NCI’s Experimental Therapeutics Program
(NExT): A Status Report

James H. Doroshow, M.D.
Director
Division of Cancer Treatment and Diagnosis
National Cancer Institute

National Cancer Advisory Board
Bethesda, MD
June 23, 2010
### Anticancer Drugs Discovered & Developed by NCI from Preclinical Stage

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug Name</th>
<th>Year</th>
<th>Drug Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Sipuleucel (Provenge®) ? Eribulin</td>
<td>1979</td>
<td>Daunorubicin</td>
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<td>2009</td>
<td>Pralatrexate</td>
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<td>Eribulin</td>
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<td>Cetuximab</td>
<td>1977</td>
<td>BCNU</td>
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<td>2003</td>
<td>Bortezomib</td>
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<td>CCNU</td>
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<td>1998</td>
<td>Denileukin diftitox</td>
<td>1975</td>
<td>Dacarbazine</td>
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<td>1996</td>
<td>Topotecan</td>
<td>1974</td>
<td>Doxorubicin</td>
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<tr>
<td>1995</td>
<td>All-trans retinoic acid</td>
<td>1973</td>
<td>Bleomycin</td>
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<td>1992</td>
<td>2-chlorodeoxyadenosine</td>
<td>1970</td>
<td>FUDR</td>
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<tr>
<td></td>
<td>Paclitaxel</td>
<td>1970</td>
<td>Mithramycin</td>
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<td></td>
<td>Teniposide</td>
<td>1970</td>
<td>Mitotane</td>
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<tr>
<td>1991</td>
<td>Fludarabine phosphate</td>
<td>1969</td>
<td>Cytarabine</td>
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<tr>
<td></td>
<td>Pentostatin</td>
<td>1969</td>
<td>Procarbazine</td>
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<td>1990</td>
<td>Hexamethylmelamine</td>
<td>1964</td>
<td>Melphalan</td>
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<td>Levamisole</td>
<td>1964</td>
<td>Actinomycin D</td>
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<td>1989</td>
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<td>Ifosfamide</td>
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<td>5-FU</td>
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<td>Mixtoxantrone</td>
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<td>Vinblastine</td>
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<td>1983</td>
<td>Etoposide</td>
<td>1959</td>
<td>Cyclophosphamide</td>
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<tr>
<td></td>
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<td></td>
<td>Thiotepa</td>
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<tr>
<td>1982</td>
<td>Streptozotocin</td>
<td>1957</td>
<td>Chlorambucil</td>
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</table>
Drug Development Programs: NCI & NIH

Efficiency sub-optimal

National Cancer Institute
Decentralized NCI Drug Development

- **Created inefficiencies** (duplication of experimental work and/or mission)
- **Fostered resource silos** (staff with expertise in an area could be unintentionally excluded from a project)
- **Confused collaborators** (which mechanisms most appropriate for entry of agent into the program? What resources available?)
- **Confused staff** (What projects had priority? What resources could be accessed? Who had decision making authority?)
The NCI Experimental Therapeutics (NExT) Pipeline: Target discovery through early stage clinical trials
NCI Experimental Therapeutics Program: Unified Discovery & Development

Where Did We Need to Go?
Rapid translation of discoveries into public health benefits

A single pipeline for all therapeutic development resources:
One Pipeline, Many Points of Entry

INCLUDES
- Investigational drugs and biologics
- Investigational imaging agents
- Academic & Biotech & Pharma projects
- Includes Phase 0, I and II Programs
NCI Chemical Biology Consortium (CBC)

- **Mission**: Dramatically increase flow of early stage drug candidates into NCI therapeutics pipeline

- **Vision**
  - Develop integrated network of chemists, biologists, and molecular oncologists, with synthetic chemistry support
  - Active management by NCI and external advisory boards
  - Unify discovery with NCI pre-clinical and clinical development
  - Linked to other NCI initiatives; CCR chemistry integral partner

- Focus on unmet needs in therapeutics: “undruggable” targets, under-represented malignancies

- Enable a clear, robust pipeline all the way from target discovery through clinical trials for academic, small biotech, and pharma investigators

