Bringing a Compound Collection into the 21st Century: *The Introduction of Automation and QC*

Myra O'Leary
Chemical Biology Platform
The Broad Institute of MIT and Harvard

June 10, 2009

BROAD INSTITUTE

Compound Management - Past

- 90K compound collection in low volume, stored in 384 and 96 well plates and vials with no routine QC.
- Manual Inventory Retrieval
- Exclusively walk up

Collaboration with HighRes BioSolutions

Compound Storage, Replication, and Reformatting

- Long-term Compound Storage System(LTS)
- Compound Management System (CM)

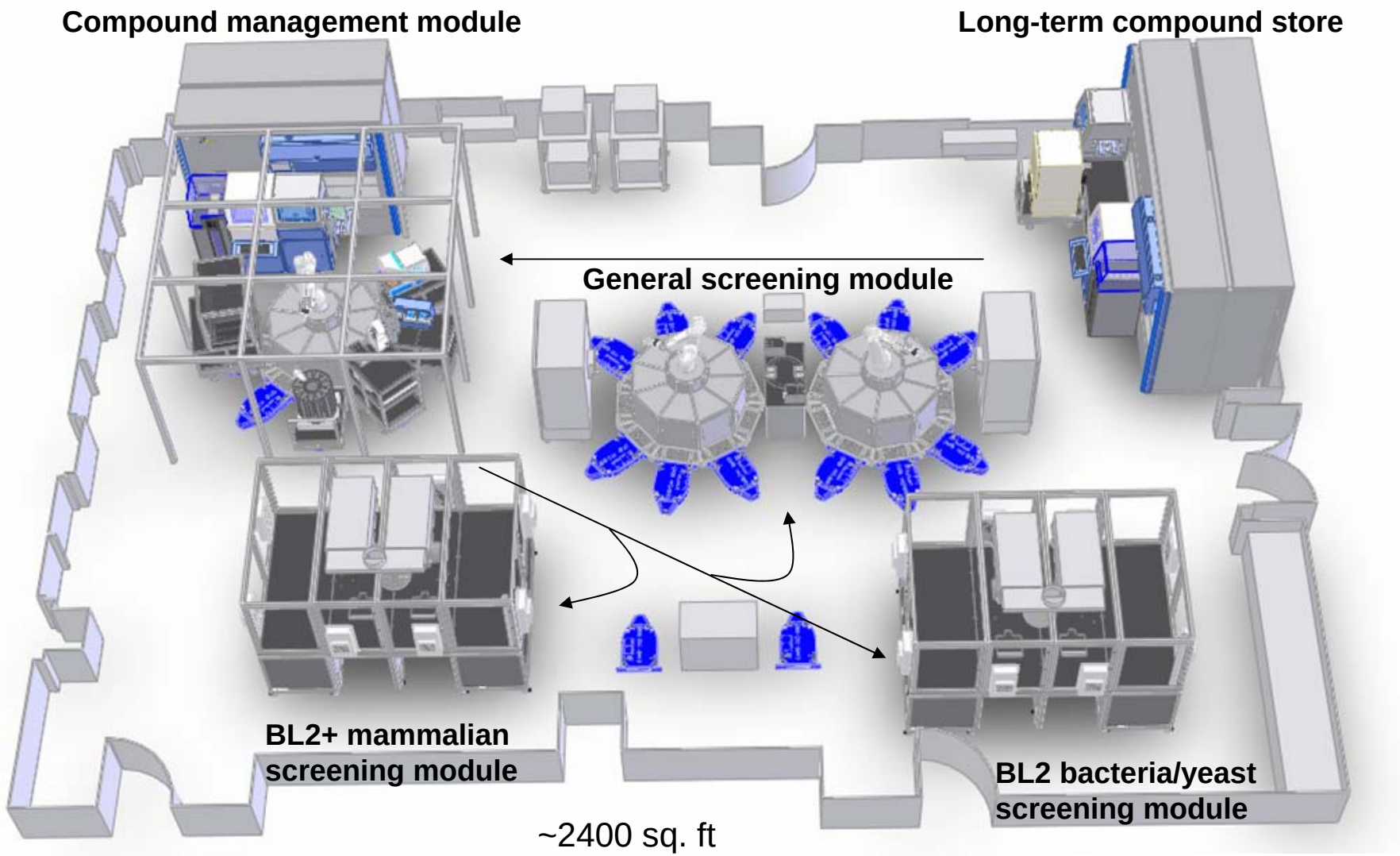
High-Throughput Screening

- BL2 Screening System
- BL2+ Screening System
- General Screening System (GS)

