MolecularLibraries
Pathways to Discovery

Molecular Libraries Implementation And Imaging Initiative (MLI)

Presentation for the Council of Councils

Francis S. Collins, M.D., Ph.D.

March 31, 2008

Division of Strategic Coordination, OPASI

NIH Roadmap FOR MEDICAL RESEARCH

- Overview
- NIH Roadmap Initiatives
- Funding Opportunities
  - Roadmap Related Activities
- Funded Research
- 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

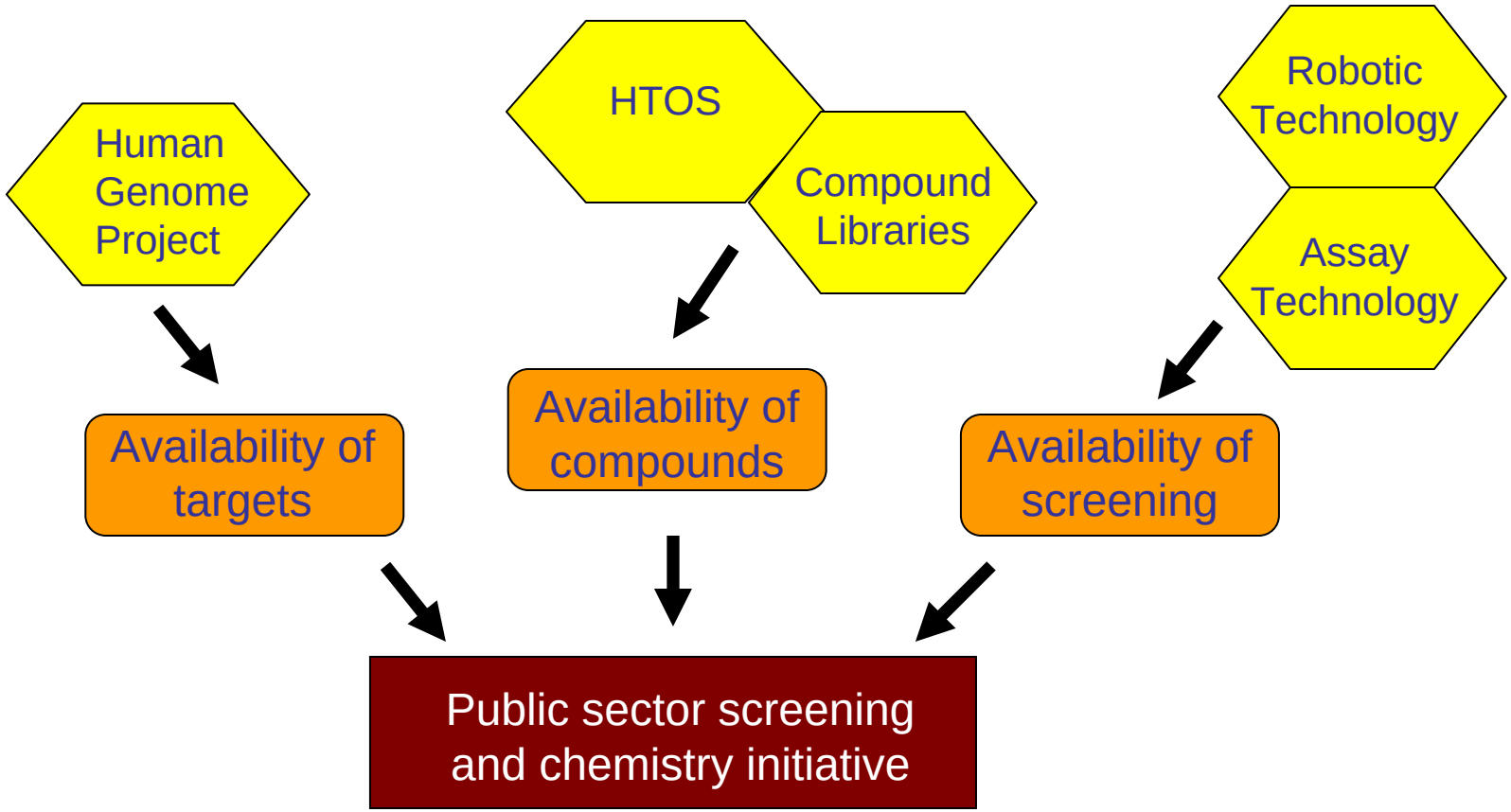
- **RFA:** Assay Development for High Throughput Molecular Screening (R21)
- **Article:** First Steps to an Intramural Roadmap
- **Meeting:** Feasibility of Expanding and Integrating the Clinical Research Networks – Roadmap Steering Committee Meeting
- **RFA:** Using Metabolomics to Investigate Biological Pathways and Networks (R01)
- **Article:** NIH Roadmap in Gear for 3rd Year: Pioneer Awards Allow 'Off-Road' Exploration
- **Meeting:** NIH Roadmap National Centers for Biomedical Computing – 2006 All Hands Meeting
- **Notice:** Multiple PI Implementation Update
- What's New – Archives
- RSS Feed XML

This page last reviewed: July 14, 2006

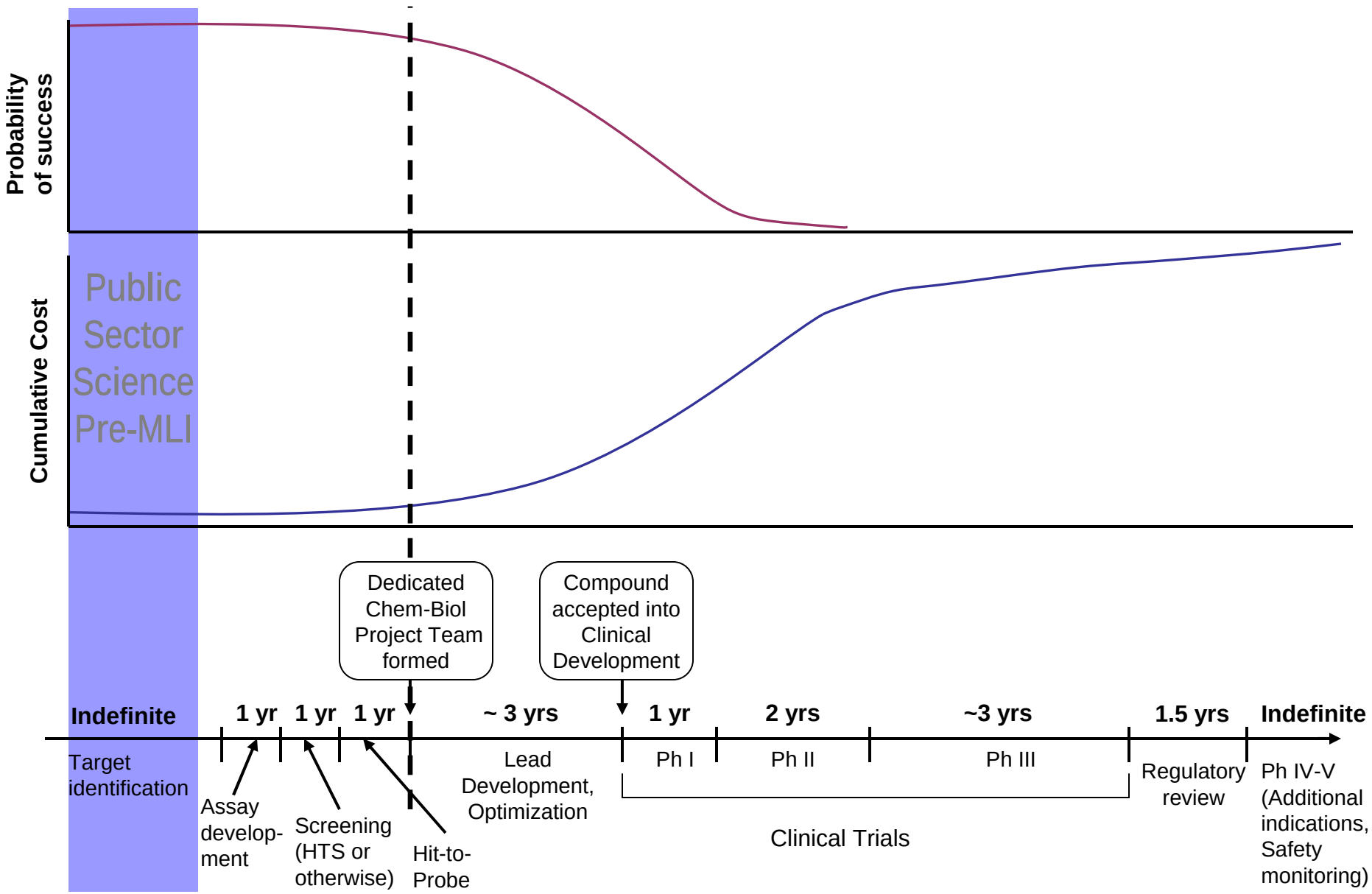
Molecular Libraries Initiative: Rationale

- Urgent need to determine function of genes, proteins, and pathways
  - Small molecules are complementary to molecular genetic tools such as siRNA
  - Small molecules generally act on a protein target, therefore most proximate to physiology
  - Can act as agonists as well as antagonists
  - Reversible in real time
- Urgent need to catalyze development of therapeutics for rare and orphan diseases
  - >6000 rare diseases
  - Genetic basis of many known
  - Treatments available for <100

Molecular Libraries Initiative made possible by recent convergent developments



How does Molecular Libraries relate to drug development?



