A NEW PARADIGM FOR LIFE SCIENCE RESEARCH

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Here we interview Jeremy Caldwell, Ph.D., of the Genomics Institute of the Novartis Research Foundation (GNF). We ask him about the work at GNF, how he thinks high-throughput technologies will change life science research, and what advice he has for young scientists in training.

Introduction

Life science research has changed dramatically over the last few decades, and the pace of that change continues to accelerate. Those of us trained in the ultralow-throughput world of "one gene: one graduate student" sometimes struggle to wrap our minds around the technologies that drive high-throughput biology and the tremendous amount of information that high-throughput biology produces.

A simple search of the HighWire Press® database for the phrase "high-throughput screening" reveals that the number of papers containing that phrase increased by 89% from the previous decade (1987–1997) to this decade (1997–2007). We have also seen the publication of an entirely new genre of peer-reviewed journal for high-throughput biology including the *Journal of Biomolecular Screening* and *Journal of the Association of Laboratory Automation*, both first published in 1996, *Combinatorial Chemistry and High-Throughput Screening*, published in 1998, and *ASSAY and Drug Development Technologies*, begun in 2002.

What does the rise of high-throughput biology mean for the future of biological research? Who is doing this research? How will this research affect areas such as public health and the training of the next generation of biologists?

To explore these questions, *Cell Notes* spoke with Jeremy Caldwell, Ph.D., Director of Molecular and Cellular Biology of the Genomics Institute of the Novartis Research Foundation (GNF).

GNF seems like a hybrid organization between industry and academia. Can you tell us more about why GNF was created and how it works?

GNF was created in 1998–99 by the Novartis Research Foundation to exploit the human genome sequencing project and develop new technologies to deconvolute the human genome at a functional level. The goal was to bring chemists, biologists and engineers together under one roof to create novel technologies and methods in protein sciences, cell biology, genomics, chemistry, computation and automation that could revolutionize life science research. Then we hired researchers to leverage these new tools to find new therapeutic targets, pathways and ways to intervene in disease. This approach has led to the successful creation of a preclinical pipeline offering new possibilities for a broad variety of diseases.

GNF is a bottom-up meets top-down, science- and technology-driven place. Many of the best ideas come from young and highly driven scientists with approaches that make the best use of GNF's technological capabilities. We proactively get involved

The automated cellular profiling system at GNF. The high-throughput automation system borrows precision robotics technology from the automotive industry.

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in fields that are relatively new and still early in their development—fields like cancer stem cells and circadian biology that are still in the hypothesis-testing stage, where our technologies lend themselves to making significant leaps. And, in suit, we look for researchers working on questions that haven't been answered that might benefit from the tools at GNF.

GNF has managed to combine the best qualities of biotech, pharma and academia. GNF started off with a biotechnology mindset to innovate. It has a culture of inspired and highly motivated people who are ready to come up with the next great thing and has managed to segue this into a preclinical pipeline so that new discoveries can be advanced towards new drug discovery. GNF also has managed to maintain an academic mindset that seeks to let the small research lab have access to ultrahigh-throughput (uHTS) technologies, but GNF does have a deliberate biomedical focus, similar to a pharmaceutical company.

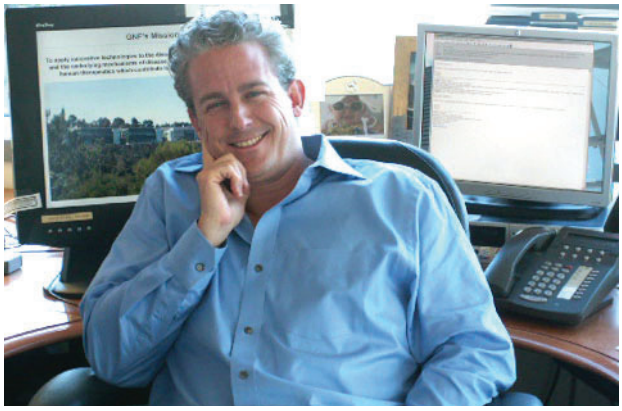
Who decides what projects GNF will pursue?

The infrastructure at GNF allows it to be independent and opportunistic. The uHTS screening system, designed by GNF engineers from the automotive industry turned biotech, allows the institute to screen about 2 million compounds per day against both biochemical and cellular targets. Through miniaturizing and streamlining the process, the cost of a screen has been dramatically reduced to a small fraction of the conventional cost.

The reduced cost to screen allows GNF to be highly opportunistic in terms of which compounds to pursue for further inquiry. The chances of coming up with an attractive chemical starting point are much higher if you can run multiple screens against different pathway members—the GNF approach allows you to do that for a fraction of the normal cost. GNF has applied this approach throughout the organization in order to focus its efforts where the technology leads toward a strategic advantage (e.g., a potent specific compound directly from the screen). Generally GNF chooses biological questions where progress can be made fairly quickly.

New high-throughput screening centers are being created around the country, centers like GNF and centers created through publicly funded initiatives like the NIH Molecular Libraries Screening Network. How will life science research be affected over the next few years by these HTS activities?

GNF is creating an impressive record of compound activity, building compound activity profiles for all of the compounds tested across all their in-house screening assays. These data can be mined, allowing researchers to make predictions about how a specific compound will interact with a given biological system. For instance, you could take a really successful therapeutic compound, like the Type II Diabetes drug Metformin, and look at its activity profile across all of the assays. Then, you can mine the database of compound profiles to look for drugs with the same activity profile as Metformin. Compounds with the same activity profile are likely to hit the same target pathway, so this method can be exploited for target identification.



