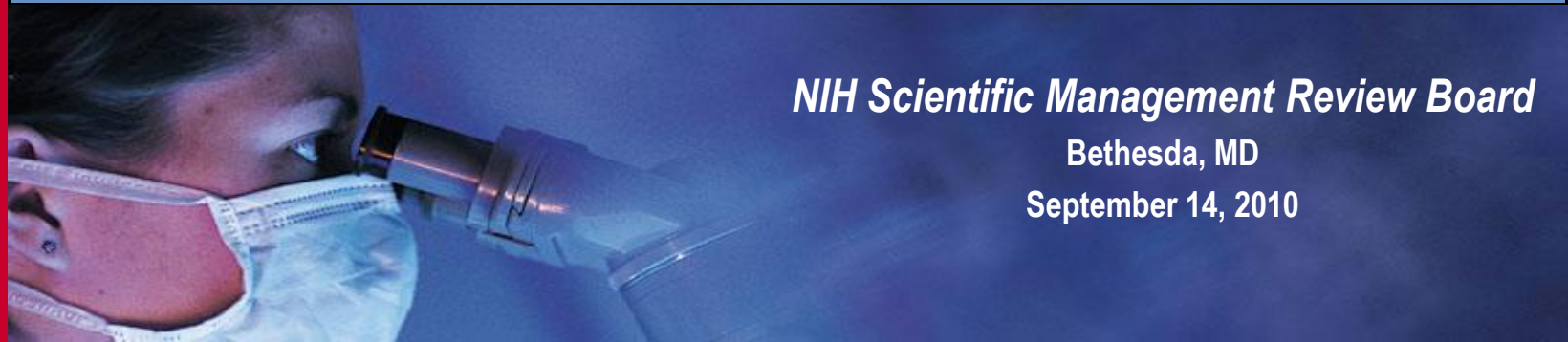




NCI's Experimental Therapeutics Program (NExT)

James H. Doroshow, M.D.
Director

Division of Cancer Treatment and Diagnosis, NCI



NIH Scientific Management Review Board

Bethesda, MD

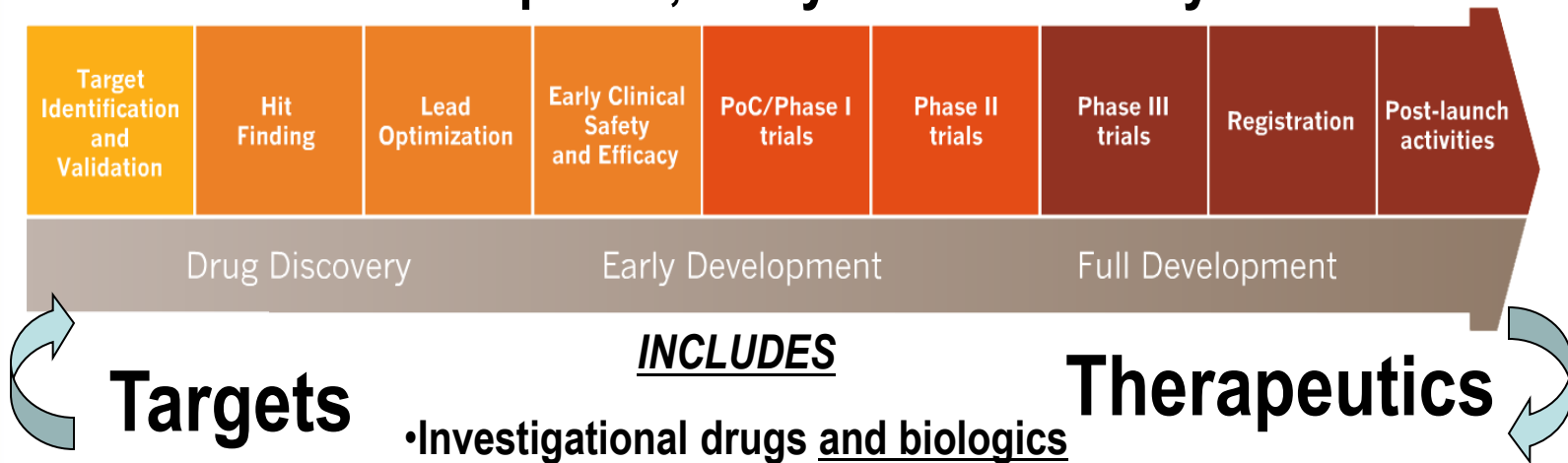
September 14, 2010

Where Did We Need to Go?

