

High-Content Screening of the NIH MLSMR Library

Susanne Heynen-Genel, Ph.D.

Director, High-Content Screening Systems
Conrad Prebys Center for Chemical Genomics
Burnham Institute for Medical Research
sheynen@burnham.org



MLPCN / MLP

• Molecular Libraries Probe Production Centers Network

- Production phase of the Molecular Libraries Program (an NIH Roadmap Initiative) supporting chemical biology efforts (<http://mli.nih.gov/mli/>)
- Nationwide network of small molecule screening centers
- Aim to produce *in vitro* chemical probes for use in biological research
- Perform HTS of bioassays submitted by the research community using a central NIH library of small molecules (**MLSMR**)
- Optimize chemistry of hits to produce useful *in vitro* chemical probes
- Data from MLPCN assays and identified probes are made publically available via **PubChem** (<http://pubchem.ncbi.nlm.nih.gov/>)

Nine Centers Funded by the NIH (Roadmap Initiative):

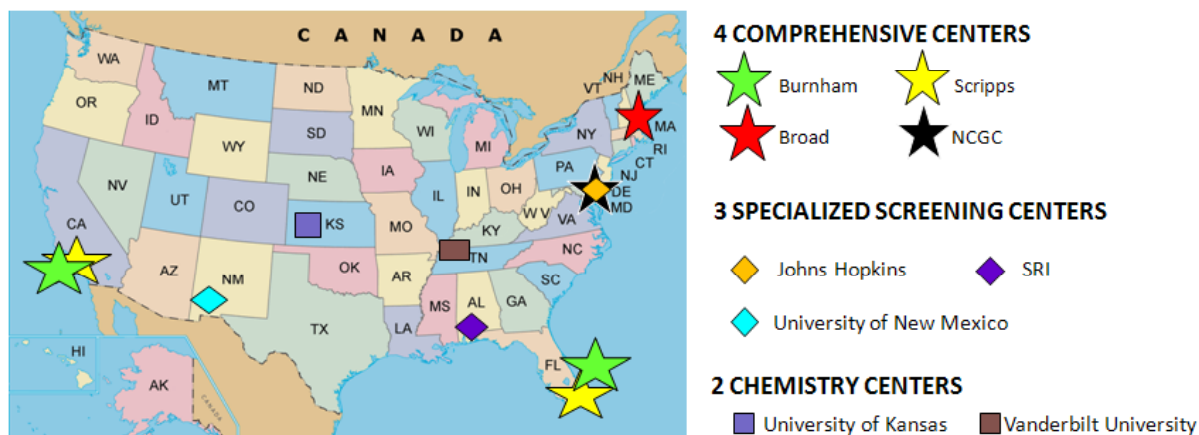


Figure courtesy of T. Chung / Burnham Institute for Medical Research

NIH MLSMR Library

- Information about the **Molecular Libraries Small Molecule Repository** can be found at :
http://mlsmr.glpig.com/MLSMR_HomePage/
- MLSMR distributes the central compound collection to MLPCN for high-throughput screening of bioassays
- MLSMR collection contains >300,000 chemically diverse small molecule compounds from 4 different compound classes:
 1. Diversity Compounds
 2. Natural Products (from known and documented natural sources)
 3. Targeted Libraries (i.e. protease, kinase, GPCR, ion channel, and nuclear receptors)
 4. Specialty Sets (known bioactives like drugs, toxins etc.)

Image-Based HCS in MLPCN/PubChem

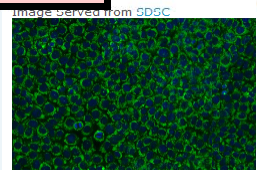
Screening Center	Type of HC Assay
SRMLSC	Secondary Only
Burnham	Primary & Secondary
Univ. Pittsburgh*	Primary & Secondary
NCGC	Primary & Secondary
Columbia*	Primary & Secondary
Emory*	Zebrafish (small screens)
New Mexico	Flow Cytometry

* MLSCN Center Only – did not continue into MLPCN Phase

HTS Workflow
 Chemistry Core
 Info/Cheminformatics
 PubChem Data
 Outreach

236421

26665841 1532



■ DAPI-Stained Nuclei
 ■ Lipid Droplets Labeled with Bodipy

[Expand Image](#)

Assay: 1656(PubChem)
 High Throughput Imaging Assay for
Assay Description:
 Data Source: Burnham Center for
 (BIMR, San Diego, CA) Network: N
 Number: 1 R03 MH083261-01A1 A
 wide now use the term "epidemic"
 estimated to occur in 30% of the
 and adolescents, which indicates

PubChem BioAssay
[PubMed](#) | [Entrez](#) | [Structure](#) | [PubChem](#) | [Help](#)

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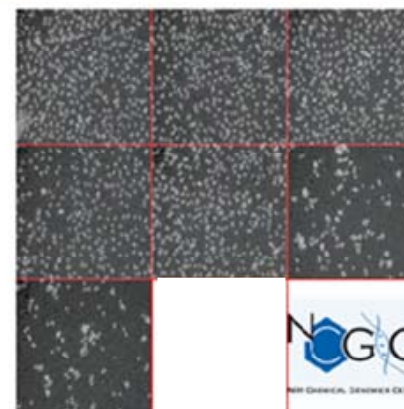
[Contact Us](#) | [Submit Assay](#) | [Sign up](#) | [Login](#)

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HTS Image View
 high content screen data

HCS Image Repository

NCGC | cellcycle_incell_041709 | PubChem



Panels starting at
 lowest concentration,
 moving left to right then
 top to bottom.

