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Genomics: when the chemistry is good

Nathan Blow

Could the latest high-throughput technologies propel chemical genomics screens forward in academic settings? After 18 months of careful design and planning, scientists at the Broad Institute's chemical biology platform are about to flip the switches and find out.

Three newly installed high-throughput robotic screening systems occupy a large air-conditioned room on the third floor of the Broad Institute building in Cambridge, Massachusetts, USA. The largest, in the center of the room, is nearly twenty feet long and is operated by two multi-jointed Stäubli robotic arms installed on honeycomb-shaped platforms and surrounded by an army of carts and trolleys carrying assorted pieces of instrumentation—microplate readers, incubators and imaging systems. Two 'smaller' robotic systems, each the size of a compact car, stand along a wall encased in protective coverings and vented to allow researchers to perform screens under biosafety level 2 conditions. Two more systems will be installed in the coming months to store chemical libraries and manage compounds.

The new robotic capabilities, along with other infrastructure changes, will increase the number and diversity of the chemical genomic screens performed at the Broad. "We are anticipating as many as 60 high-throughput screening campaigns this year," says Michael Foley, director of the chemical biology platform. Although commonplace in pharmaceutical companies, robotic systems with this capacity have only been seen from afar by most academic scientists. But as Foley sees it, the screening capacity at the Broad will now be on par with any major pharmaceutical company.

"There is a desire to build on our tradition of chemical genomics, to push toward not just discovering reagents but also probes for disease biology," says Robert Gould, director of novel therapeutics who came to the Broad Institute two years ago



Chemists in the Broad Institute's chemical biology platform make use of electronic notebooks for data entry and planning.

after spending more than 20 years at the pharmaceutical giant Merck.

This goal required not only to increase screening throughput above that of a typical academic facility but also to generate greater diversity in the chemical compound collections and to create a new informatics system to handle and interpret the volumes of data that will be produced.

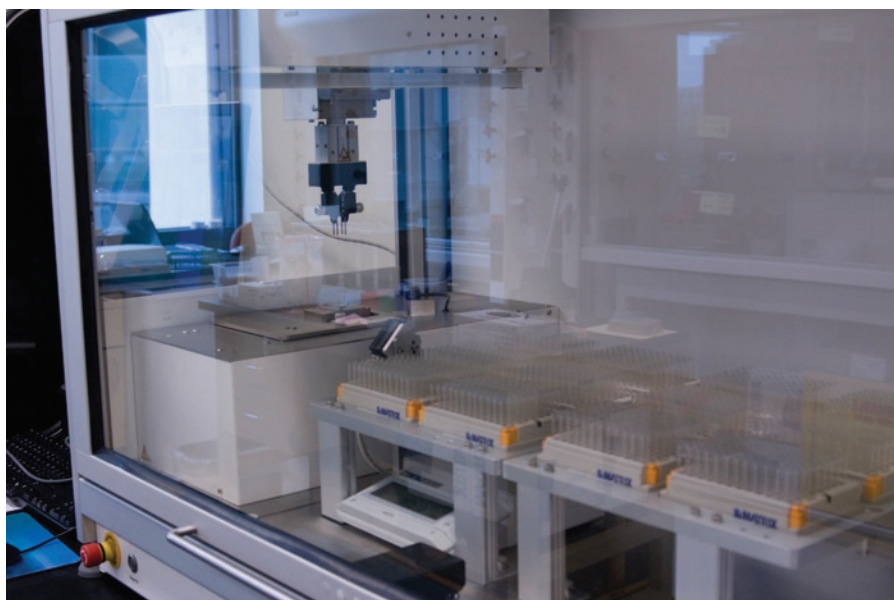
Roll with the changes

On the day I visited the facility, a group of 20 visitors were watching a demonstration of the newest robotic system. Gould says that such tours of the new facility are becoming increasingly commonplace as

more outside researchers learn about the capabilities and the unique nature of their platform.