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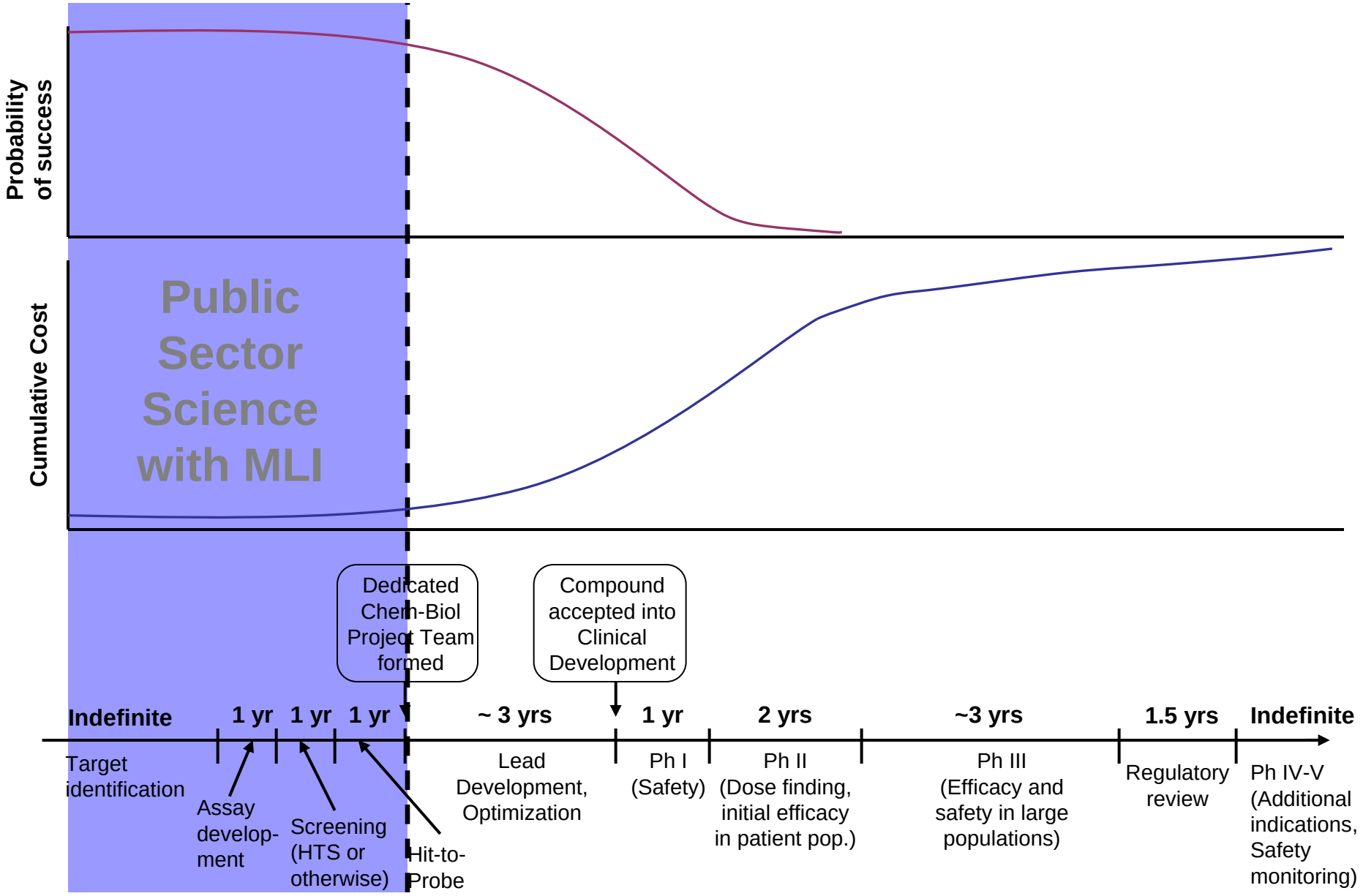
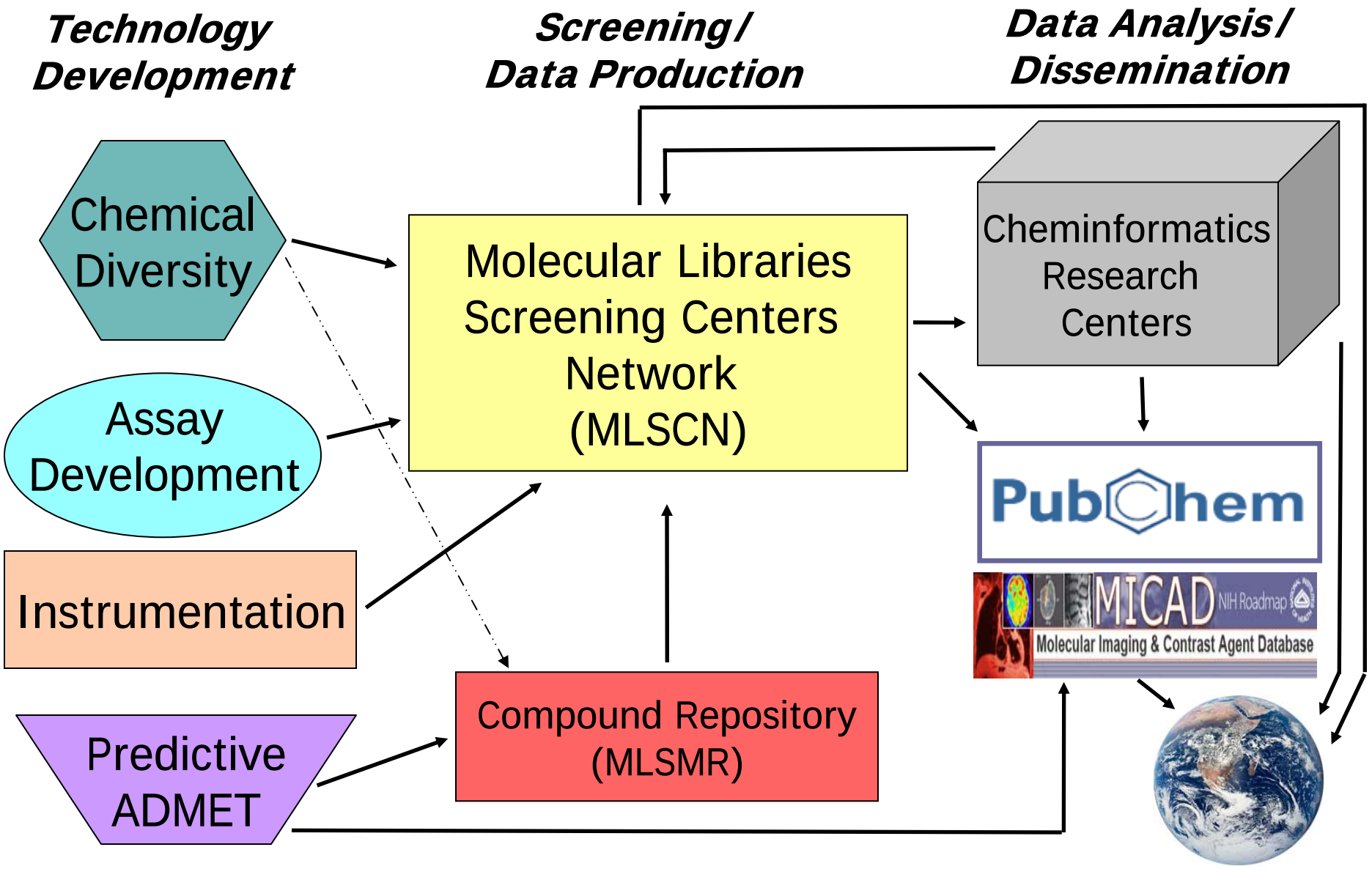


The Molecular Libraries and Imaging Roadmap: An Integrated Initiative

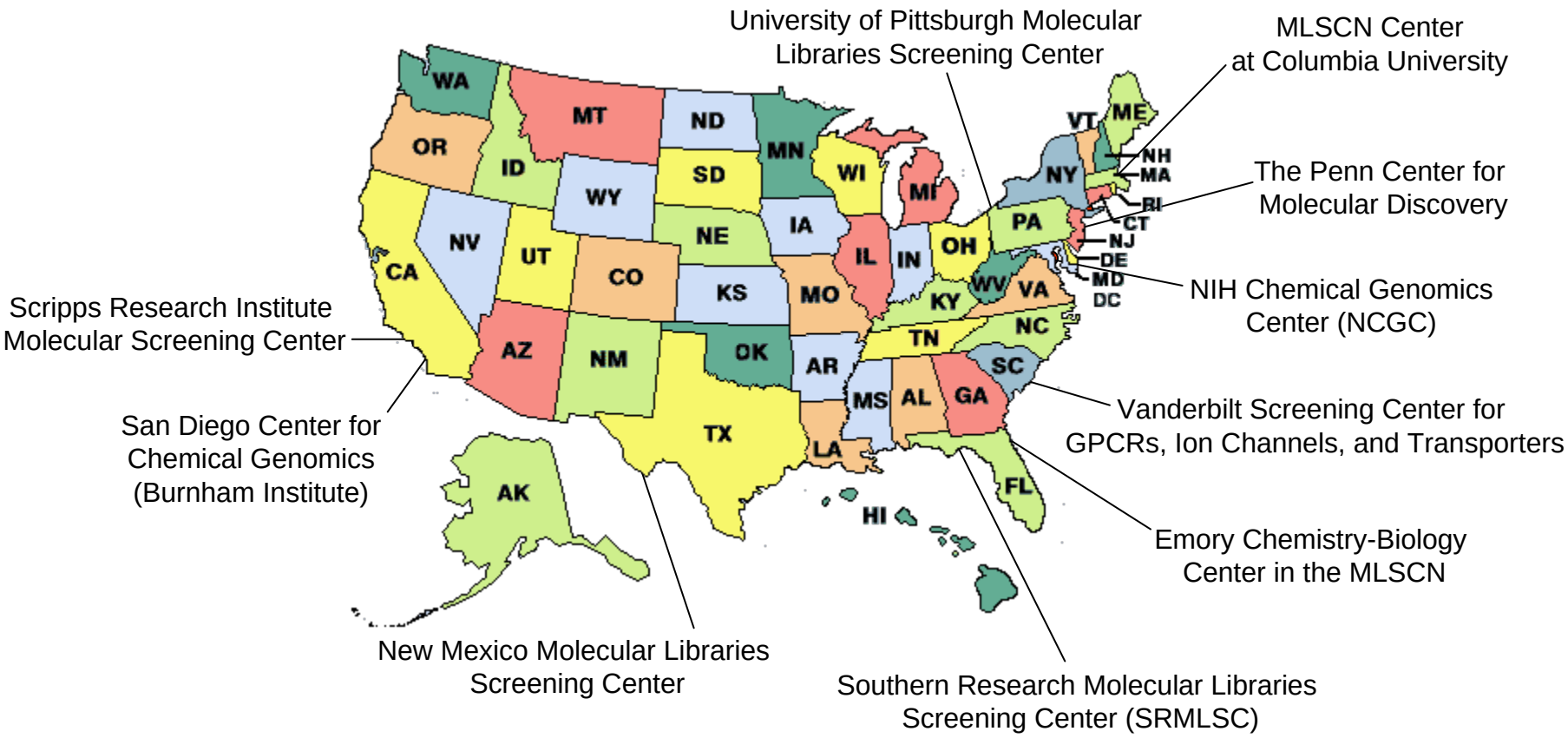


The Molecular Libraries Screening Center Network

Three year pilot phase:

- An NIH-academic partnership,
- Network of academic initiatives providing improved tools and resources for discovery of chemical probes,
- Contains a cooperative of 10 Screening Centers performing probe discovery on a common chemical library (MLSMR) and publishing results to the public chemical biology database, PubChem,
- Purpose is to enhance translational progress towards improvements in human health.

