Small Molecules and Chemical Genomics: Tools for Understanding HHT?

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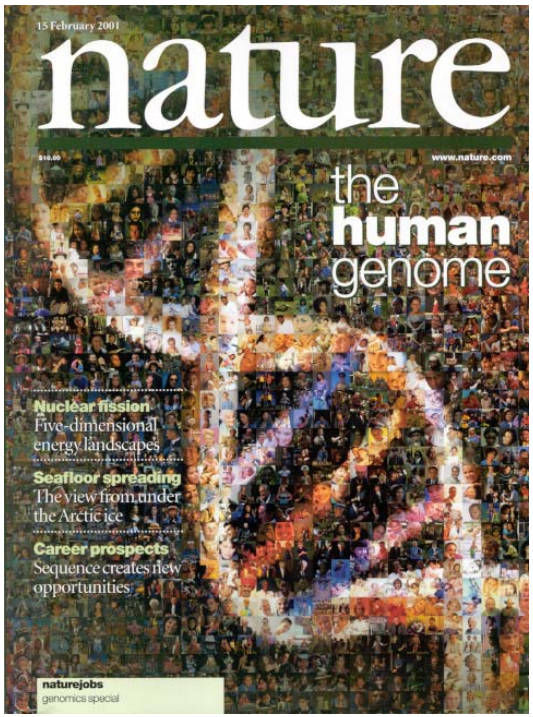
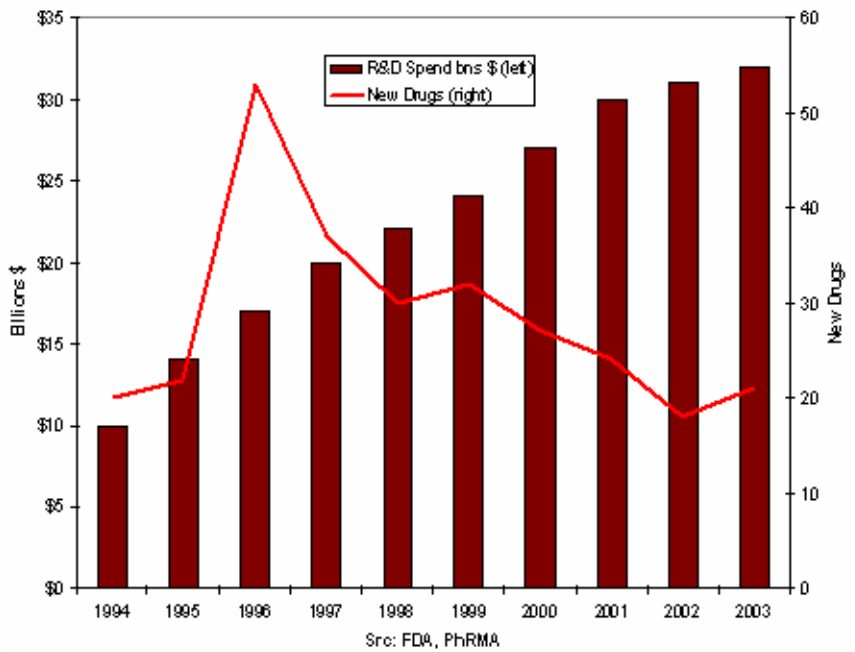
National Human Genome Research Institute
National Institutes of Health

Hereditary Hemorrhagic Telangiectasia Conference
June 8, 2006

NIH Chemical Genomics Center

The best of times, the worst of times

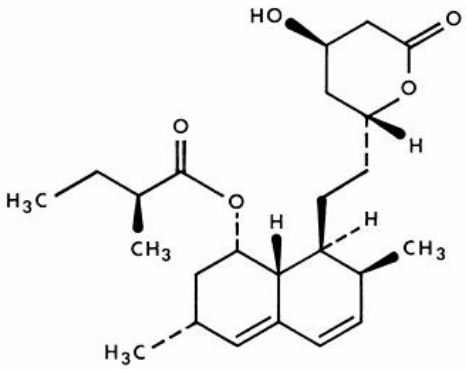




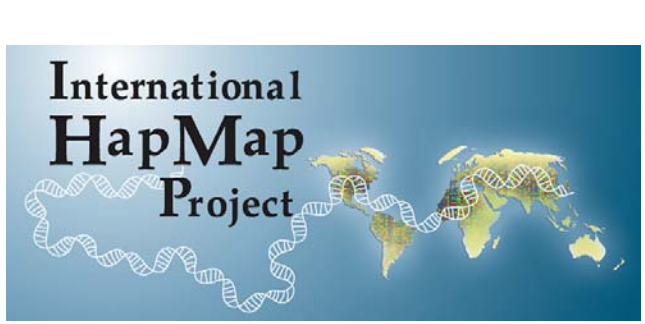
How to translate the genome into biological insights and therapeutics?

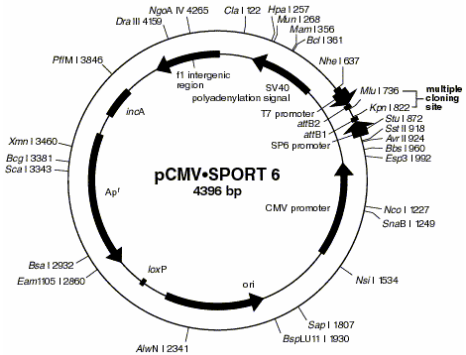
Creating the Human Genome Translation Toolbox

HumanBase

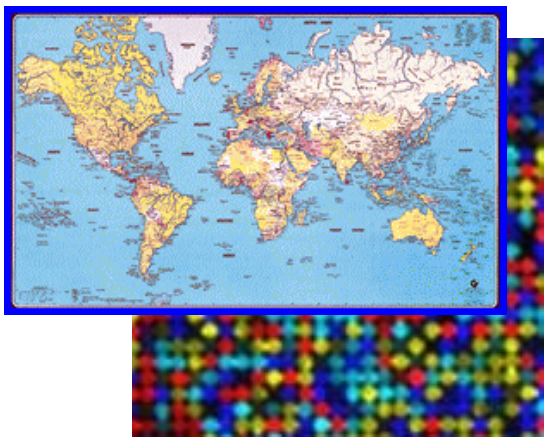


Small molecules





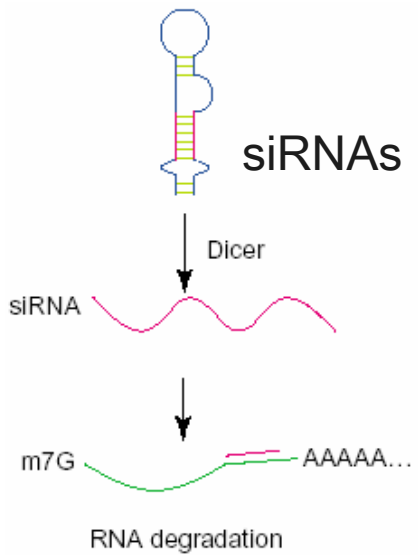
cDNA collection (MGC)



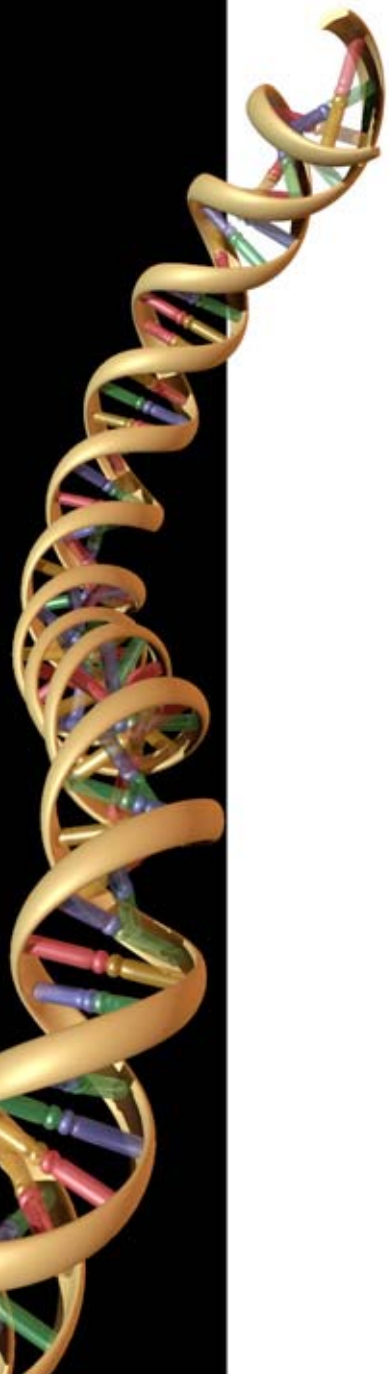
Transcriptome Reference Sets *(MRT Project)*

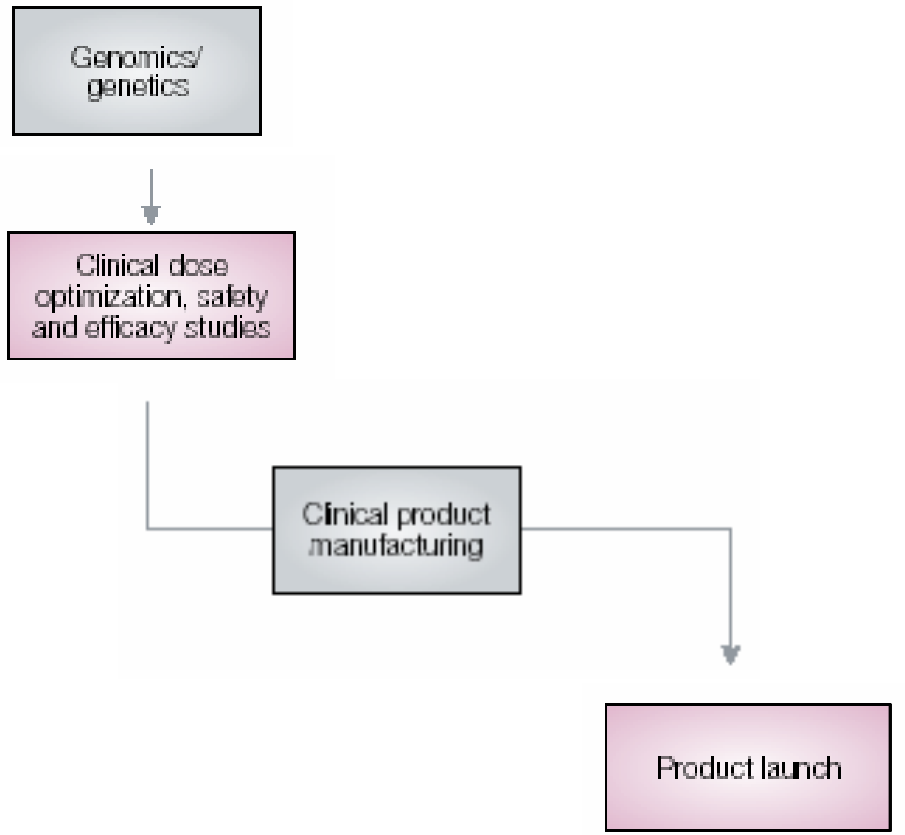
(ENCyclopedia Of DNA Elements)

