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

Conrad Prebys Center for Chemical Genomics
BURNHAM INSTITUTE for MEDICAL RESEARCH

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):

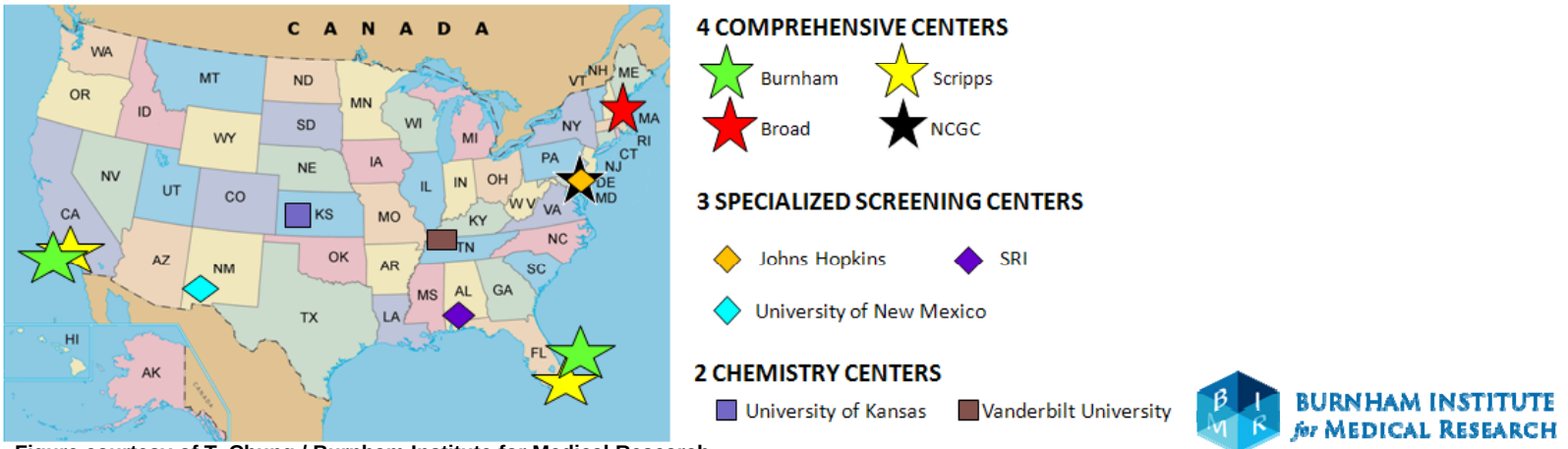


Figure courtesy of T. Chung / Burnham Institute for Medical Research

BURNHAM INSTITUTE for MEDICAL RESEARCH

Conrad Prebys Center for Chemical Genomics
BURNHAM INSTITUTE for MEDICAL RESEARCH

NIH MLSMR Library

- Information about the **Molecular Libraries Small Molecule Repository** can be found at :

  http://mlsmr.glpg.com/MLSMR_HomePage/

- MLSMR distributes the central compound collection to MLPCN for high-throughput screening of bioassays

