

ProteoMonitor

THE GLOBAL NEWSWEEKLY OF PROTEOMICS TECHNOLOGY



copyright

**THIS NEWSLETTER IS COPYRIGHTED INTELLECTUAL PROPERTY.
BY OPENING AND VIEWING THIS ADOBE FILE YOU AGREE THAT:**

- You may print and retain one paper copy. Additional copies may be printed only by specific arrangement with GenomeWeb LLC.
- You may permanently retain this Acrobat file. You may forward, copy or otherwise distribute this file only by specific arrangement with GenomeWeb LLC.
- If you have received this file under a GenomeWeb site license, your rights to print, forward, copy or otherwise distribute this file are governed by the provisions of that site license.



www.genomeweb.com
The Pulse of the New Biology

If you have questions about your use of this newsletter please contact
Allan Nixon at anixon@genomeweb.com

volume 3, number 29
July 18, 2003

in this issue

page 2

- Movers & Shakers
- New Products

page 3

- Bruker rounds up changes at open house meeting and jumps onto biomarker train.

page 6

- *ProteoMonitor's* IP Roundup: Recent Patents of Interest in Proteomics.

page 7

- Proteomics Pioneer: Forest White, assistant professor, Biological Engineering Division, MIT

page 9

- Industry Briefs:
 - Caprion and Wyeth pen biomarker collaboration.
 - Tecan US and EMD Biosciences sign co-marketing agreement.
 - Astex solves human P450 structure.
 - Waters associates to pay \$6.5M.



www.genomeweb.com
New Media for the New Biology

© 2003 GenomeWeb, LLC. All rights reserved. Copying, photocopying or duplicating this publication in any form other than as permitted by agreement with GenomeWeb, LLC is prohibited and may constitute copyright infringement subject to liability up to \$100,000 per infringement. For photocopy permission, back issues, bulk distribution or site licenses, please contact Allan Nixon at +1.212.651.5623 or anixon@genomeweb.com.

In Spite of Flat NIH Budget, FY 2004 Likely to Be Boom Year For Proteomics

IT WOULD seem like very bad news for proteomics companies and researchers that NIH funding will suffer next year, growing by only two to four percent — down from 15.9 percent growth in fiscal year 2003, according to a FY2004 draft budget approved early this month by the US Congress.

And yet it apparently isn't. Thanks to the enthusiasm that the US government has for genomics-related technologies — and to its recent willingness to fund anything with the label "biodefense" — proteomics researchers, funders, and industry analysts agree that funding for proteomics research and technologies will not suffer significantly next year, but will instead continue to grow at a steady rate.

"There's enough money for [proteomics] companies to grow in double digits," said Kenneth Goldman, an analyst who covers mass spectrometry companies for Lehman brothers.

According to Goldman, growth for NIH research projects in FY2004 will decrease by only one percentage point, from 8.5 percent growth in FY2003 to about 7.5 percent, due to the priority that the NIH puts on research. "What the NIH will do is still skew the money the way they

continued on page 3

Emmanuel Petricoin Searches For a Prince on The Road to Ovarian Biomarkers Clinical Trials

WHEN IT comes to developing an ovarian cancer biomarker test, Emmanuel Petricoin will do anything it takes to find the cleanest, most consistent model — even if it means kissing frogs.

As the co-director of the FDA-NCI clinical proteomics program prepares to send his mass spec pattern-based diagnostic test, which first made a splash in the February 2002 issue of *The Lancet* (see [PM 2-18-02](#)), into two separate clinical trials at the end of this year, he and his colleagues are first "trying to find our prince among the frogs," Petricoin told

ProteoMonitor this week. That means identifying the best combination of instruments and protocols to produce a high level of accuracy and reproducibility across platforms. "You have to be absolutely sure that the spectra [making the patterns] are reproducible," Petricoin said. "Or else your house of cards falls apart."

That reproducibility is a central problem evident from some of Petricoin's recent work. At the June meeting of the American Society for Mass Spectrometry, Petricoin's colleague Thomas Conrad introduced a paper describing a

continued on page 4

MOVERS & SHAKERS

Michael Sweeney has become a general partner of venture capital firm **InterWest Partners** of Menlo Park, Calif. In his new position, he will help the company identify investment opportunities in the life sciences. Sweeney joined InterWest in 1998 as an entrepreneur in residence and went on to become a venture partner in 2001. Among a host of other companies, he represents InterWest's portfolio company **Fluidigm**.

Clive Brown has become head of bioinformatics at Little Chesterfield, UK-based **Solexa**. Prior to that, he was a bioinformatics consultant for **Oxford GlycoSciences**, where he was involved with the Protein Atlas of the Human Genome. He also consulted for a number of other biotechnology companies. Before that, Brown held various positions at the **Wellcome Trust Center for Human Genetics** in Oxford, **GlaxoWellcome**, and the **Sanger Institute**.

