Criteria:
Association of target with disease – 40%
Availability of biochemical/cellular assays – 20%
Availability of structural data – 20%
Quality PD markers for target engagement – 20%

Targeting Mcl-1: Opportunity to modulate protein-protein interaction in cancer

Stephen Fesik (Vanderbilt University)



Mcl-1 is a highly validated target:

-Amplified in human cancers

-Over-expression associated with poor survival

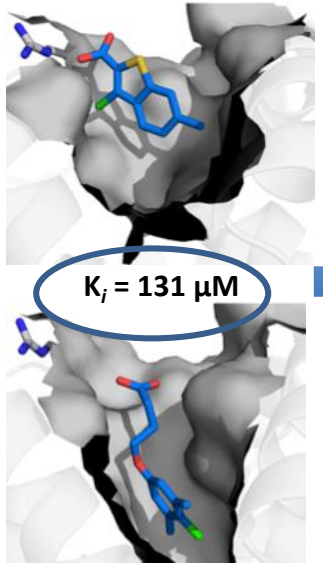
-Implicated in resistance

-Knockdown sensitizes cells to apoptosis

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

STEPHEN FESIK (Vanderbilt University)

Hit to Lead | **Lead Optimization** | ***In vivo* Optimization**

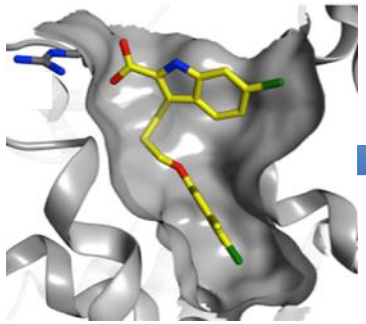


K_i = 60 µM

Fragment hits

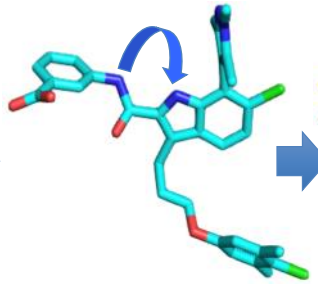
Structure-guided fragment merging

> 200,000x improvement in affinity for target



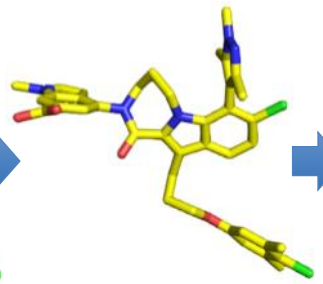
Mcl-1 K_i = 55 nM

Binding interface Expansion



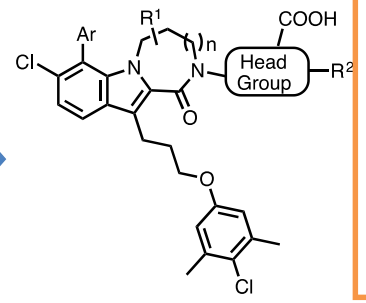
Mcl-1 K_i = 23 nM

Structure-guided Tethering



Mcl-1 K_i = 0.39 nM
H929 GI_{50} = 1.2 µM

Med. Chem. Optimization



Mcl-1 K_i = <0.3 nM
H929 GI_{50} = <0.3 µM

Likely candidate profile

- ✓ K_i < 0.3 nM to Mcl-1
- ✓ Cellular IC_{50} < 100 nM
- ✓ Oral bioavailability
- ✓ Robust pharmacodynamic response

Leads feature

- K_i < 0.3 nM to 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)
- Good PK properties

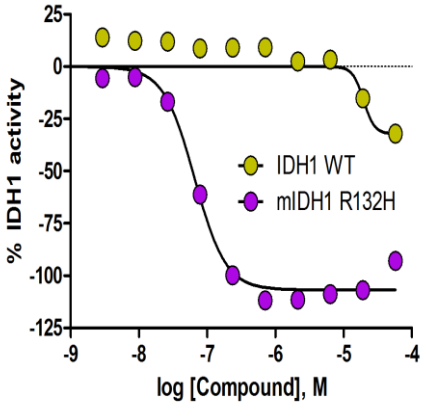
January 2018 Licensed by Vanderbilt to Boehringer-Ingelheim

Mutant IDH1 Inhibitor Program: Discovery to Out-Licensing

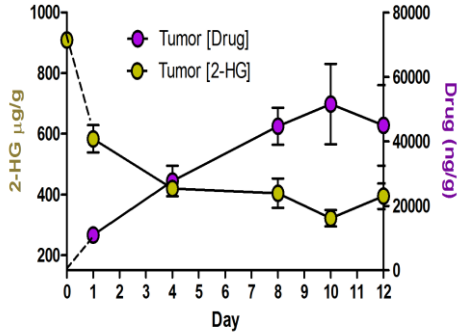
Collaboration: NCATS & UNC

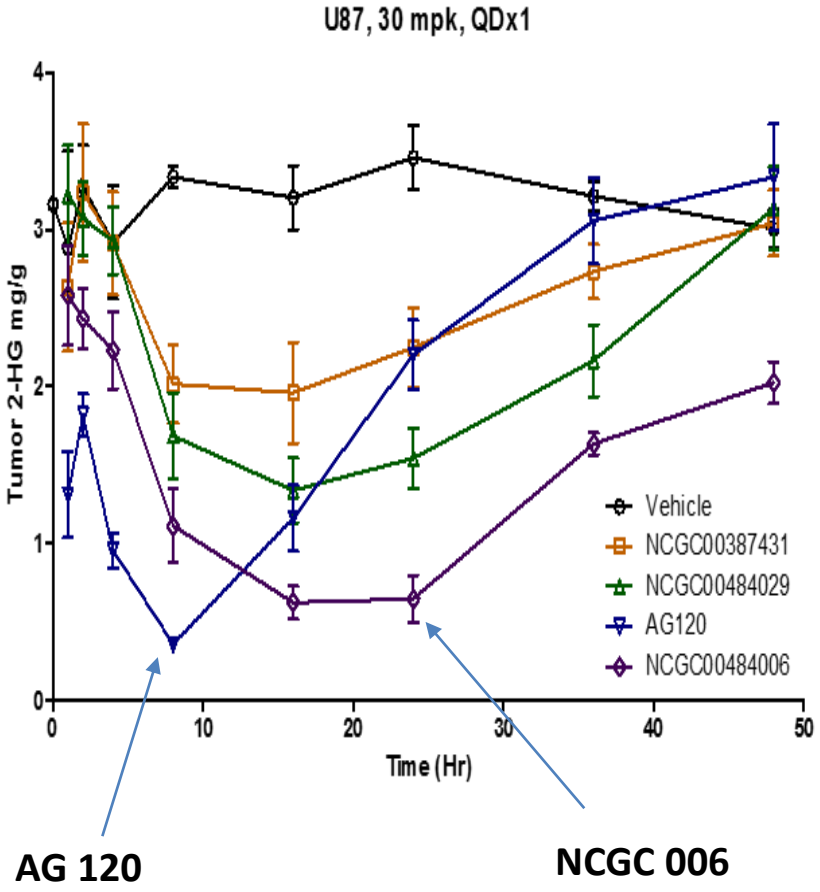
- **2011** Launch team, assay development
- **2012** HTS, hit validation
- **2013** CBC Discovery Resources Triggered
- **2014** Lead development
- **2015** In vivo PK/PD established
- **2016** In vivo models, tolerability & efficacy
- **2016** IND enabling studies
- **2018** Outlicensed Fortress Biotech 4/2018

