

ICCB-Longwood: High Throughput Screening

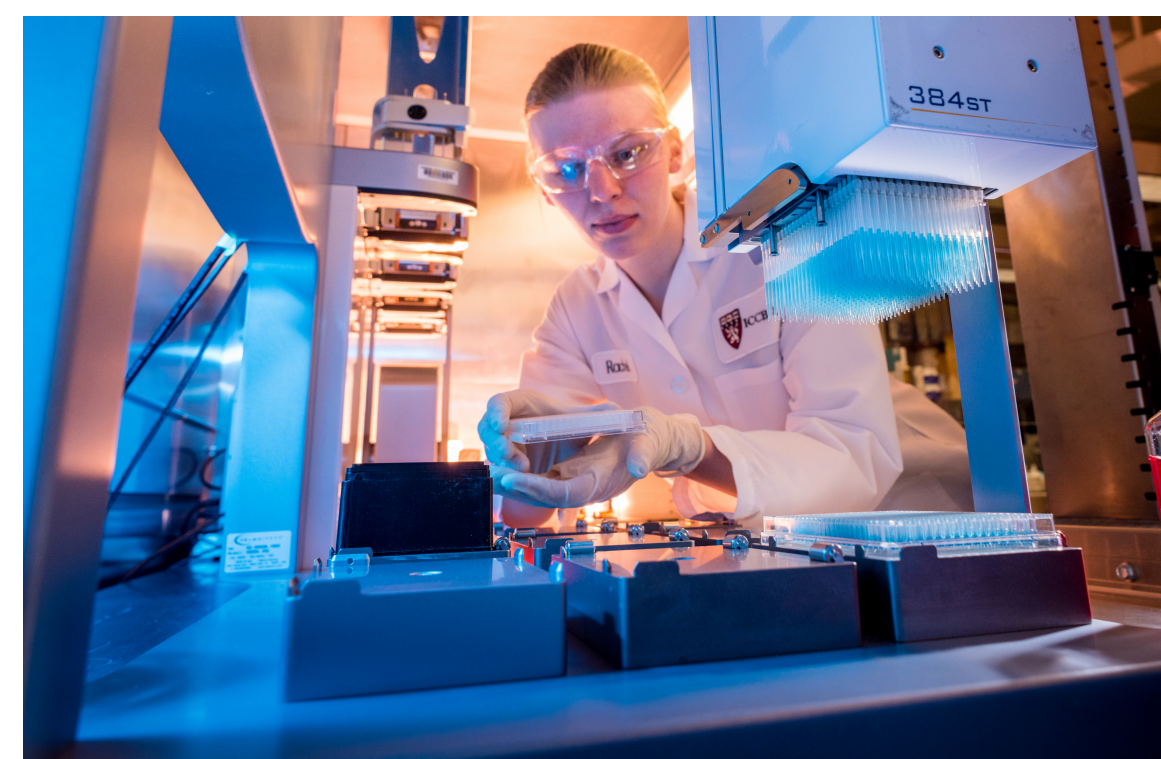
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Introduction