All the new systems for screening and compound management have been designed and installed by HighRes Biosolutions, a company based in Woburn, Massachusetts, USA. "The goal was to have a very modular design," says Gould, and the company's approach permitted the modularity that the Broad was seeking.

In HighRes Biosolutions' MicroStar system, the general screening platform installed at the Broad, the robotic arms are fixed while the other pieces of equipment in the system—for example, an



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Robotic systems at the Broad Institute are becoming essential for compound-library management and screening.

Echo 555 liquid handler from Labcyte (Sunnyvale, California, USA) and an integrated plate incubator from Liconic AG (Woburn, Massachusetts, USA)—are placed on carts around each arm. When a cart is docked into one of the multiple MicroDock stations located on the floor, a computer recognizes the cart and relays information on position and instrument type to the Stäubli robotic arm for assay implementation.

“One of the key advantages of the Broad design is the ability to move chemical inventory between screening systems and also move peripherals or devices from system to system,” says Lou Guarracina, president of HighRes Biosolutions. He also notes that the unique modularity of the HighRes Biosolutions screening system allows for the addition of new devices and for changes in configurations: “A lot of the screening changes over time; researchers often don’t know what is coming down the pipe.” Guarracina says that most common laboratory devices can be docked and implemented with these systems including larger instruments such as the ViewLux charge-coupled device (CCD) imager from PerkinElmer of Waltham, Massachusetts, USA and the FLIPR Tetra imaging system from Molecular Devices of Sunnyvale, California, USA that can weigh in excess of 1,000 pounds.

Once all the systems are installed, the center will have the capacity to screen

10 million wells per year. And with the ability to adapt and expand their screening platforms and instrumentation depending on the assay, Foley is targeting more complex chemical biology screens in the future. “Where we are hoping to differentiate ourselves at the Broad is in high-content imaging assays,” he says. For these assays there will be heavy integration of microscopy instrumentation into the MicroStar system along with additional support coming from the Broad imaging platform—directed by Anne Carpenter—which is developing software for automated cell analysis.

Chemically similar, but different

When it comes to chemical biology screens, the results can only be as good as the compounds tested. “An optimal small-molecule collection is populated with compounds that increase the probability of success in three facets of chemistry research,” says Stuart Schreiber, pointing to initial screen, follow-up analysis and large-scale, cost-effective manufacturing. Schreiber is director of chemical biology at the Broad Institute and Morris Loeb professor of Chemistry and Chemical Biology at Harvard University.

To get a handle on all three facets at once, the chemical biology platform team has adopted the method known as diversity-oriented synthesis (DOS) to generate a large proportion of their small-molecule

collection. “DOS is a way of conducting synthetic organic chemistry such that it can be most useful for biological discovery,” says Damian Young, group leader of the DOS chemistry group within the chemical biology platform. “DOS molecules can have various appendages that attach around the core periphery: they can have different stereochemical relationships, and different skeletons.” While maintaining synthetic efficiency, DOS aims to produce compounds that rival the complexity of natural products. “Combinatorial approaches generate molecules that tend to be flat, whereas DOS molecules have a more three-dimensional structure,” says Lisa Marcaurelle, manager of DOS chemistry at the Broad Institute.

Creating a DOS-based library, however, is not a trivial task. The planning stage alone, in which the successive chemical transformations are selected, is a team effort that can take a month or two. Optimizing the chemistry and synthesizing the compounds can take another year. But this upfront investment can save time at later stages. “A screening hit is never the compound that is the final drug or probe,” says Young. Making the changes to generate a usable product—the domain of a medicinal chemist—is a time-consuming process that could be sped up using DOS. “The DOS approach gives us an enormous amount of information just from a primary screen,” says Young, adding that these are “chemical relationships that can be used in the follow-up analysis.”

The Broad’s chemical collection now stands at 80,000 compounds, and Foley estimates that it should reach 400,000 by year’s end, with a minimum level of 75% purity for each compound. In addition to compounds synthesized in house, the chemical biology group has also been performing quality control analysis on compounds from several commercial vendor libraries including libraries from Chembridge and ChemDiv in San Diego.