The Molecular Libraries Screening Center Network (MLSCN)



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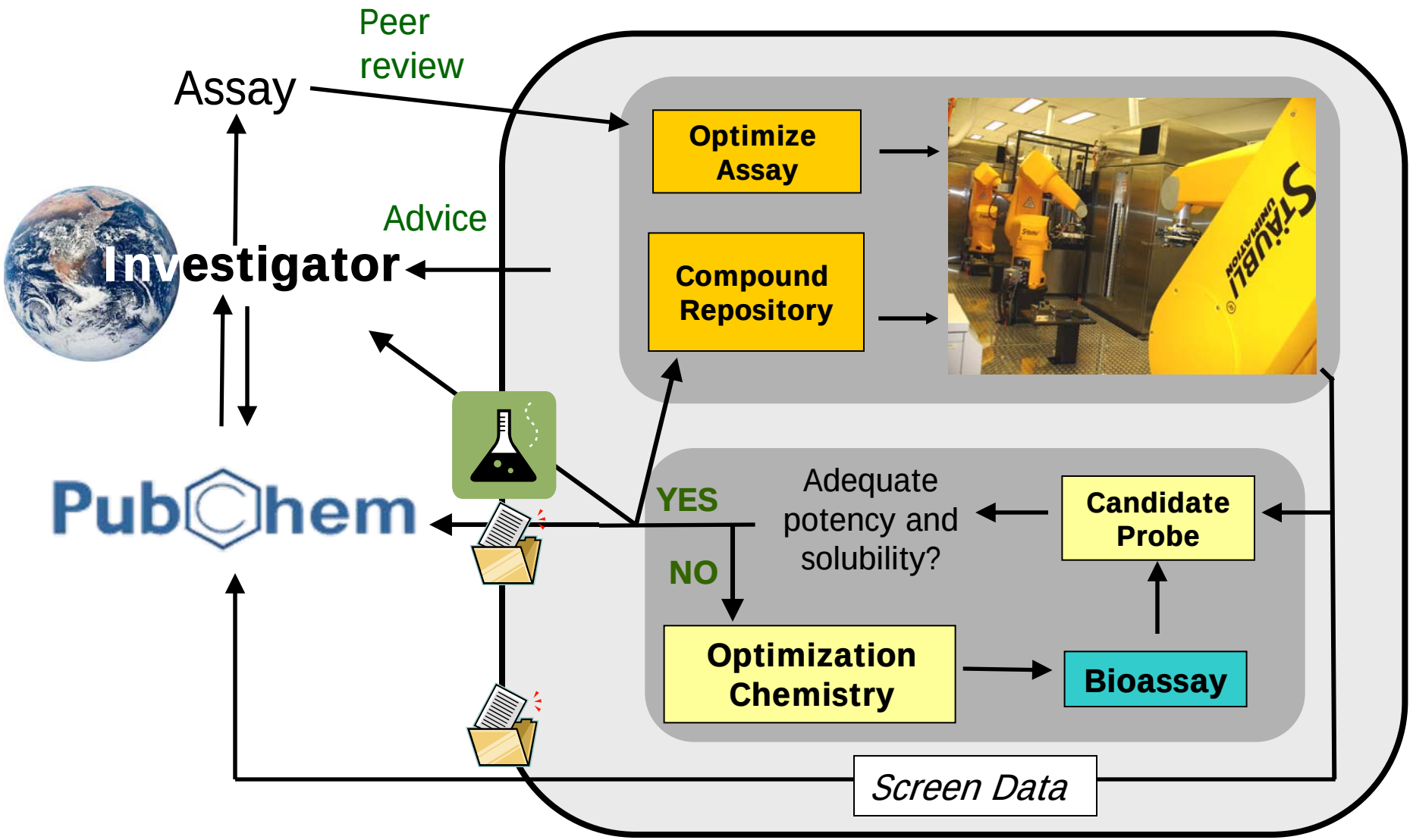
MLSCN Operation



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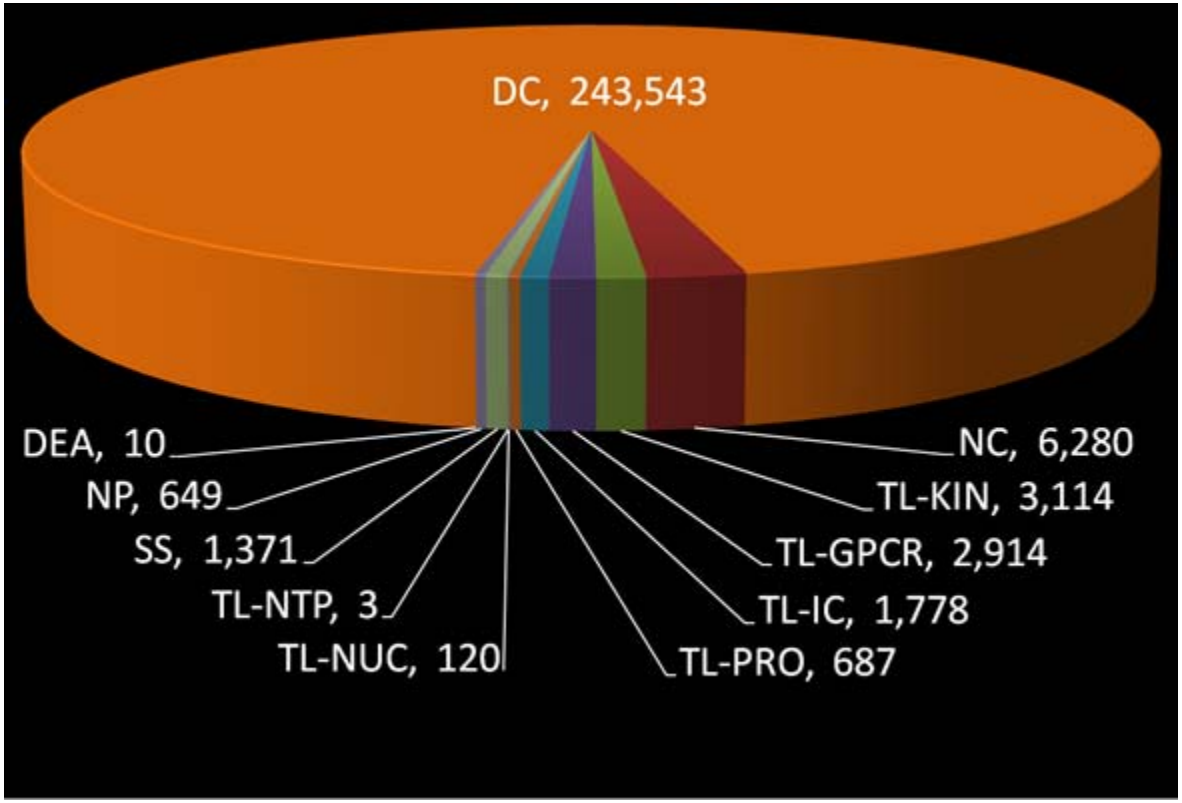
MLSMR Compound Collection (260,000 Compounds)

DC = Diversity Compounds
NC = Non-commercial
TL-KIN = Kinase Targeted Library
TL-GPCR = GPCR Targeted Library
TL-IC = Ion Channel Targeted Library
TL-PRO = Protease Targeted Library
TL-NUC = Nuclear Receptor Targeted
TL-NTP = National Toxicology Program
SS = Known Bioactives
NP = Natural Products
DEA = DEA Controlled Substances



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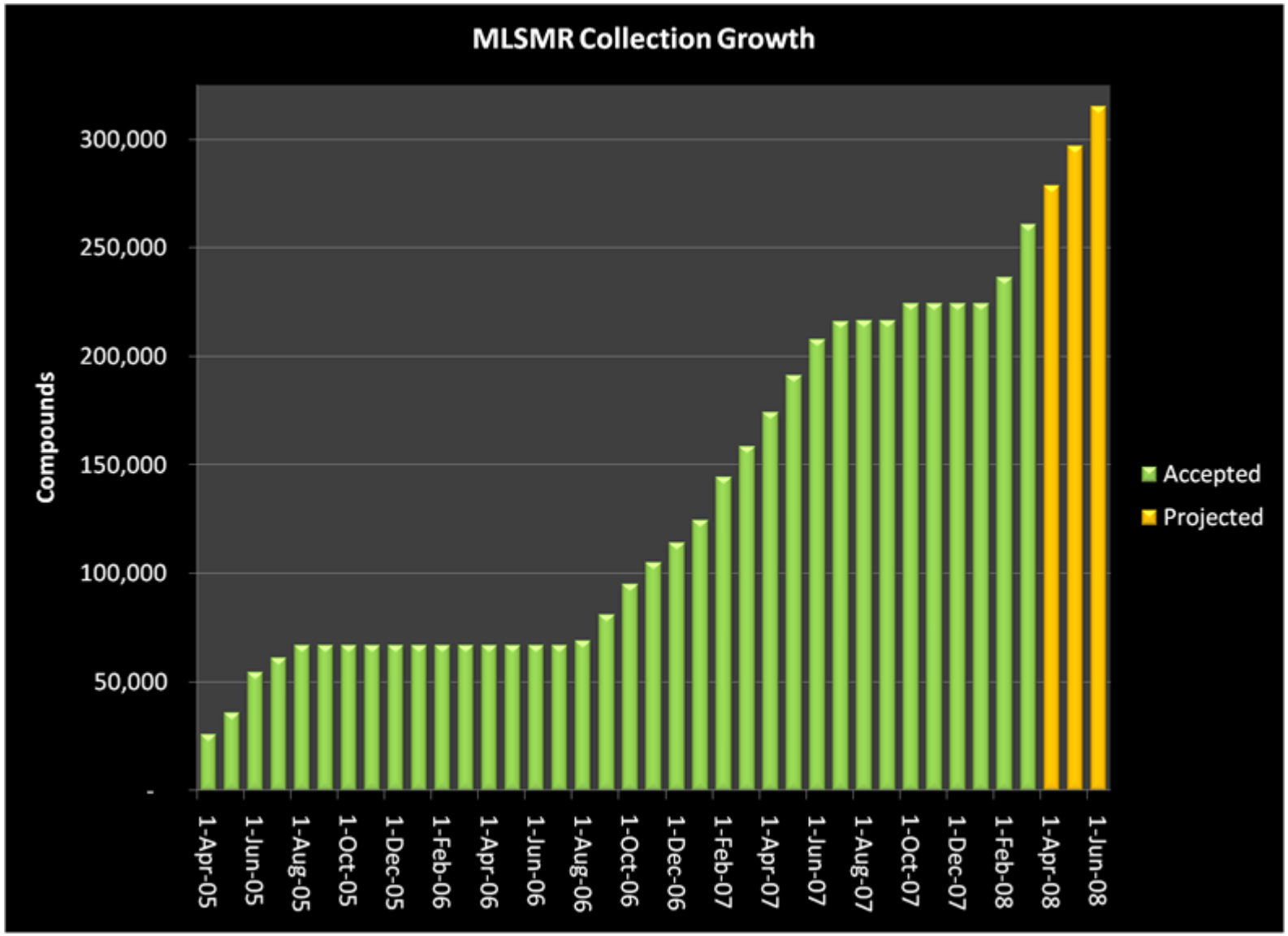
Molecular Libraries Compound Collection



