

# NIH Roadmap Molecular Libraries and Imaging:

Opportunities for Investigators to Interact  
with the Molecular Libraries Screening  
Centers Network

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# NIH Roadmap

ACCELERATING MEDICAL DISCOVERY TO IMPROVE HEALTH



## Roadmap

Since 2002, NIH has begun a series of far-reaching initiatives, NIH Roadmap, that is a vision, strategic plan and guidelines for medical research in the 21st century.

## Mission

New Pathways to Discovery sets out to build a better "toolbox" for medical research in the 21st century.

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

## 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](#)



# Molecular Libraries and Imaging Roadmap

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- A trans-NIH initiative headed by:
  - Francis Collins, NHGRI
  - Tom Insel, NIMH
  - Rod Pettigrew, NIBIB
- Participating extramural staff members from 21 institutes and offices
  - CC
  - FIC
  - NCCAM
  - NCI
  - NCRR
  - NEI
  - NHGRI
  - NHLBI
  - NIA
  - NIAID
  - NIAAA
  - NIBIB
  - NICHD
  - NIDCD
  - NIDCR
  - NIDA
  - NIDDK
  - NIGMS
  - NIMH
  - NINDS
  - NLM



# Molecular Libraries Roadmap Components

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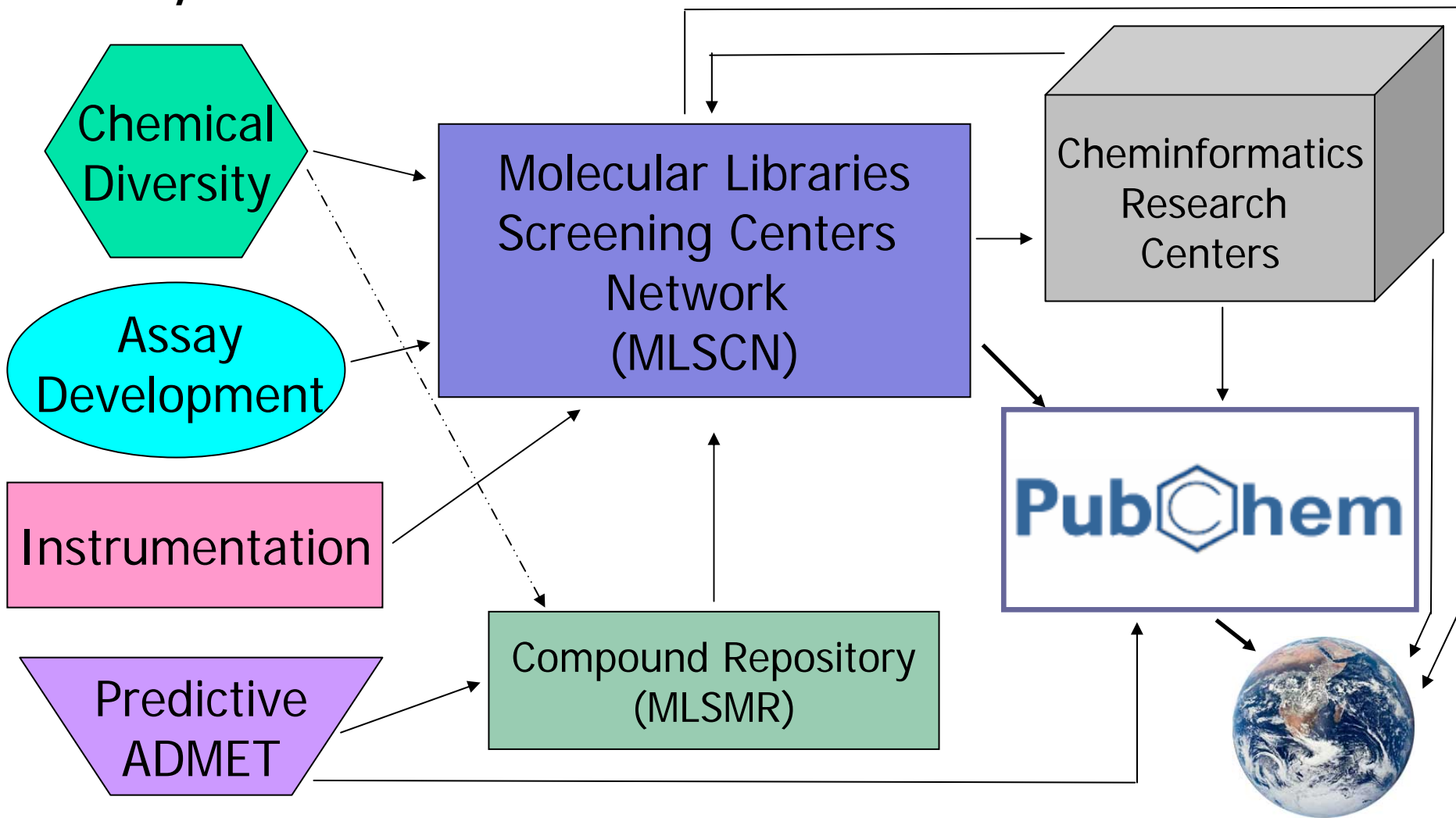
- Molecular Libraries Screening Center Network (MLSCN)
  - Small Molecule Repository (SMR)
  - NIH Chemical Genomics Center (NCGC, intramural)
  - Extramural Screening Centers
- Cheminformatics
  - PubChem
  - Cheminformatics Research Centers
- Technology Development
  - Chemical diversity
  - Assay development
  - HTS instrumentation
  - Predictive ADME/Toxicology