HighRes biosolutions

BROAD INSTITUTE

Automation Integration

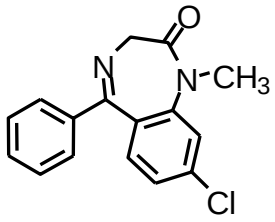


In collaboration with HighRes BioSolutions

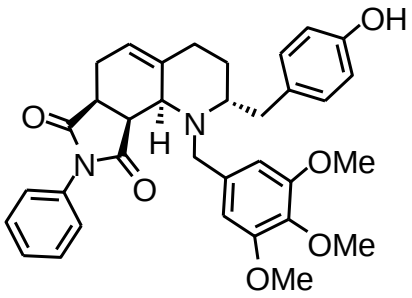
BROAD INSTITUTE

Broad Chemical Biology: DOS

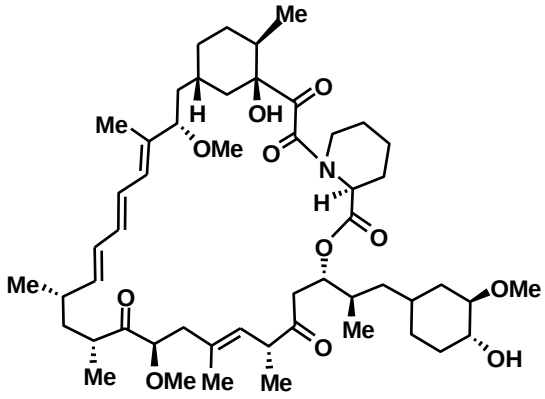
Complexity



Drug compound (Valium)
Minimal complexity
1 Chemical step

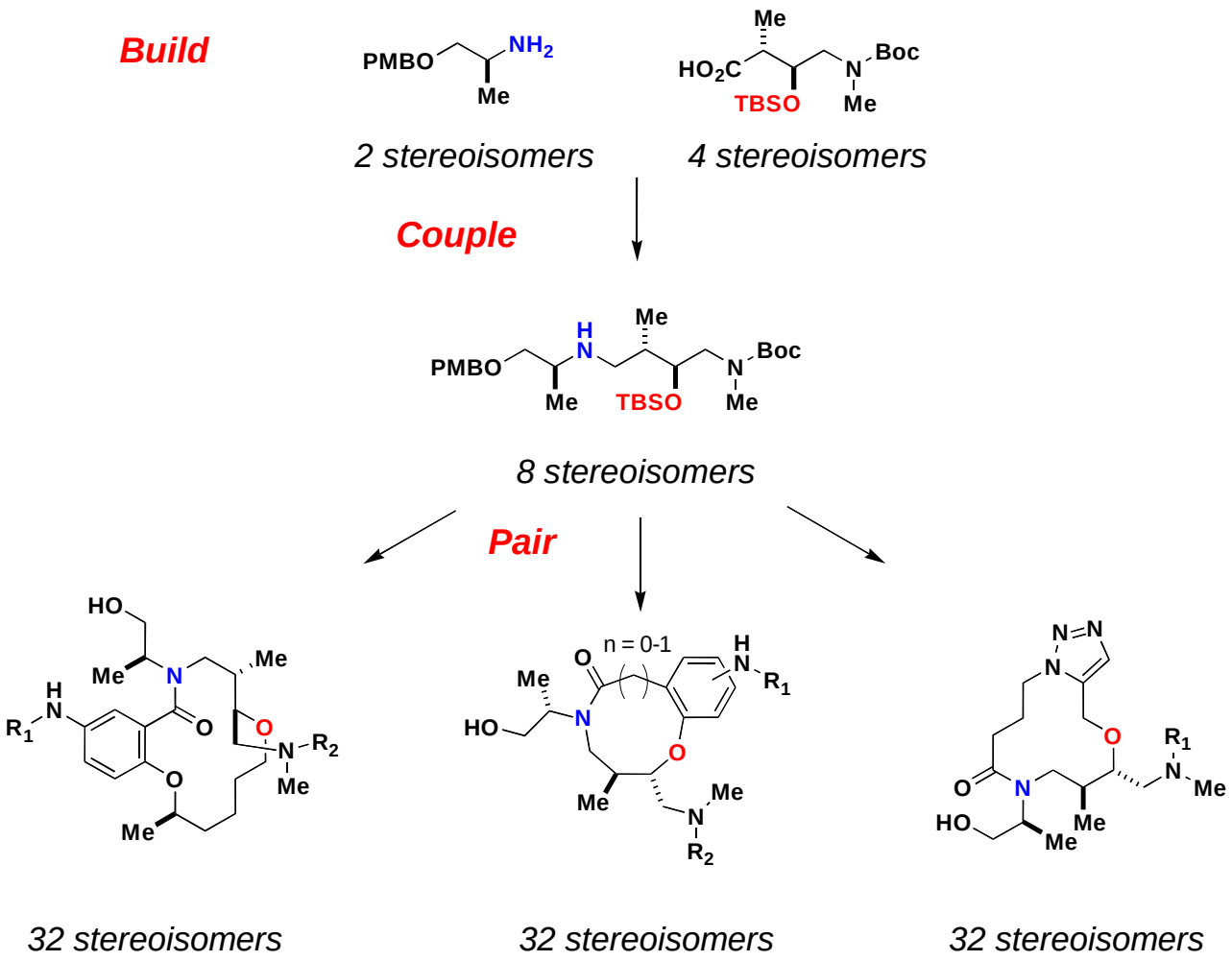


DOS compound
Moderate complexity
3 Chemical steps!