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Screening Center Goals

- Discovery and development of small molecule chemical probes to be used as research tools to interrogate existing and novel biological targets and pathways.
- Generate comprehensive datasets in PubChem for ML compounds

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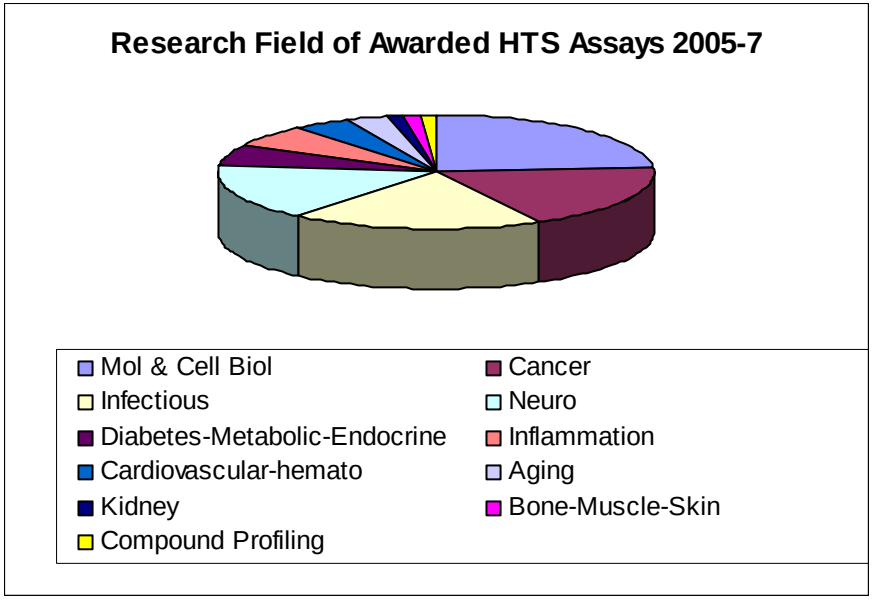
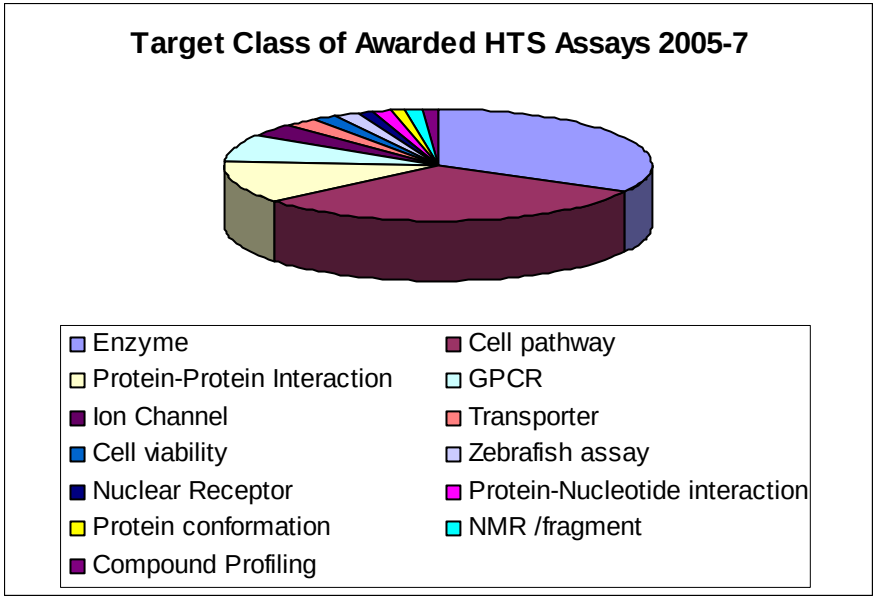
Progress on Awarded HTS Assays 2005-7

Center	Assignments	Assays	Screened	in Chemistry	Probes
Burnham	19	33	22	5	15
Columbia	9	18	12	4	2
Emory	15	20	17	6	2
NCGC	24	33	31	5	19
Upenn	10	20	13	3	8
Pittsburgh	13	14	8	4	2
Scripps	12	31	30	3	7
SRI	21	28	20	7	0
New Mexico	10	21	16	5	2
Vanderbilt	13	16	10	4	1
Totals	146	234	179	44	35

Broad Range of Assay Assignments





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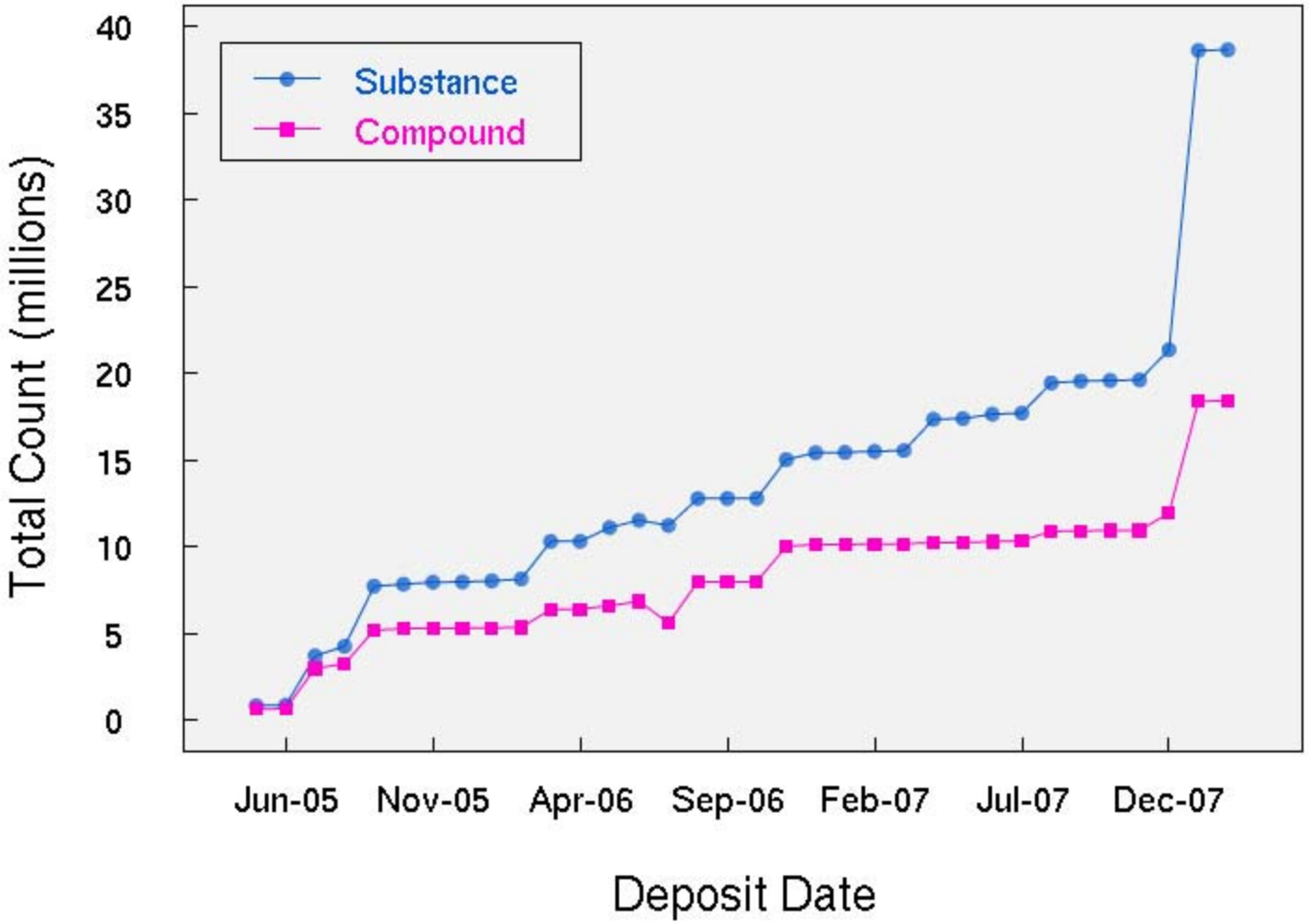
Growth In PubChem Substances / Compounds