KO mice genome-wide *(KOMP)*

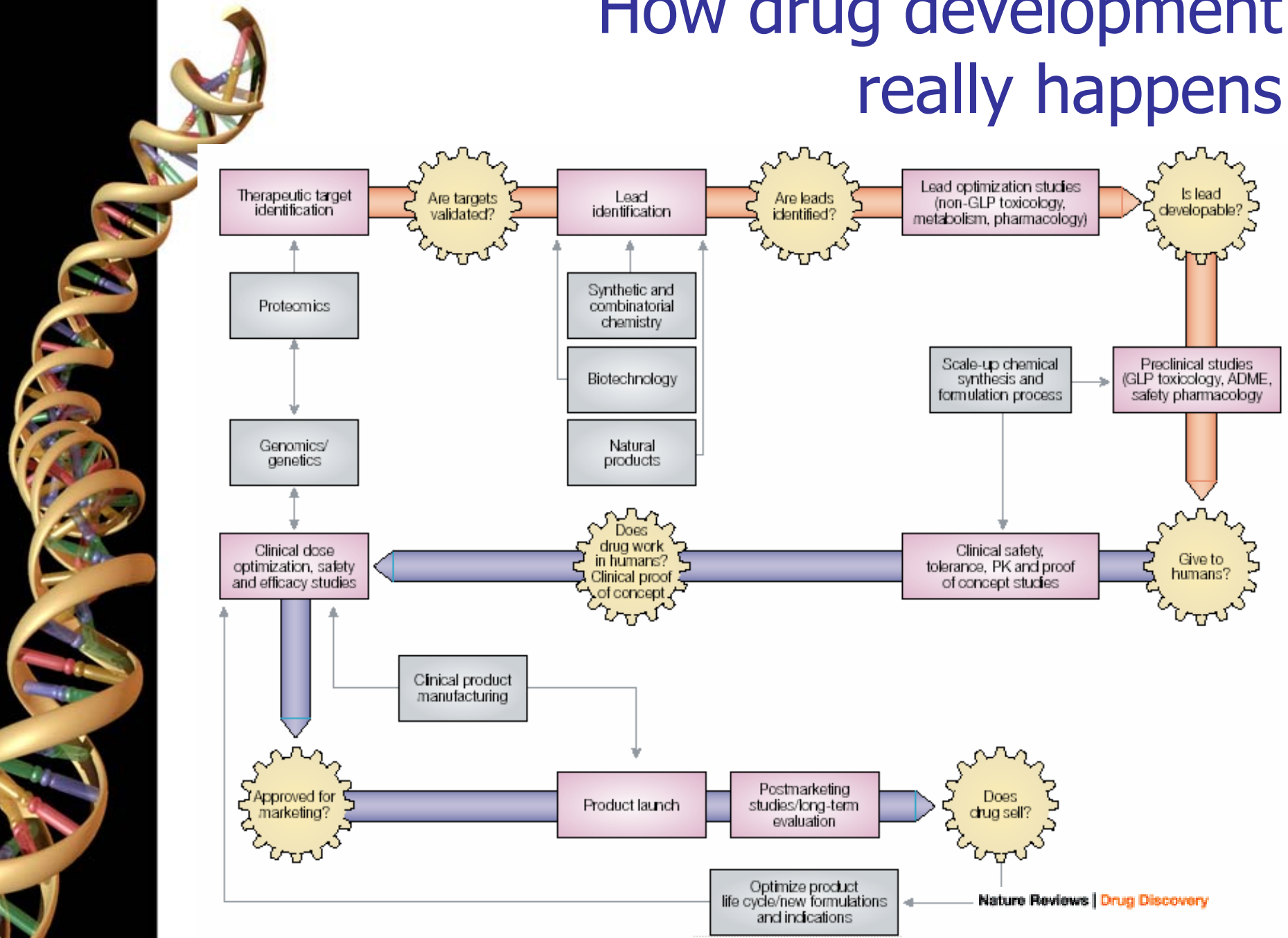


The common view of drug development





How drug development really happens



NIH's mission

- "Science in pursuit of fundamental knowledge about the nature and behavior of living systems. Foster fundamental creative discoveries, innovative research strategies, and their applications as a basis to advance significantly the Nation's capacity to protect and improve health."
  - Provide scientific underpinnings for drug development
  - No commercial imperative

The NIH Roadmap

- Initiated by Elias Zerhouni upon his appointment as NIH Director in May 2002
  - Trans-Institute strategic initiatives
- Major Roadmap themes
  - New Pathways to Discovery
  - Research Teams of the Future
  - Re-engineering the Clinical Research Enterprise

Overview of the NIH Roadmap

HISTORY AND PURPOSE

Soon after becoming the Director of the National Institutes of Health (NIH), in May 2002, Elias A. Zerhouni, M.D. convened a series of meetings to chart a "roadmap" for medical research in the 21st century. The purpose was to identify major opportunities and gaps in biomedical research that no single institute at NIH could tackle alone but that the agency as a whole must address, to make the biggest impact on the progress of medical research. The opportunities for discoveries have never been greater, but the complexity of biology remains a daunting challenge. NIH is uniquely positioned to catalyze changes that must be made to transform our new scientific knowledge into tangible benefits for people.

Developed with input from meetings with more than 300 nationally recognized leaders in academia, industry, government, and the public, the NIH Roadmap provides a framework of the priorities NIH as a whole must address in order to optimize its entire research portfolio. It lays out a vision for a more efficient and productive system of medical research. The NIH Roadmap identifies the most compelling opportunities in three main areas: new pathways to discovery, research teams of the future, and re-engineering the clinical research enterprise.

Initiatives under the NIH Roadmap will help enable the agency to sustain its historic record of making cutting-edge contributions that are central to extending the quality of healthy life for people in this country and around the world.

STEPS IN THE PROCESS

The process of crafting the Roadmap—from vision to implementation—is described in the following sections.

The initial step in the Roadmap process involved a series of five meetings in which Dr. Zerhouni and Directors of the various NIH Institutes and Centers led invited participants through lively discussions about the most compelling initiatives that the NIH should pursue over the next 10 years—those that will have the most profound impact on the progress of medical research, both in the United States and worldwide. Participants were asked:

- What are today's scientific challenges?
- What are the roadblocks to progress?
- What do we need to do to overcome roadblocks?
- What can't be accomplished by any single Institute—but is the responsibility of NIH as a whole?

NIH Roadmap

ACCELERATING MEDICAL DISCOVERY TO IMPROVE HEALTH

- Overview
- NIH Roadmap Initiatives
- Funding Opportunities
- Funded Research
- Roadmap Related Activities
- Public Meetings and Workshops
- Frequently Asked Questions
- News and Information
- NIH Roadmap Institute and Center Liaisons
- Subscribe to the NIH Roadmap E-mail list

New Pathways to Discovery

- Building Blocks, Biological Pathways, and Networks
- Molecular Libraries and Imaging
- Structural Biology
- Bioinformatics and Computational Biology
- Nanomedicine

Research Teams of the Future

- High-Risk Research
  - NIH Director's Pioneer Award
- Interdisciplinary Research
- Public-Private Partnerships

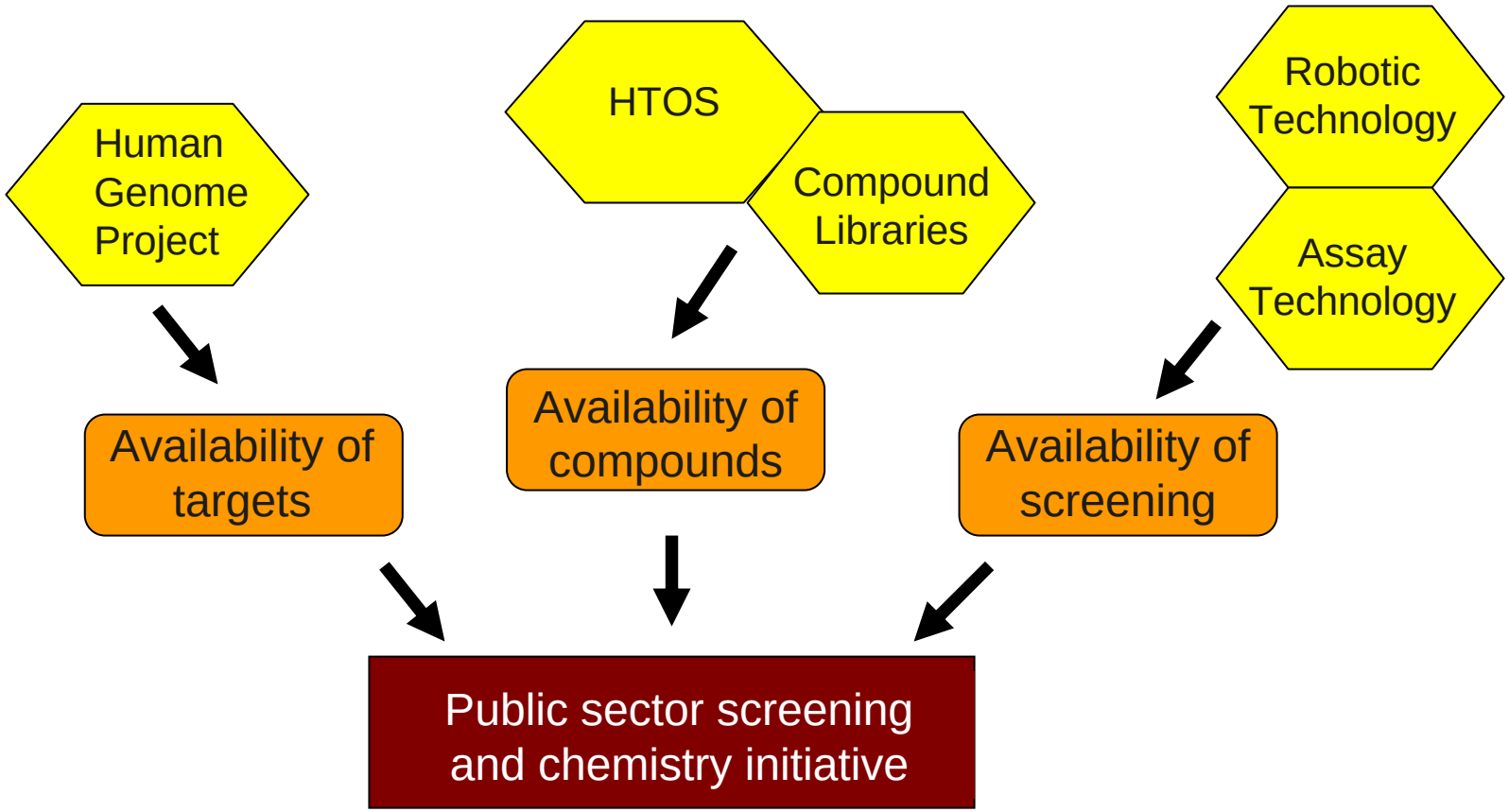
Re-engineering the Clinical Research Enterprise

- Re-engineering the Clinical Research Enterprise Initiatives
  - Clinical Research Networks and NECTAR
  - Clinical Outcomes Assessment
  - Clinical Research Training
  - Clinical Research Policy Analysis and Coordination
  - Translational Research

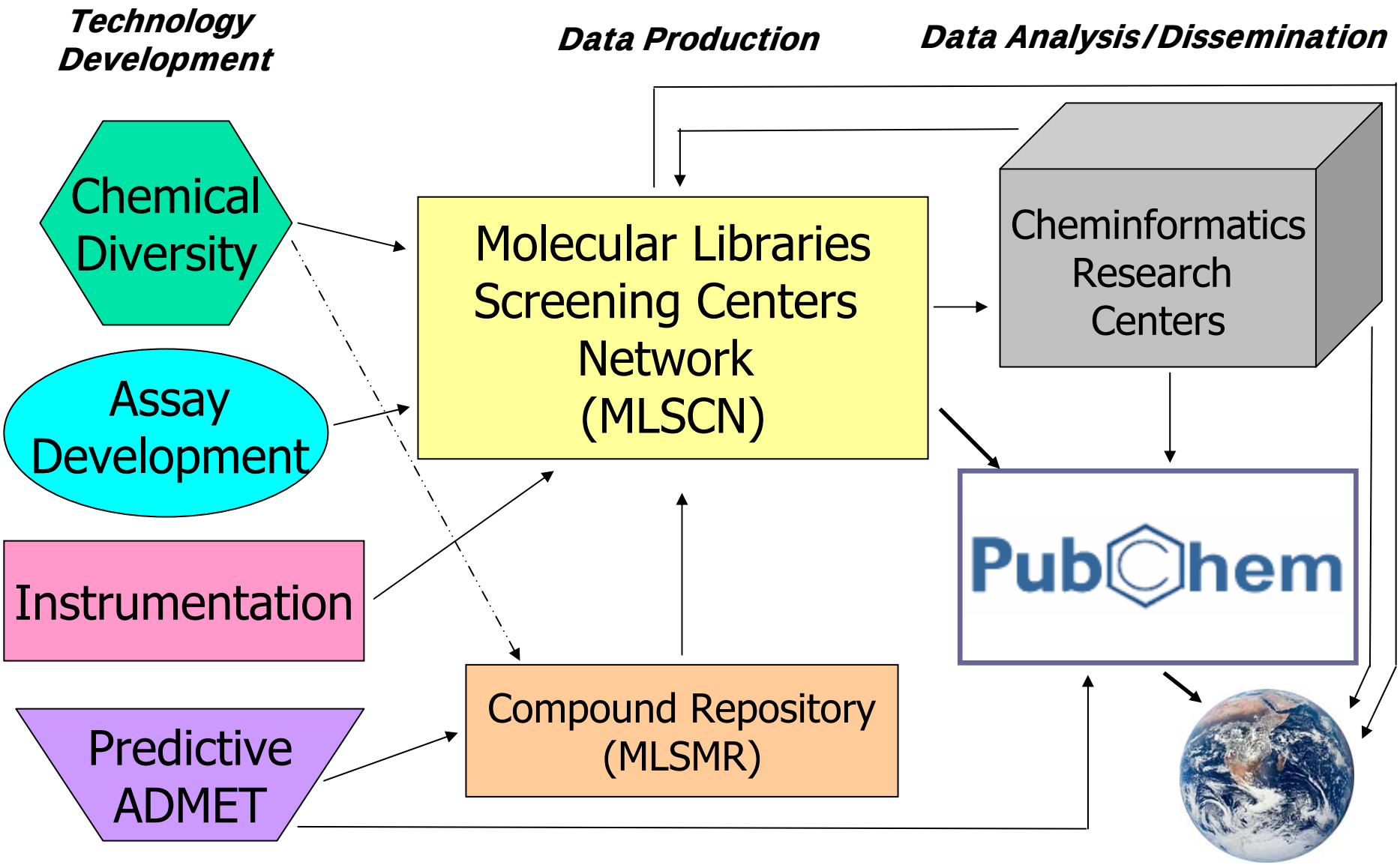
What's New

- **Notice:** Institutional Clinical and Translational Science Award (CTSA) Pre-submission VideoCast for Clinical Research Partners
- **Meeting:** Considering Usual Medical Care in Clinical Trial Design: Scientific and Ethical Issues
- **Press Release:** NIH Launches Major Program to Transform Clinical and Translational Science
- **RFA:** Planning Grants for Institutional Clinical and Translational Science Awards
- **RFA:** Institutional Clinical and Translational Science Award
- **Program:** Institutional Clinical and Translational Science Award Program Information
- **Meeting:** Interdisciplinary Research Centers Workshop
- **Press Release:** 2005 NIH Director's Pioneer Award Recipients Announced
- What's New – Archives