# The Molecular Libraries Roadmap: An Integrated Initiative

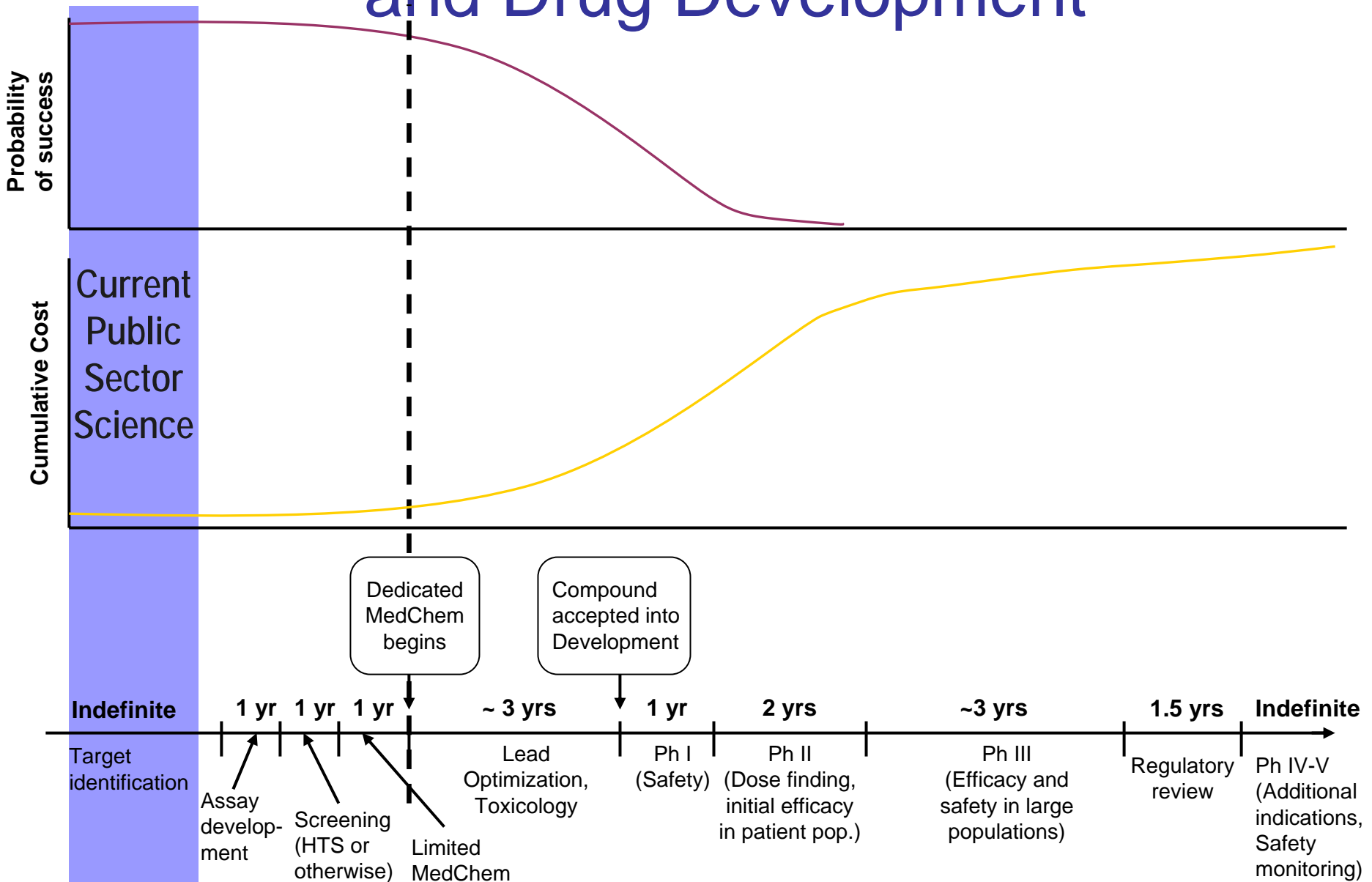
*Technology  
Development*

*Screening*

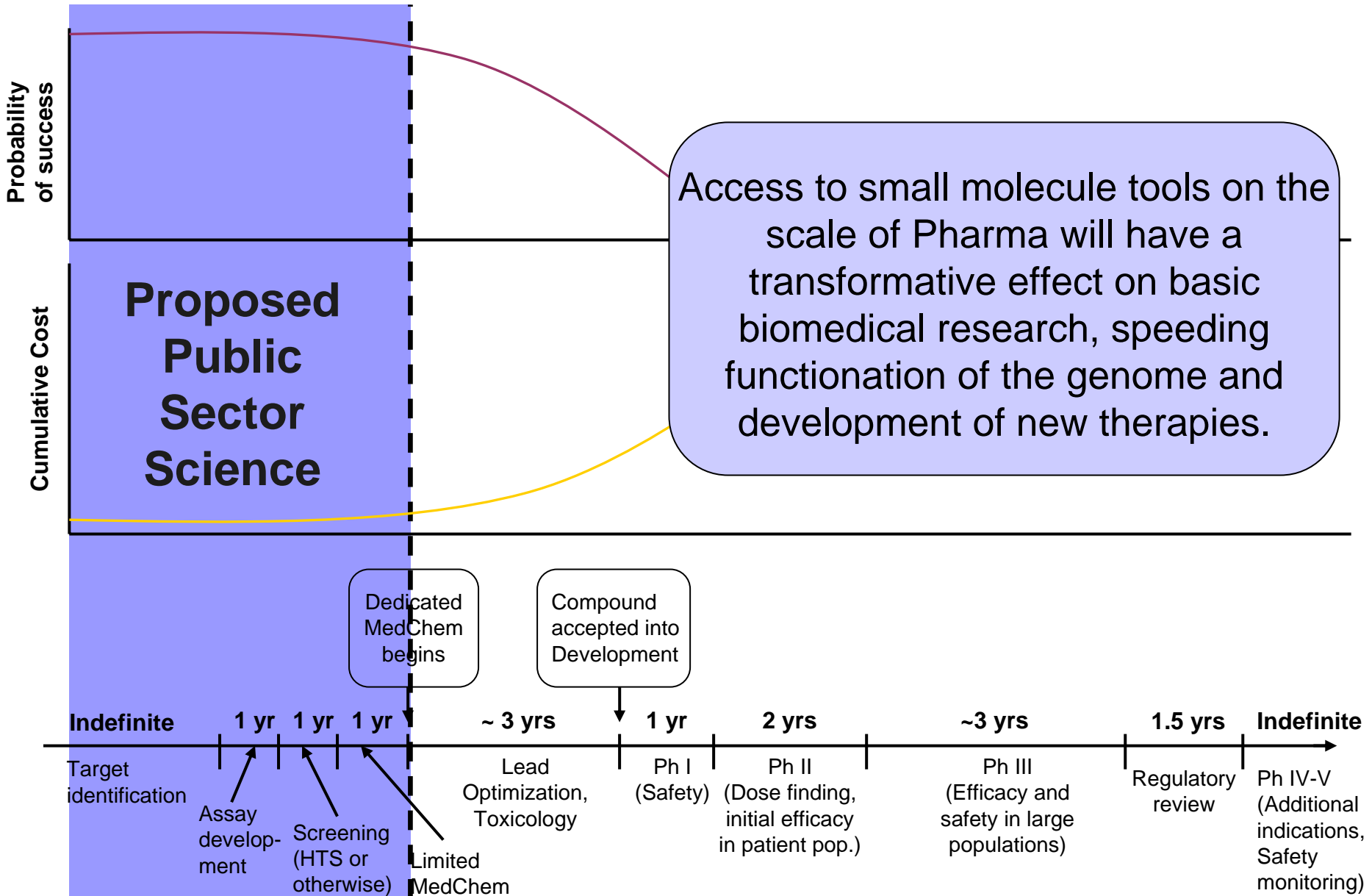
*Informatics*



# The Interface of Chemical Genomics and Drug Development



# The Drug Development Pipeline



# Molecular Libraries Screening Centers Network (MLSCN)

## is a Multidisciplinary Team Effort

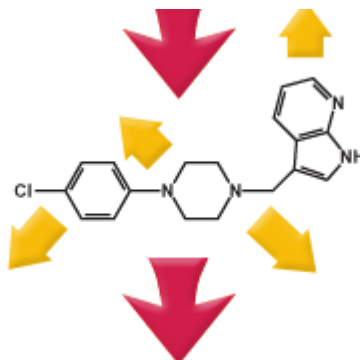


HTS Assays from the  
Community

Compounds  
from the SMR



MLSCN Screening  
Centers Network



PubChem







## Goals of the MLSCN

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- Establish a national HTS resource in the academic environment to improve the understanding of biology and disease mechanisms
  - Provide HTS approaches for identification of small organic molecules that are active in biological assays
  - Synthetic chemistry to improve the utility of small molecules as bioactive probes
  - Make HTS data publicly available in PubChem
  - Stimulate collaborations between biologists and chemists: assay providers, compound providers, and the MLSCN centers
    - Generate scientific publications, new research projects
  - Stimulate technology development
  - Provide outreach to the academic community



## To Achieve the Goals of the MLSCN

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- All data generated by the MLSCN will be deposited promptly upon data verification into PubChem
  - Data includes:
    - Assay descriptions/protocols,
    - Performance data for assays and compounds,
    - Primary data from HTS, data from secondary screening
    - Chemical structures/synthesis protocols for chemical analogs of hits and for probes
    - Biological activity of chemical analogs and probes



# MLSCN RFA and Addendum: Guidance for Sharing of Data & Resources

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## ■ Community Resources

- The usefulness of data and resources generated by the MLSCN will be of maximal benefit to public health if they are treated as a community resource and made publicly available

## ■ Shared Resources include:

- Data resulting from HTS of public domain compounds in the SMR
  - Compounds identified as “hits” are not likely to be immediately useful as research tools or as a final product
  - Screening data are deposited in PubChem with no delay
- Synthetic chemistry and probe development
  - Generation of secondary libraries around a “hit”
    - Screening data is deposited into PubChem and compounds are made available in the Small Molecule Repository
- Assay implementation
  - Assay descriptions and screening data are made available in PubChem

## ■ Exceptions for immediate data release and sharing of resources will be considered

- <http://grants.nih.gov/grants/guide/notice-files/NOT-RM-04-014.html>



# MLSCN Project Team Policy: Key Requirements for Data Sharing & IP

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- Assays and improvements in assay methods may be patented
- Primary HTS by the MLSCN
  - Compounds from the SMR identified as hits from primary HTS are pre-competitive
  - Upon verification of hit activity for a compound, the screening results, compound structure, and performance data on the hit must be promptly deposited in PubChem
  - MLSCN centers **and assay providers** will define criteria for data verification for an assay and receive acceptance from the Scientific Program Managers prior to commencing work on the assay
- <http://www.nimh.nih.gov/dnbbs/datasharing-ip.pdf>



# MLSCN Project Team Policy: Key Requirements for Data Sharing & IP

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- Secondary screening
  - Results from secondary screening of initial hits and chemical analogs of hits must be promptly deposited in PubChem
- Synthetic chemistry and chemical probe development
  - Development of chemical analogs of hits should be made solely in order to meet the specifications of a chemical probe
  - Once the specifications of a chemical probe are achieved, further optimization ceases within the MLSCN
    - Definition of a chemical probe
  - Primary and secondary screening results, and chemical synthesis protocols and data, on all rounds of chemical optimization of hits into probes must be promptly deposited in PubChem
  - Following deposition in PubChem of the chemical probe data, the centers are free to pursue chemical optimization independently of the MLSCN program and MLSCN funds



