NIH Drug Discovery and Development
NCTT and CTSAs

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NIH CENTER FOR TRANSLATIONAL THERAPEUTICS
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NIH Institutes and Centers
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NIH Institutes and Centers

NIH CENTER FOR ADVANCING TRANSLATIONAL SCIENCES
NATIONAL INSTITUTES OF HEALTH

FY 2010 Distribution

Research Project Grants: 53.0%

Intramural Research: 10.0%

R&D Contracts: 11.0%

Research Centers: 10.0%

Career Dev.: 2.5%

Other Research: 3.5%

Research Mgmt & Support: 5.0%

Training: 3.0%

All Other: 2.0%

Research Training: 3.0%

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Research Centers: 10.0%

R&D Contracts: 11.0%

Research Mgmt & Support: 5.0%

Training: 3.0%

All Other: 2.0%
Mission Statement
The mission of the National Institutes of Health Center for Translational Therapeutics (NCTT) is to translate fundamental research into patient treatments by establishing creative partnerships and developing innovative approaches to advance the science of drug discovery.

Vision Statement
Our vision is to be a pioneer in drug discovery research, developing new paradigms to transform the drug development process and exploring treatments to improve the lives of every person suffering from illness or disease.
NIH Center for Translational Therapeutics

Only a small % of genome-encoded targets and diseases are being addressed for drug development

Current drug targets:
Well understood proteins

Current targeted diseases:
Prevalent diseases that affect developed world

Human Genome
20,000 genes

Human Diseases
7000 diseases
~7,000 diseases affect humankind – but only a small fraction support commercial development of therapeutic agents

Two types of neglected diseases:

- Low prevalence, i.e., “rare” (<200,000 prevalence in U.S.)
  - There are >6000 rare (orphan) diseases
  - Cumulative prevalence in U.S. ~ 25 – 30 million
  - Most are single gene diseases
  - <200 have any pharmacotherapy available

- High prevalence but “neglected”
  - Occur chiefly among impoverished and marginalized populations in developing nations (treatment costs prohibitive)
  - Most are infectious
Therapeutic Development Pipeline

**Exploration**
- Target Identification and validation
- Assay development
- HTS Hit-to-Probe

**Discovery**
- Target
- Assay development
- HTS
- Hit-to-Probe

**Development**
- IND Enabling Studies and CMC
- Clinical Trials
- IND filing

**Clinical Trials**
- Ph I (Safety)
- Ph II (Dose finding, initial efficacy in patient pop.)
- Ph III (Efficacy and safety in large populations)

**Clinical Translation Assessments**
- Drug Target and Drug MOA Validation, Biology Efficacy, Off-Target Safety Testing in Animal Models

**Regulatory Planning**
- Probe ↓ Lead ↓ Candidate
- PK/PD Formulation Scale-up
- Toxicology, Safety, Pharm, GMP Manufacture, Process Chemistry
The Cost and “Success” of Therapeutic Development

50,000 - 5,000,000 compounds are often screened to find a single drug

>1,000 “hits”

12 “leads”

9 drug candidates

Discovery & Preclinical trials

Clinical trials: Phase I, Phase II, Phase III

12 to 24 years

$800 to $1.5M million
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What our Collaborators Bring to the Table

Gene or Protein in the disease pathway

- Validated target
- Target assay
- Lead compound
- Preclinical development candidate
- Clinical development candidate

Target Validation

Assay Dev and HTS

Probe/Lead Development

Lead Optimization

Preclinical Development

Clinical Trials

FDA approval and Drug to Patients

Licensing Partners for Therapeutic Registration Studies and Commercialization

What NCTT Brings to the Table

- RNAi
- Probe Dev (MLP, CBC)
- Assay Development
- TRND
- BrIDGs-RAID
- Clinical
- TRND-FDA Collaboration
- TOX21 Systems Toxicology Program
- Repurposing
- Paradigm/Technology Development
- Human Proof of Concept
- Approved Drug

Deliverables
The NIH Center for Translational Therapeutics (NCTT) is an *Intramural research laboratory* within the NIH with a unique business model. We conduct research, bring scientific enhancements, and incorporate value to high risk - high reward *Extramural drug development projects* across the therapeutic pipeline. Our research projects are all defined by collaborations and partnerships with investigators and organizations outside our research lab.
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How We Started

