NCI Experimental Therapeutics Program (NExT)

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Division of Cancer Treatment and Diagnosis
National Cancer Institute

Clinical Trials & Translational Research Advisory Committee
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### Anticancer Drugs Discovered & Developed by NCI from Preclinical Stage

**2009**  
Pralatrexate; Depsipeptide

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug Name and NSC Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Cetuximab (NSC 632307)</td>
</tr>
<tr>
<td>2003</td>
<td>Bortezomib (NSC 681239)</td>
</tr>
<tr>
<td>1998</td>
<td>Denileukin diftitox (NSC 697979)</td>
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</tbody>
</table>
| 1996 | Polifeprosan 20 with carmustine implant (NSC 714372)  
Topotecan (NSC 609699) |
| 1995 | All-trans retinoic acid (NSC 122758) |
| 1992 | 2-chlorodeoxyadenosine (NSC 105014)  
Paclitaxel (NSC 125973)  
Teniposide (NSC 122819) |
| 1991 | Fludarabine Phosphate (NSC 312887)  
Pentostatin (NSC 218321) |
| 1990 | Hexamethylmelamine (NSC 13875)  
Levamisole (NSC 177023) |
| 1989 | Carboplatin (NSC 241240) |
| 1988 | Ifosfamide (NSC 109724) |
| 1987 | Mitoxantrone (NSC 301739) |
| 1983 | Etoposide (NSC 141540) |
| 1982 | Streptozotocin (NSC 85998) |
| 1979 | Daunorubicin (NSC 82151) |
| 1978 | Cisplatin (cis-platinum) (NSC 119875) |
| 1977 | Carmustine (BCNU) (NSC 409962) |
| 1976 | CCNU (NSC 9037) |
| 1975 | Dacarbazine (NSC 45388) |
| 1974 | Doxorubicin (NSC 123127)  
Mitomycin C (NSC 26980) |
| 1973 | Bleomycin (NSC 125066) |
| 1970 | Flouxuridine (FUDR) (NSC 27640)  
Mithramycin (NSC 24559)  
Mitotane (o-p-DDE) (NSC 38721) |
| 1969 | Cytarabine (ARA-C) (NSC 63878)  
Procarbazine (NSC 77213) |
| 1967 | Hydroxyurea (NSC 32065) |
| 1966 | Pipobroman (NSC 25154)  
Thioguanine (NSC 752) |
| 1964 | Melphalan (NSC 8806)  
Actinomycin D (NSC 3053) |
| 1963 | Vincristine (NSC 67574) |
| 1962 | Fluorouracil (NSC 19893) |
| 1961 | Vinblastine (NSC 49842) |
| 1959 | Cyclophosphamide (NSC 26271)  
Thiotepa (NSC 6396) |
| 1957 | Chlorambucil (NSC 3088) |
T1D RAID

NIH

NIDDK

DCTD-CCR JDC

NIH RAID Pilot

DDG

DCTD

NIH

CCI

DCB

DCCPS

DCP

DCEG

CTEP

CIP

CDP

RRP

DTP

BTB

BRB (BDP)

DSCB

PRB

NPB

TPB

STB

ITB/GCOB

NCDDG

Efficiency sub-optimal
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
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
The Chemical Biological Consortium: A New NCI Initiative

- Burnham Institute
- Southern Research
- SRI International
- Vanderbilt
- Emory
- UCSF
- Univ. North Carolina
- Pittsburgh
- Univ. of Minnesota
- Georgetown
- NCI Intramural Chemical Biology
- NIH Chemical Genomics Center
- Affiliate Investigators
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
Chemical Biology Consortium: Enabling Hit-to-Lead Discovery

**Integrated Program vs. Service-Driven Program**

**Program Focus:** Cross-site “targeteers”, screeners and medicinal chemists working on high-priority targets in a team setting.
Multiple Entry Points into the NExT

1. **Novel Cellular Target**
   - Assay Development and qHTS

2. **HTS-ready Assay**
   - Optimization and qHTS

3. **Ligand or Target Structural Information**
   - Virtual Screening or Fragment Based Lead Discovery

4. **Weak Lead Compound**
   - Full Medicinal Chemistry Entry

5. **Lead Modification**
   - Focused Analog Synthesis

6. **Lead Re-Indication**
   - Large Scale Synthesis

**Target Identification**
- Primary HTS
- 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
• Exploratory development of HTS
• Screening and iterative medicinal chemistry
• Chemical synthesis of small molecules, oligonucleotides, 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/PD/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
• Production of clinical dosage forms
• Stability testing of clinical dosage forms
• Regulatory support and early phase trials
Therapeutics Discovery & Development Support
Provided by NCI (NExT)

• Exploratory development of HTS
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Agents for development

- $^{18}$F-d-cytidine
- $^{13}$N-gemcitabine
- $^{11}$C-SN-38
- $^{11}$C-AMT
- $^{18}$F-paclitaxel
- $^{18}$F-DCFBC
- $^{18}$F Her2 Affibody
- $^{18}$F-FES
- $^{11}$C-acetate
- $^{18}$F-FLT
- $^{18}$F-MISO
- $^{18}$F-Galacto-RGD
- $^{111}$In-Herscan
- Gd-chelated albumin

Synthesis and GMP Scale up (including radiolabeling)

Pre-clinical development (pharmacology and toxicology)
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](https://dctd.cancer.gov/nextapp) or [https://dctd.cancer.gov/nextregistration](https://dctd.cancer.gov/nextregistration)
Cycle 1: Total of 52 NExT proposals for cycle 1 received

<table>
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<tr>
<th>NTS</th>
<th>ESD</th>
<th>SDS</th>
<th>LD</th>
<th>CS</th>
<th>CAN</th>
<th>P0</th>
<th>PI</th>
<th>PII</th>
<th>PIII</th>
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<td>13</td>
<td>3</td>
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<td>6</td>
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**Discovery Definitions:**
- NTS = New Target Substrate
- ESD = Exploratory Screen Development
- SDS = Screening/Designed Synthesis
- LD = Lead Development
- CS = Candidate Seeking

**Development Definitions:**
- CAN = Clinical Candidate
- P0 = Phase 0
- PI = Phase I
- PII = Phase II
- PIII = Phase III
Anticipate ~20-30 projects in the 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
• 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
Success: What Will it Look Like?

Transparent, Accountable, Inclusive, & Unified
https://dctd.cancer.gov/nextregistration

NExT/CBC Implementation Team

Jeff Abrams      Sanjay Malhotra
Heba Barazi     Barbara Mroczkowski
Michelle Bennett Ralph Parchment
Jerry Collins    David Segal
James Crowell    Shizuko Sei
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Mike Difilippantonio Joe Tomaszewski
Gina Hayman      Robert Wiltrout
Lee Helman       Jamie Zweibel