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

Pharmacodynamics in Drug Discovery, Development, & Phase I Trials

Advanced Clinical Projects

J. Doroshow

Next Meeting

Early Clinical Projects

Biologics Development Program:
Antibodies, Vaccines, Cytokines

J. Moscow

R. Parchment

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

Special Emphasis Panel (SEP)

CBC Steering Committee Endorsement [Leidos/FNLCR Subcontracts]

Highly ranked projects

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

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

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

Preclinical Development
- Candidate Selection

Development
- Clinical Trials
  - Phase 0
  - Phase 1
  - Phase 2
  - Phase 3

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

Inhibitors:
- Artemis Endonuclease inhibitor
- LDHA inhibitor
- MUS81
- SHP2 inhibitor
- PHGDH inhibitor
- Taspase1 inhibitor
- WDR5-MLL1 inhibitor
- AAA ATPase p97 inhibitor
- MCL1 Inhibitor
- Mutant IDH1 inhibitor
- hAnnA1 Antibody
- WDR5-MLL1 inhibitor
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%

Legend: Low Risk
Medium Risk
High Risk
* = Recently Outlicensed
**TARGETING MCL-1: OPPORTUNITY TO MODULATE PROTEIN-PROTEIN INTERACTION IN CANCER**

**STEPHEN FESIK (Vanderbilt University)**

Signals of Cellular Damage

- **BH3-only Death triggers**
  - Bim
  - Bid
  - Puma
  - Bad
  - Bik
  - Hrk
  - Noxa
  - Bmf

- **Multidomain Executioners**
  - Bax
  - Bak

Mitochondria

- Activated BAX / BAK
- Cyt C

Caspase Activation

Apoptosis

**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

**TARGETING MCL-1:**

**OPPORTUNITY TO MODULATE PROTEIN-PROTEIN INTERACTION IN CANCER**

**STEPHEN FESIK (Vanderbilt University)**
Mcl-1 Inhibitor Discovery by Fragment-Based Methods & Structure-Based Design
STEPHEN FESIK (Vanderbilt University)

**Hit to Lead**
- Fragment hits
  - $K_i = 131 \mu M$
  - $K_i = 60 \mu M$
- Structure-guided fragment merging
  - $K_i = 55 nM$
  - $K_i = 23 nM$
- Binding interface expansion
  - $K_i = 0.39 nM$
  - H929 GI$_{50} = 1.2 \mu M$
  - Mcl-1 $K_i = 0.39 nM$
- Structure-guided tethering
  - Mcl-1 $K_i = <0.3 nM$
  - H929 GI$_{50} = <0.3 \mu M$

**Lead Optimization**
- > 200,000x improvement in affinity for target
- Leads feature
  - $K_i < 0.3 \text{ nM}$ to Mcl-1
  - IC$_{50} < 300 \text{ nM}$ 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
- Med. Chem. Optimization

**In vivo Optimization**
- Likely candidate profile
  - $K_i < 0.3 \text{ nM}$ to Mcl-1
  - Cellular IC$_{50} < 100 \text{ nM}$
  - Oral bioavailability
  - Robust pharmacodynamic response

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

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**IDH1 selectivity**

**PK/PD in Tumor Xenografts**

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**U87, 30 mpk, QDx1**

**AG 120**

**NCGC 006**
**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)

Optimization of Triazole scaffold:
- Potent cellular activity
- Observed effects on p97 pathway-related biomarkers

Early lead

Cleave 5083

Allosteric CBC 80512

HCT116 cell growth inhibition IC50 (uM)
p97 Biochemical IC50 (uM)
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

- Feb-18: Commence salt/polymorph screening and process dev.
- Mar-18: Single dose Dog eye retinography w/CB5083 positive, warrants use of dog as tox species
- May-18: Dog, Rat 28-day tox study at Covance
- Jun-18: ID appropriate salt form
- Sept-18: Commence Dog and Rat 28-day tox with 5339 including eye retinography in dogs
- Jan-19: File IND

