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- **PROTEIN BIOMARKERS**
  For protein biomarkers to have a real clinical impact requires better sample sets, new platforms and serious validation.

- **LAB REUNION**
  Mass spec guru John Yates stands by his convictions.

- **TISSUE MICROARRAYS**
  Still struggling with imaging and standardization.

- **IN THE CLINIC: CASE STUDY**
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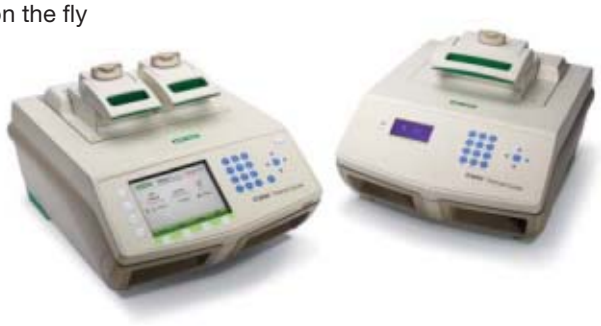

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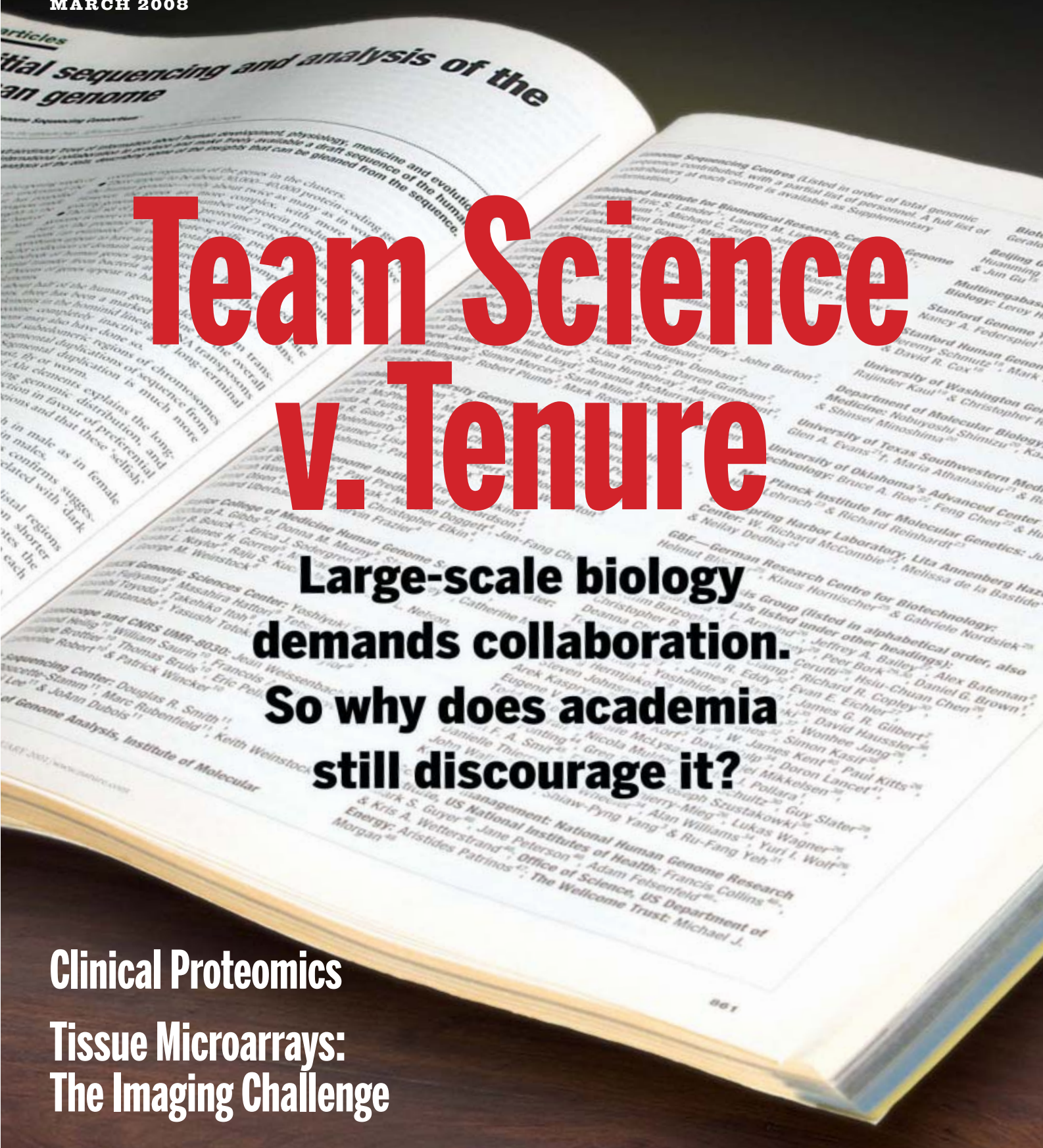

Team Science v. Tenure

Large-scale biology demands collaboration. So why does academia still discourage it?

Clinical Proteomics

Tissue Microarrays: The Imaging Challenge

MARCH 2008

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"We tell young scholars, 'Wait until you have tenure to solve very cool problems.'"

Cathy Trower, page 36

Tissue microarrays

The Awkward Adolescence of Arrays

Tissue arrays have found their footing in translational research — but scientists say they're still struggling with imaging and standardization.

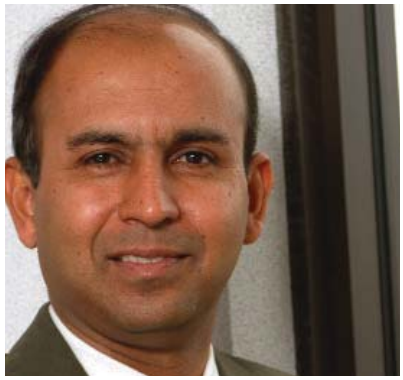
BY JEANENE SWANSON

Protein biomarkers

Toward Clinical Proteomics

Scientists say protein biomarkers stand to have a real impact in the clinic. But getting there will require better sample sets, new platform development, and serious validation.

BY MEREDITH W. SALISBURY



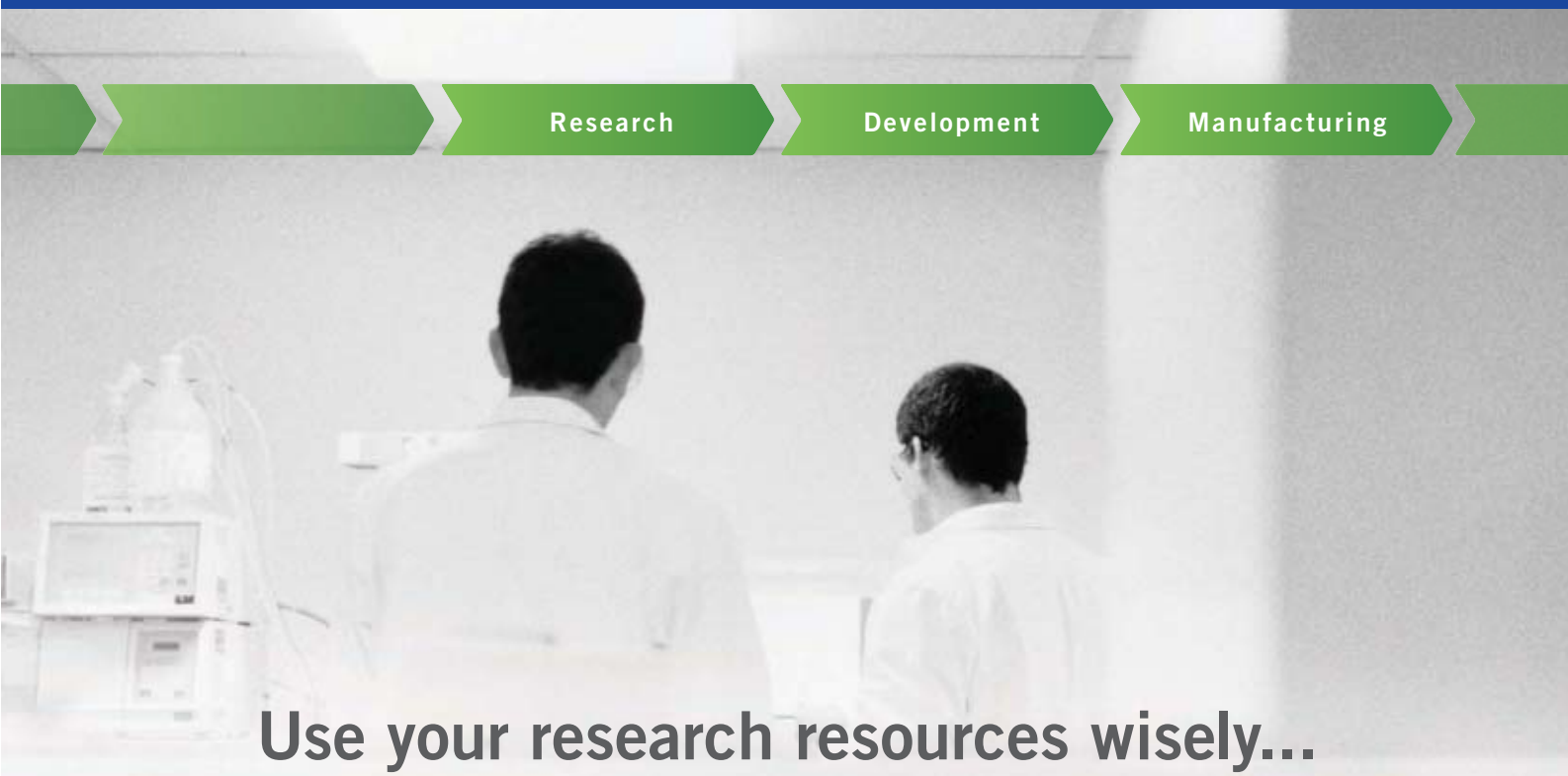
Tenure

Works Well With Others

Large-scale biology led to the advent of "team science," but tenure is still awarded for individual work. When it comes down to better science or a solid career, researchers are losing out. *GT* investigates how (and whether) to fix tenure.

BY CIARA CURTIN

On The Cover



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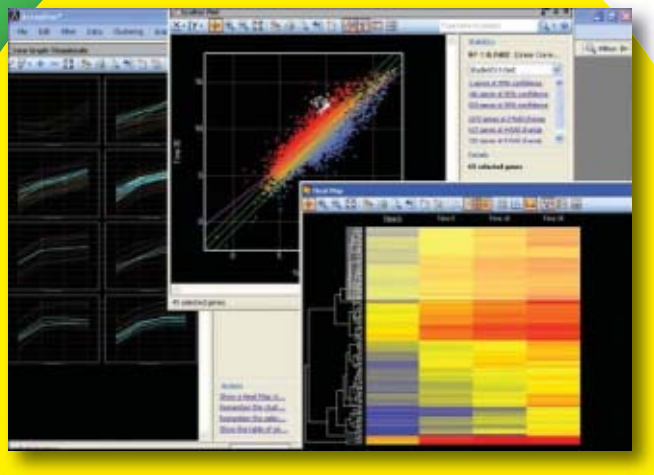

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ISSUE NO. 79

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Go Team!

For all the rah-rah talk about teamwork, teams don't always have a positive connotation. (I can attest to this as someone always among the last people chosen for dodgeball teams.)

Large-scale biology revolutionized the life sciences, shaking the comfortable model of PIs working by themselves in their labs. Ever since the Human Genome Project, teams have been the vehicle of choice for accomplishing big research programs. In science, if you get 20 or 50 or 100 minds focusing on the same thing, it actually does get done.

But recognizing the value of this work in academia has seriously lagged. Several years ago Elaine Mardis treated me to a guided tour of the Washington University Genome Sequencing Center. I was quite surprised to find that she was genuinely concerned about her chances of being awarded tenure. This top-notch scientist wasn't sure the review committee would recognize her accomplishments, since they had mostly taken place in very large collaborations.

Elaine did indeed get tenure, but the factors at the root of her worries persist. Tenure review committees base their decisions on how much a PI has accomplished solo — generally dismissing work done with or grants awarded to teams.

GT deployed senior editor Ciara Curtin (who I believe has never been chosen last for dodgeball) to investigate the disparity. Her cover story reports on the problems with the tenure system, as well as a number of novel solutions that universities and other institutions are trying out to award tenure to scientists active in collaborative research.

Also in this issue, we have feature articles on tissue microarrays — which continue to improve but still need progress in image analysis and standardization — as well as on clinical proteomics and what it's going to take for protein biomarkers to have an impact on patient care.

We've also started a new column. My Take, on p. 25, is an opinion column written by a blogger whose work we find insightful and thought-provoking. Our inaugural edition is from Keith Robison, who offers an introduction to the blogosphere and tips for finding relevant and interesting blogs. Keith's Omics! Omics! blog can be found at *omicsomics.blogspot.com* — I encourage you to check it out.

Meredith Salisbury

Meredith W. Salisbury, Editor

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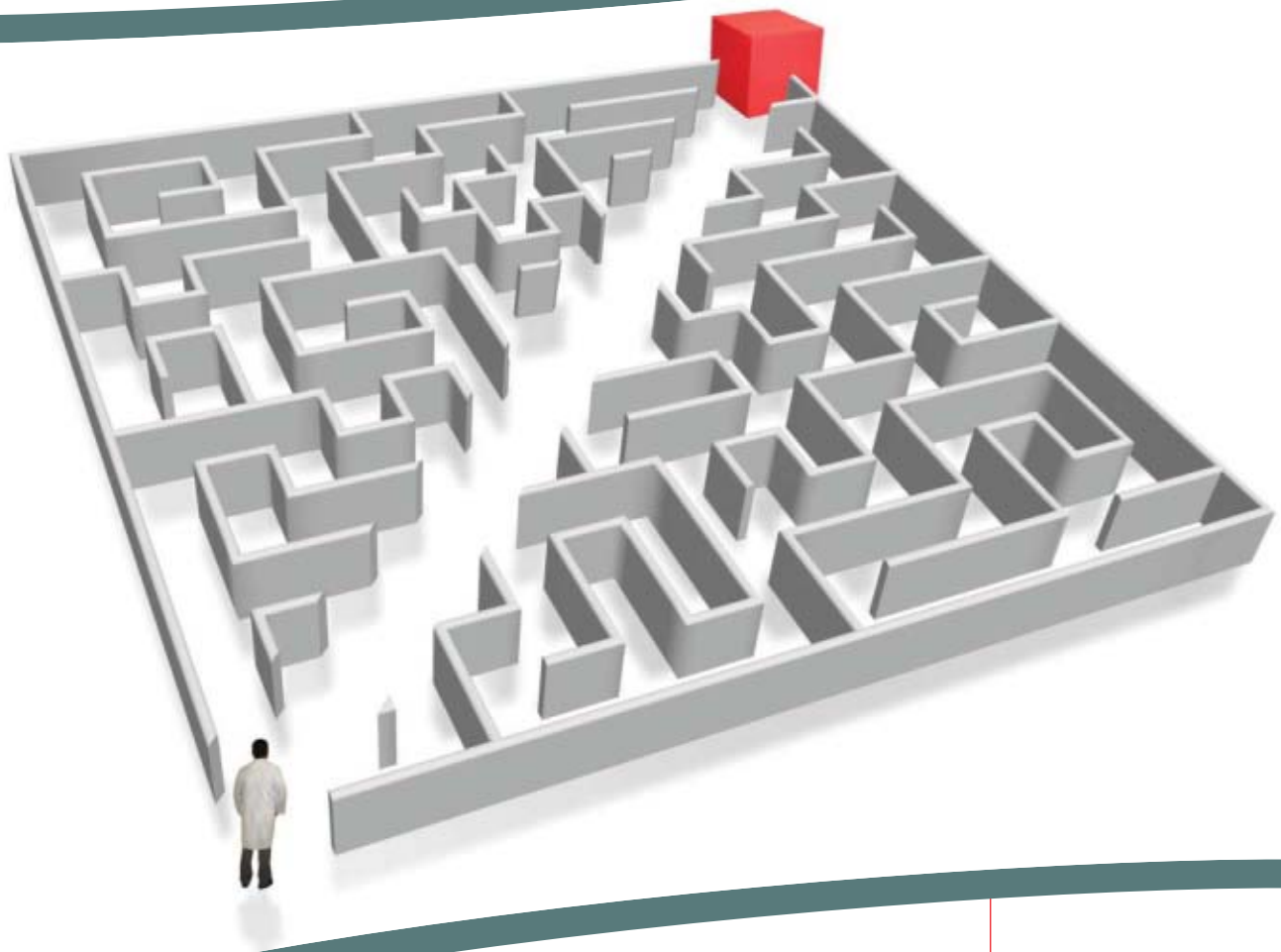

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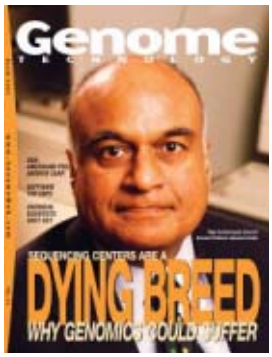
In Review: Mid-size Sequencing Centers, Amersham, Tech Transfer, and Electron Transfer Dissociation



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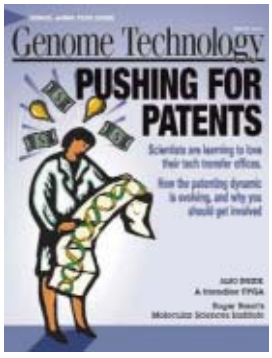

MARCH 2007

Back in 2003, *Genome Technology*'s cover story delved into NHGRI's controversial decision to ignore mid-sized sequencing facilities and give most of its sequencing grants to the Big Three: Baylor, Whitehead (now the Broad), and Washington University. Left out in the cold were Harvard's Raju Kucherlapati, Stanford's Rick Myers, CSHL's Dick McCombie, UW's Maynard Olson, and the University of Oklahoma's Bruce Roe. The fate of these smaller facilities, which housed between four and 20 sequencers and had budgets between $2 million and $10 million, seemed to hang uncertainly. But all of those researchers found a way to survive, and are still working on various sequencing-related projects. Myers, for example, participated in the ENCODE Project, and McCombie took part in annotating the rice genome.

That same issue included an interview with Amersham Biosciences' Andrew Carr. Carr was then president of Amersham, where he was trying to bring the discovery side of the company's businesses (including proteomics, bioassays, and informatics) to profitability. Carr said Amersham's mantra for 2003 would be: "We're in it for the long term." Two years later, Amersham was acquired by GE. Today, Carr holds a variety of positions. He is the chairman for Teraview, deltaDot, and Akubio's boards, and is also an independent consultant for SpinX Technologies and works with SciBridge.

In last year's March issue, *GT* looked at how scientists are beginning to take advantage of their universities' technology transfer offices. Since the 1980 Bayh-Dole Act allowed universities to patent their scientists' technology, the number of patents assigned to US universities rose from fewer than 250 prior to 1980 to 11,000 between 1991 and 2004. In that cover story, Q3's Walid Qoronfleh predicted that patent pooling would become more prevalent in the life sciences since more than one patent is usually needed for biotech companies to stay afloat.

Also in 2007, post-translational modification took center stage. *GT* spoke with Josh Coon, Akhilesh Pandey, Phil Gafken, Scott McLuckey, and Benedikt Kessler about electron transfer dissociation, a technique to uncover PTMs. Coon, an ETD pioneer, sang its praises while Pandey's lab tested its capabilites — finding 80 percent of the modification sites described in the literature. Others were more cautious, saying classical instruments still have much to offer. — *Ciara Curtin*

>SHORT READS

As of January, George Weinstock has become a professor of genetics at Washington University in St. Louis, as well as associate director of its Genome Sequencing Center. Formerly, Weinstock was a professor at Baylor College of Medicine, and co-director of its Human Genome Sequencing Center.

Florida promised $80 million to the University of Miami's Institute for Human Genomics. The institute, which opened in November, started with an initial $37 million in federal funds and an undisclosed amount from the university's medical school.

The Office of the Inspector General at the US Department of Health and Human Services reported that the NIH didn't do its homework. After being queried, the NIH couldn't come up with the number of financial conflicts of interest its extramural grantees reported between 2004 and 2006, which it is required to do.

Peter Covitz, CEO of the NCI's Center for Bioinformatics and prime initiator of the caBIG project, left the NCI at the end of February. Covitz is headed to MDS Nordion as senior vice president of innovation. MDS Nordion is a mid-sized nuclear medicine biotech company based in Ottawa, Canada.

MicroRNA: MIT's Kellis Finds Possible Genetic Switch in Dual-Direction DNA

While biologists debate the idea that most noncoding RNA serves no real function in the genome, MIT's Manolis Kellis is busy finding function in the most unexpected places. In his latest work, he's located pairs of miRNAs expressed from the same double-stranded DNA that are both functional. "What we've found out now is that, in fact, for some miRNA genes, the antisense transcript gets processed into a mature miRNA, which itself has distinct functions," Kellis says. "Both directions of the DNA are coding for distinct functions."

Kellis' work, published in the January 1 issue of *Genes & Development*, found two such miRNA pairs in the fruit fly and eight pairs in the mouse. The research is important simply because "double duty nucleotides" have never been observed before in animals, Kellis says. He adds, "It's not just that you're trying to cram in additional function in a little space — it's that antisense miRNA, sense/antisense pairs, provide a natural mechanism for a genetic switch."

"Both directions of the DNA are coding for distinct functions."

Using a computational approach, he and his team searched sequence alignment data for evolutionarily conserved miRNA elements, and isolated several that appeared to be sense/antisense pairs. In predicting that their targets would be several Hox genes — these genes play a large role in controlling the positioning of body parts — they ran several follow-up functional assays. First, they successfully matched known sequencing reads to the *in vivo* miRNA transcript. Second, upon expressing the antisense miRNA *in vivo*, they found that the targeted Hox gene was repressed. Finally, a transgenic fly built to overexpress the antisense miRNA showed marked homeotic transformation — the transformation of one body part to another is a hallmark of Hox gene regulation gone awry. "The most surprising thing was that the antisense transcript, in fact, showed a homeotic transformation that is much, much more pronounced than the sense miRNA," says Kellis. He notes that when they overexpressed the sense miRNA, there was instead a very subtle effect.

MANOLIS KELLIS

Kellis believes that the sense/antisense pairs in the Hox cluster may contribute to maintaining this tightly regulated developmental circuit. There could be more of these kinds of pairs, providing in equal measure form and function, throughout a variety of genomes. "This is pretty exciting in the sense that it's not just a *Drosophila*-specific thing and it's not just a Hox-specific thing," Kellis says. "It may be a more general regulatory mechanism for animals." — *Jeanene Swanson*

Web bookmarks: Losing Track of Journal Articles? Zotero Wants to Help

As users of Digg and other social bookmarking sites know, tracking Web pages comes in handy. Now Zotero, a Web-based tool from George Mason University, takes it a step further by providing a spot for note-taking, while also storing and organizing content such as journal articles or Web-based tools. Last fall, Zotero became compatible with all of the *PLoS* journals.

"Part of the birth of Zotero was frustration with existing tools like Endnote and RefWorks that weren't really cutting it for what we were wanting to do," says Trevor Owens, a Zotero technology evangelist.

Unlike Endnote and RefWorks, Zotero is a freely available, open-source program out of George Mason's Center for History and New Media with approximately 400,000 users. Though originally designed with humanities researchers in mind, Zotero also has appeal to scientists. "Although there is a lot of history material online, you still have to do a significant amount of research in archives, while the science community that has picked up on Zotero already has a very strong workflow in Web-based tools, like journals like *PLoS*," Owens says.

The science community that has picked up on Zotero already has a very strong workflow in Web-based tools

The launch of Firefox 2.0 also pushed the development of Zotero, since that version allows people to develop extensions to increase the browser's functionality, just as Zotero does. When installed, its JavaScript-based translators work quietly when the Firefox browser is open. An icon appears in the Web address bar and, if clicked, saves that page. All the saved items can be viewed in an iTunes-esque table where related items can be grouped, tagged, or searched. Everything — the metadata, images, and PDFs — is stored in the user's Firefox profile.

TREVOR OWENS

Last November, Zotero and the seven *PLoS* journals took a step to becoming seamlessly integrated. "We've had a significant amount of people requesting that we have a translator for *PLoS*. We were more than happy to do it," Owens says. Zotero can store the metadata, such as author names, issue and volume number, and DOI, as well as the full-text articles from all of the *PLoS* journals.

Next, the developers behind Zotero are working on getting its own server up and running so they can expand its capabilities to let users join groups, share their collections, and have Zotero suggest items for them to check out. Also, a new plug-in is in the works to allow Zotero to sync with del.icio.us bookmarks.

— *Ciara Curtin*

>SHORT READS

GE Healthcare will acquire Whatman for $713 million, adding Whatman's sample prep products to GE's protein chromatography platform and cellular analysis technologies. The purchase will up GE Healthcare's total staff of roughly 46,000 by about 1,100.

454 Life Sciences and Cold Spring Harbor Laboratory have announced plans to sequence the Tasmanian devil's genome in the hope of identifying which genes are responsible for the fatal facial tumor disease that's afflicting the wild devil population in Tasmania. Since 1996, devil numbers have been reduced by 90 percent in some parts of the state.

The NSF doled out $50 million for the iPlant Collaborative, an initiative to expand research in plant genetics. Building upon the National Plant Genome Initiative, the center will be led by the University of Arizona's BIO5 Institute, and includes researchers at Cold Spring Harbor Laboratory, Arizona State University, the University of North Carolina at Wilmington, and Purdue University.

Elisabeth Allison has joined Helicos BioSciences' board of directors. Allison is a partner at ANZI Partners, and is chief negotiator for ANZI Partners' publishing media and software ventures. She was an associate professor in economics at Harvard University.

>SHORT READS

A new FDA Subcommittee on Science and Technology report said that the FDA is unprepared to keep up with genomics and pharmacogenomics advances. If the FDA is to serve the new demands presented by today's biomedical advances, it'll need more federal resources and funding, the report said.

Abbott Laboratories will spend $20 million for an initial 10.25 percent stake in Isis Pharmaceuticals' subsidiary Ibis Biosciences, with options to acquire as much as 18.6 percent before July 31, and the remainder of the company before June 30, 2009. Ibis sells the Ibis T5000 Biosensor System, which is used for rapid identification and characterization of infectious agents.

Genetix Group has appointed Jerry Williamson to the post of president of US operations, a new position. Williamson formerly served as president of Biacore, was president of the genomics company Pyrosequencing, and was in commercial management at Genzyme and at Roche Laboratories.

Predictive Biosciences has appointed Martin Madaus to its board of directors. Madaus is president, CEO, and chairman of Millipore and he formerly was VP of development at Roche Molecular Diagnostics and a GM at Boehringer Mannheim.

Sequencing: To Solve Short Read Problem, Danes Launch Network for Data Analysis

While next-generation sequencing technology continues to push the high-throughput envelope, handling the landslide of data remains a persistent problem. Resourceful researchers have no trouble developing tailor-made tools to deal with the data deluge, but the distribution of such applications to the wider research community is often marred by the fact that not all labs use the same sequencing platforms.

In order to address this challenge, the Danish Agency for Science Technology and Innovation recently announced a $3 million grant to support a collaborative network of Danish research institutions called Seqnet. The three-year initiative aims to support the development of a national, user-friendly graphical interface platform for the analysis of next-generation sequencing data. Seqnet will be a team effort among the University of Copenhagen, the Agricultural Sciences at Aarhus University, Aalborg University Hospital, and the University of Southern Denmark, with Danish bioinformatics vendor CLC bio.

"We realized very early on that you had to develop your own applications or else rely on the slow development of comprehensive tools."

"There is a need to make a unified, next-generation sequencing platform capable of analyzing sequences for many purposes, regardless of whatever platforms they are coming from because each has their own software tied to that particular sequencer," says Kare Lehmann Nielsen, leader of the Seqnet project and an associate professor at Aalborg University. "We are already in the process of writing small scripts, but lack the capability to develop them in a user-friendly manner and make them easily distributable between labs because they are complicated, command-line based, and very specialized."

KARE LEHMANN NIELSEN

The platform will be tested in various research projects, such as metagenome analysis of bacterial systems taken from waste water treatment facilities, cancer cell typing, and tag-based expression. "We realized very early on that you had to develop your own applications or else rely on the slow development of comprehensive tools. … There is not nearly good enough software analysis for gene expression profiling," says Nielsen, who works on tag-based gene expression. "It is really important to do the visualization of the data in a way that is interpretable to regular users." Seqnet aims to eventually deploy a bioinformatics package with a slew of algorithms ported to CLC's workbench platform.

— *Matthew Dublin*

Protein alignment: New Tool Allows for Flexible Matching to Track Distantly Related Proteins

When it comes to simulating real-world conditions, most protein alignment algorithms fall short. Three researchers from Tufts University and MIT developed a new alignment tool that allows the protein to twist or move during the alignment process, more closely matching biological conditions. Lenore Cowen, from the Tufts computer science department, says her group is interested in related proteins that may be evolutionarily distant and in what those proteins' functions may be. Since no program allowed them to model proteins as they wanted, Cowen and MIT's Matt Menke and Bonnie Berger made their own program. "None of them did what we actually needed to do quite well enough when the structures were just evolutionarily a little bit too far away. We were very arrogant. We said, 'Oh well, we'll just write our own,'" says Cowen.

"We were very arrogant. We said, 'Oh well, we'll just write our own,'" says Tufts' Lenore Cowen.

Their program, called Matt for "multiple alignment with translation and twists," is an alignment fragment pair chaining program that allows for local flexibility. "Most previous methods had taken these protein crystal structures as rigid bodies and they aligned the rigid bodies, but the protein is only a rigid structure when you crystallize it. They actually are somewhat flexible," Cowen says. So instead, their program allows for a certain amount of rotation and translation.

LENORE COWEN

After a year and half of development, Cowen and her team ran benchmark tests of Matt on datasets from Homstrad and SABmark, common standard benchmarking programs, versus other alignment tools. Matt performed as well as other tools on Homstad but better on SABmark, which includes proteins that are more distantly related, as the authors reported recently in *PLoS Computational Biology*. "We're able to capture similarity even when the structures are starting to really not be that similar," Cowen says. Matt outputs its data in FASTA or PDB format, and can also output a rasmol script so users can view the protein alignment as an animated movie. The program is open-source and freely available from the Tufts or MIT websites under a GPL license.

Next up for Matt is adding support for partial alignments so it can show only the proteins that line up out of a larger group. The researchers are also adding in sequence information to appeal to users who prefer to look at sequence and alignment simultaneously.

— *Ciara Curtin*

>SHORT READS

Janelle Hoskins has been named director of the Molecular Genomics Facility at the University of North Carolina at Chapel Hill's Institute for Pharmacogenomics and Individualized Therapy.

Vivian Cheung has been named an investigator by the Howard Hughes Medical Institute. Cheung, who is a pediatric neurologist at the Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine, studies the links between gene expression and individual susceptibility to disease and treatment responses.

The National Institutes of Health has invited Thomas Kelly and Keith Yamamoto to join its advisory committee. Kelly is a director of the Sloan-Kettering Institute at the Memorial Sloan-Kettering Cancer Center, and a professor at Weill Graduate School of Biomedical Sciences at Cornell University. Yamamoto is a professor of cellular and molecular pharmacology and executive vice dean of the School of Medicine at UCSF.

Roche has signed an agreement with Ventana Medical Systems to purchase the company for $3.4 billion. The acquisition will provide Roche with a tissue-based diagnostics platform, which it sees as an important piece of the oncology diagnostics market.

>SHORT READS

James LeVoy Sorenson, a medical device inventor and founder of several companies including Sorenson Genomics, died of cancer at the age of 86. Sorenson developed or invented the first real-time computerized heart monitoring systems, disposable surgical masks, non-invasive intravenous catheters, and blood recycling and blood infusion systems.

Researchers at Philadelphia's Monell Chemical Senses Center investigated the effect of gene knockouts on mouse body weight, finding that more than 6,000 genes influence body weight. They discovered 10 times more genes associated with weight gain than weight loss, among other findings that suggest that human obesity may be equally complex.

The NIH officially rolled out its open-access policy at the end of 2007, which requires all papers funded by NIH to be made available in open access journals within 12 months after initial publication. The policy also applies to papers written by investigators whose salaries are paid by NIH.

Beckman Coulter announced it will move its existing headquarters from Fullerton, Calif., to the nearby city of Brea by the end of 2009. The firm is also cutting 158 jobs from its Palo Alto, Calif., facility, in preparation to close the site and move its centrifuge manufacturing operations to Indianapolis.

Databases: OpenHelix Wins Grant to Develop Search Portal for Open-Access Resources

If you build it, they will come. Unless they don't know where to find it, that is. Enter Seattle-based OpenHelix, which has been offering database training courses for the past five years. With a new $1 million grant from the National Human Genome Research Institute, the team will be able to step up its offering with a search portal for publicly accessible databases.

"One of the challenges with this post-genomic era is that there's tons of data and lots of resources and databases that are free [and] publicly accessible," says Scott Lathe, OpenHelix CEO. "The challenge is, researchers can't find the correct resource because there's just so many out there. And then once they find it, they're complex so they don't know how to use them."

"The challenge is, researchers can't find the correct resource because there's just so many out there. And then once they find it, they're complex so they don't know how to use them."

Initially, OpenHelix contracted with several organizations to develop and conduct on-site training courses, including classes on how to use the three big genome browsers at Ensembl, NCBI, and UCSC. The company also developed related online training and Web seminars, but found the seminars to be less valuable than the on-site and online training courses. They currently have approximately 30 tutorials, but aim to expand that number to 100.

With the onslaught of more and more publicly available databases — Lathe estimates that there are about 1,000 right now — OpenHelix has shifted its focus to creating a tool to locate them. With the new grant, the team plans to build a semantic search tool that would be freely accessible from the company's website and that would allow researchers to find both databases and associated OpenHelix training courses related to specific search terms.

"The researcher will be presented [with] a list of not only the resources but also the training on those resources," Lathe says. "Hopefully to tackle both those issues: one, to find the right resource, and two, how to use it."

OpenHelix plans a beta launch for next month, with a full launch by September 2008. "Right now, [we] are focused on the life science researcher," Lathe says. "One of the critical needs is getting this information out into the biomedical [field]. And then someday, eventually, when personal genomics really do launch, I think we'll be in a very good position to [be] filling that same niche of being able to provide training on these very complex issues."

— *Jeanene Swanson*

Clinical research: GSK's Roses Brings a New Model of Drug Discovery to Duke

Allen Roses has a sense of urgency that might come as a surprise for someone who has spent his career in academia and pharma. "I had a major heart attack in 1990," he says. "It changed the way I live my life. I wake up in the morning, I blink twice, if I'm still here I go at 120 percent."

Indeed, that's what Roses is doing at Duke University, the institution where he spent 27 years before heading off to head up genetics research and pharmacogenetics at GlaxoSmithKline in 1997. Roses leads the Drug Discovery Institute, which he says is a new model of how drug discovery could be done in a non-pharma setting.

"If big pharma's not making it, the academics aren't making them, the VCs that support many of the biotechs want a return in three to five years, they're not going to be making it — so who's making the molecules?"

When Roses went to GSK, he initially took a three-year leave of absence to work on a drug for Alzheimer's. "I was very naïve about how long it took to make a drug," he laughs. But what he saw in pharma discouraged him. Frequent changes in leadership and areas of focus — not just at GSK, but throughout the industry — meant that successful drug candidates would be shelved even after patents had been filed on them. "A lot of stuff is left on the table," Roses says.

As he surveyed the discovery and development landscape, it occurred to him that systemic problems were standing in the way of real progress. Pharmaceutical companies tend to buy late-stage molecules from biotechs rather than build them in-house, and the academics who first propose molecules as potential drug candidates don't pursue them beyond basic research stages. "If big pharma's not making it, the academics aren't making them, the VCs that support many of the biotechs want a return in three to five years, they're not going to be making it — so who's making the molecules?" Roses asks.

It won't be Roses, either, but he hopes his so-called virtual pharma will get molecules to the point where they're interesting and relatively low-risk for pharmas to take on. At his new institute, Roses has formed an executive committee of eight or 10 people with expertise in various stages of drug discovery. "It really is a group think," he says.

The idea is to form partnerships with pharmas to take over promising molecules that have been shelved, and Roses' team will farm out the stages of discovery and preclinical work to get that molecule further along the path to being an approved drug. "We're going to be trying to become a source of proof-of-concept molecules," Roses says. While the concept is definitely an experiment, he says, "one success and I think this thing becomes a model."

ALLEN ROSES

While that covers late-stage molecules — those that have already been put through the paces of early discovery — Roses says the institute will also work with earlier-stage candidates. Those will take more time and prove more costly, so Roses has secured funding from several donors — "wealthy people and small countries with a lot of money," he says.

Roses and the executive team are currently evaluating a few such deals, which are in various stages of due diligence, he says. He hopes that the first success would come in less than three years.

Another aspect of Roses' new plan is a separate entity that he calls Cabernet Pharmaceuticals, which is his own consultation company that helps pharmas handle project management for compounds in the drug development stage. Companies might come to him, for example, if they "have a molecule that's in development [and they need to] get a companion diagnostic on time for registration with the FDA." Roses says he started up this venture to fulfill his interest in late-stage pharmacogenetics and adverse events. "It took off like wildfire," he says, noting that the appointments he has lined up should keep him busy for all the time he's allotted to the consultancy for its first year of business.

— *Meredith Salisbury*

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The Month in Blogs

In the past month, bloggers have been abuzz about the 1,000 genomes project, Venter's latest foray in synthetic biology, the value of impact factors, and collaborative science.

By Jeanene Swanson

1,000 Genomes Project

In January, a consortium led by NHGRI, Sanger, and the Beijing Genomics Institute announced the 1,000 genomes project, a next-gen sequencing initiative. The news was a bit confusing, but the blogosphere cleared that up. At Genetic Future, Daniel MacArthur noted that the project will only be sequencing about 200 complete genomes, and then performing exon sequencing on portions of the rest. Ultimately, the goal is to catalog variants at as little as one percent frequency across the genome. Adaptive Complexity's Michael White responded to the news, saying that while it's a great start, creating useful, high-res catalogs of rare genetic variants might necessitate sequencing a lot more than 1,000 genomes.

genetic-future.com
adaptivecomplexity.blogspot.com

Venter Builds a Synthetic Genome

Not surprisingly, Craig Venter and his colleagues were all over the news for creating the longest synthetic genome. In response to the media coverage of what some people considered a non-event, the blogosphere couldn't hold its tongue. Carl Zimmer at The Loom acknowledged the technical challenge of creating a synthetic *Mycobacteria genitalium* genome, but notes that scientists have yet to boot it up in a live cell. As an added twist, Venter's team encoded several watermarks in the genome, which a *Wired* blog reported to be the names of the scientists themselves. MIT synthetic biologist Drew Endy commented that the watermarks would likely disappear through random mutations, making them more like graffiti than distinguishing engravings.

scienceblogs.com/loom
blog.wired.com

Learning to Share

The blogosphere was chattering about everything open access and open notebook. *Scientific American* had a long piece about the pros and cons of collaborative scientific research and blogger Pedro Beltrao announced he'd be leading an open notebook study, the data for which he's depositing at Google Code. In the *New York Times*, an opinion piece wondered whether cancer researchers shouldn't be required to open their data archives for other investigators' benefit. Moreover, with the Protocol for Implementing Open Access Data announced at Science Commons in December, blogger Deepak Singh wondered how this will change the way scientific information is distributed.

pbeltrao.blogspot.com
mndoci.com/blog

Impact Factors Take a Hit

Impact factors definitely got a bad rap this past month, as did the analysts behind them at Thomson Scientific. Rockefeller University scientists wrote an opinion piece in the *Journal of Cell Biology*, slamming the process that Thomson uses to rank publications as well as the lack of transparency in the rating process. In turn, Thomson replied with an editorial defending its methods and saying that the Rockefeller crew based its stance on misinterpreted information. Blogger Neil Saunders opined that impact factors are outmoded, while a Nature Network blog encouraged alternatives such as the SCImago Journal Rank indicator.

network.nature.com/blogs/user/mfenner
nsaunders.wordpress.com

The Path Less Traveled

In Missouri, a couple of grad students showed their university a thing or two about career training. Now the school underwrites a program to help students learn about scientific jobs outside of academia. *By Meredith Salisbury*

Denise Bouvrette, a fourth-year graduate student at the University of Missouri, thinks that after she completes her degree she might like to become a science writer or a liaison between a biomedical company and the public.

Funny thing is, a year ago Bouvrette didn't even know there were such positions — and she certainly wouldn't have known where to find one. After coming to terms with the idea that a career in academia didn't appeal to her, she realized that her knowledge of alternative scientific career options was woefully lacking. "I spent a lot of time online" looking into other paths, she says. "I realized that I could spend the next year trying to get all this information for myself."

There are a number of students and postdocs in the same situation — and, frustratingly, just as many scientists who are enjoying successful careers outside of academia and have plenty of expertise to share. The trouble is connecting these people.

Bouvrette and her labmates, including Emily Stagner, took their curiosity about alternative careers a step further than most students do. Bouvrette wrote a proposal for a training program that would bring in speakers to talk about their jobs and got "an

DENISE BOUVRETTE

How to Start Your Own Program

Whether you're a student, postdoc, or established faculty member at a university, you too might find it valuable to help set up a career exploration program at your institution. Denise Bouvrette offers advice from her experience.

What do you want to get out of it? Bouvrette says the first step is to decide exactly what you're looking to gain from such a program, and devise a plan based on that. For the kind of glimpse-of-alternative-careers series she had in mind, seminars seemed like the best way to accomplish her goal. But other goals might be better served through other means, so be flexible and creative. Don't forget to identify your target audience and make sure you're serving their needs. A quick survey could help you stay on track.

Communicate like a champion. If you're a student, the grad school may be your best bet for an ally; if you're faculty, hit up your collaborators and fellow researchers to help start up a program. Let everyone know what you're trying to do and identify your assets — who's willing to help and what they can offer.

Check the university's mission statement. Bouvrette says a good break came in the university's mission statement, which included a section about promoting training for graduate students and promotion of economic development for the state. In her proposal and other program materials, Bouvrette used those items to her advantage, arguing that good career counseling for grad students was necessary to the university's mission and would encourage students to get jobs in the state. Showing the school how it will benefit never hurts, she advises.

overwhelming response" when she circulated it among other students and postdocs.

Stagner, who helped Bouvrette launch the program, says that "as grad students here in the academic culture, we're pretty well aware of what a professor goes through," but that when it comes to looking for a career beyond the university setting, "we're doing that blindly."

Next, Bouvrette did what any university member would: she formed a committee. Through a pilot project for the training program, Bouvrette approached people who were scheduled to speak on campus for other reasons and asked if they could give another hour for a career seminar. Speakers have included an employee from a small genotyping company, a patent attorney, and a genetic counselor. Students get to hear about a day in the life of these people, as well as how to search for that kind of job. The seminars have attracted as many as 50 students, and benefits were immediate: after the patent attorney's talk, for instance, a couple of students reported switching to a joint PhD/JD program to pursue science in a legal setting, according to Bouvrette.

Bouvrette and her committee followed up each seminar with a questionnaire for attendees; the positive responses from those provided even more ammunition to support the program, which they then shopped around to a number of science departments. The group needed funding to pay for the events and reimburse speakers for their travel expenses; several science departments have contributed.

With funding in hand, Bouvrette hopes that the program — now known as ACES, for Alternative Career Exploration in the Sciences — will be active long after she's gone. She remembers that early in her research into non-academic jobs, she was flummoxed even by job titles she saw in job listings. "What does that mean, director of scientific affairs?" she remembers wondering. "What's 'Scientist I'?"

Today, the program has seminars every other month; each seminar is paired with an informal networking session as well. That helps students "work on their networking skills, which a lot of us are not very good at," Bouvrette says. The events also give students contacts for future employment or even just to get more information about certain types of careers.

A Virtual World

Linux on your Windows machine? Migrating flocks of computers? Virtual machine technology is steadily opening up new possibilities for genomics data management and bioinformatics tools. *By Matthew Dublin*

Last month we looked at cloud computing, a compute architecture that provides users with access to large amounts of on-demand computing power through an Internet connection. Amazon, Google, IBM, and a growing number of other vendors are hosting compute clouds where users can go online, open an account, and for mere cents an hour, create virtual compute clusters complete with the desired CPU type and speed, RAM, and memory capacity.

Compute clouds are made possible through virtual machine, or VM, software, which allows users to create multiple virtual computers that function completely independently on one physical machine. There are many benefits to employing VMs, and in the case of cloud computing, it gives the cloud provider more bang for the buck because a single server can host numerous virtual compute nodes simultaneously, thereby increasing optimization of resources and saving energy and maintenance costs.

VM software also has a very practical and increasingly popular application for desktop users who desire the ability to run what would normally be incompatible software in their preferred operating system environment. For example, Windows users can run a Linux distribution simply by installing it on their virtual machine software platform of choice, and run Linux applications seamlessly alongside their native Windows OS. In most cases, the VM appears as any other open application, but in reality, it is an independent, virtual computer with its own operating system running next to the host computer's operating system.

But VMs are not only useful for those looking to reach across the compatibility divide. In addition to cross-operating system application access, this technology also comes in handy if there are certain programs that may only run on older versions — or, in the case of Linux, different distributions — of your current operating system. This is especially the case when you come across a must-have application but you're not ready to install an entirely new operating system just to complete a few tasks.

Biofx on the bandwagon

In addition to VM-savvy desktop users, this technology is also finding favor with bioinformatics software developers, says Michael Brudno, an assistant professor of computational biology at the University of Toronto. Brudno believes that it may actually be more reliable and cheaper to bring the computers to these ballooning databases, rather than the other way around; operating systems, after all, are smaller and therefore easier to move over a network connection than enormous datasets. Following this logic, the machines should be in a location where it makes the most sense to do the computation, says Brudno. "A virtual machine is just like a laptop — you can suspend and resume it, just like when you close or open your laptop," he says. "But instead of carrying it with you, you send your VM to another site, where it populates to other compute nodes."

MICHAEL BRUDNO

The concept of moving a virtual computer from one physical piece of hardware to another is called migration. "The way it works is that you have a running VM on your home machine and then you migrate the whole running machine from your own site to a remote site, so the result is that you still have network connections to

the original place where it came from," Brudno says.

The trick with genomics data has always been processing in parallel, so merely migrating a single VM doesn't cut the compute mustard. Brudno's solution is Snowflock, a VM software implementation specifically geared toward parallel computation over a cluster. Like other VM software solutions, Snowflock allows users to migrate a single VM over a network connection. Its usefulness to bioinformatics resides in its ability to clone a user's VM over an entire cluster. This is achieved through an almost instantaneous cloning mechanism that creates exact replicas of the original VM sent by the remote user and then populates each clone throughout the cluster.

"We are also looking at this as a solution to multiple laboratories with different needs sharing one compute cluster," Brudno says. VMs can allow for secure, shared usage of a cluster or server farm because access by the system administrator need only be granted to the user for an allotted virtual machine account. For example, if one biological research group wants to share its cluster resources and datasets with another, the guest would merely be granted a password to migrate virtual machines onto the cluster instead of granting direct access to the cluster. If security is breached and passwords are compromised, the hacker only has access to the guest VMs and not the entire cluster.

VM apps

VMs are also good for those intimidated by the world of Linux, or those still in the learning stage with bioinformatics applications. A suite of bioinformatics tools packaged in a virtual machine distribution called DNALinux Virtual Desktop Edition offers Windows users the chance to have at their favorite applications, such as HMMER, Bioperl, NCBI Blast, and many others, all contained within a prepackaged virtual machine distribution based on Xubuntu, an alternative version of the Ubuntu Linux distribution. DNALinux uses a virtual machine platform by VMWare, currently one of the more popular VM vendors. DNALinux developer Sebastian Bassi, project leader at the National University of Quilmes in Buenos Aires, says that while there are many live CD bioinformatics software packages available, a VM implementation allows users to save their settings and data. Bassi also says that the target audience for DNALinux is the greenhorn bioinformatics software user who is either not familiar with Linux or does not want to install Linux on his or her own desktop. Users can download DNALinux for free from VMWare's official site.

"Virtual machines overcome backup challenges by encapsulating all software and databases along with a pre-configured operating system in a single convenient package."

VMs also allow users to put the machine and data together in one self-contained package. Such is the case with WormBase, the central database for *C. elegans* and other nematodes hosted by Cold Spring Harbor Laboratory. According to Todd Harris, project manager of Wormbase, virtual machines solve problems associated with the creation of efficient backups, referential access, and most importantly, easy distribution. Databases like WormBase usually consist of multiple database backends, complicated visual display layers, and a slew of third-party software libraries, all joining together to create the end-user experience. "Any backup strategy needs to capture the underlying databases but also the presentation layer and hosting environment, so simply mirroring the resource onto additional hardware is prohibitively expensive and a maintenance headache," Harris says. "Virtual machines overcome backup challenges by encapsulating all software and databases along with a preconfigured operating system in a single convenient package."

The reason for creating a VM distribution of a Web-based database is that many users like the option of running the resource on their own machine, free of network congestion or server load, or even the need to be online, says Harris. For biotech companies and pharmas involved in expensive R&D projects, VM distribution allows for a certain level of privacy when browsing the database. Harris acknowledges that while there was a small amount of salesmanship involved in getting biologists and other researchers comfortable with the idea of downloading a VM implementation of WormBase onto their desktops, the results have been positive, with a lot of interest coming from users who want to set up their own clusters to support their labs. "A lot people in the bioinformatics world were not even aware of virtualization, but all you have to do is tell them it's just like opening up a Word document and they get it," Harris says.

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KEITH ROBISON My Take

Welcome to the Blogosphere

Keith Robison introduces you to why scientists blog, how to find relevant and useful sites, and a phenomenon called the blog carnival.

It is a problem nearly as old as the written word: Given a text that is found useful or enjoyable, how does one find others like it? In the days of Gutenberg, the limited number of authors and slow process of producing texts mitigated the problem, but in the modern age the problem simply grows exponentially.

Blogs are websites consisting of a series of written posts by one or more authors. Their general tone can range from personal diaries to online columns to running journal clubs and, in most, readers are encouraged to comment on the entries.

Why do people blog — or more specifically, why do scientists blog? Certainly each scientific blogger has her or his own reasons, but in my case it was a mix. I started my blog during a difficult professional transition, having been forcibly severed from what had been my scientific home of a decade. I wanted to continue to think about some of the topics I had been working on and to expose my thoughts to the glare of professional criticism. I also liked the idea of writing something more rewarding than terse PowerPoints and hurried e-mails.

The rewards have been numerous. I do get to write something I can try to be proud of. I do get critical feedback that helps refine my thinking. And on a very personal note, I get to connect with old friends who find me through the blog and make new ones through those who comment there.

From the point of view of a professional scientist, there are many blogs that may be useful and interesting. But how do you find the right ones, and keep up with the new ones that wink into existence?