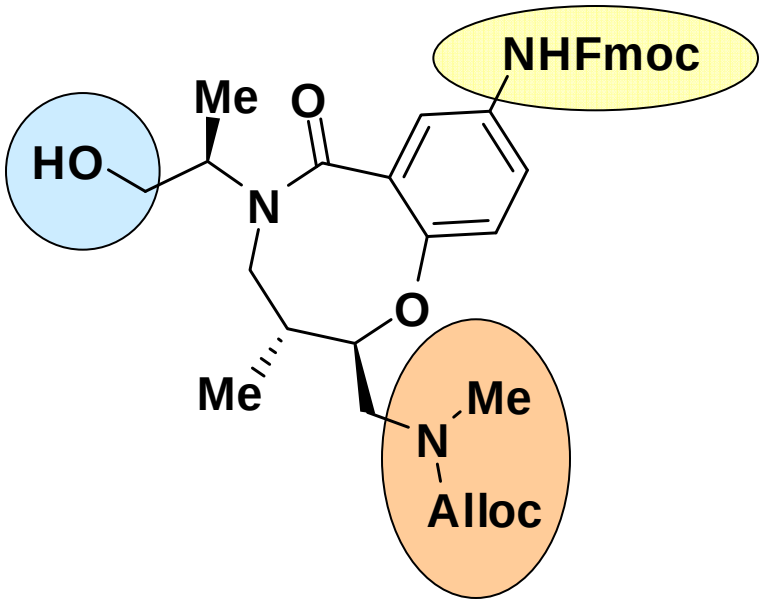


Natural Product (Rapamycin)
Great complexity
78 Chemical steps

Build – Couple - Pair



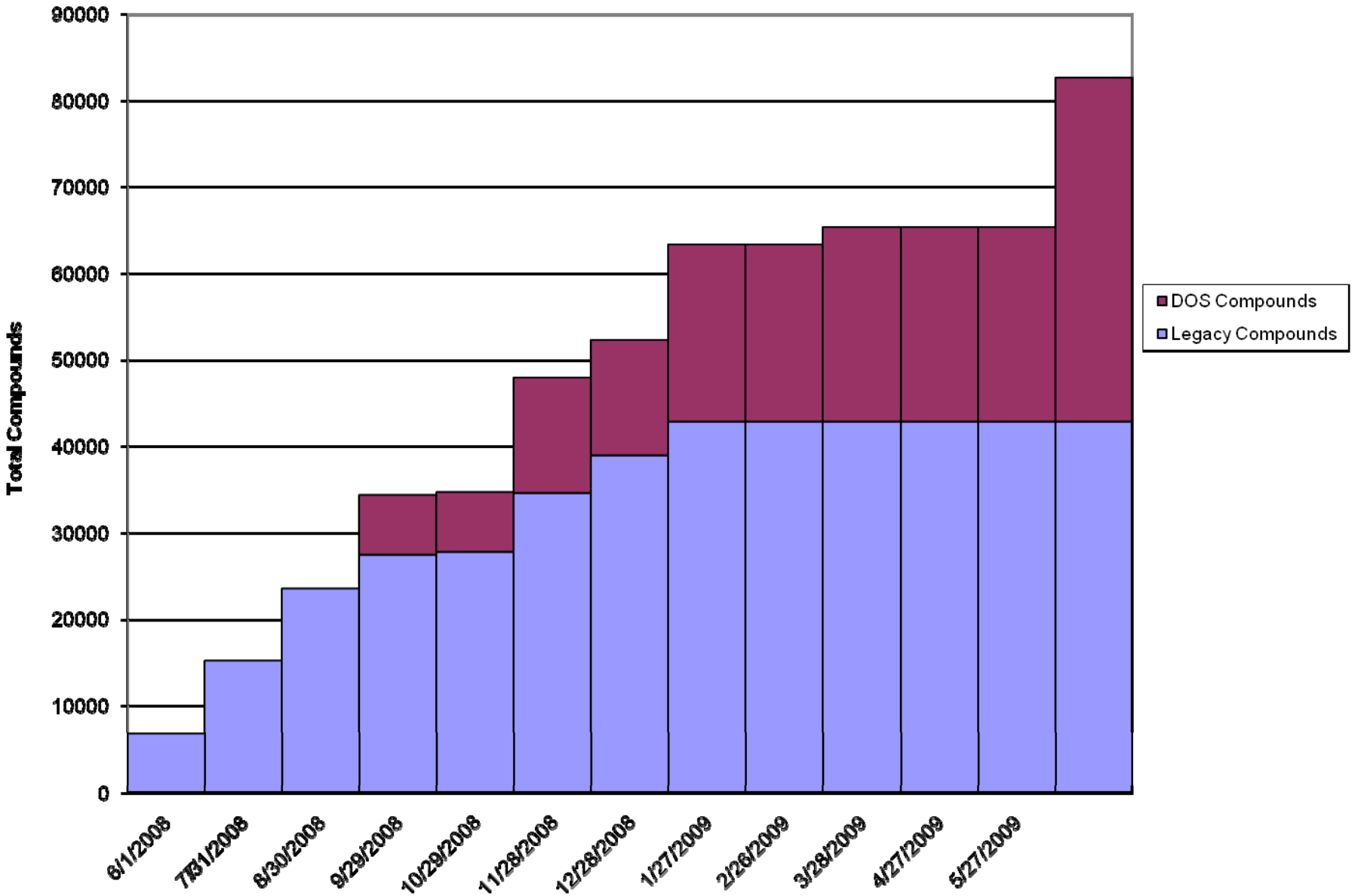
Broad Chemical Biology: DOS



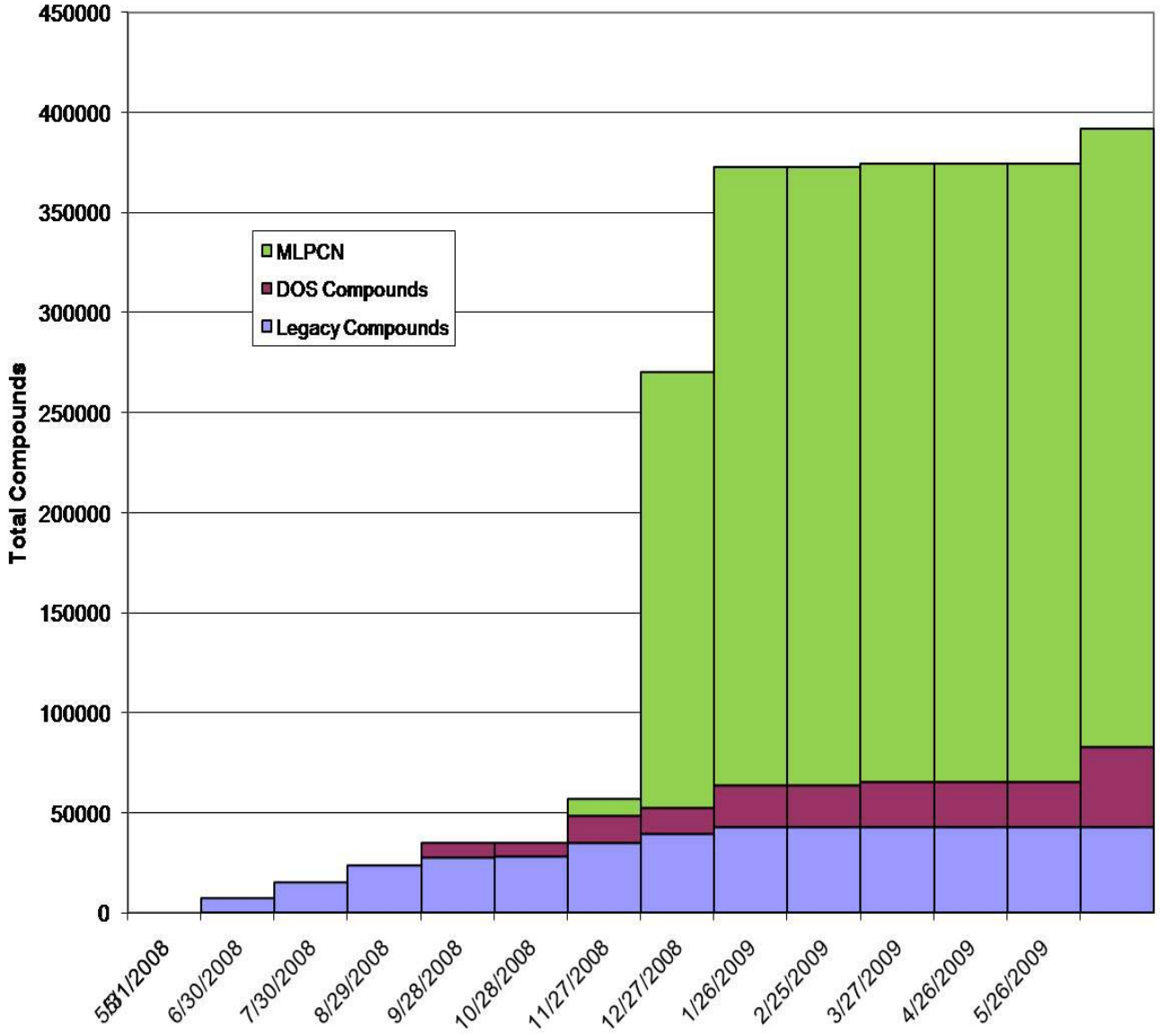
- structural complexity
- efficient synthesis
- stereochemical diversity
- skeletal diversity
- chemical handles

Synthesize diverse small molecules having structural complexity rivaling naturally occurring small molecules, and having chemical handles that enable systematic optimization or modification (e.g., for making target I.D. reagents, or for adding biasing elements).

