HMS Lab Grants to Support Computational Methods Development for Systems Pharmacology

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By Uduak Grace Thomas

NEW YORK (GenomeWeb) – Researchers in Harvard Medical School's newly minted laboratory of systems pharmacology were one of six research groups awarded a share of a $64 million grant from the National Institutes of Health that is earmarked for the Library of Integrated Network-based Cellular Signatures (LINCS) program.

The researchers, led by Peter Sorger, a professor of systems biology and the principal investigator on the grant, have been awarded $12.8 million under the program, and will use the funds to develop new measurement methods and computer algorithms that can detect and analyze perturbations brought on by therapeutic drugs in healthy and diseased cells. They'll work primarily with cancer, studying a panel of about 100 cell lines, but will also work with about 30 primary tissues including neuronal and human liver cells. In terms of treatments, the researchers will work with both approved and investigational drugs including small molecule kinase inhibitors. All the data and software tools created under the auspices of this project — as well as those from an earlier three-year pilot phase — will be made publically available.

The ultimate goal, according to Sorger, is for drug developers to perform computations on LINCS data in much the same way that Google Maps makes use of geographic information systems data. One component of that vision involves figuring out ways to combine information from disparate biological studies into a greater, more meaningful, and useful whole, he explained to *BioInform*. It also involves figuring out the best ways to represent data so that it simultaneously captures a good amount of detail without losing the bigger picture, and making data from these studies openly available for research use.

These aims, Sorger said, are written into the DNA of the LINCS grant. The program aims to catalog and analyze cellular function and molecular activity that occurs in response to perturbing agents – such as drugs and genetic factors – that are potentially disruptive to cells, and to identify patterns or signatures in these responses. According to the NIH, the new funds for the program, which is administered by the National Human Genome Research Institute and the National Heart, Lung, and Blood Institute, will be used to establish six centers collectively called the Data and Signature Generating Centers. In addition to HMS, there will be centers at Oregon Health and Science University; Icahn School of Medicine at Mount Sinai; the University of California, Irvine; and two at the Broad Institute.

The work that Sorger's lab will be doing under the LINCS grant dovetails with a second $3 million grant awarded to his team from the Defense Advanced Research Projects Agency (DARPA) under its so-called Big Mechanism program, which is intended to create an open-source software environment for building dynamic models of cancer networks. The DARPA grant explicitly focuses on expanding computational methods developed by Sorger and colleagues, and integrating them with other aspects of computer science, he said, while the LINCS grant is more about using the methods to analyze data.

Specifically, the HMS team is focused on developing "biochemical models of

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drug-target interaction and of signaling networks before and after drug exposure," he explained in an email. "These dynamic models are usually combinations of stochastic and continuum differential equations (rather like chemical engineering). However, it is very difficult to build such models by directly writing the underlying equations, so we have developed programmatic modeling methods that automate the process. Our work on this part of the field of 'rules-based modeling' … aims to replace informal reasoning about biochemistry — pictures and diagrams for example — with formalized models that make the process more rigorous and effective." His group published a paper on this subject last year in *Molecular Systems Biology*.

The HMS group is also working on modeling pharmacodynamics activities, Sorger said. Models here "need to be multiscale, capturing some features of drug activity at the molecular, cellular, and tissue levels, informed by data on distribution through the body (pharmacokinetics)," he explained. "In our work, we are particularly interested in adding single-cell data since we believe that this is essential for understanding dose-response." Additional details of these efforts are available in a *Nature Chemical Biology* paper also published last year.

The LINCS and DARPA awards are part of a group of four complementary grants — totaling about $30 million — recently awarded to HMS' systems pharmacology laboratory, which was set up as part of its therapeutic sciences program launched last year, Sorger told *BioInform*. Besides the LINCS and DARPA grant, the lab got an $11 million grant from the National Institute of General Medical Sciences, which will support efforts to investigate drug action at a single-cell level, develop a rational approach to combination therapy, and identify and quantify new drug targets. Meantime, a $3.4 million grant from the US Food and Drug Administration will be used to develop computational methods and cell culture platforms to link cellular systems' toxicology to clinical phenotypes.

Broadly speaking, researchers in the lab — which includes investigators from the Broad Institute, Massachusetts General Hospital, and other institutions — aim to use "large-scale systematic experimentation and computational modeling" to essentially "revitalize preclinical and translational pharmacology," said Sorger, who is the PI on all four grants. Specifically, the researchers will try to answer questions that underlie three broad research areas, he said.

The first involves uncovering the precise mechanisms of action of existing pharmaceuticals in existing indications. This is important because "there's a lot of patient-to-patient variability that remains unexplained." For example, some cancers have good molecular signatures but a host of others don't, he said. "It's our premise that existing genomic methods are giving us some of the top 15 percent or so of the explanatory variables but they're leaving much of the rest unclear." A systems pharmacology approach, on the other hand, "is much more rooted in cell and tissue biology so it actually looks at the dynamics of drug interaction, drug target binding, cell-to-cell variability, tissue level responses, and in animal models things like pharmacokinetics and pharmacodynamics," he said. "It's a more integrative cellular approach."

Secondly, the researchers intend to analyze drug response data from both successful and failed drugs to gain a better understanding of why medications either work or fail. At present, very little is known about the underlying mechanisms in either case, Sorger said. This is true for widely prescribed drugs and more so for failed drug classes. In fact, "there is quite a lot of evidence that quite a lot of target classes have been abandoned without really testing the therapeutic hypothesis," Sorger said. The goal for this study, he added, is "to use success and failure [data] to really develop and improve methodology for moving [drugs] up into phase one [and] we would do that by a much more sort of systematic and … computationally driven accumulation of data," with the longer term goal being "to increase predictability and reduce the rate of failure."

A third effort will focus on applying learnings from cancer pharmacology, for example targeted therapies and preclinical models to other diseases, starting with pulmonary and respiratory diseases like chronic obstructive pulmonary disorder, or neurological disease or neurodegenerative conditions, Sorger said. The idea here would be to see "if there are short-term opportunities to repurpose drugs from one indication to the next based on better science," he explained. This has been done for drugs like methotrexate, which, at different doses, is used to treat some forms of cancer and autoimmune diseases such as rheumatoid arthritis, he noted.

The research efforts at HMS grew out of ideas described more fully in a white paper published in 2011. That paper is one of the fruits of two workshops involving participants from industry, academia, and government that work in the systems biology

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and pharmacology space. Their goal was to explore "whether a merger of systems biology and pharmacology via the emerging discipline of quantitative and systems pharmacology could advance the discovery, development, and clinical use of therapeutic drugs."

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Australian molecular diagnostics firm Genetic Technologies is undertaking a restructuring aimed at ramping up its US molecular diagnostic operations and commercializing the new version of its BrevaGen breast cancer risk test. Its board has approved the sale and/or divestment of the company's non-core assets, and the firm has finalized commitments for a A$2.15 million (US$1.94 million) financing to support its US MDx plans. The firm plans to soon launch BrevaGenplus test, which would have use for African-American and Hispanic women, as well as Caucasian women.

Funding

The National Institute on Aging plans to award up to $800,000 next year to investigators' efforts to develop and plan research projects that will examine epigenetic factors involved in age-related diseases, addressing important questions in the emerging field of geroscience. The researchers will plan and design research projects that will investigate epigenetic risk factors for age-related diseases and conditions, or will undertake small-scale pilot projects focused on the same goals. NIA expects that these projects will receive more funding when they are fully developed.

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