# MLSCN Project Team Policy: Exceptions for Two Unique Circumstances

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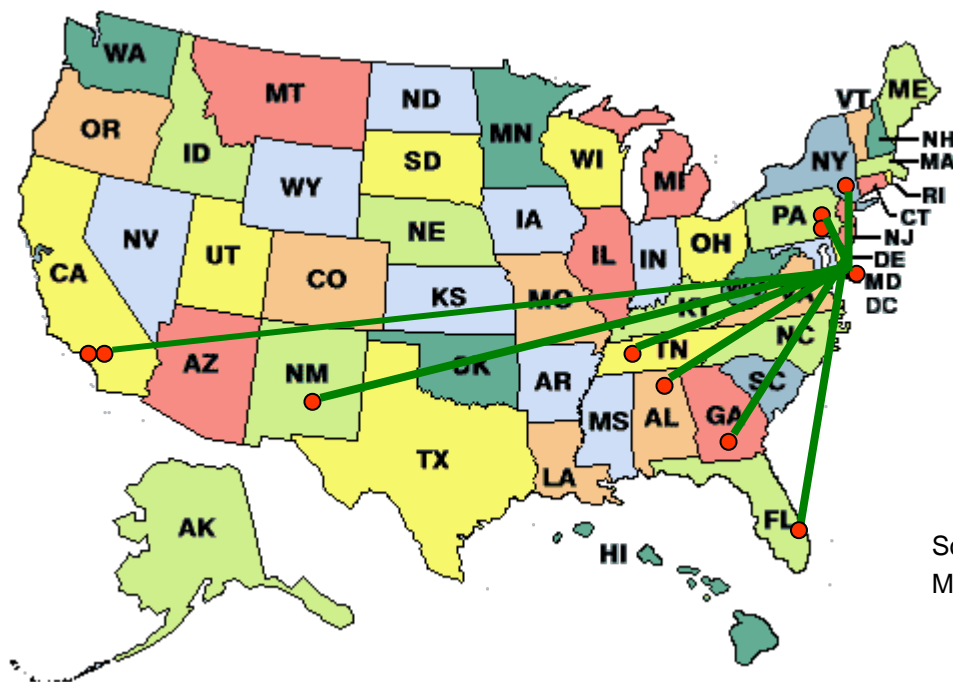
- If prompt disclosure of screening data is determined to provide an unfair advantage to scientific competitors of the assay provider
  - A waiver of the requirement of prompt deposition of screening data will be considered by the NIH Project Team to allow early publication of the screening results
  - If approved, the delay in data deposition would not exceed 60 days
- If a compound is determined to be a drug candidate without further chemical optimization
  - A waiver of the requirement of prompt deposition of screening data will be considered by the NIH Project Team to allow filing of a patent
  - If approved, the delay in data deposition would not exceed 60 days



# Molecular Libraries Screenings Centers Network (MLSCN)

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

# MLSCN Nationwide Network



MLSCN Center  
at Columbia University

NIH Chemical Genomics  
Center (NCGC)

University of Pittsburgh Molecular  
Libraries Screening Center

The Penn Center for  
Molecular Discovery

Scripps Florida  
Molecular Screening Center

Vanderbilt Screening Center for  
GPCRs, Ion Channels, and Transporters

Southern Research Molecular Libraries  
Screening Center (SRMLSC)

Emory Chemistry-Biology  
Center in the MLSCN



Scripps Research Institute  
Molecular Screening Center

San Diego Center for  
Chemical Genomics

New Mexico Molecular Libraries  
Screening Center



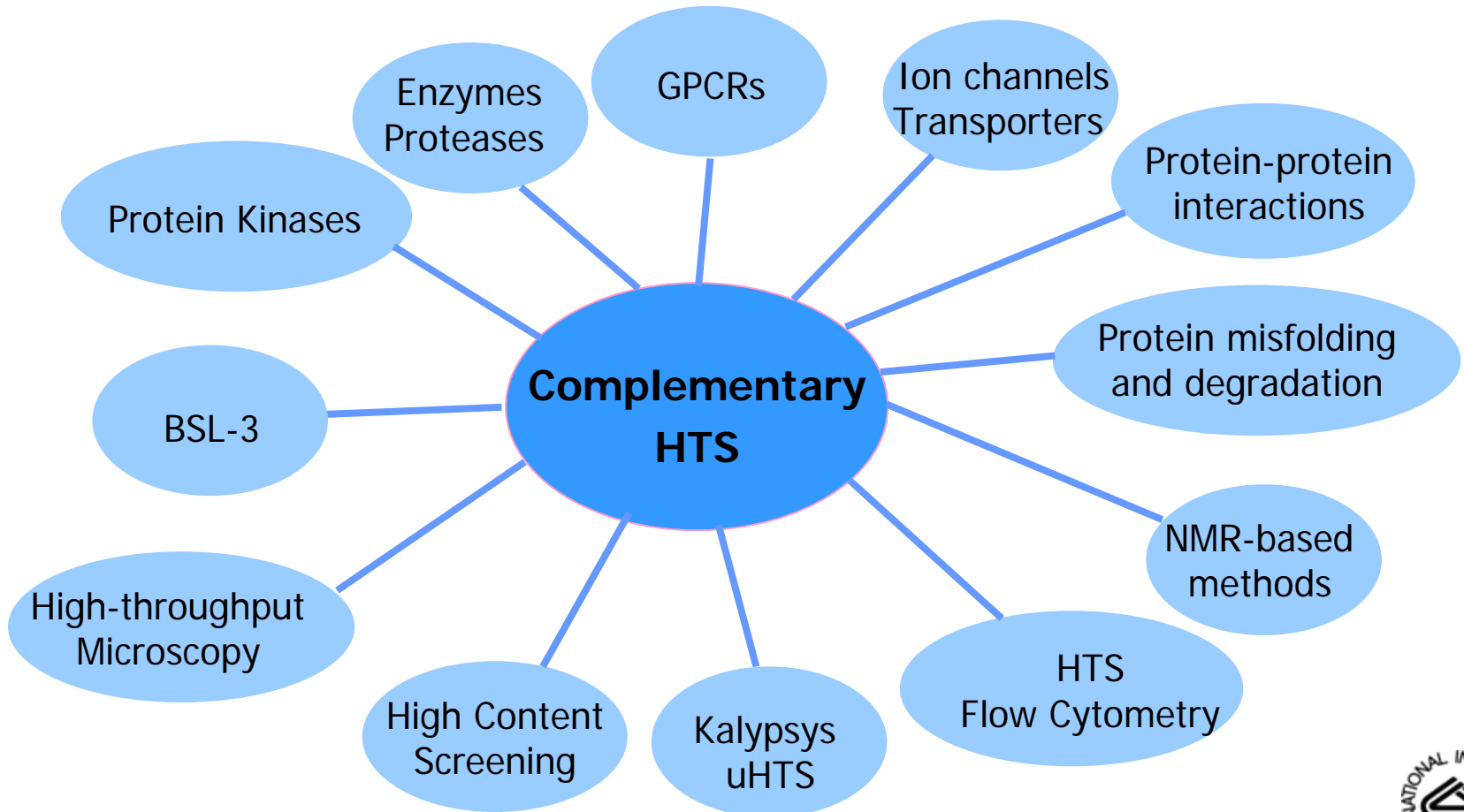


# Overall HTS Technology of the MLSCN

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- Diverse screening platform technologies
  - Cell based imaging, flow cytometry, microarray screening, ultraHTS, protein-protein, whole organism
- Detection systems
  - Luminescence, fluorescence, FLIPR, FRET, SPA, absorbance, ELISA
  - Microscopy based imaging, spectrophotometric
  - Microarray, RT-PCR

# Overall Capabilities of the MLSCN



# The NIH Molecular Libraries Small Molecule Repository (MLSMR)



The screenshot shows a Microsoft Internet Explorer browser window displaying the homepage of the NIH Molecular Libraries Small Molecule Repository (MLSMR). The browser's address bar shows the URL: [http://mlsmr.discoverypartners.com/MLSMR\\_HomePage/](http://mlsmr.discoverypartners.com/MLSMR_HomePage/). The page features a blue header with the text "NIH MOLECULAR LIBRARIES SMALL MOLECULE REPOSITORY" and the "DISCOVERY PARTNERS INTERNATIONAL" logo. Below the header, there is a navigation menu on the left with items like "Home", "MLSMR Project", "Compound Identification", "Quality Control", "Sample Storage", "Sample Arrays", "Informatics", "MLSCN Centers", and "MLSMR Contacts". The main content area includes a "Welcome" section with a photograph of a scientist in a lab coat working at a workstation. The text describes the repository's role in collecting samples for high-throughput biological screening and distributing them to the NIH Molecular Libraries Screening Center Network. A "Learn more" link is provided. Below this, there is a section titled "Registered Users Login" and a "Copyright © 1999 - 2005 Discovery Partners International" notice. The footer of the page states "Discovery Partners International operates MLSMR in South San Francisco." The browser's taskbar at the bottom shows the "Internet" icon.

NIH MOLECULAR LIBRARIES  
SMALL MOLECULE REPOSITORY

DISCOVERY PARTNERS  
INTERNATIONAL

A Roadmap Initiative

Home  
MLSMR Project  
Compound Identification  
Quality Control  
Sample Storage  
Sample Arrays  
Informatics  
MLSCN Centers  
MLSMR Contacts

Registered Users Login

Copyright © 1999 - 2005  
Discovery Partners International

Discovery Partners International operates MLSMR in South San Francisco.