NEW PRODUCTS

Varian of Palo Alto, Calif., now offers its **Omix pipette tips** for peptide extractions on a microliter scale. The pipette tips contain a monolithic sorbent, which, according to the company, allows researchers to isolate up to about 40 percent more peptide with an improved standard deviation. Also, the technology improves flow and binding capacity, according to the company.

Temecula, Calif.-based **Chemicon International**, a division of **Serologicals**, has introduced a number of **tissue microarrays** for studying proteins implicated in cancer. The company offers a series of 30 human and animal tissue arrays derived from normal and cancerous formalin-fixed and paraffin-embedded tissues. The arrays come in three formats: high density, with 180 1 mm tissue spots per slide; low-density, with 60 2 mm spots per slide, and trial size, with 10-20 2 mm spots per slide. They are designed for both high-throughput auto-mated and manual screening.

RefSeq release 1, the first full release of all **NCBI RefSeq** records, is now available by anonymous FTP

at: <ftp://ftp.ncbi.nih.gov/RefSeq/release>. The release incorporates genomic, transcript, and protein data available as of June 30 and has over 785,000 proteins and sequences from 2005 different organisms.

Imaging Research of St. Catharines, Canada, a subsidiary of **Amersham Biosciences**, has released version 7.0 revision 1.0 of its **MCID Elite** image analysis software. New features include co-localization for fluorescence microscopy, three new curve types for ELISA binding, and four point logistic and Michaelis-Menten for densitometry calibrations.

Select Biosciences of Acton, UK, has published a market report entitled "**Proteomics 2003**." The proteomics market, according to the report, has already grown from \$1.1 billion in 2001 to almost \$1.4 billion in 2002, and is continuing to grow. The study evaluates 75 proteomics companies in the US and in Europe and contains interviews with proteomics experts, three scenarios for the future of the industry, and a quantitative market model. It is available as a single user print version or as an electronic site license.

ProteoMonitor

The Global Weekly of
Proteomics Technology

www.proteomonitor.com
ISSN 1537-6079

Julia Karow, DPhil, *Editor*
jkarow@genomeweb.com

Katherine A. Mason, *Contributing Editor*
kmason@genomeweb.com

Gwen Libsohn, *Production Manager*
glibsohn@genomeweb.com

Elena Coronado, *Production Designer*
ecoronado@genomeweb.com

Dennis P. Waters, PhD,
Chairman and Publisher

Marian Moser Jones
Editorial Director

SUBSCRIPTION INFORMATION

ProteoMonitor is published weekly (50 times annually) by GenomeWeb LLC

Subscription rate: \$895.

To subscribe contact Allan Nixon
+1.212.651.5623
anixon@genomeweb.com

Or subscribe at our website at
<http://www.proteomonitor.com>

REPRINT ORDERS

Gwen Libsohn
+1.212.651.5630
glibsohn@genomeweb.com

ADVERTISING PLACEMENT

+1.212.269.4747
sales@genomeweb.com

GENOMEWEB, LLC

PO Box 998, Peck Slip Station
New York, NY 10272-0998 USA
Phone: +1.212.269.4747
Fax: +1.212.269.3686

Bruker Rounds Up Changes at Open House Meeting and Jumps onto Biomarker Train

TWO WEEKS after Bruker Daltonics and Bruker AXS officially merged, the new company — Bruker BioSciences — presented itself to investors and analysts at its headquarters in Billerica, Mass. last week

For employees and customers, changes may be subtle: According to CEO Frank Laukien, the two operating companies, Daltonics and AXS, will be the “two engines that pull the train” of Bruker BioSciences, the holding company. Both will retain their separate research and production facilities and sales forces, but hope to boost revenues by cross-selling to each other’s customers and pooling their international distribution networks. Also, the company expects to save \$1.2 to 1.5 million per year by eliminating

redundant costs, such as separate boards, public filings, audits, and insurance (see [PM 4-14-03](#)).

But Bruker is also venturing into new directions, by jumping onto a protein biomarker discovery train that appears to be dominated by CIPHERGEN at the moment. “We already have two biomarker discovery centers,” said Laukien — one in Leipzig, Germany, and another one in the US that is “nearly finished.”

Last month, the company also launched a product package for biomarker discovery called ClinProt, which includes magnetic beads for protein separation, a MALDI-TOF or MALDI-TOF/TOF mass spectrometer, and software for pattern discovery. According to Laukien, this platform — which Daltonics has

already sold to several beta-sites — not only allows users to discover protein fingerprints in clinical samples, but also to identify the peaks in these patterns. “Fingerprints are fascinating, but after a while you would like to know ‘what’s that finger,’” Laukien said.

Moreover, he claimed that Bruker’s liquid-based bead technology allows for easy automation, good reproducibility, and low analysis costs, compared to surface-based approaches (such as CIPHERGEN’s).