NCGC and the NIH Molecular Libraries Program

- Disease Biology
- Target Validation
- Assay Development and HTS
- Target Assay
- Probe/Lead Development
- Lead Optimization
- Preclinical Development
- Clinical Trials
- FDA approval and Drug to Patients

Deliverables

Probe Dev (MLP, CBC)

HTS Assays Probes
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How we started

- Founded as part of NIH Roadmap
- 85 scientists
- > 200 collaborations with investigators worldwide
  - 75% NIH extramural
  - 15% Foundations, Research Consortia, Pharma/Biotech
  - 10% NIH intramural
- Focus on novel targets, rare/neglected diseases
- Has Produced
  - chemical probes/leads
  - new paradigms for assay development, screening, informatics, chemistry
- Assay Development
  - High Throughput Assays
- High throughput Screening for Small Molecules
- Medicinal Chemistry
  - Hits to Probes
  - Probes to Leads
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Successes of our Probe Development

- 450 assays spanning >1,500 individual protocols
- 70 million dose response curves generated
- 350 million % activities
- Throughput at 45 screens per year
- Compound library at ~425,000 plated in qHTS format
- Over 35 hit-to-lead chemistry campaigns initiated
- 13 agents advanced to in vivo analysis
- 70+ publications on small molecule probes and assay technologies
- 15+ patents applications
- 4+ technology licenses granted
Chemical Genomic Profiling for Antimalarial Therapies, Response Signatures, and Molecular Targets

Jing Yuan, Ken Chih-Chien Cheng, Ronald L. Johnson, Ruili Huang, Sittiporn Pattaradilokrat, Anna Liu, Rajarshi Guha, David A. Fidock, James Inglese, Thomas E. Wellems, Christopher P. Austin, Xin-zhuan Su

Science 5 August 2011: Vol. 333 no. 6043 pp. 724-729
DOI: 10.1126/science.1205216
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Disease Areas

- Ataxia-telangiectasia
- Beta-thalassemia
- Charcot-Marie-Tooth
- Chordoma
- Chronic lymphocytic leukemia
- Gaucher disease
- Huntington’s disease
- Leishmaniasis
- Lymphangioleiomyomatosis
- Malaria
- Myotonic dystrophy
- Niemann-Pick C
- Progeria
- Retinitis pigmentosa
- Schistosomiasis
- Spinal muscular atrophy
- Trypanosomiasis
Objective
The purpose of this FOA is to promote and support discovery and development of new chemical probes as research tools for use by the research community to advance the understanding of biological functions and disease mechanisms. The MLPCN offers biomedical researchers access to large-scale automated screening centers, diverse compound libraries, medicinal chemistry resource, and information on biological activities of small molecules.
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As we Grew

Technology Development, TOX21, & HTP RNAi Screening

Gene or Protein in the disease pathway

Validated target

Target assay

FDA approval and Drug to Patients

RNAi

Probe Dev (MLP, CBC)

Assay Development

TOX21 Systems Toxicology Program

Paradigm/Technology Development

Deliverables

Validated Targets

HTS Assays

Probes

Novel Technologies
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As we Grew

- Technology Development
  - Assay
  - Screening
  - Chemistry
  - Bioinformatics
- Systems Toxicology
- Genomic Toxicology
- High Throughput RNAi Screening
## NIH Center for Translational Therapeutics

### NCTT Pharmaceutical Collection

<table>
<thead>
<tr>
<th>Drug Source</th>
<th>Current</th>
<th>Remaining</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>US FDA</td>
<td>1635</td>
<td>187</td>
<td>1822</td>
</tr>
<tr>
<td>UK/EU/Canada/Japan</td>
<td>756</td>
<td>174</td>
<td>930</td>
</tr>
<tr>
<td>Total Approved</td>
<td>2391</td>
<td>361</td>
<td>2752</td>
</tr>
<tr>
<td>INN</td>
<td>928</td>
<td>3932</td>
<td>4860</td>
</tr>
<tr>
<td>Total</td>
<td>3319</td>
<td>4293</td>
<td>7612</td>
</tr>
</tbody>
</table>