Welcome

NIH Molecular Libraries Small Molecule Repository collects samples for high throughput biological screening and distributes them to the NIH Molecular Libraries Screening Center Network.  
[Learn more.](#)

MLSMR is part of the NIH Roadmap for medical research in the 21<sup>st</sup> century. The project is funded in whole with Federal funds from the National Institutes of Health, Department of Health and Human Services, under Contract No. HHS-N-278-2004-41001C.

*In the news:*  
[Behind the Scenes at the NIH Molecular Libraries Small Molecule Repository](#)

[http://mlsmr.discoverypartners.com/MLSMR\\_HomePage/](http://mlsmr.discoverypartners.com/MLSMR_HomePage/)



# Building the MLSMR

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- Initial set of 80,000 compounds
  - Compound Selection Criteria
    - Purity > 90%
    - Stock of > 10 mg
    - Lipinski Rule of 5, if applicable
    - Solubility of 20 ug/ml based on AlogS
    - No undesirable functional groups



# Molecular Libraries Small Molecule Repository (MLSMR)

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- Initial set of 80,000 compounds purchased from commercial vendors
  - Targeted Libraries
    - Active ingredients of FDA approved drugs
  - Diverse compounds
  - Natural products
- Expanding the compound collection
  - Solicitation of compounds from academia, biotech companies, and pharma (in process)
  - NIGMS Chemical Methodologies Library Development (CMLD) centers
  - Molecular Libraries Chemical Diversity initiatives
  - Strategy being developed for acquisition of second 100,000 compounds

# To Search for the SMR Compounds in PubChem: DPISMR

PubChem Substance - Microsoft Internet Explorer

File Edit View Favorites Tools Help

NCBI National Library of Medicine NLM My NCBI [Sign In] [Register]

All Databases PubMed Nucleotide Protein Genome Structure PMC PubChem Books

Search PubChem Substance for DPISMR[sourcename] Go Clear Save Search

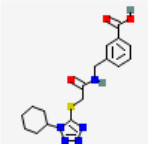
Limits Preview/Index History Clipboard Details

Display Summary Show 20 Sort by Send to

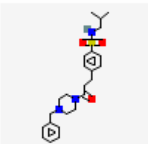
All: 52624 BioAssay: 0 Protein3D: 0 Rule of 5: 43924

Items 1 - 20 of 52624 Page 1 of 2632 Next

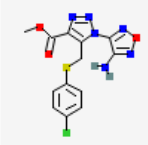
1: SID: [4265931](#) Links

  
CID: 1291615, MLS000097311, SMR000075886 ...  
Source: DPISMR(MLS000097311)  
IUPAC: 3-[[2-(1-cyclohexyltetrazol-5-yl)sulfanylacetyl]aminomethyl]benzoic acid  
MW: 375.447 | MF: C17H21N5O3S

2: SID: [4265930](#) Links

  
CID: 2951507, MLS000097264, SMR000075790 ...  
Source: DPISMR(MLS000097264)  
IUPAC: 4-[2-(4-benzylpiperazin-1-yl)carbonyl]ethyl-N-(2-methylpropyl)benzenesulfonamide  
MW: 443.603 | MF: C24H33N3O3S

3: SID: [4265929](#) Links

  
CID: 1259460, MLS000052920, SMR000082785 ...  
Source: DPISMR(MLS000052920)  
IUPAC: methyl 1-(4-amino-1,2,5-oxadiazol-3-yl)-5-[(4-chlorophenyl)sulfanylmethyl]triazole-4-carboxylate  
MW: 366.784 | MF: C13H11ClN6O3S