Mass spectrometry, he said, “is bound to have a very bright future in molecular diagnostics, not only in the next few years of research, but longer-term,” and funding opportunities are abundant. “We think we are going to be a very significant player in this fast-growing market,” he said. “It’s going to be competitive, but that’s fine.”

— JK

NIH Funding...

continued from page 1

want to,” Goldman said. That means taking money that would have been spent on buildings and facilities, for example (*the American Association for the Advancement of Science* reported that spending in this area is slated to drop by 86 percent), and spending it on research projects instead.

Among the NIH research project money, an even greater piece of the pie will go to genomics and proteomics, areas that the NIH has been consistently emphasizing recently. In addition, NIH spending

on biodefense is expected to double next year to about \$5 billion and Goldman expects half of that to go to what the NIH calls “research resources,” including genomics and proteomics-based research. “If you have the foresight to put ‘bioterrorism’ or ‘AIDS’ into your budget request, your funding will be up for genomics and proteomics about 10 percent at least,” Goldman said.

Proteomics researchers also expressed confidence that they would not be hampered by the change in NIH funding. “I don’t think [the budget] will have as much of an effect on proteomics as it does on more traditional biology fields,” said Steven Gygi, an assis-

tant professor and protein mass spectrometrist at Harvard Medical School. Gygi cited several new proteomics initiatives coming out of various institutes of the NIH as evidence that enthusiasm for the field was accelerating rather than waning. “By and large there’s more call for proteomics type research in the last year than I’ve seen in many years at the NIH,” he said.

Alexander Kurosky, professor of the University of Texas Medical Branch Biomolecular Resource Facility and director of a National Heart, Lung, and Blood Institute-sponsored proteomics center noted the same trend. “I think the NHLBI led the way with their big effort of

Recently Released NIH Proteomics Initiatives

Sponsoring Institute	Release Date	Application Receipt Date	Funds Available	Project Number
NIDDK	1/07/03	2/1/03, 6/1/03, 10/1/03	\$150 million	PA-03-052
NIDA	4/28/03	10/24/03	\$2.5 million	DA-04-004
NIDCD	7/09/03	10/1/03, 2/1/04, 6/1/04	N/A	PA-03-151

\$157 million over seven years. The institutes kind of watch each other and they need to keep up with each other," Kurosky said. Also, he noted, "I do think there is the awareness that proteomics will make an impact and that there are benefits to supporting this area of research."

Christine Colvis, director of a National Institute on Drug Abuse neuroproteomics initiative that was introduced this April (see table p. 3), said proteomics research was definitely a hot area. "Because of mass spectrometry we're actually able to do the science in a forward direction — to generate hypotheses rather than test them," she said. "There's tremendous strength in that."

A look at recent initiatives at various NIH institutes confirms Gygi's and Kurosky's observations. At least five institutes aside from the NCI and NHLBI are already funding or are planning to fund proteomics initiatives. These include the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Drug Abuse,

the National Institute on Deafness and other Communication Disorders, the National Institute of Neurological Disorders and Stroke, and the National Institute of General Medical Sciences (see table p. 3). Program directors at the NIDDK, NIDA, and NINDS all expressed confidence that their initiatives would continue to have sufficient funds — in fact, the NIDDK proteomics initiative receives additional funds outside of the normal NIDDK budget from a type 1 diabetes Special Statutory Funding Program. This program began allocating money in 1998 and just had its funding renewed to the tune of \$150 million for five additional years until 2008. Any research proposal that would use proteomics technology to study type 1 diabetes and its complications would be eligible for these earmarked funds.

Biodefense initiatives with applications to proteomics are also in the works at the NIH. The Institute has already awarded UTMB a five-year biodefense grant for \$5.5

million, and the university hopes that figure will soon grow considerably. UTMB has applied for a National Institute of Allergy and Infectious Diseases-sponsored Regional Centers of Excellence in Biodefense and Emerging Infectious Diseases grant that would total \$65 million in funding over five years. About \$2.5 million of that grant would be slated for proteomics research, according to Kurosky.

All of this is ultimately good news for companies that sell proteomics technologies. Waters and Applied Biosystems declined to comment for this story, and Bruker investor relations officer Michael Willett said the NIH budget normally has "only a very minor effect" on Bruker's business.

But Goldman said he suspected that "if NIH spending were suddenly flat in any given year, Bruker would feel it." Luckily for Bruker, FY2004 should be anything but flat for the proteomics industry.

— KAM

Biomarkers...

continued from page 1

repeat of the original study in which ABI Q-Star mass specs replaced CIPHERGEN's SELDI mass specs to successfully detect more precise — but different — ovarian cancer proteomic patterns.

Petricoin is determined to iron out these differences. "A tremendous amount of our work right now is quality control measures," he said. Upgrading mass specs was an important first step. Since switching from SELDI to the Q-Star, the models "got much much better" with 100 percent accuracy achieved in some runs, Petricoin said. The Q-Star machine's advantage is that it not only generates more peaks overall, leading to higher specificity,

but it also generates fewer background peaks. "SELDI tends to generate a lot more fragments because the mass analyzer is directly coupled to the source," Petricoin said. Still, Petricoin has not ruled out retaining the use of SELDI chips, which he used along with the Q-Star in the recent experiment. He is also interested in trying out electrospray, using Advion's source.

For FDA approval, Petricoin will have to show that the results from a sample run on one machine will be classified the same way on at least two other machines, across multiple time periods. This doesn't mean that there can't be any variability across platforms, but that variability must be recognized and controlled for. And that involves more than just controlling for different machines' sensitivities. It also

requires developing effective control measures for every step of the process.

"It's an onion of a problem — layers of problems at the clinic, chipping, software reliability that you have to address, the way the samples are handled and processed for the chip — every step introduces variability," Petricoin said. "So basically, the least number of steps you have, the better. A bicycle works almost all the time because it has a lot less parts than a spaceship."

Even after the kinks are ironed out, the ovarian biomarker pattern tests still will not be applied in a large scale, long-term general screening study anytime soon. This is not because the FDA treats pattern-based tests any differently than it would treat any other test using new technology, according to Petri-

coin. "A lot of people ask us [if that's the case]. But the FDA looks at all things on a case by case basis," he said. Given that, why not launch a big trial of thousands of people right away? "The knee jerk reaction is to say, 'let's start having big screening trials,'" Petricoin said. "But we don't want to necessarily wait a decade to see if the technology has any promise."

In one sense, they won't have to wait at all. Petricoin's partner, Correlologic Systems of Bethesda, Md., last November already licensed the pattern test to Quest Diagnostics and Laboratory Corporation of America Holdings for homebrew use. The laboratories can use any pattern test based on Correlologic's algorithms and modeling techniques in their work, so long as they don't sell the technology to anyone else.

The FDA will also consider approving Petricoin's version of the test based on two small trials set to begin within four to six months from now. Both are expected to be completed within 18 months of their start dates. In one trial, Petricoin's biomarker test will be used alongside the only existing ovarian cancer biomarker, the rather unreliable CA125, which has a positive predictive value of less than 10 percent. The trial will look at whether the pattern test as equally effective or better than CA125 at predicting whether cancer will recur among women who have already been successfully treated, and are now in danger of relapsing. Since 80 percent of ovarian cancer patients relapse within 18 months, this highly enriched population will provide very quick answers.

The second trial will couple the pattern test with an ultrasonography imaging screen, again looking at patients at risk for recurrence. Patients who are suspected of having a malignancy based on the

imaging test will all be biopsied, but Petricoin and his team will look retrospectively at whether the pattern test could have distinguished a benign growth from cancer. The idea is to eventually be able to prevent unnecessary biopsies, which can sometimes lead to morbidity. "This is not the slam dunk clinical benefit of detecting disease early, but this is an important baby step," Petricoin said.

An obvious next baby step, for many scientists, would be to identify the proteins that make up the patterns. "I think in the end it would be better to have the identities of these proteins," said David Springer, a staff scientist at Pacific Northwest National Laboratory who also works on the proteomics of

"The least number of steps you have, the better. A bicycle works almost all the time because it has a lot less parts than a spaceship."

Emmanuel Petricoin, FDA

ovarian cancer. "We should be able to get to the bottom line and understand where they're coming from and what's different."

This is something Petricoin is working on, but he insists that identifying the proteins and finding antibodies to them is not the best way to think about cancer biomarkers. "We need to stop thinking that cancer is a foreign disease," he said. "It is your own body cells acting like mini-terrorists — it doesn't make a unique protein."

Because the proteins that make up the pattern are mostly truncated versions of naturally occurring proteins, finding a specific enough antibody for diagnostic purposes is an "improbability that is not likely to happen." For this reason, mass

spec-produced patterns, Petricoin believes, are a better model for cancer biomarkers. Springer doesn't disagree. "I think there's truth to that," he said.

In any case, the pattern-based approach is picking up steam. Last week at the American Association for Cancer Research meeting, data was presented by NCI-affiliated researchers showing that similar pattern-based serum tests, when applied to prostate cancer, could classify 70 to 80 percent of benign lesions as benign without doing an unnecessary biopsy. Unnecessary biopsies often occur when PSA, the prostate cancer biomarker in use now, is in the "diagnostic gray zone," Petricoin said. Projects are also in the works to find biomarkers for breast and lung cancer that could be used to verify or refute image-based mammography or spiral CT tests. "This will probably be the next big thing to look at after ovarian cancer," Petricoin said.