**Informatics sources for NPC**
- US FDA: Orange Book, OTC, NDC, Green Book, Drugs@FDA
- Britain NHS
- EMEA
- Health Canada
- Japan NHI
- WHO ATC

**Physical sources for NPC**
- Procurement from >20 suppliers worldwide
- Synthesis

*Drug plate composition*
The NCGC Pharmaceutical Collection

Introduction

The NCGC Pharmaceutical Collection (NPC) is a comprehensive, publically-accessible collection of approved and investigational drugs for high-throughput screening that provides a valuable resource for both validating new models of disease and better understanding the molecular basis of disease pathology and intervention. The NPC has already generated several useful probes for studying a diverse cross section of biology, including novel targets and pathways. NCGC provides access to its set of approved drugs and bioactives through the Therapeutics for Rare and Neglected Diseases (TRND) program and as part of the compound collection for the Tox21 initiative, a collaborative effort for toxicity screening among several government agencies including the US Environmental Protection Agency (EPA), the National Toxicology Program (NTP), the US Food and Drugs Administration (FDA), and the NCGC. Of the nearly 2750 small molecular entities that have been approved for clinical use by US (FDA), EU (EMEA), Japanese (NHI), and Canadian (HC) authorities and that are amenable to HTS screening, we currently possess 2400 as part of our screening collection. Obtaining an authoritative listing of approved drugs was surprisingly difficult. Once obtained, the list was reduced to a non-redundant set of HTS-compatible molecular entities for sourcing. The current collection was sourced from a combination of traditional chemical suppliers, specialty collections, pharmacies and custom synthesis. All data generated through this effort will be deposited without restriction into PubChem, including the full concentration-response profile of each compound in each assay. Detailed information on the sourcing of this collection including regulatory status, supplier information, compound structures, target information and indication will be made available as time permits. As we complete this initial phase of building a definitive set of pharmaceutical compounds, we plan to expand the collection to include other compounds which target novel diseases, pathways, and classes of proteins in addition to active metabolites of known drugs.

Software

To provide electronic access to the NPC content, we have built a dedicated browser with searching and exporting capabilities. The NPC browser is currently still early in its development cycle. We plan to make regular updates to the browser as we continue to improve on the features and content. Below is a quick preview of the NPC browser.
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Latest Addition – TRND, NIH RAID, & FDA Collaborations

What our Collaborators Bring to the Table

Gene or Protein in the disease pathway

Validated target

Target assay

Lead compound

Preclinical development candidate

Clinical development candidate

Successful Licensing Partners for Therapeutic Registration Studies and Commercialization

Translational Therapeutic Pipeline

Disease Biology

Target Validation

Assay Dev and HTS

Probe/Lead Development

Lead Optimization

Preclinical Development

Clinical Trials

RNAi

Probe Dev (MLP, CBC)

TRND

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What NCTT Brings to the Table

TOX21 Systems Toxicology Program

Repurposing

Repurposing

Paradigm/Technology Development

Deliverables

Validated Targets

HTS Assays

Probes

Lead Series

Clinical Drug Candidates

Human Proof of Concept

Approved Drug
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Latest Addition – TRND & NIH RAID

- Good potency
- Consistent Structure-Activity Relationship (SAR)
- Selectivity
- Active on human and animal model targets
- Efficacy in animal/cellular model of disease, +/- biomarker
- Low plasma protein binding
- Metabolic stability
- Bioavailable in multiple species
- Good pharmacokinetics

- Acceptable liver CYP inhibition
- No hERG activity
- No gross toxicities in animal models (safety pharmacology)
- No short term toxicity in 2 species (one rodent, one non-rodent)
- Ames, 2 yr carcinogenicity negative
- Blood-brain barrier penetration, if applicable
- Chemistry scale-up and formulation adequate, with acceptable cost of goods at anticipated dose
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Scheduled Maintenance:
The proposalCENTRAL website will be offline for approximately thirty minutes starting at 6:00 AM Eastern time on Thursday, October 28th for routine maintenance and upgrades. We apologize for any inconvenience this brief interruption may cause.

