

Translational Therapeutics Discovery for Rare Diseases at NIH



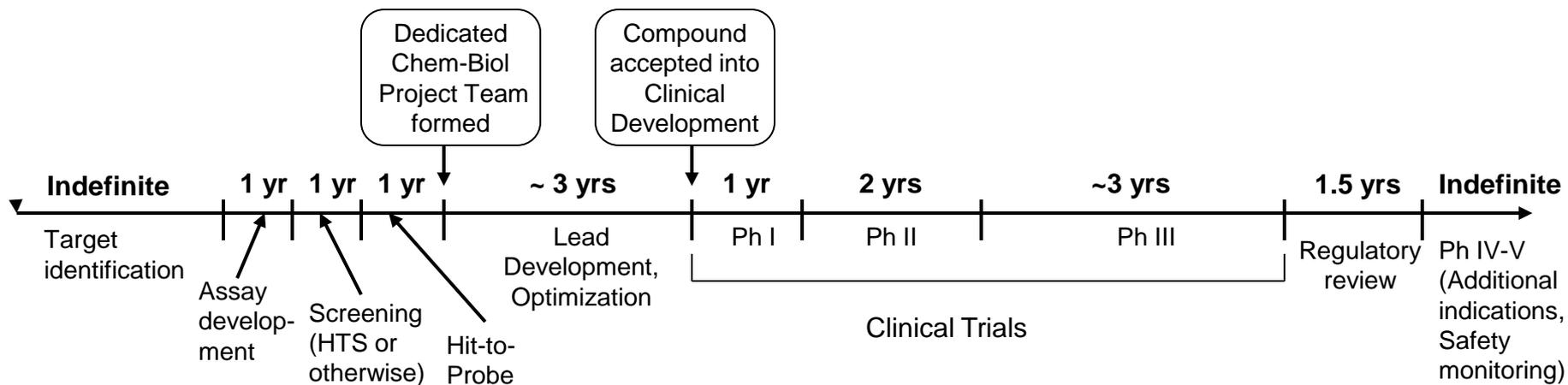
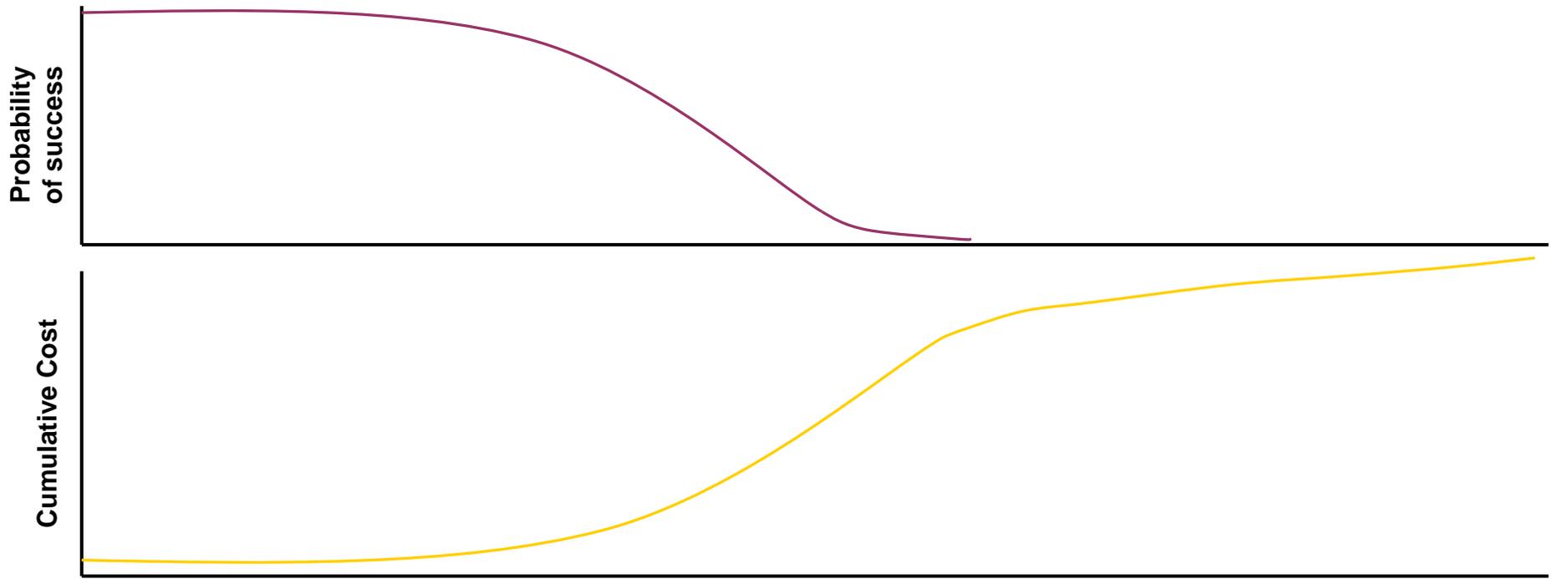
Christopher P. Austin, M.D.
Director, NIH Chemical Genomics Center
Therapeutics for Rare and Neglected Diseases Program
NIH Center for Translational Therapeutics
National Institutes of Health



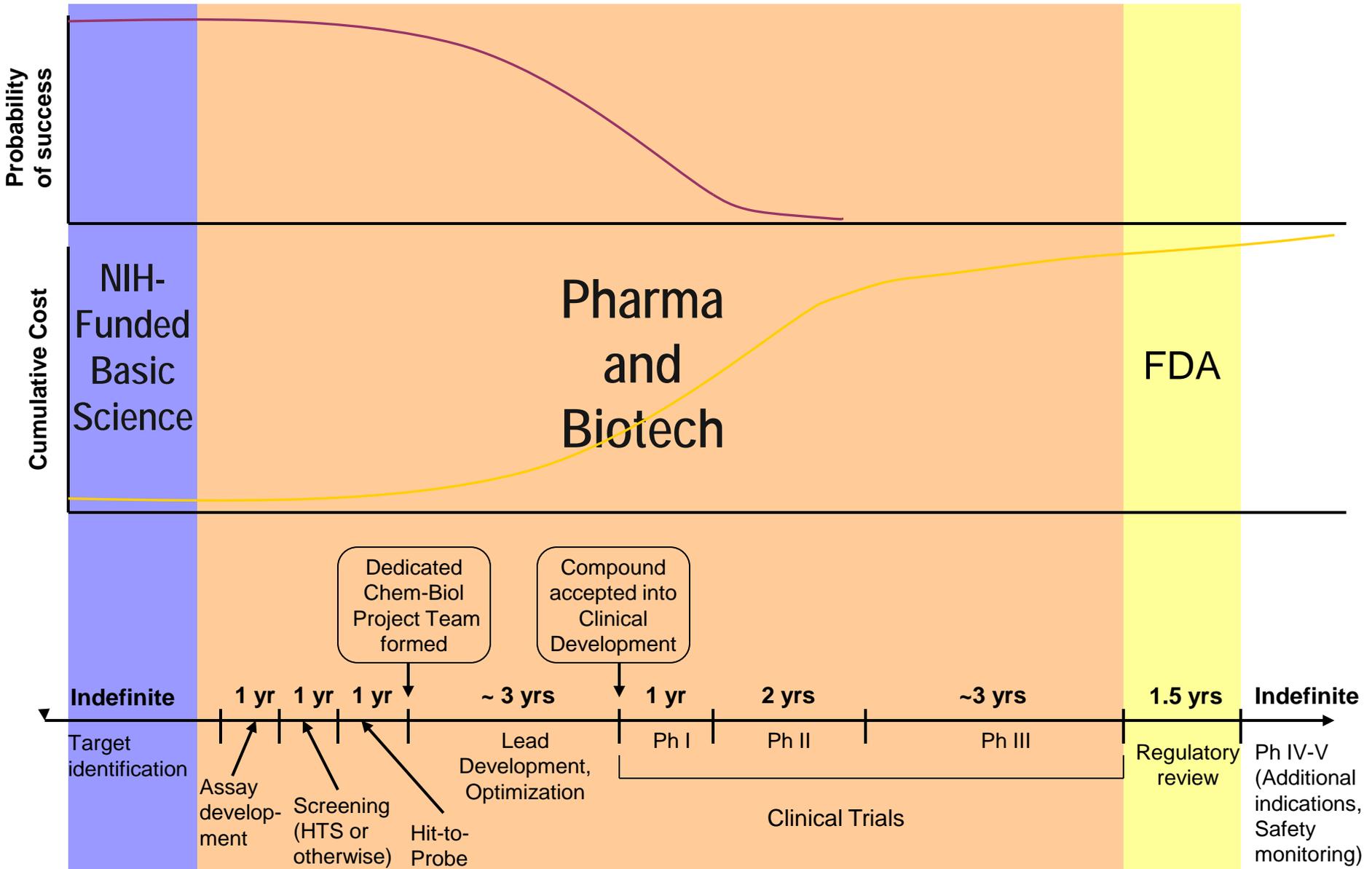
Accelerating Therapies for Rare Diseases Workshop
October 19, 2010



Economics and risks of drug development



Conventional roles of public and private sectors in drug development





Home Page



Molecular Libraries and Imaging

- Overview
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Molecular Libraries and Imaging

OVERVIEW

Small molecules, often with molecular weights of 500 or below, have proven to be extremely important to researchers to explore function at the molecular, cellular, and in vivo level. Such molecules have also been proven to be valuable for treating diseases, and most medicines marketed today are from this class.