IDH1 selectivity



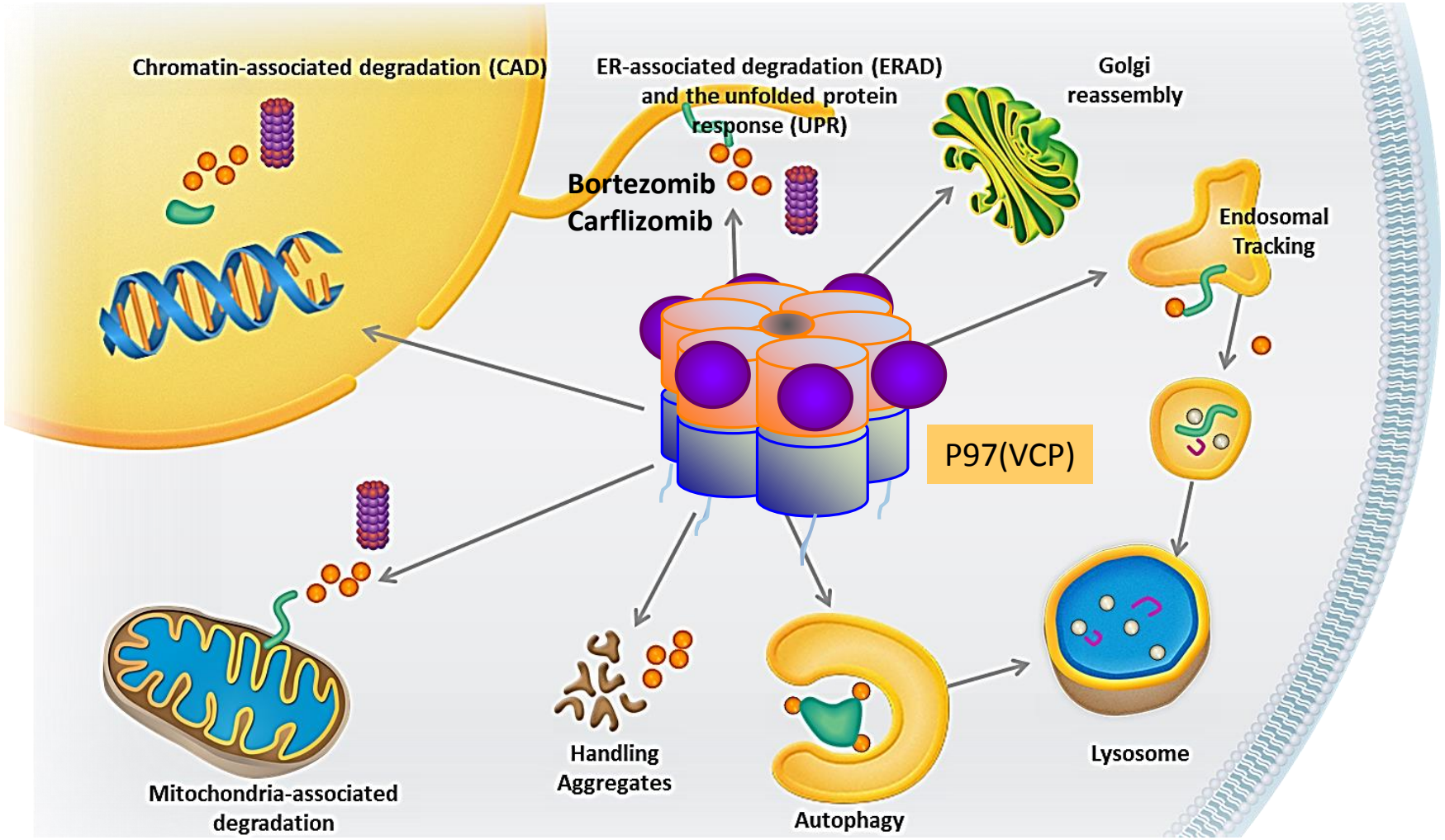
PK/PD in Tumor Xenografts





TARGETING P97: NOVEL OPPORTUNITY TO MODULATE PROTEIN HOMEOSTASIS IN CANCER

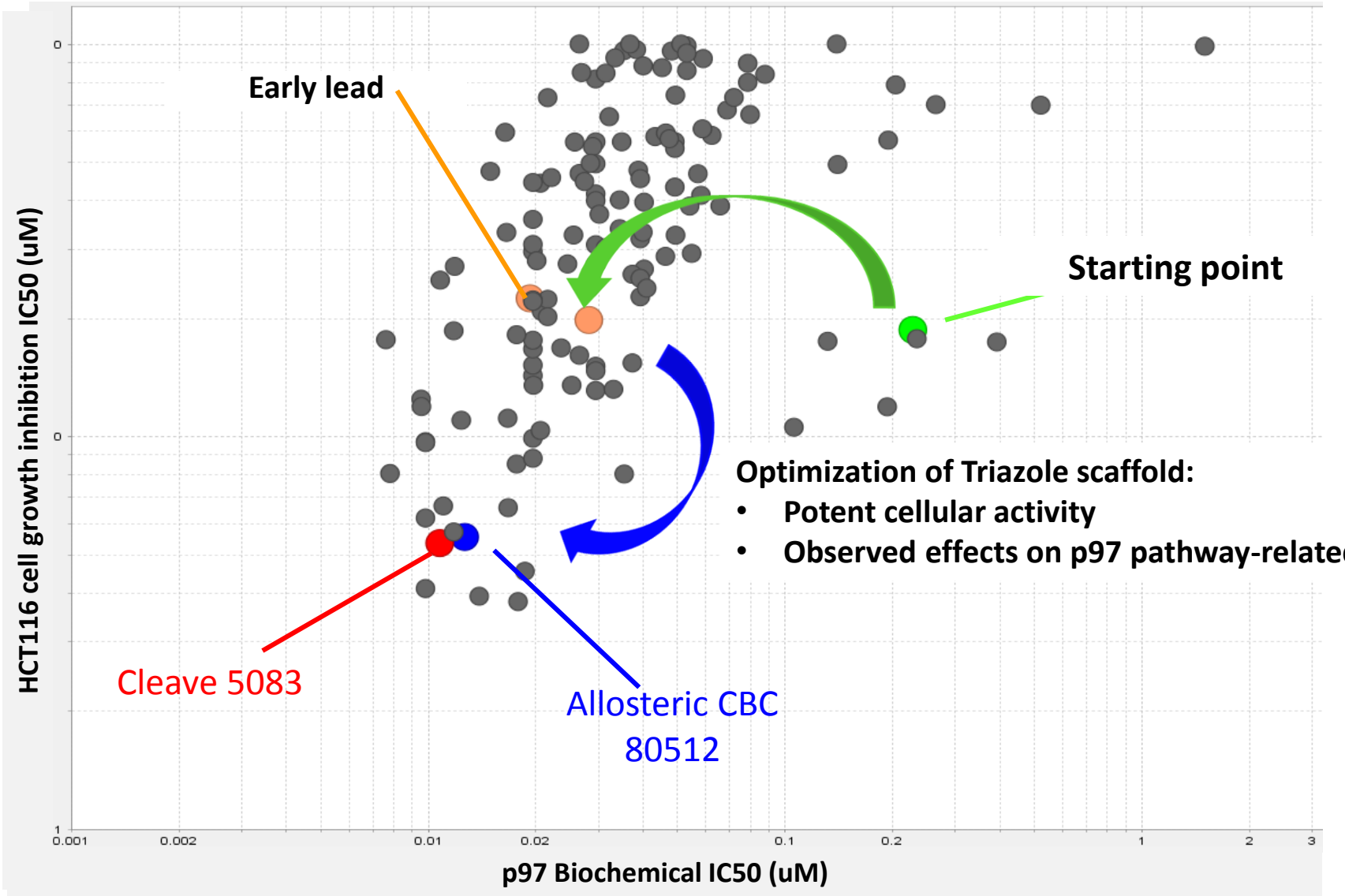
Ray Deshaies (Caltech)



P97 is a protein "machine" that uses the energy from ATP to attach and process misfolded proteins. *Proc Natl Acad Sci USA* **2011**,108:4834–4839

Evolution of CBC Allosteric p97 Inhibitors

Donna Huryn (Pittsburgh)



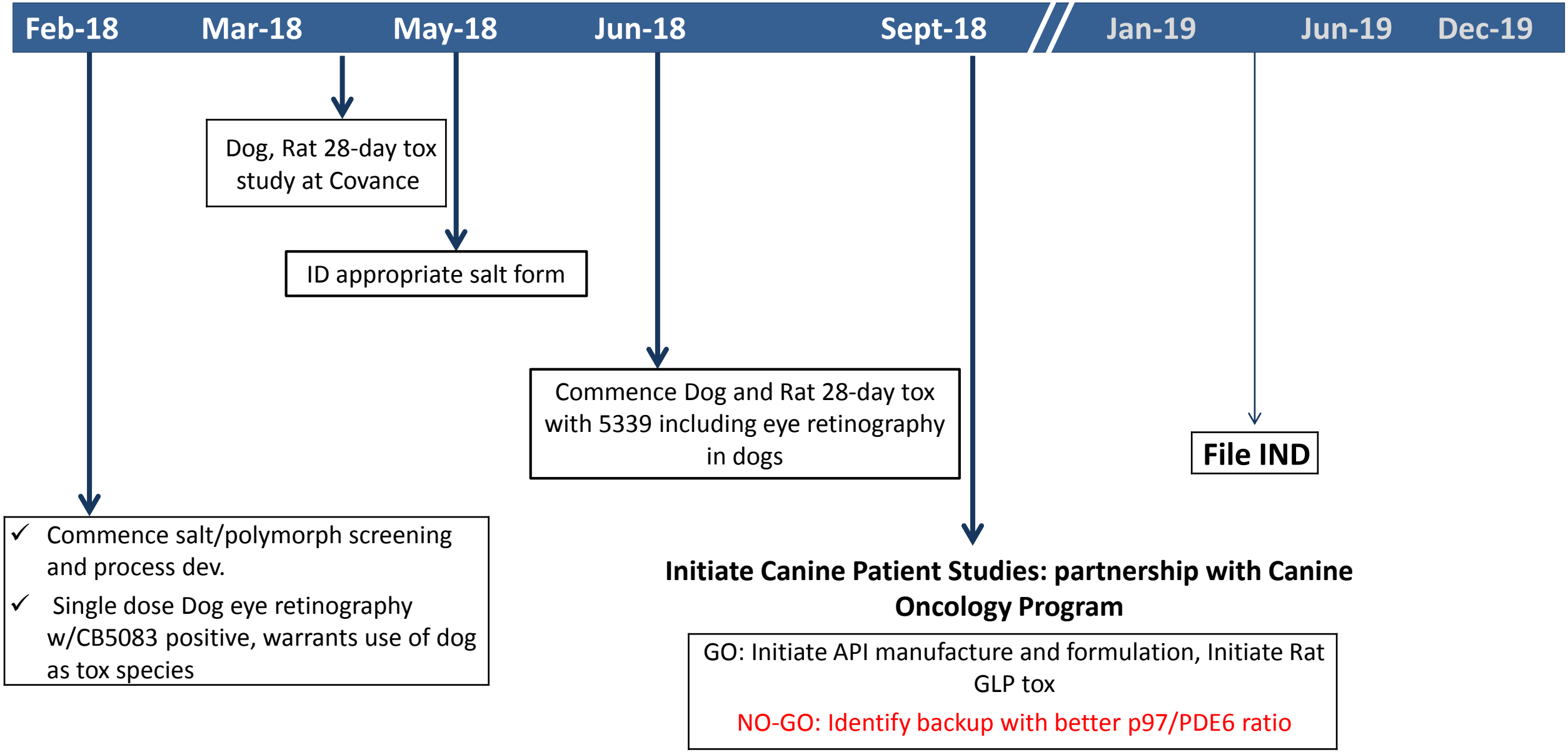
Opportunity to Position P97 Inhibitor Project for Success