A first approach is to find recommendations from back in the printed world or from a friend or colleague. This might identify a bunch of sites, and after browsing them you are likely to find a few that really click — perhaps you enjoy the commentary, or find the authors are good at pulling hidden gems out of the literature. Most blogs include a blogroll, or a list of other sites the blog author finds interesting; this can be a rich hunting ground for other sources. There are also services that aggregate multiple blogs on related themes, such as the DNA Network, which is like a newswire service for blogs related to genetics and genomics that you can subscribe to through an RSS feed.

But if you're looking for an overview of some of the recent blog traffic in a given subject area, check out the species known as a blog carnival. They don't have rides or barkers, but they're a good way to survey the field of scientific blogging. The general scheme is much like a floating poker game: a set of blogs takes turns hosting the carnival. At a given time, the host of the carnival collects recent blog entries of interest and writes a post mentioning all of them with short commentary and links back to the original articles.

KEITH ROBISON

A number of active carnivals exist that may be of interest to *GT* readers. Three that I've contributed to in the past are Mendel's Garden, which celebrates the full spectrum of genetics; Gene Genie, which has the ambitious goal of eventually having at least one post covering every gene in the human genome; and the Cancer Blog Carnival, which covers a wide spectrum of cancer research.

Keith Robison's Omics! Omics! blog frequently covers issues on the intersection of large-scale biology research with the biotechnology industry. His blog can be found at http://omicsomics.blogspot.com

The Legacy of Ling and Smith

With $250 million in funding, Marco Marra's genome center aims to deploy the latest technology in the battle against cancer — but it hasn't forgotten the mountain pine beetle. *By Ciara Curtin*

In 1997, Michael Smith and Victor Ling founded the Genome Sciences Centre, a high-throughput genomics center with a sharp focus on cancer. "Here you have two of Canada's most widely respected and well-known scientists, Victor Ling and Michael Smith, coming together and saying that they were devoted to the concept of a genomics presence in Canada," says Marco Marra, director of what is now the Michael Smith Genome Sciences Centre. Smith won the 1993 Nobel Prize in Chemistry for site-directed mutagenesis, sharing it with Kary Mullis, who was recognized for his PCR work.

In the late '90s, Ling was the vice president of research at the British Columbia Cancer Agency, which was instrumental in getting the new genomics center up and running. The British Columbia Cancer Foundation gave Ling and Smith $25 million to launch the center. "At the time, this was the single largest investment put into the field in Canada," says Marra. "The cancer foundation was persuaded to back the enterprise based largely on the belief that cancer and cancer genomics would be the next big thing."

The GSC cut its teeth on its first big project, generating a BAC fingerprint map of the mouse genome in conjunction with Washington University and the Sanger Institute. Since then, Marra says, the center has had a string of grants and contract funding, totaling approximately $250 million. It has expanded to 230 staff members, with 10 principal investigators who focus on a range of projects from proteomics to mapping.

MICHAEL SMITH GENOME SCIENCES CENTRE

"We're all collaborating at a very highly integrated level. I'm working with the cancer genomics people and the gene expression people," says Steven Jones, head of bioinformatics at the center. "When we write large applications, we are writing them together as a team. That's really how we're running the center."

The center hasn't lost its cancer genomics focus. Of the 60 or so ongoing projects, a whole host of them are looking into the genetics and genomics behind cancer, including studying the follicular lymphoma genome in deep detail as well as analyzing which genes keep people healthy by looking at octagenarians who have never developed cancer, cardiovascular disease, or pulmonary disease. "At the time [the center was founded], it seemed like a focus on cancer genomics was exactly where this field would head. And in hindsight, it looks like Victor and Michael were right," says Marra. The GSC, through Genome British Columbia, also takes on projects unrelated to cancer.

Cancer and aging

The two big projects going on right now in the cancer genetics lab at the center are population-based SNP studies of non-Hodgkin's lymphoma and of healthy aging. The GSC functions under the auspices of the BC Cancer Agency, which is responsible for all of the cancer patients in British Columbia. Angela Brooks-Wilson, who runs the cancer genetics lab, tries to keep that in mind. "What I like to do is take into account, or base our studies around, the BC Cancer Agency's mandate for cancer care

and research for the whole BC population," she says. In conjunction with researchers at the cancer agency, her lab is conducting a SNP and haplotype-based case-controlled study to uncover genetic susceptibilities to non-Hodgkin's lymphoma.

Brooks-Wilson is also looking into what it takes to grow old gracefully — that is, without developing cancer, cardiovascular disease, pulmonary disease, or diabetes. This study takes a twist on a case-control study since the cases here are people 85 years or older who have never developed any of those diseases or conditions, while the controls are middle-aged people recruited randomly from the population, regardless of their health. "The study has a genetics, rather than lifestyle, focus, and we want to find genetic factors that contribute to healthy aging," says Brooks-Wilson. In particular, her team, which includes GSC investigators Marra and Jones as well as outside clinicians, is using a SNP approach to the research.

Next-gen at the fore

Naturally, technology has a critical role at the GSC, which continues to build up its instrumentation. "Right now, perhaps not surprisingly, we're quite heavily focused on developing applications for next-generation sequencing and, in particular, the Illumina sequencer," says Marra. GSC scientists have made approximately 500 Illumina sequencing libraries and are ramping up their core instrumentation.

"The big thing is we [can] now start to attack cancer genomes fairly robustly with these new devices," adds Jones.

Marra's already got one experiment in mind to try out their new next-gen sequencers. As a continuation of their BAC fingerprint mapping projects, GSC researchers are making whole-genome, deeply redundant BAC libraries of cancer genomes that they are then fingerprinting to look for cancer mutations. Working from a library of approximately 150,000 BACs and using a combination of restriction enzymes to generate a pattern, they compare the cancer genome pattern to one predicted computationally from reference genomes. Any difference between the predicted pattern and the fingerprint gets marked as a candidate mutation to be further validated.

When they made a BAC fingerprint map of the follicular lymphoma genome and analyzed it, they found that the genome has hundreds or thousands of tiny deletions with a median size of about 5 kilobases. "It turns out that many of these itty-bitty, tiny deletions are associated with repeats," says Marra. "We think this is a fantastic structural genomics project, and we're quite keen now to take that same genomic material and analyze it on our Illumina sequencers to see what the overlap and the pickup rate is. It could be that the BAC fingerprinting gives us better detection sensitivity in these regions than the Illumina because these regions are enriched in repeat sequences and, of course, sequencing repeats with short reads is tough work."

>MICHAEL SMITH GENOME SCIENCES CENTRE

Vancouver, British Columbia

HOST: British Columbia Cancer Agency

DIRECTOR: Marco Marra

ESTABLISHED: 1997, by Michael Smith and Victor Ling

SIZE: 50,000 square feet of lab, occupying two floors of two buildings

STAFF: About 230, with 10 principal investigators

FUNDING: About $250 million from 25 sources, including British Columbia Cancer Agency, Genome Canada, Genome British Columbia, the National Institutes of Health

FOCUS: Cancer research

'OMICS TOOLS: New Illumina sequencers, BAC fingerprinting, SNP analysis, as well as bioinformatics and proteomics

The forestry branch

Another part of the GSC's mandate is to take on projects important to British Columbia as a whole. "With funding from Genome British Columbia, we are essentially a provincial platform for certain types of genomic activity, including DNA sequencing and bioinformatics," says Marra.

With the surrounding forestry community, GSC's team is working on the genome of the mountain pine beetle and the blue stain fungus it carries. This bug and its fungus have decimated about two-thirds of British Columbia's forests. Due to warmer winters, the mountain pine beetle population has exploded, says Marra. The beetle chews on the bark of the trees, weakens them, and leaves the fungus behind — which further harms the trees by interfering with water uptake and movement. At the genome center, scientists are looking for vulnerabilities in the beetle and fungus to control their spread throughout the province. "The idea is now to figure out how can we restrict spread by perhaps using genomics to study the beetle and fungus to find targets or susceptibility to agents — perhaps even biological agents that would allow us to control the infestation," says Marra.

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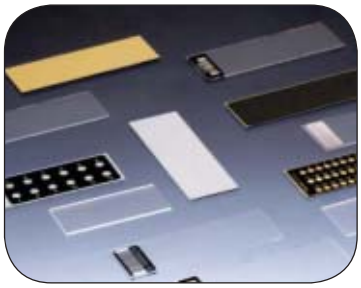

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TISSUE MICROARRAYS

The Awkward Adolescence of Arrays

Tissue arrays have found their footing in translational research — but scientists say they're still struggling with imaging and standardization.

BY JEANENE SWANSON

As far as microarrays go, gene chips might as well be considered the new kid on the block. All sorts of samples can be put down on a slide in an array format, and the longstanding tissue microarray is among the most useful to the field of clinical pathology. While these arrays are primarily used to probe large numbers of tissue samples for cancer biomarkers, many pathologists still haven't made the jump to truly high-throughput biology — they eyeball each sample individually.

The first tissue array was created more than 20 years ago, but it's taken until the last decade for automated arraying and imaging to propel the technique into the realm of large-scale biology. Still, automation has yet to be widely adopted, leaving many pathologists looking for more objective analysis. Few vendors offer such standardized, quantitative readouts, and in many cases, the automated platforms are just not affordable.

Most labs create their own tissue microarrays using archived patient samples. There are at least 20 vendors that sell prefabricated arrays; however, most of these aren't that useful because they lack archival clinical annotation. "There's a very wide range of tissue and questions and possibilities with formalin-fixed, paraffin-embedded material," says David Rimm, director of Yale's tissue array core facility. "In fact, one of the great resources that I think many institutions have … is the pathology archives. [They] represent our oil well, so to speak."

DAVID RIMM

Building blocks

The process of creating a tissue microarray is labor-intensive, whether one has automated arrayers on hand or not. Using a hollow needle, tissue cores as small as 0.6 mm in diameter are extracted from paraffin-embedded clinical biopsy samples, and then deposited into a master block in an evenly spaced array pattern. From this master block, sections are cut and mounted on a slide. Most often, researchers use immunohistochemistry to see which protein is being expressed, how much is there, and its specific location within the section. These arrays can also be used to visualize nucleic acids through fluorescent *in situ* hybridization.

Tissue arrays have found a strong footing in clinical research labs, whether for biomarker discovery and validation or for drug development studies. "Users are looking at tissue biomarkers, or looking at trying to understand protein function better. So they purified a new protein X from some gene screen and now they want to know, is it expressed predominantly in primary tumors or in metastases? Or is it expressed only in low-grade tumors or low-grade and high-grade? Or is it expressed in prostate cancer but not in breast cancer?" says Rimm. "Those are the kinds of questions they can ask."

In clinical trials, associating patient drug information with gene expression patterns is critical to making a successful drug, so the arrays are often put to use in dosage and toxicology studies. "It's condensed pathology," says Stephen Hewitt, who runs the National Cancer Institute's tissue core facility and produces arrays for both NCI and external researchers. "Instead of screening a few cases, you're screening large numbers of cases." His team tends to focus on validating biomarkers, both prognostic (Will a patient's tumor spread?) and predictive (Will the

STEPHEN HEWITT

patient's tumor respond to therapy?). While much published work has focused on localizing specific markers for disease mechanism of action, Hewitt notes that arrays have been a boon for molecular epidemiologists studying risk factors in large populations. Though the field is currently being driven by SNPs, he says, "people really do want to look at environment and protein interactions. … This is a platform where you can look at those questions — the questions you just can't answer at the DNA level."

Translational research

As a translational research tool or, as Hewitt says, "the translation point from basic science towards clinical medicine through pathology," tissue microarrays put broad population samplings to good use. NCI's Mark Sherman uses tissue arrays to classify tumors according to expressed protein biomarkers. He can then go back to find which factors impose more of a risk than others, and whether or not these can be related to all tumors. "Eventually we want to develop a risk model for breast cancer where we have factors that relate," Sherman says, in order to track how breast cancer develops, how it might be prevented, and how it could be detected more effectively.

His studies typically include thousands of patients. In one project, he is investigating 2,500 Polish women with breast cancer to correlate risk with different factors, including low penetrance genes. "If we had to look at one slide per patient, it would cost us a prohibitive amount of money," Sherman says. Not only do tissue arrays make these studies affordable, but they also increase reproducibility and accuracy, especially in light of the fact that staining many individual slides by hand can introduce error. "For efficiency, speed, standardization — very large studies have tried out this approach," he adds.

Enabling much of this research are standard assays, like IHC and FISH. For accreditation purposes, many clinical labs make use of the high-throughput nature of tissue microarrays for internal validation. At the Cleveland Clinic, Ziad Peerwani, a third-year resident in the department of pathology, is working on a project with the College of American Pathologists to standardize their IHC runs across the clinic — and thereby maintain its CAP accreditation — with specially created tissue arrays. Moreover, prefabricated arrays can also be used as internal experimental controls "for positive staining control to ensure that your techniques are working properly," Peerwani says.

With such widespread clinical use, it's hard not to wonder if tissue microarrays have potential diagnostic value. Most experts say that they predict little use as a diagnostic tool, simply because clinical diagnoses can't wait for hundreds of patient samples to come in before an IHC stain is run. Yale's Rimm sees it as basically a high-throughput research tool. However, echoing Peerwani, he's already seeing clinical use for control tissue. "Instead of putting on a single control tissue,

MARK SHERMAN

you can now put on 20 or 30 or 50 control tissues with every slide," he says. "I expect that we'll see an increase in usage in that context."

Images and standards

Technological advances during the last decade have produced platforms for automatically arraying and digitally visualizing arrays, which has cut down on time and subjective error. However, most experts interviewed still create and visualize their arrays manually.

"The big 800-pound gorilla in the room is not so much applying these materials, but actually trying to do it in a very validated, standardized fashion and then reading them," says Sherman. Most of the analysis is still done by eye, as IHC itself is difficult to standardize. IHC is not very reproducible and is very quantitative. Additionally, pathologists continue to struggle against tissue heterogeneity — trying to create an array that accurately and completely represents protein expression patterns that might differ across a tumor mass.

Rimm and colleagues have confronted these problems head-on. While automating the arraying process hasn't been that successful — tissues vary not only in protein expression patterns but also in

Hunting for Diagnostic Uses

Most pathologists are pessimistic about tissue arrays ever being used as a diagnostic tool, but try telling that to the British Columbia Cancer Agency's David Huntsman. An associate professor at the University of British Columbia, Huntsman recently finished a pilot study that tested whether arrays could be used in actual breast cancer patients to determine risk subgroups. "We considered whether we could use tissue arrays for the delivery of breast cancer biomarkers," Huntsman says. "We've done a pilot study which showed that the tissue arrays gave results which were basically similar to whole section data." While it would work in a clinical environment, he says, it would only work for laboratories where there's a very high throughput of samples being analyzed. "In the US, where the regulatory bodies are quite different, the use is likely to remain in quality assurance," he says.

DAVID HUNTSMAN

Huntsman sees more immediate challenges to the field. He thinks miRNAs and other noncoding RNAs have a lot of potential as biomarkers, "but to my knowledge there isn't an effective way of studying these using tissue arrays. And that's going to be a challenge." Another challenge is not just identifying and localizing proteins, but determining whether they're active post-translation. For this task, "there are real issues with looking at phospho-specific antibodies in archival specimens," he says.

thickness and amount of fat content — building out a platform to read the arrays in a more standard fashion has. In 2000, Rimm began working on a measurement tool that reads absolute protein concentration from an IHC stain, and it's now licensed exclusively to HistoRx under the name of Aqua. "The biggest limitation in my own mind, which is what we started working on in 2000 and now have overcome, is the reading of them," he says. "Back when they were invented, the only way to read them was to have a pathologist look at them and issue an opinion. While I am a pathologist and I respect pathologists' opinions, they will never be objective."

When using IHC to visualize protein concentration, pathologists use a subjective approach, estimating what they think might be the intensity of the spot and then grading it on a gross range. HistoRx's Aqua technology measures absolute quantity and assigns each spot a standardized score. While a much less subjective route than eyeballing, it's still difficult to get statistically relevant information from an IHC stain. "I think the biggest hurdle is capturing the true statistical power that comes from analyzing large populations on a tissue microarray," says John Tonkinson, VP of business development at HistoRx. With IHC, "you're using a very subjective, qualitative way of saying, there's a little bit there, there's a lot there — and now you're trying to apply that in a quantitative fashion to generate statistical value. The two are not compatible."

While HistoRx's is the only system that does absolute concentration, Rimm says, a number of other vendors offer digital scoring tools. However, Tonkinson notes, despite a move toward digital pathology, most people are still "doing it by eye." The equipment is, for the most part, only available to drug development companies or researchers with deep pockets.

Says Hewitt at NCI, "The image analysis field is something that is continuing to evolve. There's not going to be a winner; there's going to be a number of high-quality solutions." He's used several different systems, and acknowledges that the technology is not only expensive, but also a work in progress. "It's still a challenge. Only recently have I been willing to take my bigger projects into full, automated analysis," he says.

A major roadblock is database infrastructure. For example, Hewitt says that for each tissue array, there are 400 to 500 cores, with up to 20 gigs in images for each core. With such immense data sets, the analysis part tends to lag behind, simply because the data has more complexity and depth, he says. "It's not trivial bioinformatics."

Peerwani at the Cleveland Clinic knows that automation won't take away the need for pathological analysis — when it comes to how tumors act in living tissue and how they interact with surrounding structures, looking at tissue samples on a slide probably won't cut it. But for now, he says, "I think that the newer technologies are a very big boon to the research itself and to the art and science of using tissue microarrays." He adds, "I think the problem is their expense. As those come down, it will be more practical to utilize it."

PROTEIN BIOMARKERS

Toward Clinical Proteomics

Scientists say protein biomarkers could have a real impact in the clinic. But getting there will require better sample sets, new platform development, and serious validation.

BY MEREDITH W. SALISBURY

You've got to wonder about scientists who focus on protein biomarkers. While there are plenty of far more stable types of markers, such as DNA, these people have deliberately chosen one of the most finicky analytes out there. As if that weren't enough, they're trying to wrap up multiple proteins into an assay panel and somehow ship them off to a clinical setting.

But these scientists contend that if they can get protein biomarkers to work, their virtues will far outweigh the pains it took to usher them into the clinic. For starters, says Shawn Comella, CEO of Monarch Life Sciences, proteins provide a more direct measure of what's going on in the body than other molecules do. "Just because you have a gene mutation doesn't mean you're going to see a disease," he says. "By measuring the proteins and really correlating it with other data you get a much better picture of what's going on with the patient or with the disease."

Proteins can also be detectable long before other changes — for instance, the DNA changes characteristic of cancer cells — make themselves known, says Drake Zhang at ProtTech. "A protein gives you the best chance for early detection of cancer," he adds, noting that his service company has seen increased demand for work with these kinds of biomarkers.

Early detection is just one goal of identifying and validating protein biomarkers. Potential uses for these kinds of markers include determining drug efficacy, risk stratification, prognosis and diagnosis of patients, classifying patient populations, and toxicology, says Comella.

Current challenges

There's no shortage of hurdles to overcome in the quest to turn protein biomarkers into a clinical mainstay. Perhaps above all else, though, proper validation procedures loom over the field.

The challenge is not about discovering biomarkers, experts say. "Everyone's drowning in candidates," says Emanuel Petricoin at George Mason University. "Every lab has a series of candidate markers that they think are great."

That's in part because proteins are continually changing, so if you're looking for changes in proteins, you won't be disappointed. "I've never seen anybody do a biomarker discovery project that didn't come up with an answer," says Martin McIntosh at the Fred Hutchinson Cancer Research Center. Whether that answer will hold up through validation studies is another issue entirely.

Validation — the step of taking hundreds or thousands of candidate biomarkers and putting them through their paces to find the handful that are really indicative of the disease or condition you're trying to predict or diagnose — is the real trick. "What all of us are lacking is a facile way of validating these multiple markers in a high-throughput system rapidly so that you can really separate the contenders from the pretenders with a large number of samples," Petricoin says.

While the discovery process happens in a massively parallel way, validation is still slowed by the need for high sensitivity and good reagents. "Right now, most people approach biomarker evaluation by generating an antibody [and running] an immunoassay or a radioimmunoassay," Comella says. "It generally takes a long time to generate an antibody, or you can't get a good antibody. It's also expensive."

At Monarch, Comella and his team use a mass spec-based system to eliminate the need for antibodies, but of course that means they're using a platform that is known to be less sensitive than its immunoassay counterpart. "We have some pretty elegant methods of getting around that by depleting proteins, by fractionating or enriching," he says. "Most of the time we can develop an assay that's as sensitive as it needs to be."

Gordon Kapke, senior director of biomarker services at Covance, says that the technology for looking

Power3's Protein Biomarker Play

While everyone else debates the possibilities for protein biomarkers, the folks at Power3 Medical think they've got it worked out. Late last year, the Texas-based company launched a breast cancer test in 12 Middle Eastern countries, where the incidence of breast cancer is three to four times greater than it is in the US. The $500 test consists of a panel of 22 protein biomarkers. Steve Rash, the CEO of Power3, says the company hopes to launch the test in the US as well after it completes an ongoing 100-patient study.

STEVE RASH

The company is also validating multimarker tests for Alzheimer's and Parkinson's. "These would be the first known proteomics tests to be commercialized," Rash says. The breast cancer test has demonstrated sensitivity and specificity of 80 percent or more, Power3 says, compared to about 40 percent for the current mammography standard.

Because Power3 performs all of its testing in its own CLIA-certified laboratory, these tests do not require FDA approval, Rash says.

at biomarkers has a way to go before it reaches the necessary point for clinical utility. "Modern LC-MS techniques have appropriate precision and reasonably good sensitivity," he says, "but you still are looking at only a small fraction of the human proteome." He estimates that to look at all of the proteins and truly evaluate their biological relevance "improving the sensitivity of the assays by 10- to 100-fold or more."

Another issue facing clinical proteomics is complexity — something the genomics field is just beginning to iron out itself. Going forward, Petricoin says, it's unlikely that protein biomarker tests will be based on a single analyte; instead, panels of analytes will be studied in concert to diagnose a patient or study drug response. "A lot of people in the last decade have been searching for that elusive single-analyte marker," Petricoin says, using PSA as an example of one that's currently used in the clinic. "The sea change has been toward discovering and measuring multiple markers at once."

Which is, of course, its own can of worms. Investigators have long been familiar with the concept that each protein has its own "sweet spot" of ideal temperature and other conditions. Imagine trying to accommodate a 20-marker panel with 20 different sets of conditions, and you can see what the field is up against. "The platform that you develop to measure those has to be unlike platforms in the past," says Petricoin. "That is not like your father's PSA test."

A final hurdle for all of this work is to have good sample sets to use in validation and other studies. Most biorepositories haven't required sample collection under the conditions necessary to study proteins, Petricoin says — for instance, samples may have sat out for several hours before being stored, rendering them useless to proteomics researchers. McIntosh recommends that scientists try to establish partnerships with clinical collaborators who have access to good samples and whose own work could be furthered with good protein biomarkers.

Life in the clinic

As intimidating as those challenges are, scientists are making progress on all of those fronts, thanks to hard work and funding initiatives from agencies like the National Cancer Institute. Experts say a few key events will help catapult protein biomarkers beyond the research lab.

For starters, Petricoin says that advances in mass spectrometry could go a long way to helping get these biomarkers validated. Hybrid and other novel platforms — including immuno mass spectrometry, multiple reaction monitoring, and the triple quad mass spec — are all progress toward clinical utility, he says.

But scientists have to realize that mass specs will never be a clinician's tool of choice, says Monarch's Comella. Once biomarkers are found and well validated, clinicians will have to be given an easier-to-use assay for them, he says.

Overall, optimism reigns in this field. Comella contends that it'll take just one big success to make the concept truly viable. "The big thing that will probably move it forward is to have a protein biomarker used in a clinical trial," he says. "I don't think we're very far [from that.]"

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TENURE

Works Well With Others

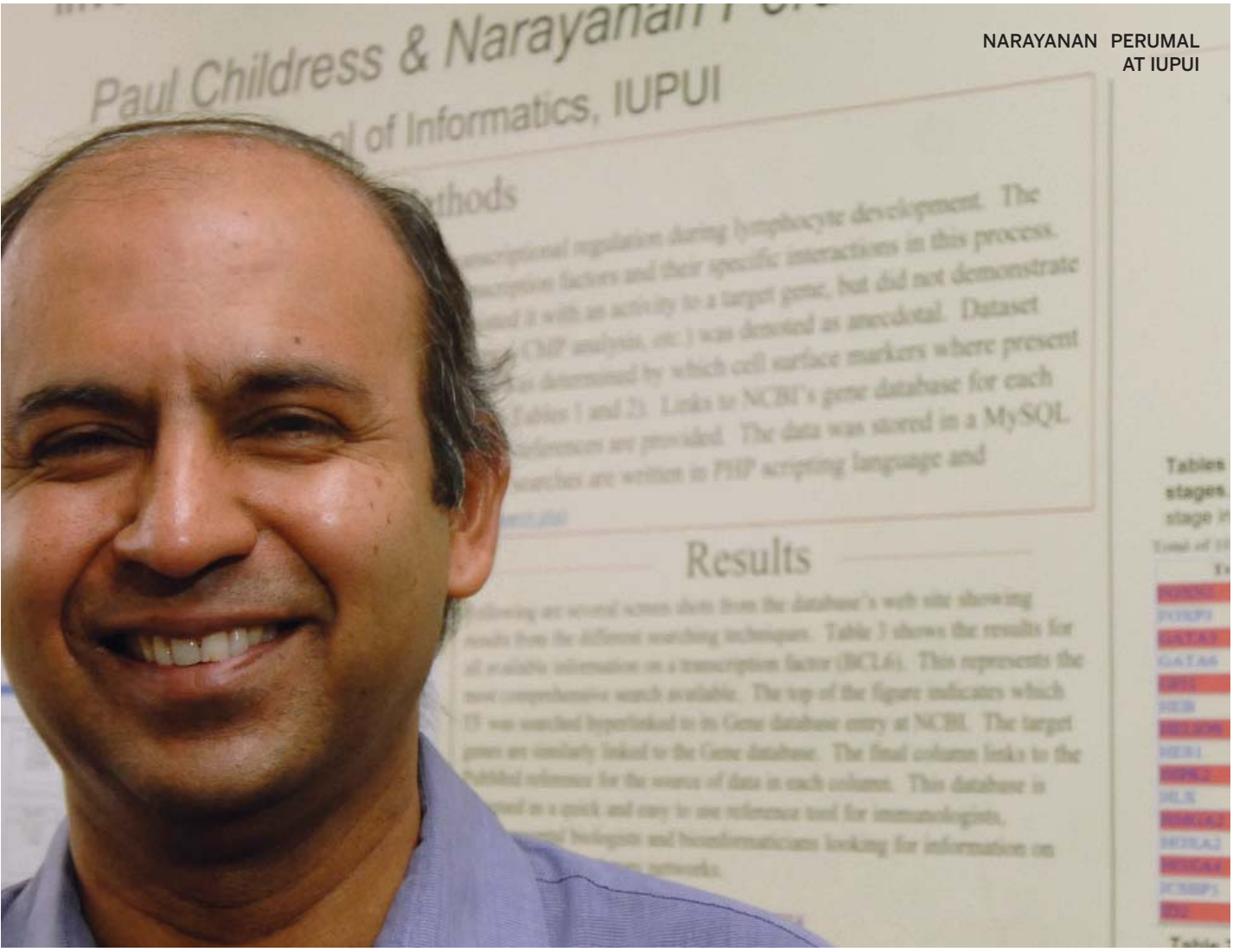
Large-scale biology led to the advent of "team science," but tenure is still awarded for individual work. When it comes down to better science or a solid career, researchers are losing out. *GT* investigates how (and whether) to fix tenure.

BY CIARA CURTIN

In two years or so, Narayanan Perumal will go up for tenure. An assistant professor at the University of Indiana/Purdue University School of Informatics, Perumal researches gene regulation and immune system development and collaborates with researchers at the medical school. Though the informatics school values working with others — really, it's the only way to be a successful bioinformaticist — Perumal still has some concerns about how the tenure review committee will assess his work.

"Informatics is a bridge between computer science and biology or computer science and healthcare," says Perumal, who has spoken to his associate dean to figure out how to make sure his contributions to the projects are recognized. "Our tenure committee has been telling us to clearly [say] what exactly is my part and what exactly was done from my collaborators' side, so they know how much credit to give me," he says.

When junior faculty members go up for tenure around their sixth year at a university, they are judged on their scholarship, the grant money they brought in, and community service and teaching. For scientists in large-scale biology who spend a lot of time collaborating or working in a consortium on a big project, it becomes difficult for review committees to parse out their individual scholarship and fundraising abilities. As one person in a large group, a particular researcher's name may not appear in that coveted first or last author position on the paper and may not be listed as a PI or co-PI on the grant. The culture of much of academia, and tenure review committees in particular, is tied to looking at a faculty member's independent work; so if researchers rarely or never



NARAYANAN PERUMAL AT IUPUI

work alone, they may miss out on getting tenure.

There's the rub. Groups and consortiums get the big questions in biology answered, but tenure committees don't evaluate groups — they evaluate individuals.

"In genomics … you do have to get out there and collaborate with people. It's really the only way to get it done. The datasets needed and the skill sets needed are too broad now. One person can't sit down and do it all themselves," says John McPherson, a platform leader at the Ontario Institute for Cancer Research. Pointing to the Human Genome Project, he adds, "Consortiums work. Consortiums get things done."

The funding is there, too, for team science. In the US, the National Institutes of Health and the National Science Foundation are giving money to collaborative groups. NIH's Roadmap Initiative includes support for collaborative team research projects and, according to a National Academies Press report on interdisciplinary research, there has been a steady upward trend in the number of PIs on grants awarded by NSF. "They are pouring millions and millions of dollars into interdisciplinary science," says Cathy Trower, a research associate who studies young faculty and tenure issues at Harvard University's Graduate School of Education.

The funding agencies have changed to accommodate teams of scientists working on one problem, but the tenure system has yet to catch up, clinging to a review system that may be outdated.

"We're training students that team science is the way to do it. It seems archaic to then attempt to judge them by a system that doesn't acknowledge that," says Hunt Willard, director of Duke University's Institute for Genome Sciences and Policy.

In fact, some junior faculty members are dissuaded from collaborat-

PHOTO: JOHN GENTRY, IUPUI

ing right from the get-go. "We tell young scholars, 'Wait until you have tenure to solve very cool problems,'" Trower says.

Gerry Rubin, the director of Janelia Farm, says this is a systemic problem. "They are told that at the best research universities explicitly by deans, by department chairs, by senior colleagues. But then [universities] want to have collaboration. They are not being internally self-consistent, in my view," he says.

By the time junior faculty receive tenure, they may no longer be interested in teamwork. "My concern is what happens [after] six years or seven years or eight years in some cases on a tenure track, which becomes a tenure rut. It gets beaten out of them and they become entrenched. … By the time they get [tenure], they go, 'Hmm, I don't remember what got me so excited,'" Trower says.

How many authors?

Collaboration is relatively new to the biomedical sciences, and the culture of academia hasn't changed to keep up. Other academic areas, such as physics, have long been involved in large collaborative efforts, and junior faculty in those disciplines still receive tenure, says Mary Lidstrom, vice provost of research at the University of Washington. She says the difference is that in those disciplines, the academic culture places value on teamwork.

Unlike physics departments, many biology and related departments have yet to internalize their value of collaboration, sticking with tenure review metrics and criteria that focus on independent scholarship. At many places, if a junior faculty member is not the first or senior author on a paper, it counts less or not at all toward his or her publication record. Here, the problem isn't with tenure, says Lidstrom, but with the values of the promotion and tenure committee.

"We're training students that team science is the way to do it. It seems archaic to then attempt to judge them by a system that doesn't acknowledge that."

HUNT WILLARD
DUKE UNIVERSITY

"Universities are extremely conservative and are self-defeating," says Rubin, whose own institution doesn't offer tenure. Universities want to promote collaborative science, he adds, but when those scientists are reviewed for tenure, universities say they cannot tell which researcher did what and who should be promoted. Rubin says he can envision review committees questioning whether to give James Watson tenure since he worked with Francis Crick on the double helix. "Maybe the double helix was just really Francis Crick's idea?" he says he would expect a tenure committee to ask.

Changing a university's tenure policy won't necessarily translate to a change in how people on the review committee think. "We tend to focus on structure because we tend to think that maybe changing structure, having policies that support the structure or support different types of work, will help. I say they help, but they don't fix it. They don't fix the culture," Trower says.

To the faculty undergoing review, the issue boils down to credit, says Perumal. If you are one of many authors on paper, you might not get recognition for the role you played in that project from your home academic department. This is especially worrying to junior faculty who are trying to amass publications and grants for their tenure dossiers, because they have learned that their names must appear first or last on the list of authors or as the PI on the grants. Otherwise, the review committee will likely dismiss that paper or grant out of hand since no one can tell who contributed what to the research.

"There are two positions that matter, no matter the size of the author list, and that's the first author and the last author," says Elaine Mardis, co-director of the Genome Sequencing Center at Washington University. Those large author lists, she says, are one of the difficulties with doing big science.

There are now numbers to back up those concerns. Jonathan Wren, an assistant member at the Oklahoma Medical Research Foundation, and his collaborators surveyed promotion and tenure committee members at medical schools in the United States, Puerto Rico, and Canada about how they perceived an author's contribution to a paper based on where the name appeared on the author list. On papers with three or five authors, the respondents gave the first author the most credit for performing the work and the last author credit for conceiv-

JONATHAN WREN

ing of and supervising the project. Half of the people who responded also thought that the more authors on the paper, the harder it is to tell if "a candidate merits promotion."

"It's a cautionary tale to people who think of co-authorship as being an equal contribution because, by our survey, it is widely recognized by people on promotion and tenure committees that positions are not equal," Wren says.

"There are two positions that matter, no matter the size of the author list, and that's the first author and the last author," says Elaine Mardis.

The same problem seems to apply to grants. Junior faculty members must show review committees that they can support themselves through the grants they receive. "In my case, I was awarded tenure not because I collaborate with people, but because I brought in one NIH R01. That was at the time the biggest R01 that the school had. They had to be nice to me," says George Plopper, an associate professor at Rensselaer Polytechnic Institute. Other researchers, like Indiana's Perumal, will share their grants with collaborators, again bringing up the question of credit.

Mardis points to getting recognition for writing sections of grants as the biggest concern she had about getting tenure. She was often a co-PI or responsible for a concept or vision of the technology portion of a grant, but she was not the main PI. Even though she played a key role, there was little recognition. "To me that was the most daunting challenge," she says. (Mardis did indeed receive tenure when the time came.)

Tenure reform

There are no shortages of ideas about how the tenure review system could be altered. First of all, the review metrics could be changed to support collaboration or innovation, perhaps by a simple addition to the review criteria. How review occurs — currently, with stacks of papers — could be replaced by, or at least include, an interview with the candidate to allow that person to present his case and answer the committee's questions. Another possibility: review committees could give more importance to letters of support from the candidate's collaborators. More drastically, the whole system could be replaced with a rolling tenure or contract system.

The tenure review process, contends Antoine Danchin, the director of the genomes and genetics department at the Pasteur Institute, is not set up to reward creativity or innovation, particularly if reviewers look mainly at past journal articles. "Creativity is very important. This can be measured, but not … by the bibliometrics approach," says Danchin.

Ontario's McPherson agrees. "I think it's more of an attitude adjustment. People have to do a little bit more work on the committees to read the letters and look at the papers and the contribution to tease it out more. You can't just count up the number of papers as first and last author; you actually have to think about what the papers are. Some people aren't willing to do that," he says.

ELAINE MARDIS

Danchin suggests that site visits by outside experts could replace much of the paper-based review. At Janelia Farm, the review process — which is not for tenure but to secure a new contract — will be based in part on site visits. Experts will come in, meet the scientist under review, and discuss the science and thought processes behind the experiments to understand what that researcher did and why.

Another avenue for change could be the metrics the review committee uses to judge tenure candidates. Rubin predicts that after adding a collaboration criterion to the review process, "team science would blossom tremendously."

That's what Lidstrom's University of Washington engineering center did. "The dean's office worked with our appointments and promotions committee to specifically add a criterion that valued this collaborative work," Lidstrom says. Assistant professors came through, she says, collaborated and did individual work, and came

The Rise of the Multi-Author Paper

In the 1950s, when Francis Crick and James Watson published their *Nature* paper on the structure of DNA, the average number of authors on biomedical papers was low — it held at 2.3 authors per paper between 1934 and 1963. Since then, there has been a rise in how many authors are on a paper. Today, papers in *Nature* or *Science* can have upwards of 100 authors. The Human Genome Project Consortium, perhaps the most famous example of megascale science, had 1,100 members.

"The number of authors per paper has been rising pretty much steadily since 1970 and it's not a phenomenon that's going away," says Jonathan Wren, an assistant member at the Oklahoma Medical Research Foundation. Two main factors drive that rise, he says: pressure to publish and the increasingly specialized skills needed to complete big projects quickly. With more authors appearing on journal articles, some journals are providing ways for joint first or senior authors to be recognized for the work they did.

Along with his collaborators, Wren studied how an increase in number of authors has affected how people perceive each author's contribution to the project. "The fact that the first and last authors get most of the credit ... that wasn't surprising," Wren says. "These two anchor positions seem to get the lion's share of glory, and the people in the middle are really perceived to contribute very little — comparatively little to everybody else."

Journals have been adopting ways for authors to indicate who should get how much credit. In 1999, *Nature* added a feature to its articles allowing authors to list their contribution to the project in the acknowledgments section. *Science* soon followed suit. The journals also allow people to share the different spots on a paper's author list. Both *Nature* and *Science* put an asterisk next to the authors' names and the footnote reads: "These authors contributed equally to this work."

"*Science* and *Nature* have done this for a very long time, but more and more journals are moving to this," says Mary Lidstrom, vice provost for research at the University of Washington. The Public Library of Science journals also include author contributions in their articles, and the *Proceedings of the National Academy of Sciences* requires authors to list their contributions.

away with tenure. Lidstrom points out, though, that no one had only collaborative work, so the system has yet to be put to the real test.

Even if no changes are made to overhaul the process, junior faculty can still use letters of support to help review committees understand that a middle author's contribution can be critical to the success of an experiment or grant. "Some people who don't work in that environment feel that there's no way to determine your contribution. I think letters of support are important," McPherson says. He adds that if they come from more senior members of the consortium — people like Eric Lander or Bob Waterston — those letters should be weighted very heavily.

Mardis gives an example of what such a letter could say. "You might have someone like Francis Collins, or someone who's chief in charge of the genome centers, providing you a letter of support saying, 'I realize that Elaine was one of 58 authors on the human genome paper, but her seminal work in high-throughput production of sequencing made it possible for us to generate the multitude of data.'"

That's just the policy that Duke University's Institute for Genome Sciences and Policy has in place for its junior faculty. In setting up the institute about five years ago, Hunt Willard negotiated with the dean and provost of Duke to ensure that teamwork and collaboration are expressly valued during the review process. On these tenure committees, people from other interdisciplinary centers serve to provide a positive view of collaborative efforts to the committee, and the person up for tenure provides letters of support from people like Willard explaining how essential their role was in the collaborative projects. "In genomics, we have a fairly young crowd of people and they grew up working together. To them, that's the style of doing science," Willard says.

However, no one has tried out the Duke system yet — the first crop of junior faculty at the institute will come up for tenure in a year or two. "In principle, it will count here, but we have to see how that goes," Willard says. "I've got my reputation on the line."

A worthwhile system?

As people go into contortions trying to make the review system work for these scientists, it begs the

What's a Junior Faculty Member to Do?

If you're aiming to become a professor but your interests in biology mean that you'll be spending a lot of time collaborating, there are a few things to keep in mind as you fight your way up the academic ladder to land tenure.

First, says Gerry Rubin, director of Janelia Farm, when you're looking for a job, ask if the institution supports collaborative research. Some places are more encouraging of this than others, though he suspects that may change for the better over time.

Cathy Trower, who studies tenure at Harvard University, urges job candidates to get everything in writing, especially if you are looking at a joint appointment between two departments. "Ensure through a memorandum of understanding [your] responsibilities and expectations for both departments are spelled out as clearly as possible so that [you] understand who [your] boss is in both departments," she says. She adds that besides the memo, you should sit down with both department heads to go over all the expectations and chart out a path to tenure — before you agree to sign anything.

CATHY TROWER

MARY LINDSTROM

Once you join a department, find a good mentor, says the University of Washington's Mary Lidstrom. Mentors can help, especially if you run into difficulties with collaborators who are more senior than you. "If you get into a bad situation, you need help to get out of it," she says. "Getting advice from more senior people is the way to go."

As for your work, pursue what interests you, though you may want to have a balance of collaborative and independent work. "Everyone should be driven by their intellectual questions that excite them, regardless of what it means in terms of team research," Lidstrom says. "It's often a very good thing to have a mix with collaborative research and a more focused [project]."

Finally, work hard, says Elaine Mardis at Washington University's genome center. "Don't be afraid if you think you have a good idea. Get out there and promote them and find ways to turn your ideas into reality," she says. "Work hard and don't be afraid to speak up."

question: is tenure worth fixing?

The arguments in favor of tenure are well known but worth considering. The professional security afforded by tenure protects faculty members from lean funding budgets and allows them to take intellectual risks. "I think [tenure] does give you a sense of security, to stick your neck out and not just write grants that you think will get funded," McPherson says. "If you've got your back covered a little bit, and you don't get that grant, at least you've still got a job."

Rensselaer's Plopper also says that professors are not as mobile as other professionals, and the stability that tenure provides helps make up for that lack of mobility. "I feel that [if] people spend enough energy and they make enough sacrifices in their careers to pursue an academic career, that there should be something that gives it a corresponding amount of both financial as well as professional security," says Plopper.

At the same time, tenure is a vote of confidence in a faculty member's work and capabilities. "You ask yourself all the time, how am I doing relative to my peers?" Plopper says.

WashU's Mardis adds, "To me, it was a very important milestone and it's certainly gratifying to have that acknowledgment from the faculty."

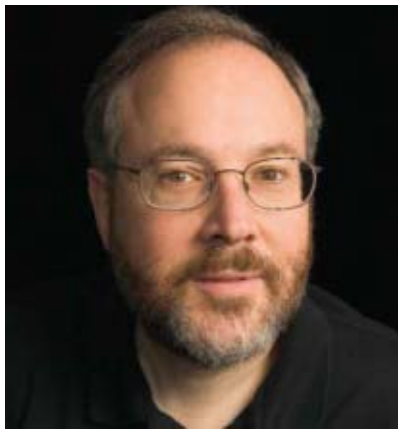
Tenure does, naturally, have its downside, namely the "deadwood" effect — those tenured professors who hang around but contribute little to the university. To avoid that, a common suggestion is to institute a rolling tenure or contract system in which researchers would have to maintain certain standards to keep their position. "I think that in order to be employed by any institution, doing anything, you have to be productive," Plopper adds.

"I'm a bigger fan of the rolling window where it protects you from lean times or allows you to stick your neck out but also it doesn't lock them into supporting you forever," says McPherson.

In essence, that's what the Howard Hughes Medical Institute's Janelia Farm has in place. When Gerry Rubin set up Janelia Farm, he made a conscious decision to abolish tenure. He argues that there is an inverse correlation between

tenure and the productivity of an institution. Sure, tenure's great at an individual level, he says, but not at the institutional level. Rubin points to Bell Laboratories, Cold Spring Harbor Laboratory, and the Medical Research Council Laboratory of Molecular Biology as evidence. These institution either had no or limited tenure during their heydays — when they did their most innovative, cutting-edge research.

When Janelia Farm hires a researcher, whether it's someone fresh out of a postdoc or someone coming out of an endowed chair, it is for a six-year contract. At the end of six years, the scientist undergoes a review — but not, Rubin stresses, just based on publications. If someone does not do well on that review, Janelia Farm provides two years of phase-out funding while the person finds a new position. If it does go well, then the researcher can stay with a five-year renewal, after which there will be another review. The first review at Janelia Farm will take place in about four years.



GERRY RUBIN

PHOTO: PAUL FETTERS

Not having tenure hasn't been a problem in terms of recruiting for Janelia Farm, Rubin says. "There's a good correlation between the people who are willing to do the research we want to do and people who have the attitude, 'I know I'm good. Just give me the resources I need, I think I can prove myself. … Tenure's not relevant. I'll always be able to find another job,'" he says.

Having tenure at cross purposes with collaborative science could turn scientists away from academia, Rubin adds. "[The problem with the academic] system is it tends to drive people who like more a teamwork approach and a collaborative approach from academics into industry or other modes of doing it. Because it's a turnoff for them."

He says the choice for institutions is a simple one. "You decide you don't want team science, or you change the review system."

BIOARRAYNEWS

SeqWright, GATC in Personal Genomics

Fueled by a belief that widespread public demand for access to personal genomic information will grow in coming years, two firms entered the nascent consumer genomics space this month, both using microarrays in their services.

Earlier this year, SeqWright, a Houston, Texas-based contract genomics firm and certified Affymetrix service provider, launched its Genomic Profiling Service, which uses an Affymetrix array to provide customers with their own personal genomic database to help infer the risk of developing specific diseases as well as access to genealogical information.

Also, Konstanz, Germany-based GATC Biotech formed a subsidiary called LifeCode to provide a similar service to European Union residents. According to the firm, the LifeCode service, which also uses microarrays, will be available in the EU in three languages — German, English, and French — by April.

The launch of these services follows the debut last year of three similar ones. November saw the launch of personal genetics services by Navigenics, which uses an Affy platform; 23andMe, which is working with Illumina; and DeCode Genetics, which has not divulged the name of its platform provider.

All five of the firms differ on how much they charge for their service, what degree of counseling they offer their clients, and from what regional markets they will accept orders. However, they are all chasing the same idea that the market for genotyping includes everybody.

"It's still very much speculative, so it's hard to say how big the market is," says SeqWright spokesperson Marc Dantone. "But I do believe [personal genomics] has a lot of movement behind it and we do believe it's a beneficial service."

Dantone says that SeqWright decided to enter the market because as an Affy service provider, it already was equipped to position itself for early entry into the consumer genomics space.

— *Justin Petrone*

DATAPOINT

$2.5

BILLION

VALUE THAT RESEARCH FIRM KALORAMA INFORMATION ESTIMATES THE GENE EXPRESSION PROFILING MARKET TO BE BY 2012.

Microarray Notes

To improve copy number analyses, **GOLDEN HELIX** will collaborate with six academic centers, including **UCLA**, **ZUCKER HILLSIDE HOSPITAL**, **MONTREAL HEART INSTITUTE**, **EMORY INSTITUTE**, **CASE WESTERN RESERVE UNIVERSITY**, and the **UNIVERSITY LUBECK**.

LABORATORY CORPORATION OF AMERICA will use Affy chips in a molecular cytogenetic-testing service that aims to correlate structural genetic variation and chromosomal rearrangements with pediatric autism, mental retardation, and developmental delay.

ERASMUS MEDICAL CENTER in Rotterdam will use **ILLUMINA**'s Infinium HD Human610-Quad BeadChips for a 10,000-subject study aimed at identifying early environmental and genetic causes of abnormal growth in fetal development.

FUNDED GRANTS

$253,500/FY 2007

DNA METHYLATION IN CANCER GENOMES

Grantee: Gerd Pfeifer, City of Hope, Beckman Research Institute

Began: Aug. 10, 2007; Ends: June 30, 2009

A small number of genes have been found to be methylated at high frequency in early stage lung cancer. In this study, they plan to identify genome-wide DNA methylation differences between normal lung tissue and early stage lung tumors using a combination of microarrays and methylated-CpG island recovery assay.

$1,438,644/FY 2007

INTERROGATING EPIGENETIC CHANGES IN CANCER GENOMES

Grantee: Tim Huang, Ohio State University

Began: Sep. 30, 2004; Ends: Aug. 31, 2009

Researchers will study complex epigenetic interactions in order to better understand neoplasms and human female cancers. They will use various microarray platforms to investigate DNA methylation, histone modifications, loss of heterozygosity, and transcription factor binding in cancer cell lines and neoplastic epithelium and the surrounding stroma. This data will also be used to build and refine data models.

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KEYNOTE PRESENTATION

RNAi, Other Mechanisms by Which Cells and Organisms Respond to Genetic Change, and the Implication of These Mechanisms on Human Disease and Health Care
Andrew Fire, PhD, Stanford University
(Nobel Prize in Physiology or Medicine, 2006)

SPECIAL PRESENTATION

Update on Infectious Disease Testing in Emerging Nations
Deborah Burgess, PhD, The Bill & Melinda Gates Foundation

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www.aacc.org/AACC/events/meeting/SanDiegoConf2008.htm

PROTEOMONITOR

Proteomic Biomarkers For CNS Lymphoma

Researchers from the University of California, San Francisco, and biomarker-discovery firm PPD have used a liquid chromatography-mass spectrometry based method to identify a battery of proteins differentially expressed in cerebrospinal fluid, in what they say is the first study in which a proteomic analysis of CSF yielded biomarkers with greater sensitivity than cytology.

The researchers combined high-resolution LC/MS data for profiling differential quantification without isotope labeling with LC/MS/MS for protein identification, and found 76 proteins in CSF associated with central nervous system lymphoma, including a majority that had not been previously identified.

The study, which appears in the Jan. 1 edition of the *Journal of Clinical Oncology*, demonstrates that "the CSF proteome contains a wealth of potential diagnostic and prognostic information," the authors report.

The researchers say trying to pinpoint the cause of focal brain lesions in patients with unexplained neurological symptoms is a clinical challenge. Diagnostic methods for CNS lymphoma include flow cytometry and, in some cases, measuring beta-human chorionic gonadotropin or alpha-fetoprotein levels.

James Rubenstein, senior author of the study and an assistant professor of hematology and oncology at UCSF, says that among approaches using CSF, cytology is the "gold standard" in diagnosing brain cancer. However, the sensitivity of the method to diagnose lymphoma and other cancers is less than 50 percent.

The diagnostic method of last resort is brain biopsy, but in addition to a risk for brain hemorrhaging, the method carriers a failure rate as high as 35 percent.

Earlier research suggests that the elevation of total CSF proteins may be associated with adverse prognosis in CNS lymphoma, although the identity of specific proteins and peptides had not been known. In addition, mass spectrometry has been shown to be able to detect such proteins to help diagnose certain cancers early in their development.

— *Tony Fong*

DATAPOINT

$6.25

MILLION

CS-KEYS, A PROTEOMICS FIRM THAT IS DEVELOPING TECHNOLOGY FOR CANCER BIOMARKER DETECTION, RAISED $6.25 MILLION IN SERIES A FINANCING.

Proteomics Notes

PLEXERA has exclusive access to **AUGURON BIOSCIENCES**' Nucleic Acid Programmable Protein Array technology for one year, with an option for a one-year extension. Plexera will be testing and developing NAPPA as a content source for its own label-free Kx Array platform.

FLUOROTECHNICS, an Australian biotech firm, announced a partnership with Japan's **WAKO PURE CHEMICAL INDUSTRIES**. Under their agreement, Wako will sell Fluorotechnics' fluorescence-based kits as well as its protease monitoring and live-cell intracellular imaging technologies.

NACALAI TESQUE and **NACALAI USA** will distribute **OLINK BIOSCIENCE**'s Duolink products in Japan. Duolink uses Olink's *in situ* Proximity Ligation Assay technology.

FUNDED GRANTS

$58,886/FY2007

A PROTEOMICS APPROACH TO STUDY THE MECHANISMS OF FAS-INDUCED LUNG FIBROSIS

Grantee: Dong Chang, University of Washington
Began: Aug. 3, 2007; Ends: Aug. 8, 2008

To study acute respiratory distress syndrome and the Fas pathway involved in lung injury, the researchers will use mice with Fas on their myeloid or non-myeloid cells to study how alveolar epithelium and alveolar macrophages contribute to lung fibrosis. Through proteomic analysis, they will look at mouse bronchoalveolar lavage fluid and determine how MMP-12 modifies profibrotic proteins.

$229,500/FY2007

PLASMA PROTEOME PROFILING OF INSULIN RESISTANCE

Grantee: Nana Gletsu, Emory University
Began: Apr. 1, 2007; Ends: Mar. 31, 2009

Under this grant, researchers will perform a proteomic analysis of insulin resistance to find biomarkers. They will study intravenous glucose tolerance tests and oxidative stress and inflammation of patients as they undergo a gastric bypass or are on a low-calorie, liquid formula diet. Also, using LC/MS/MS, they will identify proteins associated with differences in insulin resistance in obese patients who lose weight.

INSEQUENCE

'1,000 Genomes' Challenges Data Flow

Managing and analyzing the data from the recently announced 1,000 Genomes Project will pose a number of challenges, some related to the nature of the next-generation sequencing platforms, but organizers say the results will boost both medical research and scientists' understanding of human evolutionary history.

The study consortium, which aims to sequence at least 1,000 and up to 2,000 human genomes within three years, includes two data-related working groups. A data flow group will be responsible for collecting and archiving the sequence reads, helping map them to a reference genome, and making the data available to the research community in different formats and levels of detail. Meantime, an analysis group will focus on aligning the reads, reconstructing the 1,000 genomes from the data, calling genetic variants, and interpreting the results.

A major challenge will be the "sheer volume of data," according to Gil McVean, a professor of statistical genetics at the University of Oxford, who co-chairs the analysis group. The consortium expects the study to produce on the order of 6 terabases of data, or 60 times the sequence data that has been deposited in public DNA databases over the last 25 years.

According to McVean, the analytical tasks fall into three broad areas: technology-related tasks that focus on translating the raw data into DNA sequence and mapping the sequence reads to a reference genome; calling genetic variants such as SNPs and structural variations and reconstructing individual genomes; and using the results to help disease studies and other research projects.

On the technology side, data analysis experts have to grapple with the fact that the nature of the data produced by existing next-generation sequencers is still in flux. "The data that comes out of the machines is changing pretty much month by month as the engineering improves," McVean said.

— *Julia Karow*

DATAPOINT

$12

MILLION

NHLBI AND NHGRI SET ASIDE $12 MILLION IN GRANTS FOR DEVELOPING CHEAPER METHODS OF EXON SEQUENCING.

Sequencing Notes

KNOME, a personal whole genome sequencing startup, lined up its first two customers and announced a partnership with the **BEIJING GENOMICS INSTITUTE**. Based in Cambridge, Mass., Knome offers whole-genome sequencing and genomic analysis for $350,000.

DNA sequencing technology startup **GENOME CORP.** raised $250,000 in venture funding to continue work on its massively parallel Sanger sequencing tool. It also named three founding members of its scientific advisory board: **NORM DOVICHI**, **ANNELISE BARRON**, and **PATRICK DOYLE**.

PACIFIC BIOSCIENCES said it expects to commercialize a next-gen sequencer by 2010 that could eventually generate 100 gigabases of sequence per hour, or 10x coverage of a human genome in 15 minutes.

FUNDED GRANTS

$219,331/FY2007

SEQUENCING DNA BY TRANSVERSE ELECTRICAL MEASUREMENTS IN NANOCHANNELS

Grantee: Robert Riehn, North Carolina State University
Began: Aug. 1, 2007; Ends: July 31, 2009

With this exploratory grant, Riehn and his team plan to build a sequencing technology using stretched and linearized DNA in nanofluidic channels, and detection using nanoelectrodes, according to the grant abstract. Riehn says this kind of technology would enable ultra-long read frames of more than 100 kilobases.

$140,625/FY2007

EXON SPECIFIC SEQUENCING OF WHOLE GENOMIC DNA

Grantee: Darren Link, RainDance Technologies
Began: July 1, 2007; Ends: June 30, 2009

Link says his long-term goal is to build a way to simultaneously sequence thousands of different exons from a genomic DNA sample with 30 to 50 times coverage of each exon. The technology will be based on RainDance's microfluidics platform and 454 Life Sciences sequencing, according to the abstract.

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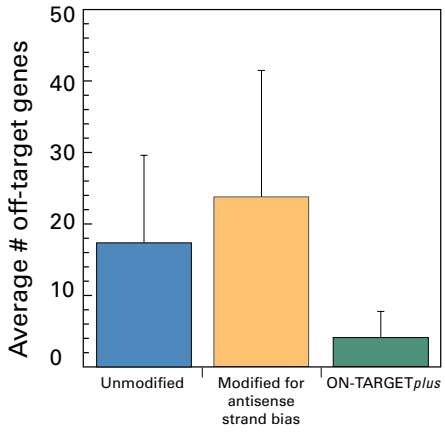

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RNAiNEWS

Photocaging to Control RNAi

While a number of technologies are being developed to turn the RNAi process on and off, these typically require introducing small molecules or other compounds into the cell. But a researcher from Louisiana State University thinks that a photoactivation technique developed three decades ago may offer a better solution.

The approach, called photocaging, involves covalently attaching blocking groups onto a nucleic acid. These groups keep the nucleic acid inert — an siRNA, for instance — while protecting it from enzymatic degradation until it is exposed to light, at which point the nucleic acid's activity is restored, according to Todd Monroe, an assistant professor in LSU's department of biological and agricultural engineering.

"There are a lot of small molecules that can drive gene expression or gene repression, but those molecules, if they are not already inherent in some type of pathway, have to be delivered" and can be difficult to regulate, he says.

With photocaging, on the other hand, researchers can control when and where in a cell a nucleic acid is activated, he says. "If we're working with an organism instead of a culture dish, we can deliver [a caged nucleic acid] in a select spot," such as the retina.

According to Monroe, photocaging was developed in the 1970s to inactivate and reactivate ATP to study the kinetics of muscle contraction. "We'd like to take those same principles [used with ATP] and apply them in cells and tissues to govern nucleic acid bioactivity," he says.

Monroe and his colleagues have been working on this concept for some time and have conducted experiments in which they attached nitro benzyl-like cage compounds to the phosphate backbone of DNA. This caging process "disrupts transcriptional enzyme machinery [and] blocks [the DNA's] degradation by nucleases," he explains. When exposed to light, the molecules reactivated.

— *Doug Macron*

DATAPOINT

$7.5

MILLION

INTROGEN THERAPEUTICS, WHICH DEVELOPS TUMOR SUPPRESSOR DRUGS, SOLD ITS APPROXIMATELY 7.5 MILLION SHARES OF SILENCE THERAPEUTICS, NETTING $7.5 MILLION.

RNAi Notes

INTRADIGM licensed the rights to the **MASSACHUSETTS INSTITUTE OF TECHNOLOGY**'s nucleic acid delivery patent. This covers a range of biodegradable polymer structures used to deliver RNAi-based therapeutics.

In a filing with the US Securities and Exchange Commission, **ARROWHEAD RESEARCH** said its subsidiaries, **CALANDO PHARMACEUTICALS**, an RNAi drug firm and **INSERT THERAPEUTICS**, a nanobiotech company, will merge.

ALNYLAM PHARMACEUTICALS announced that a double-blind, placebo-controlled, randomized study showed that its siRNA-based respiratory syncytial virus drug ALN-RSV01 is safe and well-tolerated. The results are to be presented at the International Symposium on Respiratory Viral Infections meeting.

FUNDED GRANTS

$171,881/FY2007

DEVELOPING RNA INTERFERENCE FOR GENE SPECIFIC SILENCING IN APLYSIA NEURONS

Grantee: Kelsey Martin, UCLA

Began: Apr. 1, 2007; Ends: Mar. 31, 2009

With this grant, the researchers want to develop RNAi for use in Aplysia neurons. To determine if the silencing will work, they will target four endogenous Aplysia genes and exogenously overexpressed destabilized eGFP. The researchers say that the ability to use RNAi in Aplysia will also yield information about molecular mechanisms underlying synapse formation, synaptic transmission, and synaptic plasticity.

$131,200/FY2007

TITLE: NOVEL TUMOR SUPPRESSOR GENE DISCOVERY IN PANCREATIC CANCER

Grantee: James Eshleman, Johns Hopkins University School of Medicine

Began: Sep. 1, 2007; Ends: Aug. 31, 2009

In this grant, the researchers propose to use RNAi to uncover novel pancreatic cancer tumor suppressor genes. First, they plan to construct cell lines by transducing non-tumorigenic and weakly tumorigenic pancreas cell lines with whole-genome libraries. Then, they will select tumorigenic cell clones and perform sequencing.

Bioinformatics Notes

The **NATIONAL LIBRARY OF MEDICINE** will give $5 million over a three-year period to fund several research groups aiming to advance biomedical informatics. The grant will support between 12 and 15 research programs in areas of public health, complex modeling, and clinical translational research.

The US **ENVIRONMENTAL PROTECTION AGENCY**'s National Center for Computational Toxicology will license **GENE LOGIC**'s bioinformatics platform. The EPA will use the company's Genesis Enterprise System, GXR Connect software, and parts of its ToxExpress and BioExpress systems for use in the agency's ToxCast program.

The **CDC** extended an existing deal for a multi-site license to **DNASTAR**'s sequence analysis software for use at its facilities in Colorado, Alaska, and Puerto Rico.

BIOINFORM

EU Team to Coordinate Gen2Phen Data

A consortium of European research groups and bioinformatics firms has kicked off an effort to integrate the growing body of information on human genotype-to-phenotype relationships enabled by the rise of low-cost genotyping technologies.

The five-year project, called Gen2Phen, for Genotype-to-Phenotype, began earlier this month with €11.9 million in funding from the European Union's Seventh Framework Program. The goal of the project is to create tools and standards that will seamlessly integrate numerous genetic variation databases and provide a unified view of these disparate data sources.

"This is not a database," says Anthony Brookes, a professor in the department of genetics at the UK's University of Leicester and the coordinator of the project. "It's trying to help organize, orchestrate, and coordinate the general field of genotype-to-phenotype databasing."

Brookes says that the project is a response to the "tidal wave of information" that is now coming online from low-cost genome-wide association studies that link genotypic data with phenotypic information.

Brookes says that the informatics community has not yet developed standardized database infrastructures, data standards, or data models for the rise of so-called G2P data. Unlike genomic data, which is "unidimensional, so it's very easy to design databases, and very easy to manage and handle," Brookes notes that "there are a lot more complex challenges involved in handling phenotype data because it's an infinite universe of information."

As a result, different databases have chosen to handle and represent this information in very different ways, which has made it difficult for researchers to access data from multiple studies and compare it. Current efforts to solve the problem are "nowhere near enough for the absolute torrent of genotype-phenotype information that's now flowing and will continue to flow," he says.

— *Bernadette Toner*

DATAPOINT

$50 MILLION

AMOUNT THE NATIONAL SCIENCE FOUNDATION HAS DOLED OUT TO ESTABLISH A CYBERINFRASTRUCTURE CENTER FOR PLANT BIOLOGY.

FUNDED GRANTS

$386,400/FY2007

SP BASE: A SEA URCHIN GENOME DATABASE

Grantee: Robert Andrew Cameron, California Institute of Technology

Began: Sep.1, 2007; Ends: Jun.30, 2012

Through this grant, Cameron will continue to expand and extend SpBase, a genome database for sea urchins that collects data produced by the Sea Urchin Genome Sequencing Project, composed of the Baylor College of Medicine Human Genome Sequencing Center and the Sea Urchin Genome Annotation team. SpBase is being developed to include a user interface that allows for easy updating, editing, and installation of additional features.

$529,887/FY2007

SHOTGUN LIPIDOMICS AND ALTERATIONS IN SPHINGOLIPIDOMES IN ALZHEIMER'S DISEASES

Grantee: Xianlin Han, Washington University

Began: Sep. 1, 2007; Ends: July 31, 2012

Han and his colleagues are developing a bioinformatics approach to yield high-throughput processing of complex lipidomics data, including the identification of altered lipid molecular species induced by a disease state and the construction of a lipid metabolic network map. This project will also attempt to identify the altered pathways of the sphingolipidome networks present in very mild Alzheimer's disease.

PHARMACOGENOMICS REPORTER

AutoGenomics' Warfarin Test Approved

AutoGenomics announced that the US Food and Drug Administration approved its Infiniti Warfarin XP dose-response assay for identifying patients with CYP450 2C9 and VKORC1 genetic variants.

The company, based in Carlsbad, Calif., submitted the assay to the FDA for 510(k) approval last December. The test runs on its Infiniti platform, which the FDA cleared for multiplex testing earlier this year.

AutoGenomics is entering a crowded market. Four months ago, the FDA approved Nanosphere's Verigene Warfarin Metabolism Nucleic Acid Test, which runs on the company's Verigene platform. There are also several companies, such as Clinical Data, LabCorp, Genelex, and Nanogen that market homebrew tests for this indication.

But Autogenomics' test has several points that differentiate it from these rivals, the company says. For one, its warfarin panel was validated by the Harvard Medical School-Partners HealthCare Center for Genetics and Genomics. HPCGG also used AutoGenomics' assay in the "CReating an Optimal Warfarin Nomogram," or CROWN, trial, a prospective study that used genetic tests to determine optimal warfarin dosing.

According to AutoGenomics, there can be more than a 10-fold dosing variability among patients on warfarin. The Infiniti 2C9-VKORC1 panel "has the potential to optimize warfarin dosing and lower the risk of bleeding complications," Raju Kucherlapati, HPCGG scientific director, has said of the assay.

In addition to being validated by independent researchers, the assay is able to test for variants that no other marketed test can assess. Most marketed warfarin assays test for CYP239*2 and *3 variants, and VKORC1 variant 3673 (-1639G>A).

The Infiniti assay tests for those variants plus CYP239 *4, *5, *6, and *11, as well as VKORC1 variants 5808, 6009, 6484 (1173C>T), 6853, 7566, 8773, and 9041(3730G>A). Clinical studies have linked some of these variants to warfarin sensitivity in certain ethnic populations, such as Japanese and African-American.

— *Turna Ray*

DATAPOINT

$2.5

MILLION

VALUE OF NIH GRANT FUNDING AN INITIATIVE PAIRING THE CANCER INSTITUTE OF NEW JERSEY AND IBM TO DEVELOP DIAGNOSTIC TOOLS.

PGx & Molecular Dx Notes

Three soon-to-be published studies suggest that a polymorphism in KIF6, a gene encoding a kinesin-like protein in the molecular motor family, increases the risk of coronary heart disease. **CELERA** subsidiary **BERKELEY HEARTLAB** is developing a laboratory test, which it expects to launch soon, for the gene variant.

Four papers on lupus genetics, including two large genome-wide SNP studies, one investigating SNPs that specifically predict amino acid changes and one focusing on a particular candidate gene, shed light on the molecular pathways implicated in the disease. The papers appeared in *Nature Genetics* and the *New England Journal of Medicine*.

The Canadian government licensed **CEPHEID**'s test for methicillin-resistant *Staphylococcus aureus* for use in hospitals.

FUNDED GRANTS

$162,918/FY2007

MOLECULAR TARGETED IMAGING IN COLON CANCER

Grantee: Joseph Backer, SibTech

Began: Sep. 28, 2007; Ends: Mar. 31, 2008

According to the abstract, Backer and his colleagues plan to optimize detection of colorectal lesions via VEGFR-mediated fluorescent imaging and establish the feasibility of early detection of colorectal lesions with scVEGF/Cy tracer. If all goes well, this work could lead to the clinical development of a new imaging tracer for early diagnosis of prostate cancer.

$471,753/FY2007

BIOMARKER SIGNATURES OF BIOLOGICAL, CHEMICAL, OR PSYCHOLOGICAL STRESS

Grantee: David Lawrence, Wadsworth Center

Began: Aug. 15, 2007; Ends: May 31, 2011

Lawrence will study patients with sepsis or rheumatoid arthritis as a prototype of stressed individuals to identify and quantify the presence of serum proteins that have increased, decreased, or which display epitope-modified expression, according to the abstract. These molecular features will form the basis of specific biomarker signatures characteristic of people under stress.