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Genome Technology

Jan/Feb 2005

Inside Integrated Biology

SMALL MOLECULES GO PUBLIC



INSIDE: COMPARATIVE GENOMICS
PROTEIN FRACTIONATION

NIH'S NEW CHEMICAL GENOMICS INITIATIVE SENDS RESEARCH DOWNSTREAM. HERE'S WHY

PLUS: WHO WILL BENEFIT? ACADEMICS AND PHARMA RESEARCHERS WEIGH IN

NIH's Chris Austin, Linda Brady, and James Ingleson

“...To empower the research community to use small molecule compounds in their research, whether as tools to perturb genes and pathways, or as starting points to the development of new therapeutics for human disease.”

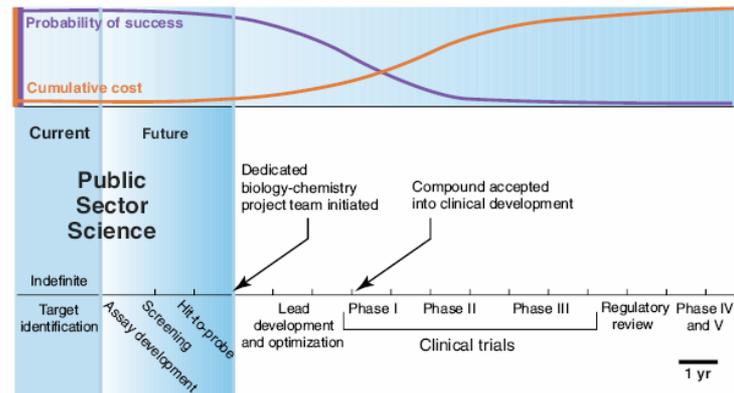
POLICY FORUM

MOLECULAR BIOLOGY

NIH Molecular Libraries Initiative

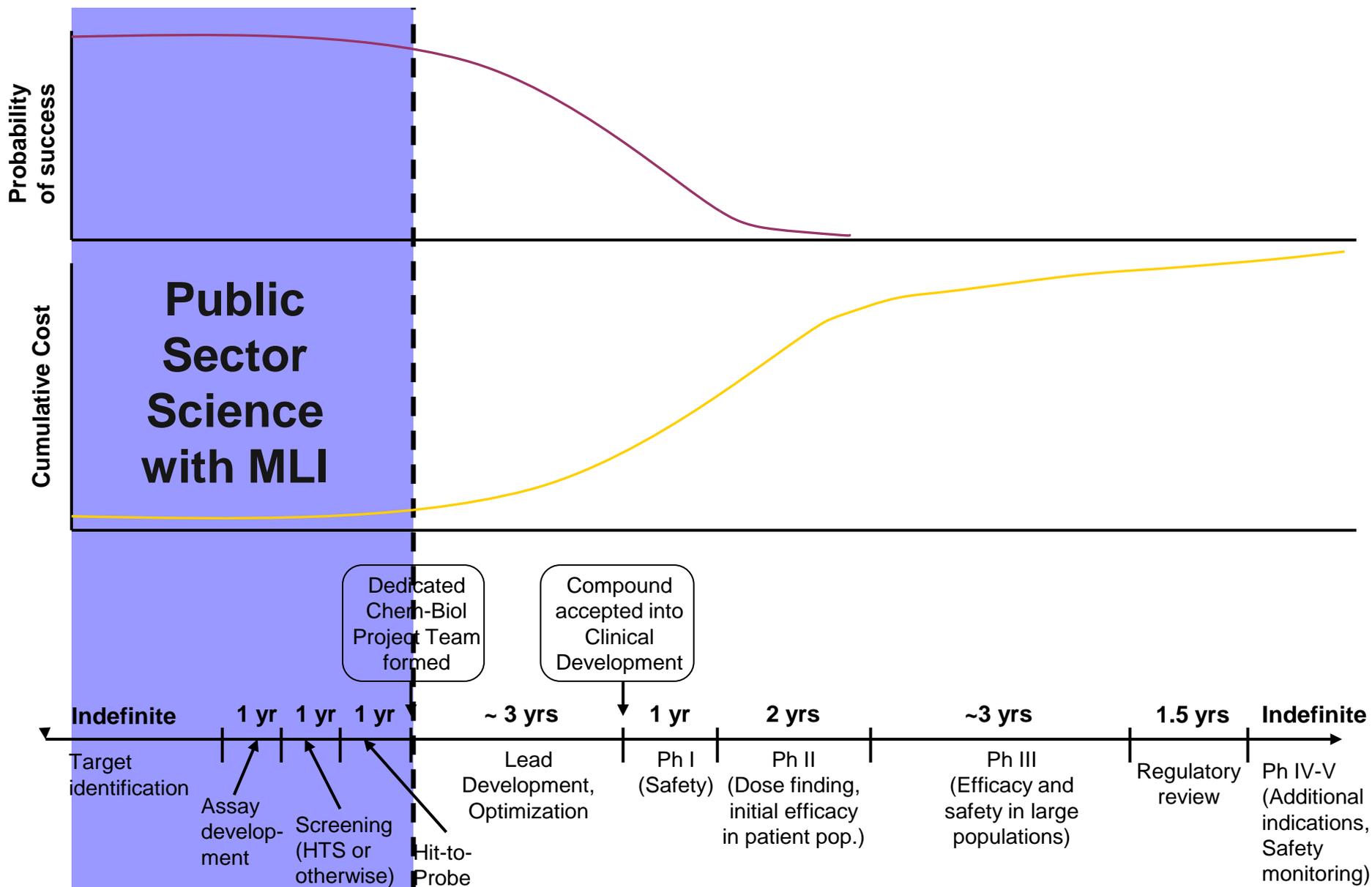
Christopher P. Austin,^{1*} Linda S. Brady,² Thomas R. Insel,² and Francis S. Collins¹

12 NOVEMBER 2004 VOL 306 SCIENCE www.sciencemag.org



Interface of the MLI and drug development.