Rapid translation of discoveries into public health benefits

NCI Experimental Therapeutics Program: Unified Discovery & Development

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



Therapeutics Discovery & Development Support Provided by NCI (NExT)

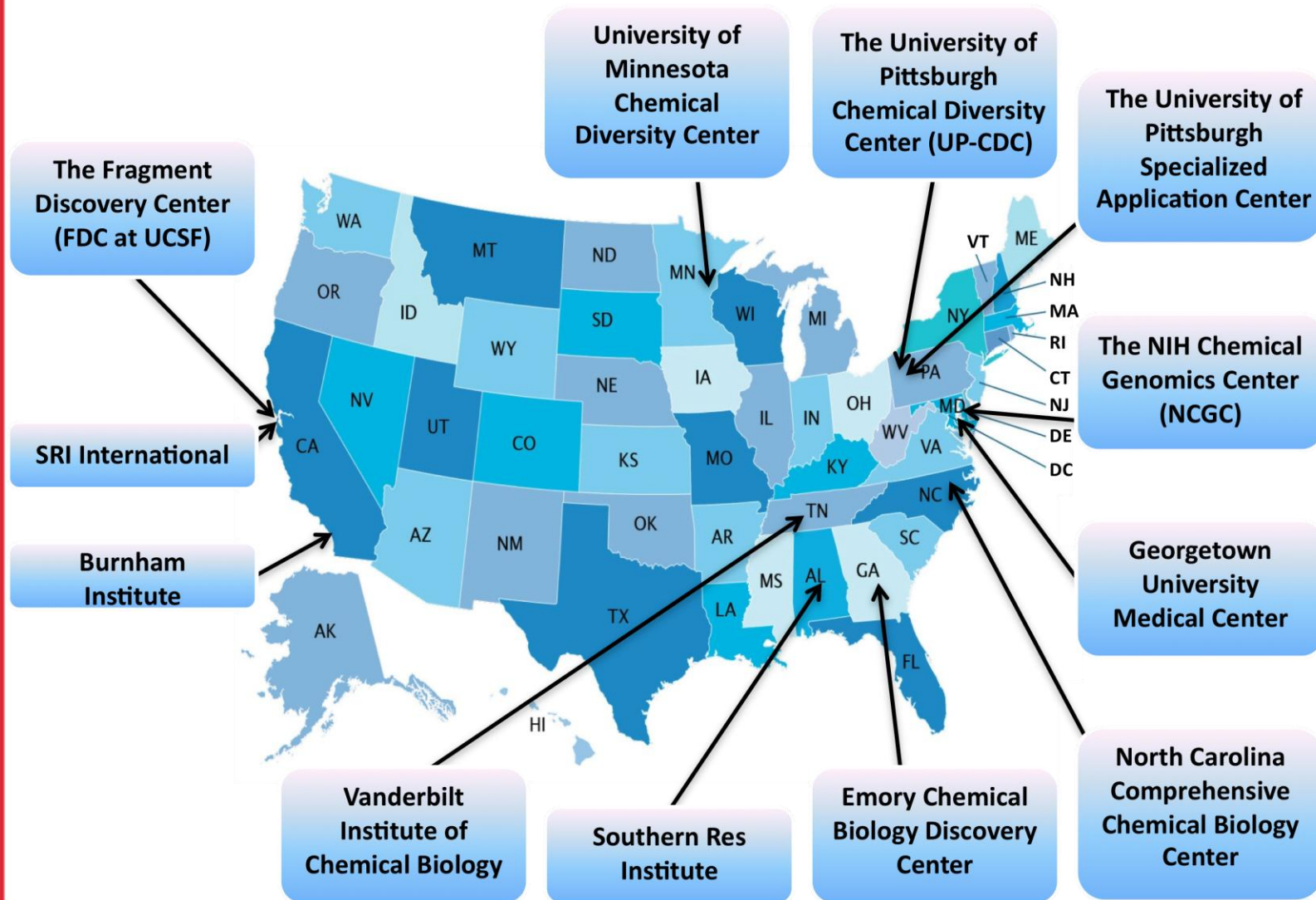
- Medicinal chemistry, HTS, lead optimization
- Synthesis of oligonucleotides
- Chemical synthesis of small molecules and peptides
- Scale-up production of small molecules and biologicals
- Development of analytical methods
- Isolation and purification of naturally occurring substances
- Exploratory 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

NCI Chemical Biology Consortium (CBC)



