protein targets as do full-sized antibodies.

Phylos, a biotech company in Lexington, Massachusetts, has its own twist on the technology. Its founders developed a system to create libraries of small antibody-mimic proteins. These mimics are as easy to produce as antibody fragments made by phage display, and they are more stable, says Albert Collinson, who heads the company's business development. Phylos also has a scheme for arraying the capture proteins in high density and with a common orientation. Because of these advantages, "Phylos appears to have the most sophisticated protein capture technology," according to the market research firm BioInsight's most recent review of the protein-chip field. Collinson says the company hopes to begin testing its chips for diagnostics and other uses early next year.

But using a protein, antibody or otherwise, to capture another protein has its drawbacks. This approach makes it tricky to detect where target proteins bind on a chip: Both the capture molecules and the targets are proteins, so a simple protein-staining technique would light up each spot. That forces many companies to use more complex assays, such as creating fluorescent compounds that have to bind to target proteins to light up. SomaLogic's Gold says a better solution is changing the probe molecules laid down on the grid to "aptamers," short stretches of nucleotides that can twist, fold, and bind to target molecules much like proteins do. A key advantage, Gold says, is that once an aptamer binds to a protein, researchers can forge a tight covalent bond by hitting it with ultraviolet light, allowing them to wash excess protein off the chip surface and scan for the tight binders that remain. SomaLogic, Gold says, doesn't plan to make chips itself but is in discussions with about 10 other companies that might market aptamer-based chips.

For now, all of these approaches are having trouble getting out of first gear to make products that compete with rudimentary protein chips already on the market. In 1990, Biacore in Uppsala, Sweden, began introducing sensor chips that use a technique known as surface plasmon resonance to investigate which proteins interact and to monitor the speed of such reactions. Ciphergen Biosystems of Freemont, California, sells a chip that screens samples for the presence of up to eight different proteins. But with both chips, researchers can look at no more than a few different proteins at one time. Ciphergen president Bill Rich is quick to admit that most researchers want more and that these chips are just the earliest examples of what is to come.

Which technology will prevail is unclear. But Zyomyx's Cohen says it's safe to assume that the nascent field will go through a shake-out in the next couple of years. Even with some success, protein chips will not match the complexity of DNA chips anytime soon, says Ruedi Aebersold, a proteomics expert at the Institute for Systems Biology in Seattle, Washington. He thinks companies will start with a limited approach, making chips to test for the presence of just tens to hundreds of proteins. Still, Aebersold and others believe even such modest gains could make the chips useful diagnostic tools. If so, protein chips could take an opposite course from that of DNA chips and be useful in the clinic long before they make a big impact in the research lab. **–ROBERT F. SERVICE**

PROTEOMICS
PATENTS

Gene and Protein Patents Get Ready to Go Head to Head

Genomics companies thought they had genetic medicine to themselves. Now proteomics firms are staking a claim

When dueling teams unveiled the near-complete human genome last February, among those cheering the loudest were companies racing to patent proteins.

Humans, the sequencers told us, may have only 30,000 to 40,000 genes, far fewer than the previous estimate of 100,000. But with proteins, the more they look, the more they find: Researchers now believe that we have as many as 2 million. Not only does this finding demolish the dogma that each gene encodes a single protein, it also throws a wrench in the business strategy of many firms that have spent the past decade furiously locking up patents on key genes involved in disease. Those patents cover what were thought to be the single proteins those genes encode—which means that any other proteins the genes give rise to may be ripe for patent lawyers' pickings. "The patent game isn't closed by any means," says Raj Parekh, chief scientist at Oxford GlycoSciences, a proteomics firm in the United Kingdom. That may be good news for protein-hunting companies like Oxford GlycoSciences, but it's likely to produce a confusing landscape of competing gene and protein patent claims, perhaps setting the stage for legal battles for control over the future of genetic medicine.

Genomics powerhouses such as Human Genome Sciences (HGS) in Rockville, Maryland, and Incyte Genomics in Palo Alto, California, have collectively filed more than 25,000 DNA-based patent applications (a number that includes both full-length genes and gene fragments). If any pharmaceutical company wants to use a patented gene and protein to develop new drugs, the reasoning goes, it has to pay royalties. This strategy makes sense as long as one gene produces one messenger RNA (mRNA) that in turn codes for one protein, as the textbooks say. But genes clearly don't tell the whole story.

Recent studies have revealed that cells often splice mRNAs together in a variety of ways to make different versions of a protein. These "splice variants" can perform separate functions in the body. One mRNA variant,

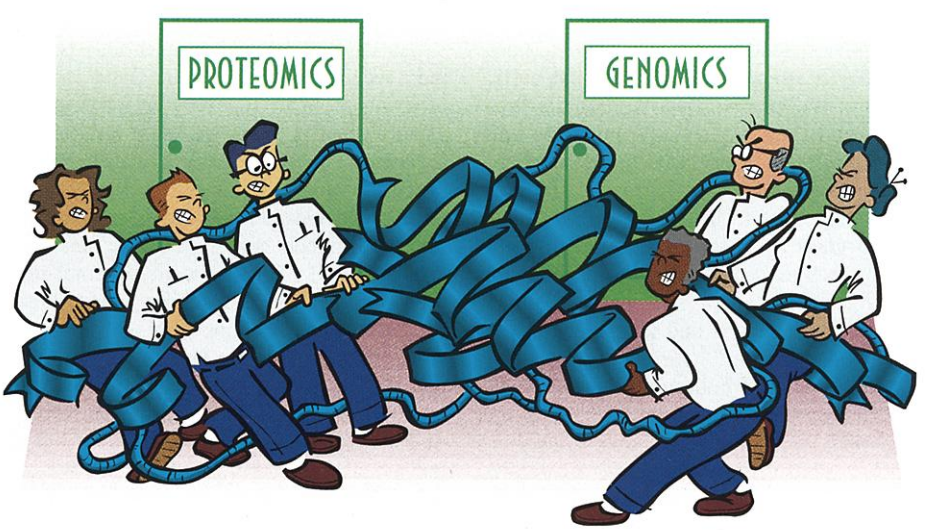

ILLUSTRATION: TIM SMITH

for example, makes calcitonin—a hormone that increases calcium uptake in bones—whereas another creates calcitonin gene–related polypeptide, which prompts blood vessels to dilate. Furthermore, once these proteins are produced, cells can also tag them with small chemical groups that aren't coded for by genes. These small changes can also have big effects on a protein's function.