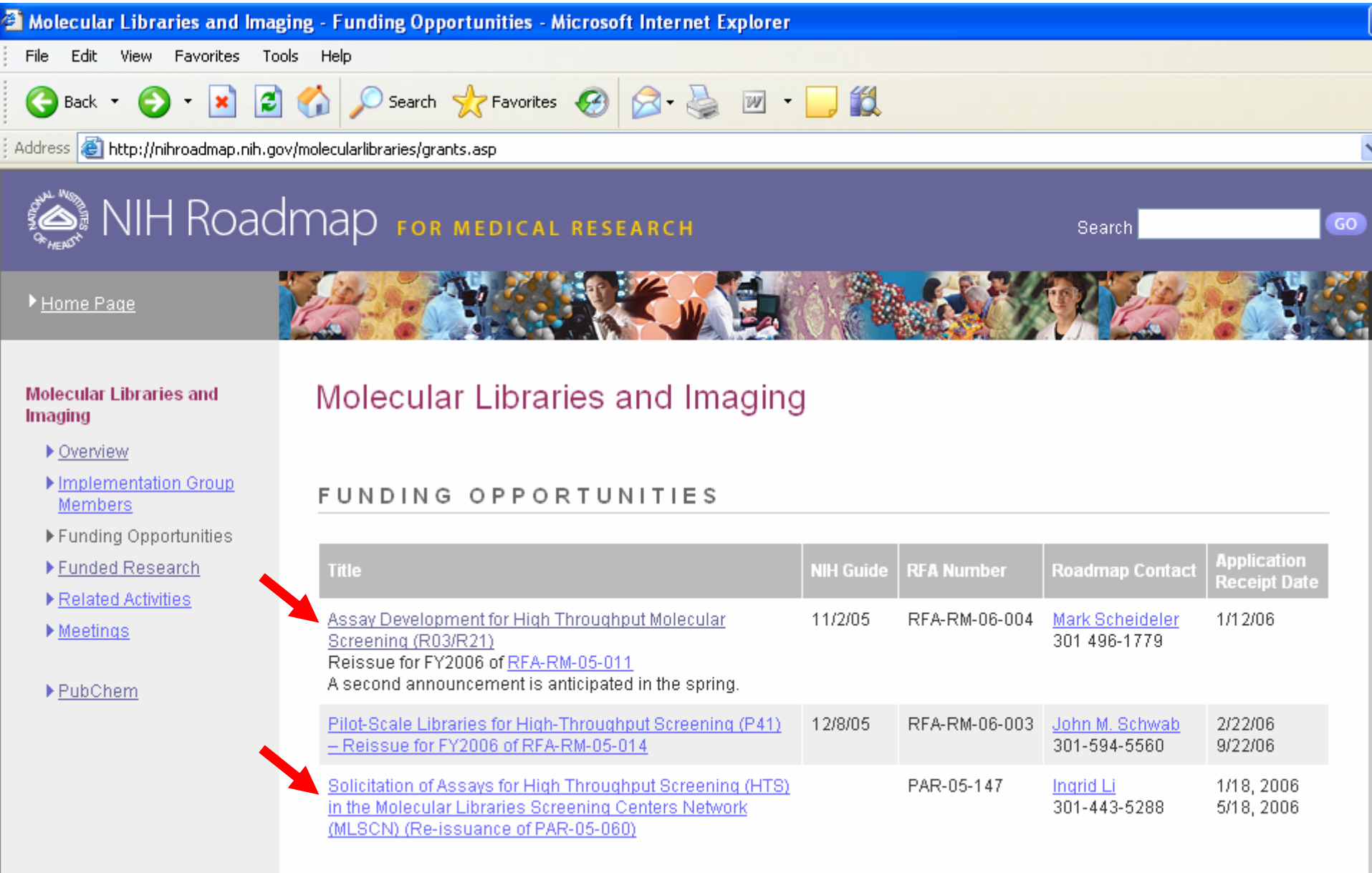
Molecular Libraries initiative enabled by recent convergent developments



The Molecular Libraries Roadmap: An Integrated Initiative



Support for assay development and access to HTS



Molecular Libraries and Imaging

- Overview
- Implementation Group Members
- Funding Opportunities
- Funded Research
- Related Activities
- Meetings

- PubChem

Molecular Libraries and Imaging

FUNDED RESEARCH

Solicitation of Assays for High Throughput Screening (HTS) in the Molecular Libraries Screening Centers Network (MLSCN) (R03)
PAR-05-060

PI Name	Institution Name	Title
MUSTAEV, ARKADY	PUBLIC HEALTH RESEARCH INSTITUTE	Development of the HTS Assay for E. Coli RNA Polymerase (RNAP)
NISWENDER, COLLEEN M.	VANDERBILT UNIVERSITY	Measurement of GPCR-mediated thallium flux through GIRK Channels
PAUMET, FABIENNE	COLUMBIA UNIVERSITY HEALTH SCIENCES	Unraveling the Molecular Mechanisms of Phagocytosis
ROTHMAN, JAMES E.	COLUMBIA UNIVERSITY HEALTH SCIENCES	Aggregation and Clearance of Mutant Huntingtin
ROTHMAN, JAMES E.	COLUMBIA UNIVERSITY HEALTH SCIENCES	Regulation of Neurotransmitter Transporter Recycling
SANNA M. GERMANA	SCRIPPS RESEARCH INSTITUTE	MLSCN HTS Assays R03 - S1P1
TEITLER, MILT	ALBANY MEDICAL COLLEGE OF UNION UNIV	Human 5HT 1E Serotonin Receptor Drug Development
WALKER, SUZANNE	HARVARD UNIVERSITY (MEDICAL SCHOOL)	Identification of O-GlcNAc Transferase Inhibitors by HTS
WHITE, E. LUCILE	SOUTHERN RESEARCH INSTITUTE	High Throughput Screen for Mycobacterium Tuberculosis Pantothenate Synthetase
WILKINSON, KEITH D.	EMORY UNIVERSITY	HTS Assay for Inhibitors of BAP1, a BRCA1 Associated Deubiquitinating Enzyme
WILLIAMS, DAVID L.	ILLINOIS STATE UNIVERSITY	HTS for Inhibitors of Schistosoma Mansoni Peroxiredoxins

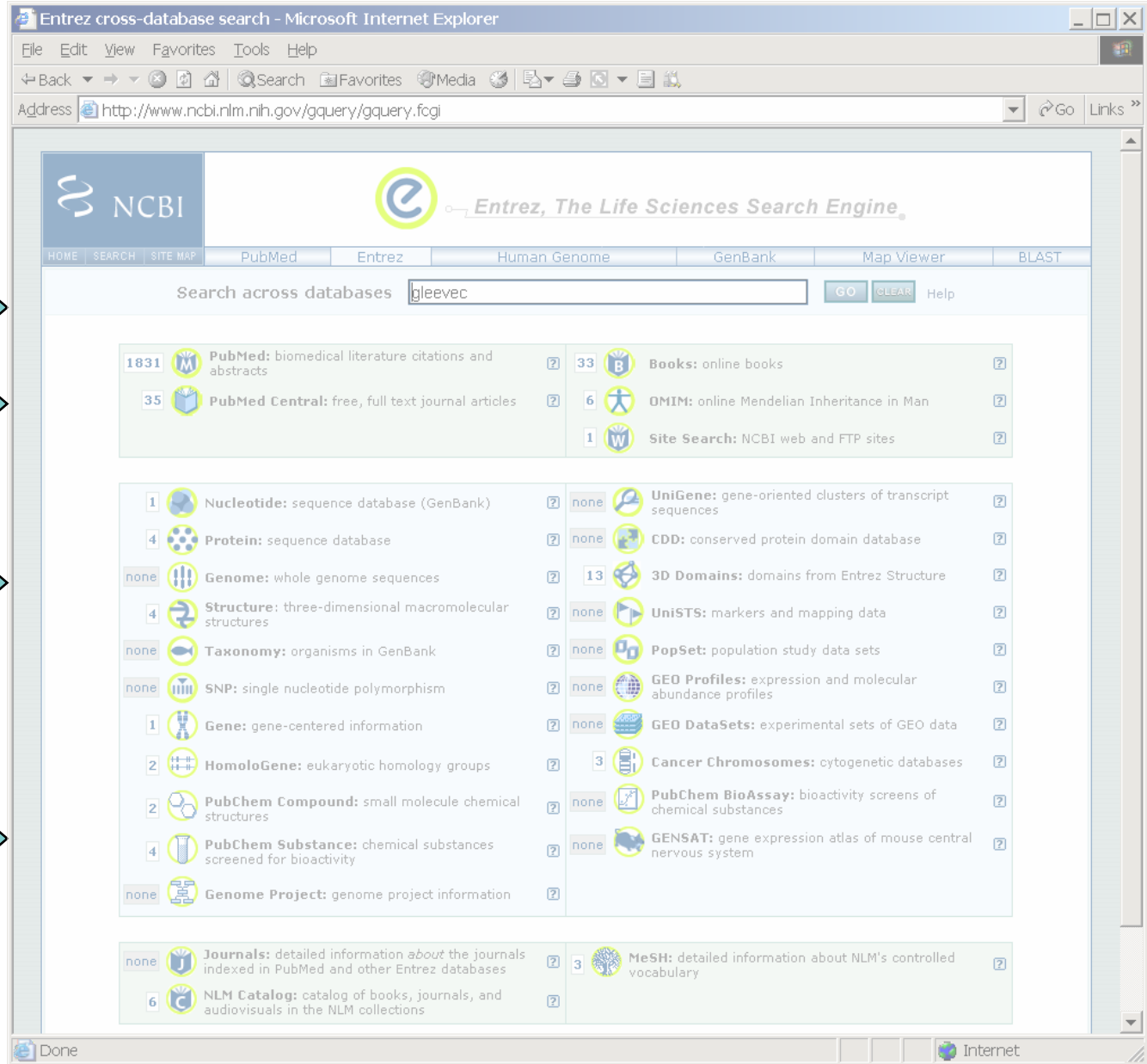
PubChem is integrated with the other NIH databases

Query for “gleevec”

Finds PubMed Articles

Finds Protein Structures

Finds PubChem Structures



NCBI

PubChem Compound

National Library of Medicine NLM

All Databases | PubMed | Nucleotide | Protein | Genome | Structure | PMC | PubChem | Books

Search PubChem Compound for Gleevec Go Clear Save Search

Limits | Preview/Index | History | Clipboard | Details

Display Summary Show 20 Sort by Send to

All: 2 | BioAssay: 0 | Protein3D: 1 | Rule of 5: 1

Items 1 - 2 of 2

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Entrez Help

PubChem
Help

PubChem Substance
Substance Database

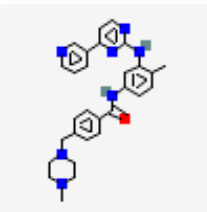
PubChem Compound
Compound Database

PubChem BioAssay
Bioactivity Database

PubChem
Structure Search

PubChem FTP

1: CID: 5291

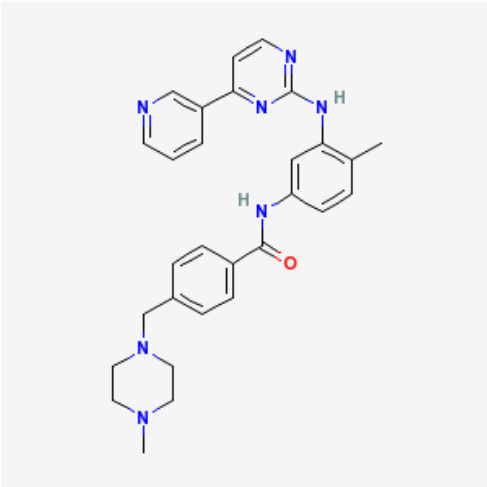


Imatinib mesilate, Gleevec ...
IUPAC: 4-[(4-methylpiperazin-1-yl)methyl]-N-[4-methyl-3-(4-py ...l)
amino-phenyl]-benzamide
MW: 493.603 | MF: C29H31N7O

Links

Links
- PubChem Substance
- Full text in PMC
- PubMed via MeSH
- Protein Structure
- Similar Compound

Compound Summary:



CID: 5291

Substances:
All: 9 Links
Same: 6 Links
Mixture: 3 Links

Protein Structures: 4 Links

NLM Toxicology: Link

Structure Search

MeSH | Synonyms | Properties | Descriptors | Exports

Medical Subject Annotations: (Total: 1)

imatinib

Pharmacological Action:
Antineoplastic Agents
Protein Kinase Inhibitors

PubMed via MeSH

Depositor-Supplied Synonyms: (Total: 12)

Display: Next 2 | All | Sort: Frequency

Imatinib
Glivec

CHEMBANK665

Items 1 - 20 of 20

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ClinicalTrials.gov

Privacy Policy

1: **Werner Syndrome Protein Phosphorylation by Abl Tyrosine Kinase Regulates Its Activity and Distribution.**
Cheng WH, Kobbe CV, Opresko PL, Fields KM, Ren J, Kufe D, Bohr VA.
Mol Cell Biol. 2003 Sep; 23(18): **6385-6395.**
PMCID: 193690
[Abstract] [Full Text] [PDF] Links

2: **Combination of rapamycin and protein tyrosine kinase (PTK) inhibitors for the treatment of leukemias caused by oncogenic PTKs.**
Mohi MG, Boulton C, Gu TL, Sternberg DW, Neuberg D, Griffin JD, Gilliland DG, Neel BG.
Proc Natl Acad Sci U S A. 2004 Mar 2; 101(9): **3130-3135.** published online before print February 19, 2004
PMCID: 365755
[Abstract] [Full Text] [PDF] Links

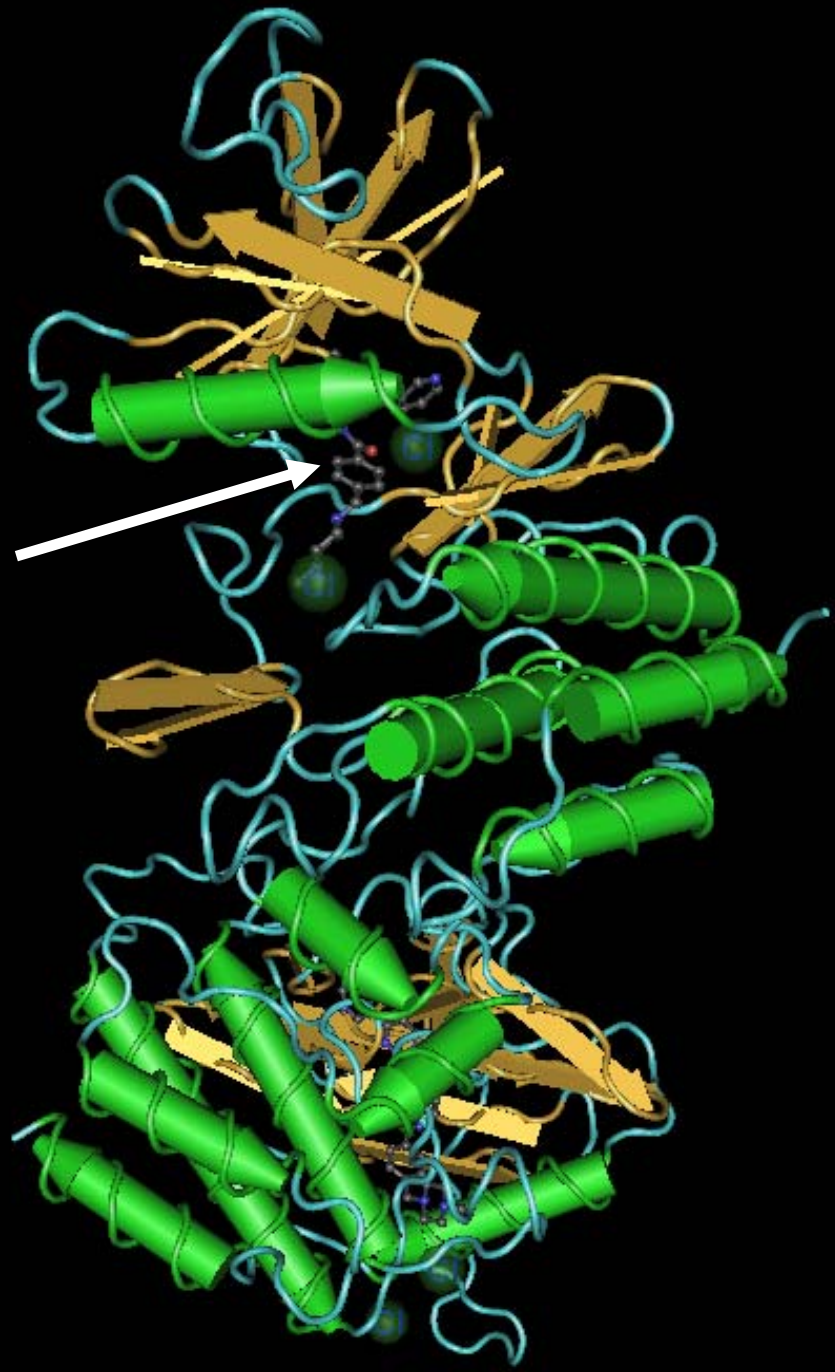
3: **Roles of Bim in Apoptosis of Normal and Bcr-Abl-Expressing Hematopoietic Progenitors.**
Kuribara R, Honda H, Matsui H, Shinjyo T, Inukai T, Sugita K, Nakazawa S, Hirai H, Ozawa K, Inaba T.
Mol Cell Biol. 2004 Jul; 24(14): **6172-6183.**
PMCID: 434248
[Abstract] [Full Text] [PDF] Links

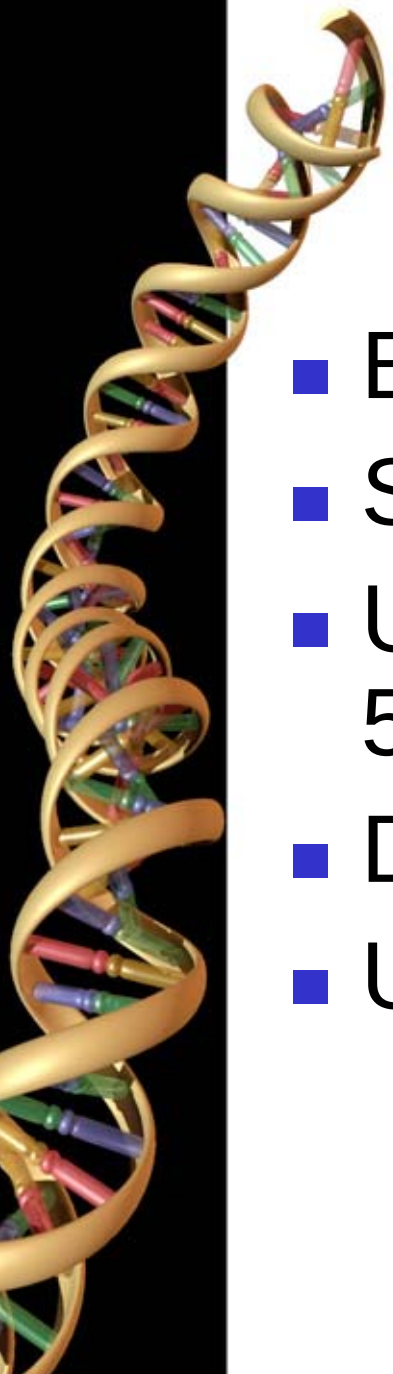
4: **Molecular-genetic imaging: current and future perspectives.**
Blasberg RG, Tjuvajev JG.
J Clin Invest. 2003 Jun 1; 111(11): **1620-1629.**
PMCID: 156118
[Full Text] [PDF] Links

5: **Gleevec (STI-571) inhibits lung cancer cell growth (A549) and potentiates the cisplatin effect in vitro.**
Zhang P, Gao WY, Turner S, Ducatman BS.
Mol Cancer. 2003; 2(): **1.** published online before print January 3, 2003
PMCID: 149413
[Abstract] [Full Text] [PDF] Links

6: **Effects of STI571 (gleevec) on pancreatic cancer cell growth.**
Li J, Kleeff J, Guo J, Fischer L, Giese N, Büchler MW, Friess H.
Mol Cancer. 2003; 2(): **32.** published online before print September 17, 2003

Gleevec complexed with its protein target



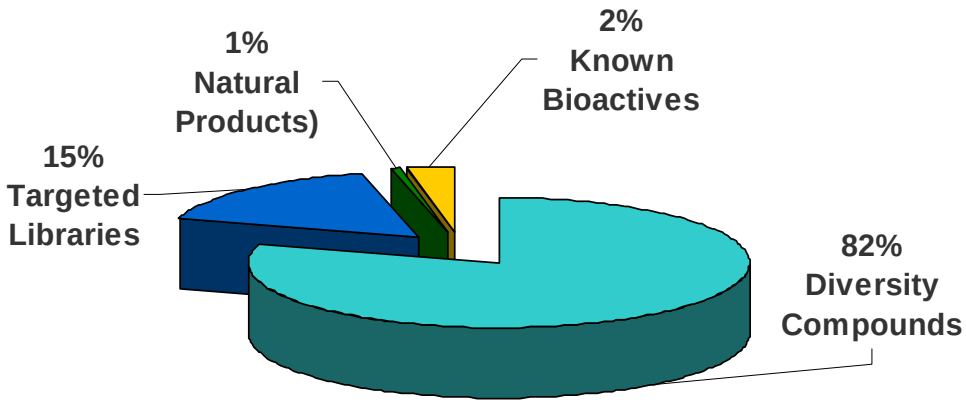


PubChem Statistics
April 2005

- Bioassays: 194
- Substances: 10,316,814
- Unique Compound Structures: 5,338,430
- Depositing Organizations: 41
- Users: >20,000/day

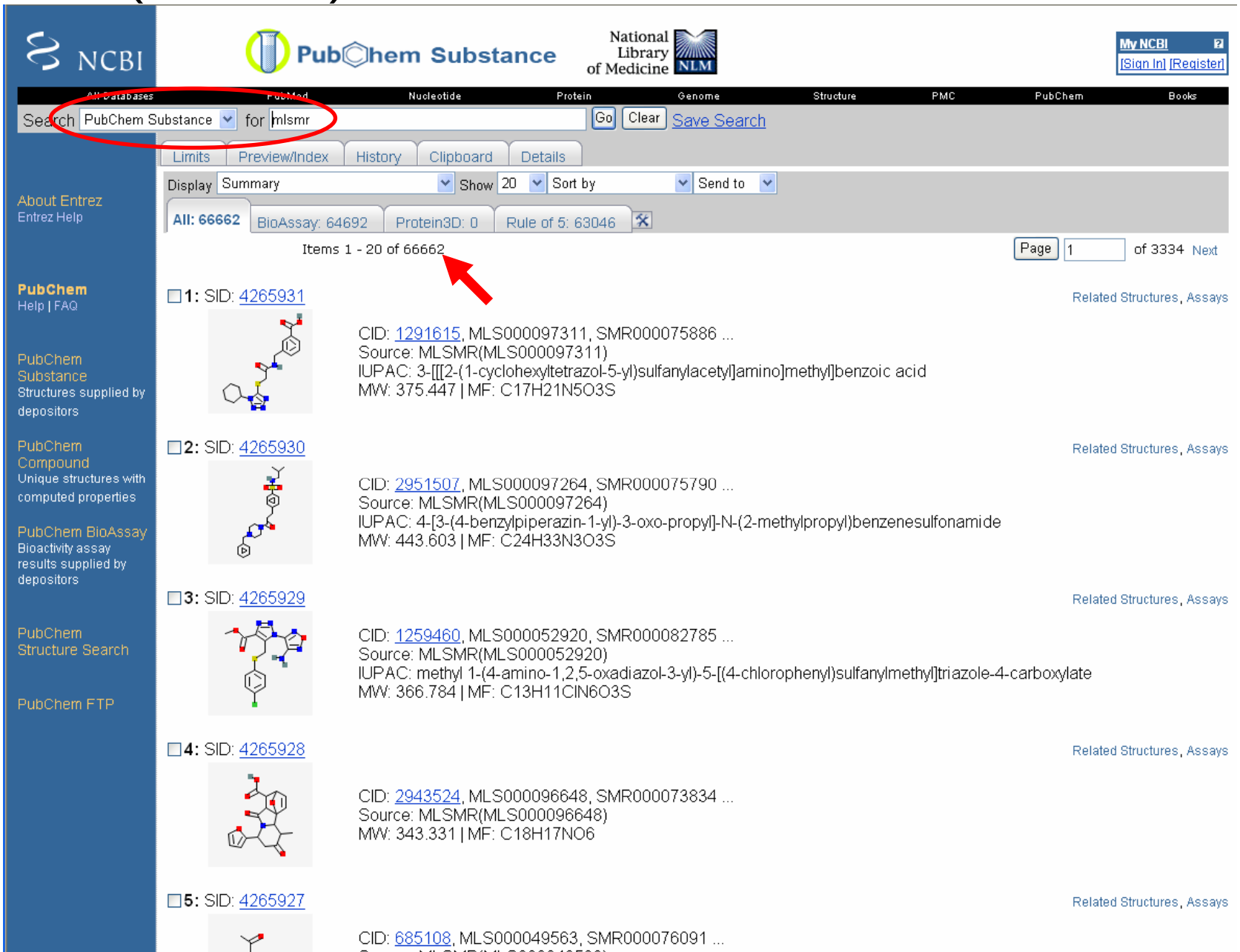
Molecular Libraries Compound Collection

- Housed at Discovery Partners International
- Initial set of ~67,000 compounds purchased from commercial vendors
  - Chosen by external advisors + DPI + NIH
  - >90% purity, >10mg, ±RO5, solubility >20ug/ml, all QCed