- **Cleave BioSciences joined CBC p97 team in December 2017**
  - First Generation Drug (CB-5083 failed in F-in-H due to off-target inhibition of PDE6 in retina with visual loss; well-tolerated otherwise)
  - CB-5339, 2nd generation p97i: selected from a group of 3 lead molecules characterized for
    - ✓ Enhanced selectivity, specifically on p97 vs. PDE6 (off target)
    - ✓ Improved DMPK properties, particularly in large species
    - ✓ Better predicted human clearance
- **Benefit of collaboration**:
  - Will maximize "shots on goal"
  - Opportunity for team to advance two chemotypes with different binding modes (allosteric and active site)
  - PD biomarkers (cleaved caspase 3) in hand at FNLCR
- **Experimental Strategy:**
  - Nominate 2nd gen Cleave inhibitor (CB-5339) as clinical candidate and advance into IND-enabling studies with potential to move to FIH 2Q19
  - Position CBC allosteric chemotypes as back-up inhibitors

CB-5339

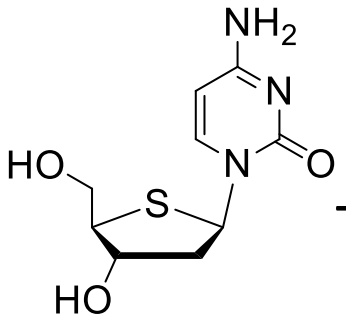
- **In vitro and in vivo potency profile comparable to CB-5083**
- **40X reduced effects on PDE6**
  - 10x less potent on PDE6 than CB-5083 and 4x lower retinal penetration
- **Improved physicochemical and DMPK properties**
  - Better bioavailability in preclinical species
  - Lower clearance across species

p97 2018/19 Timeline

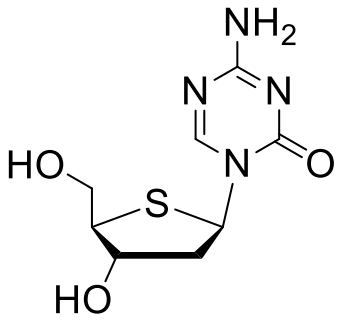


Inhibitors of DNA Methyltransferase (DNMT1)