— KAM



REPRINTS

For permission to reproduce material from *ProteoMonitor*, or to order offset printed or Web-ready PDF reprints, contact reprints@genomeweb.com

www.ProteoMonitor.com

ProteoMonitor's IP Roundup: Recent Patents of Interest in Proteomics

US Patent 6,582,965. **Method for *de novo* peptide sequence determination.** Inventors: Robert Reid Townsend, Raj Bhikhu Parekh, Sally Barbara Prime, Nick Sinclair Wedd. Assignee: Oxford GlycoSciences (now Celltech).

Covers a method for determining the amino acid sequence of an unknown peptide whose molecular mass is known. The method involves generating a virtual library of peptides with the same molecular mass as the unknown peptide, consisting of all allowed combinations of amino acids that might be present in the unknown peptide. The method involves determining a molecular mass and an experimental fragmentation spectrum for the unknown peptide, comparing its fragmentation spectrum to theoretical fragmentation spectra calculated for each member of the virtual peptide library, and then identifying a spectrum that matches the pattern most closely.

US Patent 6,586,190. **Parallel high throughput method and kit.** Inventors: Paul Bernasconi, Ray Donald Carpenter, Gary Keith Powell, Robert Michael Petrovich, Kimberly Ann White, Jennifer Audrey Hunt. Assignee: Syngenta Participations.

Covers a high-throughput method and kit for the discovery of small-molecule interactors of target proteins. A target module is prepared by selectively binding a target protein to a ligand that is linked to an individually detectable bead. Sets of target modules are mixed in each chamber of a multi-chamber container. Test compounds are added to each chamber, and the interaction of a compound with each target module is observed. A compound that is specific for a particular target protein will displace that protein from its target module. The identity of the disrupted target module is determined by identifying the bead to which the protein was attached.

US Patent 6,586,727. **Methods and apparatus for mass spectrometry.** Inventors: Robert Harold Bateman, John Brian Hoyes. Assignee: Micromass (now Waters).

Covers an improved method for parent ion scanning. In one embodiment a quadrupole mass filter upstream of a collision cell is arranged to operate in a high pass mode. Parent ions transmitted by the mass filter are fragmented in the collision cell and detected by an orthogonal time-of-flight analyzer. Ions having a mass-to-charge ratio below the cutoff of the mass filter are identified as daughter ions. In a second embodiment, the collision cell alternates between high and

low fragmentation and candidate parent ions can additionally be identified on the basis of the loss of a predetermined ion or neutral particle.

US Patent 6,586,728. **Variable width digital filter for time-of-flight mass spectrometry.** Inventors: Edward Gavin, Leonid Braginsky. Assignee: Ciphergen Biosystems.

Provides a method and system for detecting mass-to-charge ratio of ions. A control system selects a bandwidth for filtering a signal produced by the detector. The signal is then filtered with a variable width digital filter. The bandwidth for filtering the signal may be selected from a look-up table within the control system based upon the mass-to-charge ratio of an ion of interest. Alternatively, a peak bandwidth within the signal produced by the detector may be determined and the signal may then be filtered with the variable width digital filter.

US Patent 6,590,204. **Method for reducing chemical background in mass spectra.** Inventor: Valdimir Baranov. Assignee: MDS.

Protects a computer-based method for reducing chemical background in acquired electrospray and nanospray mass spectra. It involves pre-processing an acquired mass spectrum, transforming it into the frequency domain, reducing peaks at calculated frequencies, applying an inverse transformation to the mass spectrum represented in the frequency domain, further processing, and subsequent output of a mass spectrum with chemical background reduced. The invention enables rapid, automated generation of mass spectra with the component attributed to chemical background reduced. It also generates mass spectra with an improved signal-to-noise ratio and sample mass accuracy.

US Patent 6,582,969. **Microdevices for high-throughput screening of biomolecules.** Inventors: Peter Wagner, Dana Ault-Riche, Steffen Nock, Christian Itin. Assignee: Zyomyx.

Protects methods for the parallel, *in vitro* screening of biomolecular activity using miniaturized microfabricated devices. The biomolecules that can be immobilized on the surface of the devices of the present invention include proteins, polypeptides, nucleic acids, polysaccharides, phospholipids, and related unnatural polymers of biological relevance. These devices are useful in high-throughput drug screening and clinical diagnostics and are preferably used for the parallel screening of families of related proteins.



Forest White, Just Arrived at MIT, on Improving Phosphoproteomics

How did you become interested in mass spectrometry?

[I did my PhD] at Florida State University, [working with Alan Marshall] at the National High Magnetic Field Laboratory. I actually went to Florida State to do organic synthetic chemistry and did that for a semester, and then talked to Alan about switching labs. He gave me a couple of papers that he had published recently on FTMS. I read the papers and I knew: This is what I wanted to do. Mass spec was it.