*NExT FRONT END*
Chemical Biological Consortium

- **Comprehensive Chemical Biology Screening Centers (4)**
  - Identify targets, develop target assays and adapt these assays to HTS platforms, screen numerous compounds against a variety of different assays each year, and provide Structure-Activity Relationship (SAR) analysis and support chemistry

- **Specialized Application Centers (3)**
  - Provide expertise and experience in specific technologies needed to successfully develop and implement complex and technically difficult assays that may not be amenable to HTS

- **Chemical Diversity Centers (4)**
  - Capable of applying medicinal and synthetic chemistry to advance hits to lead status

- **Other (3)**
## Chemical Biological Consortium: Members

<table>
<thead>
<tr>
<th>National Cancer Institute</th>
<th>CCBSC</th>
<th>SAC</th>
<th>CDC</th>
<th>Others</th>
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<tbody>
<tr>
<td><strong>CCBSC</strong></td>
<td>Sanford Burnham Inst for Med Res</td>
<td>Southern Research Institute</td>
<td>SRI International</td>
<td>Univ. North Carolina – Chapel Hill</td>
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<tr>
<td></td>
<td>John C. Reed, Kristiina Vuori</td>
<td>W. Blaine Knight</td>
<td>Lidia Sambucetti</td>
<td>Stephen Frye</td>
</tr>
<tr>
<td><strong>SAC</strong></td>
<td>University of California, SF</td>
<td>University of Pittsburgh DDI</td>
<td>Emory University</td>
<td>Georgetown University</td>
</tr>
<tr>
<td></td>
<td>James A. Wells</td>
<td>John Lazo</td>
<td>Haian Fu, Fadlo Khuri, Dennis Liotta</td>
<td>Milton L. Brown</td>
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<tr>
<td><strong>CDC</strong></td>
<td>Vanderbilt Institute of Chem Biol</td>
<td>University of Minnesota</td>
<td>University of Pittsburgh</td>
<td>GVK Biosciences</td>
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<tr>
<td></td>
<td>Gary Sulikowski, Alex Waterson</td>
<td>Gunda I. Georg</td>
<td>Donna Huryn</td>
<td>Sreenivas Devidas</td>
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<tr>
<td><strong>Others</strong></td>
<td>NCI Intramural Chemical Biology</td>
<td>Affiliate Investigators</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>David Starks</td>
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</tbody>
</table>
Why is CBC different?

- Builds on >50 yrs of NCI experience in cancer drug development
- Not intended to replicate Pharma
- CBC members will submit own projects and take on those of other investigators
- Focus on bringing academic targets and molecules to patients
- Will not shy away from difficult targets
- Longer time horizon
- NCI committed to supporting CBC projects from inception through proof-of-concept, PD-driven clinical trials if milestones achieved: Only NCI could do this
- Inclusive involvement of CBC members in shared projects developed in parallel across consortium
Model Development and Target Validation

Biomarker validation

Target identification

Parallel medicinal chemistry

Optimal potency/selectivity

Efficacy in pivotal in vivo models

Model Development and Target Validation

Biomarker validation

Small Animal Imaging Center

Adapted with permission from the NIH Chemical Genomics Center
CBC participants sign a Consortium Agreement. This agreement details:

- How CBC participants ensure timely entry of deliverable data into the database
- How CBC participants manage IP ownership to ensure that other members of the consortium have adequate access to data for development
- The preferred mechanism by which CBC participants manage joint inventions
- CBC participant responsibilities to share research resources developed under the contract with the broader research community

The Consortium Agreement addresses:

Data Transfer  Data Sharing  Data Ownership
How Does An Extramural Investigator Access NCI’s Drug Discovery and Development Resources?
Extramural scientists may propose targets, screens, or molecules for entry into the NExT pipeline; quarterly receipt dates

https://dctd.cancer.gov/nextapp or
https://dctd.cancer.gov/nextregistration

NCI Experimental Therapeutics (NExT)

DCTD
Division of Cancer Treatment and Diagnosis

NExT Application Login

NExT application Instructions

User Name: 
Password: 
Login

Register for an account

If you have any problems or questions about this application please contact Dave Seegal
How Are Projects/Compounds Selected?

