The NIH Roadmap: *New Pathways to Discovery*

Empowering Small Molecule Research

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NIH Roadmap

ACCELERATING MEDICAL DISCOVERY TO IMPROVE HEALTH

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

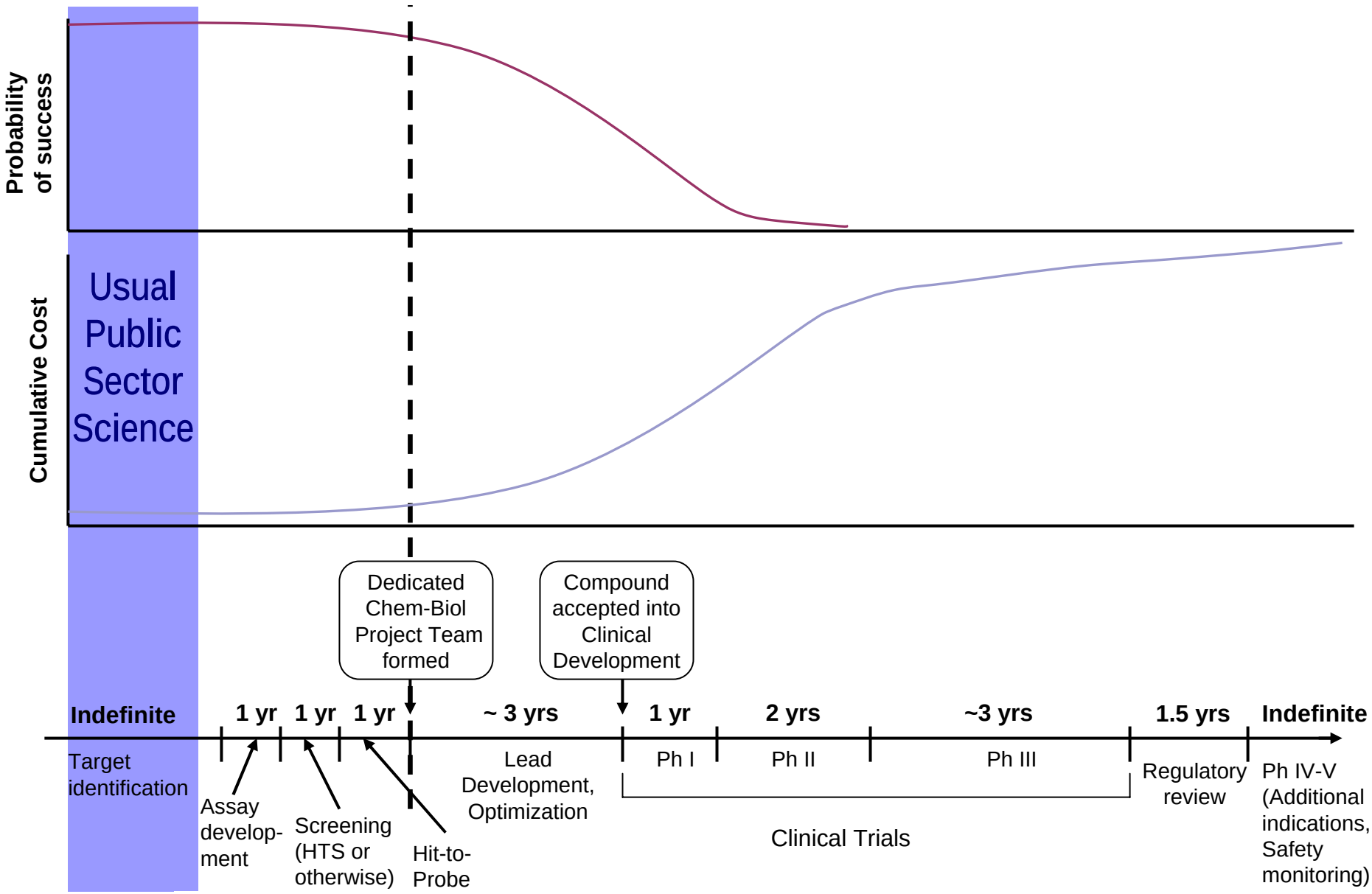
- Re-engineering the Clinical Research Enterprise

Purpose:

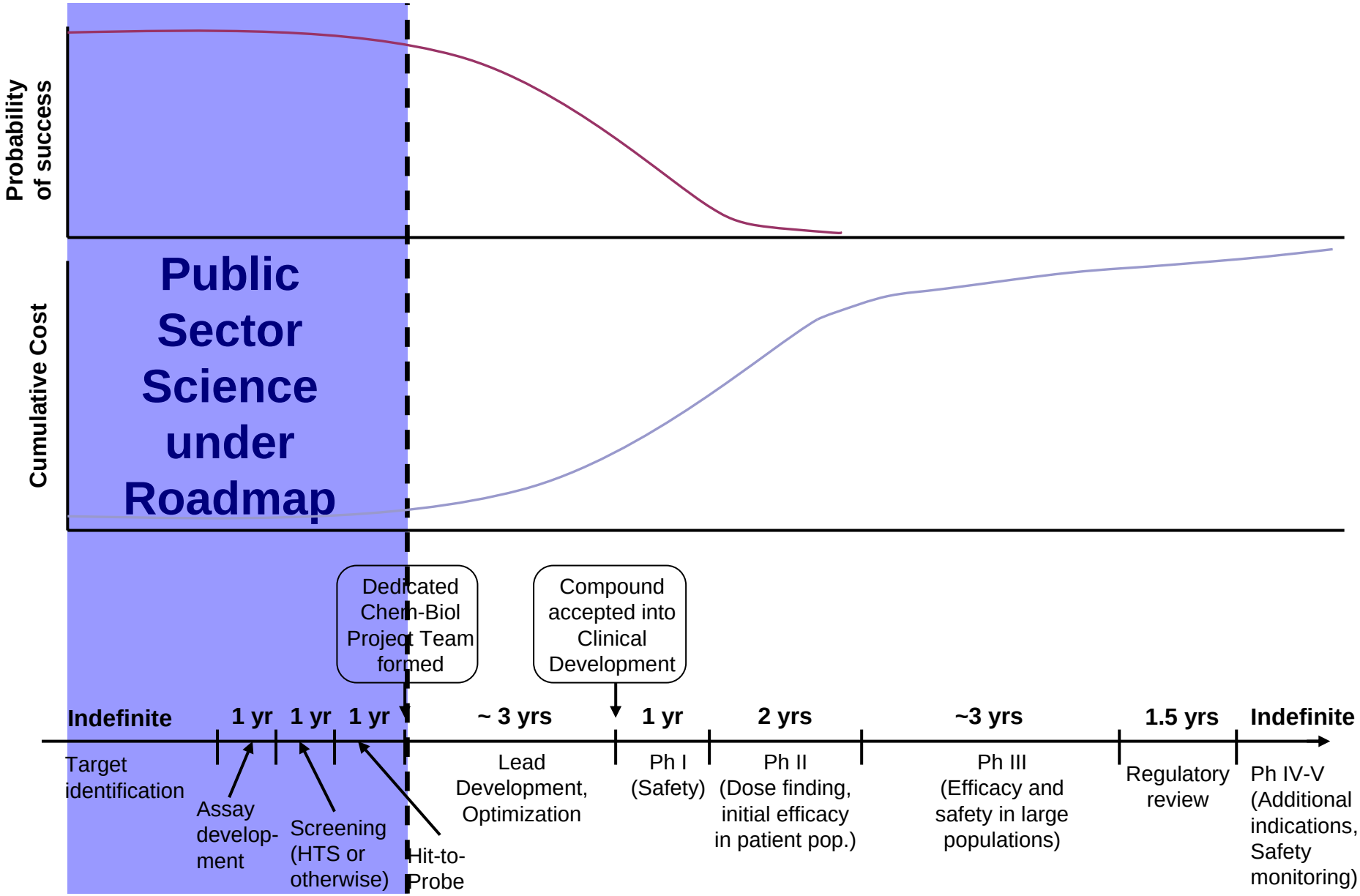
To empower the research community to use small molecule compounds in their research, whether as tools to perturb genes and pathways, or as starting points to the development of new therapeutics for human disease