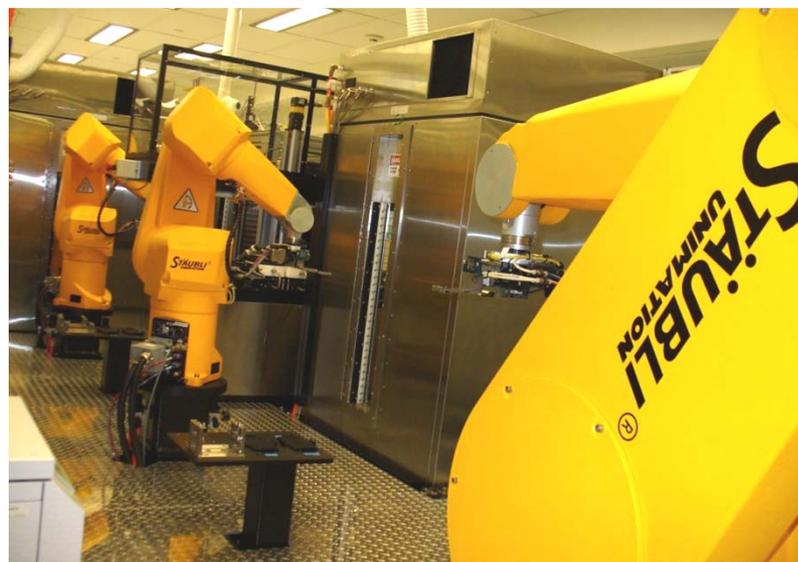
Molecular Libraries program takes first steps in drug development



NIH Chemical Genomics Center



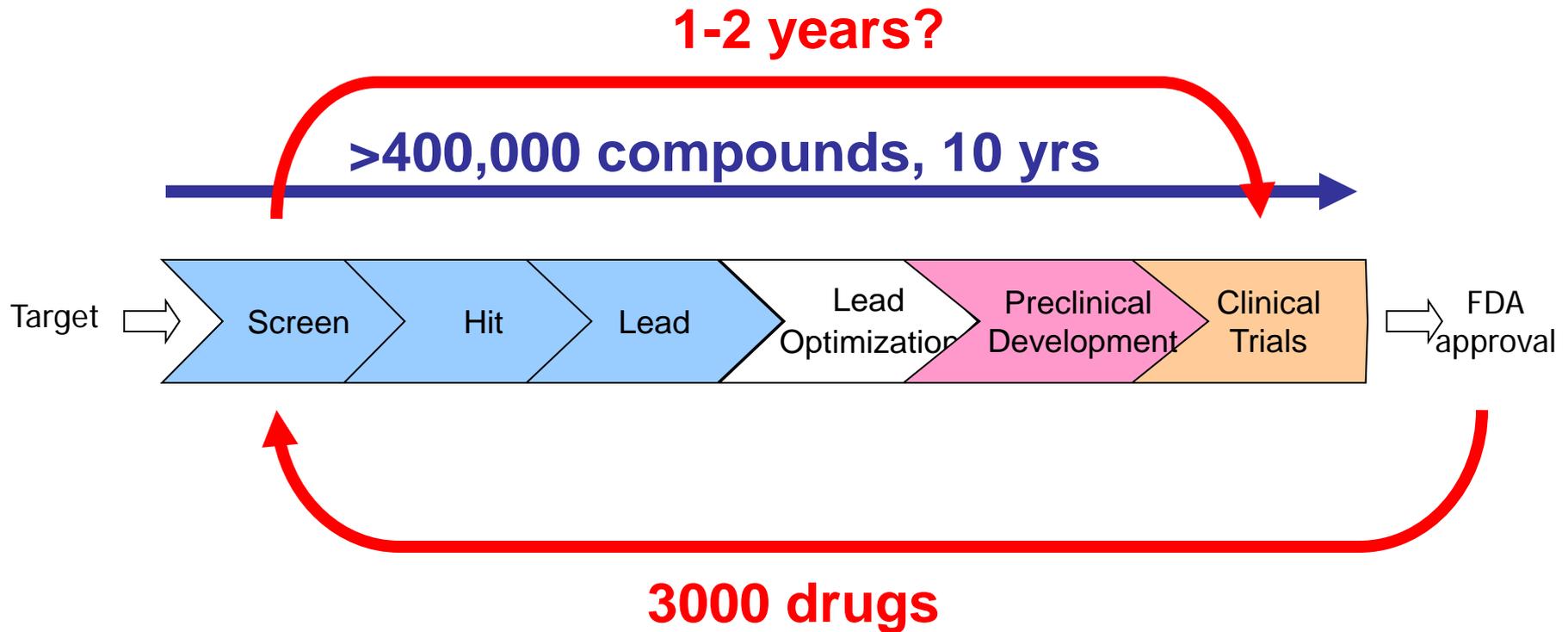
- Founded as part of Roadmap
- 85 scientists
- > 100 collaborations with investigators worldwide
 - 75% NIH extramural
 - 15% Foundations, Research Consortia, Pharma/Biotech
 - 10% NIH intramural
- Focus on novel targets, rare/neglected diseases
- Produces
 - chemical probes/leads
 - new paradigms for assay development, screening, informatics, chemistry



Rare/neglected disease projects at NCGC

- Ataxia-telangiectasia
- Beta-thalassemia
- Charcot-Marie-Tooth
- Chordoma
- Chronic lymphocytic leukemia
- Gaucher disease
- Huntington's disease
- Leishmaniasis
- Lymphangiomyomatosis
- Malaria
- Myotonic dystrophy
- Niemann-Pick C
- Progeria
- Retinitis pigmentosa
- Schistosomiasis
- Spinal muscular atrophy
- Trypanosomiasis

Two approaches to therapeutics for rare and neglected diseases

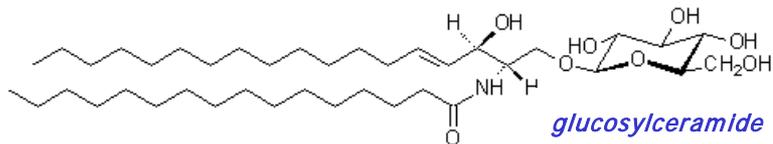


Ameliorating the Defect in Gaucher's Disease

NCGC Collaboration with Ellen Sidransky, NHGRI

- Gaucher's Disease

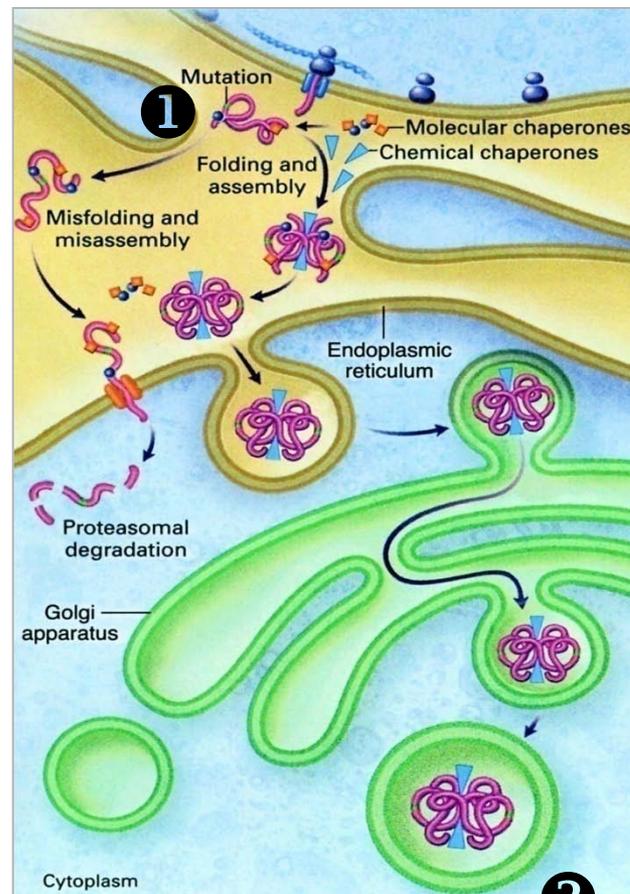
- Rare disease caused by mutations in enzyme glucocerebrosidase (GCS)



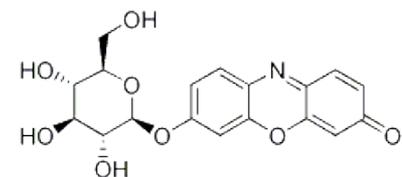
- Current treatment: enzyme replacement
 - Limited efficacy, no BBB penetration, expensive

- Many mutations are missense, leading to trafficking defect

- Pharmacological chaperones a therapeutic possibility

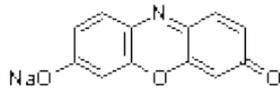


Fluorogenic substrate assay:



Resorufin beta-D-glucopyranoside

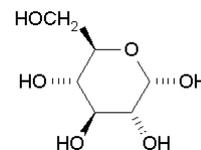
Cerebrosidase



Resorufin

Ex 570 nm / Em 590 nm

+



Glucose

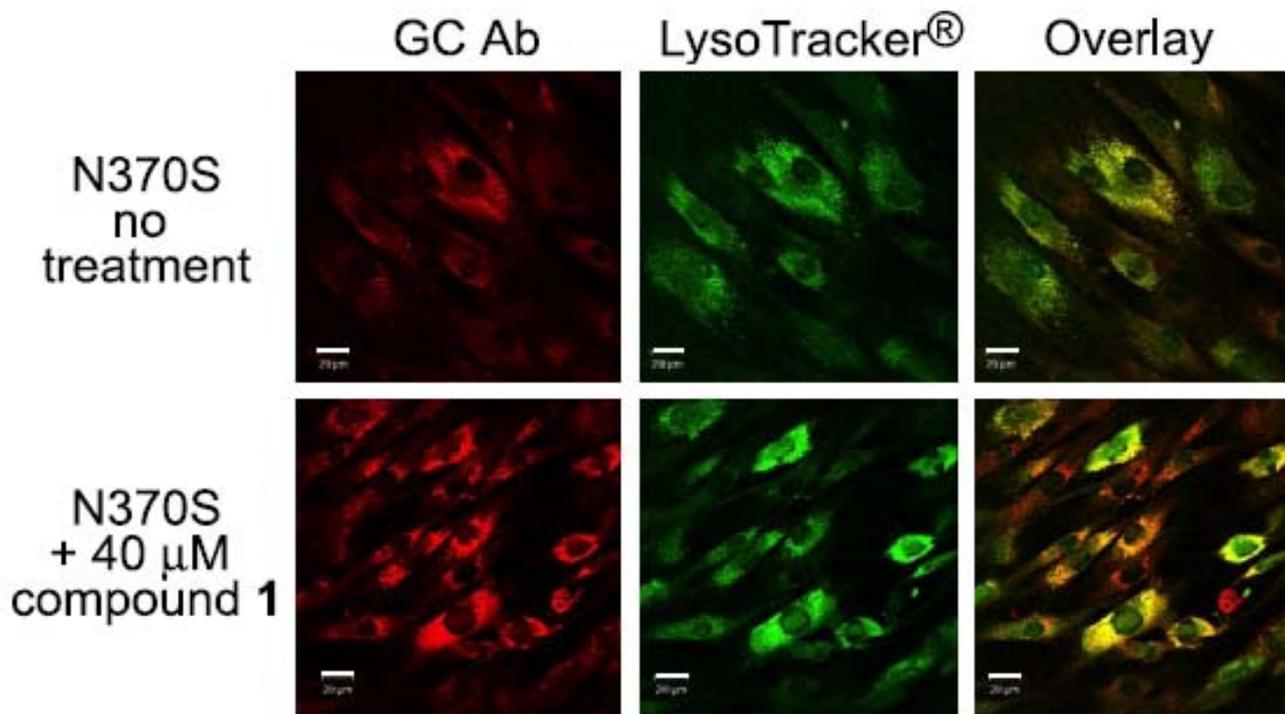
Three classes of glucocerebrosidase inhibitors identified by quantitative high-throughput screening are chaperone leads for Gaucher disease

Wei Zheng*, Janak Padia*, Daniel J. Urban[†], Ajit Jadhav*, Ozlem Goker-Alpan[†], Anton Simeonov*, Ehud Goldin[†], Douglas Auld*, Mary E. LaMarca[†], James Inglese*, Christopher P. Austin^{**‡}, and Ellen Sidransky^{†‡}

*NIH Chemical Genomics Center, National Human Genome Research Institute, National Institutes of Health, 9800 Medical Center Drive, MSC 3370, Bethesda, MD 20892-3370; and [†]Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Building 35 Rm1A213, 35 Convent Drive, Bethesda, MD 20892-3708

Communicated by Francis S. Collins, National Institutes of Health, Bethesda, MD, June 21, 2007 (received for review March 8, 2007)

13192–13197 | PNAS | August 7, 2007 | vol. 104 | no. 32



Case Study: Niemann-Pick Disease Type C

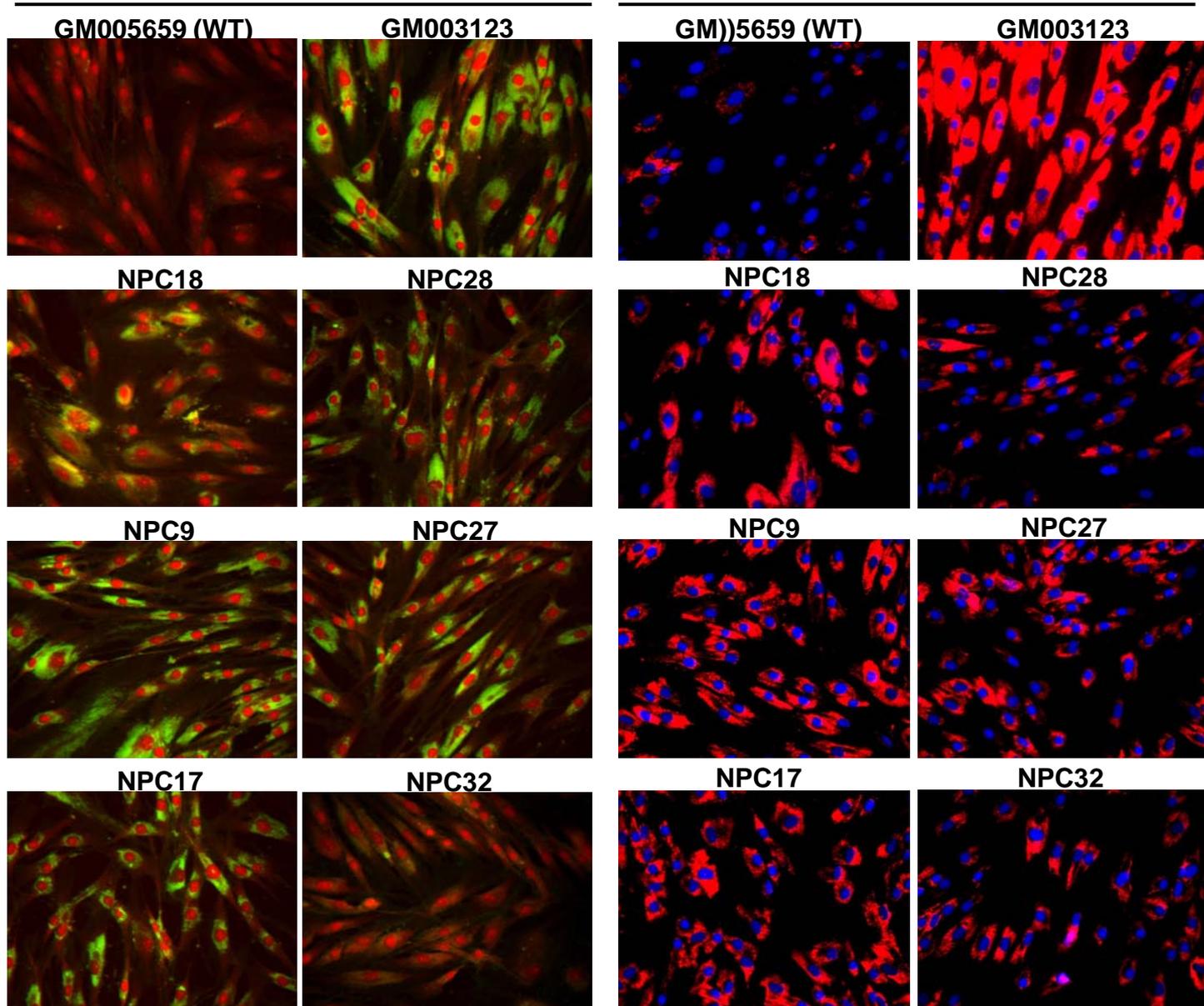
*Collaboration with Denny Porter (NICHD/NIH),
Bill Pavan (NHGRI/NIH), Dan Ory (Wash U)*

- NPC
 - Autosomal recessive disease
 - Prevalence: 1:150,000
 - Clinical manifestations: progressive neurodegeneration, hepatosplenomegaly, death by teens
 - Characterized by a lysosomal accumulation of unesterified cholesterol and other lipids.
 - Mutated genes: NPC1 (95%) and NPC2 (5%)
- Purpose of project: utilize patient cells and approved drug collection to repurpose an existing drug for NPC