Broad Compound Collection



2008: New Compound Collection



Summary of Compound QC (DOS + Legacy)

Collection	Total number of compounds	Total number of compounds passing QC (>75% purity by UV_{210})
Legacy	56,162	42,794 (76.2%)
DOS	24,491	22,445 (91.6%)
Total	80,653	65,239 (80.9%)

Current LC/MS method is general in nature,

- C18 column, detecting with UV_{210} and ESI +/- mass spec
- Unable to properly detect 5,306 legacy compounds (9.5%)

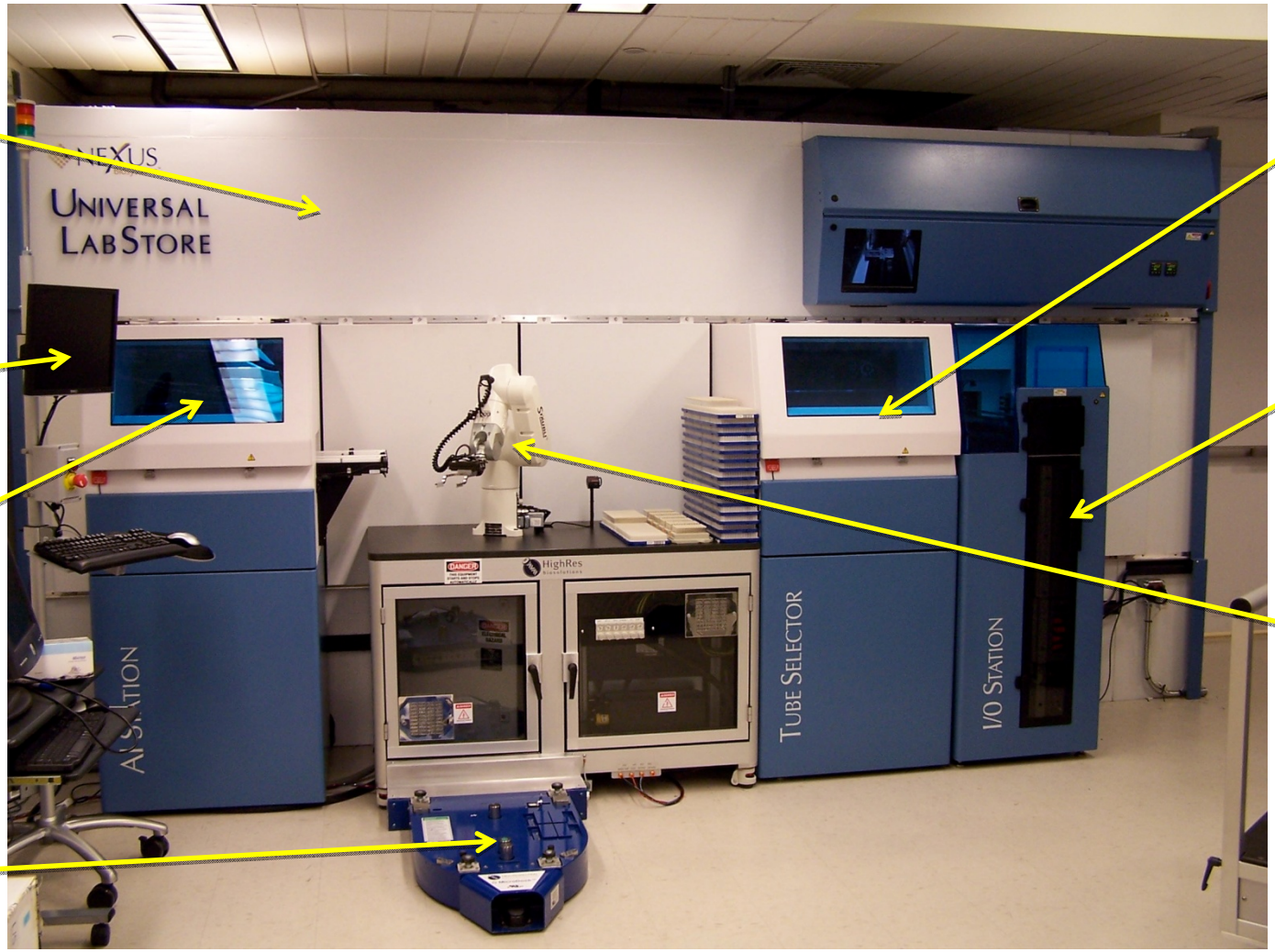
Does not adequately cover:

- Very hydrophilic or hydrophobic compounds
- Compounds lacking a UV chromophore
- Compounds that don't ionize in ESI

How do we manage all these compounds
and what do we do with them?

BROAD INSTITUTE

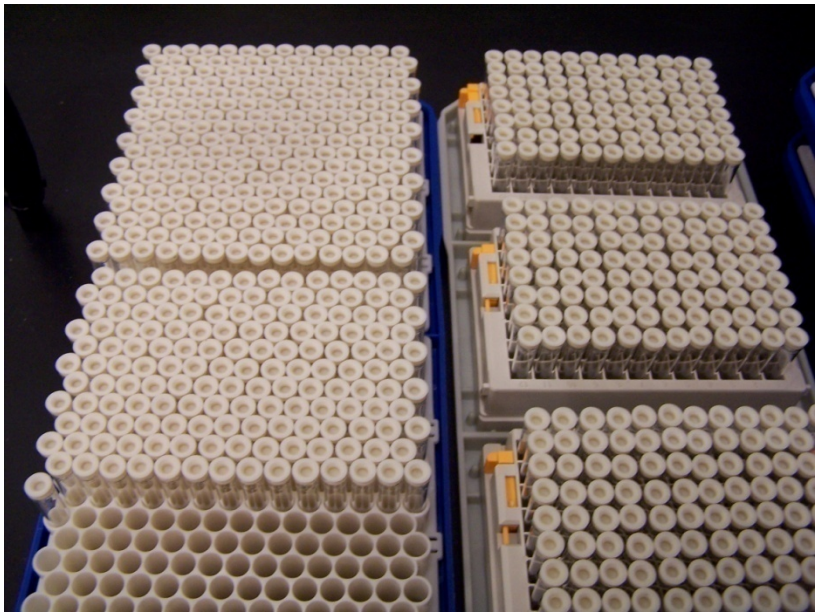
Long-term Compound Storage System



Long-term Compound Storage System

- HighRes integration of Nexus BioSystems Universal Labstore (automated freezer) with a Staubli robotic arm and a HighRes MicroDock™.
- Capacity for a fully QC'd Broad DOS compound library stored as powders in 1.4mL glass tubes at -20 degrees C.

  - Nexus Tube Selector reformats tubes into high-density tube racks (952 tubes/ rack)
  - 2D barcode scanner (on Nexus) and 1D barcode scanner (on HighRes) for sample tracking.
  - Freezer capacity ~ 300K glass tubes
  - Currently holds 65K DOS compounds and 1000 MLPCN compound plates



Compound Management System

Photo credit: HighRes BioSolutions

Compound Management System

- HighRes BioSolutions 9-sided MicroStar™ integration with a Nexus Universal Labstore, Staubli robotic arm, Hamilton Starlets, and other devices.

- Designed for:
  - Creation and -20C storage of Mother compounds in plastic Matrix tubes.
  - Random access to all wet compound stores
  - Creation of Daughter Plates, Retest plates, and Assay Ready plates
  - Fully integrated database