Initiate Canine Patient Studies: partnership with Canine Oncology Program

GO: Initiate API manufacture and formulation, Initiate Rat GLP tox

NO-GO: Identify backup with better p97/PDE6 ratio
Inhibitors of DNA Methyltransferase (DNMT1)
Southern Research

- 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)**

- **DNMT1 CRISPR U937**
  - U937
  - Clone 14
  - Clone 79

- **Tubulin**

**Generation of chimeric mice with MDS**

- Harvest BM
  - MDS/CD45.2
  - WT/CD45.1
- Transplantation
  - 1000Grad
- Wild type Donor
  - (B6, CD45.1)
  - NHD13 Tg Donor
  - (CS7/Bl6, CD45.2)

**U937, 48h**

- Cell death (%)
  - U937/sgNC
  - DNMT1/KO CL14
  - DNMT1/KO CL79

**Conversion to AML**

- % of samples converting to AML

**NO. OF WKS POST-TRANSPLANTATION**

- Percent survival
  - Td-Cyd
  - PBS
  - \( p = 0.0187 \)

**WBC PBS and T-dCyd**

- PB5
- T-dCyd

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Dr. Steven Grant  VCU Cancer Center

Dr. Peter Aplan  NCI CCR
Tdcyd: Inhibitor of DNA Methyltransferase (DNMT1)

Tdcyd (Thiodeoxyctydine)

- 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 cycles (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
Development of Endoxifen for ER+ Malignancies
Mayo Clinic SPORE

Tamoxifen (TAM) → 4-hydroxyTAM

200-300 nM (CYP2B6, CYP2C8, CYP2C19, CYP3A)

20-180 nM

N-desmethyl TAM

400-600 nM

CYP3A4/5

Endoxifen

CYP2D6

5-10 nM

MCF-7 cells: In Vitro

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)

$P < 0.001, r^2 = 0.24$

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:

<table>
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<tr>
<th>Dose (po, daily)</th>
<th>Endoxifen 28 day Steady State</th>
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<tr>
<td>Endoxifen 20 mg</td>
<td>645 ± 200 nM</td>
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<tr>
<td>Endoxifen 40 mg</td>
<td>865 ± 275 nM</td>
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<tr>
<td>Endoxifen 60 mg</td>
<td>1900 ± 550 nM</td>
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<tr>
<td>Tamoxifen 20 mg</td>
<td>20-180 nM</td>
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</table>

-¹⁸F-FES PET: pretreatment; 1-3 hrs after 3⁷⁻⁵th dose: Demonstrated POM

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?
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
**vavNHD13 mice develop MDS**

**NUP98-HOXD13 (NHD13) fusion**

**CBCs (age 4-7 mos)**

<table>
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<tr>
<th>NHD13 (n = 22)</th>
<th>WBC (10^9/L)</th>
<th>NE (10^9/L)</th>
<th>Hb (g/dL)</th>
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<tr>
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<td>1.8</td>
<td>0.44</td>
<td>11.9</td>
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<table>
<thead>
<tr>
<th>Control (n = 7)</th>
<th>WBC (10^9/L)</th>
<th>NE (10^9/L)</th>
<th>Hb (g/dL)</th>
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<tr>
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<td>6.5</td>
<td>1.4</td>
<td>14.2</td>
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*p value*: <0.001 <0.001 <0.001

**Transformation to AML**

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

- Nras mutation

**Micro-megakaryocytes**

- Multinucleate erythroblasts

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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

Discovery
- Target Validation
- Screening/Hit-to-Lead
- Lead Development

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

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

Clinical Trials

Candidate Selection

Small Molecule Imaging agent
Biologic
Amyloid light chain disease: rare, fatal illness; <2000 pts/yr; up to 80% ineligible for ASCT; 40% die in 1 yr

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

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