Southern Research



T-dCyd



Aza-T-dCyd

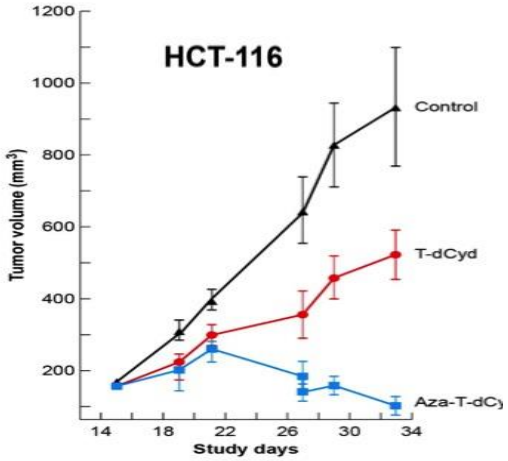
Project Start

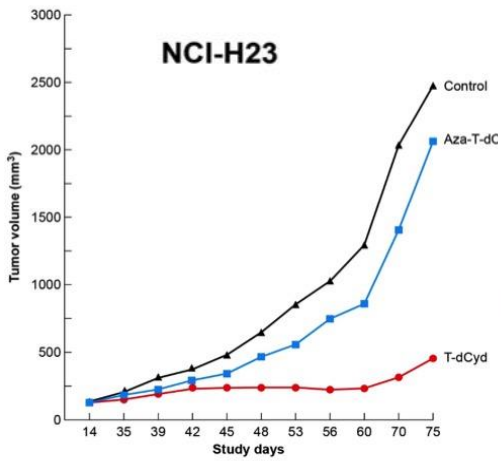
1st IND T-dCyd

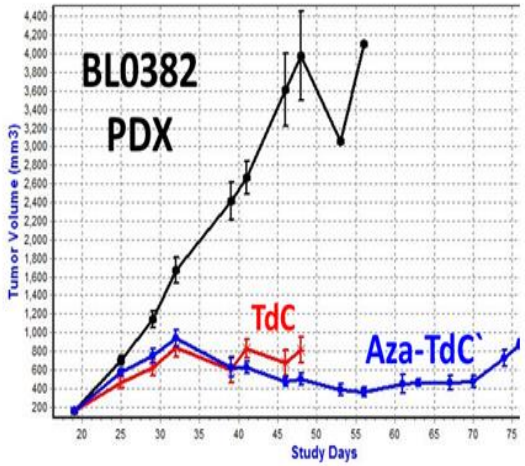
2nd IND Aza-T-dCyd

2009 2010 2011 2012 2013 2014 2015 2016 2017 2018

CBC INCEPTION

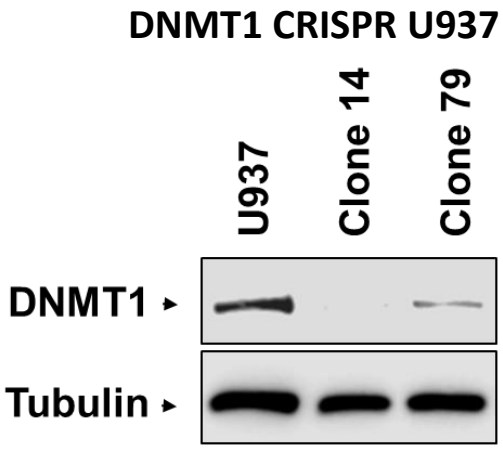


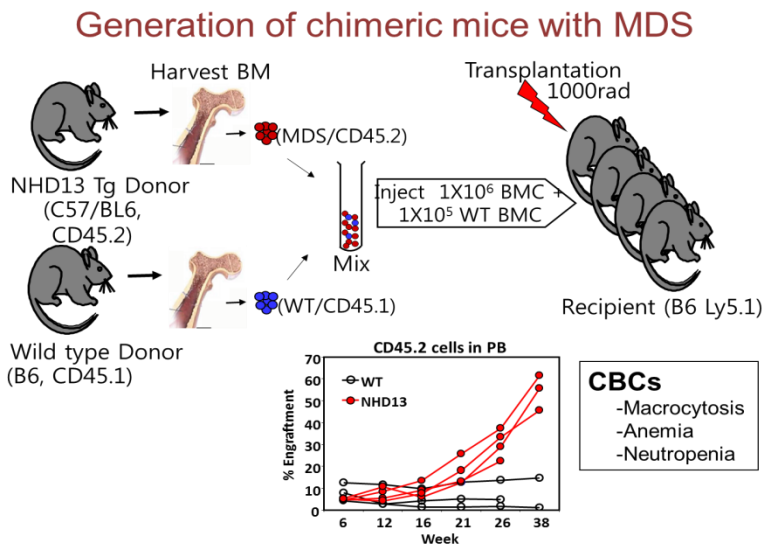


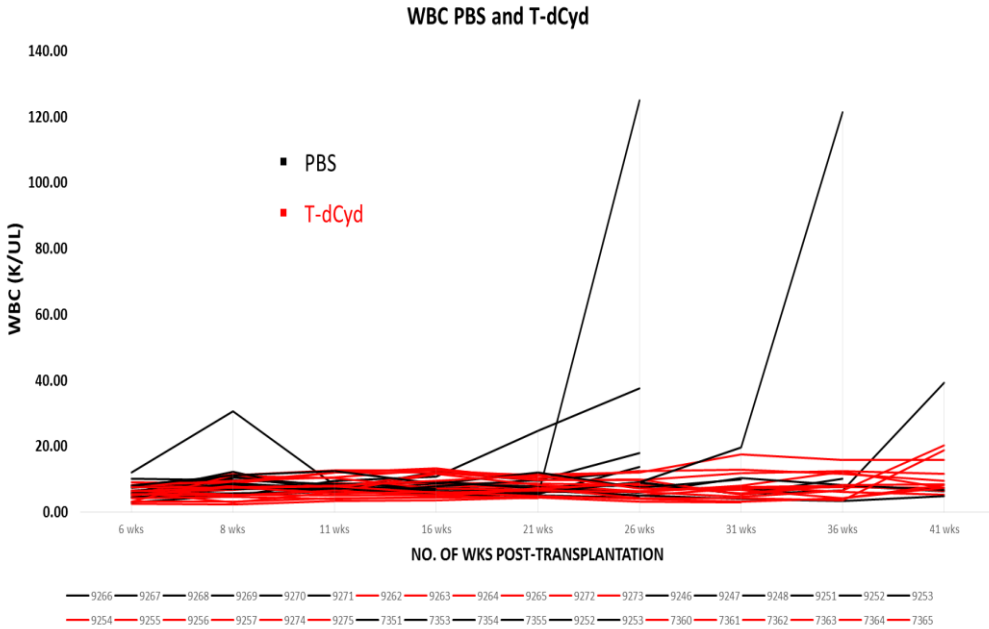


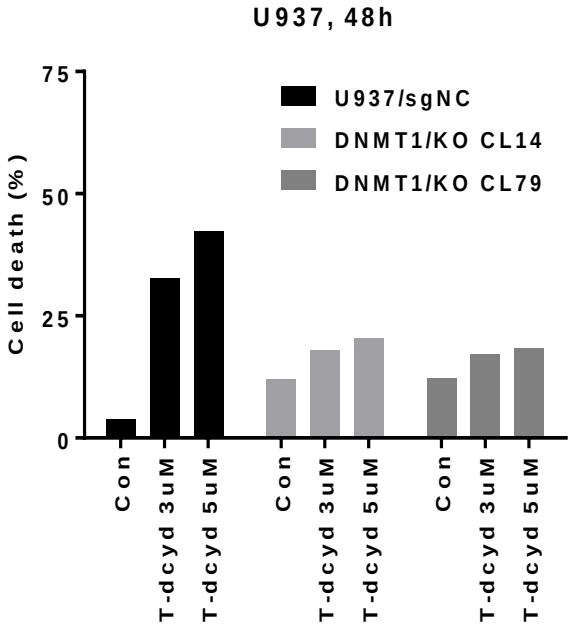
- No IP; Inhibit DNMT1 (not DNMT3) in vitro and in vivo; bioavailable po
- Demethylate RASSF1A and p16 in vivo in sensitive xenograft models
- T-dCyd Phase I Trial First Patient Treated at NCI Clinical Center in May 2016
- Aza-T-dCyd Phase I Trial Initiated at NCI Clinical Center in Feb. 2018

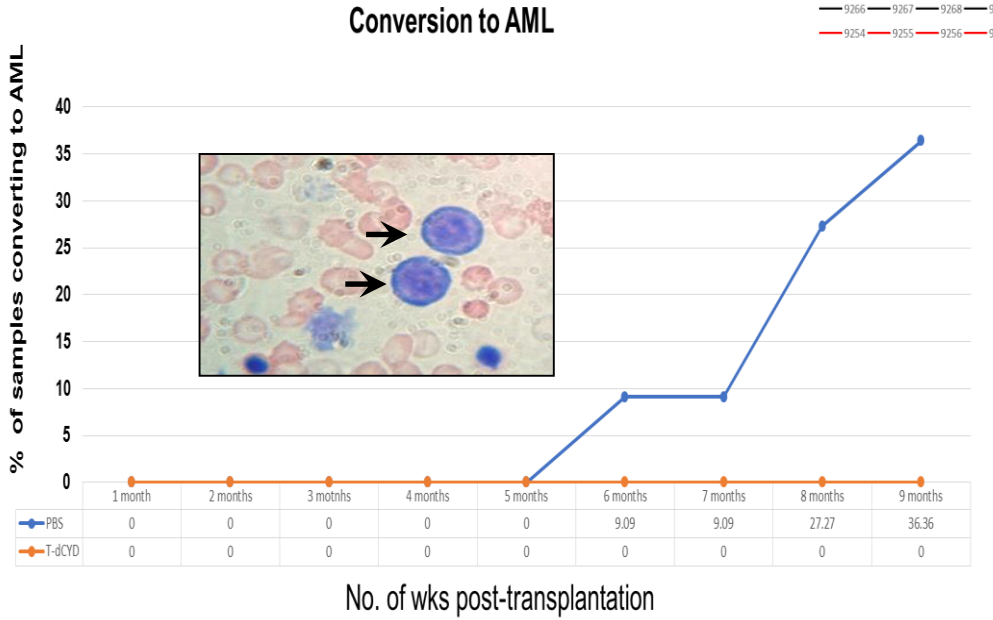
TdCyd: Inhibitor of DNA Methyltransferase (DNMT1)

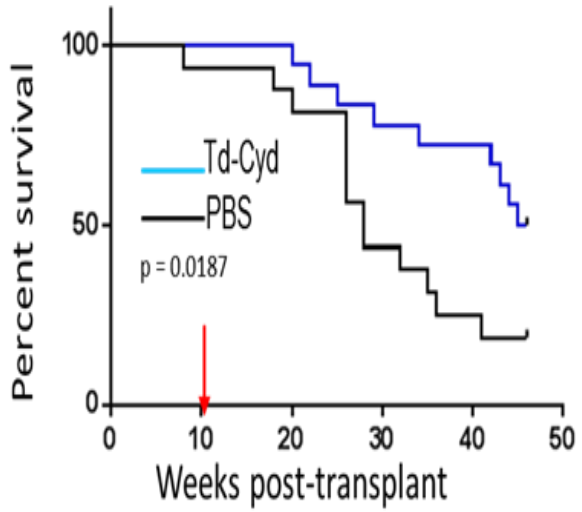












Dr. Steven Grant VCU Cancer Center

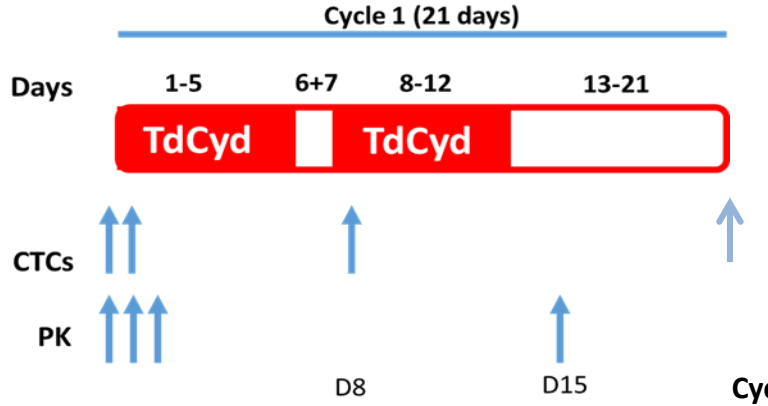
Dr. Peter Aplan NCI CCR

TdCyd: Inhibitor of DNA Methyltransferase (DNMT1)

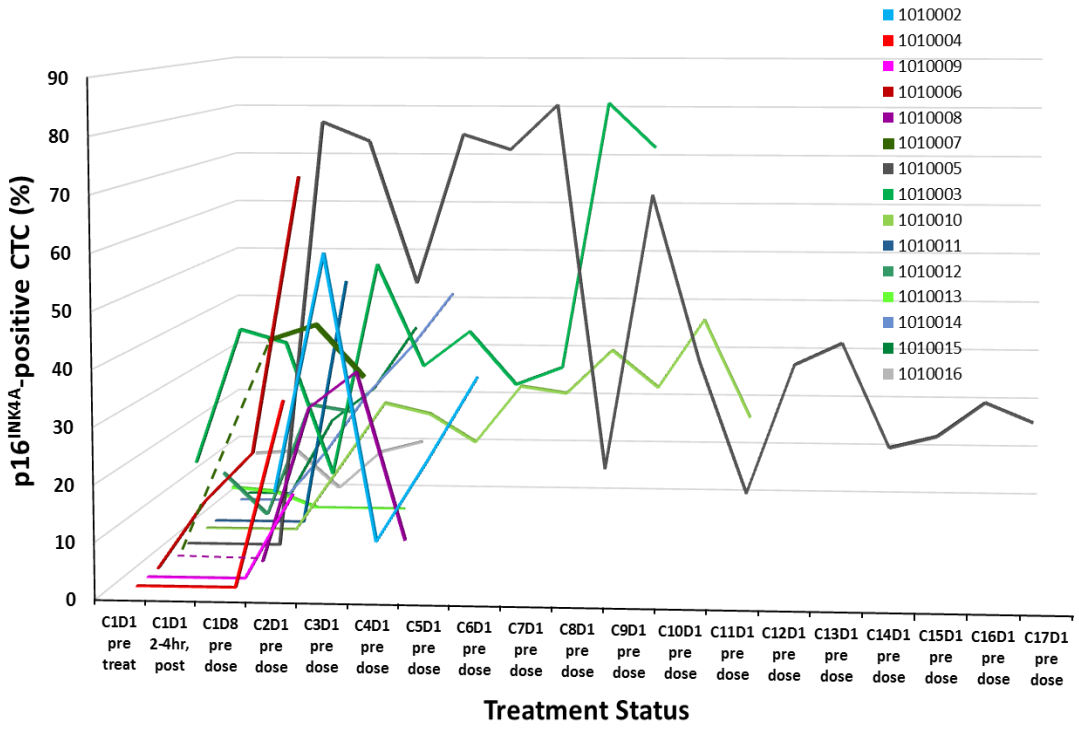
TdCyd (Thiodeoxycytidine)

