NCI’s Experimental Therapeutics Program (NExT)

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NCI Experimental Therapeutics Program: Unified Discovery & Development

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

WHERE DID WE NEED TO GO?
Rapid translation of discoveries into public health benefits

**NCI Experimental Therapeutics Program**

**Includes**
- Investigational drugs and biologics
- Investigational imaging agents
- Academic & Biotech & Pharma projects
- Includes Phase 0, I and II Programs
Therapeutics Discovery & Development Support Provided by NCI (NExT)

- Medicinal chemistry, HTS, lead optimization
- Synthesis of oligonucleotides
- Chemical synthesis of small molecules and peptides
- Scale-up production of small molecules and biologicals
- Development of analytical methods
- Isolation and purification of naturally occurring substances
- Exploratory toxicology studies and pharmacokinetic evaluation
- PK/efficacy/ADME studies (bioanalytical method development)
- Development of suitable formulations
- Range-finding initial toxicology and IND-directed toxicology
- Product development planning and advice in IND preparation
- Later-stage preclinical development of monoclonal antibodies, recombinant proteins, and gene therapy agents
- Manufacture of drug supplies, including biological agents
- Analytical methods development for bulk material
- Formulation studies
- Production of clinical dosage forms
- Stability testing of clinical dosage forms
- Regulatory support & Early phase clinical trials
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 cancer therapeutics: “undruggable” targets, under-represented malignancies, high risk projects, longer time horizon
- **Enable a clear, robust pipeline** all the way from target discovery through PD-driven proof-of-mechanism clinical trials for academic, small biotech, and pharma investigators; involve CBC members in shared project development

NExT FRONT END: Leveraged Molecular Libraries Investment
Extramural scientists may propose targets, screens, or molecules for entry into the NExT pipeline; receipt dates every 4 months

https://dctd.cancer.gov/nextapp or
https://dctd.cancer.gov/nextregistration
How Are Projects/Compounds Selected?

NCAB Experimental Therapeutics Subcommittee

- Senior Management Committee (SMC)
  - 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

Implementation
Number of Applications from Academic, Non-Profit, Biotech, Pharma or Government

All Applications (Total 193)

Top Tier (Total 30)
NExT Projects

• **Discovery:** Developing a Lactate Dehydrogenase A (LDHA) Inhibitor for Solid Tumors: Chi Dang, JHU

• **Development:** Biologics for Immunotherapy Trials

• **Early Phase Clinical:** Phase I Trial of the DMT inhibitor FdCyd + Tetrahydouridine
The proto-oncogene c-myc can drive glutamine as well as glucose metabolism. In cancer, c-myc deregulation can result in the added uptake of glucose and its conversion to lactate, thereby contributing to the “Warburg Effect”.

ChIP sequencing confirmed that Lactate Dehydrogenase A (LDHA), an enzyme that converts lactate to pyruvate, is a direct downstream target of Myc.

Knockdown of LDHA decreased colony formation and reduced the growth of tumors in breast and lung cancer xenografts.

Japanese families that completely lack LDHA are otherwise normal except for exertional myopathy.

FX11 is a selective, small molecule, active site LDHA inhibitor identified from a malarial LDH screen that provides proof-of-concept for targeting cancer metabolism in human lymphoma and pancreatic cancer models.
FX11 Treatment Leads to Regression of Tumors in Lymphoma and Pancreatic Xenograft Models

FX11

Lymphoma

Pancreas

FX11

P493

Control | FX11

Panc374

% Growth (Mean ± SEM)

Time (Days)

Panc265

% Growth (Mean ± SEM)

Time (Days)
LDHA: Next Steps

- Screen development and high-throughput screening
  - Primary uHTS
  - NIH Chemical Genomics Center

- Hit to Lead
  - NCGC: hit validation/med chemistry
  - Secondary biochemical and cell-based screens
    - Dang Lab

- Lead Optimization
  - Co-crystallization with HTS “hits”

- Candidate Seeking

- FX11 Lead Compound
  - $Ki \ 4 \mu M$

- HTS screen to identify new scaffolds
- Co-crystallization with FX11
- Optimize SAR for lead compound FX11, increase potency and improve solubility
### Prioritized Needs of the Immunotherapy Community

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

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<thead>
<tr>
<th>AGENT</th>
<th>FUNCTION</th>
<th>AVAILABILITY</th>
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<tbody>
<tr>
<td>IL-15</td>
<td>T-cell growth factor</td>
<td>NCI-in production; NCI IND approved</td>
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<tr>
<td>Anti-PD-1</td>
<td>T-cell checkpoint inhibitor</td>
<td>Commercial</td>
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<tr>
<td>IL-12</td>
<td>Vaccine adjuvant</td>
<td>NCI—in hand</td>
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<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>
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#### GMP 80L fermentation of rhIL-15:
Production and pooling in Frederick of several products from multiple fermentations needed for one 1 gram lot of rhIL-15

**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 Frederick will produce reagents that lack a commercial sponsor
Phase I Trial of 5-Fluoro-2’-Deoxycytidine (FdCyd) with Tetrahydourouridine (THU) in Advanced Malignancies

- FdCyd: an inhibitor of DNA methyltransferase
- In pre-clinical models, FdCyd administered along with THU (inhibits cytidine/deoxycytidine deaminase) activates a series of hypermethylated genes (GST\(\pi\); p16)
- FdCyd is administered as an IV infusion over 3 hours along with THU daily for 5 consecutive days of treatment per week for 2 consecutive weeks, followed by 2 weeks of no treatment, for 28-day cycles
- NCI-RAID program produced both drugs for clinical trial at USC, UC Davis, COH, and NIH CC
Phase I Activity of FdCyd + THU

61 yo F with metastatic breast cancer, high dose chemo followed by autotransplant, multiple hormonal and chemo regimens.

Pre-study

September 2006

January 2007

May 2007
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
https://dctd.cancer.gov/nextregistration

**NExT/CBC Implementation Team**

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The Consortium Agreement addresses:

- Data generated by the CBC is a defined deliverable that will be accessible to all other CBC participants via a proprietary database; management of shared IP.

- Materials generated by the CBC will also be defined deliverables and be available to the government for use and future development.

- Projects will be managed by NCI project team managers who will ensure that data delivered to the NCI is appropriately distributed among CBC members.