Putting it all together

For David DeCaprio, head of informatics at the chemical biology platform, developing the underlying informatics was a process, “walking through the entire life-cycle that connects chemistry, screening and data analysis.”

As the screening is largely automated, tracing where errors might enter the process is primordial. “You need to



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The new high-throughput general screening system from HighRes Biosolutions allows researchers at the Broad the opportunity to modify and vary their chemical screens.

understand the compound concentrations, the history of the compounds and their purity—tracing all the way back—so that when you get any anomalies you can figure out where they are coming from.”

Part of the solution was to implement electronic notebooks. Every chemist in the chemical biology group has a dedicated notebook computer mounted next to their lab bench, which they use to track day-to-day experiments. “Data are captured electronically right from the start, so we never have this bottleneck of getting data into the system,” says DeCaprio.

The chemists at the Broad are using a version of the Cambridge-based CambridgeSoft’s electronic notebook that has been modified to fit the chemical biology platform’s specialized needs such as the integration of a module to plan DOS library design.

With error-tracking measures in place and the new high-throughput screening center up and running, DeCaprio’s team is now turning their attention to the

informatics challenges of complicated high-throughput screens such as those involving high content imaging and gene expression.

With these assays, many questions can be asked, and the data can be analyzed in different ways, putting a strain on data acquisition and analysis. But the informatics team decided to take a cue from their genome sequencing counterparts upstairs: they will collect and store all the raw data so that researchers can perform different analyses as many times as they desire.

Finding that special connection

For many years, researchers at the Broad have been developing databases and tools to find biological connections between the many different datasets generated by the institute’s researchers. In 2006, Broad scientists published their connectivity map (cmap)¹, a searchable public database of gene-expression profiles in human cells treated with various drugs. The built-in

informatics tools allow investigators to find connections between disease states and small-molecule compounds.

The second version of cmap released in July 2008 contains 13 times more gene expression profiles. Justin Lamb, leader of the cmap project, says that the second version contains data for over 1,000 small molecules, including nearly all the US Food and Drug Administration–approved off-patent drugs. “With this information, you can annotate a biological query of interest in the language of chemistry, and that is very useful,” he says.

Other changes in the second version of cmap include improved algorithms to compute connectivity. “A problem with the first version of cmap is that it was a little hard to judge how specific a connection was,” says Lamb. New tools in the second version calculate a specificity measure by comparing connectivity from a user’s query signature with those from a collection of 312 publicly available gene-expression signatures.

As researchers start to explore the latest version of cmap, DeCaprio’s team is developing a new version of ChemBank, another repository for small-molecule

screens, which will include the chemical biology platform’s new high-throughput screens with a variety of end-point assays in addition to gene-expression profiling.

“ChemBank and cmap are illustrations that both the analytic tools and experimental framework are now in place for making connections between different cell states, measurements and small-molecule perturbations,” says Schreiber. And with the growing numbers of screens in human cells using different assays along with the expanding ability to establish connections between these assays and small molecule treatments, Schreiber suggests that the time might be right to rethink the idea of a good model organism. “We are excited about the idea that when you merge chemical biology, genomic biology and human genetics—although you continue to rely on model organisms—we feel like we can start to think of humans as model organisms.”

1. Lamb, J. *et al. Science* **313**, 1929–1935 (2006).

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SUPPLIERS GUIDE: COMPANIES OFFERING CHEMICAL GENOMICS REAGENTS AND INSTRUMENTATION