- http://nihroadmap.nih.gov/

How does Molecular Libraries relate to drug development?

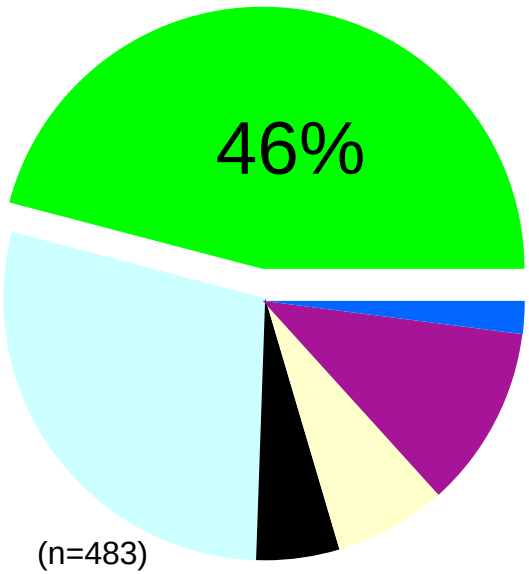


How does Molecular Libraries relate to drug development?



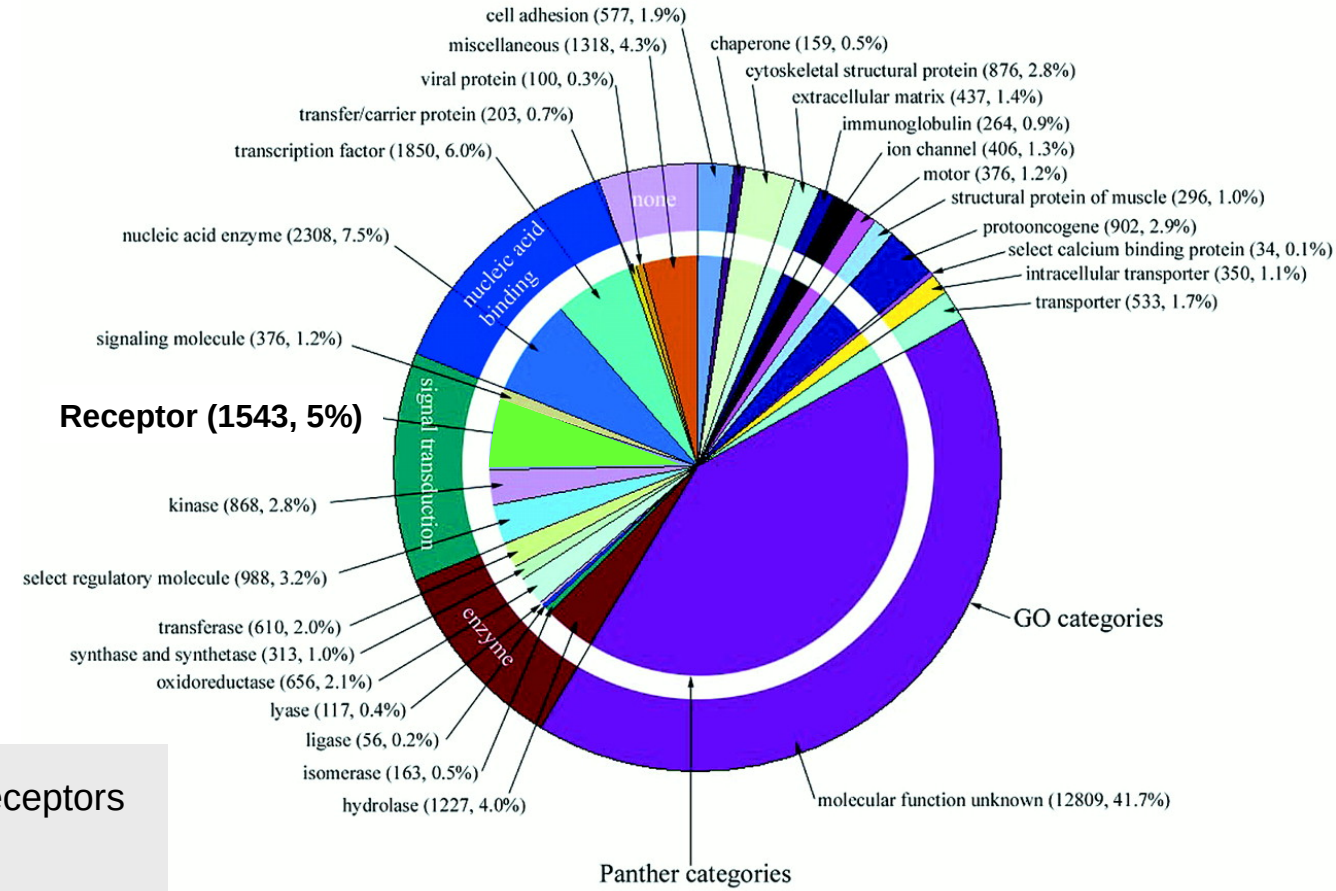
Targets Based on Current Therapies[a] and their relationship to the Human Genome[b]