- First-in-human trial activated May 2016 in our CCR clinic with NCI drug and IND
- 20 solid tumor patients accrued with limited toxicity (2 pts reversible transaminitis)
- Median time on study 2 cyles (range 1-18 cycles); ASPS (18 cycles); pheochromocytoma (11 cycles); colon ca (8 cycles); pancreas (5 cycles); tolerated well by two solid tumor transplant pts
- p16 positive CTCs also observed after 2 cycles of Rx; tumor biopsies for gene expression during expansion phase

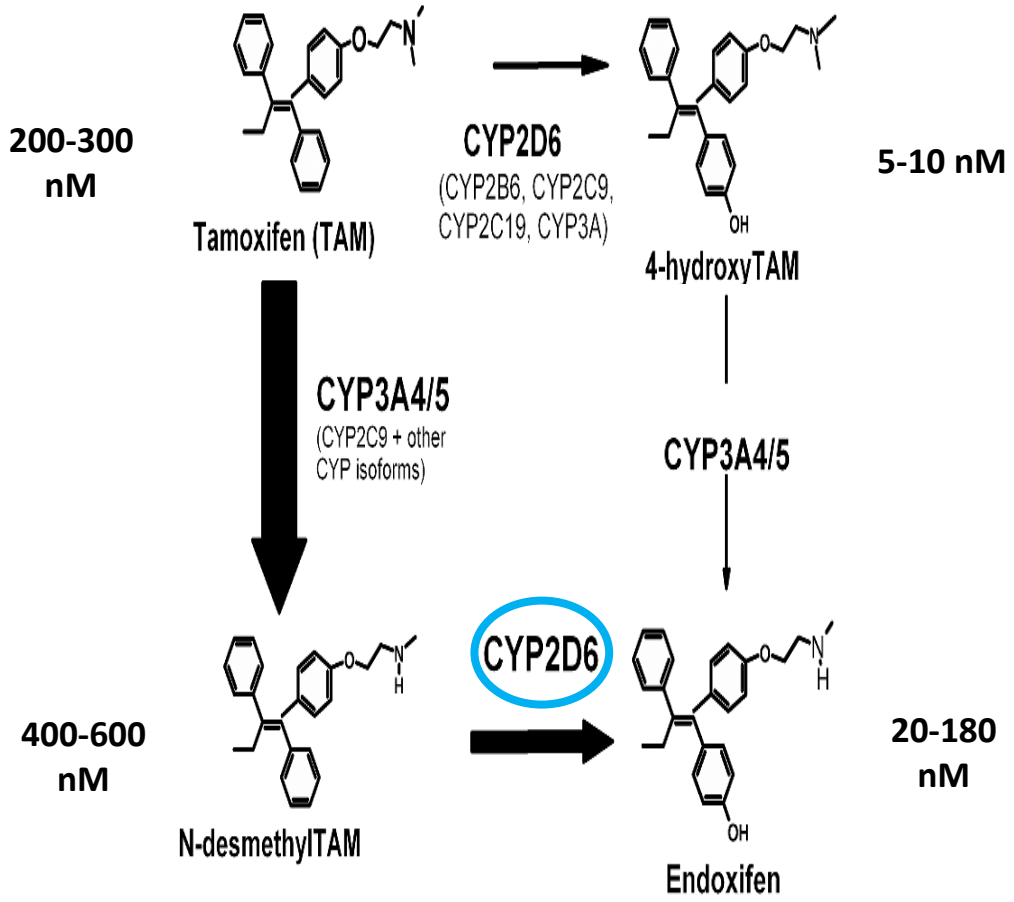
Study Schema (15-C-0116; CTEP # 9883)