Company	Web address	Company	Web address
Abbott Molecular	http://www.abbottmolecular.com/	CambridgeSoft	http://www.cambridgesoft.com/
Abgene	http://www.abgene.com/	CellProfiler software	http://www.cellprofiler.org/
Agilent	http://www.agilent.com/	Cell Signaling Technology	http://www.cellsignal.com/
AnaSpec	http://www.anaspec.com/	Cellomics	http://www.cellomics.com/
Applied Biosystems	http://www.appliedbiosystems.com/	ChemBridge	http://www.chembridge.com/
Applied Precision	http://www.appliedprecision.com/	ChemDiv	http://www.chemdiv.com/
Applied Scientific Instrumentation	http://www.asiimaging.com/	Contur	http://www.contur.com/
Andor Technology	http://www.andor.com/	Corbett Life Science	http://www.corbettlifescience.com/
Axioppe	http://www.axiophe.com/	DiscoverX	http://www.discoverx.com/
B-Bridge	http://www.b-bridge.com/	EMD Biosciences	http://www.emdbiosciences.com/
BD Biosciences	http://www.bdbiosciences.com/	Eppendorf	http://www.eppendorf.com/
Beckman Coulter	http://www.beckman.com/	GE Healthcare	http://www4.gelifesciences.com/
Biaffin GmbH	http://www.biaffin.com/	Genetix	http://www.genetix.com/
BioImagene	http://www.bioimagene.com/	Genomic Solutions	http://www.genomicsolutions.com/
Biometra	http://www.biometra.de/	Gilson	http://www.gilson.com/
Bio-Rad	http://www.bio-rad.com/	GNF Systems	http://www.gnfsystems.com/
BioTek	http://www.biotek.com/	Hamilton Robotics	http://www.hamiltonrobotics.com/
Biovision AG	http://www.peptidomics.com/	HighRes Biosolutions	http://www.highresbio.com/
Bruker Daltonics	http://www.bdal.com/	Hudson Control Group	http://www.hudsoncontrol.com/
Caliper Life Sciences	http://www.caliperls.com/	Imgenex	http://www.imgenex.com/
Cambrex	http://www.cambrex.com/	Improvision	http://www.improvision.com/

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SUPPLIERS GUIDE: COMPANIES OFFERING CHEMICAL GENOMICS REAGENTS AND INSTRUMENTATION (continued)

Company	Web address	Company	Web address
Intelligent Imaging Innovations	http://www.intelligent-imaging.com/	Promega	http://www.promega.com/
Invitrogen	http://www.invitrogen.com/	Proteodyne	http://www.proteodyne.com/
JMP Genomics	http://www.jmp.com/	Qiagen	http://www1.qiagen.com/
Kalypsys	http://www.kalypsys.com/	QImaging	http://www.qimaging.com/
Kinasource	http://www.kinasource.co.uk/	Reaction Biology Corp.	http://www.reactionbiology.com
Kinexus Bioinformatics	http://www.kinexus.ca/	Rescentris	http://www.rescentris.com
Lab Services BV	http://www.lab-services.nl/	Rigaku	http://rigaku.com
Labcyte	http://www.labcyte.com/	Roche Applied Science	http://www.roche-applied-science.com/
LaVision Biotec	http://www.lavisionbiotec.de/	Roper Scientific	http://www.roperscientific.com/
Leica Microsystems	http://www.leica-microsystems.com/	RTS Life Science	http://www.rtslifescience.com/
MBL International	http://www.mblintl.com/	Sigma-Aldrich	http://www.sigmaaldrich.com/
Micro Luminetics	http://www.cryocam.com/	Stratagene	http://www.stratagene.com/
Millipore	http://www.millipore.com/	Synoptics	http://www.synoptics.co.uk/
Mirero	http://www.gaia-zone.com/	Systat	http://www.systat.com/
Molecular Devices	http://www.moleculardevices.com/	Tecan Group	http://www.tecan.com/
New England Biolabs	http://www.neb.com/	Thermo Electron corp.	http://www.thermo.com/
Nikon	http://www.nikonusa.com/	Titertek	http://www.titertek.com/
Olympus	http://www.olympusamerica.com/	VayTek	http://www.vaytek.com/
Optronics	http://www.optronics.com/	WaveMetrics	http://www.wavemetrics.com/
Parallab	http://www.parallabs.com/	Velocity 11	http://www.velocity11.com/
PerkinElmer	http://www.perkinelmer.com/	Xiril AG	http://www.xiril.com/
Pierce Biotechnology	http://www.piercenet.com/	Zeiss	http://www.zeiss.de/