About Entrez Entrez Help

PubChem Help

PubChem Substance Database

PubChem Compound Database

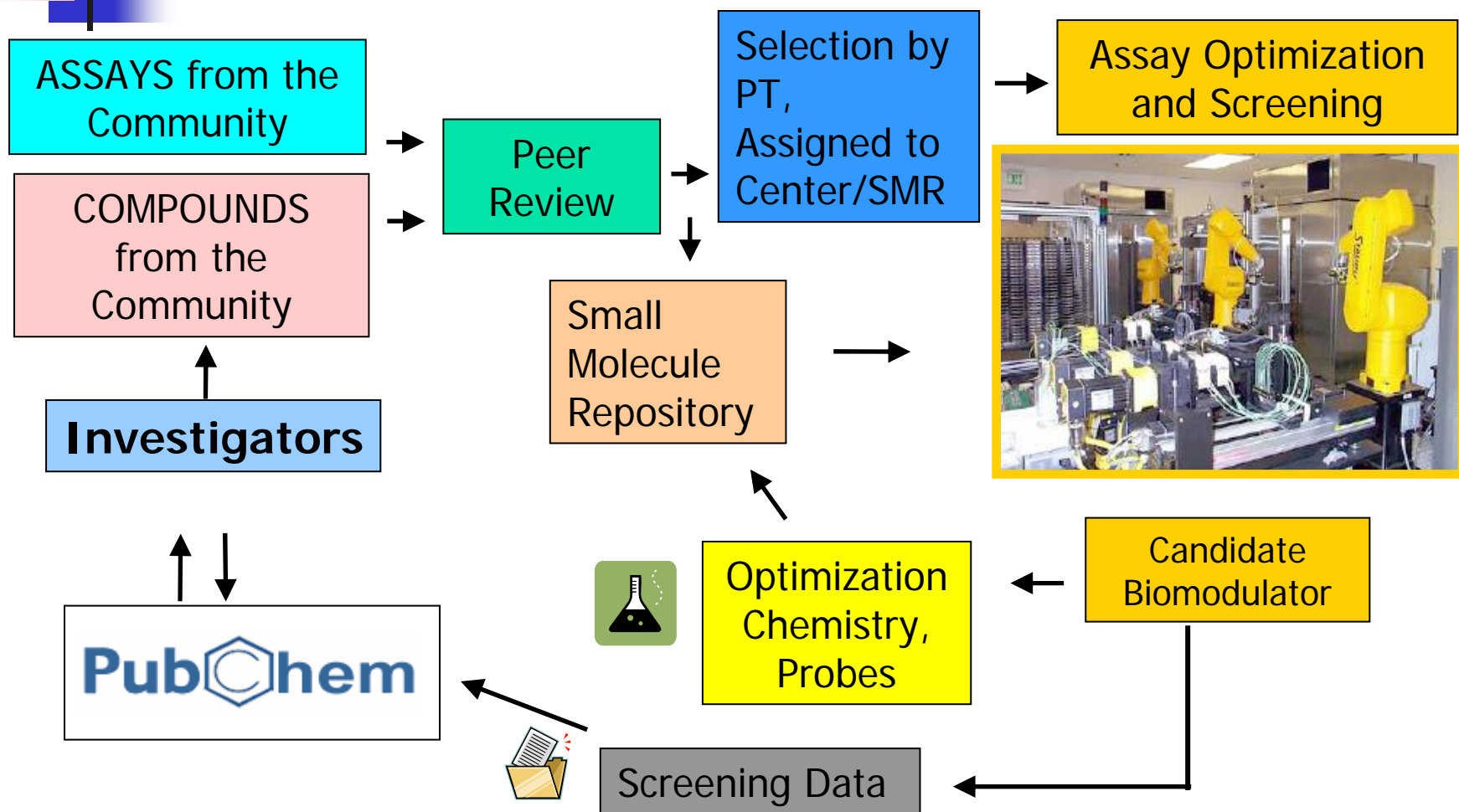
PubChem BioAssay Database

PubChem Structure Search

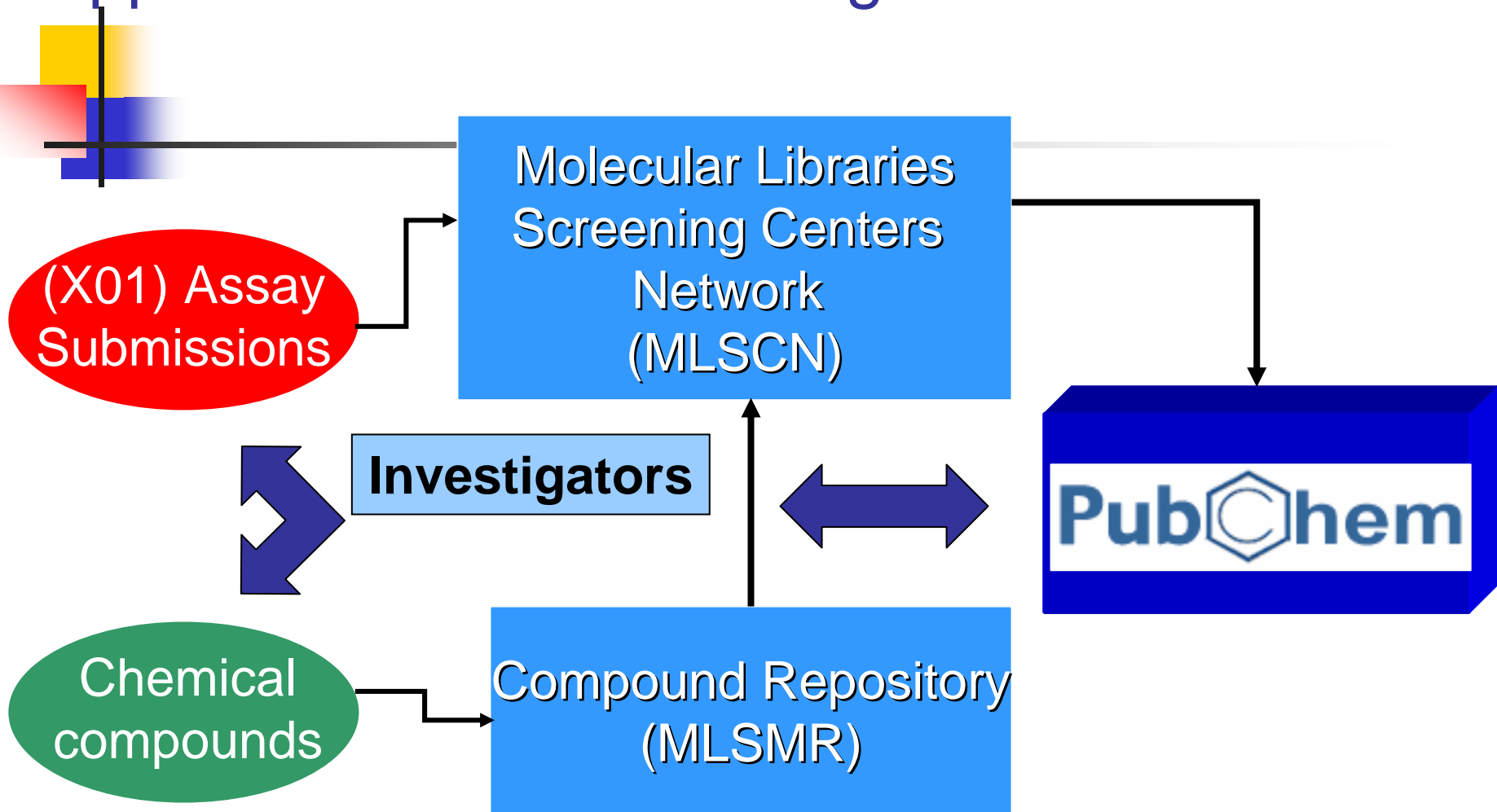
PubChem FTP

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=pcsubstance&term=DPISMR\[sourcename\]](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=pcsubstance&term=DPISMR[sourcename])

# MLSCN Resources



# Opportunities for Accessing MLSCN Resources







# Incentives for Investigators to Interact with the MLSCN

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- Access to the resources of the MLSCN Network of Screening Centers through the X01 mechanism
  - Diverse screening platform technologies
    - Cell based imaging, flow cytometry, microarray screening, ultraHTS, protein-protein, whole organism
  - Detection systems
    - Luminescence, fluorescence, FLIPR, FRET, SPA, absorbance, ELISA
    - Microscopy based imaging, spectrophotometric
    - Microarray, RT-PCR
- Availability of research tools/probes and biological data deposited in PubChem

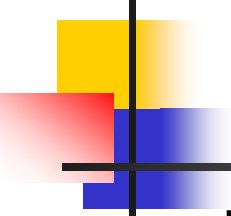


# Incentives for Investigators to Interact with the MLSCN

---

- Access to compounds in the Small Molecule Repository for HTS through the MLSCN
  - Current library of 80,000 compounds purchased from commercial vendors
    - Targeted Libraries
      - Active ingredients of FDA approved drugs
    - Diverse compounds
    - Natural products
  - Ongoing expansion of chemical diversity of the repository  
Solicitation of compounds from academia, biotech companies, and pharma (in process)
    - NIGMS Chemical Methodologies Library Development (CMLD) centers
    - Molecular Libraries Chemical Diversity initiatives
    - Acquisition of second 100,000 compounds

# Opportunities and Incentives for Investigators to Interact with the MLSCN



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- Process for access to the resources of the network of the ten MLSCN centers
  - Submission of X01 assay applications; if selected for implementation:
    - Assay adapted for HTS
    - Screened against SMR
    - Collaboration with assay provider for secondary screening of confirmed hits
    - Chemical optimization of confirmed hits
  - Submission of compound applications (to be implemented) for entry into the Repository
    - Compounds screened in HTS assays in the MLSCN

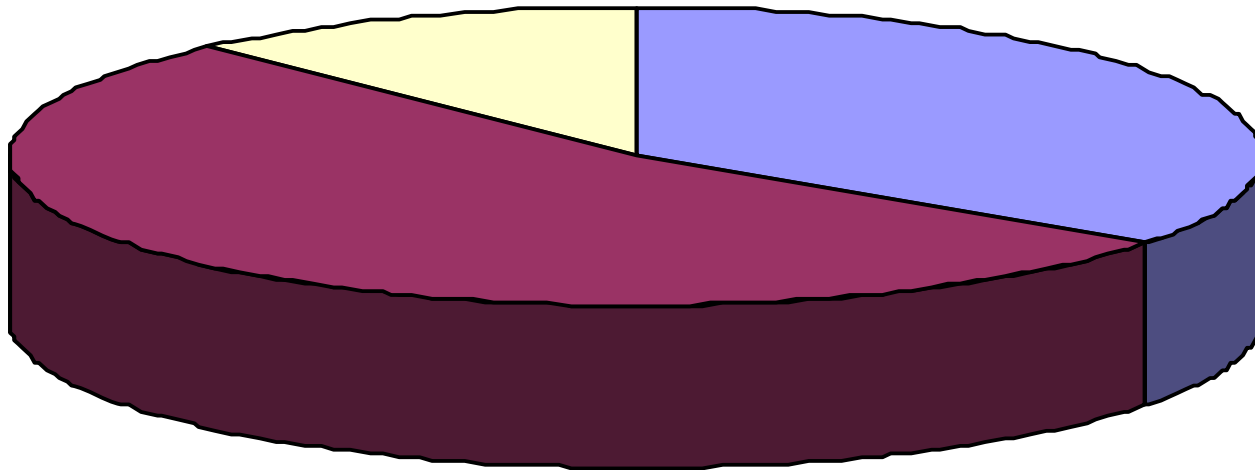
# MLSCN HTS Assay Solicitation: X01 Resource Access Award

- The MLSCN accepts assays for HTS from the broad research community, including
  - Public or private institutions and agencies of the Federal government
- The MLSCN intends to select approximately 100-200 assays per year for implementation within the network of screening centers. It is expected that each screening center will conduct 10-20 HTS assays annually
- Applications are invited from investigators who have developed innovative assays for use both in basic research and in therapeutics development programs