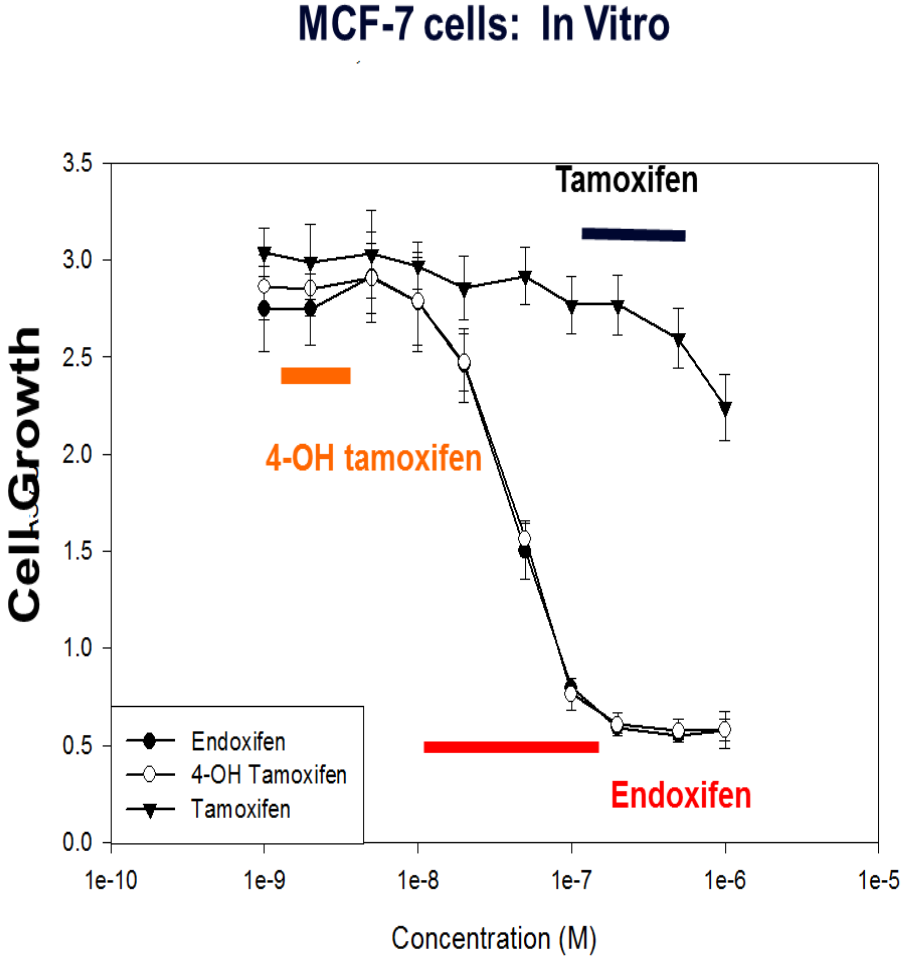


P16^{Ink4A} Responses in CK^{+}-CTC during Treatment with TdCyd



Development of Endoxifen for ER+ Malignancies
Mayo Clinic SPORE



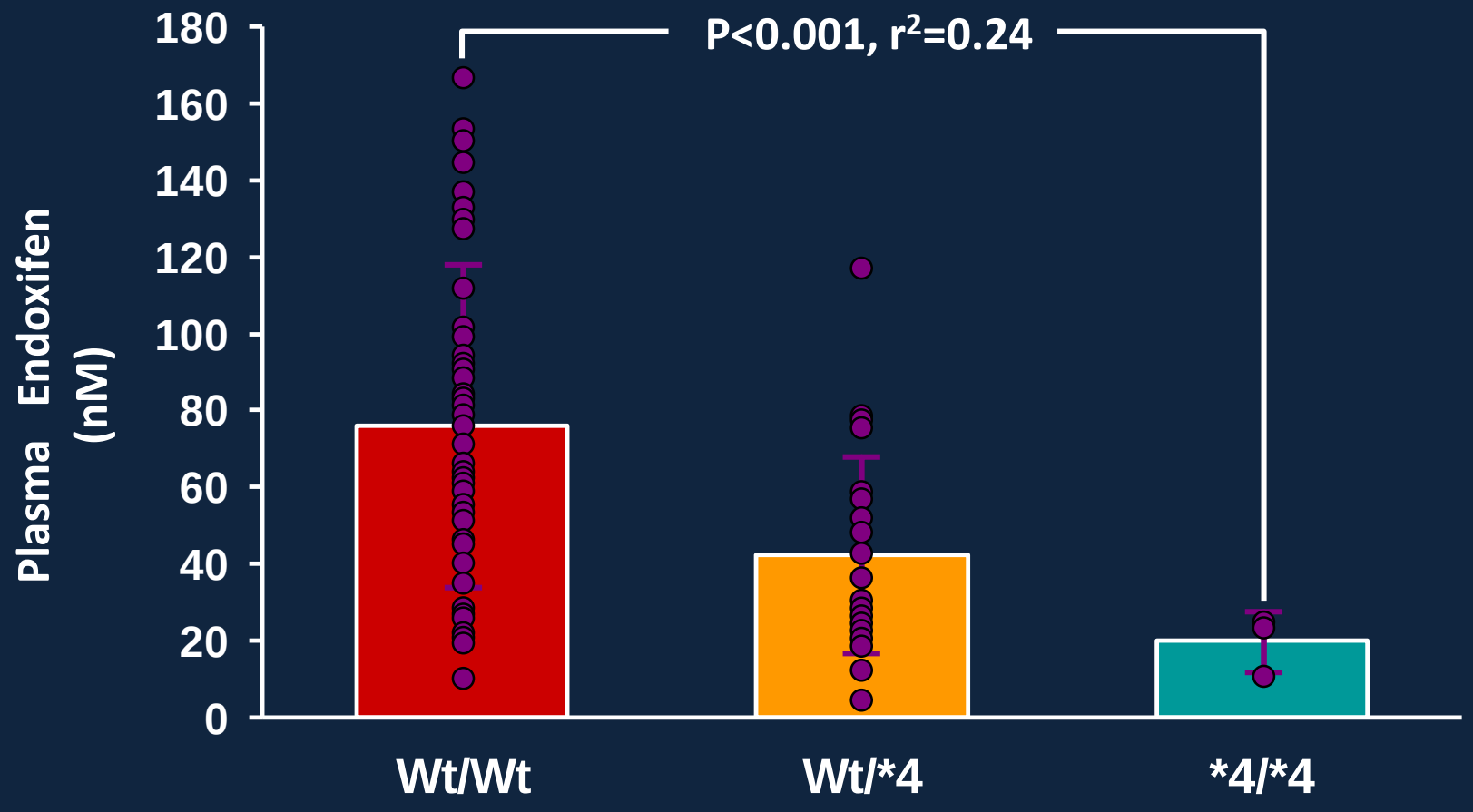


Concentrations in humans

- Tam (300-500 nM)
- 4HT (5-10 nM)
- Endoxifen (20-180 nM)

Unlike TAM, Endoxifen inhibits ER-α & overcomes AI resistance in vivo

Development of Endoxifen for ER+ Malignancies

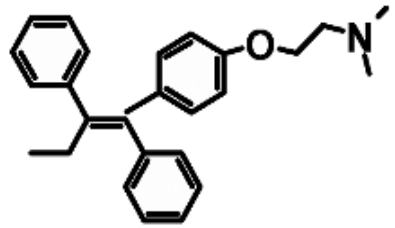


CYP2D6*4 (most common genetic variant associated with the CYP2D6 poor metabolizer state)

Development of Endoxifen for ER+ Malignancies

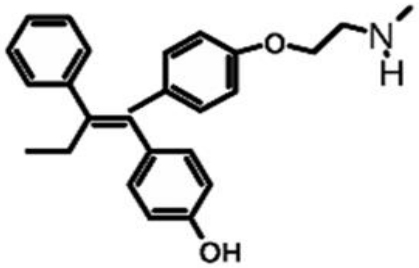
First-in-Human CCR Trial of Endoxifen for ER+ Solid Tumors

-PK not affected by presence of CYP2D6*4 and other variants (20-25% women) or use with other CYP2D6 substrates (antidepressants)
-No IP (structure known for 35+ years)
-NCI performed IND enabling studies (PK, Tox, GMP production) for Phase I trials
-36 pts entered with ER+ tumors breast (progressing on AI), ovary, endometrial, desmoid
-Grade 3/4 toxicity very modest
-PRs: ovary 12 mo; breast 8+ mo
-SD: 16; median duration 6 mo (up to 47 monthly cycles)
-PK: >10-fold increase in endoxifen levels versus TAM:



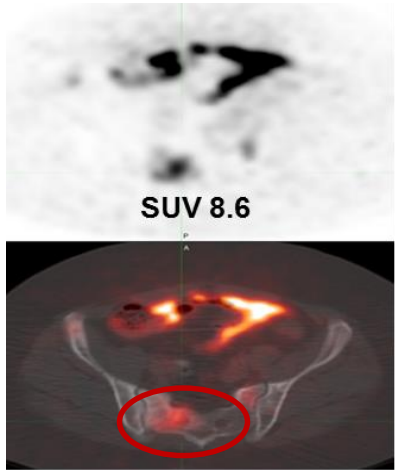
Tamoxifen (TAM)

Dose (po, daily)	Endoxifen 28 day Steady State
Endoxifen 20 mg	645 ± 200 nM
Endoxifen 40 mg	865 ± 275 nM
Endoxifen 60 mg	1900 ± 550 nM
Tamoxifen 20 mg	20-180 nM



Endoxifen

-^{18}F-FES PET: pretreatment; 1-3 hrs after 3rd - 5th dose: Demonstrated POM



Baseline

Day 6

Future Plan:

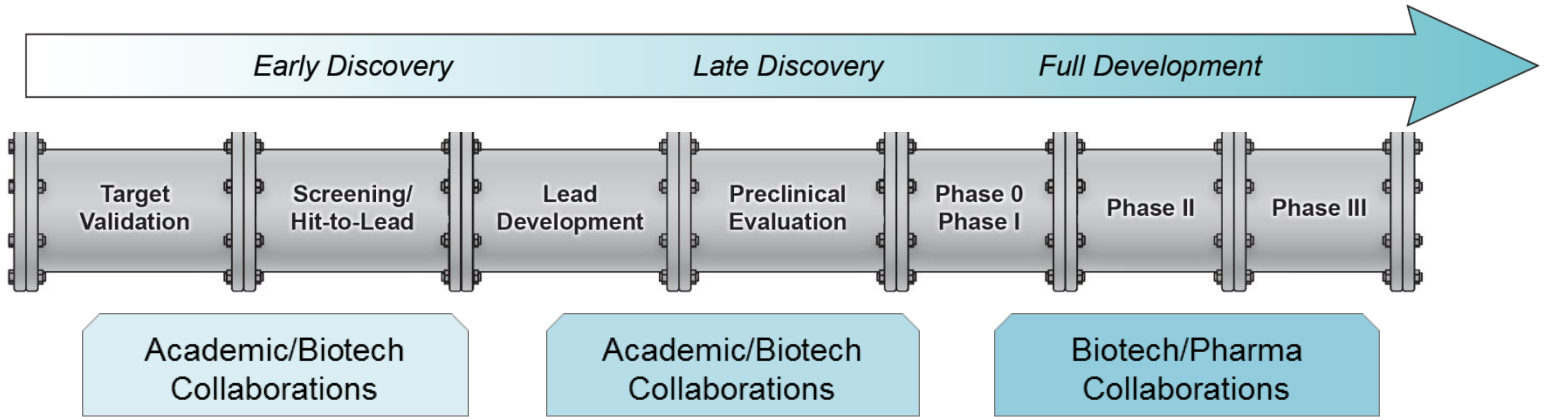
Await results of NCI-sponsored randomized phase II trial in post-menopausal patients with ER+/HER2- breast cancer: Endoxifen vs. Tamoxifen in women with disease progression on an AI (Alliance; NCT02311933)

APPRECIATION

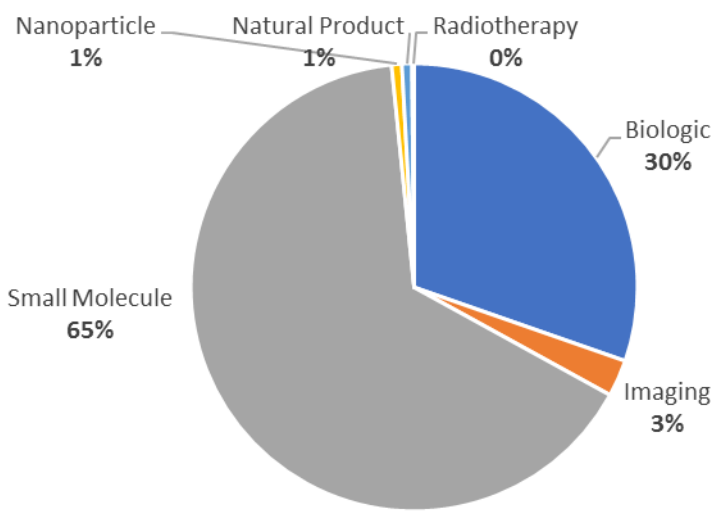
- Barbara Mroczkowski
- Michael Difilippantonio
- Alice Chen
- Naoko Takebe
- Geraldine O’Sullivan-Coyne
- Melinda Hollingshead
- Jason Cristofaro
- Ralph Parchment
- Bob Kinders
- Biological Development Program, DTP, DCTD, NCI
- Jerry Collins and DTP Toxicology/Pharmacology staff
- Peter Choyke and CCR Molecular Imaging Program
- CTEP Regulatory Affairs Branch
- Leidos Pharmacodynamics Team
- Andrew Flint and Leidos NExT Project Management Team
- CBC/NExT Project Team Members: Academic and NCI

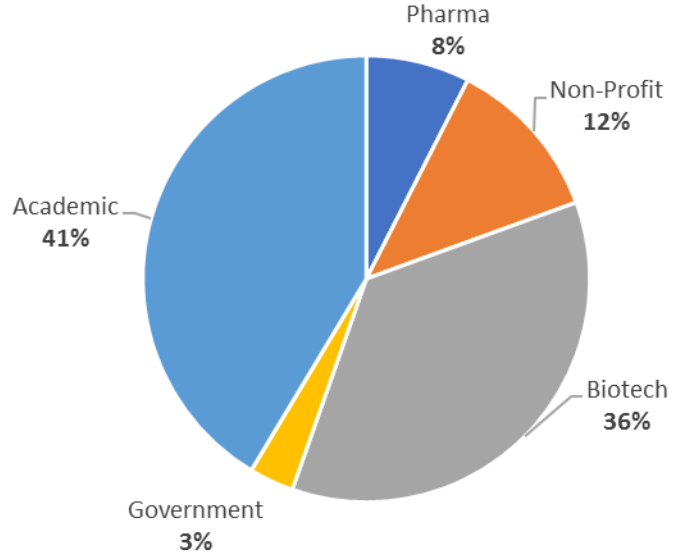
Questions?