- Discovery Special Emphasis Panel (SEP)
- NExT Discovery Committee
- NExT Senior Advisory Committee (SAC)
- NExT Development Committee
- Development Special Emphasis Panel (SEP)
- CBC Steering Committee (SC)
- Portfolio Managers
Prioritization Process Used To Ascertain Which Compounds To Move Forward?

- This selection is based on the following criteria.
  - Scientific Merit
  - Feasibility
  - NCI Mission
  - Novelty
  - Clinical Need

- A Stage Gate evaluation process to benchmark the progress and priority of projects within the portfolio.

- This evaluation process is also to provide guidance about the priority utilization of the capacity – based resources provided by NCI.

Scoring:

- 1 = Exceptional
- 3 = Excellent
- 6 = Satisfactory
- 9 = Poor
## NExT Cycle 1: September 2009

### Total Number of Applications:
- **Discovery**: 85%
- **Development**: 15%
- **Total Number of Applications**: 52

### Top Tier Applications:
- **Discovery**: 80%
- **Development**: 20%
- **Total**: 10 applications

### Applicant PI | Center | Project
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>John Frangioni</td>
<td>Beth Israel Deaconess Medical Center</td>
<td>A NIR Fluorophore for Clinical Translation of Image-Guided Oncologic Surgery</td>
</tr>
<tr>
<td>Lance Leopold</td>
<td>Ascenta Therapeutics</td>
<td>AT-406, a pan, oral IAP Inhibitor, for the Treatment of Cancer</td>
</tr>
<tr>
<td>John Reed</td>
<td>Sanford-Burnham</td>
<td>Chemical Modulators of Autophagy for Cancer Therapy</td>
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<tr>
<td>Jennifer Grandis</td>
<td>University of Pittsburg</td>
<td>Discovery and Optimization of Inhibitors of STAT3 Activation</td>
</tr>
<tr>
<td>Bert Vogelstein</td>
<td>Johns Hopkins University</td>
<td>MTAP Isogenic Drug Screen in DLD-1 Colorectal Cancer Cell Lines</td>
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<tr>
<td>Raymond Deshaies</td>
<td>California Institute of Technology</td>
<td>Development of Small Molecule Inhibitors of the AAA ATPase p97</td>
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<tr>
<td>Anne Bresnick</td>
<td>Albert Einstein School of Medicine</td>
<td>Development of S100A4 Inhibitors for the Prevention of Metastatic Disease</td>
</tr>
<tr>
<td>Shelton H. Earp</td>
<td>Univ North Carolina-Chapel Hill</td>
<td>Developing Small Molecule Mer Inhibitor Candidates for ALL</td>
</tr>
<tr>
<td>James Hsieh</td>
<td>Washington University-St. Louis</td>
<td>Optimization of Lead Small Molecule Inhibitors of Taspase 1 for Cancer Therapeutics</td>
</tr>
<tr>
<td>John Reed</td>
<td>Sanford-Burnham</td>
<td>Chemical Activators of the PML Tumor Suppressor Pathway</td>
</tr>
</tbody>
</table>
NExT Cycle 2: November 2009