Drug Target Classes



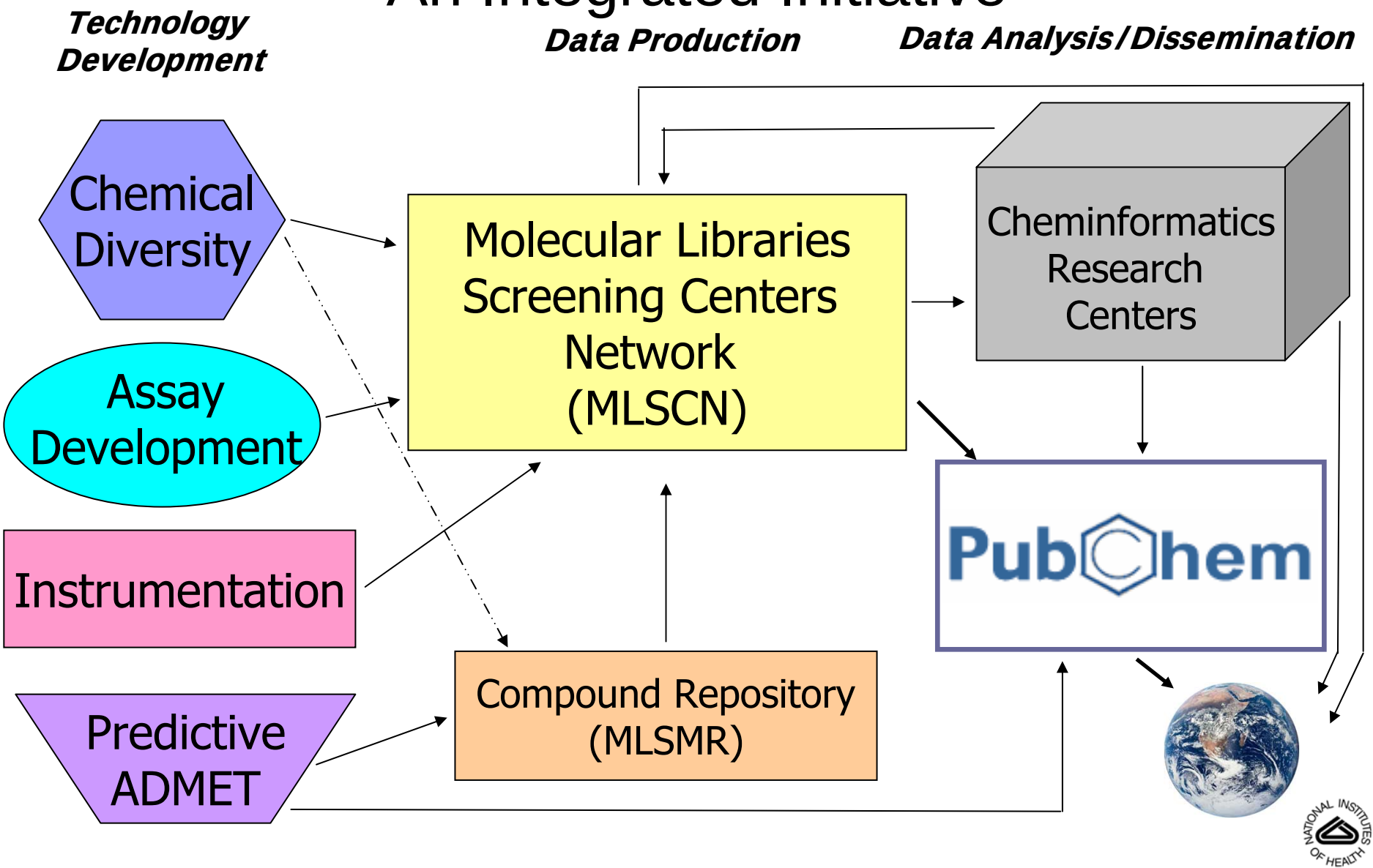
GPCRs
Enzymes
Ion Channels
Nuclear Receptors
Other
Unknown

Human Genome



[a]*Science* **287**:1962 (2000); [b]*Science* **291**:1304 (2001)

The Molecular Libraries Roadmap: An Integrated Initiative

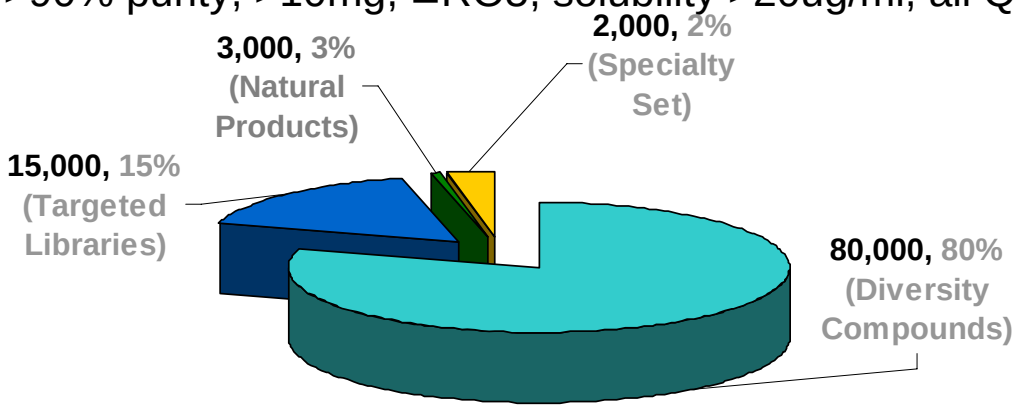


Molecular Libraries Screening Centers Network (MLSCN)
RFA-04-017

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)