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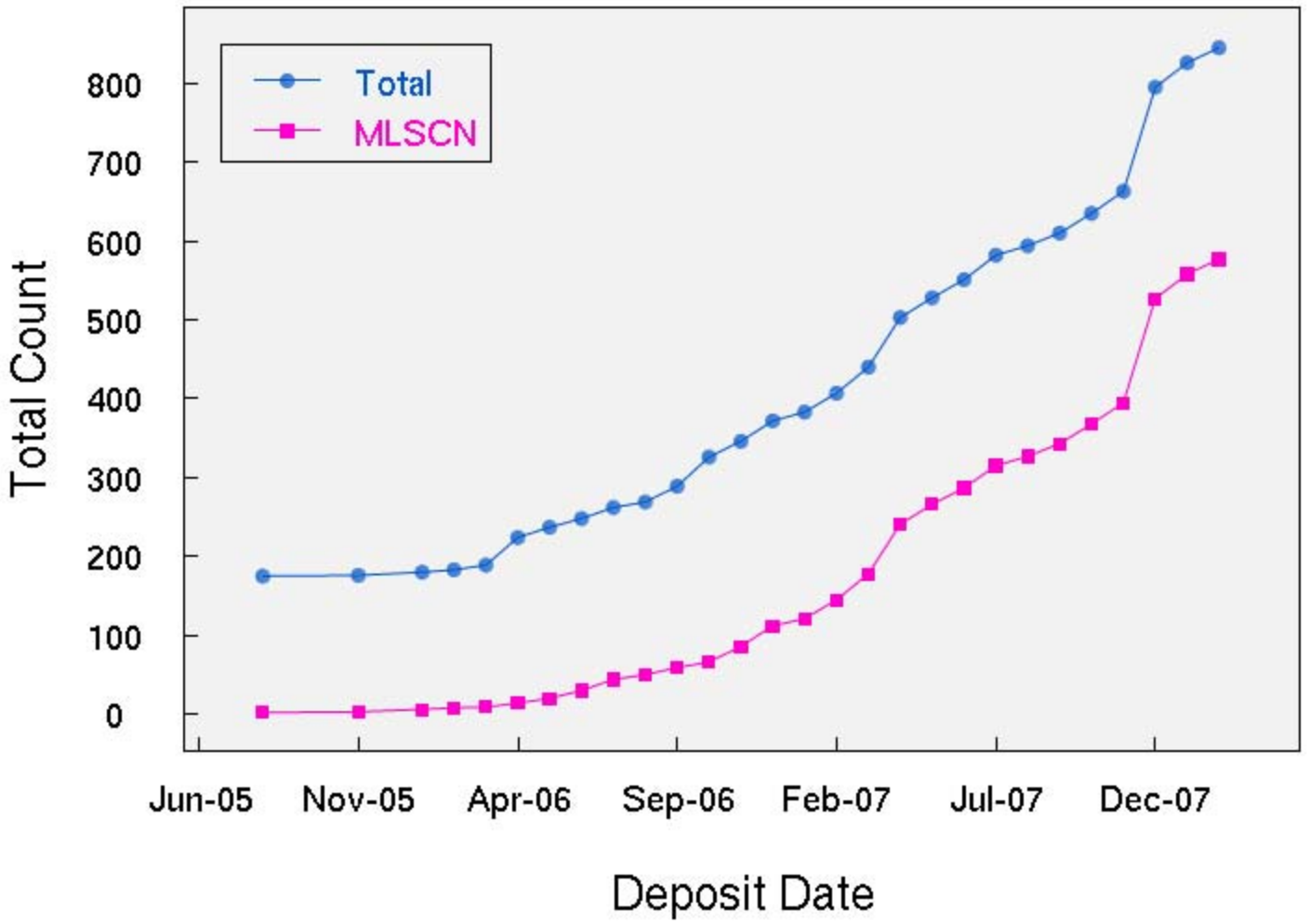
Growth In PubChem BioAssays



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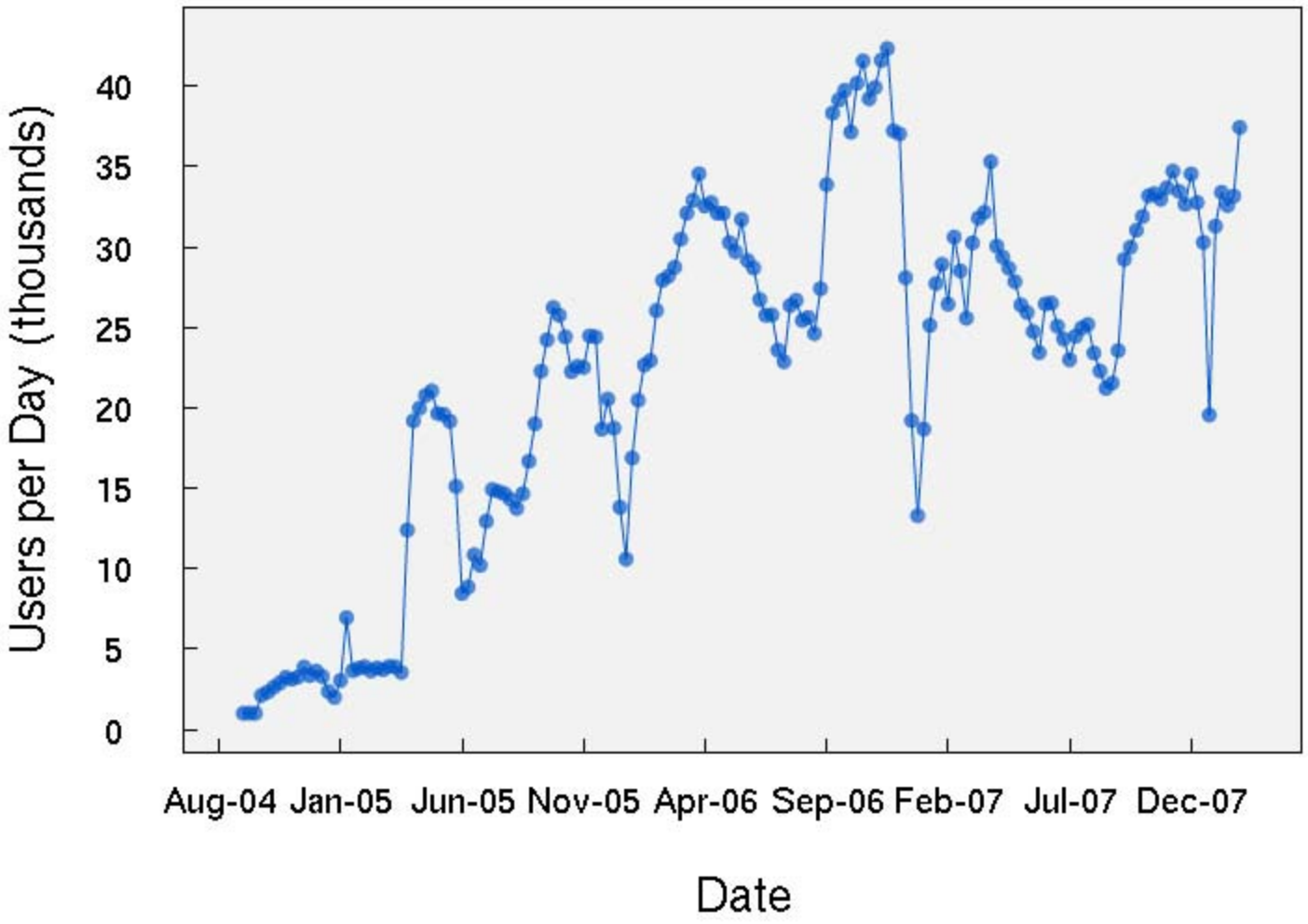
Growth in PubChem Users per Day



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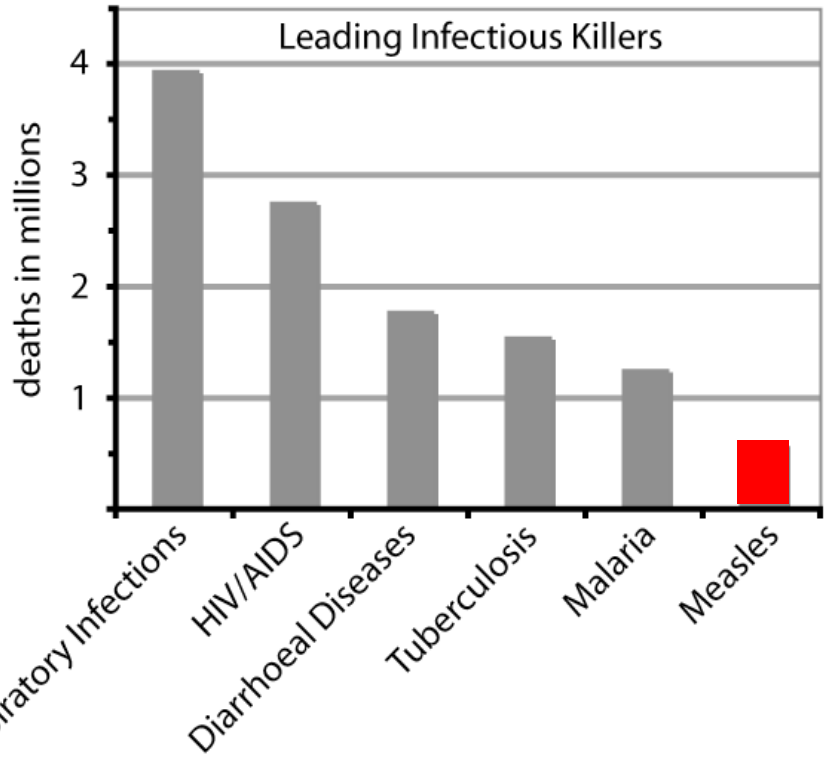
Two Examples of Projects

1. Emory University Molecular Libraries Screening Center, Ray Dingledine
   - Inhibitor of measles virus RNA polymerase
   - Assay from Richard Plemper, Emory University

Measles virus (MV) inhibitor

Despite the existence of a vaccine, MV remains among the most lethal human pathogens and accounts for approximately 500,000 deaths annually (WHO)

Novel antivirals against MV are desired to control local outbreaks.