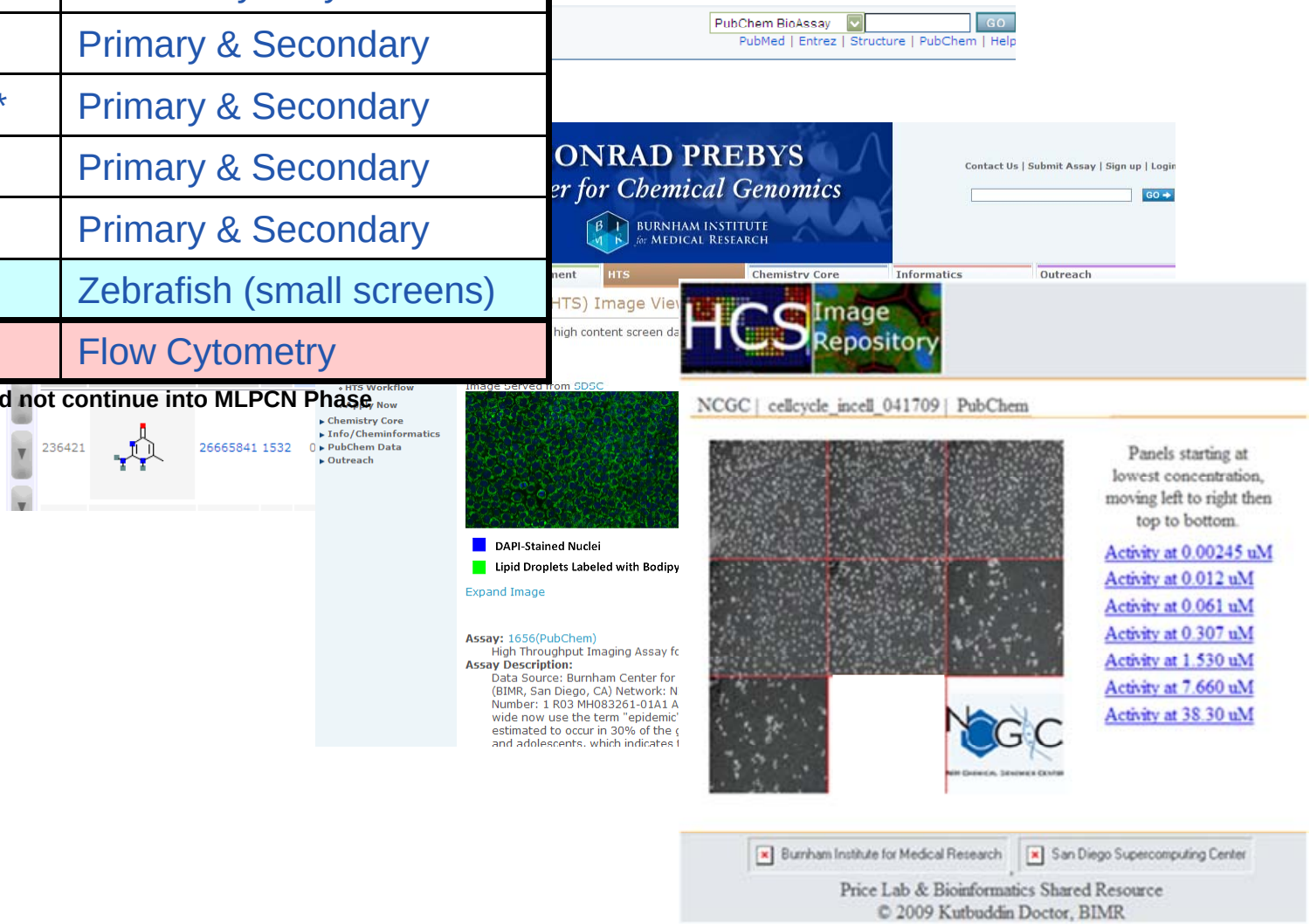
- MLSMR collection contains >300,000 chemically diverse small molecule compounds from 4 different compound classes:
  1. Diversity Compounds
  2. Natural Products (from known and documented natural sources)
  3. Targeted Libraries (i.e. protease, kinase, GPCR, ion channel, and nuclear receptors)
  4. Specialty Sets (known bioactives like drugs, toxins etc.)

BURNHAM INSTITUTE for MEDICAL RESEARCH

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**



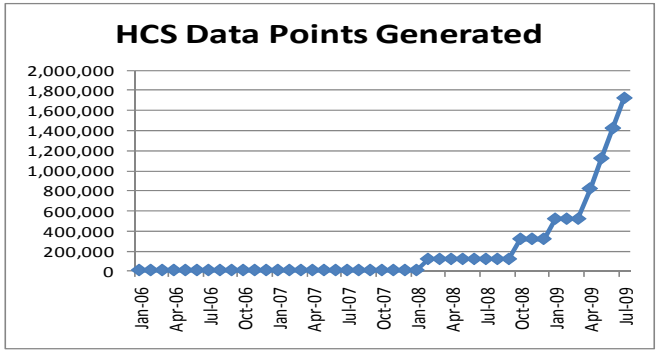
Conrad Prebys Center for Chemical Genomics
BURNHAM INSTITUTE for MEDICAL RESEARCH