- Expanding the collection
  - Purchase of next 100,000 ongoing; 500,000 at maturity
    - Less stringent property requirements, filling out SAR clusters of 3-5
  - Molecular Libraries Roadmap Chemical Diversity initiatives
    - *Pilot scale libraries for HTS*
  - Centers for Methodology in Library Development
    - Boston U., Harvard, Pitt, U. Kansas
  - Solicitation of compounds from chemists in public/private sectors

The NIH Molecular Libraries Small Molecule Repository (MLSMR) is downloadable from PubChem



Molecular Libraries and Imaging

- Overview
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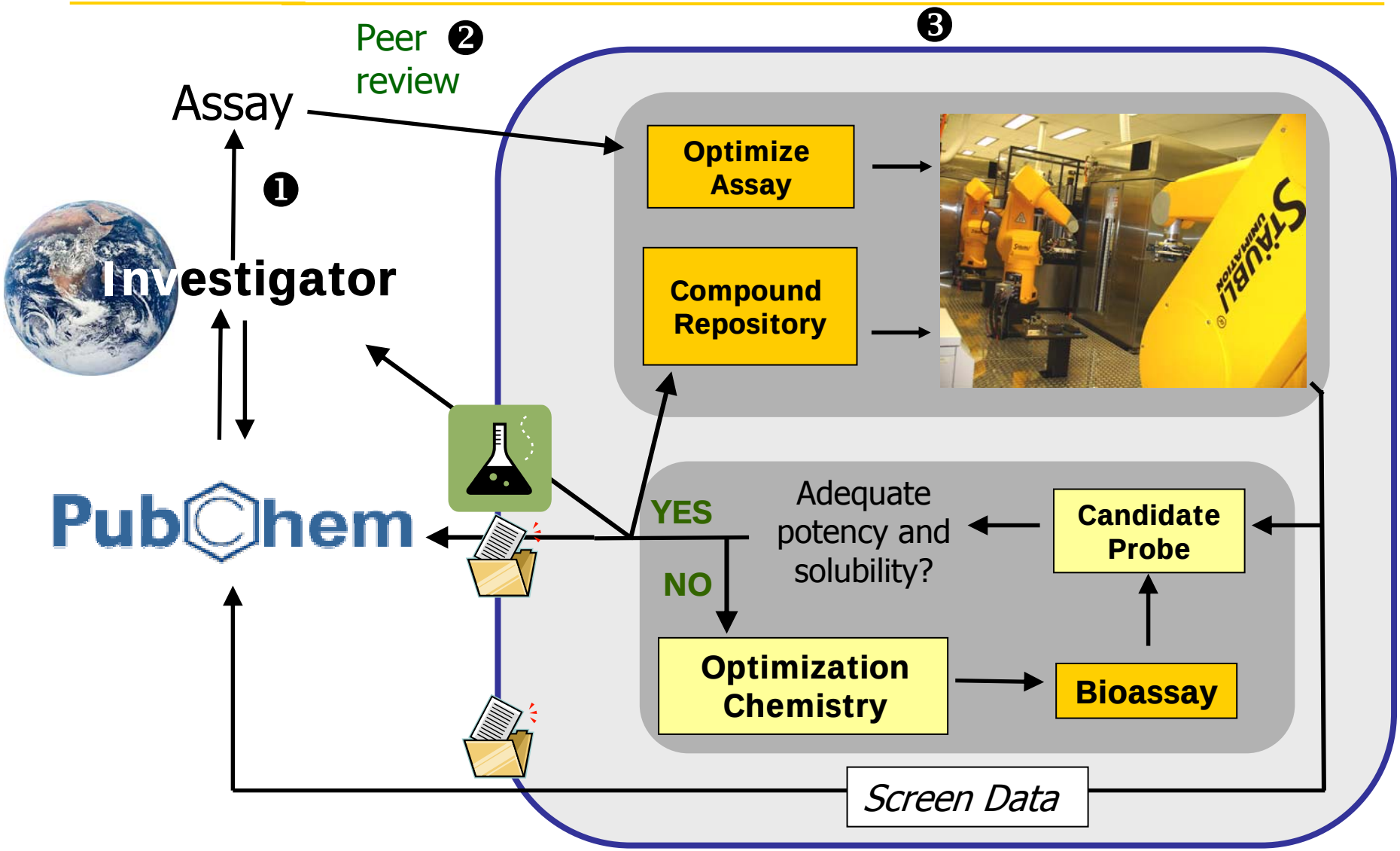
- Meetings

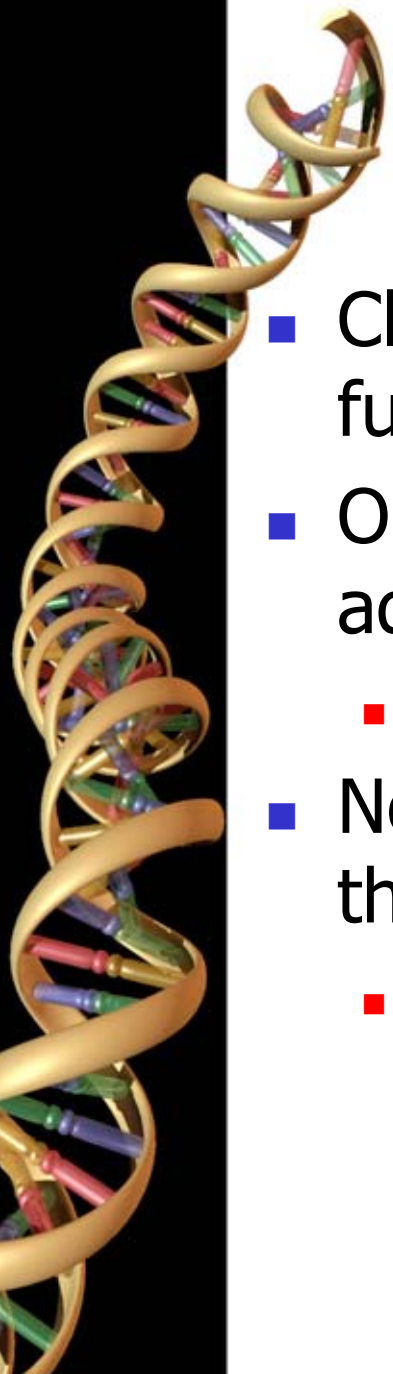
- PubChem

Molecular Libraries Screening Centers Network (MLSCN)
RFA-04-017

PI Name	Institution Name	Title
AUSTIN, CHRIS	NHGRI	NIH Chemical Genomics Center (NCGC) ■ Additional Information
DIAMOND, SCOTT	UNIVERSITY OF PENNSYLVANIA	The Penn Center for Molecular Discovery ■ Additional Information ■ Abstract (from CRISP)
DINGLEDINE, RAYMOND	EMORY UNIVERSITY	Emory Chemistry-Biology Center in the MLSCN ■ Abstract (from CRISP)
LAZO, JOHN	UNIVERSITY OF PITTSBURGH AT PITTSBURGH	University of Pittsburgh Molecular Libraries Screening Center ■ Additional Information ■ Abstract (from CRISP)
PIAZZA, GARY	SOUTHERN RESEARCH INSTITUTE	Southern Research Molecular Libraries Screening Center ■ Abstract (from CRISP)
REED, JOHN	THE BURNHAM INSTITUTE	San Diego Center for Chemical Genomics ■ Abstract (from CRISP)
ROSEN, HUGH	THE SCRIPPS RESEARCH INSTITUTE	Scripps Research Institute Molecular Screening Center ■ Abstract (from CRISP)
ROTHMAN, JAMES	COLUMBIA UNIVERSITY MEDICAL CENTER	MLSCN Center at Columbia University ■ Abstract (from CRISP)
SKLAR, LARRY	UNIVERSITY OF NEW MEXICO ALBUQUERQUE	New Mexico Molecular Libraries Screening Center ■ Additional Information ■ Abstract (from CRISP)
WEAVER, C. DAVID	VANDERBILT UNIVERSITY	Vanderbilt Screening Center for GPCRs, Ion Channels, and Transporters ■ Additional Information ■ Abstract (from CRISP)

MLSCN Operation

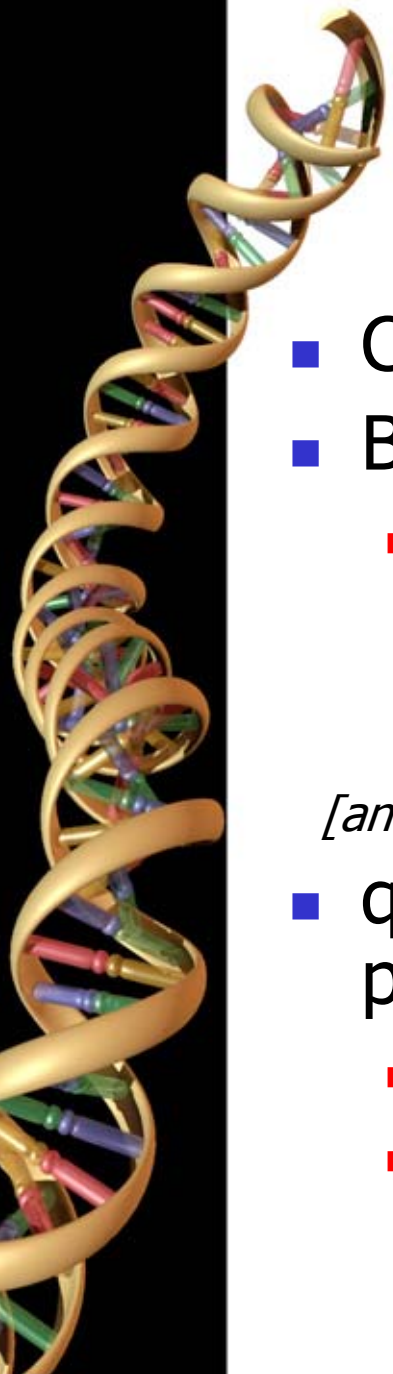




Products of the MLSCN

- Chemical probes of gene, pathway, and cell functions
- Optimized only for potency ($\leq 1\mu M$) and aqueous solubility
  - SAR ideally also present
- No IP obtained on any probes identified by the MLSCN
  - Maximal freedom of operation for
    - Basic research
    - Target validation
    - Use of results as starting points for further optimization

NIH Chemical Genomics Center



Quantitative HTS (qHTS) Paradigm

- Conventional HTS done at single [ ]
- But [ ] critical to small molecule effects
  - *"All things are poisons, for there is nothing without poisonous qualities. It is only the dose which make a thing a poison…a lot kills, a little cures ."* - **Paracelsus (1493-1521)**