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NIH - Therapeutics for Rare and Neglected Diseases

NIH - Therapeutics for Rare and Neglected Diseases – NIH - Therapeutics for Rare and Neglected Diseases

NIH - Therapeutics for Rare and Neglected Diseases

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TRND Program Evaluation Criteria

• Target and therapeutic validation (30%)
• Strength of current data package (30%)
• Feasibility to reach First in Human (20%)
• Medical impact relative to current Standard of Care (10%)
• Likelihood of external adoption (10%)
### NIH CENTER FOR TRANSLATIONAL THERAPEUTICS

#### TRND Collaborations

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type</th>
<th>Pathology</th>
<th>Collaborators</th>
<th>Compound type</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schistosomiasis, Hookworm</td>
<td>Neglected</td>
<td>Infectious parasite</td>
<td>Extramural</td>
<td>NME</td>
<td>Lead optimization</td>
</tr>
<tr>
<td>Niemann Pick C</td>
<td>Rare</td>
<td>CNS, liver/spleen</td>
<td>Disease Fnd, Extramural, Intramural</td>
<td>Repurposed approved drug</td>
<td>Preclinical Development</td>
</tr>
<tr>
<td>Hereditary Inclusion Body Myopathy</td>
<td>Rare</td>
<td>Muscle</td>
<td>Biotech, Intramural</td>
<td>Intermediate replacement</td>
<td>IND-enabling studies</td>
</tr>
<tr>
<td>Sickle Cell Disease</td>
<td>Rare</td>
<td>Blood</td>
<td>Intramural, Biotech</td>
<td>NME</td>
<td>IND-enabling studies &amp; clinical trials design</td>
</tr>
<tr>
<td>Chronic Lymphocytic Leukemia</td>
<td>Rare</td>
<td>Cancer</td>
<td>Disease Fnd, Extramural</td>
<td>Repurposed approved drug</td>
<td>Pre-IND</td>
</tr>
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</table>

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<table>
<thead>
<tr>
<th>Title</th>
<th>TA</th>
<th>Partner</th>
<th>Modality</th>
<th>Dis Type</th>
<th>Dev Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of VBP15 for Treatment of Duchenne Muscular Dystrophy</td>
<td>Muscular</td>
<td>Foundation-Backed Small Business</td>
<td>NME</td>
<td>R</td>
<td>Discovery</td>
</tr>
<tr>
<td>PAK inhibitors as disease modifying treatments for Fragile X Syndrome</td>
<td>CNS</td>
<td>Small Business</td>
<td>NME</td>
<td>R</td>
<td>Preclinical Dev</td>
</tr>
<tr>
<td>Pre-Clinical and Early Clinical Development of the Novel Antifungal VT-1129</td>
<td>Infectious Diseases</td>
<td>Small Business</td>
<td>NME</td>
<td>N</td>
<td>Preclinical Dev</td>
</tr>
<tr>
<td>A novel compound for targeted treatment of CBF leukemia</td>
<td>Cancer</td>
<td>Government</td>
<td>Re-purposing</td>
<td>R</td>
<td>Discovery</td>
</tr>
</tbody>
</table>
NCTT Projects Search Results (9 Found)

**Project Title:** A novel compound for targeted treatment of CBF leukemia

**Keywords:** Acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), chromosome translocations

**Abstract:** In this proposal, we intend to develop targeted treatments for a subgroup of leukemia based on our understanding of how the leukemia develops at the molecular level. Leukemia is a cancer of the bone marrow involving the developing white blood cells. Approximately 12,330 new cases of acute myeloid leukemia (AML) and 5,700 new cases of acute lymphoid leukemia (ALL) will be diagnosed in the U.S. in 2010 (according to the Leukemia and Lymphoma Society). Leukemia is often associated with specific, recurrent chromosome translocations and inversions that generate fusion genes, which play critical roles in leukemogenesis. The CBF subgroup of leukemia contains CBF fusion genes which have been shown to play critical roles in leukemia development. Current treatments for CBF leukemia are not optimal with long-term survival at 50%. We conducted a small chemical library screen to find inhibitors that block CBF protein interactions. Through biochemistry, cell culture, and animal model studies, we have identified three chemically related lead compounds. In particular, one of the three compounds has shown leukemia reduction capability similar to standard chemotherapy drugs in preliminary studies in a mouse CBF leukemia model. We propose to complete our efficacy studies in this mouse model, develop 1 or more back-up compounds, optimize formulation and perform preclinical trials which will lead to clinical trials.