Photo credit: HighRes BioSolutions

BROAD INSTITUTE

Compound Management - Present

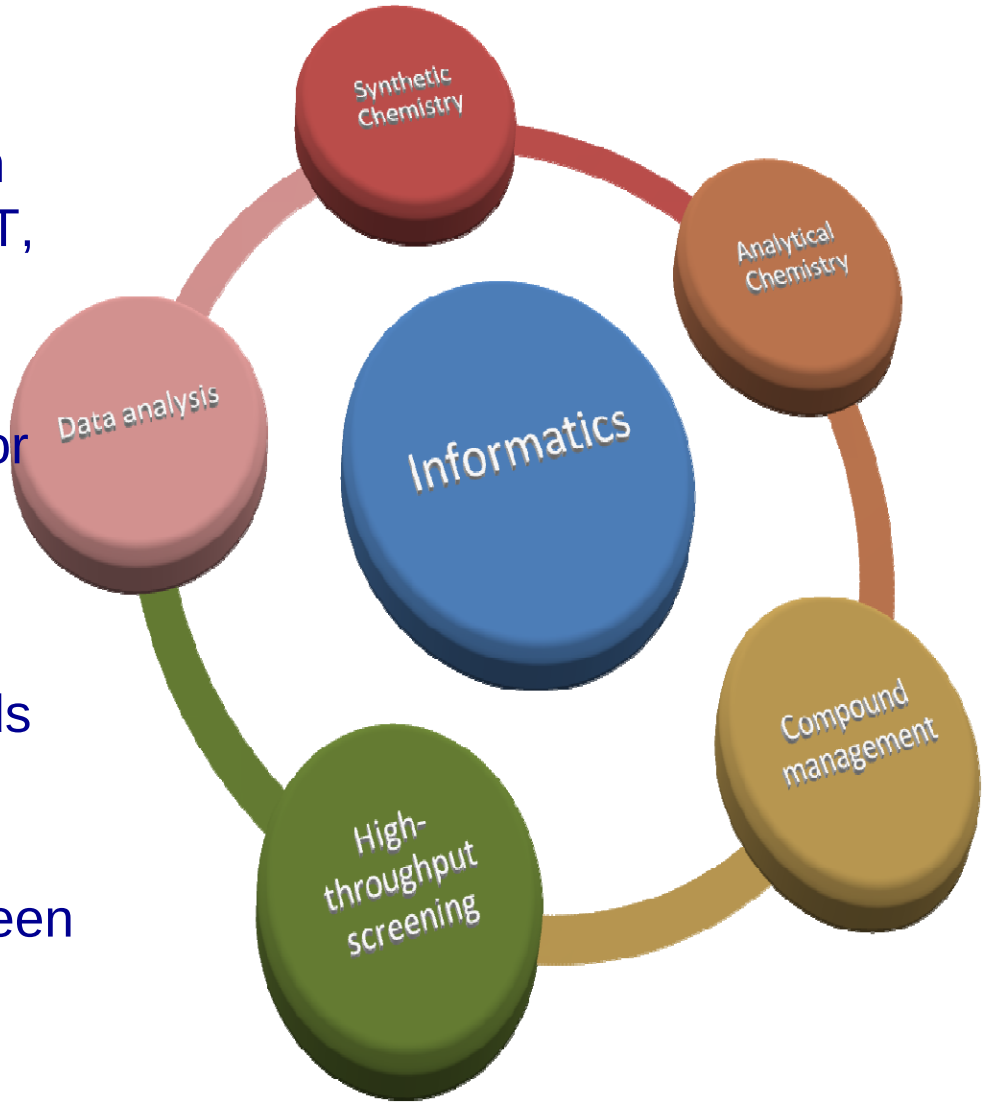
- CM System can store up to 300k Mother tubes
  - Currently holds 94k and counting
  - Also houses 300k MLPCN compounds in plates
- Can Cherry Pick any combination of compounds into plates on demand
  - Standard formats reduces turn-around time for assays and retest
- Managing 300 MLPCN compounds
- Managing growing Broad compound collection (65,000 current, 50,000 additional expected in next year)

Compound Management - Present

- MLPCN support
  - Provide logistical compound plate support for assays and retest
- Broad Screening Support
  - All screens see entire screening library in biologically useful format including 1536 assay ready plates
- Created Informatics tools to support CM
  - Support operation of the automation
  - Enable tracking of transactions and contents of the collection
  - Fully integrated database with web interface to capture and process data in real time.

Informatics Integration : Keys to Success

- Just-in-time development
  - Constantly evolving to meet current needs
  - Aligned Informatics goals with Acceptance Testing (FAT, SAT, BAT) timeline.
- Integration of all components
  - Built internal CBIP database for data processing and sample tracking
  - Acquired necessary 3rd party components for scientific needs (ELN, Cellario, Data Analysis Tools)
  - Bi-directional integration between CBIP and Cellario



Master Tubes to Mother Tubes

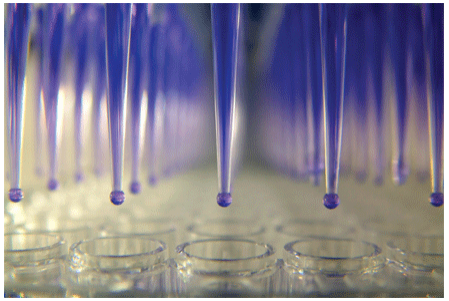
Compounds Received

NEXUS Biosystems

Sorted by Moles

Volatile Solvent Transfer

Compounds Dried



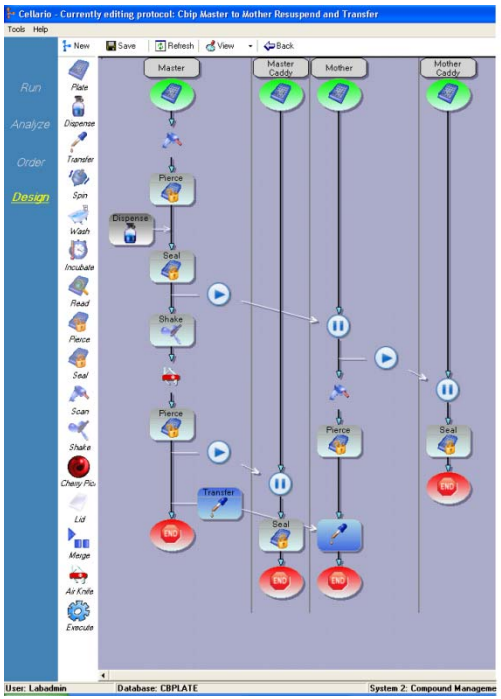
DMSO Dissolution

Daughter Plates Processing

Photo credit: HighRes BioSolutions

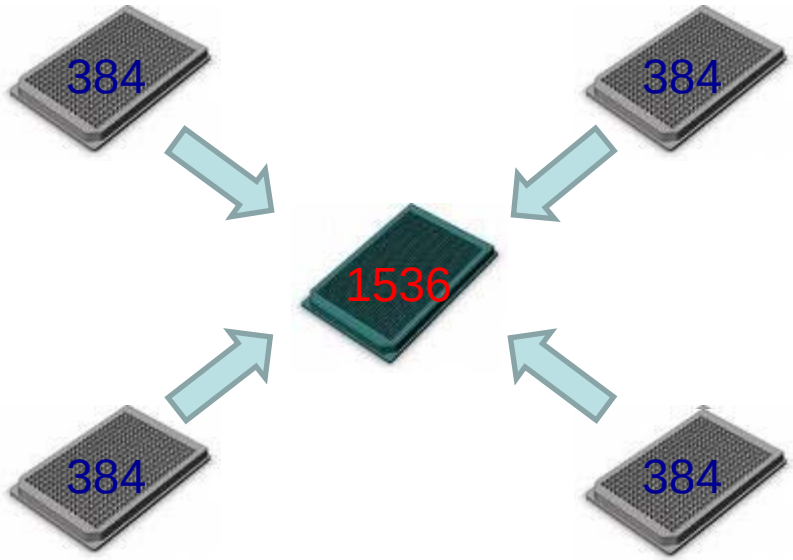
Retest Cherry picks

- Very manual process
- 1 – 2 week processing time requirement



- Random Access
- Standardization
- 48 hour processing with increased throughput!