Molecular Libraries Compound Collection

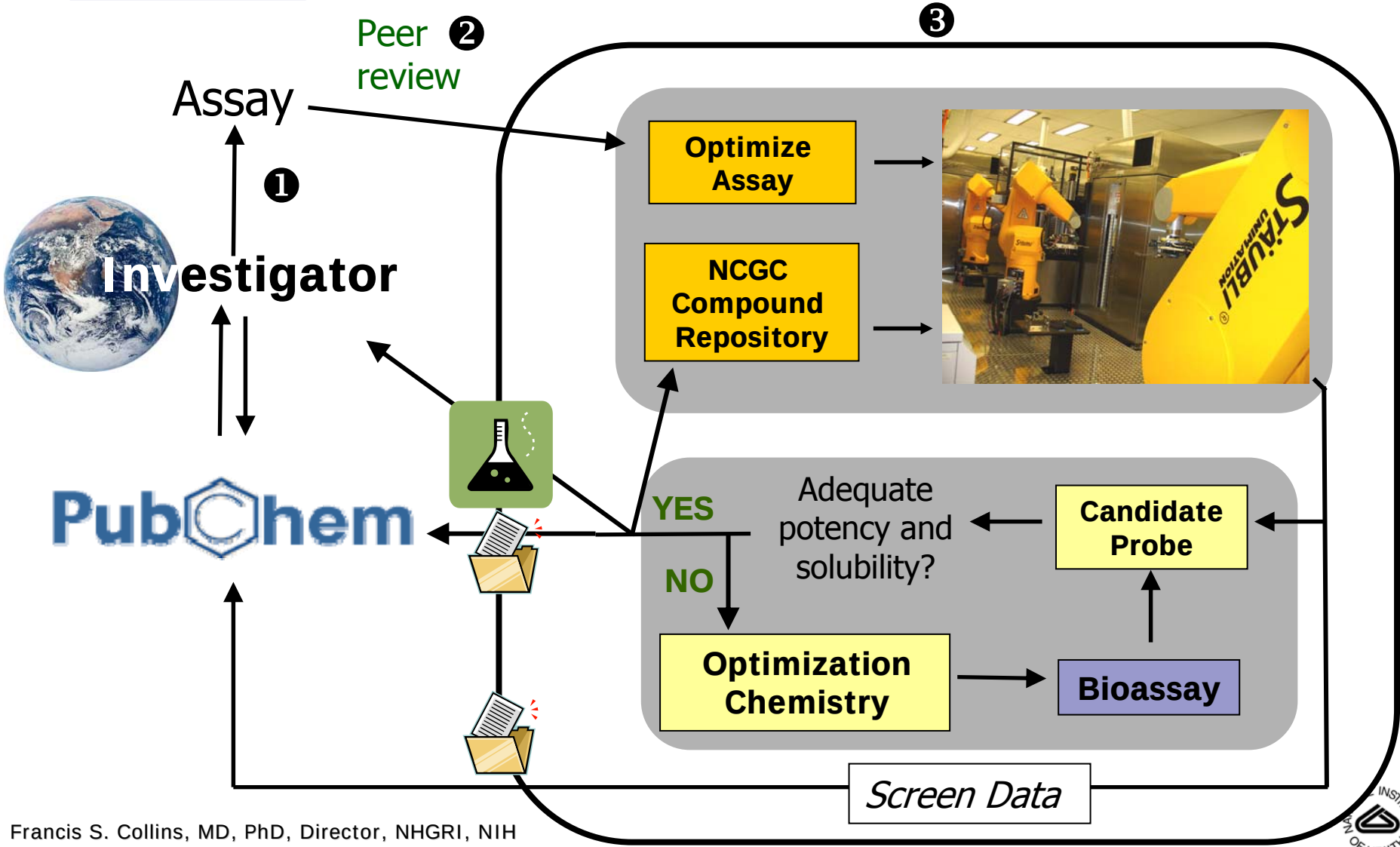
- Housed at Discovery Partners International
- Initial set of ~67,000 compounds purchased from commercial vendors
  - Chosen by external advisors + DPI + NIH
  - >90% purity, >10mg, ±RO5, solubility >20ug/ml, all QCed



- 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 academia, biotech, pharma