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 650 applications





Data to Support CB-5339 will Reach Efficacious Exposure without Visual Symptoms

- **CB-5083 reached target plasma exposures necessary for anti-tumor effects but PDE6-related visual symptoms precluded further clinical evaluation**
- **Other than PDE6 inhibition, CB-5083 was well tolerated at all doses including MTD**
  - No significant neuropathy, hematologic, cardiac, renal or hepatic toxicity observed
- **CB-5339 is approximately 40-fold more selective than CB-5083**
  - In vitro 10x less potent for inhibition of PDE6
  - In vivo 4x lower retinal penetration
- **At a similar and higher exposure in monkey via oral administration**
  - CB-5083 elicited ERG effects lasting longer than 48 hours
  - CB-5339 no ERG changes observed
- **Based on these data, CB-5339 dosed at 3200 mg would be projected to have similar visual symptoms as 80 mg of CB-5083**
  - Efficacy dose of CB-5339 is projected to not be greater than 1000 mg

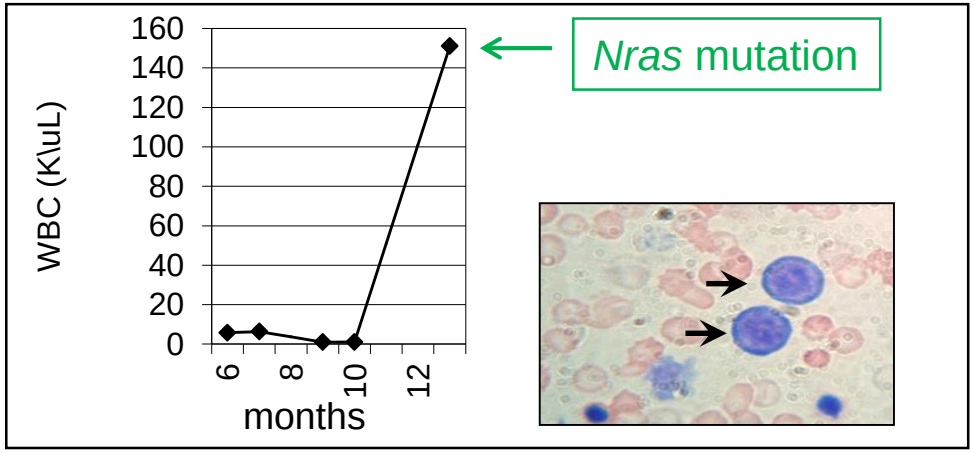
*vav*NHD13 mice develop MDS

NUP98-HOXD13 (NHD13) fusion

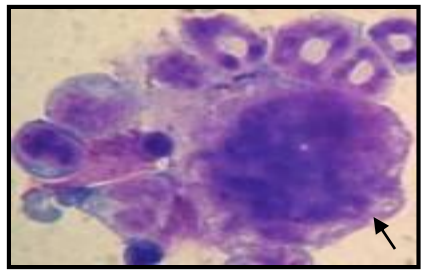
CBCs (age 4-7 mos)

	WBC (10^9/L)	NE (10^9/L)	Hb (g/dL)
NHD13 (n = 22)	1.8	0.44	11.9
Control (n = 7)	6.5	1.4	14.2
p value	<0.001	<0.001	<0.001

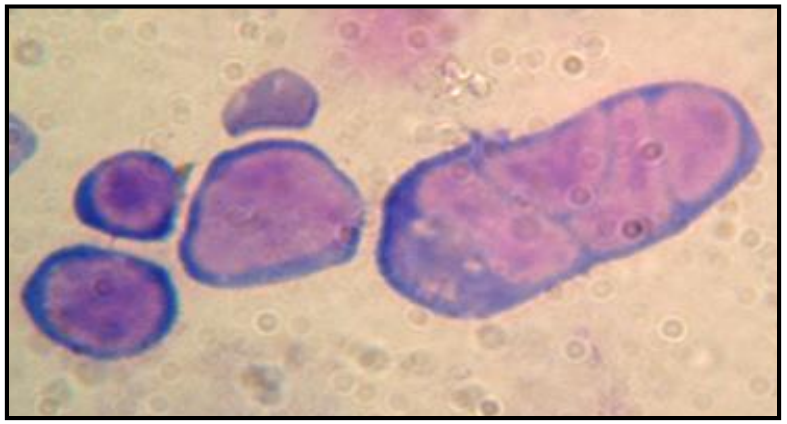
Transformation to AML



Micro-megakaryocytes



Multinucleate erythroblasts



- Expression arrays identified 10 genes 3-fold increased.
- Oas2, Ifit1, Ifi44, Hoxa9, Hoxa7, Pbx3, Hoxc6, Lin28b.

*Interferon induced *Homeodomain

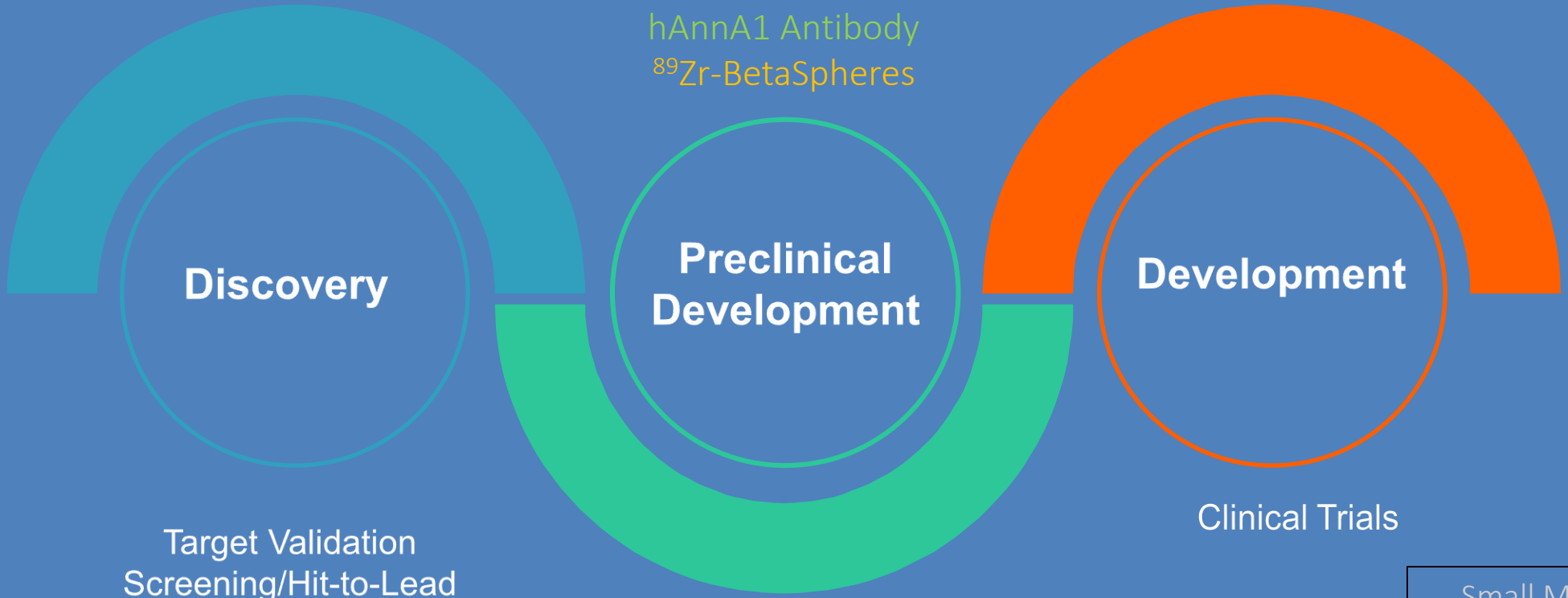
Lin et al., Blood, 2005
Chung et al., PNAS, 2008
Slape et al., JNCI, 2008
Choi et al., J Immunol, 2009
Novak et al., Exp. Hematol, 2013