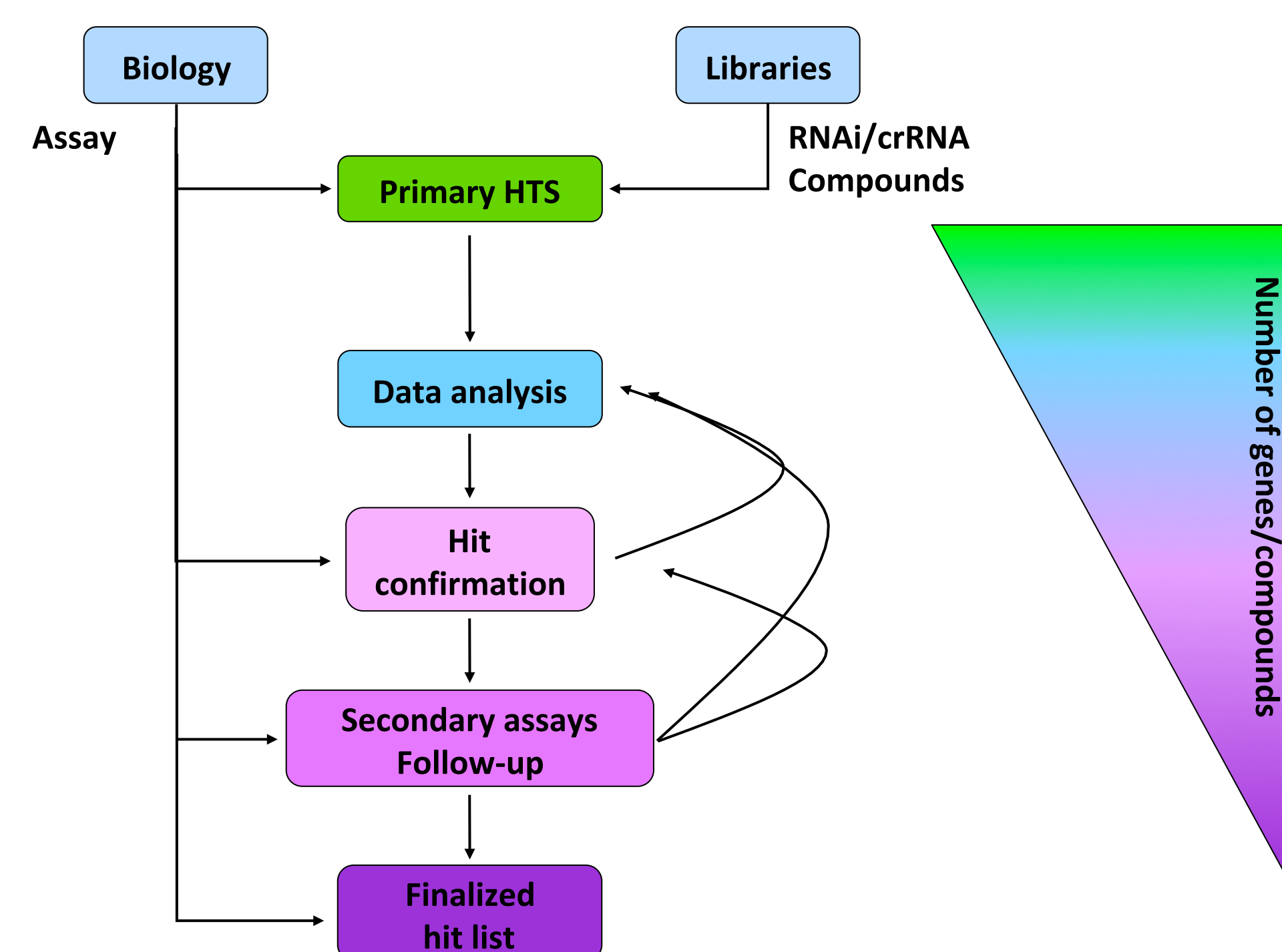
- High throughput small molecule and functional genomics screening core
- Biosafety level 2 facility on the 6th floor of the Seeley Mudd Building at Harvard Medical School
- Organized around modular workstations with online scheduling software
- Variety of assays supported by having a lab of different instruments that cover a range of technologies

Investigator-initiated, staff-assisted screening model.

- Investigator is responsible for his or her own screen, retains complete ownership of the project and provides the personnel to conduct the screen
- ICCB-L team provides advice and guidance on assay development and optimization, laboratory automation, high-throughput screening, data analysis, and follow up approaches
- ICCB-L provides training in the use of equipment, assists in developing and optimizing the HTS assay, and performs complex automation tasks
- ICCB-L maintains all equipment and libraries that are available for screening



High Throughput Screening Workflow



Access and Fees

- Fees are charged for screening and use of equipment at ICCB-L to help cover a portion of the facility operating costs.
- Each screener must cover the cost of consumables and assay reagents used in the screening project.
- Screens can typically be initiated within a couple weeks of contacting ICCB-L.

Fee summary: <https://iccb.med.harvard.edu/fees>

Small Molecule Screening

Collections	Description	# Compounds
Known Bioactives	Documented activity in cells, animals or humans <i>FDA-approved + other characterized compounds</i> Well-documented kinase inhibitors ~20 different libraries, some at multiple [] ICCB-L Mechanism of Action Library	> 13,000
Academic	Discretions from individual chemists <i>Includes:</i> LINC, BU-CMD, LDDN, Gray Kinase Inhibitors, Discrete natural product extract libraries from Clardy Lab (HMS)	~4,500
Commercial	Variety of libraries from commercial vendors <i>Most libraries diversity oriented</i> No proprietary compounds included	> 275,000
Fragments	ChemBridge library of low molecular weight, low affinity 'fragment' compounds <i>Binding requires sensitive detection methods</i>	3,000
MLP	Assembled by the NIH Molecular Libraries Initiative <i>Known bioactive, natural product and commercial compounds</i>	> 300,000