Image-Based 1° MLPCN Screens @ CPCCG

Assay Name	# of Cmpds	PubChem AID(s)	Assay Type	Assay PI
VCAM1 Activiation	~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^{o} screen
3) Faster imaging & online analysis
4) Use of HCS data management solution (still in implementation)



Conrad Prebys Center for Chemical Genomics
BURNHAM INSTITUTE for MEDICAL RESEARCH

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

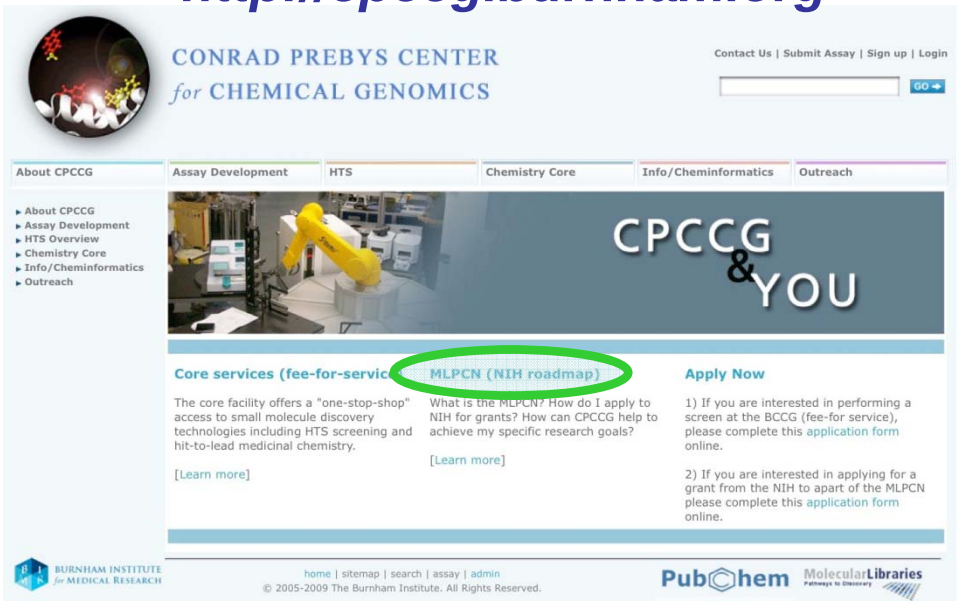
BURNHAM INSTITUTE for MEDICAL RESEARCH

Conrad Prebys Center for Chemical Genomics
BURNHAM INSTITUTE for MEDICAL RESEARCH

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



BURNHAM INSTITUTE for MEDICAL RESEARCH

Acknowledgements

- **Burnham Institute for Medical Research / CPCCG**
  - **HCS Group**
    S. Hariharan, W. Gray, L. Milan, M. Sauer, B. Azimi, I. Kalcheva
  - **Assay Dev Group** (directed by E. Sergienko)
  - **HTS Group** (directed by S. Vasile)
  - **ChemInformatics Group** (directed by Y. Su)
- **HCS Database Efforts**
  J. Price, K. Doctor, A. Kellner, E. Hunter, B. Azimi, D. Stonich (all BIMR), A. Gupta (SDSC)
- **Collaborating PIs:**
  M. Abood (Temple Univ.)
  L. Barak (Duke Univ.)
  F. Levine (Burnham Institute)
  T. Mayer (formerly Columbia Univ.)
  P. McDonough (Vala Sciences)
  M. Mercola (Burnham Institute)
  F. Paumet (formerly Columbia Univ.)

Supported by NIH MLPCN Grant# 1 U54 HG005033-02

BURNHAM INSTITUTE
for MEDICAL RESEARCH