NExT Pipeline

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

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

DNMT1 Inhibitors (TdCyd)
Mer Kinase Inhibitor
NIR Fluorophore
EGFR Panitumumab
LUM015



Target Validation
Screening/Hit-to-Lead
Lead Development

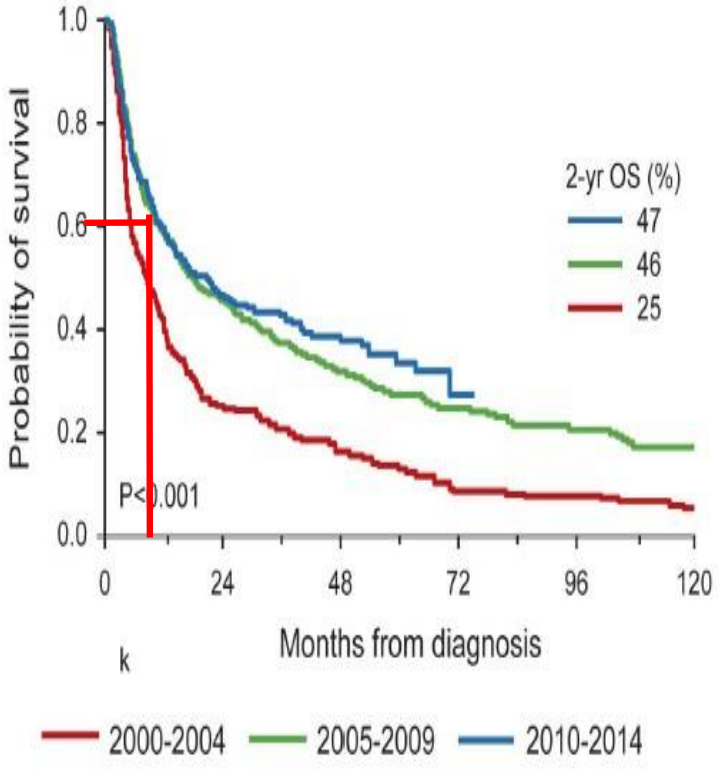
Candidate Selection

Clinical Trials

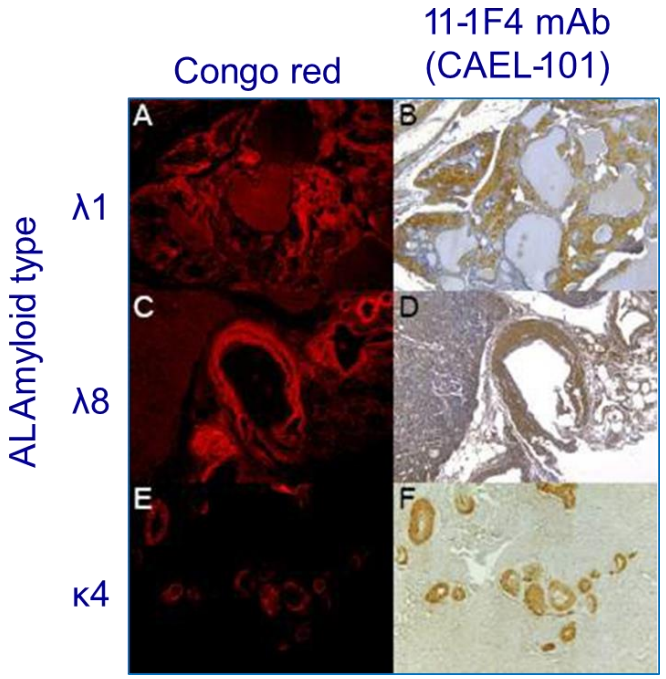
Small Molecule
Imaging agent
Biologic

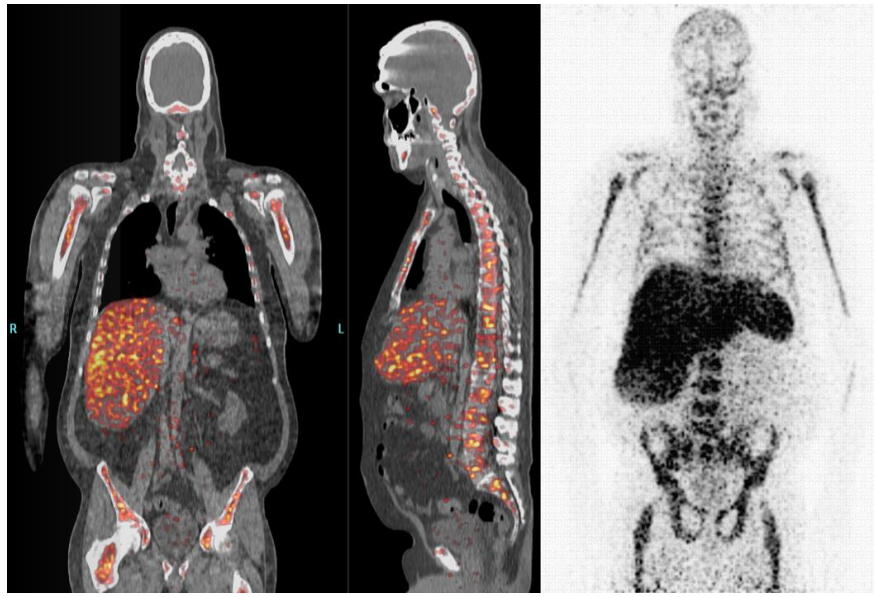
Monoclonal Antibody 11-1 F4 for Patients with Amyloid Light Chain Amyloidosis
Univ. of Tennessee & Columbia

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

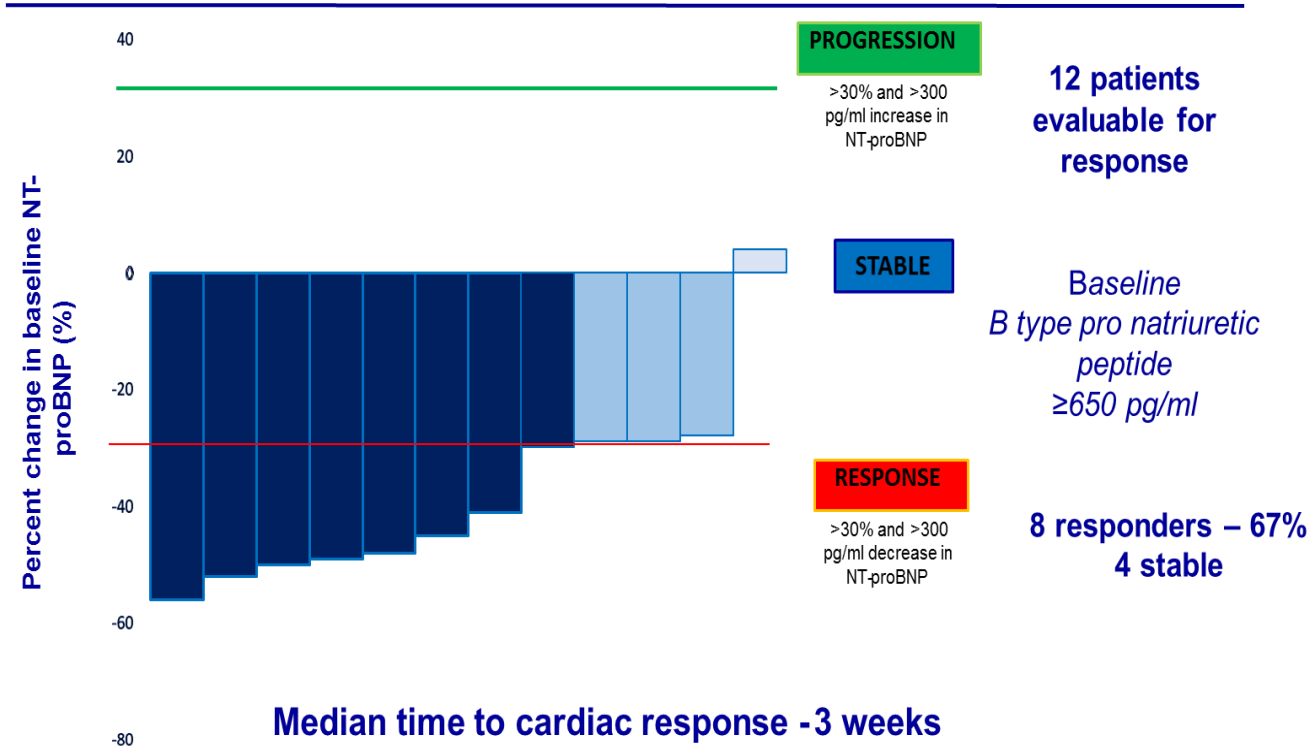
- **Used Bence Jones protein to develop human monoclonal Ab vs light chain in Amyloid fibrils not reactive with circulating light chains**
- **Reacts with Amyloid deposits in tissues**

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

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

- Phase I trial of 11-1F4 mAb for pts with refractory/relapsed amyloidosis based on dissolution of amyloid deposits in mouse model
- 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

FUTURE: SWOG supported multicenter Phase II trial



Edwards et al ASH 2017