# MLSCN HTS Assays to Date

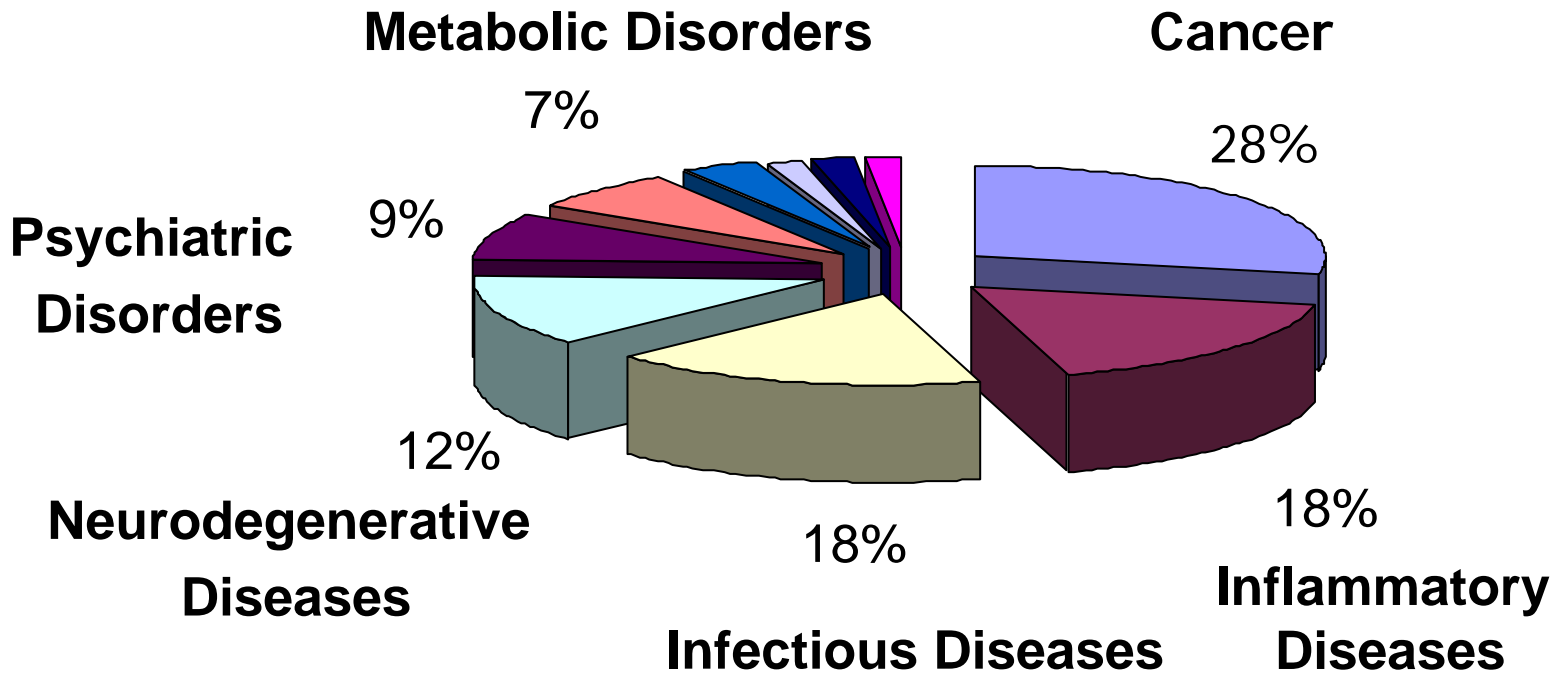
## *Assay Formats*

- Cell Based
- Biochemical
- Model Organisms



# MLSCN HTS Assays to Date

## *Disease Relevance*





# Opportunities for Investigators to Interact with the MLSCN

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- Access to and mining of data deposited in [PubChem](#)
  - Primary and secondary biological screening data
  - Assay descriptions and protocols
  - Synthesis protocols for optimization chemistry and research tools or probes generated by the MLSCN
  - Chemical structures of compounds in the Small Molecule Repository in addition to many other compound entries



# Molecular Libraries: PubChem

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- Public sector chemical database developed by the NIH National Center for Biomedical Informatics
  - Fully linked to other NCBI Entrez databases of genes, proteins, Medline
  - Coordinates bioassay data deposition from the MLSCN
  - Provides support to investigators for bioassay data deposition
  - Went live in September 2004
    - <http://pubchem.ncbi.nlm.nih.gov/>





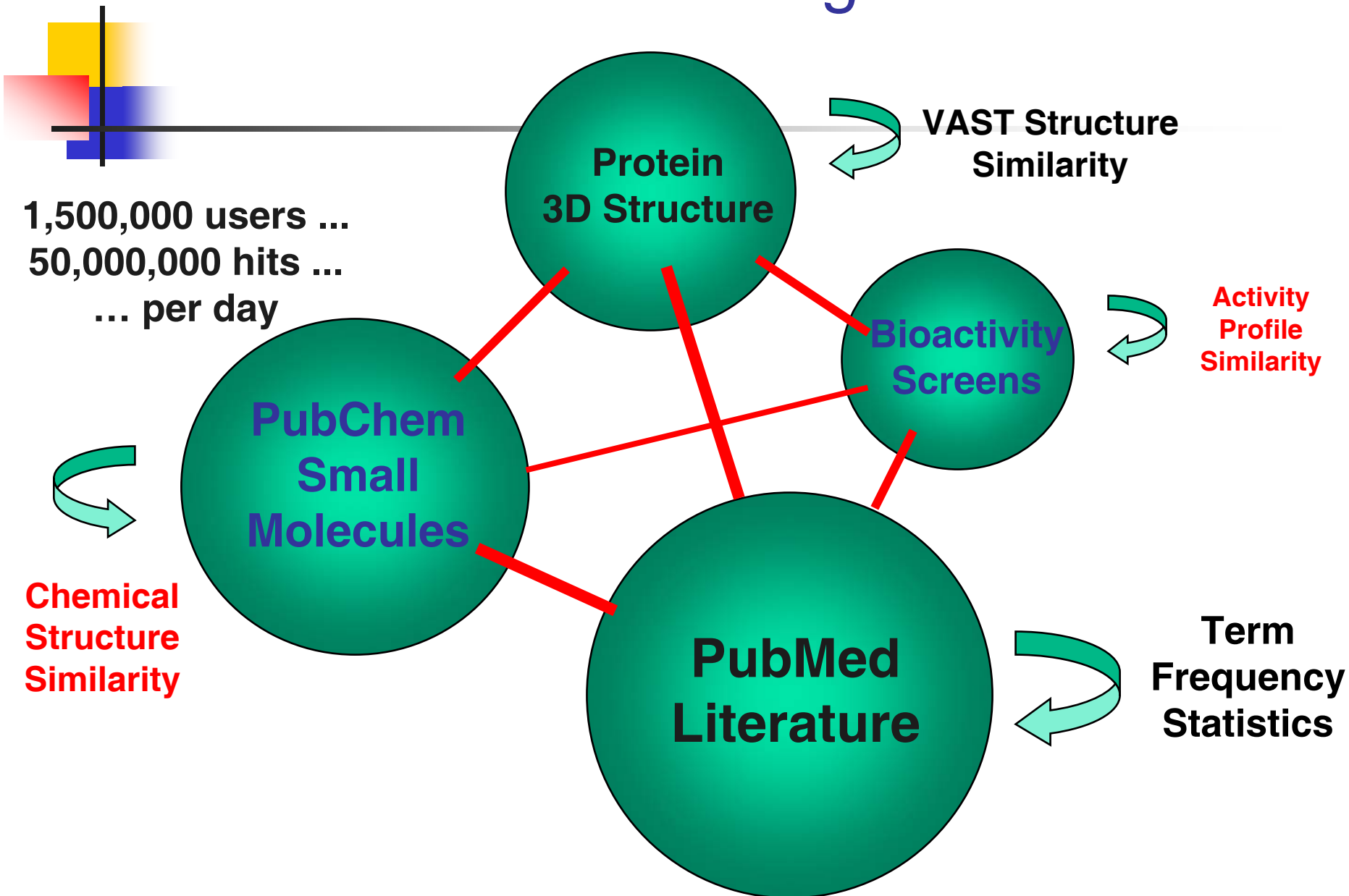
# PubChem

---

- Entrez links and neighbors:
  - PubMed-PubChem linkage
  - Unique chemical structures
    - PubChem structure neighbors
    - Structure sketching for structure searches
  - PubChem bioassay links
- Contents as of March 2006:
  - Approximately 7,848,000 substance records
  - Deposited by > 25 government, academic, and commercial organizations
  - Approximately 5,270,000 unique chemical structures
  - Approximately 200 bioassay data sets deposited
    - > 3,158,000 bioassay test results

# PubChem

## Entrez Links and Neighbors





# PubChem Information Sources

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- Contributed substance records
- Contributed biological screening results
- Contributed links to other Entrez databases
- Links created by PubMed indexing
- Computed similarities between records

# PubChem Structure Search Tool

PubChem Advanced Structure Search V1.3 - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Home Search Favorites Media Print Copy Paste

Address [http://pubchem.ncbi.nlm.nih.gov/search/compoundsearch.html?smarts=C1%3DCC%3DC2C\(%3DC1\)C\(%3DNC\(%3DN2...](http://pubchem.ncbi.nlm.nih.gov/search/compoundsearch.html?smarts=C1%3DCC%3DC2C(%3DC1)C(%3DNC(%3DN2...) Go Links »

HOME SEARCH SITE MAP PubMed Entrez Structure GenBank PubChem Help

Search Clear PubChem Advanced Structure Search

Structure Input: ?

SMARTS/SMILES:  Sketch ?

Search Method: ?

Identical structures with  ?

Similar structures with a similarity coefficient >=  ?

Substructure search:

Match SS stereochemistry:	Match SS isotopes:	Match SS charges:	Match SS tautomers:	SS ringsystems not embedded:	Single/double SS bonds match arobonds:	Chain SS bonds match rings:
<input type="checkbox"/> ?	<input type="checkbox"/> ?	<input type="checkbox"/> ?	<input type="checkbox"/> ?	<input type="checkbox"/> ?	<input checked="" type="checkbox"/> ?	<input checked="" type="checkbox"/> ?