**Project Title:** Aes-103 as a treatment for Sickle Cell Disease

**Keywords:** Sickle Cell Disease; SCD; Hemoglobin; Sickle; S-Hb; S-hemoglobin/2-carboxyglycine

**Abstract:** Sickle cell disease (SCD) is a recessive, genetic (i.e., inherited) blood disorder affecting red blood cells. Red blood cells contain hemoglobin, a protein that helps the cells carry oxygen through the body. Patients with SCD have an abnormal form of hemoglobin that causes the red blood cells to take on a rigid, sickle shape. These rigid cells can block small blood vessels, decreasing blood flow. This can result in significant and permanent damage to tissus, and can be fatal. SCD presents in childhood and affects millions of people worldwide. In the United States, SCD affects 70,000-80,000 Americans and 1 in 500 African-American births.

Although SCD was first described in the medical literature 100 years ago (James Herrick, 1910), there has never been a drug developed specifically for the treatment of SCD. A number of agents have been studied, but the only drug approved for use in treating SCD patients is the anti-cancer agent hydroxyurea. Hydroxyurea is currently approved for use only in adults, and not for children.
• Collaborators IP constitutes background IP for TRND projects
• Inventorship of new IP created in TRND collaborations will be determined according to patent law
• Potential of multi-party IP to be developed depending on when projects enter into TRND collaboration
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RNAi
- Probe Dev (MLP, CBC)
- Assay Development

Licensing Partners for Therapeutic Registration Studies and Commercialization
- FDA approval and Drug to Patients

Translational Therapeutic Pipeline

Deliverables
- Validated Targets
- HTS Assays
- Probes
- Lead Series
- Clinical Drug Candidates
- Human Proof of Concept
- Approved Drug
Chemistry
Biology
Informatics
Automation
Compound Management
Program Management
Technology Transfer
Clinical Sciences
Regulatory Sciences
Collaborative
Patient Need
“Neglected” Disease
Dedication
To catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.
Components of Molecular Libraries Program
Therapeutics for Rare and Neglected Diseases
Office of Rare Diseases Research
Rapid Access to Interventional Development
Clinical and Translational Science Awards
FDA-NIH Regulatory Science
Cures Acceleration Network
Partnership between:
NCTT and CTSA
Intramural and Extramural
Areas of Synergy:

• Public Private Partnerships
• Training Opportunities
• Collaboration on Specific Development Projects
T1 Translation: Vignettes from the CTSAs
The mission of the National Institutes of Health Center for Translational Therapeutics (NCTT) is to translate fundamental research into patient treatments by establishing creative partnerships and developing innovative approaches to advance the science of drug discovery.

**Translational Therapeutics Pipeline**

- Disease Biology
- Target Validation
- Assay Development
- Probe/Lead Development
- Lead Optimization
- Preclinical Development
- Clinical Trials
- FDA approval
- FDA
- Approved Drug
- Clinical Drug Candidates
- Human Proof of Concept
- Lead Series
- HTS Assays
- Validated Targets

**View the full illustration**

**NCTT Operational Model**

The NIH Center for Translational Therapeutics (NCTT) is an intramural research laboratory within the NIH with a unique business model. We conduct research, bring scientific enhancements, and incorporate value to high-risk, high-reward extramural drug development projects across the therapeutic pipeline. Our research projects are all defined by collaborations and partnerships with investigators and organizations outside our research lab.

**Welcome to NCTT**

Scientific Director, Dr. Christopher Austin gives a brief introduction to the NCTT research mission and how researchers can collaborate with the center on drug development projects.

**How Do I?**

NCTT wants to collaborate with you. To find out how, here are just some of our Frequently Asked Questions About NCTT: