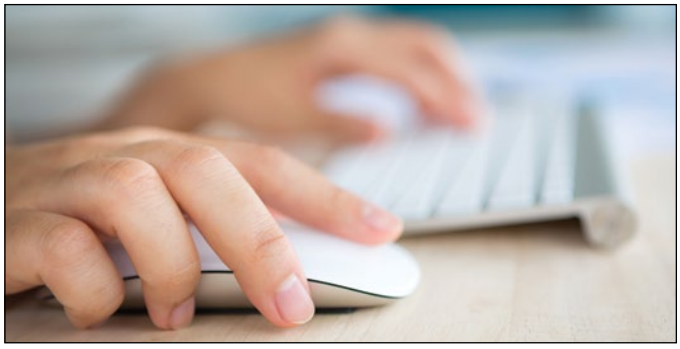


Translational cell biology careers turn on technological savvy

Translational cell biologists pursue research questions that have a direct impact on treating human diseases. But to build a successful career, young cell biologists must also be well versed in technologies, such as those for advanced imaging, data mining, and biophysics, to push their research ahead. These cell biologists must embrace skills usually found in other departments—such as programming, performing heavy-duty statistical analysis, and even building devices from scratch in the machine shop. Turning laboratory findings into the foundations for potential new therapies also takes strong communication skills and a willingness to collaborate in team science or even across academia-industry borders. **By Kendall Powell**

Bernd Bodenmiller has never been quite satisfied with the state of current technology. As a graduate student in one of the founding laboratories of systems biology, he was fascinated with the power of new proteomics tools to survey all the proteins of a cell type. But he eventually grew frustrated by the fact that these measurements had to be averaged across millions of cells.

As a postdoc, he joined Garry Nolan's laboratory at Stanford University, in large part because it was the first lab to try out a new device called a "mass cytometer," or CyTOF, which married time-of-flight mass spectrometry with single-cell analysis of cells in solution. However, he soon realized that to answer his burning questions about what influences a stationary cancer cell to strike out and invade the rest of the body, he needed the technology to be able to analyze cells sitting in native tissues.

Bodenmiller's wanderlust to find and improve technologies for analyzing cell signaling led him to develop a laser-assisted mass cytometer that could analyze up to 50 different protein signals found in a single cell within a slice of tissue. It also drove his success as an assistant professor of quantitative biology at the University of Zurich, earning him highly competitive grants.

Now, Bodenmiller encourages young scientists in his group at the University of Zurich's Institute of Molecular Life Sciences to follow in his own footsteps for shaping a career on the frontiers of cell biology: to become established at the intersection of biology and new methods development.

"Developing a novel method and then applying this bleeding-edge technology to biological questions will yield novel views in biology and important findings with little competition," he notes. Focusing only on technologies or only on biology does not push either one forward with as much momentum or potential for breakthroughs, he explains.

Successful scientists working at the intersection of cell biology and human health are following this recipe for success, too, in slightly different variations. Many of them are both developing and applying new tools to build an increasingly complex view of the cell and its signaling networks during disease. Others are sifting through massive data sets to find new ways to target diseases. And still others are using advanced imaging and computing to find the subtle patterns that govern cell behaviors.

Young researchers who want to pursue a career in translational cell biology, whether in academic research or in industry, must be comfortable with data analysis, programming, and computational biology. They must also be collaborative and be able to work well in teams, which often include physicists, bioinformaticists, and software engineers.


Anne Carpenter

Problem-solving PIs

Several cell biology principal investigators (PIs) have made their mark as Bodenmiller did, by pushing technologies forward to help them answer their own research questions. As a postdoctoral fellow at the Whitehead Institute, **Anne Carpenter** found her lab's imaging software was not up to the task she needed to tackle—identifying phenotypic changes in cell size and growth across thousands of cells in response to a genome-wide RNA interference (RNAi) screen. So she rolled up her sleeves, taught herself to program, and found a computer science graduate student from nearby MIT willing to lend a hand.

That collaboration eventually yielded CellProfiler, a software application used to do high-throughput imaging screens and to quantify phenomena observed continued>

PHOTOS (FROM TOP): © JANNOON028/SHUTTERSTOCK.COM; MARIA NEMCHUK, BROAD INSTITUTE

Upcoming Features
Regional Focus: Asia—December 11 ■ *Faculty Careers—January 29* ■ *Postdoc Careers—March 25*

> **"The most important part is figuring out what cool, exciting data sets are out there and what are the unanswered questions you can ask using them."**
> **— Marina Sirota**

by eye in the microscope. The program allows researchers to screen hundreds of thousands of drug compounds or genetic perturbations to find the conditions that give researchers the complex cellular readout they would like to see—such as a change in cell shape, organelle number, or cytoskeleton structure.

"A lot of our collaborators are trying to make in vitro systems more reflective of real biology," which often requires using more complex cell-culture systems, says Carpenter, who is now leading a computational biology group at the Broad Institute of MIT and Harvard in Cambridge, Massachusetts. Through machine learning, a biologist trains the software to recognize subtle cellular differences.

Marina Sirota knew as early as college that she wanted to take "interesting biological experiments and map computer science onto them," to perform sophisticated data analyses in order to query the explosion of genomic data. Sirota saw that researchers would need computational methods to wrangle data and to make real progress against human diseases.

As part of her Ph.D. work at Stanford University, Sirota launched a study to find potential new uses for drugs already on the market. The idea was based on matching human disease gene expression patterns with opposite or inverse drug gene expression patterns. In other words, if a disease caused a group of genes to be upregulated, was it possible to identify a drug that caused those same genes to be downregulated?

She ran an analysis of 164 drug compounds against gene profiles of about 100 diseases. One very promising hit was the antiseizure drug topiramate, which scored better against Crohn's disease in the analysis than a known treatment for Crohn's symptoms. The lab went on to show that topiramate worked better in an animal model of Crohn's disease, too.

"It taught me how to ask questions in big data science," says Sirota, now an assistant professor at the University of California, San Francisco's Institute for Computational Health Sciences. "The most important part is figuring out what cool, exciting data sets are out there and what are the unanswered questions you can ask using them"

Finding creative new ways to manipulate big genetic or imaging data sets is a key skill for translational researchers looking to make an impact on disease. Likewise, working in collaborative, interdisciplinary teams is also a must. Bodenmiller's project to adapt the CyTOF technique to image single cells in tissue exemplifies both skill sets.

"In the beginning it was a somewhat crazy idea," says Bodenmiller of his moving a laser system into his lab to add to the CyTOF equipment. By adding the high-resolution laser to the microscope, his team developed a way to peel off tiny, 1-square micron tissue areas with surgical precision.

The CyTOF mass spectrometer can read information from up to 50 different heavy metal isotope markers tagging cellular proteins and protein modifications in each tiny spot. Using the laser's coordinates, "we computationally generate an image by putting the marker information back in the right spots," says Bodenmiller. His group uses the technique to define cellular signals that initiate metastasis in breast cancer. For such projects, he needs researchers with backgrounds in analytical sciences, cancer biology, and computational biology.

"My primary advice is to become very good at one of those areas," he says. "But also to learn to interact with other people who have another expertise that you do not have." Big data science absolutely requires collaboration, whether in academia or industry. "No single person can achieve every aspect of these projects," says Bodenmiller. Successful young researchers learn to speak the different languages of a technology.

Skill building

Adam E. Cohen started his scientific life as a theoretical physicist, but became a biophysicist by immersing himself in biology's language and all of its messy details. His group's website at Harvard University has a tagline that sums up its mission: "Physical tools to study molecules, cells, and organisms."

"The number one piece of advice I would give [young cell biologists] is to learn to program," says Cohen. "If you can't program, you are dead in the water when it comes to extracting meaning from digital data and analyzing it numerically."

Researchers can take a boot camp or introductory class or simply learn by doing as Carpenter did in her work. Biology graduate students should all be learning to code as part of their training, Cohen insists.

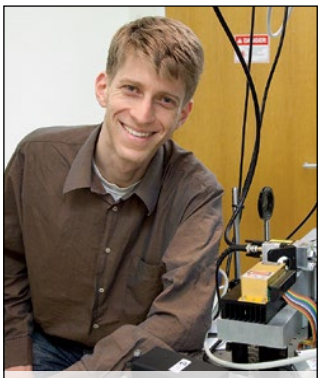
Strong quantitative skills will also help cell biologists distinguish themselves as researchers capable of extracting meaningful information from patient genomes, disease phenotypes, or cellular image-based screening. "If someone comes to me and asks, 'What can I do to make myself more marketable?' I tell them to become an expert in statistics or data mining," says Carpenter.

Along those same lines, **Jennifer Gerton,** a geneticist at the Stowers Institute for Medical Research in Kansas City, Missouri encourages every trainee in her lab to take a class in bioinformatics. "Everyone is going to have to interact with bioinformatics experts in their career—they should at least learn the language so they can communicate," she notes. She also advises trainees to think deeply about their research problem and how they might apply the latest explosion of imaging technologies toward solving it.