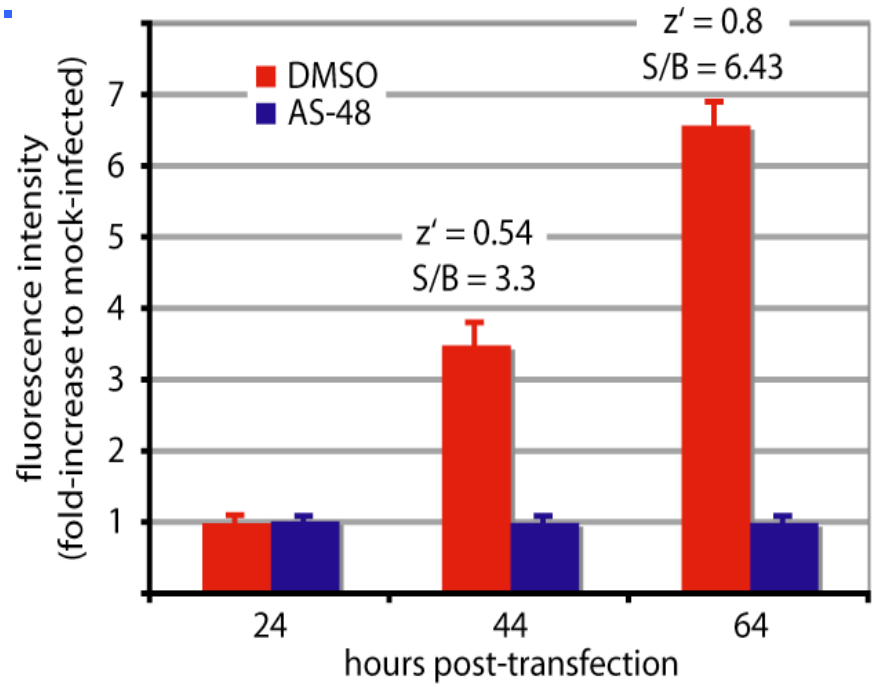


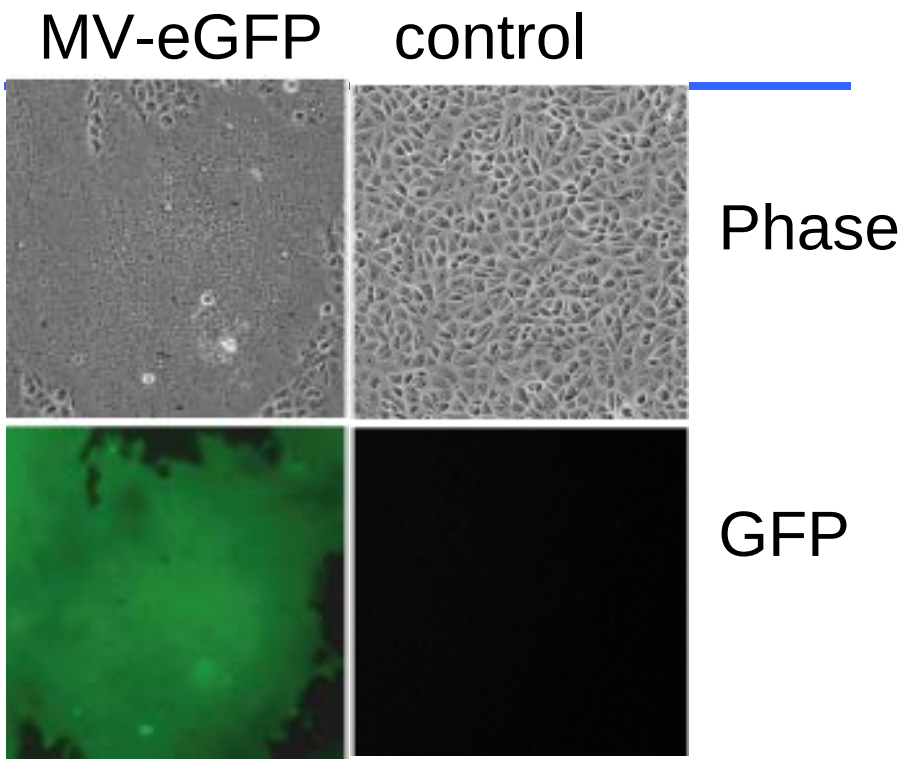
Why?

- Herd immunity is below protective levels in developing countries
- Decreased vaccination compliance in parts of the developed world
- No therapeutic strategy for management of cases of severe measles

Richard Plemper & Jim Snyder

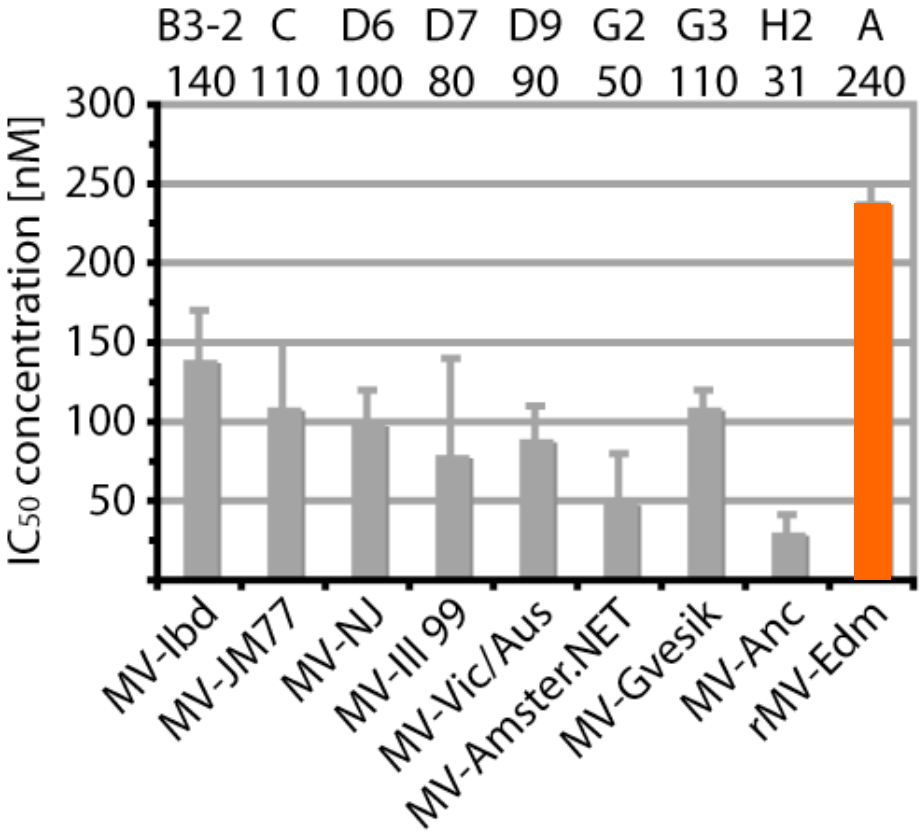
Development of a robust HTS assay





- Cellular assay based on recombinant MV, with eGFP added to the amino terminus of the viral glycoprotein
- 34,000 compounds assessed in a first-pass screen
- AS-48 is a known positive control

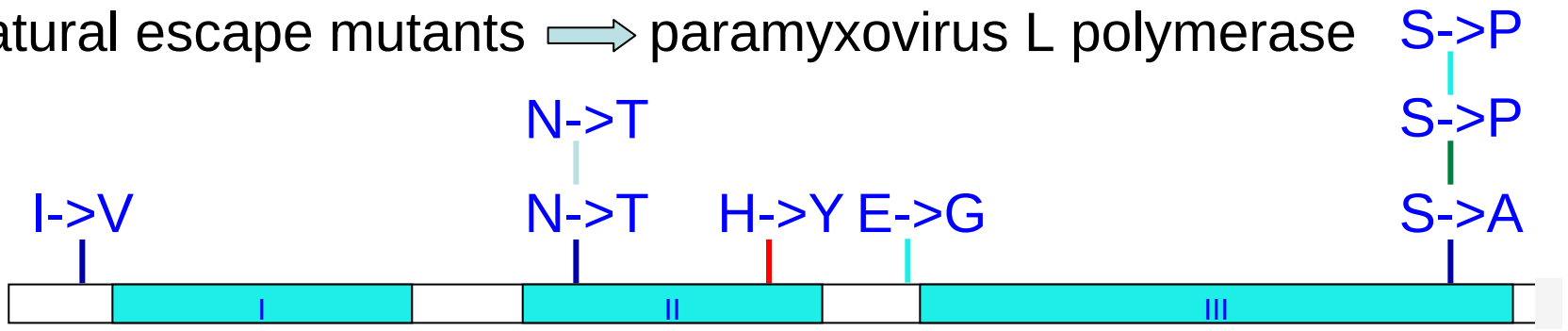
Compound #16677 shows nanomolar activity against 8 *primary* MV isolates



- IC_{50} concentrations against live MV range from 31 to 245 nM
- Compounds shown to not inhibit viral entry or host protein synthesis
- Target narrowed down to the RNA polymerase complex