Superstructure search:

Ignore	<input type="checkbox"/> ?	<input type="checkbox"/> ?	<input type="checkbox"/> ?	<input type="checkbox"/> ?	<input checked="" type="checkbox"/> ?	<input checked="" type="checkbox"/> ?
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Done Internet

# PubChem Sketcher and Other Options

PubChem Server Side Structure Editor V1.8 - Microsoft Internet Explorer

Fast connection | SMILES | C1=CC=C2C(=C1)C(=NC(=N2)C3=CC=CC(=C3)C#N)N(C4=CC=NC=C4)[H]

New Undo Cln Del Qry

S/A D/A S/D

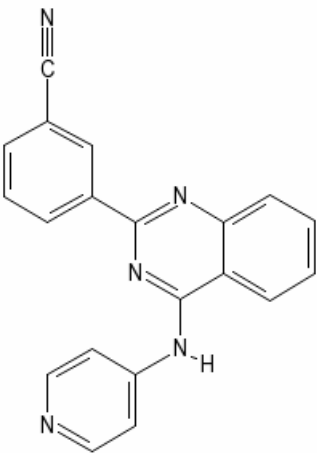
NO2 COOH COOMe SO3H

H		?	?						He
Li	Be			B	C	N	O	F	Ne
Na	Mg			Al	Si	P	S	Cl	Ar
K	Ca	Sc	Sc	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Y	In	Sn	Sb	Te	I	Xe
Cs	Ba	Lu	Lu	Tl	Pb	Bi	Po	At	Rn

Export MDL Molfile Done

Hydrogen Keep AsIs

Import Browse...



Done Internet

# PubChem Search Results

## Pass to Entrez

PubChem Compound - Microsoft Internet Explorer

File Edit View Favorites Tools Help

← Back → Search Favorites Media

Address <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Select+from+History&WebEnvRq=1&db=pccompound&WebEnv=C> Go Links »

NCBI PubChem Compound National Library of Medicine NLM My NCBI [Sign In] [Register]

All Databases PubMed Nucleotide Protein Genome Structure PMC PubChem Books

Search PubChem Compound for Go Clear

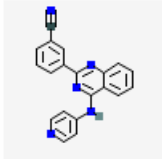
Limits Preview/Index History Clipboard Details

Display PubChem Download Show 20 Sort by Send to

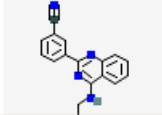
All: 72 BioAssay: 40 Protein3D: 0 Rule of 5: 68

Items 1 - 20 of 72 Page 1 of 4 Next

1: CID: [3234284](#) Links

 PCOP-586654, NCGC00011706  
IUPAC: 3-(4-pyridin-4-ylaminoquinazolin-2-yl)benzotrile  
MW: 323.351 | MF: C20H13N5

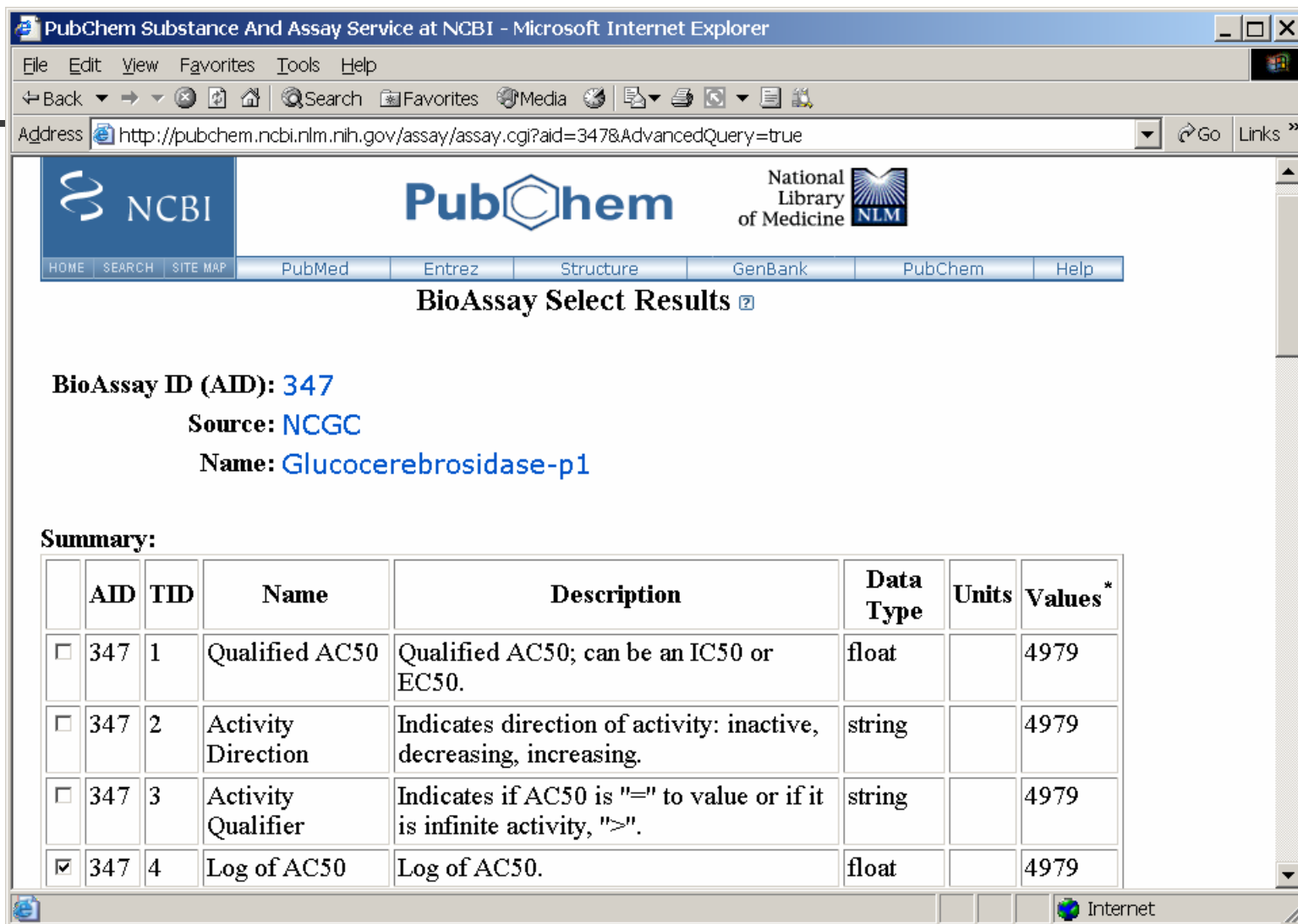
2: CID: [3232642](#) Links

 PCOP-21053, NCGC00010058  
IUPAC: 3-[4-(pyridin-3-ylmethylamino)quinazolin-2-yl]benzotrile  
MW: 327.379 | MF: C21H15N5

PubChem Compound Database

Internet

# Select PubChem BioAssay Results



PubChem Substance And Assay Service at NCBI - Microsoft Internet Explorer

Address: <http://pubchem.ncbi.nlm.nih.gov/assay/assay.cgi?aid=347&AdvancedQuery=true>

NCBI PubChem National Library of Medicine NLM

HOME SEARCH SITE MAP PubMed Entrez Structure GenBank PubChem Help

## BioAssay Select Results

**BioAssay ID (AID):** [347](#)  
**Source:** [NCGC](#)  
**Name:** [Glucocerebrosidase-p1](#)

**Summary:**

	AID	TID	Name	Description	Data Type	Units	Values*
<input type="checkbox"/>	347	1	Qualified AC50	Qualified AC50; can be an IC50 or EC50.	float		4979
<input type="checkbox"/>	347	2	Activity Direction	Indicates direction of activity: inactive, decreasing, increasing.	string		4979
<input type="checkbox"/>	347	3	Activity Qualifier	Indicates if AC50 is "=" to value or if it is infinite activity, ">".	string		4979
<input checked="" type="checkbox"/>	347	4	Log of AC50	Log of AC50.	float		4979

# For Selected PubChem Substances

PubChem Substance And Assay Service at NCBI - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Home Search Favorites Media Print Copy Paste

Address <http://pubchem.ncbi.nlm.nih.gov/assay/assay.cgi> Go Links

**Set activity search range:** ?

AID	Result Name	Values	Value range	Lower Limit	Upper Limit
347	Log of AC50	4979	-7.65, -2.94		

**Set substances search:** ?

Choose Select One:  
from #28 Similar Substance Links for PubChem Substance ( for PubChem Substance (Select 4239177)) sort by: DEP  
Entrez #27 for PubChem Substance (Select 4239177) [72 hits]  
history: #25 PubChem Substance, Active Links for PubChem BioAssay (Select 347) ... [83 hits]

Or set Entrez query:   
(example as '100:200[MOLWT] AND 5[HBDC]')

Show Results With property  MW

Sort by  ↓ ○ ↑ ○ ?