Characterization of NPC Patient Cells

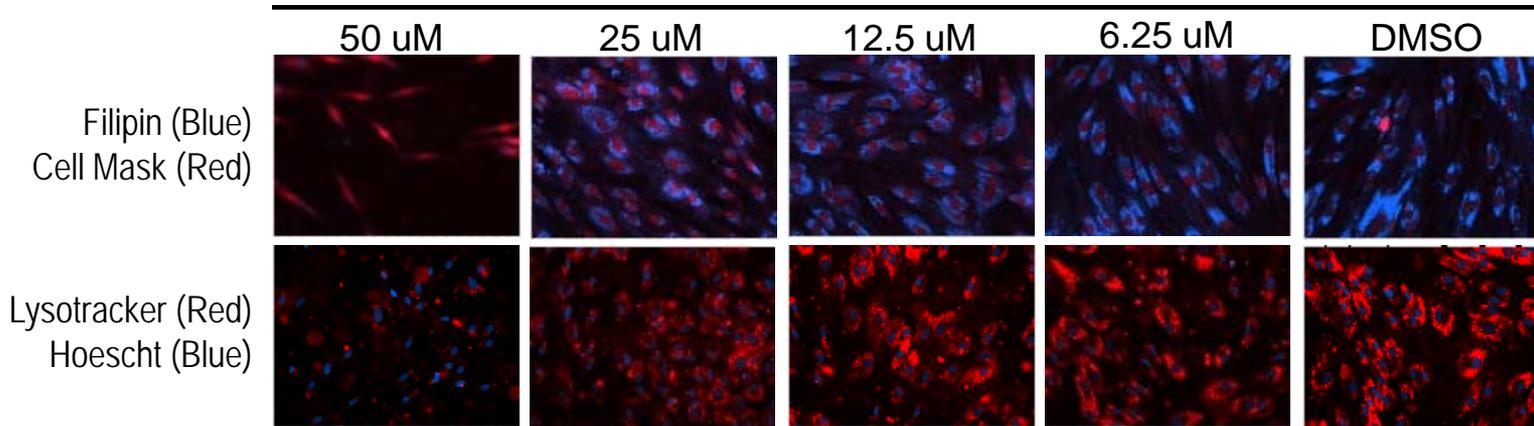
Filipin (Green)
Cell Mask (Red)

Lysotracker (Red)
Hoechst (Blue)

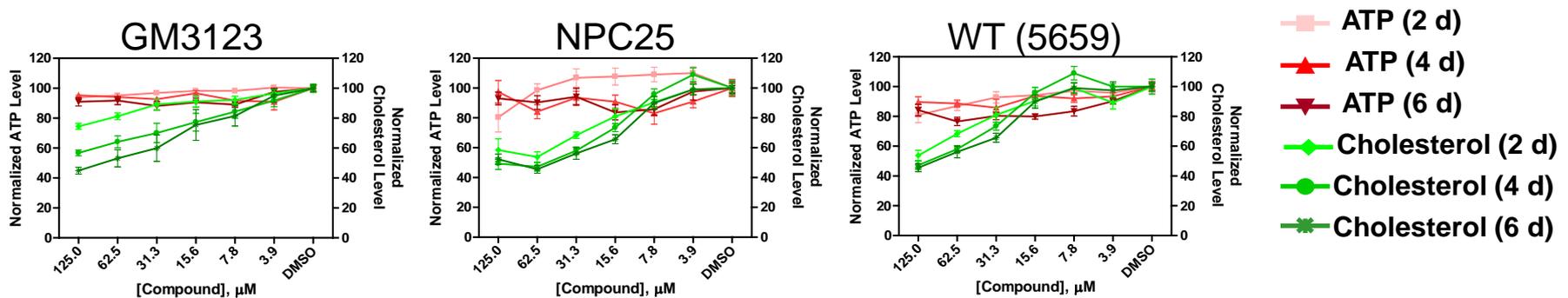


NPC "Corrector" identified from screening of pharmaceutical collection

Reduction in Free Cholesterol Accumulation and Lysosome Size

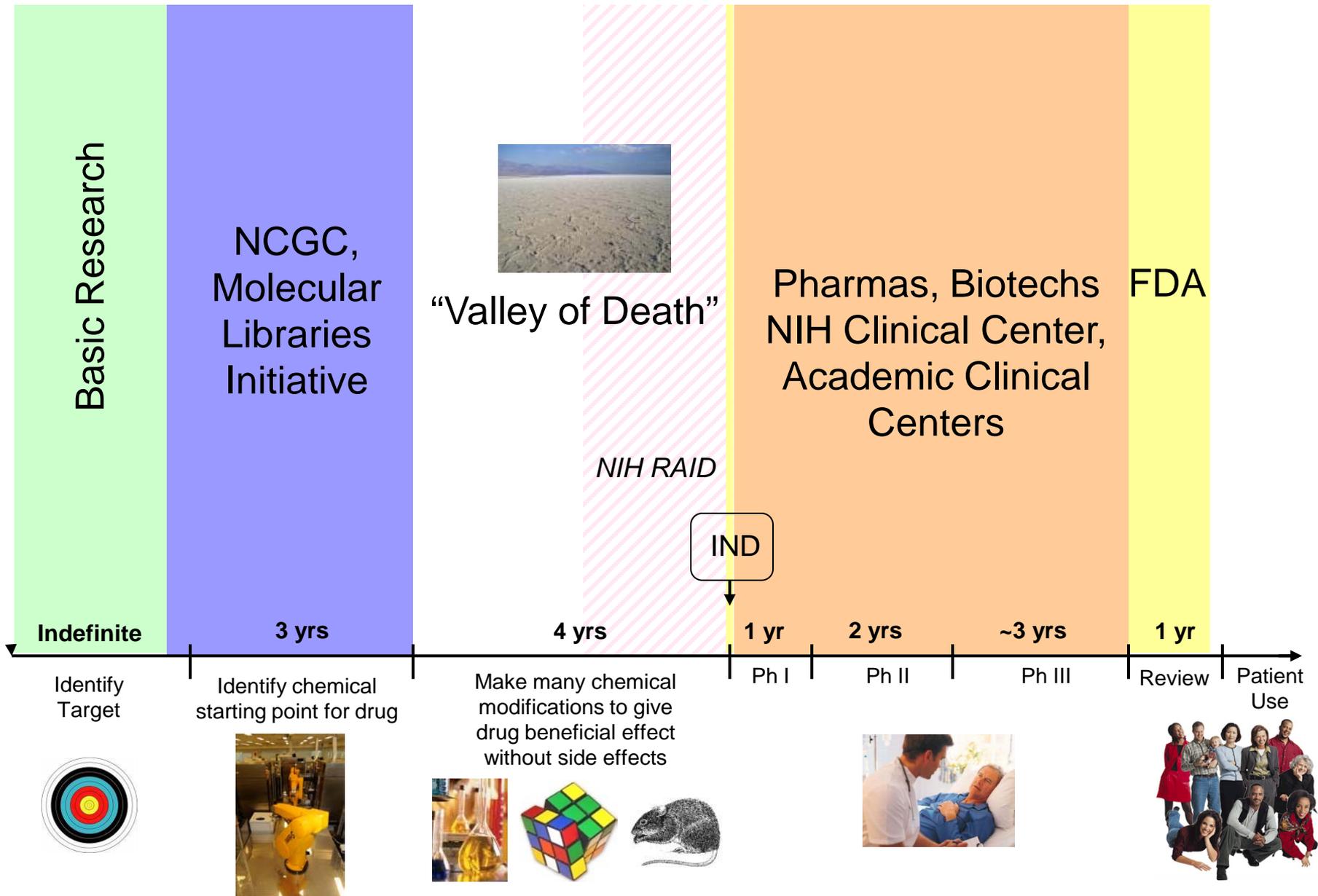


Reduction in Cholesterol Accumulation (cholesterol oxidase assay)