My PhD was basically on designing and constructing a novel FTMS instrument that would have multiple ion sources. What Alan wanted [me] to do is construct a system where you could do MALDI and then, if you weren't getting the right results with MALDI, or you wanted to switch projects completely and go to electrospray, you would have only 15 or 20 minutes of downtime.

What led you to biological applications?

I wanted to learn a little more biology because instrument design is pretty cool, but it's much better to design an instrument with an application in mind. The person who really has pushed the field of bioanalytical mass spectrometry is Don Hunt, so I went and postdoced for him. When I got there, he was still very focused on doing immunology and looking at MHC class I and class II peptides. During my time there, he switched to bringing in a large component of proteomics into his lab, and that's actually how I got started in proteomics.

One of my main projects [in Don's lab] was developing phosphoproteomics, [together] with a first year graduate student called Scott Ficarro. (see [PM 1-20-03](#)). Don came into the lab one day and said, "I want you to analyze protein phosphorylation sites on blood platelets." We went and read the literature, and there are a lot of papers published on IMAC. We applied the standard methodology and saw instantly what a lot of other people had seen, that there is [a lot of] nonspecific binding to an IMAC column. Don [suggested] that if you block the carboxylate groups, you [could] get rid of the

AT A GLANCE

NAME: Forest White

AGE: 32

POSITION: Assistant professor, Biological Engineering Division, Massachusetts Institute of Technology, since July 2003.

PRIOR EXPERIENCE: Senior research scientist, MDS Proteomics, Charlottesville, Va., 2001-2003

Institute for Proteome Research, University of Virginia, 1999-2000

Postdoc, University of Virginia, 1997-1999. Worked with Don Hunt.

PhD, Analytical Chemistry, Florida State University, 1993-97. Studied with Alan Marshall.



nonspecific binding. Scott and I went back into the lab and spent the next several months implementing Don's suggestion. A couple of years of development later, we applied it to yeast, and published a paper in *Nature Biotechnology* last year (March 2002;20(3):301-5).

After my postdoc, I spent two years in Don's Institute for Proteome Research, which was funded by Novartis Agricultural. They presented a broad variety of very interesting problems, including posttranslational modifications, [and] phosphorylation was one of the main projects there. It was actually all in plants, so it was a completely different ballgame. The overall level of phosphorylation is much lower [and] there are a lot more issues with dynamic range. Overall, it was much

more difficult looking at the phosphoproteome of a given plant than it is to look at the phosphoproteome of yeast. We looked at several other projects, and developed a technique for mapping novel sites of ADP ribosylation on proteins.

Does the institute still exist?

It was around for about two years, and then MDS Proteomics came in. They hired several postdocs from Don's lab, and several of us who were in the institute, and that pretty much was the end of it. [The institute] was funded very well by Novartis Agricultural, but that was the only partner. So at any point they could have pulled funding, and it wasn't a stable atmosphere.

I think [MDSP's] main goal was to get Don Hunt's technology for phosphoproteomics that we had developed, and also the differential analysis technology, and to be able to tap into Don as a mass spec consultant.

What did you do at MDSP?

We were pushing quantitative phosphoproteomics forward in human cells. We worked on several pilot projects for a variety of pharmaceutical companies. We would take a given kinase inhibitor and look at the phosphoproteome either before or after its addition and

look at changes. If the kinase inhibitor was very specific, you would inhibit a given pathway. It's a really nice technique for figuring out what a specific signal transduction pathway is.

How did you improve the technology?

Our mapping of a given phosphoproteome [became] much more comprehensive. [In the] yeast [study, which] was actually done at MDSP, we mapped 270 or so phosphorylation sites. At the end, right before I left the company, we were mapping on the order of 1,000-1,200 phosphorylation sites from a given sample.

The quantitation is the other thing we pushed forward, being able to do reproducible quantitation from cell state A to cell state B. [For this], we use isotope-coded derivatization. During the esterification procedure, you add a methyl group to the carboxylate. We can use either a non-deuterated, or a deuterated form of methanol and put on three deuteriums on each of the carboxyl residues. Not only does this give you quantitation, but it also gives you a check on your sequencing, because now you know that you have a certain number of aspartic acids or glutamic acids in your sequence.

You have just become an assistant professor at MIT. Why did you decide to go back to academia?

The main reason was that I really want to develop the phosphoproteomics technology beyond what we can do in a company. We had pushed the technology to a point where we were able to apply it to many different problems, but we still are not [able to deconvolute] the signal transduction pathways in the cell. To do that, there needs to be quite a bit of technology development, and the nice thing in academia is that you don't necessarily have a timeline for that, you don't have to do it in two months or six months. Plus, I tend to be excited by a broad variety of different projects.

What are your plans for the next few years?