[Activity at 0.00245 uM](#)
[Activity at 0.012 uM](#)
[Activity at 0.061 uM](#)
[Activity at 0.307 uM](#)
[Activity at 1.530 uM](#)
[Activity at 7.660 uM](#)
[Activity at 38.30 uM](#)



☒ Burnham Institute for Medical Research
 ☒ San Diego Supercomputing Center

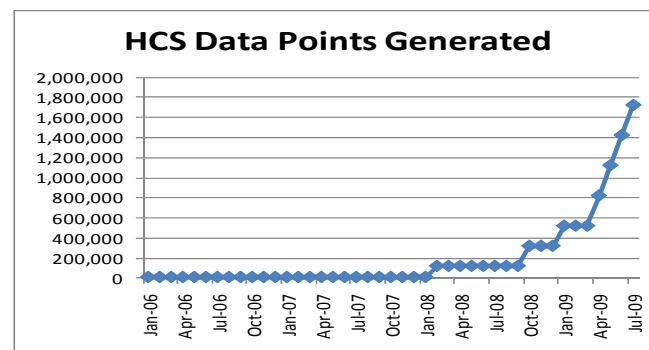
Price Lab & Bioinformatics Shared Resource
 © 2009 Kutbuddin Doctor, BIMR

Image-Based 1° MLPCN Screens @ CPCCG

Assay Name	# of Cmpds	PubChem AID(s)	Assay Type	Assay PI
VCAM1 Activation	~10k	457	Protein Expr.	T. Mayer / Univ. Columbia
VCAM1 Inhibition	~10k	456	Protein Expr.	T. Mayer / Univ. Columbia
Phagocytosis	~100k	1029,1618,1643	Phenotypic	F. Paumet / Univ. Columbia
Beta-Catenin	~200k	1665,1685	Protein Expr. / Transloc.	P. McDonough / Vala Sciences
MIN6 Up-Regul.	~200k	1625,1642,2124	Protein Expr.	M. Mercola / Burnham
MIN6 Down-Regul.	~200k	1628,1647,2122	Protein Expr.	M. Mercola / Burnham
Lipid Droplet Modul.	~240k	1656	Phenotypic	P. McDonough / Vala Sciences
GPR55 Agonist	~300k	1961,1965	GPCR	M. Abood / Temple Univ.
GPR55 Antagonist	~300k	2013,2026	GPCR	M. Abood / Temple Univ.
GPR35 Antagonist	~300k	2058,2079	GPCR	L. Barak / Duke Univ.

Increase in HCS project throughput due to:

- 1) Better assay concepts / HCS project quality
- 2) Larger # of FTEs & instrument resources for 1° screen
- 3) Faster imaging & online analysis
- 4) Use of HCS data management solution (still in implementation)



How to get your Assay into MLPCN?

1) R03 (PAR-09-129) mechanism: *For Assays which are screening ready*

“Solicitation of Assays for High Throughput Screening (HTS) in the Molecular Libraries Probe Production Centers Network (MLPCN) (R03)”

<http://grants.nih.gov/grants/guide/pa-files/PAR-09-129.html>

2) R21 (PAR-08-024) mechanism: *For Assay development (not screening ready)*

“Assay Development for High Throughput Molecular Screening (R21)”

<http://grants.nih.gov/grants/guide/pa-files/PAR-08-024.html>

Also browse the NOT-RM-09-008: Guidance on Submitting Applications to PAR-08-024:

<http://grants.nih.gov/grants/guide/notice-files/NOT-RM-09-008.html>

3) Fast Track Entry (NOT-RM-09-011) mechanism (extension): *Bootstrap an existing R21 that is ready for screening, or an R01 which has some type of screening context in the application*


“Notice of Opportunity for Fast Track Entry of Assay Projects for High Throughput Screening into the NIH Roadmap Molecular Libraries Probe Production Centers Network”

<http://grants.nih.gov/grants/guide/notice-files/NOT-RM-09-011.html>

MLPCN Advantages & Deadlines

- Assays accepted into MLPCN are screened against the MLSMR collection and identified hits are advanced to probes via chemistry efforts
- Deadlines;
 - R03 – 2010: Jan 4, May 4, Sep 3; 2011: Jan 4, May 4, Sep 2; 2012: Jan 4
 - R21 – 2010: Mar 20
 - Fast-Track from existing R01/R21 – Reviewed monthly

<http://cpccg.burnham.org>



The screenshot shows the website for the Conrad Prebys Center for Chemical Genomics (CPCCG). The header includes the CPCCG logo, the text "CONRAD PREBYS CENTER for CHEMICAL GENOMICS", and navigation links: "Contact Us | Submit Assay | Sign up | Login". Below the header is a navigation bar with tabs: "About CPCCG", "Assay Development", "HTS", "Chemistry Core", "Info/Cheminformatics", and "Outreach". The main content area features a large banner with the text "CPCCG & YOU" and a background image of a laboratory. Below the banner, there are three columns of text. The first column, "Core services (fee-for-service)", describes the center's offerings. The second column, "MLPCN (NIH roadmap)", is circled in green and describes the MLPCN program. The third column, "Apply Now", provides instructions on how to apply for a grant. The footer includes the Burnham Institute logo, copyright information, and links to "home | sitemap | search | assay | admin".

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- **HCS Group**

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- **HTS Group** (directed by S. Vasile)

- **ChemInformatics Group** (directed by Y. Su)

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