MV escape mutants and directed mutagenesis identify the target

Natural escape mutants ⟹ paramyxovirus L polymerase

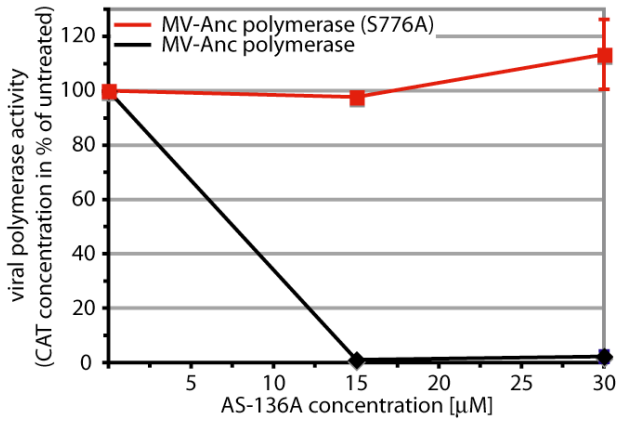


Site-directed mutagenesis of polymerase domain confirms ID

765-R I A S L V Q G D N Q T I A-778

A A

P



GDNQ motif is the active center for phosphodiesterase bond formation

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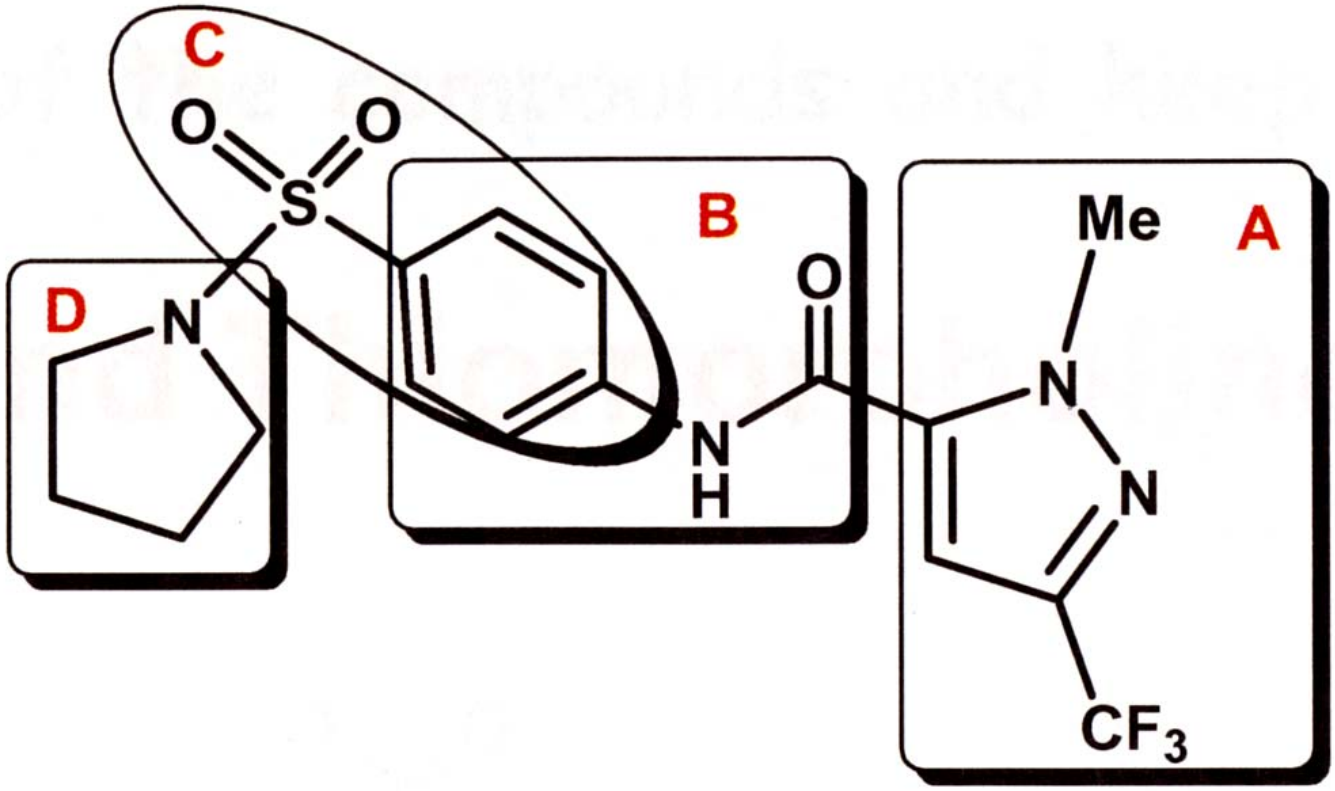
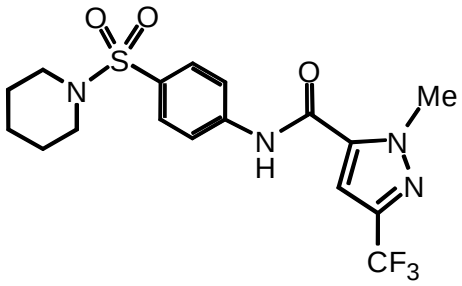
Hit to probe development

- Iterative rounds of analog generation and cell-based bioassay
- Approx. 150 analogs created in increasingly focused libraries



First measles virus probe

CID 16122506

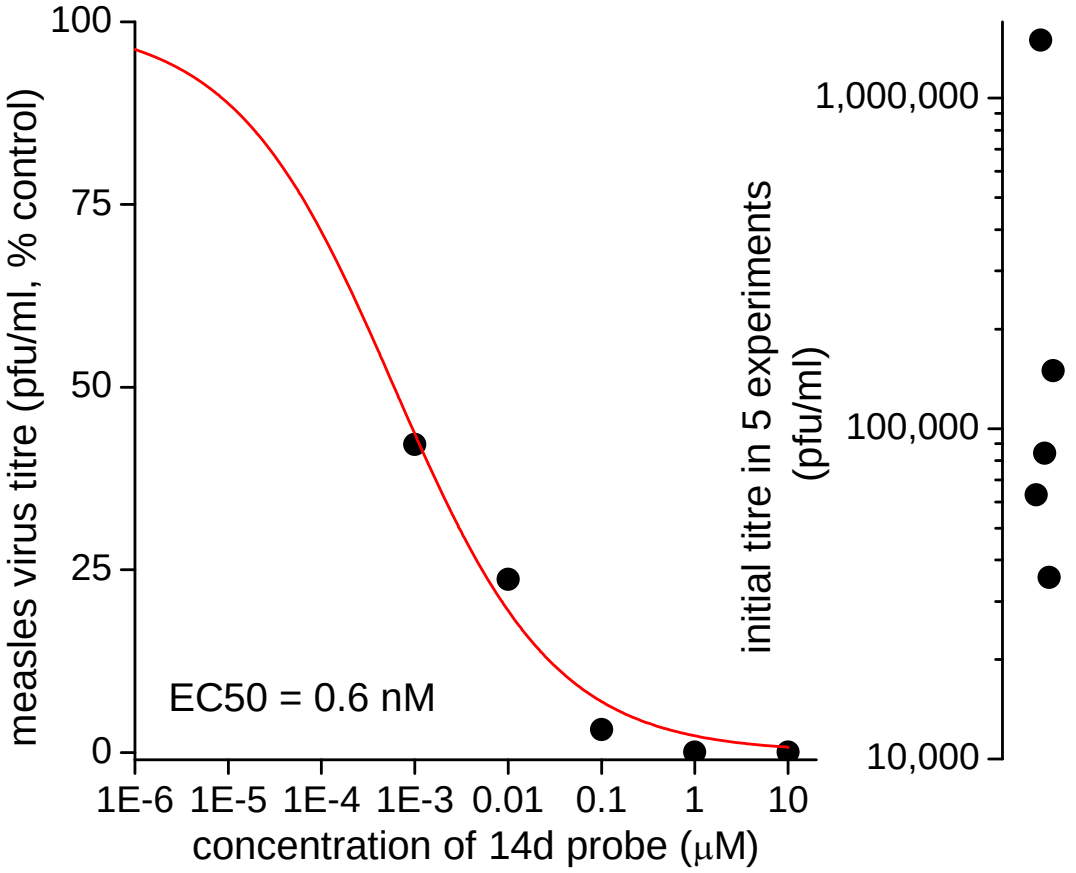


Mean EC_{50} = 3.8 nM
(n=5 experiments)

Cell toxicity >300 μM

Mechanism: viral
polymerase inhibitor

Shows in vivo efficacy
rats against intranasal
infection with MV



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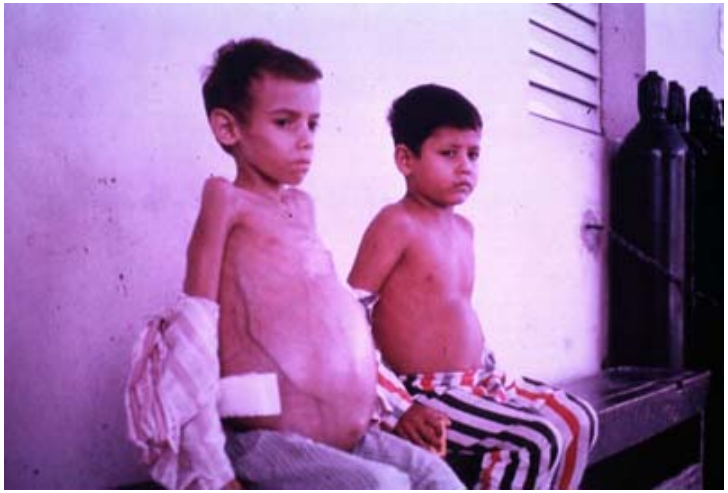
2. NIH Chemical Genomics Center, Chris Austin
   - Inhibitors of *S. mansoni* peroxiredoxins
   - Assay from David Williams, Illinois State University

NIH Chemical Genomics Center

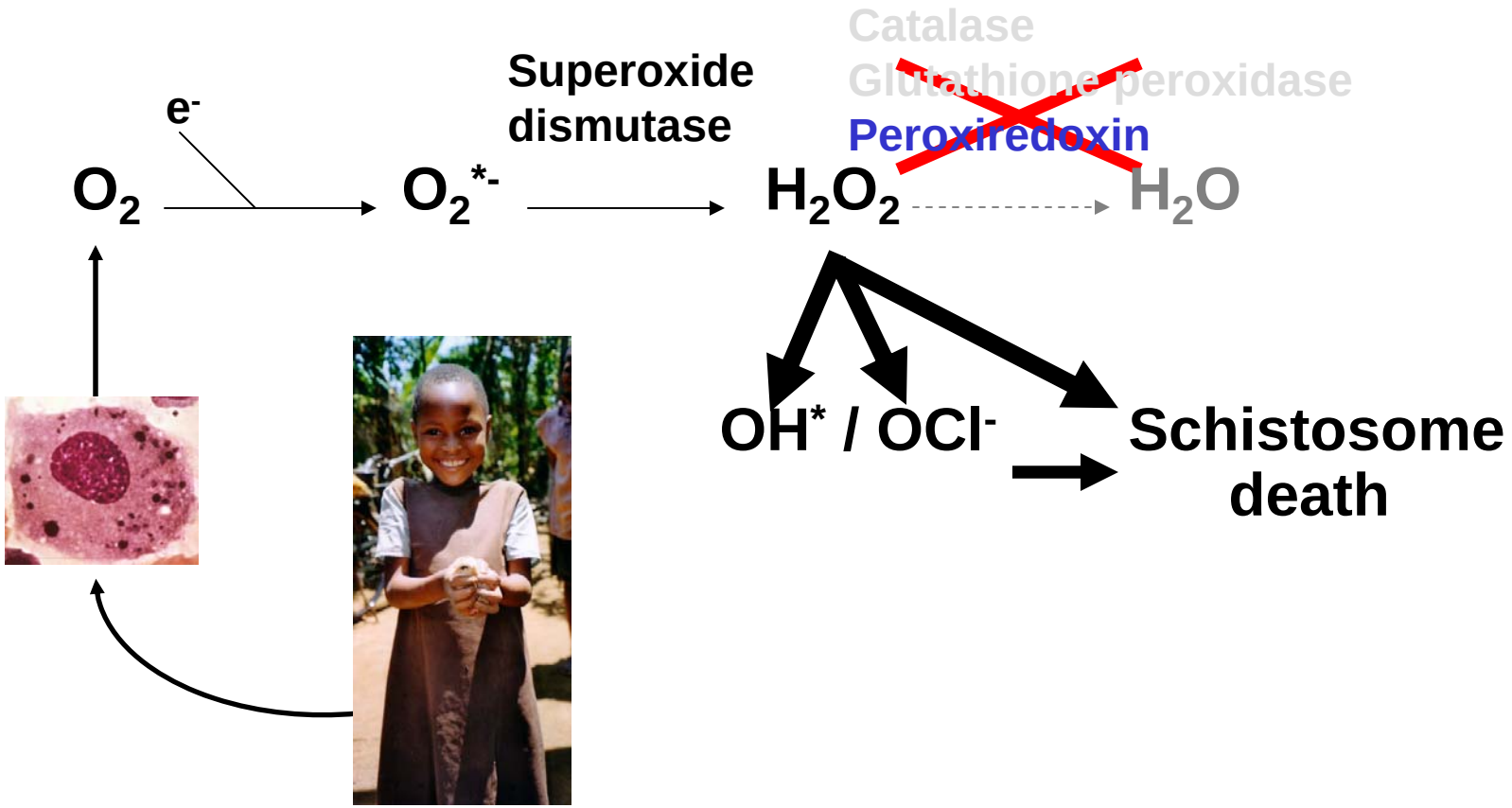
Developing drugs for Schistosomiasis



- Parasitic disease that affects 250 million people, mostly in Africa
- Dr. David Williams at Illinois State University identified potential new target
- The NIH Chemical Genomics Center and Dr. Williams worked together to successfully identify targeted chemicals that provide a starting point for new drugs