One of the initial projects will be looking at the yeast cell cycle. If we arrest yeast at some given point in the cell cycle and then release them and take samples at discrete time points and look at the phosphoproteome, we should be able to figure out the signal transduction that's going on at each of these time points. A lot of people have obviously looked at the yeast cell cycle and identified phosphorylation sites on given proteins, but no one has really taken a system approach, trying to figure out exactly how the different signal transduction networks are talking to each other. The nice thing about being at MIT is, there are some excellent biologists here

who are experts in looking at the cell cycle, and there are also some very good modelers who can use the data to model signal transduction pathways. There is an effort here called CSBI, which is the Computational and Systems Biology Initiative, [and] I am going to be part of that. It's basically a tie-in of a lot of different approaches to systems biology, including RNA expression biology, proteomics, and some very high-powered computing.

What I like to do initially is some technology development, so we can go in and map a larger fraction of the phosphoproteome. When we published that paper with a couple of hundred phosphorylation sites, we were looking at maybe one percent, or less, of the yeast phosphoproteome. What we would like to be able to do is look at maybe 20 percent of the yeast phosphoproteome and then track that 20 percent throughout the cell cycle and see how it changes with this quantitative approach.

The [ultimate] goal is to start looking at cancer, to figure out the signal transduction that occurs as you go from carcinogenesis and then progress through the various stages of cancer to metastasis. That should yield a broad variety of drug targets, so industry would be interested in this. Once we work on the yeast cell cycle, we will be moving into humans quite a bit, looking at breast cancer to begin with.

What challenges remain in proteomics?

There are three big problems: Sensitivity, so we need to develop more sensitive instruments and more sensitive sample handling techniques on the front end. There is dynamic range, which again can be addressed at the instrument side, and at the sample handling side by fractionation to simplify the mixture. The last one, that's huge right now, is going to higher throughput [analysis]. That was one of the main issues within the company. After a while, you realized that your throughput is not enough to do what a lot of pharmaceutical companies wanted you to do, which was to analyze 30 samples or 50 samples and do it ten times over for each sample, so that you had real statistical numbers, and go down deep into the phosphoproteome on each sample. I think with the right instrumentation developments, and [advancements] on the software side, we can start addressing a lot of these problems. FTMS is the way that it has to go right now. Your peak capacity in FTMS far exceeds peak capacity in any other instrument, so you can look at more species with higher dynamic range and more accurate mass than you can on other instruments. This allows you to probe deeper into the proteome, and you are able to quantitate from one sample to another. If you can go deep into the proteome in a single analysis, now your throughput has increased quite a bit.

AMERSHAM AND GENEPIO EXPAND 2D GEL SOFTWARE ALLIANCE

Amersham Biosciences and Geneva Bioinformatics have signed an exclusive proteomics software agreement, the two companies said this week.

GeneBio's Melanie 2D gel analysis software, which is developed by the Swiss Institute of Bioinformatics, will be integrated into Amersham's ImageMaster image analysis software platform and will be available upon its next release.

The companies also plan to develop further imaging software collaboratively.

The new agreement expands a strategic alliance to develop and distribute novel proteomics analysis software, databases, and training tools that Amersham and GeneBio announced in January (see [PM 1-13-03](#)).

CAPRION AND WYETH PEN BIOMARKER COLLABORATION

Caprion Pharmaceuticals and Wyeth have started a collaboration to identify biomarkers, the companies said this week.

Under the agreement, Caprion will study the effect of pharmaceutical compounds from Wyeth on plasma proteins in a preclinical model of inflammation, using its CellCarta proteomics discovery platform.

The companies hope to learn about the mechanism of action of these compounds and to be able to optimize their action.

TECAN US AND EMD BIOSCIENCES SIGN CO-MARKETING AGREEMENT

Tecan US of Research Triangle Park, N.C., and EMD Biosciences of Madison, Wis., have agreed to co-market a number of products for protein extraction, screening, and purification, the companies said this week.

EMD, an affiliate of Darmstadt, Germany-based Merck, provides reagents for molecular biology and proteomics through its Novagen brand. The two companies will combine Tecan's automated platforms for recombinant protein purification with Novagen's reagent kits. As part of the collaboration, they formed a technical applications team that will provide technical support.

AGILENT AND BATTELLE TO DEVELOP PROTEIN ID SOFTWARE

Agilent Technologies has signed a Cooperative Research and Development Agreement with Battelle

Memorial Institute, the operating and management contractor for the DOE's Pacific Northwest National Laboratory, the company said this week.

The goal of the collaboration is to further develop an artificial neural network technology for protein identification that was developed by Richard Smith at PNNL, and to adapt it to Agilent's LC/MS systems.

The technology predicts how long it takes individual peptides to elute from a liquid chromatograph. This increases the confidence in the identification of peptides and the proteins from which they are derived.

Agilent will supply its LC/MS platform to PNNL, which plans to use DOE funding to demonstrate the peptide retention time capability on these instruments. Under the CRADA, Agilent has the option to negotiate an exclusive license for the patent-pending IP, and for any inventions that may result from the collaboration.