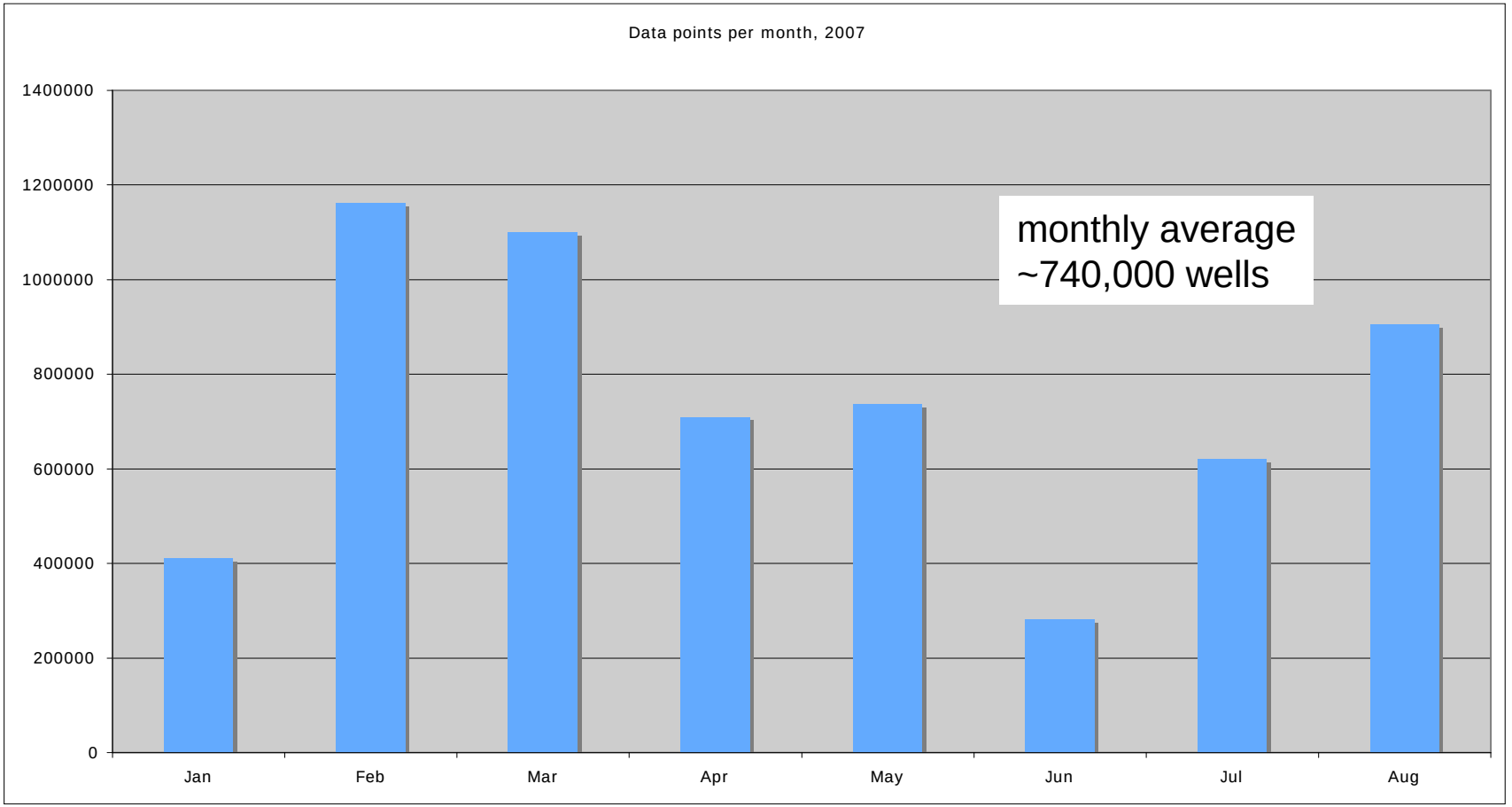
Assay Ready Plates



- 40 % all screening in 1536
- 300,000 compounds in 200 robot hours

- No risk of carry over contamination
- Lower dead volume

HTS Statistics



- ~ 5,300,000 total wells pinned in 2006
- ~ 6,000,000 wells pinned Jan-Aug 2007

Screening Commitments

- 30 Broad screens/year
  - Screen 25k compounds & retest
- 25 MLPCN screens/year
  - Screen 300k (supplied by NIH), retest, secondary assays, follow-up chemistry = “Probe development”
- Total wells/year = 15M to 20M (compounds in duplicate plus controls and retests)

BROAD INSTITUTE

Compound Management – Future

- Support of Follow-Up Chemistry efforts
  - Ability to “Sequester” compounds as private to specific group
  - Dispensing small numbers of compounds on-demand to variety of groups
  - Handling of dry powers
- Compound support to programs in Cancer, Infectious Disease, Psychiatric and Metabolic Disease areas

Chemical Biology staff: an emphasis on experience

DOS Chemistry
Lisa Marcaurelle Ph.D.
Eamon Comer Ph.D.
Siva Dandapani Ph.D.
Jeremy Duvall Ph.D.
Mark Fitzgerald Ph.D.
Baudouin Gerard Ph.D.
Ann Kelly Ph.D.
Sarathy Kesevan Ph.D.
Haibo Liu Ph.D.
Maurice Lee Ph.D.
Jason Lowe Ph.D.
Jean-Charles Marie Ph.D.
Carol Mulrooney Ph.D.
Tiffanie Murillo
Bhau Pandya Ph.D.
Troy Ryba Ph.D.
Byung-Chul Suh Ph.D.
Jingqiang Wei Ph.D.