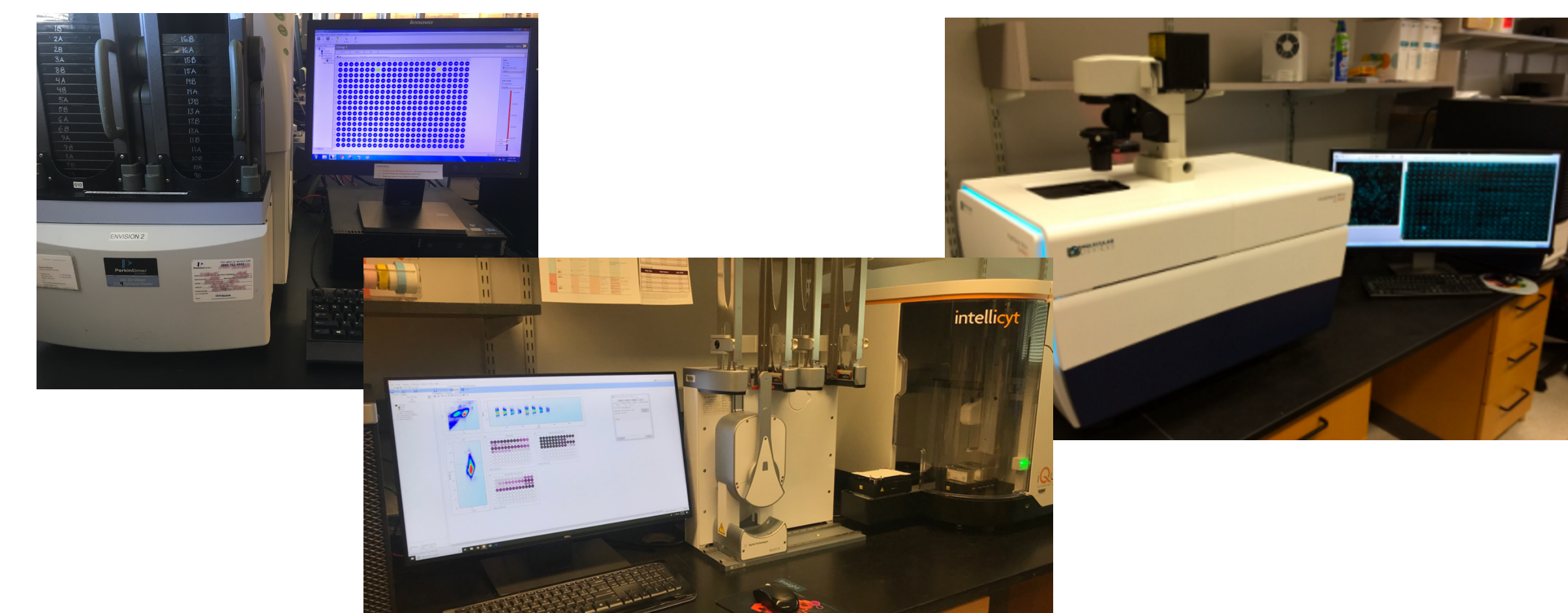
Screens Supported

Small molecule screening

- > 600 primary screens completed
- Range from small and focused to > 600,000 compounds
Average ~55,000 compounds/screen
- 67% cell-based, 27% biochemical, 6% organismal

Functional genomics screening

- 114 primary screens completed
- Initial screen is 1 gene/well
- Deconvolution, secondary screens 1 duplex/well
- 65% high content microscopy and 35% plate reader-based assays