ASTEX SOLVES FIRST HUMAN CYP450 STRUCTURE, OPENS NEW RESEARCH FACILITY

Astex Technology of Cambridge, UK, has published the first three-dimensional crystal structure of a human cytochrome P450 protein, the company said this week.

The structure of the protein, CYP450 2C9 — in the absence and presence of the anticoagulant warfarin — was published online in *Nature* on July 13. CYP450 2C9 is one of four enzymes that are responsible for metabolizing more than 90 percent of drugs. Astex has filed patents on the use of the crystal structure and is now sharing this information with a number of pharmaceutical partners.

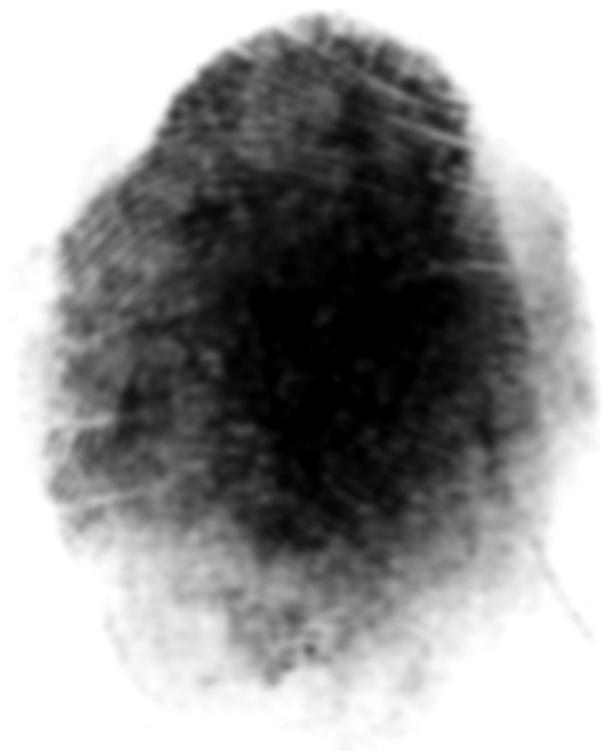
Last week, Astex opened a new, 36,000-square-foot research and development facility at Cambridge Science Park, which will house up to 150 research scientists, and which can be extended by another 30,000 square feet.

WATERS ASSOCIATES TO PAY \$6.5M

Waters Associates, a subsidiary of Waters, is settling an air and water pollution complaint for \$6.5 million, according to a newspaper report.

Last week, the *Herald News* of Fall River, Mass., reported that Waters Associates, located in the Myles Standish Industrial Park of Taunton, Mass., is settling the complaint, filed by state attorney general Tom Reilly. According to the news report, the company was accused of increasing its airborne emissions after changing production procedures and of filing incorrect data on airborne emissions for 20 years. It also allegedly discharged contaminated water without the proper permits.

MALDI-TOF TECHNOLOGY



MALDI O-TOF TECHNOLOGY



A breakthrough in **peptide mass fingerprinting**
– only from **PerkinElmerSCIEX**.

Introducing prOTOF™ 2000, featuring MALDI O-TOF,



a new class of MALDI-TOF that leaves current technology behind. Designed for proteomics research, this new orthogonal MALDI-TOF brings unprecedented clarity and accuracy to your results.

prOTOF's unique design delivers:

- Improved mass accuracy and resolution over a wide mass range.
- Stable platform which does not require internal calibration or frequent optimization.
- Higher rates of successful protein identification through PMF.

For more information, visit www.O-TOF.com or call us at 1-800-762-4000.


PerkinElmerSCIEX™

800-762-4000 (U.S. & Canada)
(+1) 203-925-4600

ProteoMonitor

THE GLOBAL NEWSWEEKLY OF PROTEOMICS TECHNOLOGY



3 easy ways to order!

1. Print and fax completed order form to: +1-212-269-3686
2. Print out and mail completed order form to:
GenomeWeb LLC
 PO Box 998
 Peck Slip Station
 New York, NY 10272-0998
3. If you're a first-time subscriber, [sign up online](#) for our introductory offer!

yes! Sign me up for a full year of *ProteoMonitor*! That's 50 weekly issues plus access to the *ProteoMonitor* website (includes current issue and complete archive access) — the most comprehensive news resource in the proteomics industry — for **\$895!**

subscription form

Please indicate your preferred method of payment:

- My check or money order is enclosed.
- Please bill me.
- Charge my credit card (see below).

Name _____

Job Title _____

Company _____

Address _____

City _____ State/Province _____

Zip/Post Code _____ Country _____

Phone _____ Fax _____

E-mail _____ @ _____

URL _____

Please indicate your preferred method of payment:

- Visa
 - Mastercard
 - American Express
- Number _____ Exp. _____
- Signature _____



www.genomeweb.com
The Pulse of the New Biology