NExT Application Process

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>

The screenshot shows the NCI Experimental Therapeutics (NExT) application process page. At the top, there is a red header with the National Cancer Institute logo and the text "National Cancer Institute" and "U.S. National Institutes of Health | www.cancer.gov". Below the header, the page title is "NCI Experimental Therapeutics (NExT)". Underneath the title, there are two logos: "DCTD Division of Cancer Treatment and Diagnosis" and "CENTER FOR CANCER RESEARCH". The main content area features a banner with the text "NExT Application Login" and a molecular structure image. Below the banner, there is a button labeled "NExT application Instructions". Further down, there are input fields for "User Name:" and "Password:", followed by a "Login" button. Below the login fields, there is a button labeled "Register for an account". At the bottom of the page, there is a footer with the text "If you have any problems or questions about this application please contact [Dave Segal](#)". The footer also contains a navigation bar with links: "DCTD Home | Text-only | Contact DCTD | Site Map | NCI Home | Accessibility | Policies". At the very bottom, there are logos for the National Cancer Institute, the U.S. Department of Health and Human Services, and the USA.gov logo.

NATIONAL CANCER INSTITUTE National Cancer Institute U.S. National Institutes of Health | www.cancer.gov

NCI Experimental Therapeutics (NExT)

DCTD
Division of Cancer
Treatment and Diagnosis

CENTER FOR
CANCER
RESEARCH

NExT Application Login

NExT application Instructions

User Name:

Password:

Login

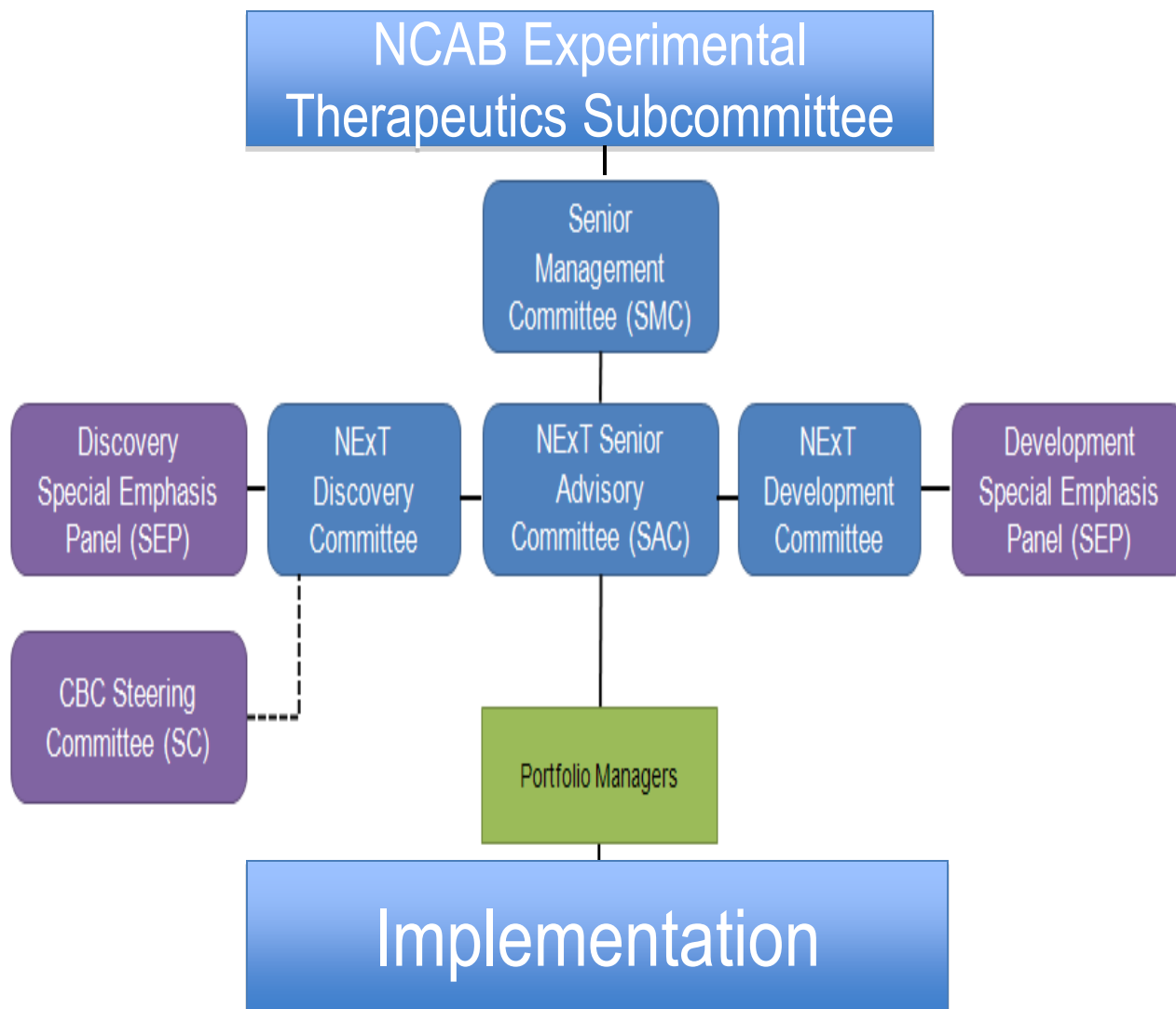
Register for an account

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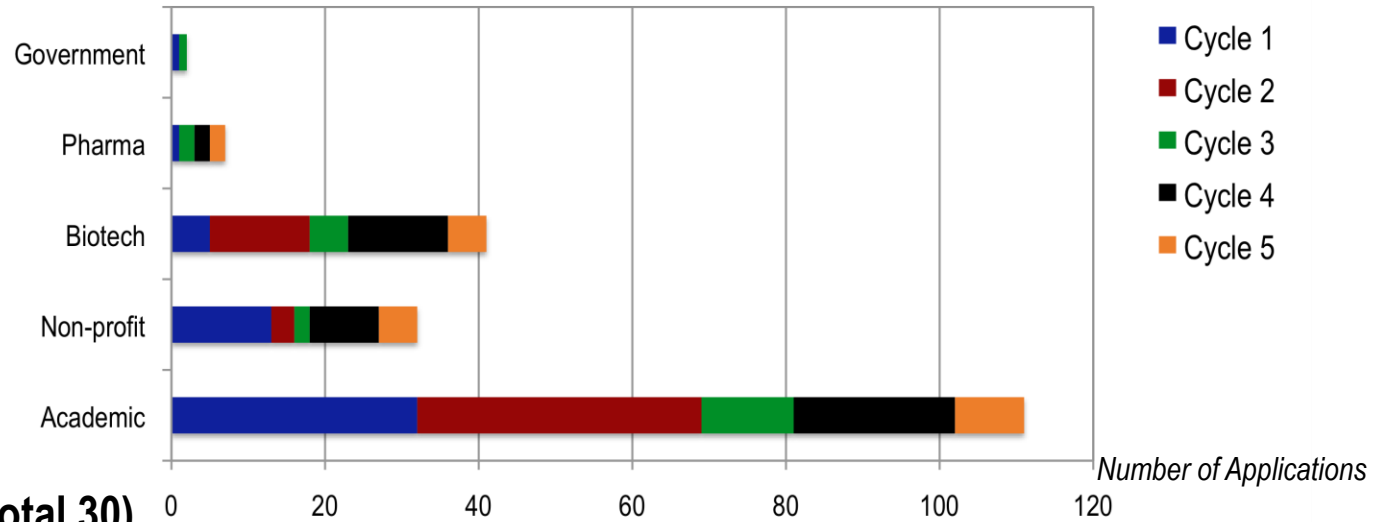
NATIONAL CANCER INSTITUTE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES USA.gov

How Are Projects/Compounds Selected?