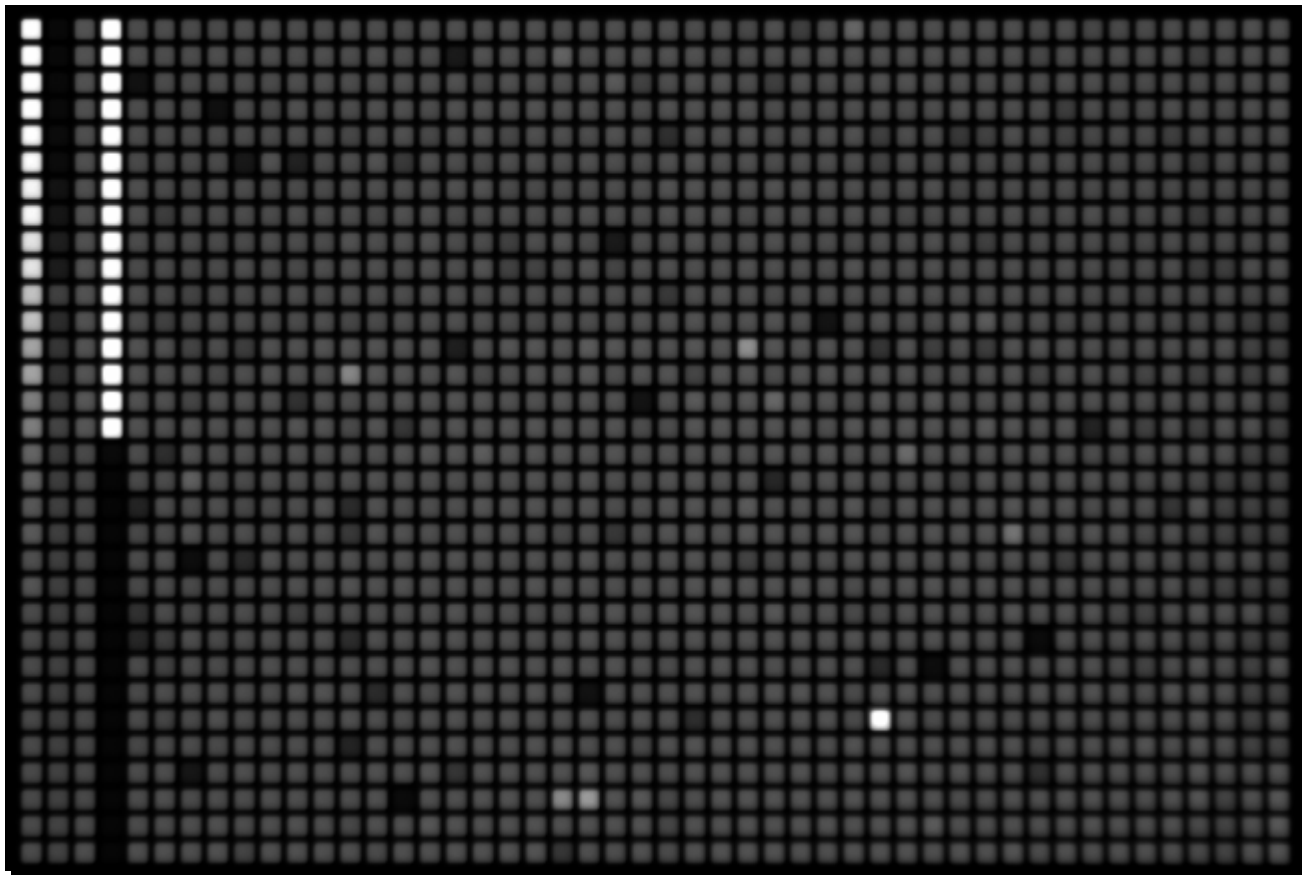
NCGC Operation

NIH Chemical Genomics Center



Titration screening: Raw luminesence data

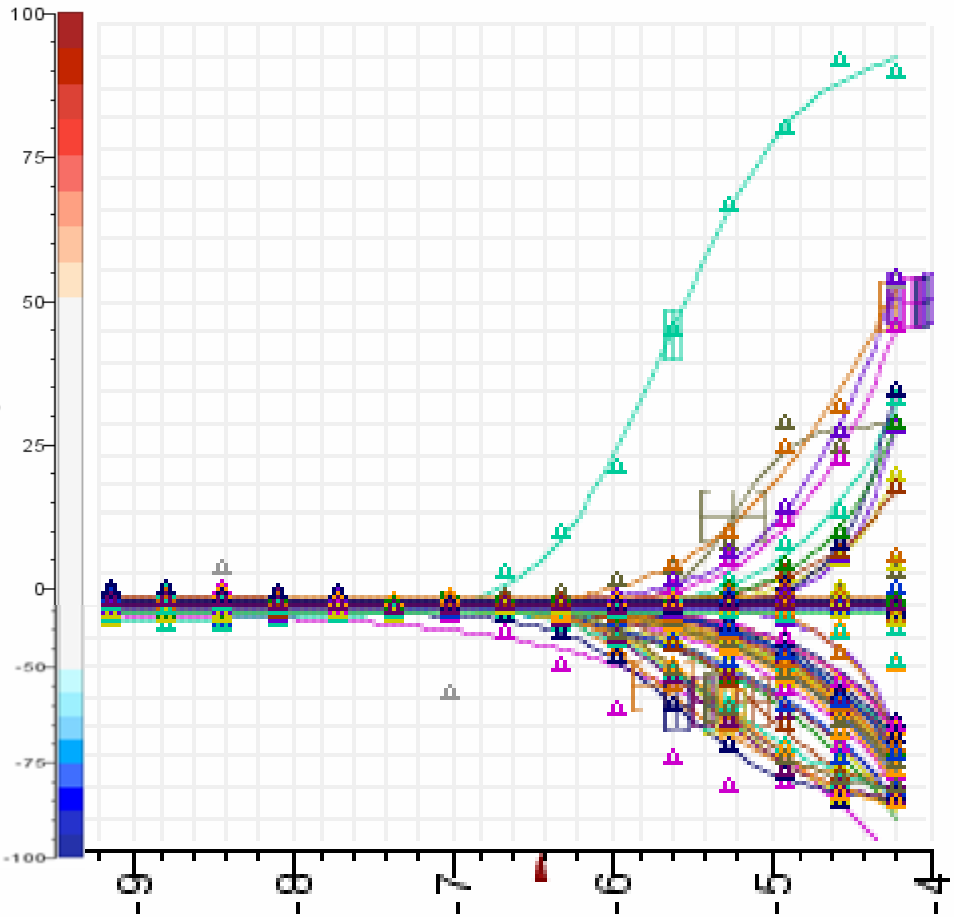
57 μM



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

Positive modulation

Assay: Pyruvate kinase
Library: LOPAC



Negative modulation

Products of the MLSCN

- Chemical probes of gene, pathway, and cell functions
- Optimized only for potency (≤ 1μM) 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

PubChem

- PubChem is a free, publicly available database that provides information about potential starting points for the development of new medications.
- PubChem connects chemical information with biomedical research and clinical information in a connect-the-dots fashion.
- PubChem is a critical part of the NIH Molecular Libraries initiative.
- PubChem is the latest member of the powerful family of integrated databases operated by the National Library of Medicine.
- The integration of these databases makes the whole much greater than the sum of its parts

PubChem Contents ...