Data Analysis Resources

Screensaver, Laboratory Information Management System

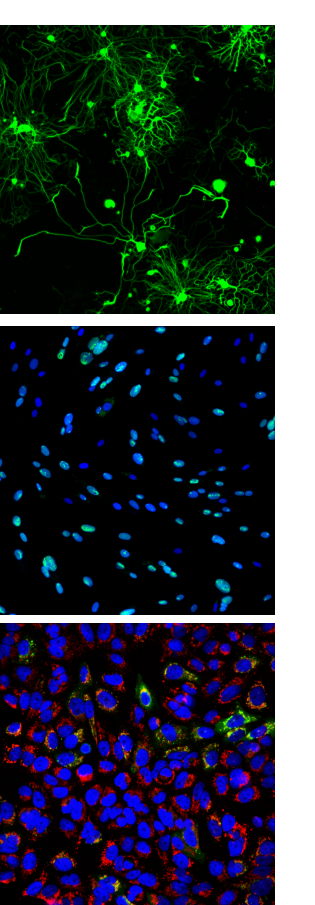
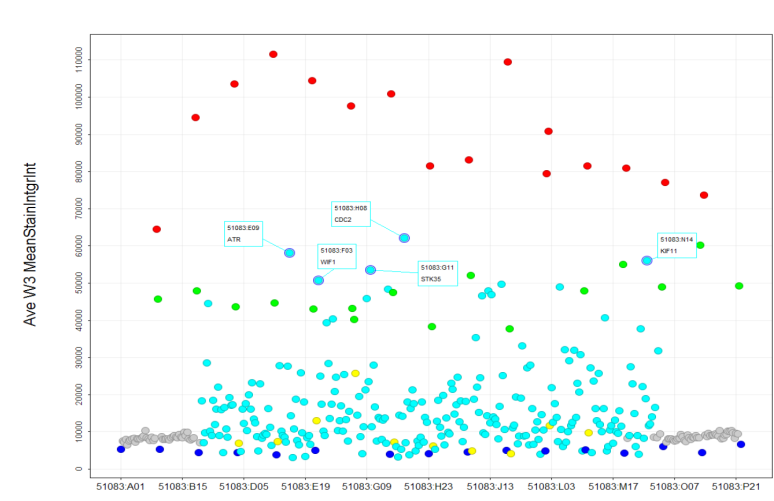
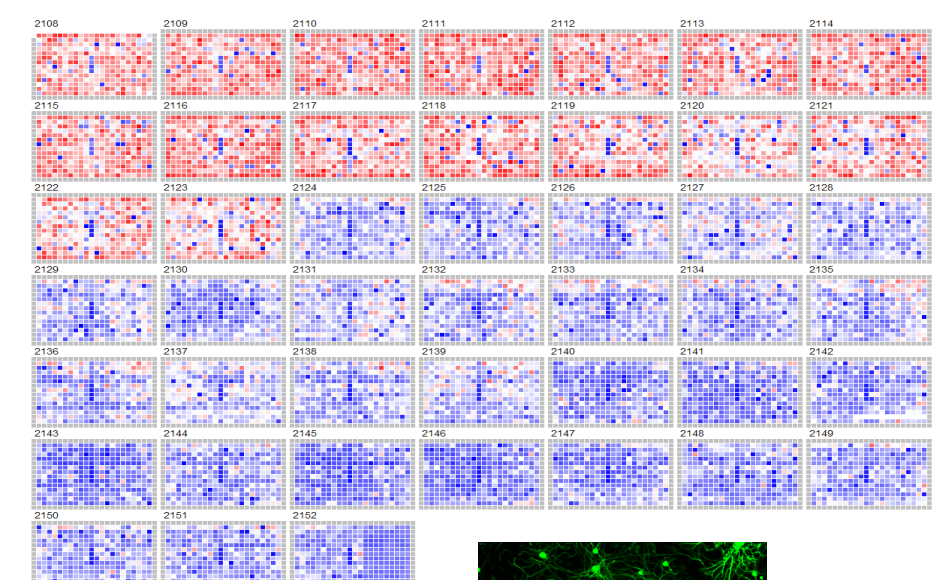
A. Tolopko et al., 2010, "Screensaver: an open source lab information management system (LIMS) for high throughput screening facilities," *BMC Bioinformatics*, 11:260 doi:10.1186/1471-2105-11-260. PMID: PMC3001403

Data analysis and visualization software

Dotmatics Vortex
Pipeline Pilot
KNIME
Online GESS
Haystack
CARD

Image analysis software

MetaXpress
Cellista
CellProfiler
ForeCyte



Functional Genomics Screening

siRNA Reagent Libraries:

Vendor	Library Name	# Genes Targeted
Dharmacon	Updated Human siGENOME	18,152
Dharmacon	G-protein Coupled Receptors	390
Dharmacon	Human Kinases	720
Dharmacon	Human Ion Channels	349
Dharmacon	Human Proteases	480
Dharmacon	Human Phosphatases	256
Dharmacon	Human Ubiquitin Conjugating Enzymes #1	89
Dharmacon	Human Ubiquitin Conjugating Enzymes #2	115
Dharmacon	Human Ubiquitin Conjugating Enzymes #3	390
Dharmacon	Human Lincod NR IncRNA siGENOME	2,231
Dharmacon	<i>Mouse siGENOME</i>	20,552
Ambion	Silencer Select Human Library	21,584

Custom siRNA libraries available

miRNA Reagent Libraries:

Vendor	Library Name	# miRNAs Targeted
Ambion	Human 1: Mimics	851
Qiagen	Human 1: Mimics	875
Exiqon	Human 1: Inhibitors	918

Synthetic arrayed CRISPR library, druggable genome

Funding Opportunities

- Letters of support can be written for investigators preparing grant applications
Email Jennifer Smith, jennifer_smith@hms.harvard.edu
- Relevant funding opportunities posted on ICCB-L website as they are received

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