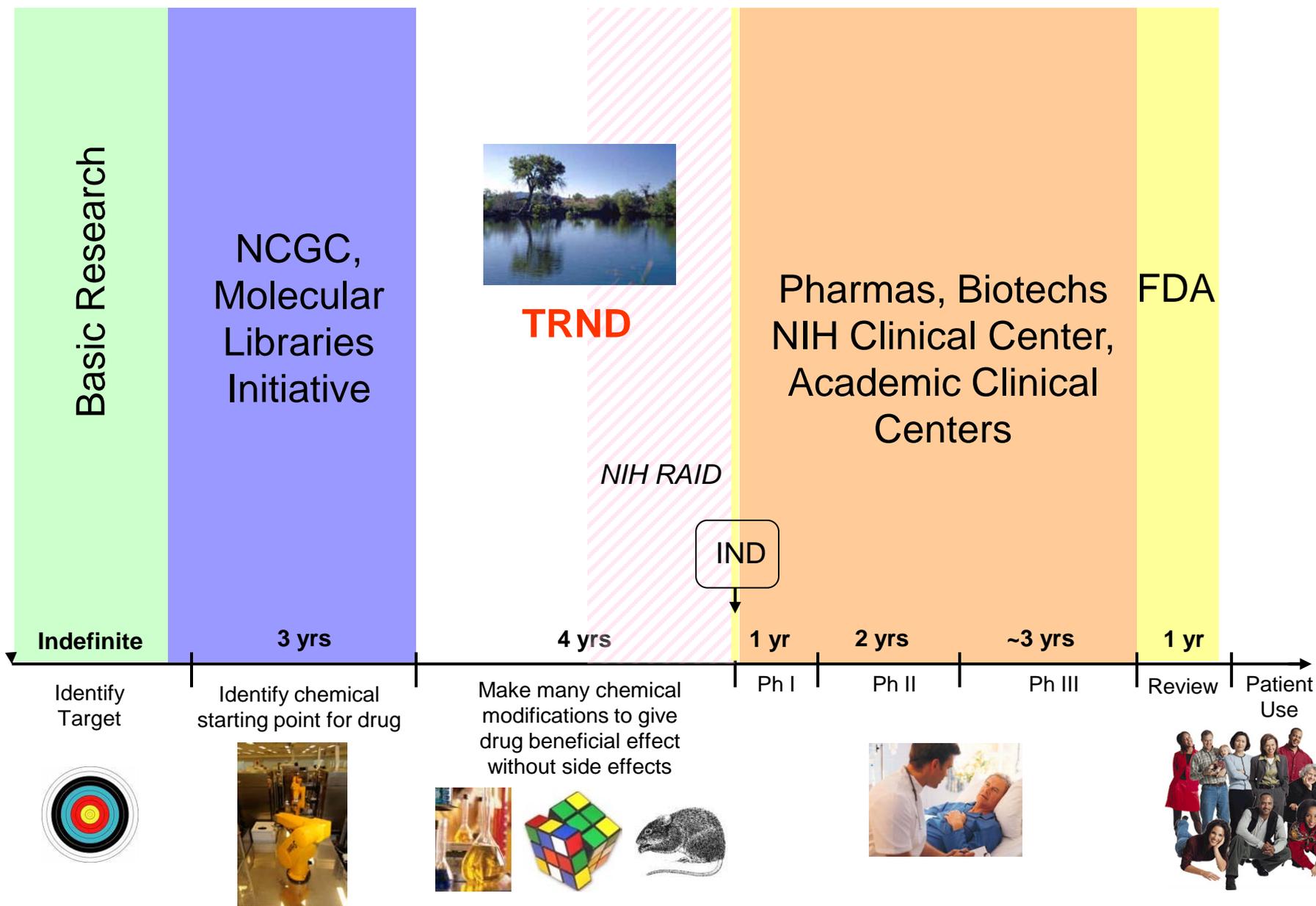


Drug now in mouse model; clinic Fall 2010

The long pathway to drug development



The long pathway to drug development



NIH Therapeutics for Rare and Neglected Diseases (TRND) Program

Creating a Drug Development Pipeline for RND at NIH

- Congressionally-mandated effort to speed development of new drugs for rare and neglected diseases
- Administration and governance at NIH
 - Governance/oversight by Office of Rare Diseases Research
 - Administered by NHGRI
- Operations: collaboration between intramural and extramural labs with appropriate expertise
- Projects will:
 - Enter TRND at a variety of stages of development
 - Be taken to phase needed for external organization to adopt for clinical development

TRND Science

- In-house laboratories with expertise in preclinical drug development will collaborate with external laboratories with expertise in disease/target
- Distinguishing features
 - Disease agnostic, take advantage of cross-cutting mechanisms
 - “Diseaseome” approach
 - *Science* of preclinical drug development
 - Reasons for successes and failures will be investigated and published
 - Technology/paradigm development
 - 20% of effort, toward improving success rates
 - Large-scale systematic repurposing
- Project-specific activities
 - Medicinal chemistry
 - Efficacy, pharmacology, ADME, toxicology, PK/PD
 - Compound scale-up, formulation
 - First in human clinical trials as needed for project

TRND Timeline

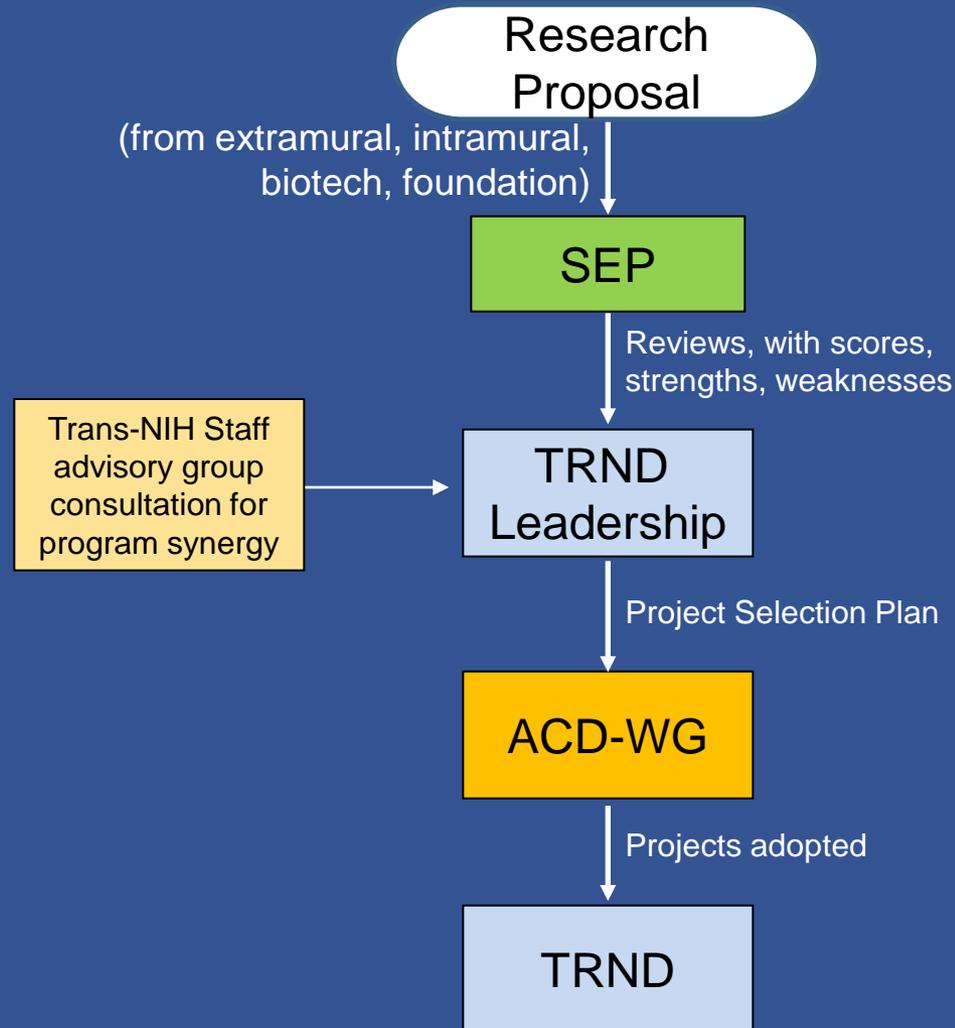
- FY09: infrastructure
- FY10: governance, hiring, research community outreach; pilot projects
- FY11: solicitation of projects for adoption; 4-5 new projects expected
- FY12: fully operational
 - Work on several new projects per year
 - Average project should take ~2 years
 - Projects will be monitored closely for progress