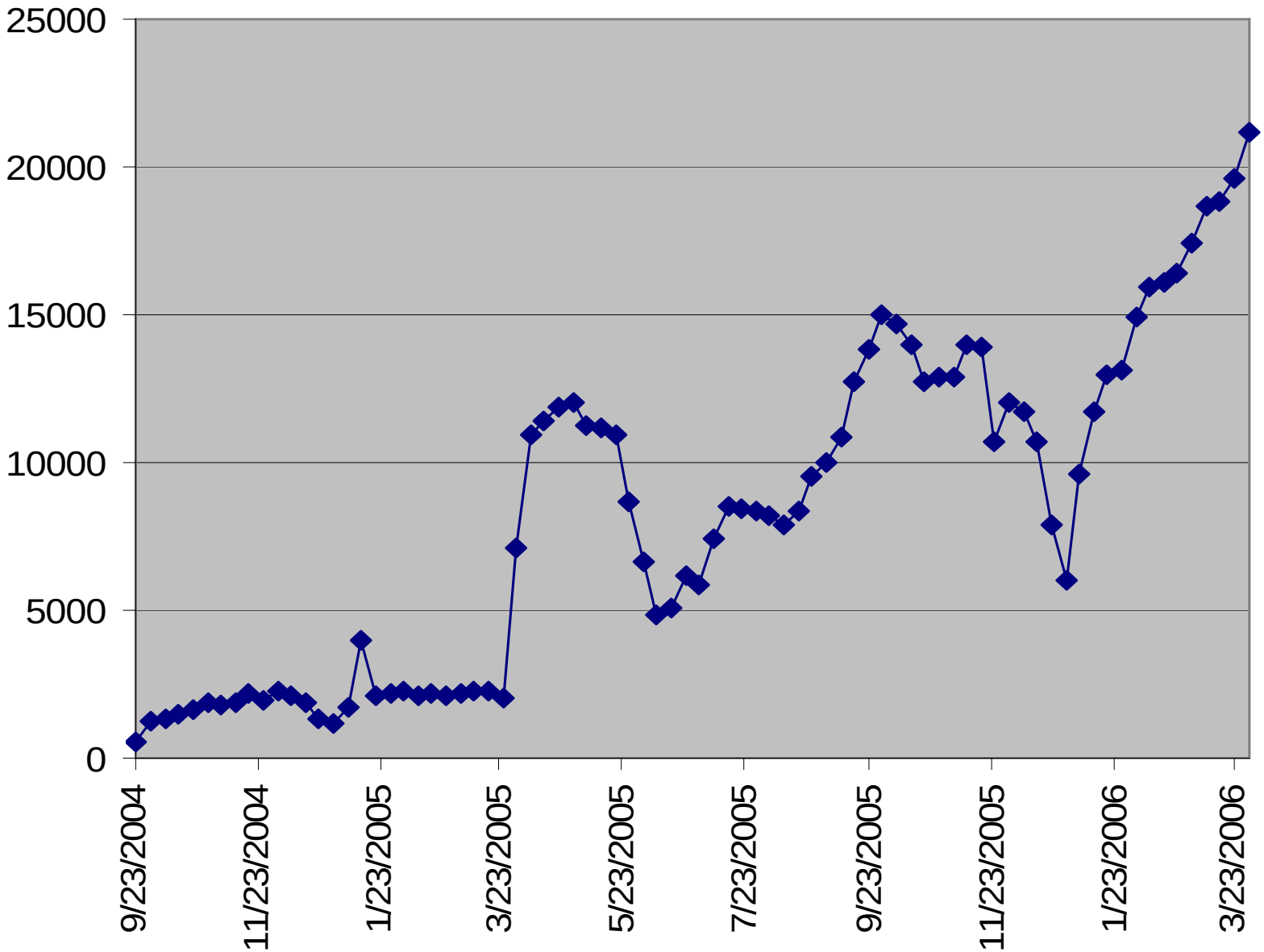
… 194 Bioassays Contributed

… 10,316,814 Substances Contributed

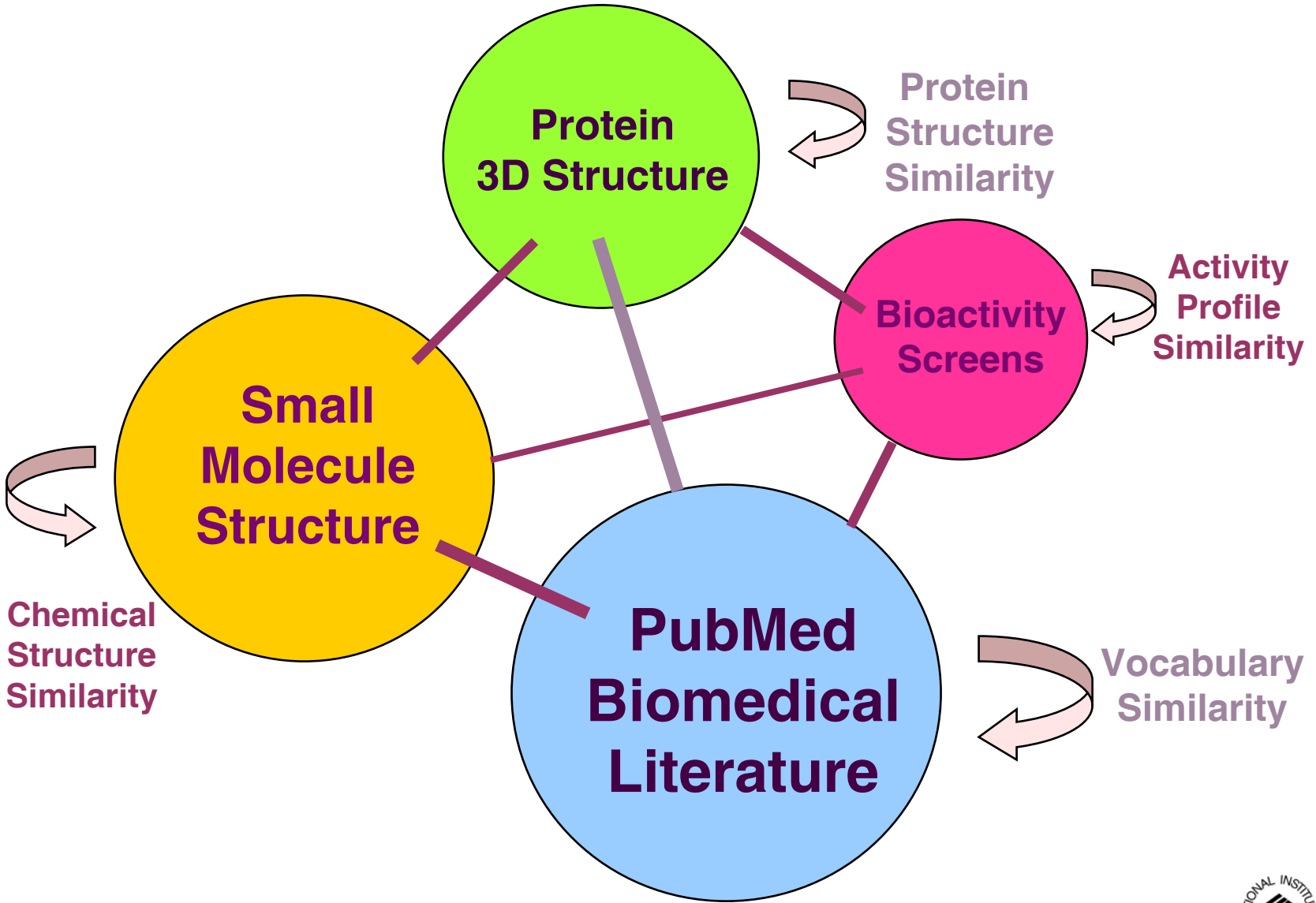
… 5,338,430 Unique Compound Structures