That means that a patent on a specific DNA sequence and the protein it produces may not cover some biologically important variants. "If you find a splice variant that is different at the protein level, you can patent that variant," says Scott Brown, chief patent counsel at Millennium Pharmaceuticals in Cambridge, Massachusetts. John Doll, who heads biotechnology patents for the U.S. Patent and Trademark Office in Arlington, Virginia, says that the same holds true for patents on proteins modified by chemical groups. As long as these changes lead to proteins with new and unclaimed functions and uses, researchers can stake separate patent claims on them, he says.

So far, genomics firms say they aren't too concerned that their gene patents will wind up being worthless. One reason is that "most of these splice variants don't have very different activity from the main protein," says James Davis, general counsel for HGS. And if some variants do turn out to have critical functions, several genomics firms plan to be the first to find and patent them. HGS, Incyte, and Celera of Rockville, Maryland, are all building their own proteomics facilities to ensure that they find the most important protein variants linked to disease-related genes.

Still, showdowns may be inevitable. Some companies will undoubtedly find novel protein variants that correlate better with disease than those another company claimed earlier in gene patents, leading to competing claims over very similar molecules.

If that happens, "I think in the vast majority of cases, people will work out a deal" to cross-license each other's patents, says Davis, who notes that that's how microelectronics companies typically deal with competing claims. "Nobody likes litigation," agrees Parekh. "Cross-licensing is far cheaper than going to court."

But Davis and Brown admit that gene and protein patents may well prove different. Microelectronics researchers can often engineer their way around using particular inventions. But that's not so easy for drugmakers, who target specific proteins. That gives pharmaceutical companies little choice but to use those proteins—and the genes that make them—in searching for new medicines. That may make gene and protein patent holders a little less willing to back away from a legal battle. **–ROBERT F. SERVICE**

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PROTEOMICS
▶INDUSTRY RECRUIT

Rockefeller's Star Lured to San Diego Company

A crystallographer who leads a public consortium, Stephen Burley surprised colleagues by taking a private-sector job—and taking NIH funds with him

Stephen Burley doesn't look like someone getting ready to leap into the jungle. His bow tie, polished manners, and British accent (a blend from Australia, Canada, and Oxford University) speak of prudence and deliberation. His record as a structural biologist—21 years devoted to measuring the precise shape of protein molecules—doesn't suggest risk-taking, either. But Burley has decided to plunge into a new career. In January, he will quit an endowed professorship at Rockefeller University in New York City, resign his appointment as a Howard Hughes Medical Institute investigator, and begin directing research at a small company in San Diego called Structural GenomiX (SGX). He's stepping into a biotech melee, helping a young company analyze proteins rapidly for drug development—and possibly for a profit.

In transition. Stephen Burley is leaving Rockefeller after 11 years to direct research at Structural GenomiX.

Many biologists have trodden the path to industry, but Burley's route is a little different. Unlike other university stars, Burley will not be joining the gray ranks of a pharmaceutical company. He is leaving the pinnacle of his field for a firm that's still scrambling to prove itself. And his switch from academia to industry raises questions about the propriety of mixing public and private funds and ways to ensure public access to key biological data.

As one of Burley's colleagues says, he's heading into "a kind of East Coast–versus–West Coast battle" that's broken out in San Diego, pitting the cream of New York's crystallographers against California's. SGX, just 2 years old, is competing against several talented rivals, including one down the road called Syrrx. SGX was founded by top structural biologists Wayne Hendrickson and Barry Honig of Columbia University in New York City. Syrrx, also founded in 1999, includes among its partners and leaders structural biologist Ian Wilson of the Scripps Research Institute in La Jolla, California, and company co-founders Raymond Stevens of Scripps and Peter Schultz, formerly at the University of California, Berkeley, and now director of the Genomics Institute of the Novartis Research Foundation in San Diego. Both companies are specializing in automated, rapid determination of protein structures by x-ray crystallography.

Academic peers say they're not surprised that Burley wants to work in industry; after all, companies can throw money and talent at problems to solve them in a hurry, whereas academics are limited by the grant system and university fiefdoms. But they are amazed that he will become an officer at a start-up company. "We were all surprised," says Helen Berman, a structural biologist who runs the Protein Data Bank at Rutgers University in New Brunswick, New Jersey. (Burley chairs her advisory committee.) "Steve is one of the shining stars in structural biology," she notes, marveling at how this will "change his whole life and career." Lawrence Shapiro, a structural biologist at Mount Sinai School of Medicine in New York City who also consults for SGX, says: "Before this, we were betting that he would become the president of Rockefeller or director of the National Institutes of Health [NIH]."

In addition to being a top biologist—known for his work on RNA transcription factors—Burley has also been a community leader, says protein modeler Tom Terwilliger of Los Alamos National Laboratory in New Mexico. "Steve was one of the people who got involved early" in an NIH plan to fund pilot projects in high-throughput protein