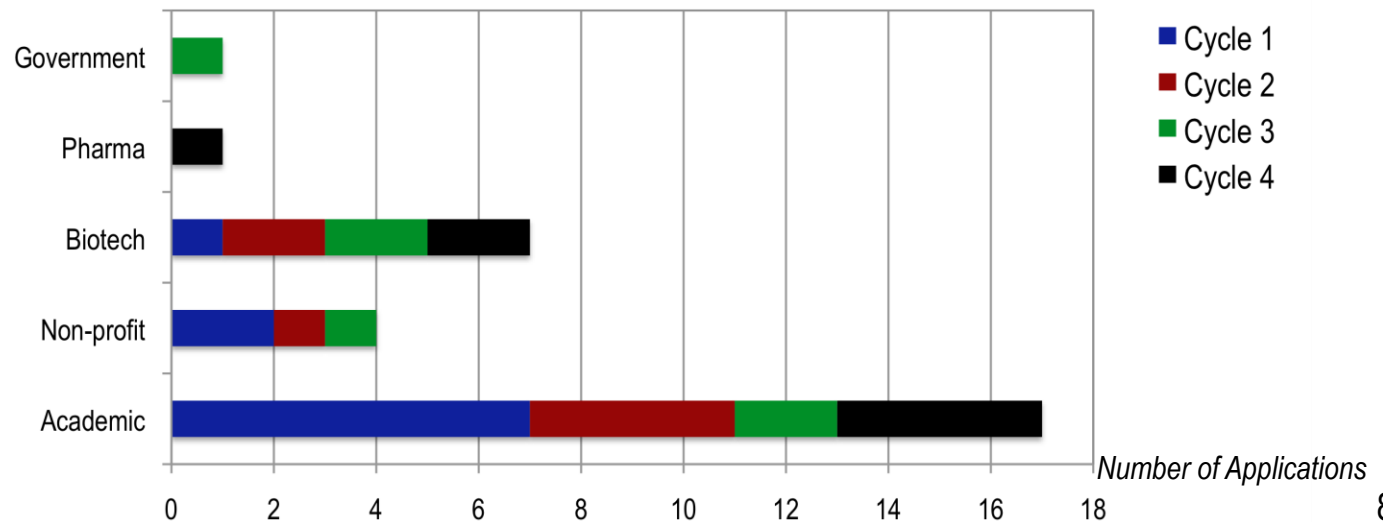


Number of Applications from Academic, Non-Profit, Biotech, Pharma or Government

All Applications (Total 193)



Top Tier (Total 30)



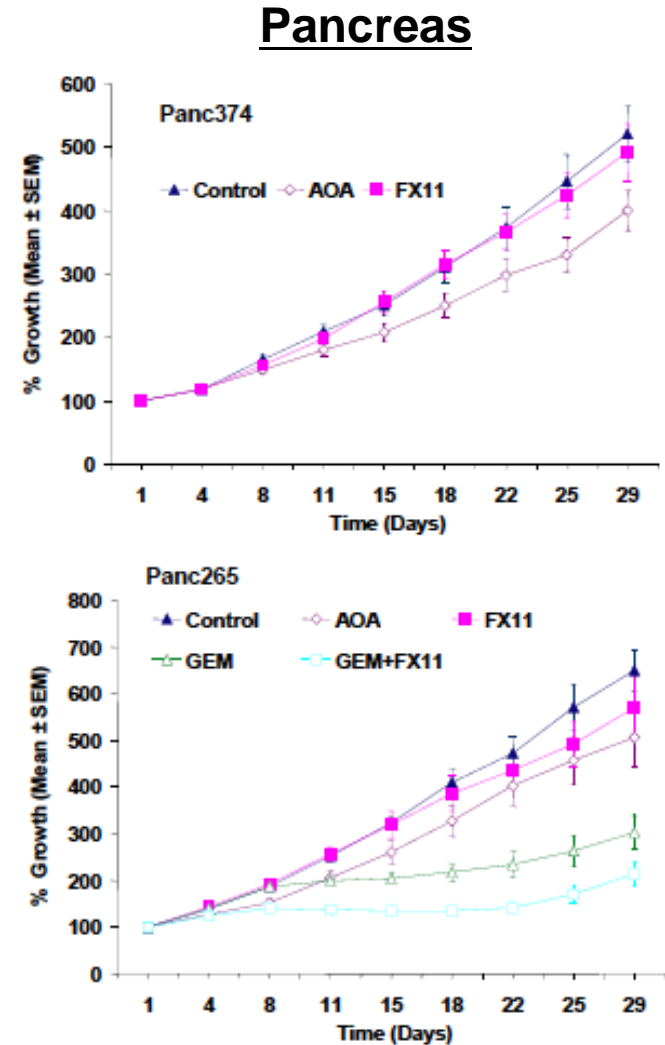
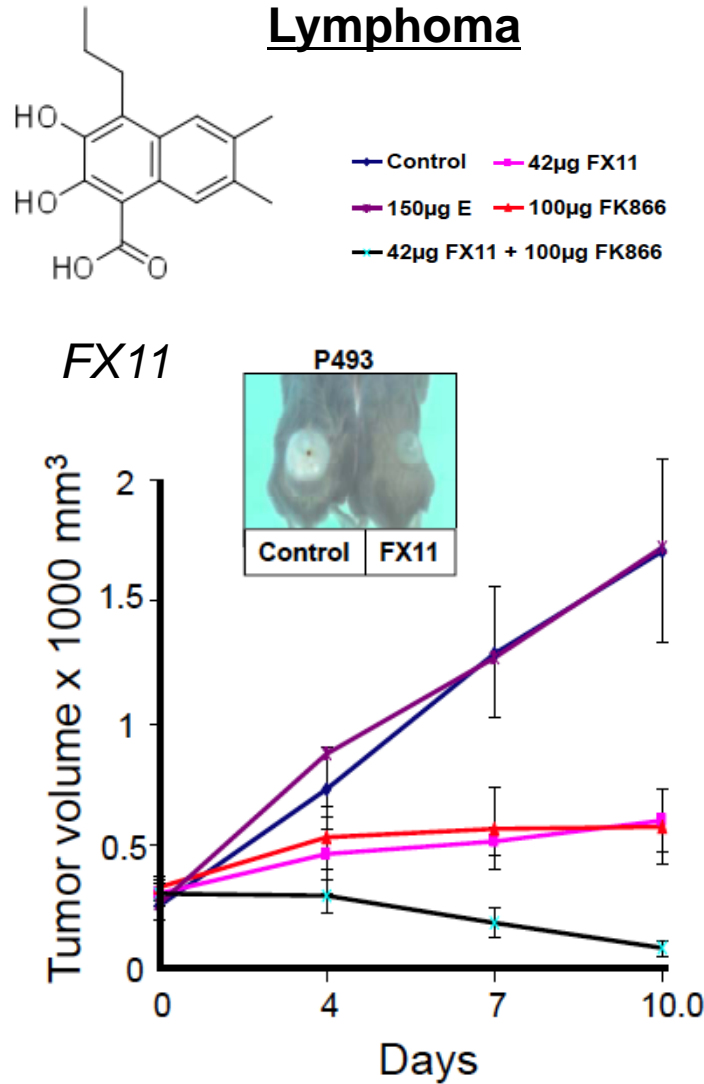
NExT Projects