… 41 Depositing Organizations

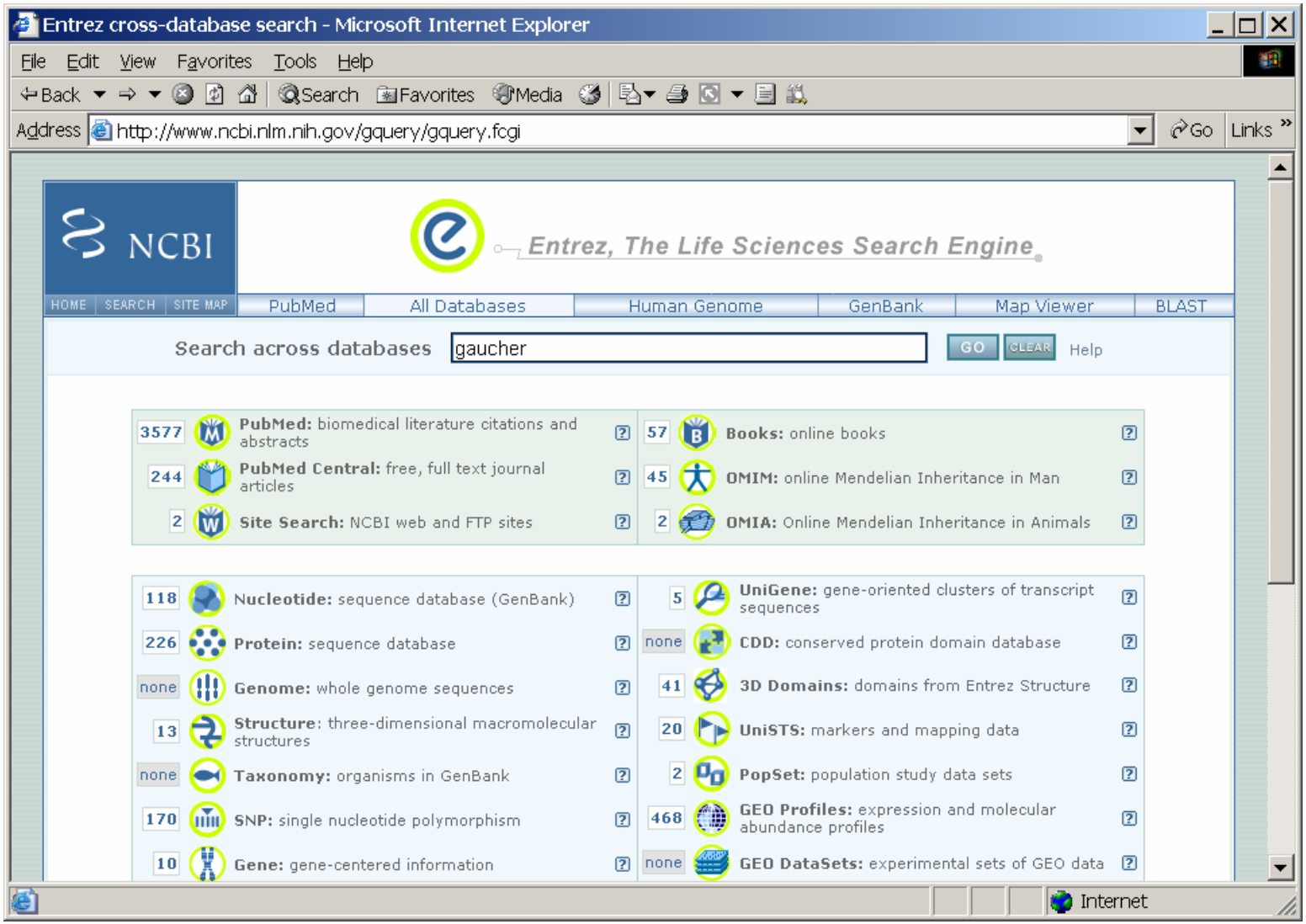
Growth in PubChem Users per Day



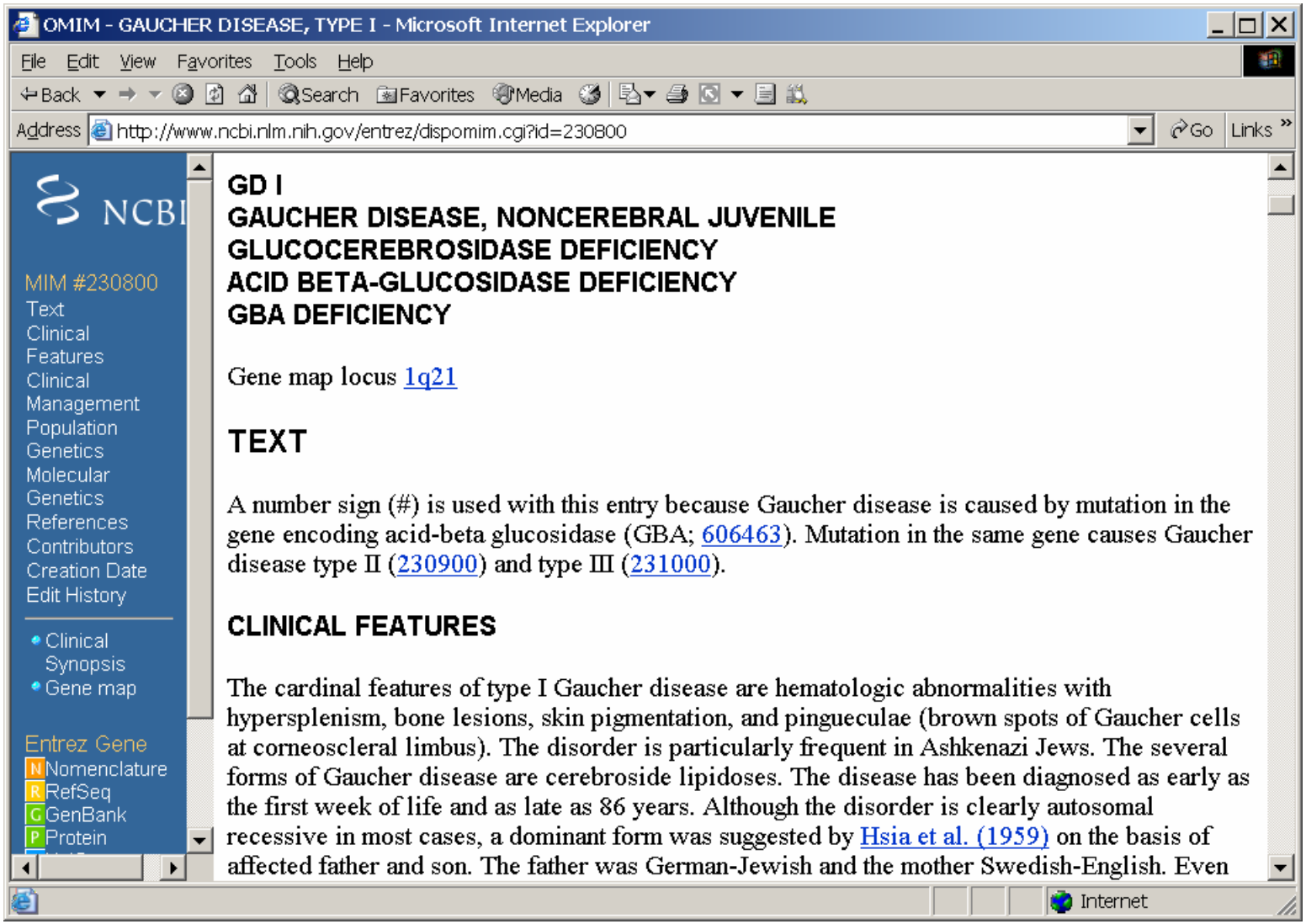
PubChem Database Integration



Search for “Gaucher” ...