Show  Records/page

Ignore substances with missing readouts

Done Internet





# Molecular Libraries Technology Development Initiatives

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- Cheminformatics Research Centers
- Chemical diversity
- Assay development
- HTS instrumentation
- Predictive ADME/Toxicology



# Cheminformatics Research Centers

## Technology Development

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- Substantial unmet need for publicly available cheminformatics research tools
  - Virtual screening, virtual synthesis, other applications, R&D on new tools
- Exploratory Centers for Cheminformatics Research, [RFA RM-05-012](#)
  - FY05: 6 Exploratory Centers awarded
    - P20s, 2 years

# Chemical Diversity

## Technology Development Supporting the MLSCN and SMR

- Pilot-Scale Libraries for High-Throughput Screening ([RFA-RM-05-014](#))
  - Rationale: Probes for novel proteins require novel chemical structures
  - Pilot chemical libraries from RFA will be deposited in the MLSMR and tested for bioactivities in MLSCN centers and expanded if active
  - FY05: 8 Biotechnology Resource Grants awarded
    - P41s, 3 years
  - FY06 [RFA-RM-06-003](#)



# Assay Development Technology Development Supporting the HTS Assay Pipeline

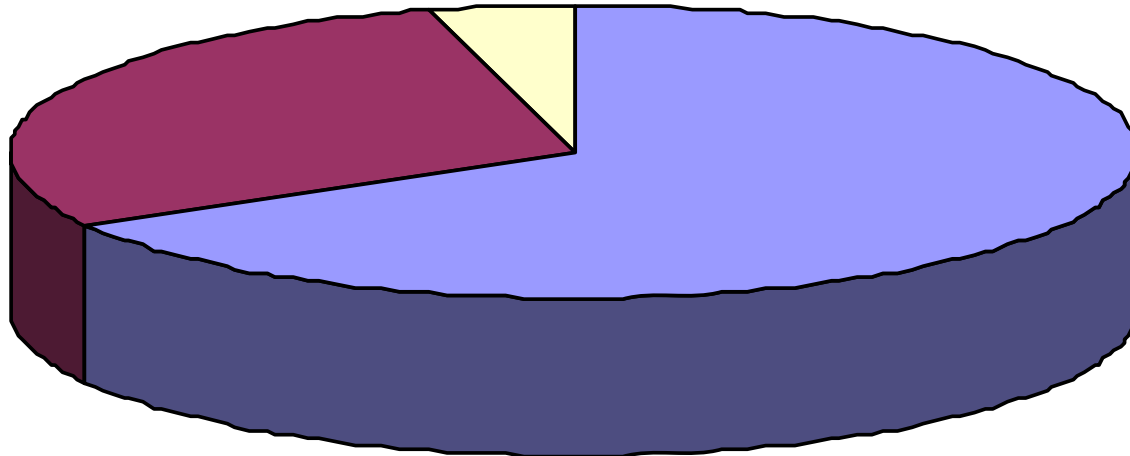
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- Assay Development for High Throughput Molecular Screening ([RFA-RM-06-004](#))
  - <http://nihroadmap.nih.gov/molecularlibraries/grants.asp>
  - Facilitate the development of innovative assays
  - Provide a continuously evolving stream of assays that can enter into the MLSCN via the HTS solicitation
    - Biochemical or cell-based assays of activity or interaction involving proteins and/or other biological molecules
    - Assays of cellular or molecular phenotypes
    - Modulation of expression of genes of interest, including effects on transcription, translation or RNA splicing
    - Assays involving mutant proteins associated with disease
    - Cell-based assays of cell signaling or biosynthetic pathways
  - FY04: 29 R03s awarded (1 year)
  - FY05: 38 R03s/R21s awarded (1 year)

# Assay Development Awards To Date

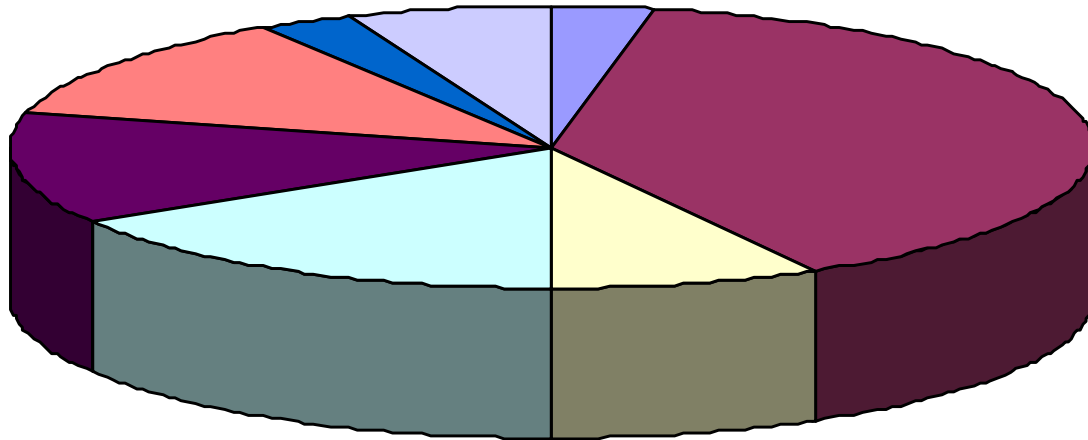
## *Assay Formats*

■ Cell Based                      ■ Biochemical  
■ Model Organisms



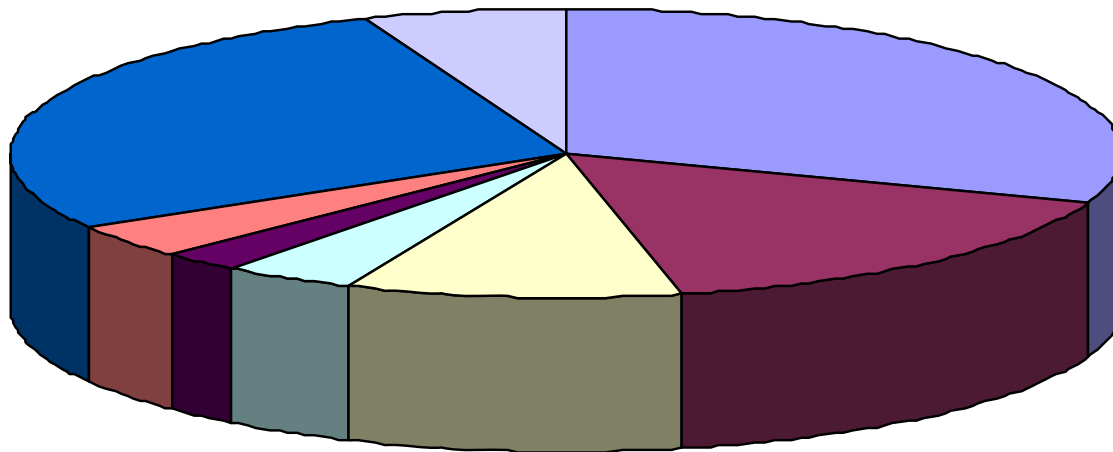
# Assay Development Awards To Date

## *Detection Technology*



# Assay Development Awards To Date

## *Molecular Assay Targets*





# Chemical Diversity Technology Development

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- New Methodologies for Natural Products Chemistry ([RFA-RM-05-013](#))
  - Rationale: Natural products have higher rate of bioactivity than novel synthesized compounds
    - most small molecule new chemical entities introduced as drugs worldwide 1981–2002 were NPs or NP-related
    - but Pharma has largely abandoned NPs in favor of synthesis because NP chemistry is slow and NP supply problematic
  - New methodologies needed to address these problems
    - Rapid isolation, purification, and identification
    - Chemical and genetic strategies for derivatization
    - Rapid isolation of genes for biosynthesis
    - Universal expression systems
  - FY05: 6 R01s awarded (3 years)





# HTS Instrumentation

## Technology Development

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- ML Screening Instrumentation ([RFA-04-020](#))
  - Purpose: Support for technology development in HTS instrumentation necessary to achieve MLI objectives for throughput and for diversity of biological targets and approaches
  - Research emphasis in 3 areas
    - overcoming bottlenecks in HTS production, *e.g.*, improved robotics and systems integration
    - increasing efficiency, *e.g.*, miniaturization
    - innovation in detection methodologies, *e.g.*, protein-protein association measurement, cell imaging
  - FY05: 6 Exploratory Centers awarded
    - P20s, 2 years



# Predictive ADME-Toxicology Technology Development

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- Novel Preclinical Tools for Predictive ADME-Toxicology ([RFA 04-023](#))
  - Objectives
    - Seek novel preclinical tools to improve predictive evaluation of new chemical entities
    - Improve understanding of how drug molecules are absorbed, distributed or excreted from the body
    - Understand mechanisms by which drug molecules cause toxicities
  - FY05: 5 Exploratory/Developmental Grants awarded
    - R21, 4 years

# Summary of MLSCN Opportunities

## The New Interface of Chemistry and Biology