TRND Pilot Projects

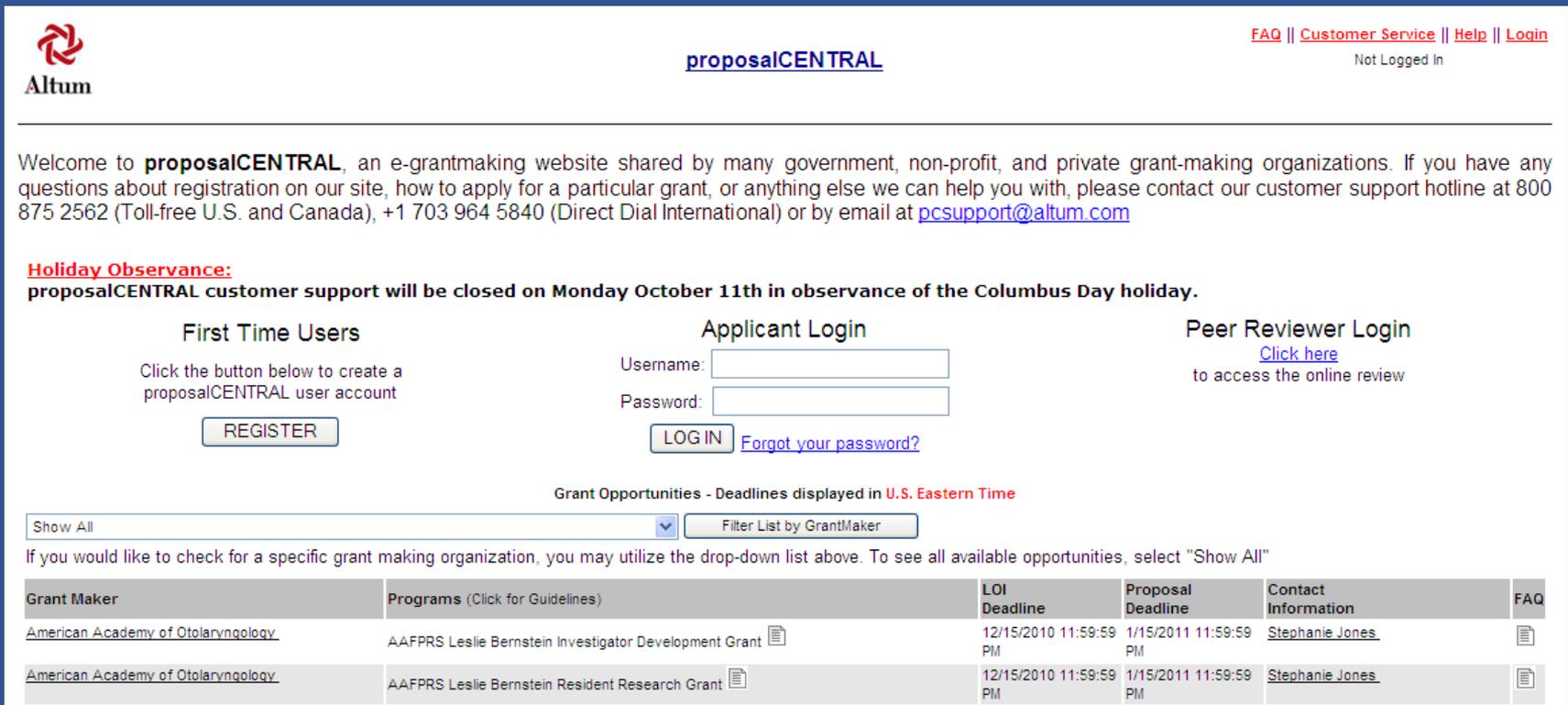
Chosen to establish processes in advance of solicitation, with diversity of project stage, type of disease and collaborators

Disease	Type	Pathology	Collaborators	Compound type	Stage
Schistosomiasis, Hookworm	Neglected	Infectious parasite	Extramural	NME	Early (lead optimization)
Niemann Pick C	Rare	CNS, liver/spleen	Disease Fnd, Extramural, Intramural	Repurposed approved drug	Mid-stage
HIBM	Rare	Muscle	Biotech, Intramural	Intermediate replacement	Pre-IND
Sickle Cell Disease	Rare	Blood	Nonprofit, Intramural, Extramural	NME	Mid-stage
Chronic Lymphocytic Leukemia	Rare	Cancer	Disease Fnd, Extramural	Repurposed approved drug	Pre-IND

TRND: Project Selection



TRND Project solicitation released last week on ProposalCentral!



The screenshot shows the proposalCENTRAL website interface. At the top left is the Altum logo. In the center is the text "proposalCENTRAL". At the top right are links for "FAQ", "Customer Service", "Help", and "Login", along with the text "Not Logged In". Below the header is a welcome message: "Welcome to proposalCENTRAL, an e-grantmaking website shared by many government, non-profit, and private grant-making organizations. If you have any questions about registration on our site, how to apply for a particular grant, or anything else we can help you with, please contact our customer support hotline at 800 875 2562 (Toll-free U.S. and Canada), +1 703 964 5840 (Direct Dial International) or by email at pcsupport@altum.com".

Below the welcome message is a "Holiday Observance" notice: "proposalCENTRAL customer support will be closed on Monday October 11th in observance of the Columbus Day holiday.".

The main content area is divided into three sections: "First Time Users", "Applicant Login", and "Peer Reviewer Login".

- First Time Users:** Includes the text "Click the button below to create a proposalCENTRAL user account" and a "REGISTER" button.
- Applicant Login:** Includes "Username:" and "Password:" input fields, a "LOG IN" button, and a link "Forgot your password?".
- Peer Reviewer Login:** Includes the text "to access the online review" and a link "Click here".

Below the login sections is a section for "Grant Opportunities - Deadlines displayed in U.S. Eastern Time". It features a "Show All" button and a "Filter List by GrantMaker" button. Below this is a table of grant opportunities.

Grant Maker	Programs (Click for Guidelines)	LOI Deadline	Proposal Deadline	Contact Information	FAQ
American Academy of Otolaryngology	AAFPRS Leslie Bernstein Investigator Development Grant 	12/15/2010 11:59:59 PM	1/15/2011 11:59:59 PM	Stephanie Jones	
American Academy of Otolaryngology	AAFPRS Leslie Bernstein Resident Research Grant 	12/15/2010 11:59:59 PM	1/15/2011 11:59:59 PM	Stephanie Jones	

- Will be great deal of outreach before due date Dec 6
- Please spread the word to rare disease community!

http://trnd.nih.gov



THERAPEUTICS FOR RARE & NEGLECTED DISEASES

Bridging the Gaps in Discovery and Development of Therapeutics for Rare and Neglected Diseases

Posts Comments

HOME ABOUT TRND RESOURCES APPLY TO TRND CURRENT PROJECTS RELATED PROGRAMS AT NIH FAQ CONTACT US



Home

The **National Institutes of Health** (NIH) Therapeutics for Rare and Neglected Diseases (TRND) program is a congressionally mandated program to encourage and speed the development of new drugs for rare and neglected diseases. This unique program creates a drug development pipeline within the NIH and is specifically intended to stimulate research collaborations with academic scientists, non-profit organizations, and pharmaceutical and biotechnology companies working on rare and neglected illnesses.

The TRND program provides an opportunity to partner with, and gain access to, drug development scientific capabilities, expertise, and resources in a collaborative environment with the goal of moving promising therapeutics into clinical testing. TRND will use an application evaluation process to select collaborators. If the application is successful, the applicant(s) will partner with TRND staff to advance a drug development program. TRND investigators will provide drug development expertise and operations, and the applicant investigator(s) will provide starting points for the project and ongoing biological/disease expertise throughout the project.