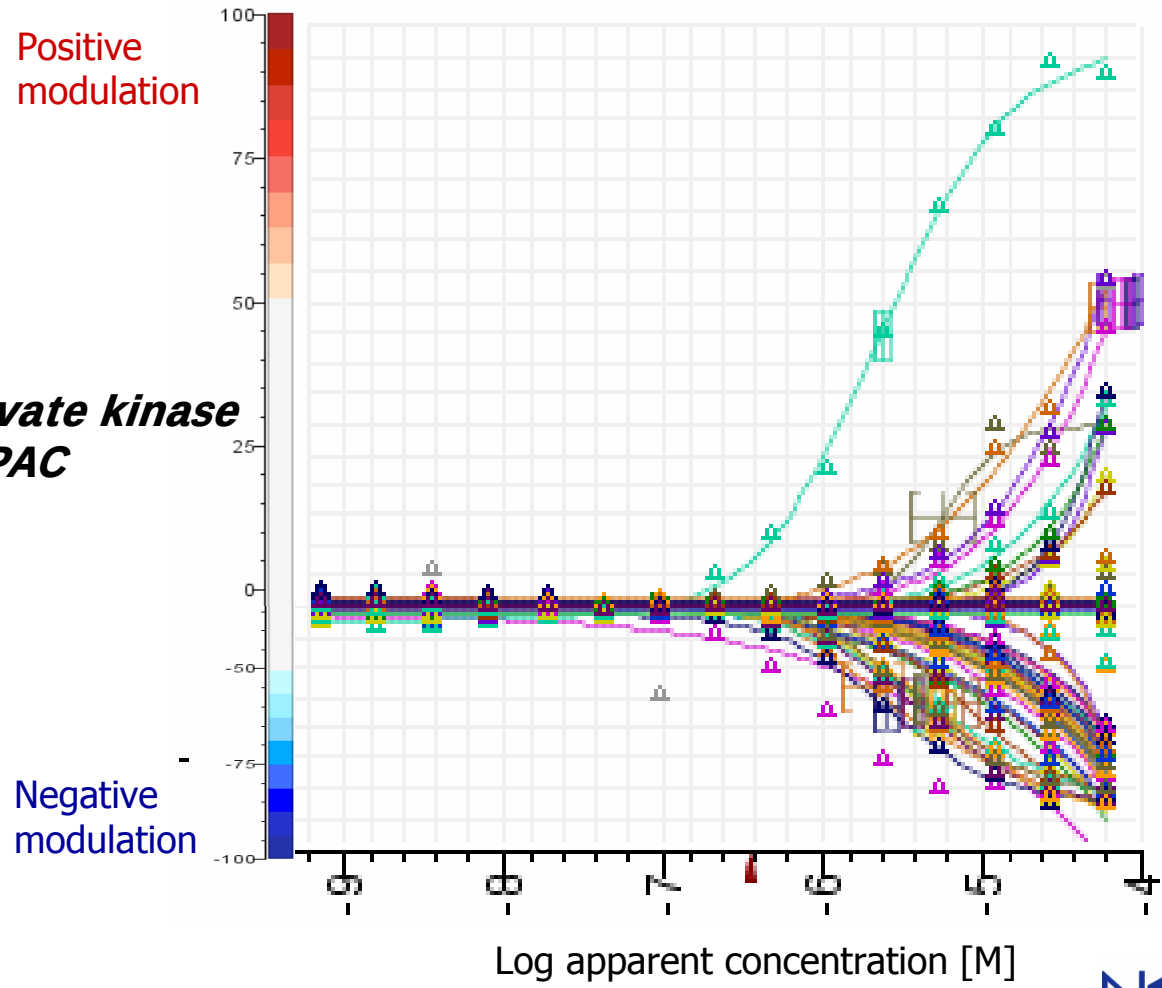
[and less does nothing]

- qHTS tests all compounds in titrations in primary screen
  - HTS as high-throughput pharmacology
  - Rich positive and negative activity data on chemical libraries

NIH Chemical Genomics Center

Data from a test primary screen: 1280 concentration-response curves

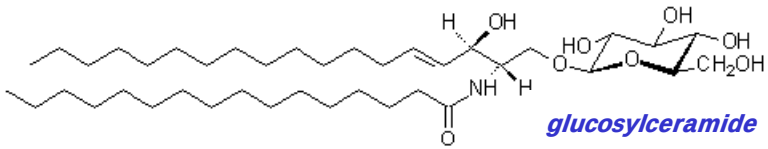
Assay: Pyruvate kinase
Library: LOPAC



Ameliorating the Defect in Gaucher's Disease

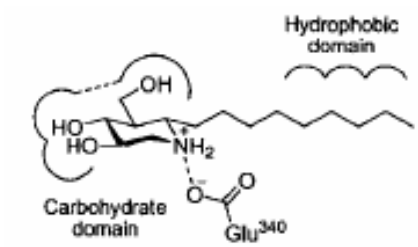
NIH Chemical Genomics Center – Ellen Sidransky, NHGRI

- Gaucher's Disease
  - Caused by mutations in glucocerebrosidase



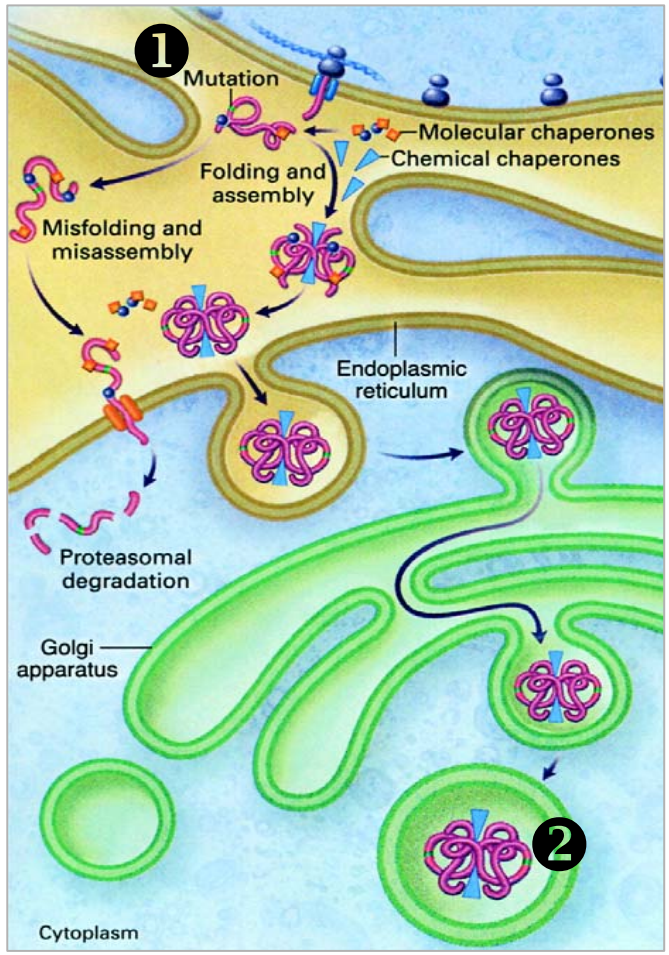
glucosylceramide

  - Some mutations exhibit trafficking defect
  - Current treatment: enzyme replacement
    - Limited efficacy
    - Expensive
- Pharmacological Chaperone Concept
  - Small molecules act as reversible binders, stabilizing protein's native conformation
  - Correct trafficking restored, enzyme exhibits physiological activity

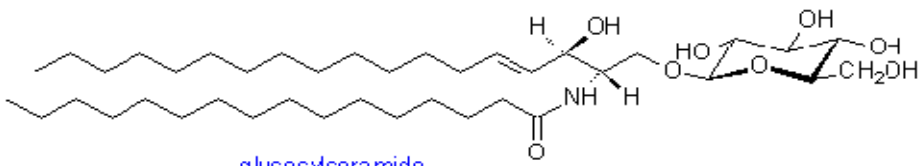


6-nonyl isofagomine

Zhu et al. *Angew Chem. Int. Ed.* **2005** 44 p7450

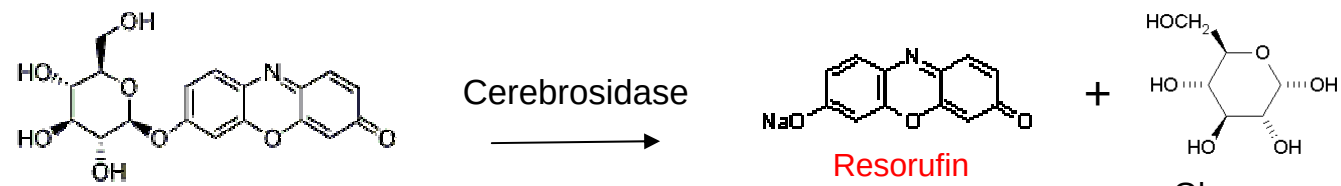


Glucocerebrosidase Enzyme Assay

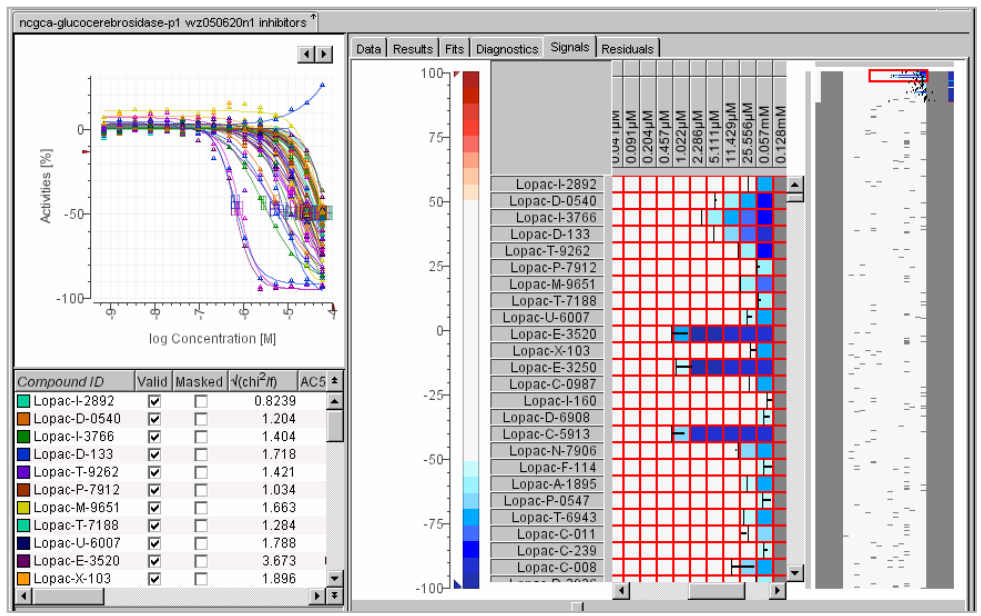


glucocerebrosidase catalyzes the hydrolysis of glucosylceramide to glucose and ceramide

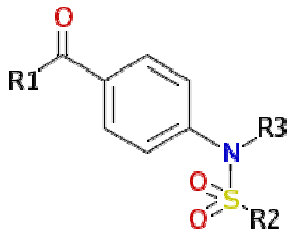
Red fluorogenic substrate assay:



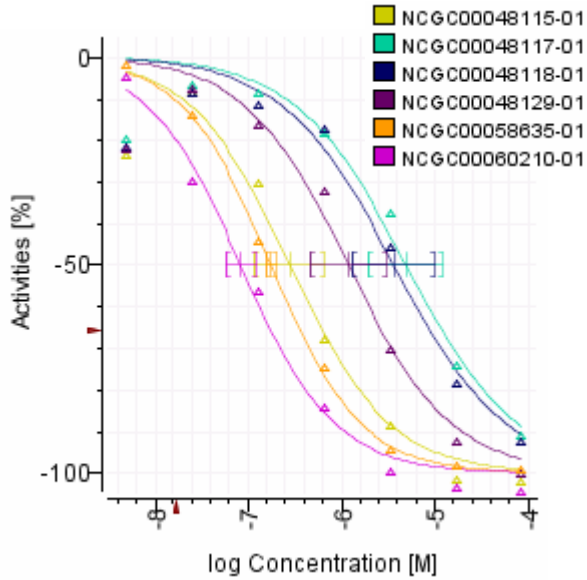
1536-well Assay Protocol		
Step	**Value**	**Description**
1	2 µL	Enzyme
2	1000 rpm, 1 min	centrifugation
3	20 nL	**40 µM – 0.5 nM**
4	1 µL	substrate
5	1000 rpm, 1 min	centrifugation
6	20 min	RT incubation
7	548nm /600nm	ViewLux reader



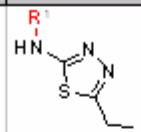
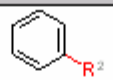
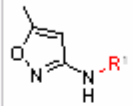
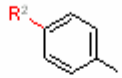
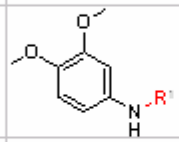
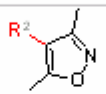
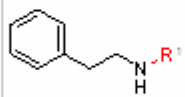
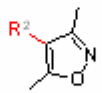
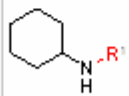
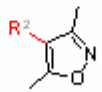
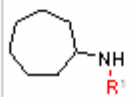
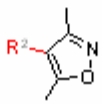
Glucocerebrosidase inhibitors: Aryl Sulfonamide Series



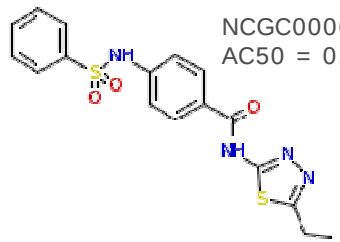
MW Range: 243 to 497
ALogP Range: 0.4 to 5.0
Potency Range: 70nM to >77uM