**Total Number of Applications:**

- **Discovery**: 63%
- **Development**: 38%

**Top Tier Applications:**

- **Discovery**: 33%
- **Development**: 67%

**Applicant PI** | **Center** | **Project**
--- | --- | ---
Richard B. Roden | Johns Hopkins University | Production of an HPV16 L2E6E7 Vaccine with GPI-0100 Adjuvant for the Treatment of HPV-Associated Disease
Ari Melnick | Joan & Sanford I. Weill Medical College | Clinical Translation of a BCL-6 Inhibitor
Dario C. Altieri | University of Massachusetts Medical School | Clinical Development Of Mitochondria-Targeted Hsp90 Antagonists, Ganimetrins
Donald W. Kufe | Dana-Farber Cancer Institute | The Development of a Novel Anti-Cancer Agent Against the MUC1 Oncoprotein
Bryan Leigh | Tracon Pharmaceuticals | Development of TRC105 as a Novel Anti-angiogenic Monoclonal Antibody
John Kovach | Lixte Biotechnology Holdings, Inc. | Novel Inhibitor of PP2A Potentiates Chemotherapy
Chi Dang | Johns Hopkins University School of Medicine | Development of FX11, a Lactate Dehydrogenase A (LDHA) Inhibitor, as an Anti-neoplastic Agent
Cyrus Vaziri | University of North Carolina at Chapel Hill | Inhibition of the DNA Repair Enzyme Rad18 as a Novel Strategy for Sensitizing Tumor Cells to Platinum Drugs
Edward V. Prochownik | Children's Hospital of Pittsburgh | Evaluation of Rationally-Designed Small Molecules Directed Against the c-Myc Oncoprotein
NExT Cycle 3: February 2010

Total Number of Applications: 23

Discovery 48%
Development 52%

Top Tier Applications: 6

Development 50%
Discovery 50%

Applicant PI | Center | Project
--- | --- | ---
Thomas Waldmann | National Cancer Institute | Anti-IL-15 Receptor Antibody Therapy of Celiac Disease Associated Lymphoma
Raveen Marapaka | MedImmune | HA 22 Randomized PIII-HCL
Thomas Davis | Celldex Therapeutics, Inc. | Clinical Development of CDX-1308 Vaccine Regimen
Marianne Sadar | BC Cancer Agency/British Columbia Cancer Agency | IND-Directed Preclinical Studies of EPI-001 for Prostate Cancer Treatment
Shyam Biswal | Johns Hopkins University | Development of NRF2 Inhibitors for Cancer Chemotherapy
Stephen Fry | University of North Carolina at Chapel Hill | Assay Development and Hit Discovery for IDH1-based Approaches Targeting Glioblastoma
NExT Cycle 4: May 2010

Total Number of Cycle 4 Applications: 46

Development 61% (28)
Discovery 39% (18)
Resubmissions 33% (15)

New Applications 67% (31)

Total Number of Cycles 1 to 4 Applications: 174
### NCI RAID and NExT Programs: Statistics

<table>
<thead>
<tr>
<th></th>
<th>NCI RAID</th>
<th>NExT</th>
</tr>
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<tbody>
<tr>
<td><strong>Time Period</strong></td>
<td>9.5 yrs</td>
<td>10 months</td>
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<tr>
<td><strong>No. Applications</strong></td>
<td>428</td>
<td>128 (174)</td>
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<tr>
<td><strong>No. Approved</strong></td>
<td>137</td>
<td>25</td>
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<tr>
<td><strong>% Approved</strong></td>
<td>32.0</td>
<td>19.5</td>
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<tr>
<td><strong>Discovery Apps</strong></td>
<td>(0)</td>
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<tr>
<td><strong>Development Apps</strong></td>
<td>137</td>
<td>11</td>
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</table>

1. Approved Applications
2. Total number Cycles 1-4
Goals of the NCI’s Therapeutics Platform

- Develop treatments for unmet medical needs (e.g., rare cancers and pediatric tumors)
- Provide resources for natural product development and the development of high risk targets
- Move discoveries from TCGA into drug discovery
- Support development of biological agents

Success measured by:
- IND filings (first in human studies)
- Licensing of novel therapeutics
- Improved cancer therapeutics success rate
- Approved NDA’s developed from academic and small biotech research
# Top 20: Immunotherapy Workshop Reagent List

Input from AAI and its members helped compile this list; NCI now acquiring reagents.

