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Profiles written by Jennifer Crebs, Matthew Dublin, and Meredith Salisbury
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You’re a busy person. If you’re like most of our readers, you probably spend your day scrambling from one meeting to the next, squeezing in experiments and data analysis whenever you can, and after your long, hard day, you finally go home — where you catch up on all of your work e-mail. Sound familiar?

In a field where speed is essential — you need results now, you have to release your data immediately, and there’s always a grant application or project presentation looming — it’s a rare thing indeed to step back and actually take a moment to appreciate what you and your colleagues have accomplished.

It’s that rare moment we offer to you with this issue of Genome Technology, aimed at celebrating the accomplishments of a select group of researchers in this community. In the past several months, readers have asked me for more profiles of up-and-coming scientists. So when we decided to add a bonus tenth issue to our calendar, choosing the theme was simple: who would be the PIs of tomorrow’s labs? Who are the rising stars people should be watching right now?

We tapped today’s leading PIs to you find out, and they had no shortage of recommendations, their criteria were simple: they had to be involved in the disciplines that comprise systems biology, and could be no more than five years into their first faculty or equivalent post.

In what has been perhaps the most promising scientists whose profiles you will find on the following pages. Our heads who recommended people for inclusion in this issue, and also GT staff got to spend hours talking with these bright researchers not only about what they’re doing today, but also about where they see the field going in the years to come (we did get mocked soundly, though, for my own favorite question: “If you were to one day win the Nobel Prize, what accomplishment would you like that to be for?”). What we found was that these scientists are already fluent in some key attributes: if you read the profiles carefully, you’ll notice a theme of highly collaborative people who understand the importance of networking and surrounding themselves with other very smart people.

I’d like to thank all of the current lab heads who recommended people for inclusion in this issue, and also GT reporter Matt Dublin for heading up this project. And though we keep our editorial and advertising departments completely separate, I will take a moment to thank our advertisers, whose contributions for this issue have allowed us to give travel stipend honoraria to our profiles investigators.

You’ll notice that this issue doesn’t look like a typical Genome Technology. With different content comes a different designer, and GenomeWeb’s own Elena Coronado has done an outstanding job in giving our bonus issue a very special look. We’ll be back to our usual heads who recommended people for inclusion in this issue, and also GT reporter Matt Dublin for heading up this project. And though we keep our editorial and advertising departments completely separate, I will take a moment to thank our advertisers, whose contributions for this issue have allowed us to give travel stipend honoraria to our profiled investigators.

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Finally, for those of you who thought we’d forgotten about the cartoon caption contest we offered earlier this year, don’t miss the Blunt End. We held a project. And though we keep our editorial and advertising departments completely separate, I will take a moment to thank our advertisers, whose contributions for this issue have allowed us to give travel stipend honoraria to our profiled investigators.

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Finally, for those of you who thought we’d forgotten about the cartoon caption contest we offered earlier this year, don’t miss the Blunt End. We held results till now since so many entries were plays on the PI/postdoc dynamic. Check out p. 50 for the winning caption and our honorable mention.

Meredith W. Salisbury
Thanks For Your Support.

*Genome Technology* extends its sincere thanks to the advertisers in this issue, whose sponsorship helped provide a travel stipend honorarium for each of Tomorrow's PIs
By all accounts, Nathan Price had a pretty successful career as a graduate student. Upon finishing his PhD in bioengineering with Bernhard Palsson at the University of California, San Diego, where he published some 20 papers in computational biology, Price was offered a faculty position in the department of Chemical and Biomolecular Engineering at the University of Illinois at Urbana-Champaign. The majority of Price’s grad work was centered on metabolic systems, mitochondria, and red blood cells, but he wanted to do something more relevant to disease research, specifically cancer. So Price decided to defer the job offer and applied instead for a fellowship to work with systems bio guru Lee Hood.

“The rationale for that is that Lee is one of the best persons in the world for thinking about systems approaches to medicine,” says Price. “What I wanted to do was to harness computational models and high-throughput technologies to [be] able to get a better grasp of understanding of cancer from [the] systems perspective.”

In Hood’s lab, Price has set about developing algorithms that harness information external to the cell. “What we really want to learn is how to read secreted protein patterns in blood, not only to distinguish between health and disease at various stages, but also we hope to be able to link that back into causal perturbations and networks to use these patterns to identify states,” he says.

He sees blood as a window into human health and disease that’s just teeming with data. The problem, of course, is getting it. Price notes that one of the biggest challenges is measuring protein concentration in the blood. “It’s very important that you identify your candidate markers in advance because when you go into the blood, it’s much easier to measure proteins that you know you’re looking for,” he says.

And although Price says that researchers often refer to “deluges” of data in biology, that’s not a problem he faces. “Relative to what we want to do, and the kind of algorithms that we want to run and the kinds of predictive capabilities that we want to generate, we often find that we have much less data than we would like,” says Price. “That’s a fairly universal problem that almost anyone in modeling faces.”

Looking ahead

In the future, Price would like to see small microchips that can measure 1,000 to 2,000 proteins in the blood. His vision is to be able to take blood measurements, run them through various algorithms, and detect patterns that will essentially read out a person’s health, what kind of diseases that individual might have, and the state of those diseases. “So we hope that eventually, the blood can be used as a window to track the development of various diseases and even to assess drug efficacy,” says Price. “We hope to be able to see those kinds of things very early on.” Price sees the blood not only as a way to monitor network perturbations and screen for diseases like brain cancer, but also as a means to determine how well a particular treatment will work.

Publications of note

Price and his colleagues recently submitted a paper entitled “Highly accurate two-gene classifier to differentiate gastrointestinal stromal tumors and leiomyosarcomas.” Using a novel classifier based on a simple relative expression reversal between the expression of two genes, the paper reported 100 percent accuracy in differentiating between GIST and LMS in all patients tested.

And the Nobel goes to …

Price says if he were to win the Nobel Prize, he would want it to be for developing good systems models and algorithms that could assess vulnerability in cancer as a dynamic system and effectively treat it in a variety of settings.

— MD

Title: Postdoctoral Fellow, Institute for Systems Biology

Education: PhD, University of California, San Diego, 2005

Recommended by: Harris Lewin
A computer scientist by training, Manolis Kellis has always been fascinated by machines that can adapt to the environment. Before getting into genomic research, Kellis’ work centered on reconfigurable robots, artificial intelligence, and pattern recognition. But after becoming interested in the mechanics of the cell, he had a career-altering conversation with a fellow researcher who told him that the cell’s algorithm — nature’s own program — was already available. “He opened up a file that had pages and pages and pages of ACGT and I was caught staring at my own program, the code that actually makes me work,” says Kellis.

It was also the sheer volume of data that got him intrigued. For his dissertation, Kellis set about mapping the first genome-wide comparison of four complete yeast genomes. He says, “Only after I had published this work and gotten my PhD did I actually hear, ‘Hey Manolis, we never told you this, but we all thought it was impossible!’”

Kellis is now focused on elucidating the human genome using model organisms, including yeast. “The power of model organisms is that they allow you to tune in to the particular level of resolution that you’re interested in understanding,” he says.

But Kellis and his team are moving beyond what he calls “comparative genomics 101” by discovering specific evolutionary signatures. “By studying these evolutionary signatures of protein coding genes, we can now start to recognize new types of gene events and we can recognize that some segments used a protein with new kinds of signals,” he says. Because many genes don’t follow the evolutionary signatures he’s finding, Kellis believes that there may be plenty of erroneous genes currently listed in databases. He’s already proven that for the yeast genome. After developing gene signatures with the yeast genome, Kellis went back and revised the gene catalogue. Prior to revamping it, researchers had been including 6,300 genes in microarray experiments; after Kellis was through, it turned out only 5,700 genes were real. “This has had a tremendous impact on yeast genetics,” he says. “When you probe baker’s yeast, everything points to the fact that these are not genes; they are just intergenic regions that were previously mis-annotated.”

Kellis maintains that the only way to continue such refinements is by taking biological discovery in silico. He hopes that soon, instead of relying on traditional genetics to reveal novelties in the genome, computational biology will be at the forefront of discovery.

Looking ahead

At some point, Kellis would like to be able to access every step of the evolutionary history of all species. This would include the ability to reconstruct every single ancestral state and to recognize how they transformed over time — as well as where and how every single region is stored in the nucleus. “Basically understanding the 3D state of the nucleus and how DNA is stored and packaged would be tremendous,” he says.

Publications of note

In 2005, Kellis and his collaborators published a paper in *Nature* called “Systematic discovery of regulatory motifs in human promoters and 3’ UTRs by comparison of several mammals.” In it, they showed that it was possible to discover a battery of human motifs at the genome-wide level. They found that roughly 50 percent of 3’ UTR motifs are miRNA-associated with the remainder playing other diverse roles in post-transcriptional regulation.

And the Nobel goes to …

Kellis has grand plans for his Nobel commendation: he aims to win it by reaching an understanding of how to computationally code the geometry for any body plan, including organs and neuro-connections. — MD
S

till early in his career, Hiroki Ueda has already worked on both sides of the public-sector/private-sector divide. He completed both his MD and PhD at the University of Tokyo, and also spent time working as a researcher for Yamanouchi Pharmaceutical as well as Sony Computer Science Laboratories. That’s not the only divide he has crossed: Ueda has worked both in computer science — training under Hiroaki Kitano — and in the wet lab, learning about “high-throughput ‘omics” technologies during his time at the Pharma firm, he says.

Today, he hangs his hat at RIKEN, where he serves as head of the Laboratory for Systems Biology and as manager of the institute’s functional genomics division in the Center for Developmental Biology.

Born in Fukuoka, Japan, Ueda’s current experimental focus is on circadian rhythms, and how to better understand them using systems biology approaches. “My favorite system is the mammalian internal clock,” he says. Using high-throughput tools, he can monitor as many as 4,600 samples at a time, which he does to trace the network composed of clock genes. Ueda has fine-tuned the mammalian cells he uses in these experiments by introducing a receptor for light recognition, so his cells have literally seen the light. “We can control the clock in the cell by using light,” he says. “We can control the cell state … and then derive the mechanisms, the logic of the clock, by perturbation.” The careful monitoring and rigorous controls he employs for this result in comprehensive and quantitative data, he adds.

Ueda recognizes that his work stands on the shoulders of all those scientists who slogged through genetic experiments long before “high-throughput” was part of the lexicon. In the days when his own teachers and mentors were in grad school, “the focus was to identify the important genes,” he says. Thanks to their work, he doesn’t have to identify genes one at a time or seek out the most important genes — so his work can focus on examining these genes in large sets, or better understand them using quantitatively oriented research.

As his work evolves, Ueda says that he will incorporate developmental biology research as well, expecting to take on questions about how cells differentiate into various types of cells.

Looking ahead

A challenge facing current biology, Ueda says, is dealing with the question, “What is life?” He believes that “to address that question, we maybe need to create the cell.” That will require more than a little technology development, Ueda says, pointing to tools that would “produce functional proteins” as well as “manipulate the membrane and the membrane proteins” as just two examples of what would have to be invented before scientists can build their own cell from scratch.

Publications of note

Ueda has already contributed significantly to the scientific literature. Recently, he and John Hogenesch of the Scripps Research Institute were corresponding authors on a paper in Nature Genetics this year called “Requirement for feedback repression in mammalian circadian clock function.” In this paper, the authors discussed a molecular genetic screen they developed to identify mutants of two circadian transcriptional activators in mammalian cells, from which they demonstrate evidence that the mammalian clock function relies on transcriptional feedback.

In another paper entitled “An improved single-cell DNA amplification method for efficient high-density oligonucleotide microarray analysis” (published this year in Nucleic Acids Research), Ueda and colleagues describe a strategy that will globally amplify mRNAs from individual cells, using both PCR and linear amplification techniques, for analysis on an oligo-based array.

— MWS

Title: Head, Laboratory for Systems Biology, RIKEN
Education: PhD, University of Tokyo, 2004
MD, University of Tokyo, 2000
Recommended by: Hiroaki Kitano
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Kimberly Stegmaier is a pediatric oncologist who, frustrated with the still-elementary state of drug treatments for rare cancers affecting her patients, decided to take drug discovery efforts into her own hands.

Take acute myelogenous leukemia, for instance. AML cells are immature cells that spread like wildfire in bone marrow, incapable of becoming normal blood cells. “We actually know a lot about the molecular pathogenesis of AML, yet the treatment is still extremely primitive,” Stegmaier says. Currently, the only curative treatment available for AML is high-dose chemotherapy, which has terrible toxicity and an unimpressive cure rate. “We have treatments that haven’t changed much since the 1980s, so I felt like we really needed to have more of a focus on this in [academia] and we need to try and develop new tools to find lead compounds.”

Stegmaier considers the methods for doing small molecule screening rather limited due to their focus on either target-based screening or phenotype-based screening. Target-based screening requires prior knowledge of the particular biological process and the target of the process that needs to be altered. Phenotype screening is also limited because it requires new screens and assays every time there’s a new and complex biological question, she says.

Along with Todd Golub of Dana-Farber and the Broad, Stegmaier developed a way to work around these limitations using gene expression-based high-throughput screening. In this method, gene expression signatures serve as surrogates for various biological states. She and her colleagues were aware that a particular subtype of AML had good cure rates when treated with differentiation agents such as ATRA (all-trans retinoic acid) and cytotoxic drugs. It followed that other subtypes of AML might respond just as well. They started out using microarrays to define one signature for AML and another for mature white blood cells. Next, they looked for compounds that would trigger a change from the expression signature of leukemia to that of a mature white blood cell. After screening more than 1,500 chemicals, they arrived at eight compounds that reliably induced the gene signature of mature cells. Much to their delight, one of the most promising compounds they identified was gefitinib, an FDA-approved drug already in use for lung cancer patients.

Stegmaier is now applying this same approach to identify compounds that could be used to treat Ewing sarcoma. “We’ve been very excited about how this actually seems to be working—in that the platform is feasible and we can go from a screen concept to a candidate for clinical trial,” she says.

Looking ahead

Stegmaier hopes that in the next 10 years, cancer treatment modalities will be based on specific genetic information and not a one-size-fits-all mentality. She would like to see researchers and clinicians thinking more in terms of therapies that target genetic regions instead of being concerned with merely what type of tumor or cancer they’re faced with.

Publications of note

Stegmaier published a paper in a clinical hematology journal earlier this year entitled “Genomic approaches in acute leukemia.” This study traced how expression-based approaches to research have been used, with particular attention paid to hematologic malignancy. A signature-based screening approach, which eliminates the need to have prior knowledge, is also discussed.

The Nobel goes to...

Stegmaier hopes her legacy will be having a significant impact on disease through genetically targeted treatments that result in higher cure rates, better quality of life, and a longer relapse-free time. “That would be amazing ... to really have a clinical impact on disease,” she says.

Title: Pediatric Oncologist, Dana-Farber Cancer Institute
Education: MD, Harvard Medical School, 1996
Recommended by: Gary Gilliland
A
dolfo Ferrando has a mission to understand and eventually subvert the mechanisms of malignant leukemias. It’s an ambitious undertaking, but it’s one for which the physician-scientist seems well equipped — both in terms of clinical expertise and technological savvy.

Ferrando’s two-year-old lab at Columbia University is primarily engaged in teasing apart the cellular and molecular biology of aggressive malignant leukemias through the use of a variety of genomic tools, including expression arrays and ChIP-on-chip technology. Ferrando started work on this topic as a postdoc in Thomas Look’s lab at Dana-Farber. While in Boston, he also picked up powerful gene analysis techniques through collaborations with Todd Golub’s MIT lab. Ferrando is now interested in building on his postdoc work by “trying to decipher the actual effectors of the oncogenic program” in lymphoblastic leukemias, he says.

His team has found that a limited amount of oncogenic factors can turn on the program for human T-cell leukemia. The oncogenes operate by controlling the development of immune system progenitor cells, so it was a natural step to look into the activation of one gene in particular: Notch1, which is crucial for immune system formation. At Look’s lab, Ferrando’s research helped establish that Notch1 mutations were indeed involved in a high proportion of tumors. At this point, Ferrando’s team has “identified that Notch1 appears to be working as a key regulator of cell growth in T-cell development and T-cell leukemias.” The next step will be to fine-tune the extent of this role, with the ultimate goal of translating such a finding into clinical use.

To that end, Ferrando is at work on getting his new lab off the ground while generating data to support his research goals. These objectives may hinge on integrated analysis techniques, especially for expression and ChIP-on-chip data, which Ferrando cites as one of the field’s bottlenecks.

Looking ahead

Ferrando sees the field moving rapidly toward a point where the consolidation of data from disparate origins will help researchers investigate the functions of genes at the level of whole organisms, rather than only at the cellular level. It’s just what the doctors are ordering. “We need to understand how genes work, how tissues work, how organisms work — ultimately that will give us an amazing understanding of how to intervene and provide therapy for cancer and other diseases,” Ferrando says.

Publications of note

Ferrando’s postdoctoral work on the Notch1 gene helped establish that its mutations are involved in more than half of all T-cell acute lymphoblastic leukemias, as was reported in a Science paper entitled “Activating mutations in Notch1 in acute myeloid leukemia and lineage switch leukemias.” Ferrando went on to collaborate with Todd Golub’s group on a systematic expression analysis of several human cancers. This work, published in Nature last year, showed how microRNA profiling can be used for understanding molecular pathology and improving cancer diagnosis. Together these findings opened up a raft of new questions as to the mechanisms of Notch1 activation, as well as how to harness gene signaling inhibitors for therapeutic use. These are a couple of the directions Ferrando’s own lab is now pursuing.

The Nobel goes to …

Ferrando notes that although the Nobel is awarded for very basic science, his ideal findings “would have a very direct impact on global human health.” In his view, “the best Nobel Prize you could win would be the one where they wouldn’t know whether they were giving it to you on the science side, the medicine side, or on the peace side. That would be really amazing.”

— JC
It was at the urging of his PhD advisor that John “Trey” Fondon first came upon the question which he has pursued to this day. Fondon’s advisor, Skip Garner, suggested that he run their newly developed repeat polymorphism prediction algorithm on coding sequences to find human coding polymorphisms. At first, Fondon says, he was rather skeptical. “But when I saw the results, I was amazed.”

“It wasn’t just the large number of human proteins with slippage-prone repeats, but the identities of the proteins — Hox genes, BMPs, signal transducers — all genes whose names and roles were familiar to me from my background in developmental biology,” he says. The question that was staring him in the face: do these repeats facilitate evolution?

“Potential solutions to longstanding problems in evolution, such as D’Arcy Thompson’s transformations and the astounding speed of vertebrate evolution, suddenly seemed within my grasp,” he says.

Fondon has pursued this evolutionary question using dogs as a model system. “What we’ve learned is that dogs have this very interesting feature in their genome in that they mutate their microsatellites at a higher rate than humans or even cats do,” he says. He is currently using computer simulation to determine the conditions under which having such a slippery genome would be advantageous. The computer model takes into account factors like the size of a population and the cycle of climatic changes over the last few million years, and how those connect to changes in selection.

For Fondon, having a great core sequencing facility within arm’s reach is a boon to his research. Most of his budget is basically split down the middle between sequencing and mouse work. Although he says it would be nice not to have to fork over so much money for in-house sequencing, he is quick to point out that it’s the quality control and easy access that make the slightly higher cost worthwhile. “We really like to be able to walk over to the person actually doing the sequencing and talk to them about troubleshooting,” he says. Fondon and his team, who work with highly repetitive, GC-rich regions, are looking for microsatellites that are heterozygous. The problem is that these result in a very messy read, which most commercial sequencing outfits aren’t used to handling. “Advances in DNA sequencing that make it less expensive would be great, and they’re coming, and periodically we go and evaluate commercial sequencing companies,” he says. “But we don’t have much confidence in the data.”

Looking ahead

Over the next 10 years, Fondon would like to identify the possible mutations that allow for variation in how mammals evolve, as well as in their morphological variation. Fondon says it would be “a dream come true” if he could pair high-throughput morphological phenotyping of mice, dogs, and humans with morphometric software capable of analyzing skeletal elements. He also notes that measuring the dimensions of bones and other subtle mutational effects definitely slows down the workforce in his lab.

Publications of note

Fondon and his UT Southwestern colleague Skip Garner published a study in *PNAS* entitled “Molecular origins of rapid and continuous morphological evolution” which proposed their hypothesis on tandem repeats and evolution. The study presents a comparison of repetitive elements in the developmental genes of 92 dog breeds. The paper suggests that tandem repeat slippage mutations speed up the evolution process. The researchers used data from his study of DNA repeats influencing morphological variations in domestic dog breeds.

The Nobel goes to …

“Discovering the means by which genomes guide the evolution of their host organisms,” he says.

— MD
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Ever since his graduate days at the University of Michigan, Elliott Margulies has been just as interested in developing technology as he has in answering biological questions. That makes his new post in the Genome Technology Branch at NHGRI a perfect fit, he says.

His just-opened lab “focuses on trying to identify and characterize functional sequences that are in the human genome,” he says. His team is working on new approaches — both computational and experimental — to extract information from the genomes of multiple species and find patterns or alignments to indicate evolutionarily conserved sequences that are likely to be functional. “There’s strong evidence that because these sequences have stayed so similar over millions of years, that those bases must be important for something,” he says. And unlike searching for protein-coding genes or other well characterized genetic elements, “it’s a very unbiased way for approaching what parts of the genome might be functional,” he adds.

There is certainly no shortage of people in the field using evolutionary studies to track possible functional elements, but Margulies has plans to take the usual sequence comparisons a step further. “I’m going to be working on [trying] to develop new ways of looking at parts of the genome that have been conserved throughout evolution,” he says. Current studies focus entirely on the primary order of nucleotides, he notes, but little attention has gone toward the physical structure of the DNA in question. “We know that sequence has a three-dimensional structure to it,” Margulies says. “I’m trying to develop more sensitive methods that take the structure of the DNA into account” — in part by collaborating with scientists who specialize in DNA structure.

It’s no wonder Margulies is looking for new ways to compare DNA. Comparative genomics is an approach he has well in hand, not only from his postdoc position in Eric Green’s lab but also from his service, since 2004, as group leader of the ENCODE Consortium’s Multi-species Sequence Analysis Group.

Looking ahead

Margulies has a short wish list for his research: more sequence data. He believes the community is poised on the brink of a major change in how much sequence data is available. Right now, he says, “there are questions that we would like to be able to ask … but they require a tremendous amount of sequencing data, so we don’t even ask the questions.” But as promising new sequencing technologies ramp up output and slash costs, he says, “we’re going to see a completely new revolution of how we can ask genomics questions and how we can answer them. I’m hoping to ride that wave.”

That sequencing capacity will help increase the number of genomes that can be compared in functional studies, he adds. “I think we’re going to go way beyond comparing tens of genomes to comparing hundreds of genomes,” he says. “We also need newer technologies to figure out where these functions are, regardless of how they might be evolutionarily conserved.”

Publications of note

While Margulies has a number of papers currently submitted or in press, he feels that a paper published in 2003 "laid the foundation for a lot of the work I’m doing right now." That paper, entitled "Identification and characterization of multi-species conserved sequences," can be found in Genome Research.

And the Nobel goes to ...

Margulies hopes his crowning scientific achievement is “to find some function that the genome does that we never knew existed before.”

— MWS
Babak Parviz believes it's high time to get serious about applying readily available nanotechnology to genomics. "We have a lot of very interesting tools and capabilities that people have developed over the years [in the semiconductor industry]," says Parviz. "I think it would be wonderful to take advantage of these unique capabilities to make tools for biology to enable medicine."

Just head down to your local Best Buy, Parviz says, and you can find any number of cheaply made electronic products containing high-speed components smaller than an average virus. "We can now build microprocessors that have tens of millions of transistors, and chips that have billions of transistors," he says. "I think it's historic because we've never been able to make such complicated things work, and [now] they're available to us for just a few hundred dollars."

Parviz is currently leading an effort to develop a portable DNA sequencer using the same kind of commercially available semiconductor technology. The device functions on a quantum mechanics principle known as tunneling current, which can be measured when electrons move through a thin barrier that they normally shouldn't be able to penetrate. The sequencer works by placing a single strand of DNA on either a gold or graphite substrate that is then scanned with a platinum iridium tip. The tunneling current measurement provides an electronic signature that is then deciphered to determine the bases. "This is quite different from more conventional sequencing methods that involved quite a few steps of biochemistry," Parviz says. "There's no amplification; all the complexity has been shifted from biochemistry to electronics." His sequencer holds serious potential for both biological field research as well as personalized medicine.

But even with the most bleeding-edge nanotechnology and powerful microprocessors, Parviz still needs software. At some point, he would like to see the same kind of design simulation programs engineers have for logic circuit design made available for biochemistry. "I don't have any programs right now where I can ask, 'I want this molecule; tell me how to synthesize it,'" says Parviz.

Looking ahead

Parviz says there are still quite a few kinks to work out. "Electron transport through DNA, that's something people have worked on quite a bit, but we need to do more," he says. "We really need to understand this and be able to model it and use those models to figure out how to get our sequencing systems to work properly."

The top two priorities are figuring out how to properly develop parallel scanning probe microscopy — and how to do it cheaply. Although that has yet to be done with microfabrication, he says, it is possible. Parviz is equally confident that his portable sequencer will soon become a reality, cost being the only real stumbling block. "I'm actually quite confident that it will happen, but it remains to be seen if we can make it cheap enough, reliable enough, and profitable for people to use it out in the field," he says.

Publications of note

Parviz and his colleagues recently published a paper in PNAS called "Self-assembled single-crystal silicon circuits on plastic" in which they describe their approach to building complex microsystems for biological research. The researchers are using this same technology to develop thousands of individually controlled fluorescent microscopes at the microscale through self assembly.

And the Nobel goes to...

Babak Parviz would be quite pleased to accept his award for developing a way to electronically interface with millions of live cells and monitor and alter their action.

— MD
Leading the Legume Charge

It's not everyone who thinks of legumes as "a group of plants I just have a personal affinity for," but it's that interest that makes Steven Cannon especially happy to be at his post as a research geneticist at the USDA's Agricultural Research Service. "The main focus in this position will be soybean sequencing and assembly," he says. Most of the sequence will come from the Joint Genome Institute, "but because it's a big and complex genome it's going to require a lot of additional work" to whip it into a finished assembly.

Legumes represent the only plant family with three completed genomes — Medicago truncatula, Lotus japonicus, and now soybean — and that provides Cannon with an enviable vantage point. "We want to make all-by-all comparisons between those genomes, and out to other dicot genomes [too]," he says. As that work progresses, he adds, "we'd like to be able to correlate the genome structural comparison and evolutionary phylogenetic comparison for all of these gene families."

Cannon has background that may be unique in this field: before his days as a sequence-comparing fiend, he was an educational software designer working on projects such as the popular children's game Oregon Trail. While admittedly genome analysis can't be helped by knowing when to caulk your wagon and cross a river, Cannon says that his experience with interactive, multi-user games is important in establishing large-scale collaborations requiring biocuration "where each person is contributing a small piece."

The aspects to keep in mind, he says, are things like ontologies as well as "what are appropriate incentives for each person to contribute their piece of the Arabidopsis 2010 project? … Once you have the incentives right, how do you store and organize and provide access to this data?" he says. The traditional means revolve around publication and relying on scientists to keep up with the literature, "and I'm not sure that's the most efficient way," he says.

Looking ahead

The future holds massive genomic comparisons, says Cannon — and that includes much more than just sequence data. Right now, he thinks about making comparisons between four genomes, maybe five, he says. But as the price of sequencing drops, it'll be open season on generating terabytes upon terabytes of sequence data for organisms that aren't now considered a priority. Within the next couple of years, Cannon hopes to have "whole proteome sets for 10 species within the legumes" — a comparison that he knows dwarfs his current work on the three legume genomes. "It won't just be the gene sequences," he says. "If I'll be expression data" and whatever else biologists can get their hands on.

Publications of note

Cannon is the lead author on his most recent paper, due out soon from PNAS (it was published online in late September) called "Legume genome evolution viewed through the Medicago truncatula and Lotus japonicus genomes." In this paper, the authors report results of full-genome, sequence-based comparisons between Medicago and Lotus, including data about synteny, chromosomal relationships, and genome regions that don't seem to map across organisms. The team also reported evidence for a genome duplication that predated speciation between Medicago and Lotus.
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Jens Kurreck may have a master's degree in philosophy, but his focus has been firmly in the realm of empirical science for more than 10 years.

Kurreck received his doctorate at the Technical University of Berlin, where his research centered on the molecular mechanisms of photosynthesis. After spending a postdoc year in the United States, Kurreck joined Volker Erdmann’s lab at the Free University of Berlin. Since 1999, he has led the molecular medicine group in Erdmann’s biochemistry lab, where his team investigates the structure and function of RNAi molecules. Just this year, Kurreck completed his habilitation — Germany’s post-doctoral qualification for full professor status — and he’s now on the search for his first tenure-track position.

It’s a good bet that wherever Kurreck ends up professionally, novel findings on the frontlines of RNAi research will likely follow. As a lead investigator in Erdmann’s lab, Kurreck’s work has already resulted in unique discoveries on two fronts: the use of siRNAs as an antiviral tool and target validation in pain research.

In collaboration with Grunenthal, a Germany-based pharmaceutical company interested in developing new drugs for pain alleviation, Kurreck’s team “took a validated target — the vanilloid receptor — and optimized siRNAs and shRNA expression cassettes against it.” The idea was to identify silencing molecules capable of reducing pain sensitivity in animal models. The approach has been widely accepted as a means to prevent the emergence of mutant genes upon long-term silencing by RNAi, but Kurreck isn’t resting on his laurels. “Together with our cardiology partners, we also have a five- to 10-year prospective plan to [develop] therapeutic approaches for delivery of shRNA cassettes,” he says.

### Publications of note

In 2003, Kurreck reported an unbiased comparison of antisense and siRNAs, showing that “antisense oligonucleotides are better than conventional phosphorothioates, but siRNAs are even better,” he says. It was also in this paper, “Comparison of different antisense strategies in mammalian cells using locked nucleic acids, 2’O-methyl RNA, phosphorothioates and siRNA,” that Kurreck’s team first selected an efficient siRNA against the vanilloid receptor.

### Making of a great scientist

Kurreck’s recipe for successful science is simple: one must focus on the project at hand while forging fruitful collaborations. “Definitely an important part [of being a good scientist] is being able to share your enthusiasm with co-workers in the lab in order to create new ideas.”

— JC

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**Title:** Group Leader, Institute for Chemistry and Biochemistry, Free University of Berlin

**Education:** Habilitation, Free University of Berlin, 2006
Postdoc, Arizona State University PhD, Technical University Berlin, 1998

**Recommended by:** Muhammed Soheil
In his work to understand the genetics of chemotherapeutic resistance, Mike Hemann has two main objectives: to understand the key genetic determinants of drug response and to formulate strategies to overcome drug resistance. To do so, Hemann's team at MIT employs large-scale RNAi screening techniques with mouse systems of tumor development to generate mouse models that closely resemble human cancers.

Hemann's interest in tumor development dates back to his graduate research in Carol Greider's lab at Johns Hopkins, where he worked on telomeres and telomerase. "It was a fantastic graduate experience," he says, but there was just one drawback: telomeres in mice are very long, so it takes a long time — five or six generations of breeding — to see a phenotypic response to telomere dysfunction. "Whenever you want to make a combination of telomere dysfunction into another tumor-prone background, you add an additional year or two years onto an experiment," Hemann says.

At Scott Lowe's lab at Cold Spring Harbor, Hemann was able to work with a more tractable system, this time using the hematopoietic system to model tumor development. In early collaborations with Greg Hannon's lab, Hemann commenced postdoc work on finding a way to "use RNAi to knock down genes in vivo, in either an organ system or a tumor system in a recipient mouse."

These days, Hemann is working to expand his in vivo RNAi work using shRNA vectors to suppress and assess tumor development in mouse systems. Thanks to targeted RNAi libraries, Hemann's lab is able to assess the role of thousands of cancer genes in different tumors to an array of cancer drugs. "What we really want to do is get away from this idea of one gene to one mouse, or one knockout to one mouse, to where we can start to introduce complex lesions into an individual mouse, which really recapitulates what we see in [human] cancers," Hemann says.

Looking ahead

In order to really have an impact on human health, Hemann thinks that researchers need "more tractable models, specifically to model patterns of events as they're seen in human cancers." That's precisely where he sees the field headed. "We have spent a long time looking at germline mouse models of tumor development" such as single gene knockout mice or transgenics, he says — "but that's simply not how cancer arises in most people." For the most part, cancer stems from a small set of cells incurring genetic alterations in a normal system, he says, so the field continues to move toward introducing a complexity of alterations in model systems to "monitor fine changes at the stages of tumor development."

Challenges in the lab

Hemann says that his major research challenges are similar to those that accompany any kind of major genetic screen. "We face a lot of the problems that the traditional genetic screeners faced, which are issues of representation," he says. Key questions include determining the number of shRNAs that can be introduced into a system, he says, or ascertaining the power of such screens in vivo. "It's an even greater challenge when we talk about screens designed to look at tumor development," he says. Although the lymphoma system is relatively less problematic for studying tumor development, Hemann is effectively breaking new ground by taking these approaches into a mammalian system, which adds a whole new layer of issues.

And the Nobel goes to...

Hemann's ideal Nobel would be awarded for developing personalized cancer therapies. He says, "Cancer therapies for the last 50 years have been extraordinarily generic and based on tumor pathology, not molecular biology; we're now at a point where we can begin to determine what makes a given tumor respond or not respond [to treatment]."

— JC
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Michael MacCoss’ three-year-old lab is focused heavily on targeted proteomics — the result of frustration with fractionation techniques. “I had gotten some grant support to study the effect of the insulin signaling pathway in *C. elegans*, and how it affected protein turnover,” he recalls. “I figured we would just fractionate like crazy and monitor the turnover of all the proteins that we possibly could.” But 8 million MS/MS spectra later, “we identified no proteins in the pathway that we were interested in studying. That caused us to think a little differently about how we did it,” MacCoss adds. By using a more targeted approach using selected reaction monitoring to target specific proteins of interest, he says, “now we have methods that can, within an hour, measure all known components of the pathway.”

But the mass spec wunderkind didn’t start out in proteomics; he credits his entry to the field to meeting John Yates while he was an intern working with Pat Griffin at Merck Research Laboratories. Yates was just starting his own lab at the time, and MacCoss headed back to the University of Vermont, where he did his graduate work in Dwight Matthews’ lab on a project developing “technologies for measuring amino acid metabolism using stable isotope tracers in humans.” After that project wrapped up, he realized that proteomics had grown to be the monkey on his back — so he contacted John Yates and asked to be a postdoc in his lab.

His work with Yates would shape MacCoss’ early career. In fact, his own lab at the University of Washington is situated in what used to be Yates’ lab there, and MacCoss contends that his work at the Yates lab is “the main reason why I was even considered” for his current position at Washington. Indeed, MacCoss says Yates has been such a supportive mentor to him that when he has questions even today, “he’s still one of the first people I ask.”

At that lab, MacCoss and his crew are gearing up to make the transition from model systems — *C. elegans* and yeast, in particular — to human studies, thanks to the biomarker work they’re just beginning. His team will use rodent studies as the stepping stone to human systems, he says.

The MacCoss lab is also knee-deep in technology development projects. In a collaboration with David Muddiman from North Carolina State University, MacCoss’ team is testing technology from the Muddiman lab that “increases the number of ions that make it from the air into the vacuum system,” MacCoss says. The goal, of course, is to increase the ion transmission in mass spectrometers.

Looking ahead

MacCoss says that targeted proteomics will be the way to go, and points in particular to Leigh Anderson’s work as a great example of it. As far as technology goes, he says the field needs to address the critical problem of speed before proteomics can make the impact its proponents believe is possible. “Right now, most comparisons are done just by comparing two or three samples,” he says. That needs to be upsed to tens or even hundreds of samples, but “using technologies that take a day of instrument time per sample isn’t going to cut it.” MacCoss says the ideal tool would have “the peak capacity of MudPIT but could be done in about an hour.”

Title: Assistant Professor of Genome Sciences, University of Washington

Education: PhD, University of Vermont, 2001
Postdoc, Scripps Research Institute

Recommended by: Steven Carr, David Muddiman

Publications of note

MacCoss recently published “Analysis of peptide MS/MS spectra from large-scale proteomics experiments using spectrum libraries” in *Analytical Chemistry* (2006 Aug 15) in which he and his colleagues demonstrate searching peptides against a library instead of a database.

— MWS
Armed with a PhD in physics and a desire to apply his technology savvy, Alexey Nesvizhskii is shaping a career around seeking out the more interesting questions in science. This drive led him to bring his expertise to proteomics, specifically in the development of computational tools to parse out the seemingly endless stream of data generated by mass spectrometry-based technologies.

“This is a really active field,” he says, “and when you have an active field [in which] people are developing new technologies, new chemistries, new ways of generating data — they end up with data and no really good way to analyze it. That’s where I come in.”

Nesvizhskii dove into this proteomic imbroglio first as a postdoc and later as a research scientist in Ruedi Aebersold’s lab at the Institute of Systems Biology. There, he worked to develop algorithms and computational tools for processing and validating proteomic data, as well as for mining and integrating information derived from proteomics, genomics, and metabolomics. He’s continued to extend these approaches at his current post in the University of Michigan’s pathology department. “Probably most applications are going to be disease-related,” he says, “but the methods can be applied in general to proteomic data generated from model or human systems.”

In his current work, Nesvizhskii says that identifying post-translational modifications from mass spec-based data is an increasingly salient problem, especially considering his new clinical post and the relevance of phosphorylation and glycosylation to cancer. His aim instead is “to go beyond this typical proteomics-based approach, where you collect data and compare it by searching across databases to identify peptides and proteins.”

Looking ahead

Nesvizhskii sees the field moving toward more targeted analyses, by which researchers may evaluate data they’ve accumulated to seek out interesting trends that will dictate strategies taken at the experimental level. He notes that earlier researchers were more interested in exploring the proteome and seeing what could be identified using mass spec. “In the last five years, we’ve realized that there are a lot of challenges in terms of the dynamic range,” and that getting down to the level of biologically or disease-relevant proteins is the current challenge.

Publications of note

Nesvizhskii, along with co-investigators at ISB, pioneered a method designed to increase the amount of information that can be extracted from MS/MS datasets. The method picks up spectra where conventional sequence database searching falls short, with the result that iterative searches can pave the way to new insights drawn from existing datasets. The paper, entitled “Dynamic spectrum assessment and iterative computational analysis of shotgun proteomic data,” published in Cellular Proteomics earlier this year.

Last year, Nesvizhskii co-authored a paper with Ruedi Aebersold reviewing the difficulties of interpreting shotgun proteomic data. This kind of data is “peptide-centric,” the authors wrote in Molecular and Cellular Proteomics, leading to problems in determining the true nature of proteins in a sample. Aebersold and Nesvizhskii also touched on the state of protein sequence databases, and the need for a common computational infrastructure to integrate proteomic and transcriptional data.

How to succeed in science

“If you’re a computational scientist like me, the key is to be really interdisciplinary, to know as much as you can about biology so you can speak the same language [as biologists], and, at the same time, to know as much as you can about technology so that you can suggest ways to design experiments,” Nesvizhskii says.

— JC
Martin Larsen says that his forte is mass spectrometry methods development, which is a brief explanation for a wide research mandate. His team of three graduate students and one technician at the University of Southern Denmark works on the development of techniques to characterize phosphoproteins and glycoproteins, as well as to elucidate the molecular mechanisms responsible for beta cell destruction in insulin-dependent diabetes mellitus.

One such technique that Larsen is putting the finishing touches on before submitting for publication is “basically a method to pull out sialic-acid containing peptides from very complex samples.” Sialic acid-bearing glycoproteins are implicated in many human diseases, such as metastatic cancer, so the approach itself “has nice potential for biomarker discovery,” he says.

Larsen was introduced to this corner of proteomics by Peter Roepstorff, who supervised Larsen’s doctorate work at Odense University. Roepstorff remains an influence on Larsen’s work, as does another collaborator based in Australia.

“I did a postdoc in the Australian Proteome Analysis Facility, and there I met this guy who had lots of ideas,” Larsen says. “It turned out that he’s also very, very clever.” That clever collaborator and friend is Philip Robinson, head of the cell signaling unit at the Children’s Medical Research Institute in Westmead. Robinson and Larsen have occasion to brainstorm in person at least once a year, as they both review for the *Journal for Biological Chemistry*, which brings them together for annual editorial board meetings. “I always come home with lots of ideas,” Larsen says.

**Looking ahead**

Larsen is hard-pressed to predict where proteomics may be headed in the years to come, only because the field is developing at such a fast pace. “I almost wish it would go slower so that we would have the time to actually find and read all of the nice articles that are coming out these days,” he says. Because of his group’s wide remit, which includes projects on phosphorylation, glycosylation, biomarker discovery, and mass spec, he says that “there are simply too many things to keep track of.”

That said, Larsen does voice a request for the future of methods development. “If you want to do as much quantification as possible,” he says, “you need more than one quantification technique … so it would be really nice to have a robust method for quantification.”

**Publications of note**

Earlier this year, Larsen reported the identification of seven new phosphorylation sites in spinach stroma membrane via the use of illumination. To purify the light-derived phosphopeptides, Larsen’s team developed a sensitive method using titanium dioxide microcolumns, which results in minimal non-specific binding and can contend with even complex mixtures. In most cases, Larsen says, this method returns “between 70 and 90 percent pure phosphopeptides.” Details of the method can be found in a paper appearing in the *Journal of Proteome Research*.

Last year, Larsen’s work with Peter Roepstorff resulted in a paper describing a newer, faster, and more sensitive technique to characterize low amounts of glycoproteins. Published in *Molecular and Cellular Proteomics*, the paper calls for the use of sequential specific and non-specific enzymatic treatments to reduce the peptides, followed by microcolumns packed with graphite powder to isolate the small glycopeptides.

— JC
In some circles, it’s probably enough to say that Joshua Coon did his postdoc in Don Hunt’s lab to illustrate the potential of this young mass spectrometry expert-in-the-making. But for everyone else (not to mention for the sake of filling this page), some elaboration is in order.

Coon, who set up his lab at the University of Wisconsin about a year ago, is looking to make waves in the proteomics community. To be fair, he’s already started that thanks to his work on a technique known as electron transfer dissociation, or ETD. He was involved in that project with John Syka, another UVA scientist, while in Hunt’s lab — and since then, the novel ion fragmentation technology has been exclusively licensed to Thermo Electron.

The goal of ETD, and the big need for proteomic scientists in general, is to enable the analysis of larger peptides or even whole proteins by systematically breaking them up at specific sites in the protein. “There’s a pretty big limitation in current proteomic technology,” says Coon: modern proteomic tools chop proteins into such tiny fragments that their context in the original protein is lost. That means larger motifs, such as peptide or protein patterns and alternative splicing, are “for the most part invisible right now,” Coon says. As many as three-fourths of all proteins are expected to have a splice variant, and many proteins will have several splice variants, he adds. But a single peptide under analysis in a mass spec is likely to be common to all splice variants, so today scientists can’t tell the various protein personalities apart. “This is the level of detail that is missing from today’s proteomic analysis,” Coon says. “What is the context [of these peptides]?” To that end, Coon’s lab will be busy “working on new tools that will analyze large peptides or even whole proteins,” giving scientists “a better chance [to] detect very relevant events,” he says.

But technology development won’t happen in a vacuum in Coon’s lab, where proteomic work in developmental and stem cell biology represents the applied half of his projects. Coon’s team is collaborating with other Wisconsin scientists to analyze the proteomic changes that take place when, for instance, “an embryonic stem cell commits to differentiate and goes into a specific lineage,” he says. Understanding post-translational modification patterns and fleshing out the signaling pathways in stem cells will be top priorities.

Looking ahead

Traditional proteomics is simply not going to allow scientists to understand exactly what proteins are doing and how they’re doing it, Coon says. The ideal technology for this field would have “the capability to characterize all proteins from a biological sample in their intact form, and … do that with a dynamic range of 10⁹,” he says. It’s only with that kind of dynamic range that researchers will be able to “see the very abundant things and the single-copy-per-cell things,” he adds, noting that being able to study intact proteins will be an essential step for scientists in this discipline. “That’s not easy,” he says. “That’s the next frontier.”

Publications of note

The best way to get a good idea of what Coon will be up to is to read “Advancing proteomics with ion/ion chemistry,” a review he wrote for BioTechniques (June 2006). “It’s intended for a wide audience,” Coon says, “and describes my vision.”

And the Nobel goes to …

Coon knows that no matter how interesting technology development is, it’s not the ultimate goal of all this work. That’s why he says he’d like to accept the Nobel for “a key contribution to understanding developmental biology and stem cell differentiation and lineage commitment.”

— MWS
Frank Grützner was introduced to lab research and chromosome evolution earlier than most. Even before going to college, Grützner had a chance to dive into research on human and animal chromosomes at a human genetics institute in his native Germany. By the time he was an undergrad in Freiburg, he was already hooked on studying the evolution of chromosomes.

From that point, Grützner went on to do a doctoral degree at the Max-Planck Institute of Molecular Genetics in Berlin. It was a fairly young institute then, and the interactive environment fostered Grützner's interest in "comparing evolutionary with pathological aspects of genome change." As a grad student, he was also fascinated by interspecific hybrids, by which he could view the results of two divergent genomes conflicting in one animal. His main project involved pufferfish chromosomes, for which Grützner set up a technique called chromosome microdissection to physically isolate DNA and recover clones and genes for regions of interest.

Doctorate in hand and comparative genomics specialty in place, Grützner felt the call of Canberra. He had met Jenny Graves at a seminar in Freiburg and, knowing well her comparative genomics work, decided to get in touch for a postdoc position. Graves took him on at her lab at the Australian National University. There he imported the chromosome microdissection technique, and also mastered the art of chromosome painting for taking a closer look at platypus chromosomes, which he says were "difficult to distinguish and [remain] unresolved." The technique helped the researchers uncover a "complex sex chromosome system" in platypus, and also allowed them to follow those chromosomes through stages of meiotic cell division.

Grützner's newly minted lab is now extending this chromosome work by focusing on the sex determination and embryology of the platypus. It's not easy work, Grützner says, as "things just don't work as easily in more distantly related species as they do in human or mouse." But when things finally do come together, Grützner says, "you normally discover something new" — and that's as good a payoff as anyone could want.

Looking ahead

"People are seeing that just having sequence information is not enough," Grützner says, pointing out that researchers are more eager than ever to peer into nuclei to see how complexity in a genome translates into myriad behaviors on the level of organism. The tools and techniques of comparative genomics may well shed light on these phenomena, he says. It doesn’t hurt that evolutionarily divergent species, such as the platypus, are great for "unraveling the conserved functions of individual genes and regulatory elements," he says.

Publication of note

During his PhD, Grützner was involved in work that showed that chicken and mammalian sex chromosomes are not homologous, suggesting that they evolved independently. This proposal was blown out of the water a couple of years ago, when Grützner's work on platypus essentially provided an evolutionary link between mammals and birds.

Using chromosome paints, Grützner and the Graves-led team tracked male platypus sex chromosomes as they form a meiotic chain — a very rare setup in vertebrates — that sports regions that are homologous at one end and human X on the other. The full story on the organization of this sex chromosome system is reported in *Nature* in 2004.

Grützner's current work builds on this, which he considers "an amazing system to look at the evolution of sex determination and to possibly identify new sex-determining genes in humans and other mammals."

— JC
Joshua Akey was interested in genetic variation long before he had filled out an application to graduate school. “Even when I was a kid, the thing that fascinated me the most was just looking around and seeing how much variation there was between humans, animals, and just different species in general,” says Akey. That fascination grew after his undergraduate days in a population genetics lab. “I quickly became appreciative of the perspective that population genetics and evolution has on explaining phenotypic diversity and natural populations,” he says.

Now that Akey has his own lab, he’s set about trying to explain the connection between genetics and natural diversity. The goals of his lab are to gain an understanding of genetic variation patterns within and between species and by doing so, to address some fundamental problems in biology and evolution. Currently, Akey is conducting genome-wide analyses to uncover evolutionary forces that have shaped the human genome as well as the dog and yeast genomes. “In our human studies, we have primarily been focusing on identifying regions of the genome that have been affected by natural selection and then trying to correlate patterns of selection with patterns of phenotypic variation, ultimately connecting this to disease susceptibility,” says Akey.

He hopes to gain an understanding of the genetic structure of human populations and identify genes that result in disease susceptibility. “Signatures of selection delimit regions of the genome that are functionally important so by finding such regions, it might help to narrow in on places that are relevant to disease,” he says.

Akey is also interested in the incredible amount of variation across the canine species, which contains more than 400 different breeds. “I’m really fascinated by looking at the evolutionary history of dogs because of their extreme amount phenotypic diversity,” he says. So far, his lab has collected roughly 150 dog samples from 10 different breeds and has begun to integrate the signature of domestication in dogs, leaving him one step closer to illuminating how man’s best friend became so friendly.

Publications of note

Earlier this year, Akey and his partners published a paper in Human Molecular Genetics entitled “TRPV6 exhibits unusual patterns of polymorphism and divergence in worldwide populations.” For this study, the researchers conducted a population genetic analysis of TRPV6, a calcium-permeable ion channel believed to mediate part of the calcium absorption process in humans. The paper showed that the rate of the channel’s evolution is accelerated in the human lineage, but only for a haplotype defined by three non-synonymous SNPs that are virtually fixed for the derived alleles in non-African populations. Their data suggested that the TRPV6 haplotype has a selective advantage that varied spatially during human history.

Looking ahead

Akey says that locating hundreds of gene loci that appear to have been targets of natural selection is no problem. The stumbling block lies in moving beyond what he calls “superficial” genome-wide analyses and understanding the evolutionary history of each locus. “I think it’s really important to begin to have more in-depth, focused studies on these regions, because otherwise you’re left with this kind of unsatisfying list of places in genomes that might have been subject to selection — or maybe they’re just outliers because of the nature of evolution,” says Akey.

For Akey, writing a Perl script and looking through the genome for unusual patterns of variation is easy. The hard part is connecting that variation to a functional effect and phenotype. “I think that the next five to 10 years will be spent in following up these analyses that have arisen from a genomics perspective and then actually understanding the biology and biomedical significance associated with them,” he says.

— MD
Adam Siepel is developing algorithms to identify novel functional elements in mammalian genomes, with a focus on the human genome. He is zeroing in on new protein-coding genes, RNA genes, and regulatory elements. Through simultaneous modeling and analysis, he aims to reveal how evolution and function interact to affect genomic sequences.

Siepel has always been fascinated by the intersection of mathematical methods and models of living systems, but says he’s had a rather circuitous route to his present position.

Upon graduating from Cornell with a dual major in agriculture and bioengineering, Siepel began work in the Los Alamos National Laboratory doing HIV sequence analysis. After working as a software engineer in the late ’90s, he decided to get back to science and pursue his PhD with David Haussler at Santa Cruz. His timing couldn’t have been more perfect.

“The comparative analysis of the human and mouse genome was going on and Santa Cruz was heavily involved in that... It really was a great area for me because it involved a lot of creative algorithms work and it also involved a lot of evolutionary analysis,” says Siepel. “It was an area that’s time had come.”

While working in Haussler’s lab, Siepel designed a program called Exoniphy, which predicts evolutionarily conserved protein-coding exons from multiple aligned genomics sequences. The program discerns between coding and noncoding sequences using the phylogenetic hidden Markov model and other techniques. Siepel and his collaborators identified thousands of potentially novel human exons after running the program on alignments of the human, mouse, and rat genomes.

Siepel is also known for leading development of PhastCons, another hidden Markov model-based program. Using PhastCons, Siepel and his team have conducted one of the most extensive studies to date of conserved elements in vertebrate, insect, nematode, and yeast genomes. They found that as organism complexity increases, larger fractions of conserved bases fall outside of coding regions, potentially reflecting the increasing importance of regulatory functions.

“We’re working on really basic scientific questions which I think ultimately affect all of biology, although the impact is not always immediate,” he says. “So one of the things I’m working on is filling out the catalogue of human genes. There’s still a lot of human genes that aren’t yet known, and that just has a lot of obvious consequences for biology and medicine.”

Looking ahead

Siepel would like to see evolutionary biology, comparative genomics, and population genetics join forces in the near future. Population genetics has a lot of potential for detecting selection and understanding changes that take place over shorter time scales within populations, says Siepel. “I think there’s a general feeling that those two areas need to come together,” he says. He would also like to see more of a systems biology approach take hold in his field. “We’re still just trying to identify the sequences in the genome that are important for one reason or another and trying to annotate them,” he says. “But it’s clear that we need to move a lot farther in terms of understanding how they interact and actually result in living organisms.”

Publications of note

In 2005, Siepel and his colleagues published a paper entitled “Evolutionary conserved elements in vertebrate, insect, worm, and yeast genomes.” This Genome Research paper introduced PhastCons as a method for identifying evolutionarily conserved sequences, now widely used in the comparative genomics community.

And the Nobel goes to...

Siepel says if he were to win the Nobel Prize, he hopes it would be for “fundamental contributions to the functional annotation of the human genome.” — MD

Title: Professor, Biological Statistics & Computational Biology, Cornell University

Education: PhD, University of California, Santa Cruz, 2005

Recommended by: Eric Green, David Haussler
A
tul Butte and his team are tasked with developing methods to integrate disparate disease-related data sets garnered from more than 30 types of high-throughput measurement technologies currently available. Butte sees his mission as pushing nosology, the disease classification system first developed in the 18th century, into the 21st century via a genomics approach. He believes that the nosology system still in use today is long overdue for a genomics overhaul.

That's why Butte and his team set out to develop a genomic classification scheme for medicine called “genomed”: genomic nosology for medicine. “Why don't we think about classifying diseases based on genomics?” Butte says. “Instead we use symptoms: all the cancers go together, or things that cause headaches go together, but it has nothing to do with modern science.”

His team's aim is to develop an automated network capable of drawing inferences across the breadth, depth, and width of molecular biology data, including entire sets of transcripts, proteins, and genes. Butte, who is also a physician, is primarily concerned with bringing his integrative methods to bear on what he sees as the coming health crisis: obesity and type 2 diabetes mellitus. Currently, his lab works in conjunction with the Joslin Diabetes Center on integrating multiple types of genome-scale data across experiments and phenotypes to identify genes involved in these diseases.

To begin the momentous task of reclassifying diseases based on genomic data, Butte and his lab will collect disease-related data sets from international repositories such as the Gene Expression Omnibus, which has more than 100,000 microarray samples. “What we did was literally download every single experiment that's out there, we figured out every single piece of experimental details that they've done: Did they look at aging? Did they look at injury? Did they look at leukemia? We were trying to figure out the experimental context using microarray annotations and figure out the gene measurements simultaneously,” Butte says. He and his team have written software that correlates the experimental descriptions and codes them according to a structured vocabulary built by the National Library of Medicine.

Looking ahead
Butte would like to see bioinformatics eventually move away from a service mode to exploring the seemingly endless connections among disease data. But the hurdle practitioners face is finding a lab collaborator to validate those findings. “I see too many bioinformaticians just working on the next great method to analyze microarray data, or the next best way to analyze mass spec data from proteomics, but instead they could ask a question like 'What's in common between this disease and this disease?'” says Butte. “You're not beholden to any one biologist, and when you have an idea about a disease, you go to a biologist and say ‘You know, I've got 100,000 microarrays and I feel that these genes are in common and this is what it means, wouldn't you like to help validate me?’ I bet no one would say no to that. It puts you in the driver's seat.”

Publications of note
This year, Butte and Isaac Kohane published a paper entitled “Creation and implications of a phenome-genome network” in Nature Biotechnology. In it, they used what Butte calls “traditional informatics tools,” such as ontologies and structured vocabularies, to connect every part of every disease and environmental factor to the genes that go along with those factors.

And the Nobel goes to...
Butte would like to accept his Nobel for “finding a cure for type 2 diabetes mellitus by applying methods we created for use in integrative biology.”

— MD
Ben Raphael wasn’t looking for an opportunity to apply his algorithmic and computational know-how to cancer research. It found him, and he’s grateful.

Back in 2003, Raphael was busy examining rearrangements of the mouse and human genome in an evolutionary context when a group from the University of California, San Francisco, approached him with an unexpectedly scrambled cancer genome. “It actually happened somewhat serendipitously,” remembers Raphael. The researchers, having analyzed the genome using clone end sequencing, were surprised with the results, having based their expectations on earlier cytogenetic studies. So Raphael began helping to develop computational techniques to analyze the mixed-up data.

“It’s been quite a lucky thing for me to be part of such a great collaboration. Starting this project really set me on this direction, which is now becoming a pretty hot area,” he says. His initial work on the tumor data produced the first high-resolution reconstruction of a tumor genome. He has continued to develop algorithms for genome rearrangement analysis using clone end sequence profiling. By understanding the large-scale changes that take place in tumor genomes due to extensive rearrangement, he hopes to contribute to the development of targeted cancer treatments. With many sequencing centers now shifting their focus toward cancer and tumor sequencing, Raphael believes that genomic cancer research will receive quite a boost. “I got involved a couple of years ago, slightly before it was becoming a big thing,” he says. “And I think it’s really kind of at this tipping point where there’s going to be a lot of exciting things coming out in the next few years.”

Raphael’s other main focus is producing algorithms to address DNA and protein sequencing problems, such as multiple sequence alignment and motif finding. He recently helped to develop a new method for multiple sequence alignment called A-Bruijn Alignment. According to Raphael, ABA is an improvement upon similar algorithms for multiple sequence alignment because it permits the alignment of sequences with self-similar or shuffled subsequences.

Looking ahead

Raphael is eager for the day when people can walk into the clinic, have their tumors sequenced, and get information on the important mutations that point to a specific treatment program within minutes. But until that time, he is looking forward to tackling the computational problems associated with sequencing tumor genomes. “When you’ve got something like a cancer genome where there’s extensive duplication, it’s even more challenging,” he says.

— MD

Title: Assistant Professor, Center for Computational Molecular Biology, Brown University

Education: PhD, University of San Diego, 2002

Recommended by: Bud Mishra

Publications of note

Early this year, Raphael and his colleagues published a paper in Genome Research called “Decoding the fine-scale structure of a breast cancer genome and transcriptome.” The study demonstrated advantages of end sequence profiling to map the rearrangements of tumor genomes using the MCF-7 breast cancer cell line; those include the ability to generate tumor-specific reagents for in vitro and in vivo studies as well as detection of rearrangement and copy number changes.

— MD
Heidi Rehm’s longtime enthusiasm for genomics lies in the potential to bring bench work findings to the clinic. “I’ve always been interested in genetics, since I was a young child,” says Rehm. “Throughout my life, I’ve wanted to see the practical applications of genetics.”

After finishing her PhD, Rehm became a board certified molecular geneticist. “Basically that means I can run a molecular diagnostic lab and sign out patient cases,” Rehm says. She is involved in both research and developing diagnostic tests for diseases of hearing loss and cardiovascular disease. With the help of an NIH grant, Rehm is currently validating a hearing loss microarray to test for deafness. Earlier this year, she helped launch the first genetic test in the US for Usher syndrome, a disorder that involves both hearing loss and retinitis pigmentosa, a genetic eye condition that causes gradual blindness. “It’s pretty devastating because the families initially don’t realize that they have Usher syndrome, they just think that they have isolated hearing loss, which is much more common,” she says.

Rehm and her colleagues were able to translate data collected by other researchers on this disorder into clinical reality. Recent studies have shown that the ability to diagnose Usher syndrome in its early stages greatly increases the chances of being able to delay blindness through dietary changes.

Rehm has also been involved in an effort to determine the cause of an early childhood hearing loss syndrome due to a gene called Connexin 26. Rehm and her colleagues have tested hundreds of patients with hearing loss for various genes and characterized their phenotypes. Her lab is also the first to offer a clinical screen for hypertrophic cardiomyopathy, a heart disease that causes sudden death. The test, which looks for a number of different genes, requires three screens and costs upwards of $5,000. “There are some cases where insurance companies will pay for some or part of it, but in many cases they won’t,” she says. “The test is very limited in terms of who can get it — yet it’s our highest volume test because there’s very direct clinical utility.” But regardless of the scarcity of some of these tests, Rehm is dedicated to bringing personalized medicine to patients by integrating genomics into clinical medicine and practice. “That’s really mine, and the center’s, major goal: realizing personalized medicine,” she says.

Looking ahead

While Rehm is committed to getting to personalized medicine, she acknowledges that until sequencing technology gets a little cheaper, launching a test that can be afforded by patients and insurance companies is still a challenge. “It’s a combination of convincing insurance companies to pay for genetic tests and bringing the technology to a point that makes it affordable,” she says.

Publications of note

In a paper entitled “Connexin 26 studies in patients with sensorineural hearing loss,” Rehm and her colleagues tested children with sensorineural hearing loss or mixed hearing loss for mutations in the entire coding region of the Connexin 26 gene. The patients that were tested had no obvious etiology for their hearing loss. The results found that Connexin 26 mutations were most common in children with sensorineural hearing loss and patients with biallelic Connexin 26 mutations had a higher incidence of milder hearing loss than in previous studies. The study, which was published in the Archives of Otolaryngology — Head & Neck Surgery, recommended that children with sensorineural hearing loss or mixed hearing loss should be tested for Connexin 26 mutations early in their evaluation.

— MD
The fascination with duplication-rich regions of the human genome hit Tera Newman during graduate school. “That was before everything had been sequenced, but it was obvious that there were these regions of the genome that were duplicated,” she says. “I came to realize that these were incredibly plastic and dynamic regions of the genome, and they were likely to be associated with large-scale structural changes.”

After completing her PhD, that fascination led her to the recognized expert in the duplication field: Evan Eichler. She joined his lab as a postdoc and is currently conducting a nucleotide-level analysis of the break points of common structural variation in humans. She is particularly interested in the mechanisms behind the creation and insertion of these deletions and inversions. “On average there may be as many as 150 to 200 structural variant sites that differ between any two humans. These can range in size from 8 kb all the way up to 200 kb,” Newman says. She adds that anywhere from half to two thirds of those sites are most likely common among humans. “What we are talking about here is really common changes that are potential very large [and] that have some genetic impact in the population,” she says. “These are genes that may play a role in phenotype such that one person can better tolerate the carcinogens from smoking compared to another person; it’s fine-scale variation leading to subtle differences in phenotype.”

The practical applications of her work immediately point to answering questions about which segment of the population will respond favorably to a particular drug and why. “The most important thing we want to try and decide is which of these changes are going to be important at a phenotypic level, so which of these changes really make a difference for how someone metabolizes a drug, for example,” she says.

“We’re good at finding these variant structures,” she adds. “But tying the structures to function is difficult because there are a lot of variables in the biology.” Taking one change in the DNA and discerning what it means to an organism at the molecular level is the real challenge, she says.

Looking ahead

Newman expects that the next three to five years will be spent cataloguing all structural variation sites that exist between humans. After the discovery phase, the next step will be pinning down which structural variant connects to which biological trait. “I think we’re going to spend a lot of time out front figuring out what they are and then we’re going to spend a lot more time figuring out why they matter,” she says.

In thinking about technology needs, she says that both faster sequencing — getting a genome in two hours — and a nanotechnology that would follow a protein or chemical through the body to provide a glimpse of all the interactions that it has with a cell in its normal life cycle would be vast improvements for the field.

Publications of note

In the paper “High-throughput genotyping of intermediate-size structural variation,” published in Human Molecular Genetics, Newman and her colleagues describe a pilot study to launch a high-throughput method to correlate differences in individuals with various phenotypes. The study attempted to answer whether structural variation between humans relates to disease susceptibility or other important traits.

And the Nobel goes to...

Newman says discovering structural variants might not warrant a Nobel Prize. But she does think that investigating structural variation could get us closer to big questions about why species diverge from each other. “A goal of my future is to try and see whether or not structural variation has been a factor in speciation in the past,” she says. — MD

Title: Postdoctoral Fellow, University of Washington, Eichler lab
Education: PhD, University of Washington, 2004
Recommended by: Evan Eichler
When Holger Kirsten evaluates technology, such as the mass spectrometry-based genotyping tools used in his lab, he doesn’t just think about how well it works in the lab — he’s also looking at how robust the instrumentation is and asking whether it will fit in a clinical setting.

Kirsten knows that the final goal for even the basic research going into association studies and SNP tracking is to hit the clinic and have a real impact on the medical treatment people receive. A member of Peter Ahnert’s molecular diagnostics lab at the University of Leipzig, Holger and his colleagues are working to uncover the genetic mechanisms behind common but complex diseases, such as rheumatoid arthritis and systemic sclerosis. They use various technologies, including what Kirsten calls “mid-throughput MALDI-TOF” and tandem mass spectrometry, to evaluate genotypes and carry out association studies.

Kirsten says the lab currently doesn’t have the power to do whole-genome association studies, so he and his teammates are using the candidate gene approach. In one project, he’s studying about 30 candidate genes in a population of about 500 samples. Kirsten notes that complexity increases in bridging genetic characteristics with phenotypic ones, and that’s an area he’d like to see become more tractable in the field. A disease like rheumatoid arthritis, for instance, is likely to be detectable as several different genetic subtypes which are confusingly presenting in patients as a single phenotype. Treatment options and efficacy stand to improve by leaps and bounds if scientists and clinicians can clear that hurdle.

It’s that very view of disease as a complex connection between genotype and phenotype that lured Kirsten into this scientific path, he says. As his work — and the research going on in the rest of the community — progresses, he hopes to see a continued emphasis being placed on the integration of “genomic data with the mRNA and expression data and with network construction” to really get a comprehensive and clear view of how diseases function. “That’s a very exciting and also demanding aspect of getting new knowledge,” he says.

Kirsten credits Ahnert, his lab head, with providing an environment that encourages innovation and scientific exploration. “If you’ve got an idea, you get a certain amount of resources to follow [that] idea” — even if it’s not really related to the focus of the rest of the lab’s work, he says.

Looking ahead

This community places a high priority on both collaboration and open access, two values that Kirsten has taken to heart. He believes that the pharmacogenomics field will succeed only if “different groups really pool their resources together … to understand or be able to detect complex disease,” he says. But he also knows that collaborations are only as good as the data they have access to, so he encourages all researchers to make their data as openly available as possible. He notes that his group publishes data from its experiments — “even the primary data from the first experiment,” he says.

Publications of note

Kirsten is first author on a paper titled “Robustness of single-base extension against mismatches,” currently in press at the *Journal of Molecular Medicine*. Earlier this year, he was first author on another paper, this one in *BioTechniques*. Entitled “CalcDalton: a tool for multiplex genotyping primer design for single-base extension reactions using cleavable primers,” that paper came out in February 2006.

And the Nobel goes to …

Kirsten skips right past the Nobel for scientific or medical achievement. If he wins the Nobel, he’d like it to be the peace prize, he says.

— MWS
Marilyn Ritchie’s lab at Vanderbilt is focused on pinpointing susceptibility genes for common, albeit complex, human diseases. These run the gamut from hypertension and cardiovascular disease to diabetes and cancer. To make sense of the gene and protein expression data that fuels her search, Ritchie resorts to a home-grown arsenal of statistical techniques and computational tools to make meaning of gene-gene interaction or whole genome association data.

One such tool in development is a research platform designed to integrate multiple analytical techniques at the same time. “The idea is that no one method is going to work best for all data,” Ritchie says, “so we’re trying to combine the successes of lots of different groups … so that we can intelligently do analyses of whole genome association data.” The tool — known as the Platform for Analysis, Translation, and Organization (PLATO) of large scale data — exists as a prototype and is capable of discovering gene-gene interactions in genome-wide data.

The hard part isn’t just a matter of taming algorithms or applying statistics, according to Ritchie. “I think a lot of what we work on is kind of cutting-edge — sometimes bleeding-edge — so trying to make other people understand the techniques we’re using can be a challenge,” she says. So far, though, response to Ritchie’s posters and talks on the whole genome association research platform has been enthusiastic.

Ritchie, now an assistant professor, knew she wanted to do biomedical research even as an undergrad, though she didn’t have a specific focus at the time. That came when a turn in Vanderbilt’s interdisciplinary graduate program brought her to Jason Moore’s lab, where she found a research program that capitalized on her talents in mathematics and statistics to resolve biological questions. Moore, who is now at Dartmouth, remains a collaborator and one whom Ritchie credits as having a major impact on how she approaches her own research.

Looking ahead

Ritchie sees cost-effective whole genome sequencing as likely in the not-too-distant future, although she’s hesitant to hazard a date. However, she does predict that the data analysis challenges of whole genome-level data will be immense. Ritchie also cites the integration of data across fields — from microarrays to protein and biomarkers — as another research trend.

In terms of genetics proper, Ritchie says that researchers are starting to realize that genes don’t work in isolation, and that the environment plays a large role in their expression. “There’s a lot of grumbling about looking for gene-environment interactions,” she says, “and I think that a lot of that is going to take off.” In fact, she’s already involved in a proposal researchers at Vanderbilt are putting together for the NIH’s Genes and Environment Initiative. “It’s certainly a high-risk, high-payoff type of proposal,” Ritchie says, “but we figured that even the effort we put into planning how we would do it is helpful for how we are facing these studies in our own research.”

And the Nobel goes to…

If Ritchie ever receives an early morning call from Stockholm notifying her of a certain prize, she would want it to be “for developing a methodology to dissect the genetic architecture of complex disease.”

Great scientists communicate

Ritchie says that being an organized, creative thinker with a gift for communication is key to being a great scientist. “The nature of science these days is very collaborative,” she says, “and if you can’t communicate with people — both in your field and in other fields — you’re not going to go far very fast.”

— JC
Taekjip Ha’s work sits at the fore of experimental biophysics, and that’s been the case ever since he broke new ground on single-molecule fluorescence resonance energy transfer as a graduate student. Trained as a physicist, Ha didn’t exactly aim to get the ‘bio’ prefix added to his PubMed results. “Back then I wasn’t interested in biology at all,” Ha recalls. “I was just using DNA as a way of putting the two dyes close to each other so I could measure this transfer.”

Measure it he did in Scott Weiss’ lab at the University of California, Berkeley; by the last year of his PhD, Ha’s work resulted in a paper on single-molecule FRET in PNAS. Despite getting into print, Ha was skeptical of FRET’s biological applications. In fact, he “didn’t believe a word of it” when Weiss suggested in the paper’s abstract that the technique could be used to measure the conformational dynamics of single molecules. “I was wrong,” laughs Ha, whose current work builds on just that.

Ha’s research draws on physical concepts to tease out the answers to decidedly biological questions. In terms of helicase, for instance, Ha is working to understand directionality of the enzyme by physical and computational approaches. The endgame is the “rational design of a mutant that will go backward” on a single strand of DNA as a means to understanding why helicases move in one direction versus another.

Ha is also interested in extending his work by “combining single-molecule FRET imaging with optical tweezers,” by which small forces can be applied very precisely. The dynamics of DNA molecules can be altered dramatically when force is applied, says Ha, whose group is studying such fluctuations with a model system known as a Holliday junction, an intermediate made up of four strands of DNA. “What’s unique about our approach is that we’re actually measuring the effects of force by fluorescence,” he says.

Looking ahead

Right now, Ha’s lab is working on “extreme in vitro” studies, but Ha would like to see the field move toward doing all measurements in a single cell. Difficulty in measuring conformational changes at the single-cell level has been in the probes. Fluorescent dyes on the market are not bright enough, and they don’t have staying power. “There’s tremendous background fluorescence and they photobleach very quickly,” Ha notes. So although one can perform imaging in individual cells with conventional fluorescence, it’s not ideal, as fluorophores themselves limit the information you can glean from single-molecule measurements.

Quantum dots are another possibility — they’re bright enough and Ha’s team has already succeeded in making them non-blinking — but the problem is they’re just too big for the sort of techniques Ha has in mind. Once layered with materials like polymer to make the dots water-soluble and streptavidin to make them attach to proteins, a fully loaded quantum dot could be about 200 Å. “If someone makes a next-generation quantum dot that is small, water-soluble, and bioconjugable, that would be a dream,” Ha says.

Publications of note

Two recent publications by Ha’s team highlight topics that are “really new and of biological interest,” he says. These include results concerning a bacterial helicase and its sometimes snappy travels along single-stranded DNA, which the team reported in Nature last year. More recently, in a Cell paper entitled “Real-time observation of RecA filament dynamics with single monomer resolution,” Ha and colleagues used single-molecule fluorescence assays and hidden Markov modeling to investigate the growth and goings-on of RecA and its homologues.

— JC
Anne Carpenter never meant to get into software development, but her goals for doing genome-wide screens left her with little choice. Her goal when she joined David Sabatini’s lab was to find all the genes that regulate cell size, but “it turned out at the time that we could not find any commercial software that could accurately analyze the images of cells that would be produced in this type of project,” she says. The problem: Carpenter would be using Sabatini’s living-cell Drosophila technology, and at the time, imaging software wasn’t optimized for correctly analyzing and determining the size of Drosophila cells. So she started writing her own solution, and managed to find a collaborator at MIT to help out. The result is CellProfiler, “an open source, freely available software package for high-throughput cell image analysis.”

The software has become so popular that Carpenter runs a small group within Sabatini’s lab to work with external scientists who are performing the type of genome-wide RNAi screens that Carpenter originally had in mind. “We’re routinely helping people with a couple of screens a month now,” she says. “We’re able to almost all the time get the image analysis to work well, so biologists aren’t spending months and months scoring by eye.”

That also fit in nicely with Carpenter’s longtime interest in automation and quantification. “For quite a while I was a little frustrated by the fact that we’d look at images” by eye and qualitatively score them, she says. “It’s so rare for biologists to find tools that will help them to be quantitative.”

Currently a postdoc, Carpenter is just now determining her next step in the field. She expects that to be a position within academia, but knows for certain that “this unique ability to do almost any image-based screen that people would want to do” will be a key focus of her work in the coming years. “Another major focus of my future research will be really mining that data for all it’s worth,” she adds. “You’ve actually got a whole lot of information present in the images that is usually ignored” when scientists look for one particular phenotype. Carpenter believes comprehensive data mining of these images could lead to identification of new gene families, for instance. “I’ll be moving a little bit more toward the systems biology level to mine this data,” she says.

Looking ahead

The rate-limiting step for high-throughput imaging is currently the microscope part of the equation, says Carpenter; at this point, sample prep and other steps are quite robust. She’d like to see “a higher-throughput robotic microscope” that would help push the field forward. She also says that more sophisticated data mining will be a critical component in getting better and more comprehensive information out of images.

Publications of note

Carpenter’s key paper explaining the software and its utility has been submitted but not yet published. In the meantime, several collaborators who have used CellProfiler have published papers that include their findings from Carpenter’s software, such as “A lentiviral RNAi library for human and mouse genes applied to an arrayed viral high-content screen” in Cell from David Root’s group at the Broad Institute.

And the Nobel goes to...

Carpenter says if she could one day win the Nobel Prize, she’d like it to be for “generating a gigantic data set of all the genes knocked out and their phenotypes, analyzed in a number of ways that would include image-based data, transcriptional data, proteomics data — and using that data set to … get a lot of information about the genome and the networks that control how cells function.”

— MWS
Kicking off his career with a project that may have been enough to drive other people away didn’t faze Pablo Rabinowicz. He started working on the maize genome during his postdoc with Robert Martienssen at Cold Spring Harbor Laboratory and acknowledges that the bench work might have turned most people off. “In the beginning, for somebody with not much experience in genomics, it might seem boring to work on [such a] large-scale, simple problem,” he says. “But I found it interesting to look at genomes from a big perspective, rather than a single gene.”

So began his interest in elucidating the large genomes of two potential biofuel sources: maize and the castor bean — with an eye toward how these plants tolerate such large genomes. Like many plants, the maize genome is predominately composed of retro-transposable elements that are most likely silenced epigenetically in order to avoid significant genomic damage. That makes targeting gene-rich regions much more practical than whole genome sequencing. To this end, Rabinowicz employs methylation filtration, a targeting method he helped develop while still at Cold Spring Harbor. “It’s basically a means for selecting genes out of large genomes in an efficient way,” he says. “Therefore, you can clone and sequence genes more efficiently than in a whole genome shotgun approach.”

Methylation filtration is based on a protein system in E. coli that recognizes and destroys incoming foreign DNA only if it is methylated. As most plant genes are unmethylated, a clone of plant DNA can be made in E. coli, recovered, and then sequenced. Methylation filtration also screens out repetitive DNA, which is often methylated, thereby lowering the proportion of repetitive DNA in a methylation filtration library.

Rabinowicz’s other focus, the castor bean, is perhaps best known as a ricin toxin-producing plant, despite its potential as a biofuel. “The goal of castor bean as a crop is to produce high-quality oil,” he says. “But because of this toxicity, the production of the crop is minimized and the oil is imported.” Due in part to these biosecurity interests, the National Institute of Allergy and Infectious Diseases recently funded Rabinowicz to sequence the castor bean genome at a low-pass coverage. But when the time comes that there really is a need to tap biofuel sources like the castor bean, plant genomics will be there to help, says Rabinowicz. “When that happens, knowing the genetics and genomics of the plant will allow you to improve whatever problem you have at that time,” he says.

Looking ahead

With large genomes comes a need for substantial funding. Rabinowicz says there is funding for crops native to the US, like maize, but money for researching a tropical plant like castor bean is hard to come by. He hopes that if, at some point, the necessity for biofuel ends up requiring tropical crops, research will have already been funded before it’s too late. “You should start earlier … to cover the knowledge so when the moment comes to use these crops, you already know how to modify them,” he says.

Publications of note

Rabinowicz and Martienssen published a *Nature Genetics* paper in 1999 entitled “Differential methylation of genes and retrotransposons allows shotgun sequencing of the maize genome,” describing methylation filtration as an efficient method to clone and sequence genes while avoiding unwanted repetitive DNA. In 2003, they published “Maize genome sequencing by methylation filtration” in *Science*, a follow-up study showing that methylation filtration is still effective when conducted at a large scale, on the order of 100,000 sequences.

— MD
While much of structural genomics can be considered still in its infancy, the study of structures in proteins has a significantly longer track record. Brad Bernstein, an assistant professor of molecular pathology at Mass General, is making strides in understanding genomic structure by relying on his background in structural biology. “In many ways there’s a parallel between protein structure and genome structure,” he says. “You’re really dealing with a physical entity that is adopting a primary, secondary, and even tertiary structure.”

Bernstein’s main interest lies in epigenomics, in which he and his team are using “genomic technologies to obtain global views of epigenetic modifications as they occur across the genome,” he says. In particular, his focus is on how these epigenetic changes play a role in cell identity and cell lineage — which leads his work directly to the intersection of genomics and stem cell research. Not only are epigenetic marks critical to determining whether a cell will turn out to be a liver cell or a skin cell, but recent research indicates that epigenetics may also be at the root of how stem cells stay in their pluripotent state. “You can find signatures of chromatin plasticity [in stem cells] that we think help maintain their ability to turn into almost any different cell type,” he says.

The upshot of all of his research is simple: he hopes one day that all of this will have a positive impact on the landscape of human health. To that end, Bernstein’s year-old lab at MGH is just starting to use epigenetic studies in cancer research as well. He posits that a systems-level understanding of chromatin domains and how those domains are regulated and misregulated might lead to a better awareness of how epigenetics factors into cancer.

After completing his MD/PhD at the University of Washington, Bernstein fulfilled a “little over a year” of his residency at Brigham & Women’s Hospital before becoming a postdoc in Stu Schreiber’s lab at Harvard. Bernstein, who currently has affiliations with the Broad Institute, also collaborated with Eric Lander’s group during his postdoc.

Looking ahead

There’s still technology development in the offing for Bernstein’s field. “We really want to be able to take these tools for profiling the epigenetic state of a cell towards physiologically relevant cells and tissue,” he says. “[But] the technologies aren’t quite there yet.” If Bernstein and his team are able to hone their research and tools as they hope to, those studies could play a significant role in oncology, regenerative medicine, and the basic biological understanding of the embryonic stem cell genome, he adds. The ideal tool for the field would give “a single-cell readout of the epigenetic state of a gene — a master regulator gene or critical genomic loci,” says Bernstein. That kind of information would be instrumental not only in identifying stem cell populations but also in obtaining clinically useful diagnostic data about tumor samples, he adds.

Publications of note

In April, Bernstein and his colleagues published a paper in Cell entitled “A bivalent chromatin structure marks key developmental genes in embryonic stem cells.” A year earlier in the same journal, he published another paper explaining how epigenetic and related technologies could help obtain that sort of information.

And the Nobel goes to ...

Bernstein says that if a trip to Sweden is in the works for him one day, he’d like to be rehearsing a speech about “gaining another level of understanding of fundamental epigenetic mechanisms in a way that could really translate into having an impact on human health.”

— MWS
She's studied marine life, blood, feces, and the human gut — but don't think Mya Breitbart has been struggling to find her niche in the genomics community. “The environment’s changing,” she says of her experimental subjects, “[but] it’s the same or similar methods all along.”

Breitbart started out in metagenomics before the field even had a name. In grad school, she focused on viral communities in oceans thanks to an early interest in marine life from a summer stint she had at the Scripps Institute of Oceanography in Farooq Azam’s lab. Later she made the transition to human studies when scientists got interested in the volume of bacteria in the human gut. The concept, she says, is to figure out what state is considered normal or healthy so that the state of the bacterial environment in the gut, for example, can be factored into understanding human health.

Today, Breitbart is happily back into marine work with her not-quite-year-old lab at the University of South Florida, where she has four grad students and a goal of focusing on the interface between human health and the health of the environment. One of her students is studying bacteria living on coral reefs, while another is working to determine if plant viruses contained in human waste can actually survive water treatment processes and get passed, fully infectious, back onto lawns and fields through the recycling of water. The idea in these and all of the projects her lab will take on “is to use genomics to identify what’s present in an environment” — and use that information as a baseline to help determine emerging threats or changes to an environment going forward.

Looking ahead

When Breitbart scans the horizon for what might be in store for metagenomics, she homes in on the attribute that’s really lacking today: speed. “Right now it’s pretty slow and intensive,” she says. “It’s a pretty big process to be able to concentrate enough sample” for these studies. But five or 10 years from now, she says, “this is all going to happen really quickly, and we’ll be able to work with much smaller concentrations.” As speed of experiment and analysis increases, she notes, that will pave the way for routine monitoring of environments — whether it be ocean or human gut — so scientists can see changes or problems and respond right away, Breitbart says.

Publications of note

To get a sense of Breitbart’s work, don’t miss a paper she helped write entitled “Genomic analysis of uncultured marine viral communities” (PNAS, 2002). She says it’s the first metagenomic analysis to be published — and was such an early step in this field that her team didn’t even call it “metagenomics.”

Breitbart says her favorite paper came out of a collaboration with scientists in Singapore. The paper, published in PLoS Biology this year, is called “RNA viral community in human feces: Prevalence of plant pathogenic viruses” and represents the first realization that human feces contain significant amounts of plant viruses. Breitbart says it’s also a great example of the strength of the metagenomics approach. “If we just went looking for a specific animal virus, we would’ve found it or not found it — but we would’ve completely missed the big picture,” she says. “I don’t think we really expected that we would be full of plant viruses.”

And the Nobel goes to …

“If I could win the Nobel Prize, I would like it to be for elucidating the diversity of marine viruses and their critical roles in the oceans,” says Breitbart. “Or for developing a global surveillance system to allow monitoring of the environment for emerging virus.”

— MWS
Move over, SNPs. Until recently, the main focus of clinically oriented genetics has been on single nucleotide changes and their connection to genetic diseases such as diabetes and obesity. But Andy Sharp says that’s about to change. “Now that we’re studying structural variation, we’re realizing how much is out there, how variable one human is to another in terms of large rearrangements in their genome,” he says. “It’s becoming clear that the structural variation in the human genome is probably just as, if not more important than, single nucleotide variation.”

Sharp, a member of Evan Eichler’s lab at the University of Washington, expects that structural variation data will someday be routinely used in the clinical environment. “The more people are looking at the structural variation of the human genome, the more that we’re appreciating that it’s going to be involved in common human diseases,” he says.

His focus on structural variation and novel disorders in the human genome — “specifically recurrent ones,” says Sharp — has meant confronting challenges in studying the kinds of rearrangements he and his colleagues are interested in.

New types of studies require new techniques for analysis, and looking at structural variation is no different. One breakthrough came in the form of a pioneering technique called fosmid paired-end mapping, which Sharp feels is probably the best technique available for looking at structural variation across the entire genome. The method works by taking end sequences from high-density fosmid libraries, mapping them against a reference genome, and looking for discordances, Sharp says. “The power of that technique is that it can detect all types of rearrangements, including balanced rearrangements such as inversions, which the vast majority of other techniques can’t,” he adds.

“It also enables you to then go in, fully sequence that individual rearrangement — which … most techniques don’t allow you to do — so you get very high precision and very high sensitivity to all different types of things you’re interested in,” he says.

Looking ahead

“Right now, we’re kind of at a stage where we’re trying to find out what in the human genome is there,” says Sharp. “It looks like maybe 5 percent of the genome is structurally variant in different individuals, so right now we’re characterizing that, and trying to understand what type of variation is there and more importantly, what effect this might have on us as human beings.” Sharp and his colleagues are still very much in the initial stages of this characterization, but he predicts that in the near future, researchers will move from the current discovery phase to determining the influence of these changes in human phenotypes.

Publications of note

Sharp won the Student Award at a recent meeting of the American Society of Human Genetics for a study entitled “Discovery of previously unidentified genomic disorders from the duplication architecture of the human genome” (published in Nature Genetics). The study describes the identification of several new genetic syndromes caused by the deletion of specific chromosomal regions that occur as a result of the architecture of the genome.

Sharp’s team investigated 130 regions that they believed to be possible candidates for undescribed genomic disorders based on the duplication architecture of the genome. The team tested 290 individuals with mental retardation using array comparative genomic hybridization. Their efforts demonstrated that sites of recurrent chromosomal rearrangement that cause genomic disorders could be successfully identified using an informed, duplication architecture-based approach. Sharp and his colleagues identified the deletion of a piece of chromosome 17q21.31, which appears to be the most common recurrent cause of mental retardation in humans.

— MD
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Veterans from the field offer practical advice for scientists early in their careers. Genome Technology invited readers to submit career-related questions, and then tracked down experts who could provide clear, useful answers.

I’m a bench scientist but I’d like to get into the marketing or management side of the company. What’s the best route? Should I get an MBA?

Nate Lakey, CEO of Orion Genomics, started out on the technology and science side of the field and made the transition to the business front. He credits much of that with the volume of business reading he did, including topics like statistical process control and total quality management. “I was interested in the processes behind science,” he says. “Pretty quickly you find yourself getting into business questions.” That led him to accept and excel in an operations position, which paved the way for his business career.

Linda Kirsch, a professional executive recruiter who specializes in life sciences, says she considered getting an MBA when she realized she wanted to go from science to the business side, but decided that for her, the cost/benefit analysis didn’t make sense. She recommends that scientists take executive and other business training classes, noting that most highly regarded management schools offer short weekend or evening programs on very specific business topics.

Jane Krug, a former scientist who now runs her own marketing consultancy, says her path involved spending time in the sales department as her transition period. “I was really glad I had that experience,” she says. She also notes that this kind of move can be easier in a startup environment, where boundaries aren’t as rigid as they may be in large companies with long-established infrastructure and organization.

I’m about to start my own lab. What factors should I consider?

Rob Mitra, assistant professor in the genetics department at Washington University, says that the most practical considerations are equipping your lab, choosing staff, and selecting a research goal. “Be focused and figure out exactly what you’re going to do in the next two, three, four years,” he says. That information will help you with the other key steps: “Figure out what equipment has to go in the lab. … [And] try to get the best graduate students and postdocs and technicians that you can,” he says.

I am an unhappy postdoc. How do I get out of this lab before my project is completed?

Mitra at WashU advises people in this position to sit down with their PI and talk candidly about the situation. “I think it’s important to have a frank discussion as to what it is that makes you unhappy,” he says. “Your PI shouldn’t be surprised.” He says that in a case where there is no clear way to come to an agreement, a PI would be likely to release, and even help find a new position for, the postdoc. “It’s the honorable thing to do,” Mitra says.

How do I know when it’s time to move on?

“If you’re feeling stale or bored or underutilized, it’s time to look,” says Laurie Irwin, a biotech recruiter who works for Fortune Personnel Consultants. She says if you find that you’re no longer being challenged, you’ve accomplished what you set out to do, or that the organization is not doing well, you should take stock of your situation and seriously consider a move to another place.

Kirsch says obvious situations include those where “your needs aren’t being met [or] when there are situations that you know you can’t correct.” She says it’s common for people to try to ride out bad times with a company, but it may be time to go in cases where that’s actually hurting your livelihood or ability to provide for your family.

Should I get a PhD? Will just having a master’s limit my advancement?

“A PhD in the sciences really takes you a long way,” says Kirsch, noting that very few senior level people in academia or industry don’t have a doctorate. She says opportunities are more open in areas like sales, marketing, or field operations for people who do not have a PhD.

Laurie Irwin says smaller organizations, like small pharma or biotech, are more likely to advance people who have a master’s degree. Jodi Greco, senior employment administrator at the Broad Institute, says that having a PhD is more critical for academic careers than industry ones.

“Often [organizations] still weed people out that don’t have PhDs,” says Rhonda Knudsen, HR director at the Institute for Systems Biology, adding that that trend is slowly changing. “It’s fundamentally hard to change that bias.”

I know networking is important, but how do I do it?

Often [organizations] still weed people out that don’t have PhDs,” says Rhonda Knudsen, HR director at the Institute for Systems Biology, adding that that trend is slowly changing. “It’s fundamentally hard to change that bias.”
There’s no trade secret for how to become a well-connected person, but experts agree that many simple steps can help the process. Consultant Jane Krug says when she gets someone’s business card, she writes a note on the back about where she met the person or about some aspect of their conversation that she wants to follow up on. In cases where she wants to keep in touch with the person, she says, “I’ll often e-mail them right after and say it was great to meet you.”

Krug also encourages people to walk the exhibit hall floors and attend social functions at conferences — and don’t stand “with the people you know,” she says.

Meeting people at a conference may seem about as appealing as cold-calling for a telemarketing firm, but once you get past any reluctance it can be quite painless. “If you’re shy, you can overcome that by asking people questions about them — people like to talk,” says Nate Lakey at Orion Genomics. “I try to really reach out. If I meet someone who’s new I proactively introduce them to everyone I know. They’ll return the favor and introduce you to people that they know.”

Lakey also cautions scientists to keep their expectations reasonable. “It takes about three to five years” for most people to feel solidly connected, he says. “You’ve got to pick a meeting and go to it for three to five years.” At the end of that, he says, you’ll come away “tired but with a great network.”

ISB’s Knudsen recommends joining associations — alumni, scientific, social — to meet more people. She points out that if you move, often associations have other regional branches and become a great way to plug in to a new community. “You have to put yourself out there,” she says.

Which areas are poised for growth or slowdown in the next several years?

Laurie Irwin sees hiring trends in academia and government more so than industry at the moment. Within the field of bioinformatics, she says, she sees companies looking for expertise in specific therapeutic areas and statistics in particular.

Kirsch says that “employers are spending more money closer to the product, no matter what the product.” She’s noticed people who were in earlier-stage research heading down the pipeline to pharmacogenomics, for instance, or other clinical areas.

I want to stay at my institution, but I’d like a promotion. Is it wise to get an offer from another organization to use as leverage?

No way, says Laurie Irwin. “It’s like a cheating spouse,” she says, pointing out that arriving on your supervisor’s doorstep with a competing offer “could be perceived as a threat.” The better course of action, she says, is to “sit down with your boss or manager and talk about reasons why you’re feeling a little stale.” She notes that in a case where somebody did use another offer as leverage, a company that six months down the road had to downsize might look at that person less favorably.

The content here is excerpted from Genome Technology’s annual salary survey, which ran in our June 2006 issue. For this version, GT editors selected the questions and answers best suited to scientists early in their careers.
Young Investigator Awards

American Federation for Medical Research Foundation Awards

Focus: The AFMR presents two annual awards to honor outstanding young investigators in biomedical research.

Award specifics: The AFMR Outstanding Investigator Award is presented in recognition of excellence to a researcher 45 years old or younger. The award recipient will receive a prize of $5,000 and must be available to present his or her work at the Experimental Biology 2007 meeting. The foundation’s Junior Physician Investigator Award honors medical school researchers whose projects “complement an overall program of research, teaching, and clinical medicine.” Candidates must submit abstracts to the Experimental Biology 2007 meeting, and have held their full-time faculty appointment for five years or less. Two winners will each receive $2,500 and a plaque.

How to apply: OLA nomination forms are available on the AFMR web site. Applicants for the JPI award must submit an application and a letter of support from their mentor, division chief, or department chair.

Deadline: Applications are due January 19, 2007.

Website: http://www.afmr.org/awards

American Society of Nephrology/American Heart Association Young Investigator Award

Focus: The AHA and ASN co-present the Young Investigator Award annually to an individual with an outstanding record of achievement and creativity in basic or patient-oriented research related to the functions and diseases of the kidney.

Award specifics: The award is limited to individuals who are less than 41 years old on the first day of the ASN meeting at which the award is presented or who have received an MD degree not more than 15 years before the calendar year of the ASN meeting. The award prize consists of a certificate of recognition, an unrestricted grant of $5,000 to the awardee’s lab, and paid travel expenses to the meeting. The Young Investigator Award recipient will also be invited to give a presentation at the annual meeting’s plenary session.

How to apply: Nominators should submit a letter of nomination and a copy of the candidate’s CV prior to the award submission deadline. The nomination letter, not to exceed two pages, should emphasize the significance of the candidate’s scientific accomplishments and identify three or four of the nominee’s most important publications.

Deadline: Applications are due to the ASN by January 31, 2007.

Website: http://www.americanheart.org/presenter.jhtml?identifier=11121

Irving Sigal Young Investigator Award

Focus: Presented by the Protein Society and sponsored by Merck Research Laboratories, this award recognizes a significant contribution to the study of proteins by a scientist who is in the early stages of an independent career and, generally, not more than 40 years old at the time of the award.

Award specifics: The 2008 recipient will be recognized at the 22nd Annual Symposium of the Protein Society and invited to present a plenary lecture on the structure and function of protein science as it relates to his or her field of study.

How to apply: Anyone can nominate an individual by submitting one copy of the required materials via mail or e-mail. Application materials consist of nominee and nominator information, three letters of support, and copies of selected key articles.

Deadline: Nominations should be sent to the Protein Society’s executive officer, Cindy Yablonski, by November 1, 2007.

Website: http://www.proteinsociety.org/pages/page03a.htm

Michael and Kate Bárány Award for Young Investigators

Focus: Established by the Biophysical Society in 1992 and renamed six years later for an endowment gift from Michael and Kate Bárány, the young investigators award is for an outstanding contribution to biophysics by a person who has not achieved the rank of full professor at the time of nomination.

Award specifics: Each year one winner is selected to receive a $2,000 award.

How to apply: Nomination forms may be downloaded from the society’s website. Applications should include a letter summarizing the nominee’s qualifications for the award, two letters of support, and the nominee’s curriculum vitae.

Deadline: Nominations are due by April 1, 2007.

Website: http://www.biophysics.org/opportunities/bpsawards.htm#barany
### Deadlines

#### December 2006

- **December 11** — Abstract submission deadline for Oncogenomics 2007. The meeting will take place from January 31 to February 3 in Phoenix, Ariz.
- **December 12** — Letters of intent due in response to the funding announcement for Targeting Diseases Caused by Protein Misfolding or Misprocessing (R01 and R21, PAR-06-479 and PAR-06-480). Applications should be received by NIH no later than January 12, 2007.
- **December 15** — Early registration closes for LabAutomation 2006, which is scheduled for January 27-31 in Palm Springs, Calif.
- **December 19** — Advance registration deadline for the AAAS annual meeting, which will be held in San Francisco from February 15-19.
- **December 20** — Letters of intent due for second round of funding for Bioengineering Research Partnerships, PAR-06-456. Applications should be received by NIH no later than January 22, 2007.

#### January 2007

- **January 1** — Last day to register for the Fifth Asia-Pacific Bioinformatics Conference at the University of Hong Kong, January 15-17.
- **January 9** — Abstracts due for the American Society of Clinical Oncology meeting, scheduled to begin June 1, 2007.
- **January 12** — Full proposal target date for NSF’s Genes and Genome Systems Cluster (PD-04-1112), which supports studies on genomes and genetic mechanisms in all organisms, whether prokaryote, eukaryote, phage, or virus.
- **January 12** — First full proposal due date for NSF’s Developmental Systems Cluster (PD-05-7471). Studies that explore the evolution of developmental mechanisms are encouraged; genomic approaches, gene networks, the integration of gene pathways, and computational approaches are included.
- **January 12** — Another full proposal due date at NSF, this time for the Cellular Systems Cluster (PD-04-1114), a program focusing on the structure, function, and regulation of plant, animal and microbial cells, and their interactions with the environment and with one another.
- **January 26** — Early registration closes for the 58th Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, scheduled to run from February 25 to March 2.
- **January 26** — Poster abstract submission deadline for the Society for Biomolecular Sciences Annual Conference in Montréal beginning April 15.

#### February 2007

- **February 1** — Closing date for applications to the DOE’s systems biology research program, Genomics: GTL. Project goals include developing science and technology to use microbial and plant systems for cost-effective renewable energy production, carbon sequestration, and environmental remediation. Award ceiling is set at $125,000,000.
- **February 2** — Deadline to get papers in for the ISMB/ECCB 2007 meeting, set to begin July 21, 2007 in Vienna.
- **February 14** — Late-breaking abstracts due for the American Association for Cancer Research 27th Annual Meeting. Advance registration for the meeting will end March 9.
- **February 14** — Abstracts due for the Biology of Genomes meeting, set to take place May 8-12 at Cold Spring Harbor Laboratory.
- **February 16** — Abstracts due for HUGO’s 11th Human Genome Meeting in Montreal, starting May 21, 2007.
- **February 16** — Full proposals due in response to the Frontiers in Integrative Biological Research program (06-579). FIBR supports projects to identify major under-studied or unanswered questions in biology and use integrated research tools and concepts to address such questions. NSF is specifically targeting young scientists trained in an interdisciplinary environment or in non-biological disciplines for this program.

#### March 2007

- **March 1** — Poster submission deadline for the 11th Annual International Conference on Research in Computational Molecular Biology (RECOMB), scheduled to kick off on April 21 in San Francisco.
- **March 11** — Posters due for the RNAi World Congress, set for Philadelphia beginning on April 24.
- **March 11** — Last day to submit posters for the Cancer Proteomics World Congress, scheduled to start April 26 in Philadelphia.
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Early-Career Grant Opportunities

Sure, it’s tough to break your way into the world of R01s. Fortunately, the US NIH and several other grant providers have funding programs targeted at young investigators. Here, Genome Technology rounds up several — now it’s up to you to hone those grantsmanship skills.

Organization: National Institutes of Health

Details: NIH offers a slew of opportunities for young investigators, the newest of which is the Pathway to Independence Award Program, a grant of up to five years. NIH expects to award 150 to 200 of these grants in the first year; almost all institutes and centers are participating.

Check out: nih.gov — see the New Investigators Program in the Grants and Funding category.

Also of interest: Other NIH grants for this demographic include the Mentored Career Development Awards; Mentored Research/Clinical Scientist Development Awards; Career Transition Award; and the Mentored Quantitative Research/Clinical Scientist Development Award.

Organization: National Science Foundation

Details: The agency’s Faculty Early Career Development Program is a foundation-wide funding theme for junior faculty members.

Check out: nsf.gov

Also of interest: NSF also supports early-career scientists through its Research Initiation Grants and Career Advancement Awards.

Organization: PhRMA Foundation

Details: The PhRMA Foundation Support Awards are intended to support scientists beginning their faculty careers in computational or experimental research in genetics, genomics, and proteomics.

Check out: pharmafoundation.org/awards

Organization: Human Frontier Science Program

Award: Up to $450,000 per team

Details: HFSP’s Young Investigators’ Grants are designed for teams of two to four scientists, all of whom are no more than 10 years past their PhD and have had independent labs for no more than five years. Research grants last for three years and go to “novel, daring ideas” in interdisciplinary collaboration.

Check out: hfsp.org

Organization: Arnold and Mabel Beckman Foundation

Award: Typically about $264,000

Details: The Beckman Young Investigators Program supports promising life science faculty members at research institutions (no more than three years into tenure-track or comparable post).

Check out: beckman-foundation.com

Organization: The McKnight Foundation

Award: $75,000 per year

Details: McKnight Scholar Awards are for neuroscientists early in their careers who are focusing on learning or memory disorders. Applicants must have an MD or PhD and have completed a postdoc.

Check out: mcknight.org

Organization: American Association for Cancer Research

Award: Two-year grants of $50,000 per year

Details: The AACR Career Development Award is open for junior faculty at an academic or medical institution who are no more than three years into their first appointment after a postdoc.

Check out: aacr.org

Organization: American Diabetes Association

Award: $150,000 per year, up to five years

Details: ADA’s Career Development Awards help investigators seeking to establish their independence in diabetes research. Applicants must be an assistant professor at the time of the award.

Check out: diabetes.org

Organization: Alzheimer’s Association

Award: Up to $100,000 for one or two years

Details: The group’s New Investigator Research Grants help fund investigators who are no more than 10 years past their doctoral degree.

Check out: alz.org

Organization: Cure Autism Now

Award: Maximum of $40,000 per year for up to two years

Details: The group’s Young Investigator Awards are for scientists no more than four years past an MD or PhD. Research must have relevance to autism, but applicants do not have to be in an autism-focused lab to win the award.

Check out: cureautismnow.org

Organization: Office of Naval Research

Award: Up to $100,000 per year for three years

Details: The ONR Young Investigator Program (ONR BAA 07-002) supports life sciences basic and applied research for a number of interests: marine life sciences, neuroscience, biorobotics, and biosensors, among others.

Check out: onr.navy.mil
Genome Technology extends its sincere thanks to the leaders who generously took the time to recommend the up-and-coming investigators profiled in this special issue. We’re delighted to have such a noteworthy group of scientists to point us in the right direction.

Peter Ahnert  
University of Leipzig

Phil Andrews  
University of Michigan

Andrea Califano  
Columbia University

Steven Carr  
Broad Institute

Evan Eichler  
University of Washington

Claire Fraser-Liggett  
The Institute for Genomic Research

Skip Garner  
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University of Washington

Bud Mishra  
New York University

David Muddiman  
North Carolina State University

Gene Myers  
HHMI’s Janelia Farm

Gene Robinson  
University of Illinois at Urbana-Champaign

Bruce Roe  
University of Oklahoma

David Sabatini  
Whitehead Institute

Phil Sharp  
Massachusetts Institute of Technology

Muhammad Soheil  
University of Oxford
Earlier this year, GT hosted a caption contest for readers. This is the original cartoon with the winning caption and an honorable mention.

"You'd better get on these soon. If you wait they'll start clumping together."

Submitted by: IDRL students from the Animal and Natural Resources Institute at the US Department of Agriculture

And the honorable mention goes to Gary Latham for best analysis:

“All the backup databases failed. That's chromosome 21.”

(Note: The pile looks like about 15 reams of paper. That's about 7,500 pages. At 6,000 letters per page, which is manageable without a painfully small typeset, that's 45 million letters. Chromosome 21 is the smallest at about 50 million bases, so it could well be that chromosome.)
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