LINKS

- [Home](#)
- [About TRND](#)
 - [Governance](#)
- [Resources](#)
- [Apply to TRND](#)
 - [Application Instructions](#)
 - [Project Management](#)
 - [Selection Process](#)
 - [IP & Data Access](#)
 - [Resubmissions](#)
- [Current Projects](#)
- [Related Programs at NIH](#)
- [FAQ](#)

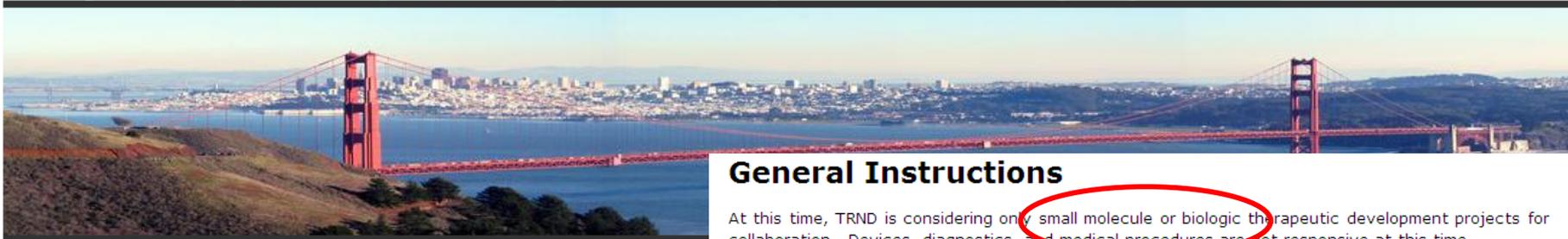


THERAPEUTICS FOR RARE & NEGLECTED DISEASES

Bridging the Gaps in Discovery and Development of Therapeutics for Rare and Neglected Diseases

Posts Comments

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- ABOUT TRND
- RESOURCES
- APPLY TO TRND
- CURRENT PROJECTS
- RELATED PROGRAMS AT NIH
- FAQ
- CONTACT US



General Instructions

At this time, TRND is considering only **small molecule or biologic therapeutic development projects** for collaboration. Devices, diagnostics, and **medical procedures** are not responsive at this time.

Proposed projects must target an untreated or poorly treated rare or neglected disease, as defined here:

- http://rarediseases.info.nih.gov/files/Rare_Diseases_FAQs.pdf
- http://rarediseases.info.nih.gov/files/Neglected_Diseases_FAQs.pdf

Special consideration will be given to projects with the potential to address more than one rare or neglected disease by virtue of shared pathophysiology, and projects with a well-developed strategy to exit TRND and complete clinical development, registration, and marketing.

Projects must be at least at the stage of a validated lead series in order to be considered for TRND. Projects requiring earlier-stage resources, including assay development, high-throughput screening, and initial medicinal chemistry optimization of screening hits, are not appropriate for TRND; researchers interested in these resources are directed to other NIH resources including the **Molecular Libraries Program** and the **NCI Chemical Biology Consortium/NEXT program**.

This "TRND Concept Application" includes six (6) sections as described in detail below; additional material can be uploaded as an appendix. Please use the TRND Concept Application Template, available only when the solicitation is open, at **proposalCENTRAL**. Please convert all documents to searchable PDF files before submission. All materials submitted to proposalCENTRAL are considered confidential. All reviewers will sign conflict of interest and confidentiality agreements before being given access to applications.

TRND encourages potential applicants to contact TRND staff via our webpage at http://trnd.nih.gov/?page_id=121 prior to submitting a proposal in response to this solicitation.

Required Documents for Therapeutics for Rare and Neglected Diseases Program Applications

A. TRND Concept Application

The concept application document **should not exceed 5 pages** (Arial 11pt, single space, 1" margins). Graphs, pictures and tables **should be included in the text**. The application should succinctly define the scientific nature and rationale of the proposed project and the current stage of its development, and should include the following:

Home

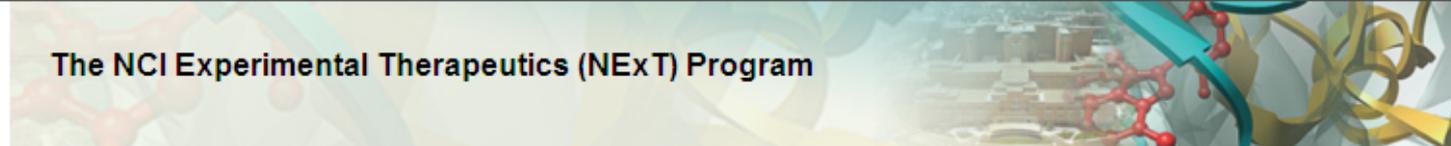
The **National Institutes of Health** (NIH) Therapeutics for Rare and Neglected Diseases program is a congressionally mandated program to encourage and speed the development of new drugs for rare and neglected diseases. This unique program creates a center within the NIH and is specifically intended to stimulate research collaboration between scientists, non-profit organizations, and pharmaceutical and biotechnology companies to address rare and neglected illnesses.

The TRND program provides an opportunity to partner with, and gain access to, the scientific capabilities, expertise, and resources in a collaborative environment to bring promising therapeutics into clinical testing. TRND will use an application process to select collaborators. If the application is successful, the applicant(s) will participate in the development and advance a drug development program. TRND investigators will provide scientific and operations, and the applicant investigator(s) will provide starting materials and ongoing biological/disease expertise throughout the project.

<http://trnd.nih.gov>

<http://next.cancer.gov/>

About NExT	Entry to Pipeline	Pipeline Management	Discovery	Development	Biomarker
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The NCI Experimental Therapeutics (NExT) Program

A Unique Partnership with the NCI to Facilitate Oncology Drug Discovery and Development

Do you need

- A partner to complete development of an orphan drug for a pediatric or rare cancer?
- Exploratory screen development and optimization?
- Preclinical development for an agent with a specific molecular target?
- A different formulation of your agent for it to be clinically useful?
- Pharmaceutical-grade investigational drug to conduct clinical studies?
- A pharmacodynamic assay or imaging technique to determine if your agent is modulating its target?
- Proof-of-concept or first-in-human studies?
- Other resources to support drug discovery and

Who: Researchers in academia, government, and industry, nationally or internationally.

What: Drug discovery and development projects will enter an NCI pipeline focused on unmet needs in therapeutics that are not adequately addressed by the private sector. *The NCI is committed to moving high-priority discovery and development projects through to proof-of-concept clinical trials.* For more information, visit [About NExT](#).

When: Submission deadlines occur three times per year: Feb 15, June 15, and Oct 15. For more information, visit [Entry to Pipeline](#).

Where: Online submission of [NExT application](#).

How: Entry into NExT can occur at any stage of the drug discovery or development pipeline, but depends on favorable review of the application's scientific merit. For more information, visit [Entry to Pipeline](#). Approved discovery and preclinical development activities may be performed by the [NCI Chemical Biology Consortium](#).

<http://neuroscienceblueprint.nih.gov/>

NIH Blueprint

for Neuroscience Research



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Blueprint Neurotherapeutics Network

What is the Neurotherapeutics Grand Challenge?

Most nervous system disorders lack effective treatment, and there is no clear solution:

- ▶ Basic researchers often lack the resources to develop novel therapeutics strategies to the point where they can attract industry interest
- ▶ Biopharmaceutical companies often hesitate to invest in neurotherapeutics development because there are few clinically validated targets or strategies, there is a long track record of failure, and many nervous system disorders affect relatively small populations.

What is the Blueprint Neurotherapeutics Network?

The Blueprint established the Neurotherapeutics Network to bridge the gap in drug development between academic and industry research ([View the project pipeline](#)). The Network offers neuroscience researchers a "virtual pharma" to develop promising hit compounds from chemical optimization through Phase I clinical testing ([View the program structure and services offered](#)). Successful applicants will receive:

- ▶ Funding to conduct biological testing
- ▶ Access to a full range of industry-style drug development services and expertise
- ▶ Control of the intellectual property for drug candidates

Quick Links



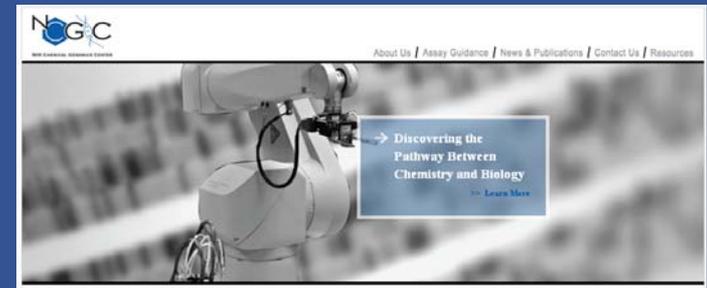
- ▶ The application deadline for [RFA-NS-11-002](#) has passed. The next Request for Applications will be issued in Spring 2011.
- ▶ [Frequently Asked Questions](#)
 - ▶ [Who Should Apply?](#)
 - ▶ [How will intellectual property be handled?](#)
 - ▶ [What are my chances of getting funded?](#)
 - ▶ [More >>](#)
- ▶ [Contact Information](#)
[Dr. Jill Heemskerk](#)
(301) 496-1779

Further Information

austinc@mail.nih.gov



<http://ncgc.nih.gov>



<http://trnd.nih.gov>