<table>
<thead>
<tr>
<th>National Cancer Institute</th>
<th>Top 20: Immunotherapy Workshop Reagent List</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-15</td>
<td>Flt-3 Ligand</td>
</tr>
<tr>
<td>Anti-PD-1, Anti-B7-H1</td>
<td>TNF Receptor (GITR)</td>
</tr>
<tr>
<td>IL-12</td>
<td>CCL-21 Adenovirus</td>
</tr>
<tr>
<td>Anti-CD40, CD40L</td>
<td>Mono-P Lipid A (MPL)</td>
</tr>
<tr>
<td>IL-7</td>
<td>Poly IC, Poly ICLC</td>
</tr>
<tr>
<td>CpG</td>
<td>Anti-OX40L</td>
</tr>
<tr>
<td>1-Methyl Tryptophan</td>
<td>Anti-B8H4</td>
</tr>
<tr>
<td>Anti-CD137 (anti-4-1BB)</td>
<td>Resiquimod,852A</td>
</tr>
<tr>
<td>Anti-TGF-beta</td>
<td>LIGHT, LIGHT vector</td>
</tr>
<tr>
<td>Anti-IL10 receptor, Anti-</td>
<td>Anti-lymphocyte activation</td>
</tr>
<tr>
<td>IL10</td>
<td>Gene -3 (LAG-3)</td>
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# Prioritized Needs of the Immunotherapy Community

## Agents with High Potential for Use in Cancer Therapy and Infrastructure

<table>
<thead>
<tr>
<th>AGENT</th>
<th>FUNCTION</th>
<th>AVAILABILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-15</td>
<td>T-cell growth factor</td>
<td>NCI-in production; NCI IND approved</td>
</tr>
<tr>
<td>Anti-PD-1</td>
<td>T-cell checkpoint inhibitor</td>
<td>Commercial</td>
</tr>
<tr>
<td>IL-12</td>
<td>Vaccine adjuvant</td>
<td>NCI—in hand</td>
</tr>
<tr>
<td>Anti-CD-40</td>
<td>APC stimulator</td>
<td>Commercial</td>
</tr>
<tr>
<td>IL-7</td>
<td>T-cell growth factor</td>
<td>NCI-in production</td>
</tr>
</tbody>
</table>

## Cancer Immunotherapy Network:
- established to stimulate multisite phase I and II clinical immunotherapy trials across a range of malignancies
- bring novel immunotherapy agents, combinations, and approaches to the clinic
- up to 25 institutions
- standardized immunomonitoring and biomarker studies
- funded end of 2010
- NCI will produce reagents that lack a commercial sponsor

GMP 80L fermentation of rhIL-15: Production and pooling of several of products from several fermentations needed for one 1gram lot of rhIL-15
ch14.18 (anti-GD2 monoclonal antibody)

- Over 99% of neuroblastomas express GD2
- ch14.18 demonstrated preclinical activity in neuroblastoma cell lines and xenografts
- ch14.18 manufactured by NCI-DCTD-DTP for Phase I, II, and III clinical trials
- NCI’s Children’s Oncology Group conducted ANBL0032 phase 3 trial to determine efficacy of ch14.18 for high-risk neuroblastoma
COG-ANBL0032, - EFS randomized patients treatment 1 (n=113) & treatment 2 (n=113)

RA only, trt 1
RA + anti-GD2, trt 2

p=0.0115

66% 63%
46% 46%

ch14.18 Immunotherapy Improves Survival for Children with High Risk Neuroblastoma
ch14.18 for Neuroblastoma

- Results define a new standard therapy for children with high-risk neuroblastoma who have completed autologous stem cell transplantation
- NCI is manufacturing additional ch14.18 to make it available through COG clinical trials for all children who meet eligibility criteria, and, in consultation with FDA, to complete registration trial
- NCI is taking the necessary steps to license ch14.18 for high-risk neuroblastoma
Recently-Approved NExT Small Molecule Projects

- Targeting mutant IDH1 in glioblastoma multiforme
- STAT3 in head and neck cancer
- Mer kinase as a target in pediatric leukemia
Targeting mutant IDH1 in glioblastoma

- Heterozygous mutations in isocitrate dehydrogenase-1 occur in glioblastoma multiforme (and in AML)

