PROTEOMICS
GENEPROT

A Proteomics Upstart Tries To Outrun the Competition

By assembling an arsenal of technology, GeneProt aims to identify proteins associated with disease

GENEVA, SWITZERLAND—"Proteomics is something you either do in a big way or putter around in a corner," says Keith Rose. He should know. Last year, along with fellow proteomics pioneers Denis Hochstrasser, Amos Bairoch, Ron Appel, and Robin Offord, Rose launched GeneProt, the biggest proteomics test-bed to date in this young field. Armed with 51 mass spectrometers—protein sequencing machines that can cost over $150,000 each—and a massive supercomputer, the company is already a proteomics powerhouse.

And that's just for starters. In addition to the research lab here in the outskirts of Geneva, the company is constructing an even bigger facility in North Brunswick, New Jersey, slated to open next year. Moreover, it's considering plans to open a third site in Japan. All this for a deceptively simple goal: finding proteins involved in disease.

The company is banking that these proteins will produce a string of lucrative drugs aimed at top killers such as cancer and heart disease. GeneProt will use the proteins either as drugs themselves—like Amgen's top-selling protein therapeutic erythropoietin—or as targets for making their own small-molecule drugs.

GeneProt is sprinting out of the blocks, says Rose, because drugs, patents, and profits will go to those who are first with discoveries or can fish out the most important disease-related proteins. And GeneProt execs are convinced that the technology for analyzing proteins en masse has finally come of age. "You can either drop a line in or drain the whole area and see what is on the bottom," Rose says. The company, obviously, is taking the second tack.

Despite GeneProt's fast start, fellow proteomics firms Oxford GlycoSciences (OGS) in the United Kingdom and Large Scale Biology Corp. (LSBC) in Vacaville, California, are already in hot pursuit. OGS has protein-hunting collaborations with Pfizer, Bayer, GlaxoSmithKline, and the agricultural firm Pioneer Hi-Bred; LSBC has teamed up with Proctor & Gamble and Dow AgroSciences, among others. Celera's footsteps are also getting louder. This genomics powerhouse in Rockville, Maryland, raised nearly $1 billion in a March 2000 stock offering, much of it slated for proteomics. The company is now completing a seperate proteomics research center. And it recently formed a joint venture with equipment dynamo Applied Biosystems—which helped Celera sequence the human genome—giving it early access to the latest mass spectrometers, among other tools. To stay ahead, concedes GeneProt president Cédric Loiret-Bernal, the company will have to cut several deals with firms willing to have GeneProt be their primary proteomics source. He says the company is in discussions with 11 possible partners, six of which are "very interested."

Gamblers. GeneProt execs including Keith Rose (*top*) and Denis Hochstrasser are betting that banks of high-speed mass spec machines and supercomputing power will put them ahead of the pack.

CREDITS: (ROSE) MARY RITCHIE; (HOCHSTRASSER) COURTESY OF DENIS HOCHSTRASSER; (LAB) GENEPROT

GeneProt's moves have inspired both awe and skepticism among other proteomics researchers. "They are going to industrialize the process," says David Hachey, a proteomics expert at Vanderbilt University in Nashville, Tennessee. "I think it will work." Ruedi Aebersold of the Institute for Systems Biology in Seattle, Washington, gives them a shot as well. The expertise of GeneProt's founders in proteomics is "very, very good," he says.

But John Yates, a proteomics researcher at the Scripps Research Institute in La Jolla, California, wonders whether the company is starting too fast with talk of three research centers: "It seems like a lot given that proteomics is still unknown as a business strategy." Hochstrasser's response: "If you want to place a satellite in orbit, you have to have a rocket of a certain size."

Hochstrasser concedes, however, that "there are not that many customers" for his business—perhaps 40 pharmaceutical companies that would be willing to strike deals. But he thinks they will, because to maintain their recent run of strong returns to investors, they must discover an ever larger number of blockbuster drugs: "The drug industry is ready because they want to go faster and can't do everything internally."

GeneProt has already lured one big customer. Last October, while its labs were still under construction, the company struck an $84 million deal with Novartis Pharmaceuticals. Backed by these resources, the company plans to work its way through a series of "twin proteome" studies, which can take up to 6 months apiece. Each will carefully analyze a pair of tissues—such as normal lung tissue and tissue from a lung cancer—and look for changes in expressed proteins that correlate with disease. For its investment, Novartis will receive three twin proteome studies, on diseases the company declines to specify.

GeneProt plans to keep its lead, says Rose, by producing a better product faster. He claims that GeneProt can analyze several hundred thousand proteins a year. That's on par with numbers by competitors such as OGS. But when GeneProt's new U.S. facility comes on line next year, its output will double, the company claims. At the Geneva site alone, this stream of proteins is expected to generate a torrent of some 40 terabytes, or 40 trillion bytes, of data per year. To handle that flood, the company has teamed up with Compaq to create one of the largest civilian supercomputers in the world, comprising 1400 separate processors capable of carrying

out 2 trillion operations per second.

And GeneProt will offer its partners something its competitors don't: synthesized proteins. Not only will this strategy help jump-start drugmaking efforts, asserts Rose, but it may also help GeneProt researchers dodge patent disputes. Companies such as Incyte Genomics in Palo Alto, California, and Human Genome Sciences in Rockville, Maryland, claim rights to certain genes that can be used to make proteins in bacteria. By synthesizing proteins directly, Rose asserts, GeneProt can navigate around those claims. "The genomics companies thought they would stake out acres of virgin land," Rose asserts. "I'm not sure that will cover chemical protein synthesis."