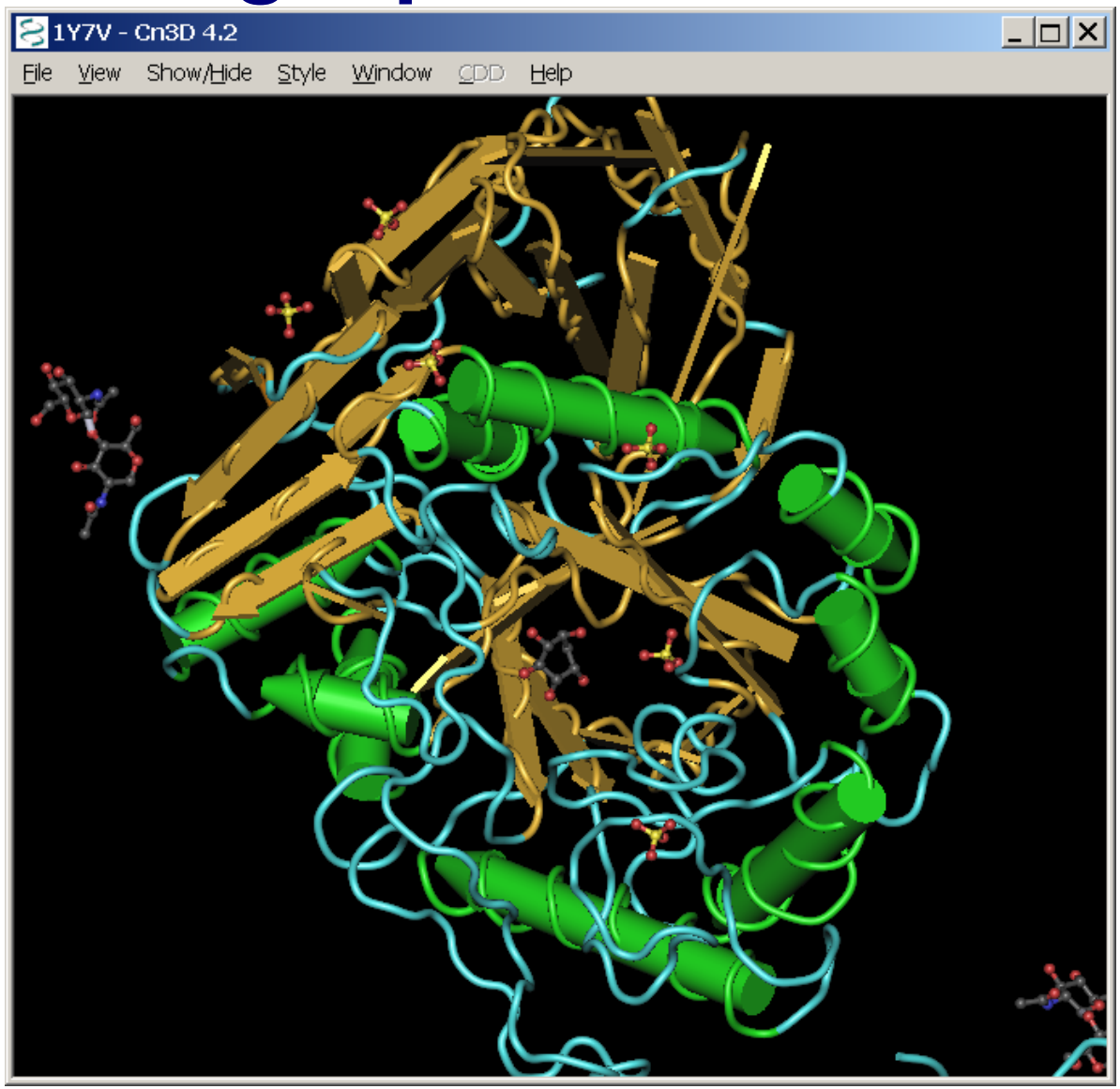


OMIM link to Gaucher disease ...

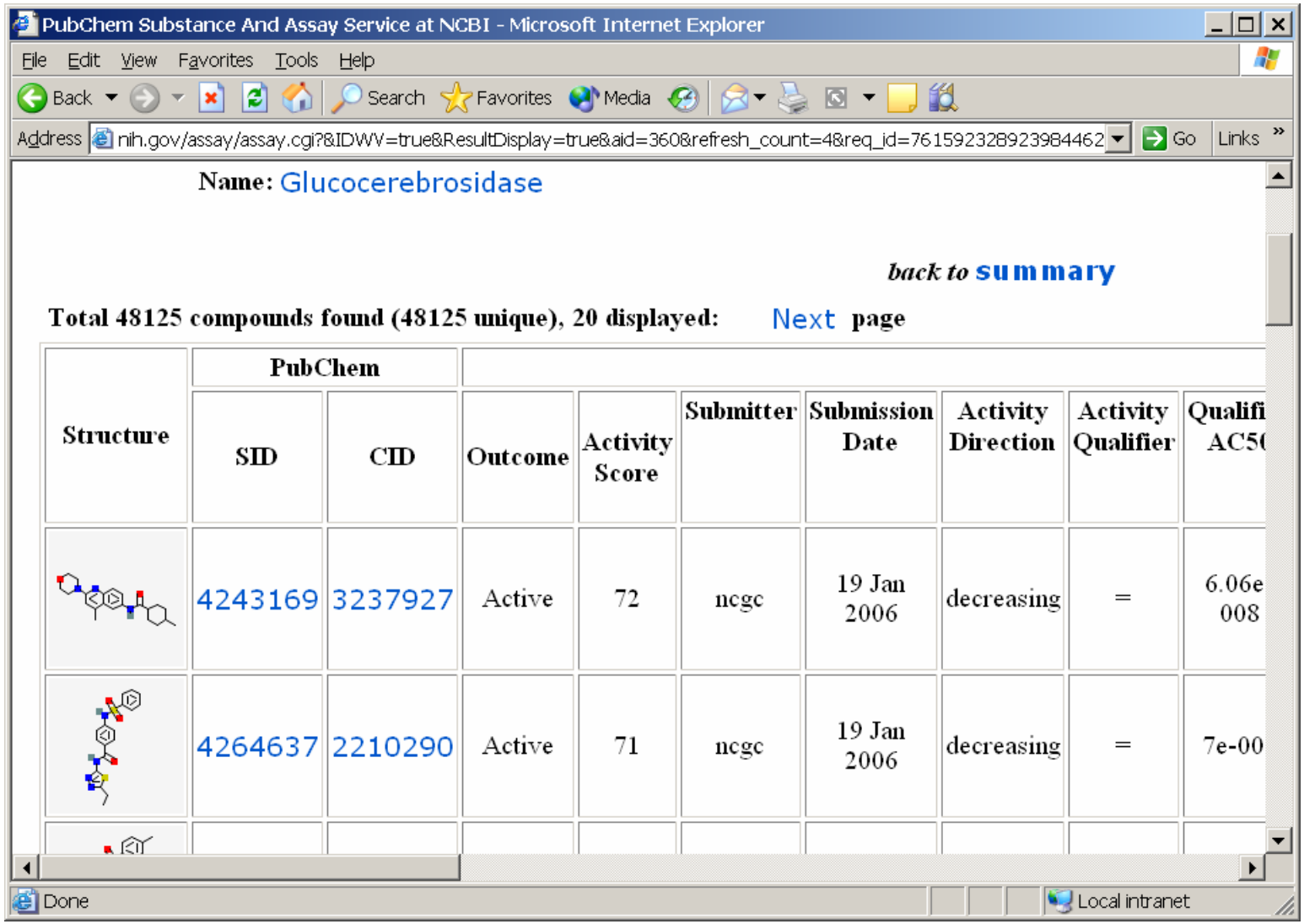


PubChem BioAssay Record ...

Link to target protein 3D structure ...



PubChem BioAssay Results ...



Structure	PubChem SID	PubChem CID	Outcome	Activity Score	Submitter	Submission Date	Activity Direction	Activity Qualifier	Qualifi AC5(
	4243169	3237927	Active	72	ncgc	19 Jan 2006	decreasing	=	6.06e 008
	4264637	2210290	Active	71	ncgc	19 Jan 2006	decreasing	=	7e-00

Fundamental Changes in Biomedical Research due to the Molecular Libraries Roadmap

- Small molecule high-throughput screening, chemistry, and informatics are available to the academic and nonprofit sectors on a scale previously available only to pharma and biotech
- Biological activities of small molecules are available to the research community and fully integrated with other medical informatics resources for the first time
- New resources for synthetic and natural products chemistry are being supported by NIH at an unprecedented level
- Researchers in the public and private sectors can get grant support to turn their basic discoveries into assays for small molecule high throughput screening for the first time
- Pharma and biotech have public sector screening data to advance their own drug discovery programs for the first time
  - Directly facilitates developing new drugs on new targets from the Human Genome Project
- Small molecules are being viewed as pre-competitive research tools rather than protected intellectual property due to the unprecedented sharing data sharing policies of the MLSCN

NIH Roadmap for Medical Research

IDEAS, PEOPLE, RESOURCES, LEADERSHIP