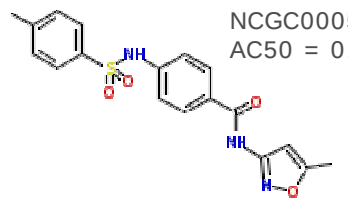


R-Group Table

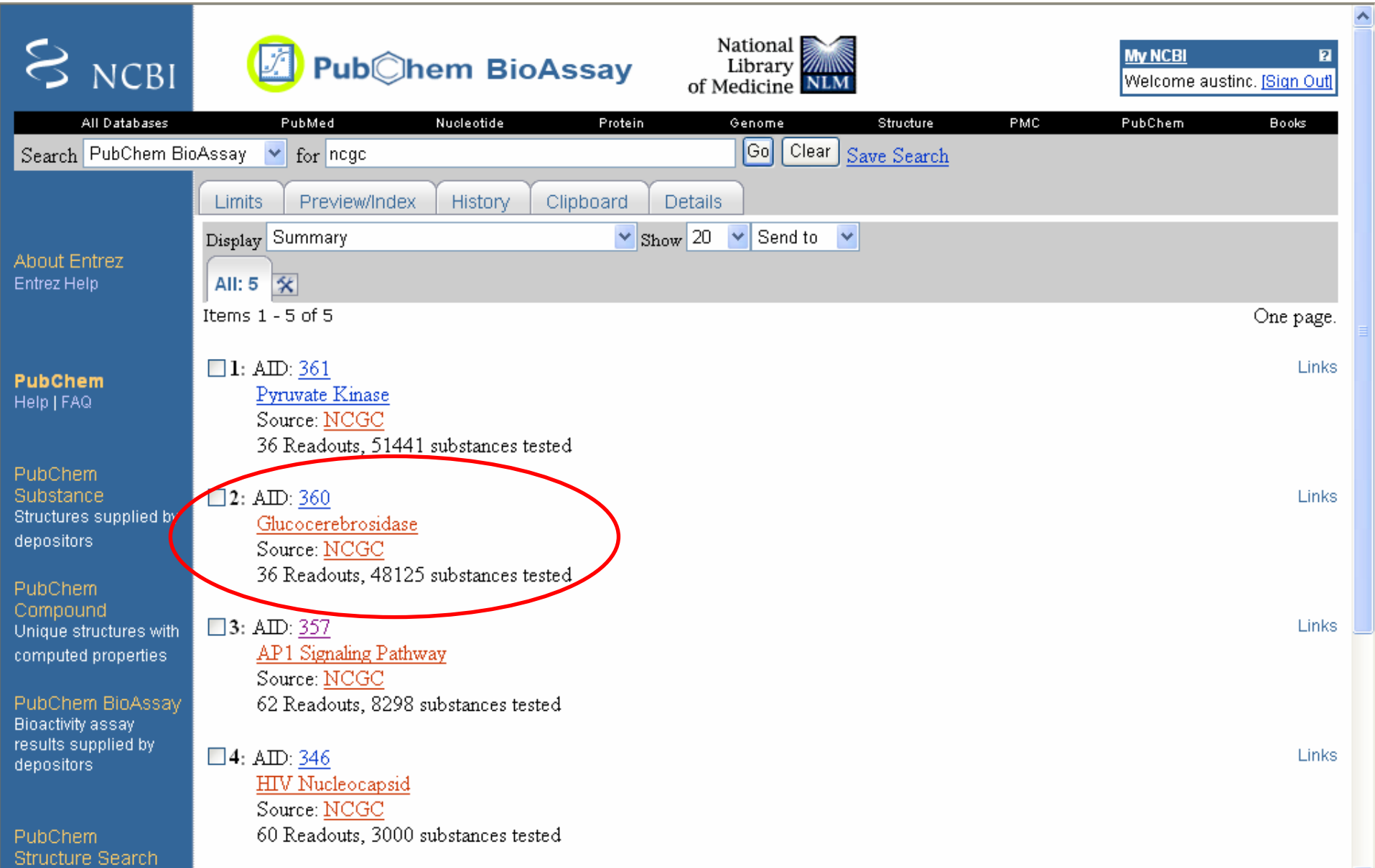
Compound	R_1	R_2	R_3	AC_{50}	Hill Slope
NCGC00060210-01			H	7.00E-08	0.66
NCGC00058635-01			H	1.55E-07	0.85
NCGC00048115-01			H	2.95E-07	0.85
NCGC00048129-01			H	1.62E-06	1.02
NCGC00048118-01			H	4.09E-06	1.11
NCGC00048117-01			H	5.80E-06	0.98

…150 analogues…





All data are deposited into PubChem



BioAssay Summary

BioAssay ID (AID): 360
Source: NCGC
Name: Glucocerebrosidase

Links | Description | Protocol | Show Data | Select Data

Links:

Substances tested: 48125 ; active: 549 ; inactive: 45736 ; inconclusive: 1840

PubMed: 4

OMIM: 3

MMDB: 1

Description:

NCGC Assay Overview:

Beta-glucocerebrosidase catalyzes the hydrolysis of beta-glucocerebroside to glucose and ceramide. The inherited deficiency of beta-glucocerebrosidase results in Gaucher disease, which is characterized by a wide variety of symptoms including hepatosplenomegaly, anemia, thrombocytopenia, bony lesions and bone marrow infiltration with characteristic storage cells, known as Gaucher cells. There are also forms of the disorder affecting the central nervous system. Patients with the same genotypes can manifest with diverse clinical presentations and it is believed that improper folding and trafficking of beta-glucocerbrosidase may contribute to the phenotypes observed.

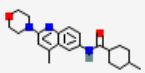
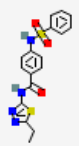
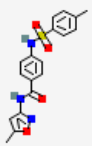
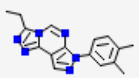
Low molecular weight molecules, acting as chaperones, may potentially restore trafficking of misfolded beta-glucocerebrosidase from the endoplasmic reticulum to the lysosomes, thereby enhancing functional lysosomal beta-glucocerebrosidase activity.

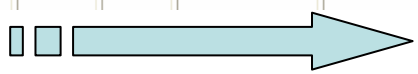
BioAssay Results

BioAssay ID (AID): 360
Source: NCGC
Name: Glucocerebrosidase

back to summary

Total 48125 compounds found (48125 unique), 20 displayed: Next **page**

Structure	PubChem		Outcome	Activity Score	Submitter	Submission Date	Activity Direction	Activity Qualifier	Qualified AC50	Log of AC50	Hill Coefficient	Curve R2	Data Type	Compound Type	Compou QC
	SID	CID													
	4243169	3237927	Active	72	ncgc	19 Jan 2006	decreasing	=	6.06e-008	-7.22	0.87	1	qHTS	NIHSMR	QC'd by [
	4264637	2210290	Active	71	ncgc	19 Jan 2006	decreasing	=	7e-008	-7.16	0.66	1	qHTS	NIHSMR	QC'd by [
	4261164	1300581	Active	68	ncgc	19 Jan 2006	decreasing	=	1.55e-007	-6.81	0.85	1	qHTS	NIHSMR	QC'd by [
	862780	664013	Active	66	ncgc	19 Jan 2006	decreasing	=	2.14e-007	-6.67	0.99	1	qHTS	NIHSMR	QC'd by [



BioAssay Results

BioAssay ID (AID): 360
Source: NCGC
Name: Glucocerebrosidase

back to summary

Full CRC

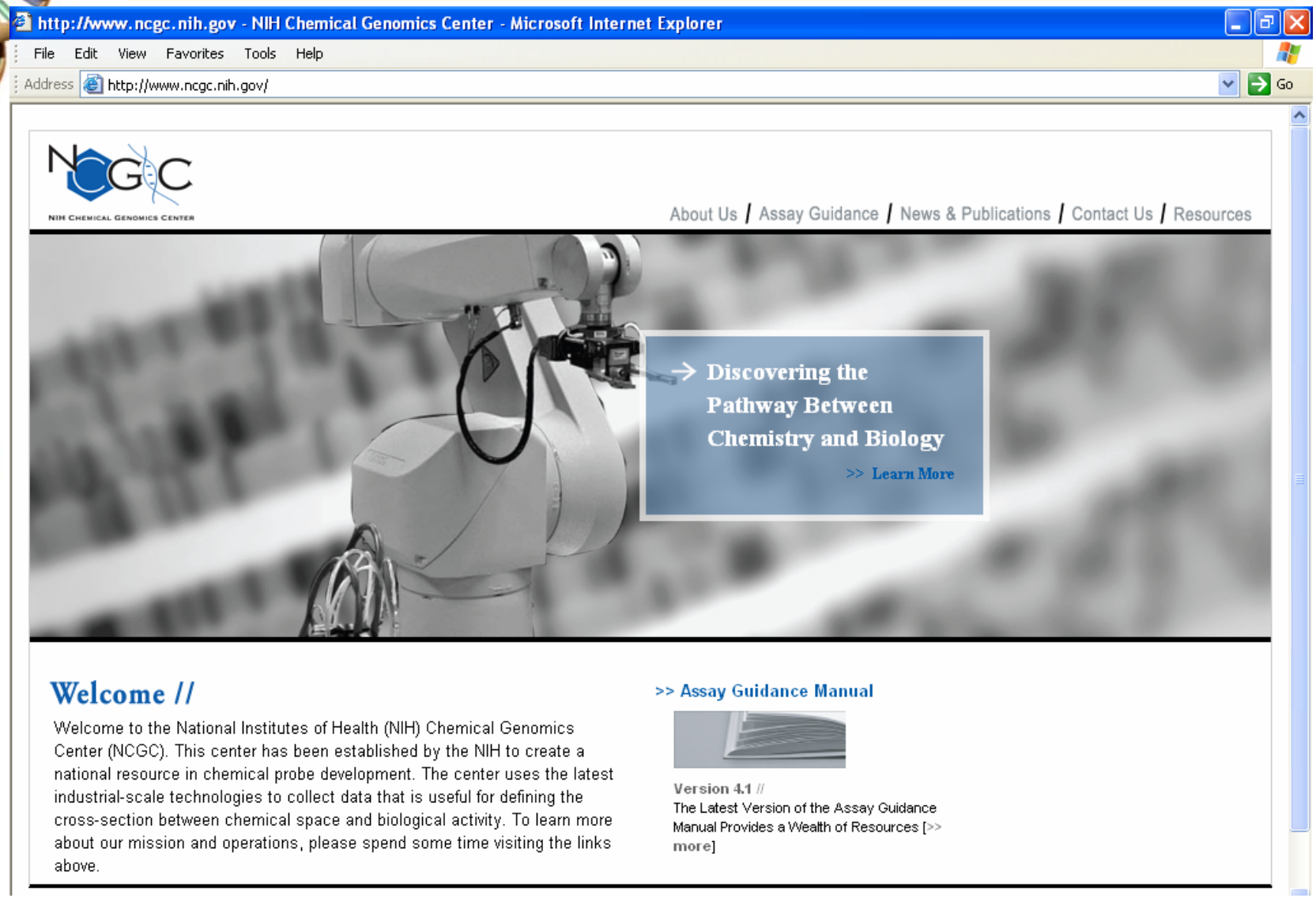
Total 48125 compounds found (48125 unique), 20 displayed: Next page

AID: 360

Compound Type	Compound QC	Curve Fit Model	Hill S0	Hill Sinf	Hill dS	Log AC50 Std Error	Curve Chi2f	Excluded Points	Number of Points	Activity at 4.925nM (%)	Activity at 24.623nM (%)	Activity at 0.123uM (%)	Activity at 0.615uM (%)	Activity at 3.077uM (%)	Activity at 15.386uM (%)	Activity at 0.077mM (%)
NIHSMR	QC'd by DPI	4pHill (AC50,n,S0,Sinf)	-1.23	-100.1	98.92	0.02	0.5	{}	7	-11.3	-31.9	-65.8	-88.4	-96.4	-99.6	-100.2
NIHSMR	QC'd by DPI	4pHill (AC50,n,S0,Sinf)	11.41	-107.2	118.6	0.1	2.04	{}	7	-5.5	-30.2	-56.9	-84.4	-100	-103.7	-105
NIHSMR	QC'd by DPI	4pHill (AC50,n,S0,Sinf)	2.97	-100.6	103.5	0.04	1.4	{}	7	-2.4	-14.2	-44.7	-74.8	-94.6	-98.5	-99.4
NIHSMR	QC'd by DPI	4pHill (AC50,n,S0,Sinf)	-1.83	-95.57	93.74	0.04	1.8	{}	7	-2.9	-13.4	-35.5	-70.9	-90.7	-94.9	-93.7