Analytical Chemistry
Stephen Johnston Ph.D.
Galina Beletsky
Chris Johnson
Michael Lewandowski
Emeline Tissot
Anita Vrcic

Screening
Michelle Palmer Ph.D.
Nicky Tolliday Ph.D.
PJ Aspesi
Jason Burbank
Frank An Ph.D.
Josh Bittker, Ph.D.
Nathan Ross Ph.D.
Kate Hartland
Andy Stern Ph.D.
Lynn VerPlank Ph.D.
Leigh Carmody Ph.D.
Joe Negri
Jim Spoonamore Ph.D.
Ken To
Tom Hasaka
Shailesh Metkar
Hanh Le

Medicinal Chemistry
Mikel Moyer Ph.D.
Ed Holson Ph.D.
Lawrence MacPherson Ph.D.
David Pearlman Ph.D.
Florence Wagner Ph.D.

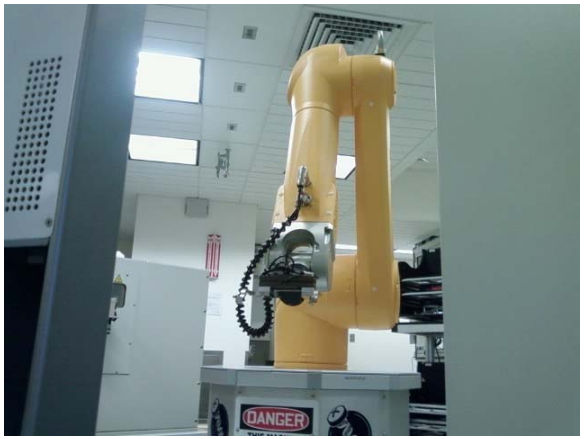
Informatics & compound management
Dave DeCaprio
Greg Wendel Ph.D.
Lakshmi Akella Ph.D.
Jacob Asiedu
Nurgees Banu Sulthan
Santhosh Kumaraswamy
Bob Brady Ph.D.
Steve Brudz
Dan Durkin
Mary Pat Happ Ph.D.
David Howe Ph.D.
Corrie Lade
John McGrath
Dennis Moccia
Phil Montgomery
Christopher Moore
Joshua Nichols
Alex Orlovsky
Myra O'Leary
Karen Rose
Raza Shaikh
Gil Walzer
Patti Aha

HighRes BioSolutions
Lou Guarracina
Michael Nichols
Vlad Zhirnov
John Smyka
Art Ming
Christian Soule
Scott Rehlander
Matt Woodward
Chris Pappas
Ira Hoffman

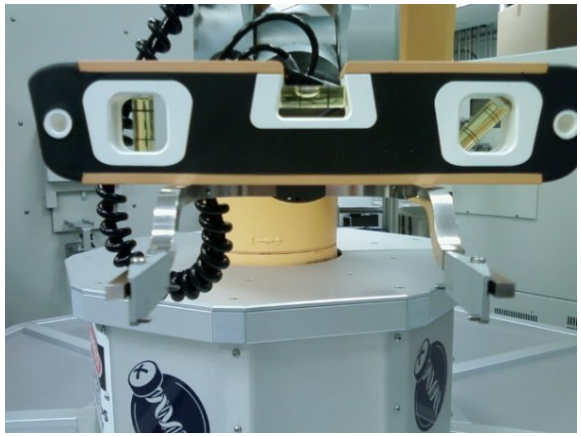
Chemical Biology Platform:
http://www.broad.mit.edu/node/139

Director, Chemical Biology Platform **Michael A. Foley Ph.D.**
Director, Novel Therapeutics **Robert Gould Ph.D.**

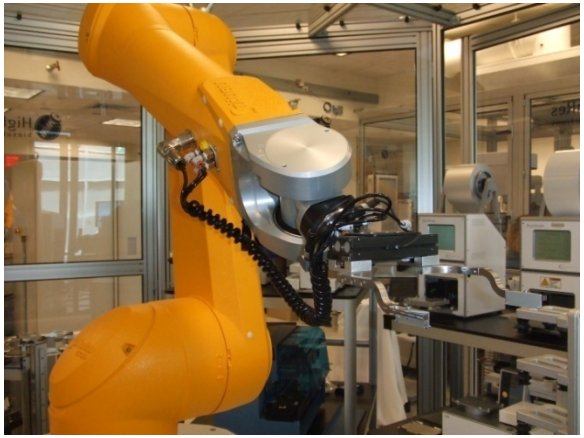
Special Thanks



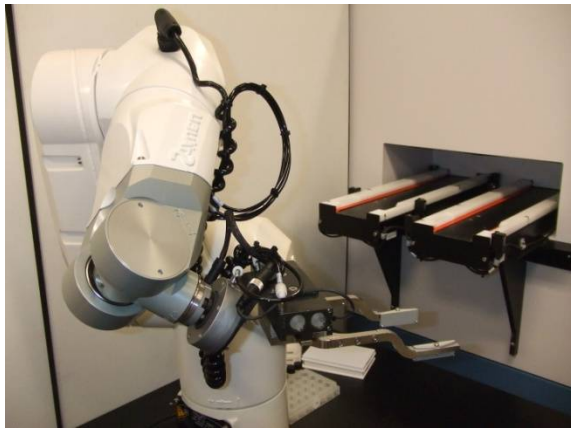
Stäubli Yo



Stäubli No



Stäubli Go



Le Petit Stäubli