Targeted Redox Pathway

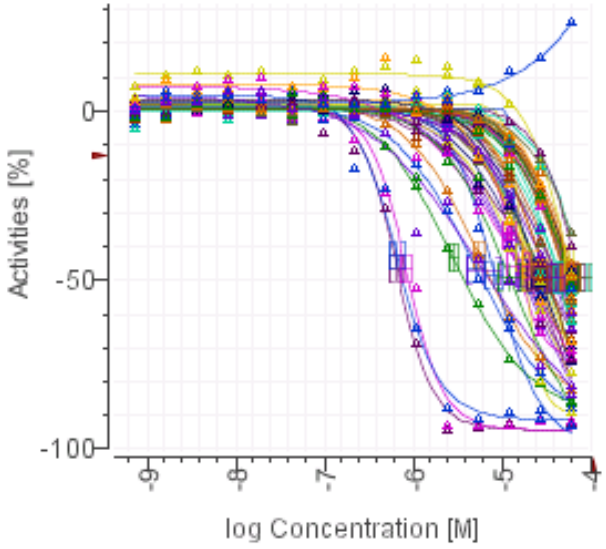
Inhibition of *S. mansoni* peroxiredoxin would prevent worm degradation of hydrogen peroxide and kill schistosomes



NIH Chemical Genomics Center

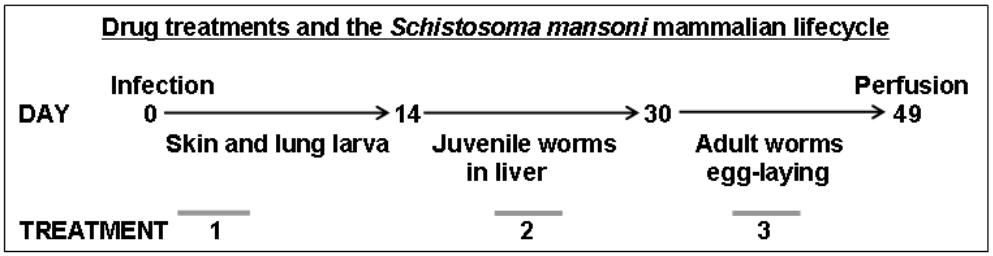
Quantitative HTS

- 70,000 compounds at 7 concentrations (qHTS)
  - Dose-response curve for all compounds (PNAS 103, 11473-8 (2006))
  - ~10,000,000 data points (16 Time-Point Reads)
  - 31 hours of robot time
- Results: 100 compounds with IC50 < 40 μM
  - 71 compounds
  - 6 different structural classes

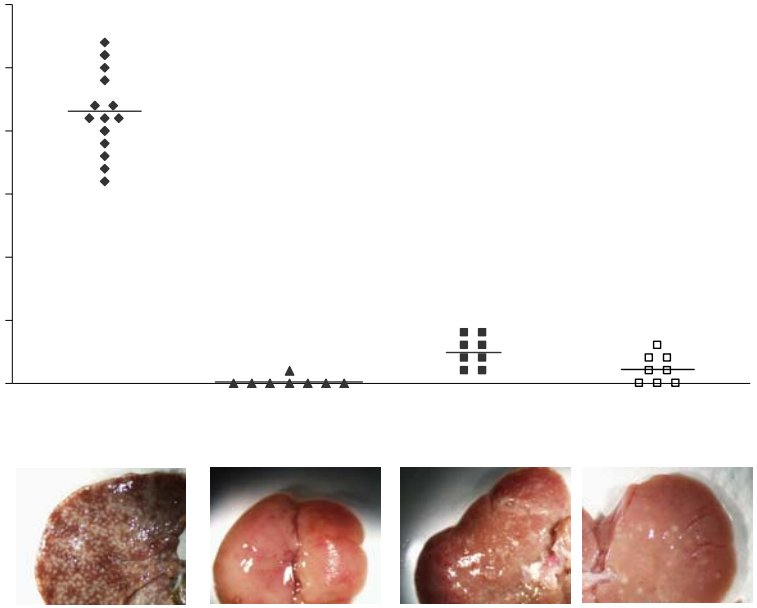


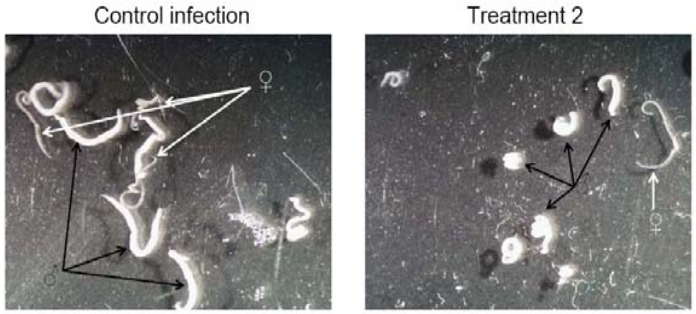
NCGC1597

Inhibitor of Schistosoma mansoni Peroxiredoxins



NCGC1597 was administered by intraperitoneal injection at 10 mg/kg for 5 days at different points during the development of Schistosoma mansoni in the mouse.





Nature Medicine, March 2008

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ML Production Phase, starting summer 2008

- Three different types of Centers
  - Comprehensive Screening Centers
  - Specialized Screening Centers
  - Specialized Chemistry Centers
- With advent of Chemistry Centers, increased emphasis on network communication
- Each Center may have center-defined research
- Screening Centers will provide outreach and greater support for assay implementation
- Screening Centers will be expected to run all primary and secondary screening assays

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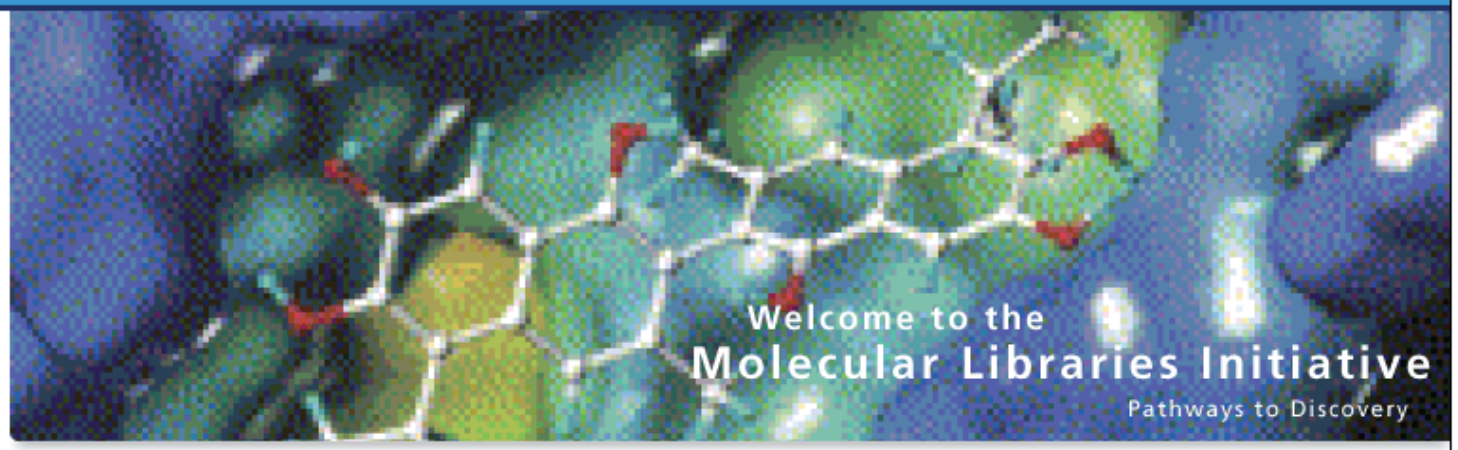
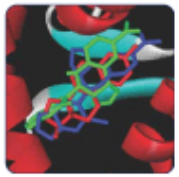
MLSCN | MLSMR | PUBCHEM | TECHNOLOGY | FUNDING | NEWS & EVENTS | RESOURCES



MOLECULAR LIBRARIES ROADMAP

The major components of the Molecular Libraries include the establishment of the Molecular Libraries Screening Centers Network (MLSCN), the Molecular Libraries Small Molecule Repository (MLSMR), a public Cheminformatics database (PubChem) and a series of technology development initiatives.



MOLECULAR IMAGING ROADMAP

To compliment the Molecular Libraries Roadmap, the NIH has developed the Molecular Imaging Roadmap, which focuses on imaging molecules or molecular events in biological systems that span the scale from single cells to whole organisms.

National HTS Resource (MLSCN)

High-tech screening methods implemented by a nationwide consortium of ten small molecule screening centers will be used to screen assays solicited from the public and private sectors against compound libraries housed within the Molecular Libraries Small Molecule Repository (MLSMR). The centers also perform optimization chemistry for the production of in vitro chemical probes used to explore the function of genes, cells, and pathways in health and disease.

Public Cheminformatics Database (PubChem)

PubChem is a public database with annotated information about the biological activities of compounds in the Molecular Libraries Small Molecule Repository (MLSMR) as well as compound probe information. A related cheminformatics initiative is developing novel cheminformatics tools, improved methods of investigation and approaches to cheminformatics research, and creative ways of translating learned experience to the larger biomedical research community.

Technology Development

To foster the development of new tools and technologies for the study of small molecules, the Molecular Libraries Roadmap focuses on technology development in the following areas: Chemical Diversity, Assay Development, Instrumentation and Predictive ADME/Toxicology.

http://mli.nih.gov/