- **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 + Tetrahydrouridine

LDHA: Therapeutic Target in Cancer

- 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



LDHA : Next Steps



Primary uHTS

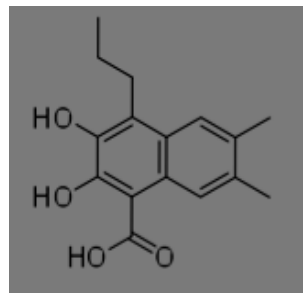
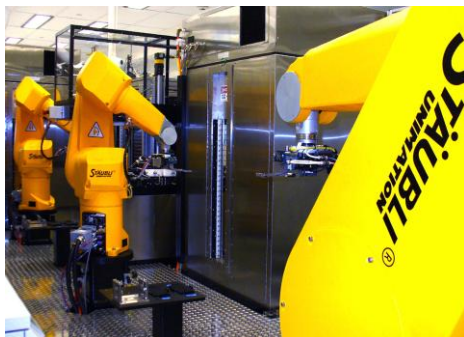


NCGC: hit validation/med chemistry

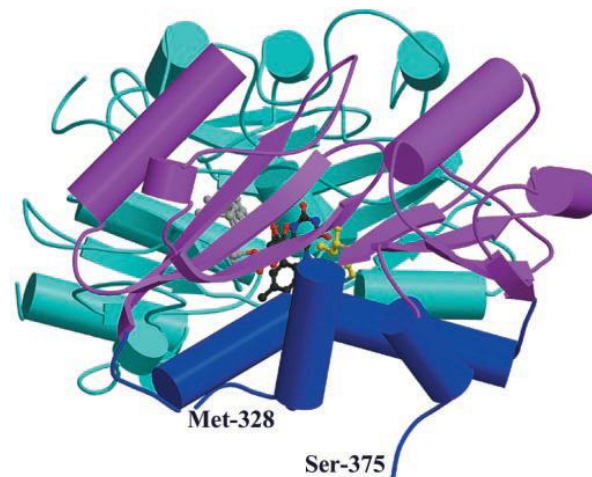
Co-crystallization with HTS "hits"

NIH Chemical Genomics Center

Secondary biochemical and cell-based screens
Dang Lab



FX11 Lead Compound
Ki 4 μ 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

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



GMP 80L fermentation of rhIL-15:

Production and pooling in Frederick of several products from multiple fermentations needed for one 1gram 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 Tetrahydrouridine (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 π ; 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