Plasma Is the New Risk Factor

With a new protein study, Mayo Clinic scientists demonstrate the potential for a biomarker test of Alzheimer's susceptibility.

By Jeanene Swanson

It may not be right around the corner, but a biomarker test for increased susceptibility to Alzheimer's disease might be waiting down the road. In a recent study, researchers at the Mayo Clinic Jacksonville found that blood levels of amyloid beta proteins were higher in young relatives of patients with late onset Alzheimer's disease than in non-relative controls, which suggests that genetic factors controlling the Aβ proteins — including the APOE4 genetic variant, a well known risk factor — are related to higher risk of developing the disease. The team's research was published in the journal *Neurology* last month.

In comparing control groups to first-degree relatives of 25 extended multigenerational families with a history of late onset Alzheimer's disease, and an additional approximately 100 first-degree relatives of patients with Alzheimer's, they found elevated levels of both Aβ40 and Aβ42 compared to non-related control groups. To find out whether these elevations were caused by any of the genes known to contribute to late onset Alzheimer's, the scientists sequenced the Aβ proteins and found no mutations. They then genotyped the participants for the APOE4 allele, hypothesizing that having this risk factor might have something to do with their higher Aβ levels. "We found that, in fact, it was those individuals with lower amyloid beta levels that had the APOE4 allele," says Nilufer Ertekin-Taner, the study's lead author. "What we postulate … might be going on there, possibly APOE4 might be promoting deposition of amyloid beta in the brain, and with the deposition of amyloid beta in the brain, the plasma levels drop. That's one postulate — but certainly it tells us that the elevations are not due to the E4, leading us to conclude that it must be some other genetic variant or variants leading to that."

Taner likens plasma amyloid beta protein to cholesterol, in that it's a quantitative trait that varies in the general population. While it's not a given that someone with a high blood cholesterol level will end up with heart disease, it's a good predictor. In many cases, Taner believes, a test to track the levels of plasma Aβ in people with a family history of Alzheimer's disease might help with early diagnosis and treatment of the disease. "When you compare the young first-degree relatives to the control population, you see that the young first-degree relatives have higher levels," Taner says. "[That] tells us that there must be genetic factors underlying elevations in amyloid beta levels that you can detect years before people develop Alzheimer's disease."

NILUFER ERTEKIN-TANER

Taner sees the possibility for a clinical biomarker test that would track plasma Aβ levels and use that information to determine the probability of getting Alzheimer's disease, but not before classic longitudinal tests are performed to measure these levels through generations of large populations. "I think that there may come a day when we follow the amyloid beta levels in individuals and be able to say that if you have a family history of Alzheimer's disease, if you have higher amyloid beta levels at earlier ages — and perhaps we might be even able to say if you have genetic risk factor A, B, or C — then your likelihood of getting Alzheimer's disease is higher compared to if you didn't have those risk factors."

The Biomarker Black Box

Lawrence Jennings just wrapped up a study on biomarker validation. He shares some of his newfound insight into molecular diagnostics, testing assays, and more.

Lawrence Jennings, director of molecular pathology and diagnostics at Northwestern University's Children's Memorial Hospital, is just putting the finishing touches to a study on validating molecular assays in diagnostic laboratories. How people find biomarkers and bring them to use in a clinical setting is of great interest to him, and it's why GT's Meredith Salisbury caught up with him for a conversation about best practices and common mistakes in validation.

GENOME TECHNOLOGY: Are there some best practice guidelines you'd offer readers?

LAWRENCE JENNINGS: I don't know if there's anything that's perfect. The things that we reference most often are the FDA websites themselves — they have specific recommendations. Usually it's directed toward industry, but for clinical laboratories that are developing tests they also fall under the purview of FDA to some degree. The FDA has jurisdiction over clinical laboratories and the results that come out of them; however, they have not really enforced their authority for a couple of reasons. One of them is that clinical laboratories are overseen by CLIA, and they also regulate the reagents — the ASRs and other reagents that go into the clinical laboratory.

In addition to the FDA, there are published guidelines — manuscripts that talk about bringing assays into a clinical laboratory. I think the problem is that with the FDA and with the people who write these standards, they view everybody who's developing a test and offering a test in the same regard. And for the smaller labs [the resource requirements] may be overwhelming. [They'll ask,] what do I need to do? Can I do fewer samples? Ultimately it's up to the director of the clinical laboratory to determine whether it meets the requirements for validation.

GT: What are some of the most common mistakes you see labs make?

LJ: I think the biggest mistake that most people have is distinguishing between analytical validation and clinical validation. It's really the clinical validation that matters. Analytical validation is of course required — but without getting to the clinical validation aspects, it means nothing. For example, analytical validation pertains to having an assay that identifies whatever analyte it's intended to identify and does that reproducibly and accurately — whereas clinical validation would take that result and give it clinical meaning. A lot of the laboratory tests that we see in our own institution began in a research laboratory where they might've done a research study that might have shown that this biomarker has some value. They might even decide this is clinically valuable — and it might be valuable within that laboratory under very specific circumstances. As long as they define those circumstances and they stay within that range then it's probably OK. But the problem comes when they start extrapolating to other patients or other analytes or when it's done in another institution that might not be doing it the same way.

GT: More recent tests look at several analytes in a panel. Is this proving to be more complex?

LJ: The challenge is on the clinical interpretation side. The technology and the techniques are advancing where that's not going to be the issue at all — whether people can do it. The FDA [statement on IVDMIAs] is meant to address specifically this point, that it's dangerous when people begin to offer tests that cannot be validated simply because they're operating in some kind of a black box. We brought this up within a committee meeting: at what point does this have to be an FDA-approved test? Among our committee members the feeling was that if the methods and clinical validation data are not publicly available — well, then, that's not acceptable.

Events

MEETINGS AND DEADLINES

Conferences

DATE	CONFERENCE	ORGANIZER	LOCATION	CATEGORY
Mar 1-7	59th Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy	PITTCON	New Orleans	Proteomics
Mar 6-7	Advances in Synthetic Biology	Select Biosciences	Cambridge, UK	Synthetic biology
Mar 10-11	MicroRNA in Human Disease and Development	CHI	Cambridge, Mass.	RNAi
Mar 10-12	2008 AMIA Summit on Translational Bioinformatics	AMIA	San Francisco	Bioinformatics
Mar 16-19	Fourth Annual US HUPO	US HUPO	Bethesda, Md.	Proteomics
Mar 17-19	Genomes to Systems 2008	Consortium for Post-Genome Science	Manchester, UK	Genomics
Mar 25-26	Genomic Technologies at the Interface of Diagnostics and Therapeutics	AACC	San Diego	Clinical
Mar 25-28	Molecular Medicine Tri Conference	CHI	San Francisco	Genomics
Mar 25-30	RNAi, MicroRNA, and Non-Coding RNA	Keystone Symposia	Whistler, British Columbia	RNAi
Mar 27-30	Systems Biology: Global Regulation of Gene Expression	Cold Spring Harbor Laboratory	Cold Spring Harbor, NY	Systems biology
Mar 30 - Apr 2	RECOMB		Singapore	Bioinformatics
Apr 2	From Genome to Proteome and Biological Function	BioSapiens Network of Excellence	Brussels	Functional genomics
Apr 5-9	Experimental Biology	FASEB	San Diego	General
Apr 6-10	235th National Meeting of the American Chemical Society	ACS	New Orleans	Chemistry
Apr 6-10	Society for Biomolecular Sciences Annual Meeting	SBS	St. Louis, MO	Screening
Apr 7-8	GenBank 25th Anniversary Celebration	NCBI	Bethesda, Md.	Bioinformatics
Apr 7-12	Molecular Basis for Chromatin Modifications and Epigenetic Phenomena	Keystone Symposia	Snowmass, Colo.	Epigenetics
Apr 12-16	AACR	AACR	San Diego	Cancer
Apr 20-23	Quantitative PCR	CHI	San Diego	PCR
Apr 23-24	Next-Generation Sequencing	CHI	San Diego	Sequencing
May 1-2	RNAi World Congress	Select Biosciences	Boston	RNAi
May 6-10	The Biology of Genomes	Cold Spring Harbor Laboratory	Cold Spring Harbor, NY	Genomics
May 7-8	Advances in Microarray Technology	Select Biosciences	Barcelona	Microarrays
May 19-21	Biomarker World Congress	CHI	Philadelphia	Biomarkers
May 19-21	GOT Summit	CHI	Boston	Genomics
May 28 - Jun 1	American Society of Gene Therapy	ASGT	Boston	Gene therapy
Jun 1-5	56th ASMS Conference on Mass Spectrometry	ASMS	Denver, CO	Proteomics
Jun 1-5	American Society for Microbiology General Meeting	ASM	Boston	General
Jun 9-11	Beyond Genome	CHI	San Francisco	Genomics
Jun 16-21	Pathways, Networks and Systems Medicine Conference	Aegean Conferences	Chania, Crete, Greece	Systems biology
Jun 18-21	BIO Annual Meeting	BIO	San Diego	General
Jun 22-26	Drug Information Association Annual Meeting	DIA	Boston	Clinical
Jun 23-25	caBIG Annual Meeting	caBIG	Washington, DC	Bioinformatics
Jun 27 - Jul 2	Pharmacogenetics and Pharmaco-genomics: Adverse Drug Reactions	European Science Foundation	Sant Feliu de Guixols, Spain	Clinical
Jul 11-13	Genetic Alliance Annual Conference	Genetic Alliance	Bethesda, Md.	Clinical
Jul 19-23	Symposium of the Protein Society	Protein Society	San Diego	Proteomics
Jul 19-23	International Conference on Intelligent Systems for Molecular Biology	ISCB	Toronto	Bioinformatics
Aug 4-7	Drug Discovery and Development of Innovative Therapeutics	IBC	Boston	Clinical
Aug 17-21	Meeting of the American Chemical Society	ACS	Philadelphia	Chemistry

Deadlines

MARCH 6
Application deadline for the NIH Deep Sequencing and Haplotype Profiling of Mental Disorders grant. This grant will support large-scale research that uses in-depth sequencing and candidate gene studies to examine the genetic risk factors of seven major mental disorders: anorexia, ADHD, autism and related autism spectrum disorders, depression, bipolar disorder, obsessive compulsive disorder, and schizophrenia.

MARCH 8
Application deadline for the grant, Reference Epigenome Mapping Centers. The NIH will support applicants to develop comprehensive reference epigenomes from human embryonic stem cells, human differentiating and differentiated cells, cell lines, and tissues.

MARCH 14
Application deadline for the Non-coding RNAs and Other Post-transcriptional Regulatory Mechanisms in Neuroplasticity and Addiction grant. The purpose of this NIH grant is to promote research on noncoding RNAs pertaining to addictive processes.

MARCH 14
Application deadline for Assembling the Tree of Life grant. This NSF grant will support projects in data acquisition, analysis, algorithm development, and dissemination in computational phylogenetics and phyloinformatics.

MARCH 17
Abstract deadline for the second annual RNAi World Congress meeting.

MARCH 19
Application deadline for the Protein Data Bank Management grant. These NSF funds will support a plan to lead, administer, and coordinate community datasets for the Protein Data Bank.

MARCH 19
Application deadline for the NIH grant, Drug Docking and Screening Data Resource. This grant aims to increase the amount of high-quality drug target data for the development of ligand docking and screening software.

MARCH 28
Application deadline for the HIV-1 and Host Genetics in Drug Using Populations and Model Organisms grant. This NIH grant will fund research into molecular mechanisms of HIV-1 infection.

Lab Reunion | THE YATES LAB

The Proteomics Pedigree

John Yates is known for being a mass spec guru — and in his lab, he's known as the guy who stands by his scientific convictions. *By Meredith Salisbury*

When Michael MacCoss started his proteomics lab at the University of Washington a few years ago, he discovered that he had been assigned his postdoc advisor's old lab space. "[It] was actually pretty intimidating," he says.

Small wonder: MacCoss' former PI was proteomics great John Yates, who ran a lab at Washington for eight years before heading to the Scripps Research Institute.

Yates, who began his career studying "protein sequencing using tandem mass spectrometry," did his own postdoc at Caltech with a high-profile PI: Lee Hood. When Hood moved to the University of Washington and started the molecular biotechnology department, he offered Yates a faculty position.

Yates recalls that being a newbie in Hood's star-studded department meant not being a top pick for students. The department had "fairly famous faculty," he says, "and if the students had half a brain they went to work with those guys." He began his lab with several postdocs and a single student, a pattern that has continued throughout his career. "I only ever had one student at a time," he says. "I've come to call it Jedi knight training."

If that's a reflection of quality over quantity, Yates' postdocs say they're grateful for the high-quality lessons they learned during their time in his lab. Ashok Dongre, now an associate director at Bristol-Myers Squibb, remembers that Yates was a "hands off" manager. "He gave a broad idea of what he wanted," Dongre says, "and he gave us the latitude to go ahead and try different things." He adds that he found the environment so rewarding that he's fostered the same atmosphere in his own lab ever since.

In fact, Yates says that this trait was an inheritance for him as well. He remembers his PhD advisor being "really good about … letting me explore ideas in the lab," he says. "That's something that I brought to my lab." Yates says a quality he really values in his lab members is being vocal and willing to speak their minds.

Dongre says what impressed him most about Yates was his refusal to follow the path that most people were taking if it didn't make sense to him; he was known among his staff as someone who carved out his own path. When he had an idea that didn't match up with what most

>NAMING NAMES

As one of Lee Hood's postdocs, John Yates is no stranger to a high-profile pedigree. The students and postdocs who have gone through his lab have also parlayed their experience into successful careers. To name just a few:

ASHOK DONGRE
After his postdoc with Yates, Dongre packed up for Bristol-Myers Squibb, where he is currently an associate director.

LAURENCE FLORENS
As managing director of proteomics at the Stowers Institute, Florens was awarded the Hudson Prize in recognition of innovative research in 2006.

MICHAEL MACCOSS
MacCoss runs a mass spectrometry lab at the University of Washington, and was named one of the up-and-coming scientists in *Genome Technology*'s 2006 Tomorrow's PIs issue.

MICHAEL WASHBURN
Washburn continues his work in quantitative proteomics, and serves as proteomics director at the Stowers Institute. Along with Florens, he won the Hudson Prize in 2006.

CHRISTINE WU
An assistant professor of pharmacology at the University of Colorado, Wu works with membrane proteins and biomarker profiling, as well as improvements of proteomics methods.

FUQUAN YANG
Yang works on quantitative proteomics and protein dynamics as a professor at the Chinese Academy of Sciences' Institute of Biophysics.

other proteomic scientists were doing, Dongre says, Yates would analyze "the pros and cons of what he was proposing and say, 'There's a good chance that we'll fail at this, but that shouldn't stop us from trying it out.'"

MacCoss remembers that Yates "always really liked those aggressive, high-risk ideas" — a characteristic that encouraged his students to conduct research as innovative and unique as his own. "[What] you learn from being in John Yates' lab is thinking big," MacCoss says.

But it's not all blue-sky science. Yates says he's a stickler for making sure his students learn the instrumentation inside and out. "The key for them is to learn as much about the technology as they can," he says. In his lab, everyone's required to "run their own samples and maintain the instruments."

MacCoss says that for him, one of the major lessons he learned early on was the importance of software for processing proteomics data — no one going through the Yates lab was going to emerge without a real appreciation for, and grasp of, good analysis procedures. "That's something you learn right off the bat — you're not going to be able to sit there and process all your data by hand," he says.

Both MacCoss and Dongre say they've kept in touch with Yates, who has been very supportive of his postdocs as their careers unfold. MacCoss says, "I remember the first couple grants I was writing, and I was getting bad reviews." He would send the proposals to Yates for feedback, and "he was always very positive with his comments," MacCoss says.

JOHN YATES

That candor (along with a dry sense of humor) is something Yates' students know well, says Dongre. "The thing I liked about him was that I always knew where I stood with him," he says. "If he doesn't like something, he'll tell you so."

Blunt End

HUMOR, WE HOPE

"Behind one door is tenure. Behind the other is flipping burgers at McDonald's."

BPA Genome Technology (ISSN 1530-7107) is published ten times a year (monthly except combined issues in Jul/Aug and Dec/Jan) by GenomeWeb, LLC, 125 Maiden Lane, New York, NY 10038. Periodicals postage paid at New York, NY, and additional mailing offices. Genome Technology is sent free of charge to qualified professionals in life sciences research. Non-qualified rate is $149 per year. POSTMASTER: Send address changes to Genome Technology, Peck Slip Station, PO Box 998, New York, NY 10273.

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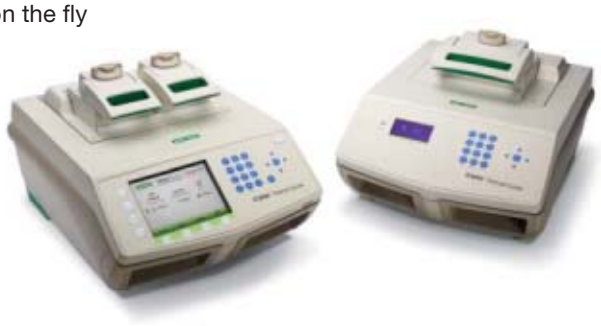

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