NCGC Website resources

www.ncgc.nih.gov



>> Assay Guidance

Assay Guidance Manual - Version 4.1

Introduction

Transfer of Validated Assays

Assay Operations for SAR Support

Enzymatic Assays

Receptor Binding Assays

GTPγS Binding Assays

Tissue Culture Assays

Cell-Based Elisa (C-Elisa) and Westerns Blots for Quantitative Antigen Detection

FLIPR™ Assays to Measure GPCR and Ion Channel Targets

Immunoassay Methods

Data Standardization for Results Management

Glossary of Quantitative Biology Terms

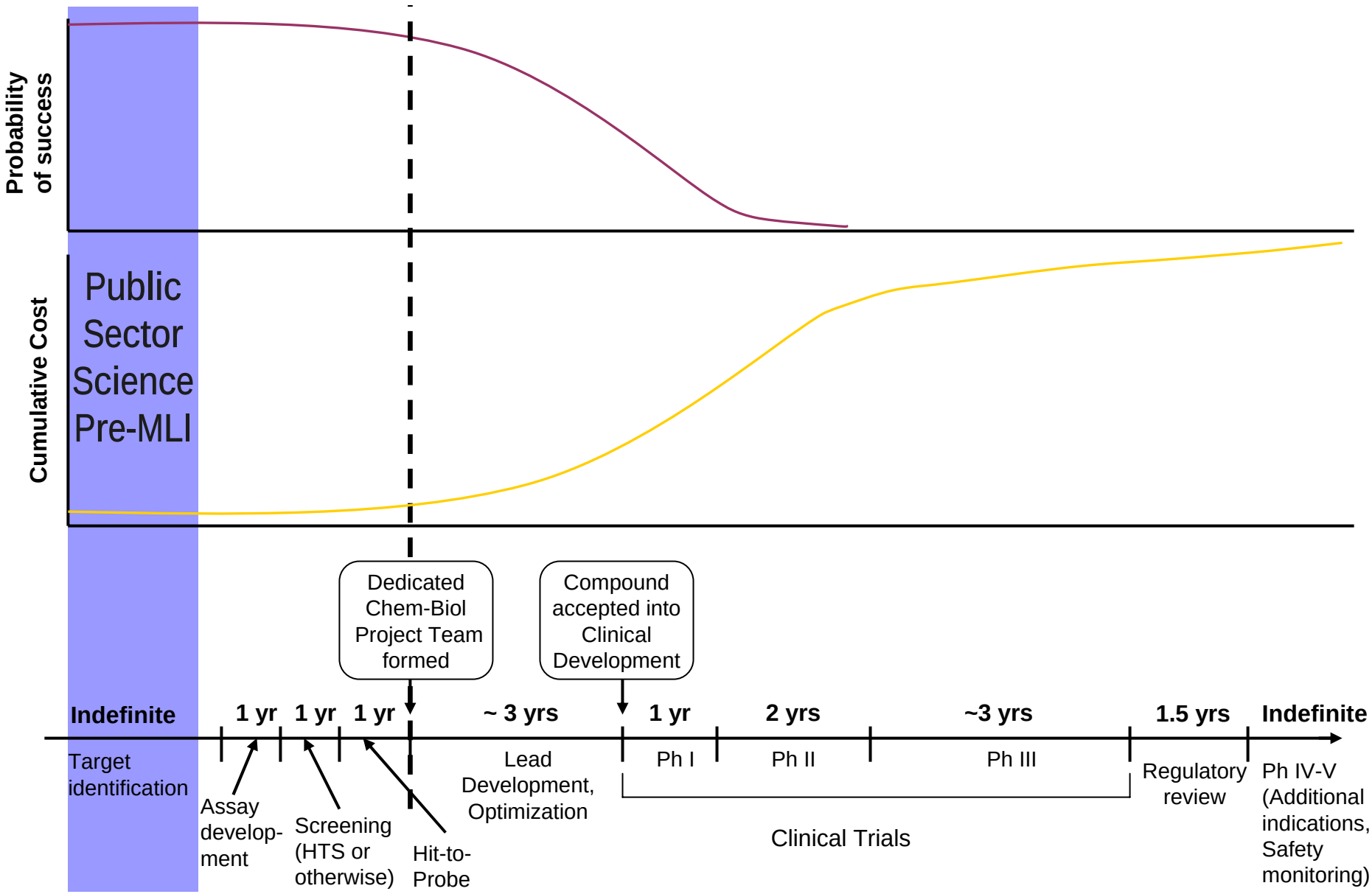
Comment Form

Table of Contents

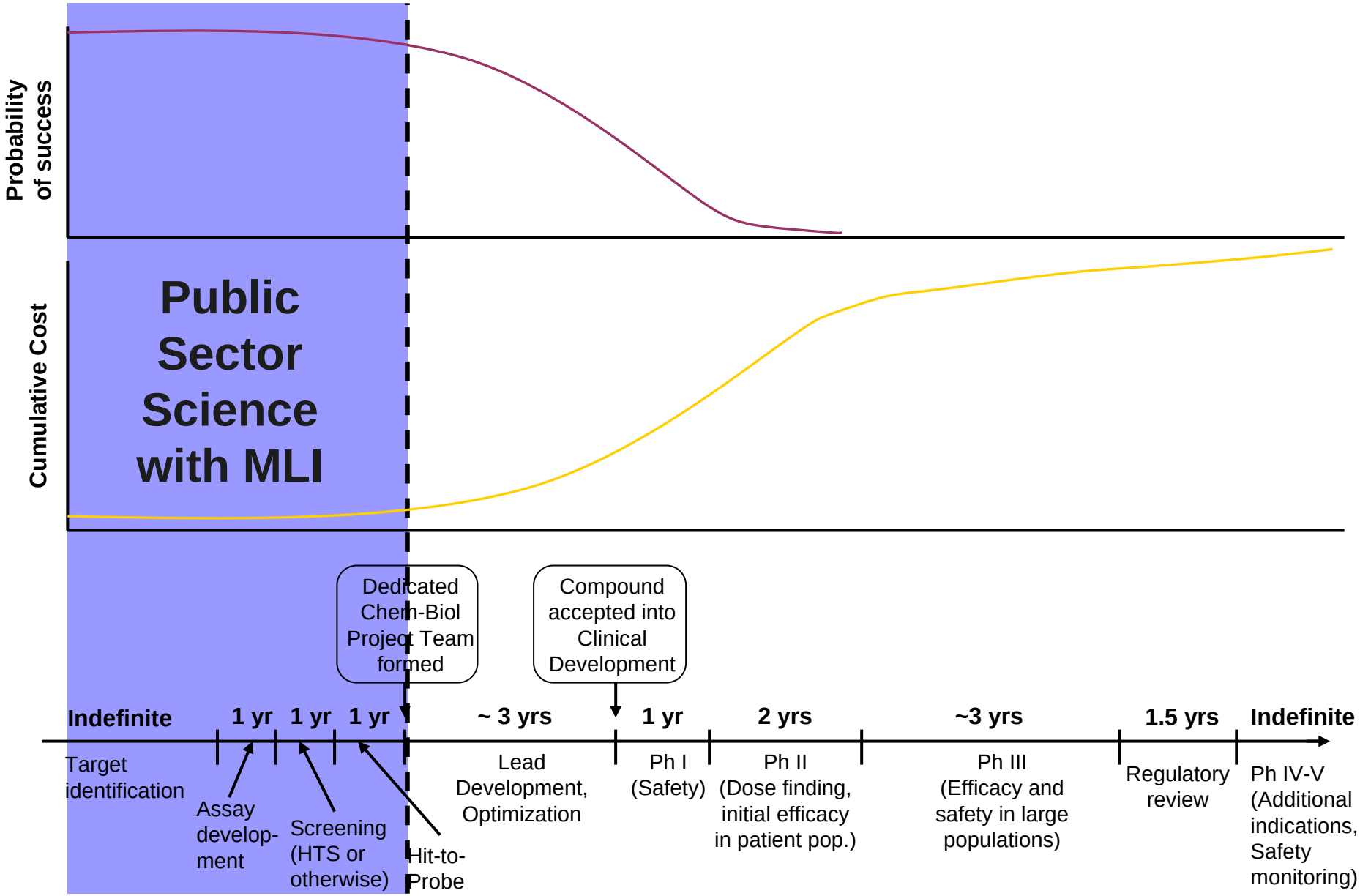
Distinguishing the NCGC from Pharma and Biotech

Private Sector	NCGC
Develops drugs *10 yrs & $800MM*	Develops probes *$50MM for MLSCN*
Compound collection selected for "Drug-like" potential *'rule-of-five'; IP novelty*	Compound collection contains "broadly diverse" substances *'Sigma catalog x Merck Index'*
Target validation pre-requisite for screening *clinical validation; medical need; market*	Target validation can be poor or non-existent *probes used for target validation*
Results & structures are corporate assets *limited access in corporate database*	Results & structures are public assets *immediately deposited to public database*
Target class is generally 'druggable' *e.g., GPCR; NHR; enzyme*	Preferred class is 'non-traditional' *e.g., PPI; aberrant splicing; phenotypic assays*
Shareholder funded *profitable drugs*	Publicly funded *biological insights; enabling drug disc.*

How does Molecular Libraries relate to drug development?



How does Molecular Libraries relate to drug development?



Re-engineering the Clinical Research Enterprise

- Overview
- Implementation Group Members
- Funding Opportunities
- Funded Research
- Meetings

Re-engineering the Clinical Research Enterprise

Translational Research

OVERVIEW

To improve human health, scientific discoveries must be translated into practical applications. Such discoveries typically begin at "the bench" with basic research—in which scientists study disease at a molecular or cellular level—then progress to the clinical level, or the patient's "bedside."

Scientists are increasingly aware that this bench-to-bedside approach to translational research is really a two-way street. Basic scientists provide clinicians with new tools for use in patients and for assessment of their impact, and clinical researchers make novel observations about the nature and progression of disease that often stimulate basic investigations.

Translational research has proven to be a powerful process that drives the clinical research engine. However, a stronger research infrastructure could strengthen and accelerate this critical part of the clinical research enterprise. The NIH Roadmap attempts to catalyze translational research in various ways, including:

Enhancing the Discipline of Clinical and Translational Science

Growing barriers between clinical and basic research, along with the ever the increasing complexities involved in conducting clinical research, are making it more difficult to translate new knowledge to the clinic -- and back again to the bench. These challenges are limiting professional interest in the field and hampering the clinical research enterprise at a time when it should be expanding.

Through discussions with deans of academic health centers and recommendations from the Institute of Medicine, the NIH recognizes that a broad re-engineering effort is needed to create greater opportunity to catalyze the development of a new discipline of clinical and translational science. The result will be a bolder transforming vision for 21st Century.

NIH Rapid Access to Interventional Development (NIH-RAID Pilot)

NIH-RAID Pilot Program

- Overview
- Request Process
- Submission Form
- Tech Transfer Form
- How to Contact Us
- Critical Dates
- Log In

E-mail questions to
NIH-RAID@niddk.nih.gov

OVERVIEW

Summary

The National Institutes of Health (NIH) Roadmap is establishing a pilot program called the NIH-RAID Pilot (Rapid Access to Interventional Development), similar to the National Cancer Institute's (NCI) RAID program, to make available, on a competitive basis, certain critical resources needed for the development of new small molecule therapeutic agents. This program, part of the Translational Research component of Reengineering the Clinical Research Enterprise, will use resources of NCI's Developmental Therapeutics Program. The services provided will depend upon the stage of the project and the strength of the preliminary

What specific services are available for the pilot program?

The main tasks that are supported by the NIH-RAID Pilot are as follows:

- Synthesis in bulk of small molecules and oligonucleotides, chemical synthesis of small peptides (GMP and non-GMP)
- Scale-up production from lab-scale to clinical-trials lot scale
- Development of analytical methods for bulk substances
- Isolation and purification of pharmacologically active entities from natural sources
- Development of pharmacology assays;
- Conduct of pharmacology studies with a pre-determined assay
- Development of suitable formulations
- Physicochemical characterization of formulations developed, including tests of stability, disintegration, dissolution, and lot-to-lot variability
- Range-finding initial toxicology
- IND-directed toxicology, with correlative pharmacology and histopathology
- Product development planning and advice in IND preparation

The tasks necessary will vary from project to project. In some cases the NIH-RAID Pilot will support only one or two key steps for early stage preclinical efficacy testing; in other cases it may be possible to provide assistance with most of the development tasks needed to file an IND.

The output of NIH-RAID activities, both products and information, will be made fully available to the originating investigator for support of additional studies or of an IND application and performance of clinical trials. Data and product will be transferred to the applicant under the terms of an NIH Materials Transfer Agreement (see Intellectual Property below). For those projects approved for production of a clinical batch, the final vialed drug product will be delivered in a single shipment; the NIH-RAID Pilot cannot distribute drug product in multiple shipments or on a per patient basis.

Institutional Clinical and Translational Science Awards (RFA-RM-06-002) NIH released an RFA on October 12, 2005, soliciting grant applications for Institutional Clinical and Translational Science Awards (CTSAs). The purpose of the CTSA initiative, which NCRR is leading on behalf of the NIH Roadmap for Medical Research, is to assist institutions to forge a uniquely transformative, novel, and integrative academic home for Clinical and Translational Science that has the consolidated resources to: 1) captivate, advance, and nurture a cadre of well-trained multi- and inter-disciplinary investigators and research teams; 2) create an incubator for innovative research tools and information technologies; and 3) synergize multi-disciplinary and inter-disciplinary clinical and translational research and researchers to catalyze the application of new knowledge and techniques to clinical practice at the front lines of patient care.

These new Clinical and Translational Science entities are expected to serve as a magnet that concentrates basic, translational, and clinical investigators, community clinicians, clinical practices, networks, professional societies, and industry to facilitate the development of new professional interactions, programs, and research projects. It is anticipated that these new institutional arrangements, coupled with innovative advanced degree programs, will foster the nascent development of a new discipline of Clinical and Translational Science that will be much broader and deeper than the classical and separate domains of translational research and clinical investigation.

To ensure the successful establishment and long-term sustenance of these ground-breaking programs, it is important that the developed program accrue significant institutional support, be granted status as a major administrative entity within the applicant institution, and that the program director have authority, perhaps shared with other high-level institutional officials, over requisite space, resources, faculty appointments, protected time, and promotion.

NIH anticipates that many diverse models will be proposed for the fulfillment of these goals and welcomes applicants to develop innovative programs that meet the needs of both the local institution and of the wider research community. Grant applications are due on March 27, 2006 and awards are expected by September, 2006.