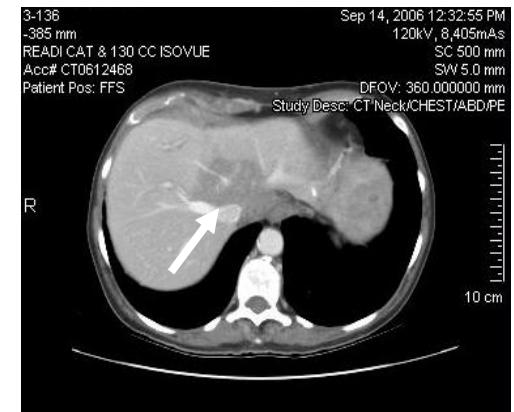
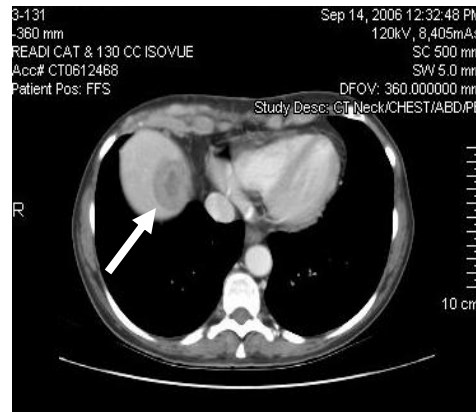
Phase I Activity of FdCyd + THU

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

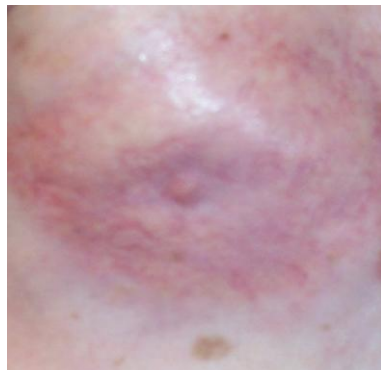
Pre-study



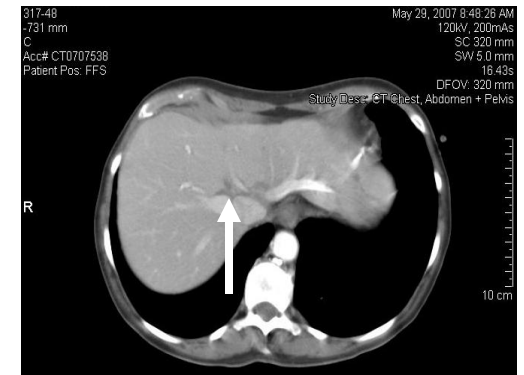
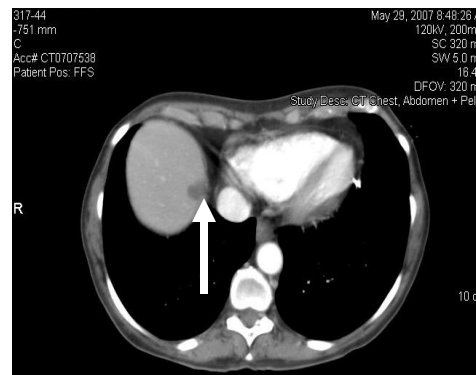
September 2006