  ✓ Missence mutations at a single residue
  ✓ Zhao and colleagues (UNC): *Glioma-derived mutations in IDH1 dominantly inhibit IDH1 catalytic activity and induce HIF-1α* Science 324: 261-265, 2009
  ✓ Dang and colleagues: *Cancer-associated IDH1 mutations produce 2-Hydroxyglutarate* Nature 462: 739-744, 2009

- UNC investigators proposed the development of mutant enzyme inhibitors

Stephen Frye
Shelley Earp
Yue Xiong
University of North Carolina
Targeting IDH1–Mutated Glioblastoma Multiforme

Normal cells

IDH1

ICT

OH

HIF-1α

↓

HIF-1α ubiquitination

↓

HIF-1α Degradation

ICT

α-KG

IDH1 mutated

IDH1

mutant

ICT

OH

HIF-1α

↓

2-HG

HIF-1α ubiquitination

↓

HIF-1α Degradation

Angiogenesis

Increased metabolism

Tumor development

Inhibitors of mutant dimers and heterodimers will block 2HG accumulation and restore PHD and other 2OG-Ox activities.
Targeting IDH1: Rationale and Current Status

RATIONALE
- IDH1 is a high-risk target
  - by-product of TCGA program
  - focuses on an unmet need: GBM
- Excellent partnership with laboratories at forefront of field
- Answer the question: “Is mutant IDH1 a druggable target”

STATUS
- α-KG and 2-HG prodrugs prepared for further biochemical studies
  - mechanism of oncogenesis
  - downstream 2-oxoglutarate oxidases
- Mutant (R132H) and wildtype clones available for assay development
- Diversity screening library (100K) will be supplemented via structure-based virtual screening
- Anticipate 18 months to develop assays, run HTS, and work-up hits
STAT3 in Head and Neck Cancer

**NExT Project:** “Discovery and optimization of inhibitors of STAT3 activation for the treatment of squamous cell carcinoma of the head and neck”

Pl: Jennifer R. Grandis, MD
University of Pittsburgh
• Constitutively activated STAT3 mediates cellular transformation

• Increased activated STAT3 is found in many different human cancers where activation levels are associated with reduced survival

• STAT3 activation induces survival, angiogenesis, proliferation, and invasion/metastasis

• Caveat: STAT3 is highly homologous to STAT1, which in contrast to STAT3, functions as a tumor suppressor gene
Assay Development: IL-6 induces STAT3 Tyrosine Phosphorylation and Nuclear Translocation in H&N Cancer Cells
HCS Assay Distinguishes pSTAT3 from pSTAT1 Activation and Nuclear Translocation

pSTAT3-Y705 Antibody
Nuc/Cyt Average Intensity Ratio

Average Nuc:Cyt Intensity Ratio
pSTAT3-Y705 (45 min)

Cytokine/Growth Factor
Media IFN-γ IL-6 EGF

Average Inner/Outer Intensity Ratio
pSTAT3-Y705

0 10 20 30 40 50
[IL-6] ng/mL

Time Min

pSTAT1-Y701 Antibody
Nuc/Cyt Average Intensity Ratio

Average Nuc:Cyt Intensity Ratio
pSTAT1-Y701 (30 min)

Average Inner/Outer Intensity Ratio
pSTAT1-Y701

Cytokine/Growth Factor
Media IFN-γ IL-6 EGF

0 5 10 15 20
[IFNγ] ng/mL

Time Min

pSTAT1-Y701 (10 ng/mL IFNγ)

Average Nuc:Cyt Intensity Ratio
pSTAT1-Y701 (10 ng/mL IFNγ)

Average Inner/Outer Intensity Ratio
pSTAT1-Y701

0 10 20 30 40 50 60
Time Min
Schema of Phase 0 Trial of STAT3 Decoy

Resectable HNC (primary or recurrent) → Pre-treatment Biopsy in OR → INJECT DECOY