If GeneProt's technology is as powerful as its executives claim, the first drug targets, and even drug candidates, should show up over the next year. "Expectations are very high," says Loiret-Bernal. "People are really looking at us to see if we are going to be successful or fail." Whatever the outcome, it's likely to serve as a bellwether for other firms looking to cash in on industrial protein analysis. **–ROBERT F. SERVICE**

PROTEOMICS
▶PROTEIN CHIPS

Searching for Recipes for Protein Chips

Protein arrays could be the basis for new diagnostics and research tools, but the technology has been slow to develop

When medical visionaries talk about the future, many offer up the image of a computer chip or CD-ROM that stores your complete DNA sequence. Interested in your odds of getting Huntington's disease or breast cancer? Just have your doctor scan your DNA.

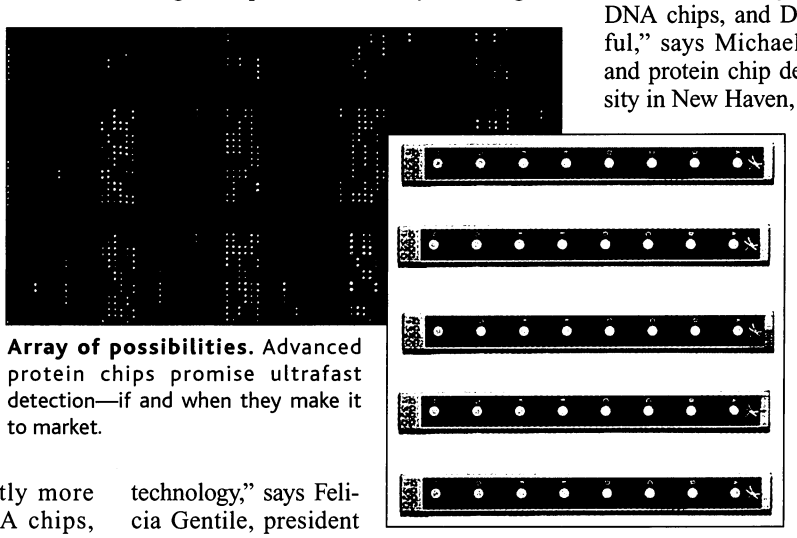
In most cases, however, we want to know what we've got right now, not what we might face in 30 years. DNA and genes won't always provide immediate answers, but looking at proteins just might. That's because proteins reflect the chemistry taking place inside cells, chemistry that is altered in potentially diagnostic ways by different diseases. The problem is that such diagnoses depend on technology that does not exist today: chips that can spot hundreds or thousands of distinct proteins at a time from a sample, say, of blood or urine.

Both academic and commercial labs around the globe are furiously competing to perfect such next-generation biochips, postage stamp–sized devices that would track many proteins in a single step. Rudimentary versions that spot a handful of proteins are already on the market. But making more complex versions is vastly more complicated than creating DNA chips, popular research tools for analyzing suites of genes involved in everything from cancer to normal cell development.

Despite the difficulty, a handful of academic groups and adventurous companies, from small start-ups to research powerhouses, are pursuing the technology. "Everyone is working on this so aggressively because it's so potentially useful," says Larry Gold, who recently stepped away from a decade of mixed success chasing biotech drugs to launch a protein biochip start-up called SomaLogic in Boulder, Colorado.

So far there hasn't been much to show for these efforts. But two recent studies offer hope that protein arrays will succeed. "I think it's virtually a sure thing," says Pat Brown, a Stanford University biochemist and pioneer of both DNA and protein chips. "But what will be the best technology, and how soon, remains to be seen."

If and when protein chips hit the market, they stand to make a big impact. "We believe there is a pent-up demand for these things. People are anxiously awaiting the technology," says Felicia Gentile, president of BioInsights, a market research firm in Redwood City, California. BioInsights predicts that the market for protein chips will grow to $500 million by 2005; other market watchers put that number as much as 10 times higher.



Array of possibilities. Advanced protein chips promise ultrafast detection—if and when they make it to market.

CREDIT (LEFT TO RIGHT): H. ZHU *ET AL.*; CIPHERGEN BIOSYSTEMS INC.

Much of the allure surrounds the diagnostic tests these chips might make possible. Proteomics companies are working overtime to find novel protein and peptide biomarkers whose expression correlates with particular diseases. If they succeed, a single scan of a drop of a patient's blood or urine could reveal whether the person is making proteins linked to cancer, arthritis, or heart disease. DNA chips are limited as diagnostic tests, in part because most diseases don't have a distinctive genetic signature.

Beyond the doctor's office, protein chips might also help reveal the web of protein-protein interactions in different cell types, thereby enabling researchers to work out the complex chains of chemical communication inside cells. Versions of the technology might illuminate how much of a given protein is expressed at a given place and time, offering insights into, say, cellular development or aging. And drug screening could be thrown into overdrive if researchers are able to quickly test whether new compounds bind to particular proteins immobilized on chips. "Protein chips will be orders of magnitude more useful than DNA chips, and DNA chips are very useful," says Michael Snyder, a biochemist and protein chip developer at Yale University in New Haven, Connecticut.

Second wave

Protein chips are made in much the same way as DNA microarrays. Researchers dot a glass or plastic surface with an array of molecules designed to grab specific proteins; the grabbers can be other proteins such as antibodies or even snippets of DNA. Then fluorescent markers or other detection schemes reveal which spots have snagged their prey. Because researchers keep track of the identity of each protein-grabbing molecule as it's laid down in the grid, when they see that a particular spot on the grid lights up, they know which protein has been captured.

It sounds simple enough. But getting all the elements to work is far more difficult than with DNA arrays. "Measuring nucleic acids [in an array] is a simple and stream-