Dr. Jeremy Caldwell, Director of Molecular and Cellular Biology at the Genomics Institute of the Novartis Research Foundation. "GNF is a bottom-up meets top-down, science and technology-driven place. Many of the best ideas come from young and highly driven scientists with approaches that make the best use of GNF's technological capabilities."

A great deal of life science research will probably center on such database-generated hypotheses, hypotheses about compound activities and effects that are based on the genomic and small molecule information. For better or for worse, in the future, researchers will probably be spending even more time in front of the computer.

Experiments will increasingly be designed to look at the impact of compounds on multiple pathways and systems they impinge upon. This will require investigating how groups of genes act functionally in different contexts. Ultimately, scientists will be able to describe how different groups of genes work in collaboration to affect a physiological response or condition by illuminating the entire landscape of the transcriptome or genome, not just one gene at a time.

What are some of the challenges facing high-throughput research?

Scientists will be thinking more in terms of networks, systems and constellations of genes, protein modifications and metabolic products to identify meaningful patterns. High-throughput biology will help find compounds that can perturb these networks and combinations of compounds that affect complementary pathways from a therapeutic standpoint. One of the major challenges of looking at compound activity profiles is in how to access as many pathways and assays as possible to test your compound libraries. In order to look broadly at how small molecules work and prioritize which small molecules to investigate, researchers will need new research tools such as cell-based assays against pathways and target classes that have previously been difficult to tap into. This is where

companies like Promega and other reagent providers can have a big impact.

We are rapidly learning from genetic association studies and systems approaches that diseases are multigenic in origin, and that multiple gene regulatory networks are affected. It follows that these diseases likely will be best treated with drugs that affect different networks, which combined can address multiple aspects of the disease. This is where compound activity profiling comes into play. With the ability to have a more complete profile for a compound, we will be able to recognize compounds or combinations of compounds that affect multiple systems. This is the way of the future disease treatment—combination therapy as seen in cancer and polypharmacy with the aging population. It's already happening, but the effective combinations are discovered serendipitously.

With all of this emphasis on high-throughput translational research, what role does the small academic lab have in the future?

Basic research is where some of the most important insights happen, the paradigm-shifting, revolutionary finds. And they are usually the product of someone noodling over an interesting, but often esoteric, question, having the freedom to pursue sometimes tangential lines of inquiry.

The smaller lab can be just as good a training ground for scientists as the larger labs with twenty-one post docs. What we want scientists to do is know how to ask a good question, think deeply about it, and design effective ways to answer it. A good question, even on a seemingly esoteric subject, can still train scientists' minds.

Just for fun, how did you get interested in science?

Well, my English literature classes just weren't keeping me awake so I had to find something else. Actually, a fellow undergraduate at Berkeley and good friend was interested in neurobiology at a time when I was still exploring my undergraduate major. We got together and talked about neurobiology. I realized that there is an underlying order to things, and that by studying science I could discover the way things work. Of course, I couldn't start the neurobiology program immediately because I had developed this interest in the wrong semester. I had to start with plant biology, and I discovered "Wow, plants are just as complex and fascinating." Eventually, I went on to earn my Ph.D. from Stanford working on NFκB signaling in the laboratory of Dr. Garry Nolan, a fellow closet horticulturist.

Do you have any advice for scientists in training?

Yes, look and see what other people are doing at the leading edge of life science research, but let it inspire you, not turn you off. It's easy to read a *Nature* paper and come away feeling that all of the important questions have been answered. There is a never-ending parade of questions to pursue, probably even several related to that work you just read in *Nature,* which seems so complete on its face.

Also, realize that new technologies can be seductive, promising fast discoveries and a fast track to a successful career. However, often times technologies are built in a vacuum, devoid of a killer application or biological question to address. Usually the investigators who understand the biology enough to ask interesting questions will be the ones in a position to develop the most useful technologies, not the other way around.

Recent Publications from GNF

1. Peters, E.C. and Gray, N.S. (2007) Chemical proteomics identifies unanticipated targets of clinical kinase inhibitors. *ACS Chem. Biol.* **2**, 661–4.
2. Konig, R. *et al.* (2007) A probability-based approach for the analysis of large-scale RNAi screens. *Nat. Methods.* **4**, 847–9.
3. Miller, A.T. *et al.* (2007) Production of Ins(1,3,4,5)P4 mediated by the kinase Itpkb inhibits store-operated calcium channels and regulates B cell selection and activation. *Nat. Immunol.* **8**, 514–21.
4. Nguyen, D.G. *et al.* (2007) Identification of novel therapeutic targets for HIV infection through functional genomic screening. *Virology.* **362**, 16–25.
5. Dhaka, A. *et al.* (2007) TRPM8 is required for cold sensation in mice. *Neuron* **54**, 371–8.
6. Warmuth, M. *et al.* (2007) Ba/F3 cells and their use in kinase drug discovery. *Curr. Opin. Oncol.* **19**, 55–60.
7. Caldwell, J.S. (2007) Cancer cell-based genomic and small molecule screens. *Adv. Cancer Res.* **96**, 145–73.
8. Mitro, N. (2007) The nuclear receptor LXR is a glucose sensor. *Nature* **445**, 219–23.

For more information about the Genomics Institute of the Novartis Research Foundation, visit the Web site at: www.gnf.org/

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