STAT3 decoy was produced by NCI’s Developmental Therapeutics Program

STAT3 Decoy Decreases Target Gene Expression in Human HNSCC

Patient 1  Patient 2  Patient 3  Patient 4

Pre  Post  Pre  Post  Pre  Post  Pre  Post

Bcl-xL  Cyclin D1  β-actin
STAT3: Rationale and Current Status

RATIONALE
- STAT3 decoy molecule (GMP oligomer produced by NCI) inhibited target gene expression following direct injection in human head and neck cancers demonstrated by PI, Dr. Jennifer Grandis
  - focuses on an unmet need: head and neck cancer
- Excellent partnership with laboratory at forefront of field
- Focuses on use of both high content (cellular imaging) screens as well as HTS

STATUS and GOALS
- High content screening assays in hand but require optimization
- Confirm and validate hits with appropriate secondary and counter-screening assays
- SAR and MOA studies
Mer kinase as a target in childhood leukemia

- Mer kinase – a member of the Tyro3/Axl/Mer RTK family
  - Expressed in monocytes, functions to clear apoptotic material
  - Never expressed in normal T or B lymphocytes
- Mer kinase expressed in most T and B cell ALL lines
- Mer expression in childhood leukemias
  - Mer mRNA expressed in 30-40% T cell ALL (Clin Cancer Res 2006, 12:2662)
  - New data: Mer protein expressed in 41% B ALL (16 of 16 E2A-PBX1 ALLs)
  - Mer protein expressed 54% T cell ALLs and 68% pediatric AML

Shelley Earp
Yue Xiong
Stephen Frye
University of North Carolina
Doug Graham
University of Colorado
Inhibition of Mer Expression Alters Chemosensitivity and In Vivo Outcome

697 B cell (E2A-PBX) chemosensitivity altered by Mer knockdown

In vivo leukemia model: injection of $5 \times 10^5$ 697 cells in Nod/SCID mice. Enhanced survival with Mer shRNA knockdown.

Target validation with shRNA, Linger et al., Blood, 2009 114:2678
Therapeutic Strategy – Mer kinase inhibitor

- Protein kinases are tractable targets for small molecule drug discovery – rich target-class knowledge base exists
- UNC has significant expertise in kinase drug discovery
  - Dr. Frye’s kinase/cancer department at GSK discovered two of the nine FDA approved kinase inhibitors (Lapatinib and Pazopanib)
  - Drs. Earp and Graham’s labs are the leaders in understanding the biology, survival signaling, and clinical relevance of Mer
- Initial goal is to discover multiple, tractable mer kinase inhibitor hit series in order to successfully optimize one series to a drug candidate suitable for i.v. administration (3 year time line); followed by an orally available candidate (4 year time line)
- Clinical utility will be chemosensitization of ALL in patients ectopically expressing Mer – other indications will likely emerge
- Unmet need; Pharma not interested in chemotype
Targeting Mer Kinase: Current Status

STATUS

- Project has been underway for 1.5 years
- Structure-based hit generation has yielded one lead series:
  - low nanomolar $K_i$'s, robust structure-activity relationships
  - Promising initial dmpk (UNC569, mouse, 4.4h $t_{1/2}$, 57% F)
  - Broad kinase profiling underway
  - Cellular assays being optimized – compounds appear to have <1 µM IC50's
  - Lead optimization on UNC569 series is top priority
  - Compounds suitable for in vivo testing are in hand
- Additional hit generation is ongoing via focused screening and further structure-based design
  - Typically need 2-3 lead series to deliver one candidate due to attrition of series during lead optimization
  - Expect 1-2 additional leads during the next 12 months
- Initial crystals of the Mer kinase domain have been obtained – optimizing conditions to develop a system for routine co-crystal structures
- Cellular assay optimization for IC$_{50}$ determination and cellular mechanism of action (UNC, Earp, Johnson)
  - In vitro metabolism and p-450 interactions (underway)
Success: What Will it Look Like?

Transparent, Accountable, Inclusive, & Unified

- Hypothesis Generation
- Clinical Candidate Development
- Commercialization

- PoC in >50% of Phase II trials

- Target/Molecule Discovery
- Assay Development
- Lead Optimization
- Preclinical Development
- Phase I
- Phase II
- Phase III
- Registration
- Global Launch
- Global Optimization

- Risk

Cumulative Investment

Lead Generation
Target Validation
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<thead>
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