And sometimes it's not a specific technical skill that's required for success in these technology-based projects, but rather a fearless personality to handle whatever needs doing. Cohen's lab experiments can run the gamut, from cell

PHOTO: JAMES PAN

culture to building lasers and doing hefty numerical analysis. So he looks for trainees with a "can do" attitude—including researchers who aren't afraid to build things in the machine shop with the lathe and milling machine when needed.


Adam E. Cohen

Gerton adds another personality trait that all translational cell biologists should possess: a love of learning new things. Gerton studies cohesinopathies, a group of rare human developmental disorders. "I love sitting down with a big pile of papers. I did a lot of reading to try to understand the human diseases and the available models," Gerton says.

Featured Participants

Broad Institute of MIT and Harvard
www.broadinstitute.org

Harvard University
www.harvard.edu

Institute of Molecular Life Sciences, University of Zurich
www.imls.uzh.ch

National Institute of Neurological Disorders and Stroke
www.ninds.nih.gov

Pfizer
www.pfizer.com

Stowers Institute for Medical Research
www.stowers.org

University of California, San Francisco
www.ucsf.edu

Strategic career planning

Another key characteristic of successful investigators in this realm is the ability to think strategically about handling the high-risk nature of projects. Cohen says that because many of these projects do not ultimately succeed, he tries to steer his group to "fail as quickly as possible" by finding the weakest, most challenging nodes of an effort.

For academic job searches, Cohen advises candidates to build a nice balance between being visionary and realistic in their research proposals. "Propose things that are straightforward that you know you can do and things that are more exploratory or speculative. And be clear about those differences," he says.

Both strategic thinking and deliberately acquired skills helped **Sam Hasson** achieve his desired career path in drug discovery in the pharmaceutical industry. Exceptional mentoring also secured his success.

Several experiences during graduate school, including a three-month internship immersed in drug discovery at Schering-Plough, showed Hasson that he belonged in the team-based and technology-driven research found in the pharma industry. So when looking for a postdoctoral fellowship, he asked himself, "How can I build up a skill set to make me attractive to industry?"

He found that opportunity at Richard Youle's laboratory at the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland. Youle's lab had found that the protein Parkin normally translocates to the outer mitochondrial membrane when there is mitochondrial stress or damage. However, certain mutations in Parkin block this movement and are associated with an early-onset, inherited form of Parkinson's disease.

Hasson took on a project to run a high-throughput imaging screen to find other genes that, when inhibited, either boosted or blocked Parkin's normal activity. With Youle's encouragement, Hasson designed and ran the screen with co-mentors at the National Center for Advancing Translational Science (NCATS), a National Institutes of Health (NIH) center located just 10 miles north in Rockville. Youle knew that learning all the ins and outs of the entire functional genomics screening process would give Hasson experience that is highly valued by industry.

In addition, when Youle was invited to give a talk at a Pfizer forum on mitochondrial health, he sent Hasson to give the presentation instead. "Because of his act of advocacy, I had an opportunity to be seen in front of a large crowd of people at Pfizer," says a grateful Hasson. "Getting exposure from an industry audience is one of the hardest things to do as a [young scientist]."

Sure enough, when a position opened up within Pfizer's neuroscience team at the end of 2013, Hasson was invited to apply. Now, as a principal investigator at Pfizer in Cambridge, Massachusetts, he applies emerging technologies to find new drug targets for neurodegenerative diseases.

Translational scientists can also gain that crucial exposure by attending the same scientific conferences as industry researchers, says Carpenter. These include meetings such as those held by the American Society for Clinical Oncology and the Society for Laboratory Automation and Screening. Casual conversations over posters or meals can give scientists a glimpse into the day-to-day operations at specific companies.

Sirota says no matter which environment a translational researcher might be aspiring toward, "Figure out who you will be working with and how to make a good team with them."

"The lines between academia and industry are blurring more and more and in many different ways," notes Sirota, whose career has included successful stints in both arenas. As someone who has hired researchers in both spaces, too, Sirota says it's extremely difficult to find the gems among the piles of résumés that come with each open position. So how to shine in a tough market?

Sirota advises: "Quantitative skills that are unique, personal connections, and very targeted applications that show me your research interests are a good match for the position will all make an application stand out if I have to go through a hundred of them."

Kendall Powell is a freelance science writer based in Lafayette, Colorado.

DOI: 10.1126/science.opms.r1500161

PHOTO: MARTHA STEWART