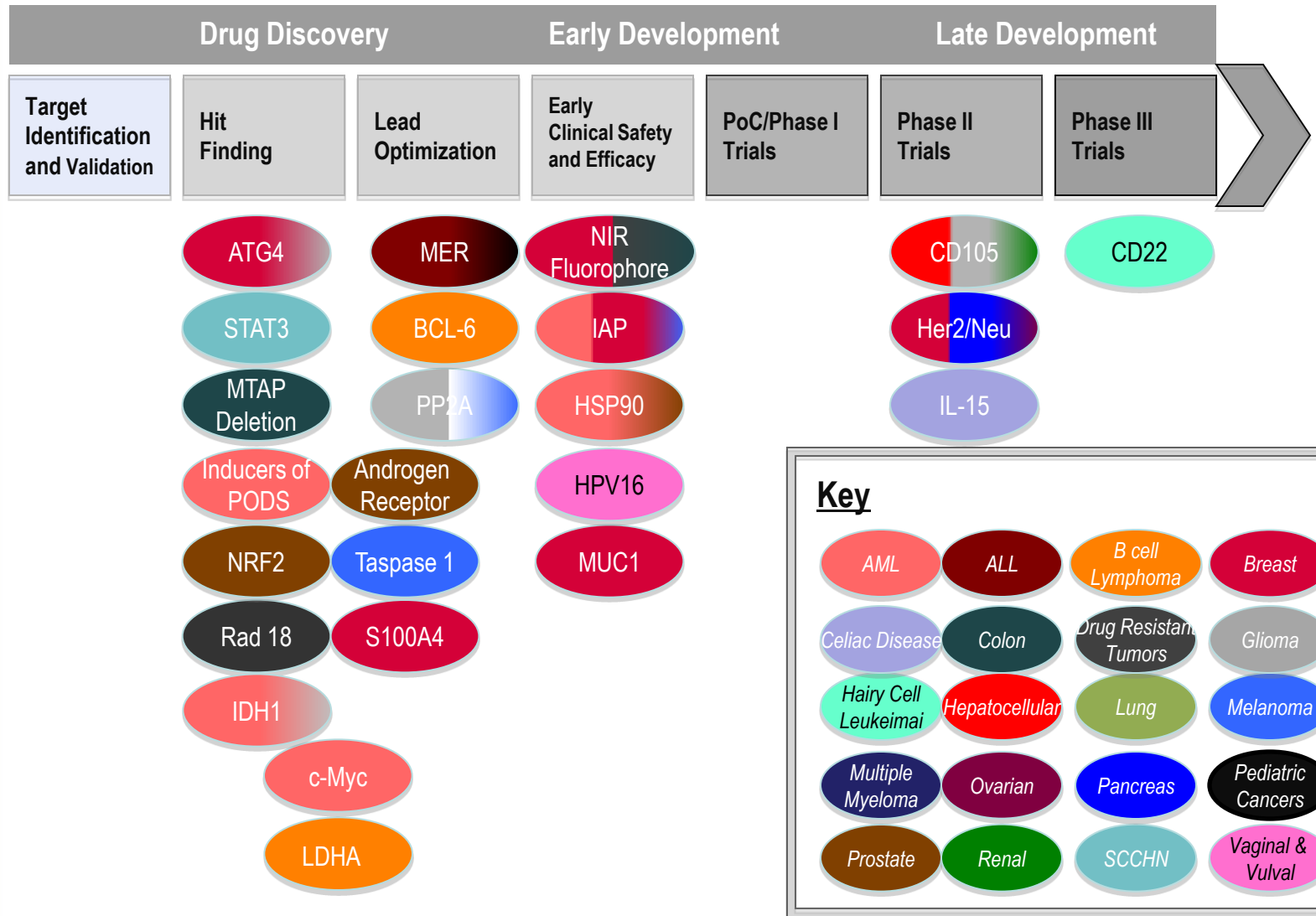
January 2007



May 2007

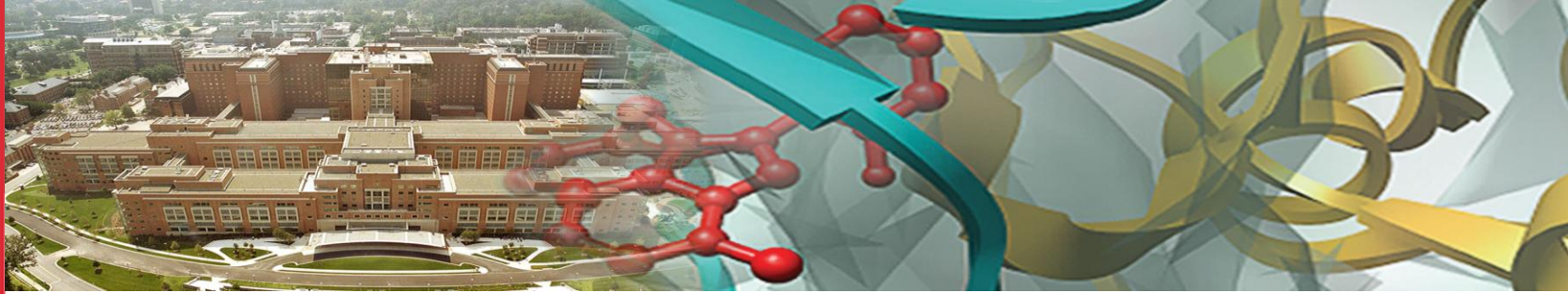


NCI Experimental Therapeutics Pipeline



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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Jason Cristofaro

Tom Stackhouse

Mike Difilippantonio

Joe Tomaszewski

Gina Hayman

Robert Wiltrout

Lee Helman

Jamie Zweibel

Intellectual Property: CBC Participants Agreement

The Consortium Agreement addresses:



Data Transfer

Data Sharing

Data Ownership

- 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.