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**

CREDIT: ANTONIO MARI

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

crystallography (*Science*, 29 September 2000, p. 2254). The program, run by the National Institute of General Medical Sciences (NIGMS), funds nine teams, each of which will get on average $4.5 million per year for up to 5 years. The teams must make data public. One of the grantees is the New York Structural Genomics Consortium, which Burley helped form and for which he is the principal investigator (PI).

That may be another reason why Burley's decision to move to San Diego startled people. The champion of high-volume analysis and public data release will now be answerable to investors who may not be enthusiastic about giving away protein structure information. Burley is trying to straddle the fence.

Although Burley will be an officer of SGX, he also plans to remain a PI on the grant to the New York consortium. "The scenario which I presented to NIGMS," Burley said in a recent interview at Rockefeller, "is to do target selection within the academic enterprise in New York. The cloning, protein analysis, protein purification, crystallization, and x-ray measurements would all be done in the company using the robotic platform that already exists" in San Diego. When the x-ray data files are complete, they would be sent back to New York, according to Burley, where academic labs "would actually complete the structure determination and take responsibility for deposition of the atomic coordinates in the Protein Data Bank." NIH would pay for the robotic work at SGX, but the "final stage of structure determination where the information becomes most sensitive" would remain in academia—and academia would control the intellectual property. The company would "work on its own targets" and "not on publicly funded targets," Burley said. SGX president Tim Harris says this plan "doesn't faze me at all ... I welcome it."

The deal has raised an eyebrow or two among Burley's academic peers, however. "It poses a challenge to the definition of conflict of interest," says structural biologist Gaetano Montelione of Rutgers. He notes that other people seeking grants from NIGMS have had to comply with rules that didn't allow them to be company officers. Eaton Lattman of Johns Hopkins University in Baltimore, Maryland, a member of NIGMS's structural genomics advisory panel, says that in public-private ventures, "you want to be sure that the company doesn't eat the results." He'd like to see a written version of the data-sharing plan. NIGMS staffers note that there is a precedent for company involvement: Syrrx is a "subcomponent" of a NIGMS grant for which Wilson is PI, under terms approved before the award was made. NIGMS director Marvin Cassman isn't commenting.

Burley argues that the new arrangement should help the field because it will speed up protein-structure determination. The public will benefit by using the company's excess capacity. "Not only do I want this to be right, in terms of U.S. law," Burley said, "I want this to look right." He's waiting for Rockefeller to spell out the intellectual-property terms before sending the written plan to NIGMS.

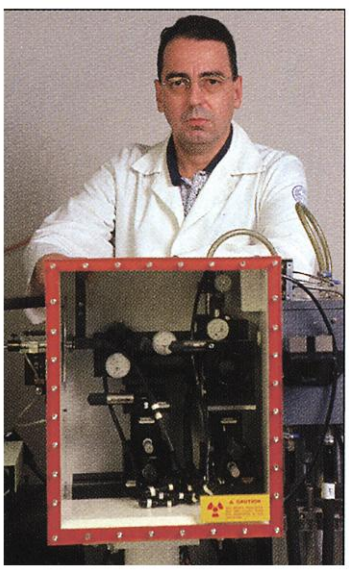
Given the resources already at his fingertips at Rockefeller, why would Burley want to tangle in such controversies—or in any industrial concerns, for that matter? Salary was not a major incentive: According to a New York City executive recruiter, Burley opted for equity holdings as his main remuneration and a salary of $200,000 to $400,000. The basic reason, Burley says, is that he wants to use structural biology to solve medical problems—especially to create new antibiotics and other drugs. Although such work is being done in academic labs, he says, "the scale is the problem." He wants to move faster.

"The aspect of structural genomics that most interests me," Burley explains, is "trying to find small molecules that you can target to particular protein families and try to restrict binding as much as possible. This can only really be done in an industrial context," because so many different resources must be brought to bear. The challenge, Burley says, is to find a compound that "binds to a target of interest and doesn't bind to everything else." To do this—and not take a quarter-century—one needs lots of talent and computing power focused on candidate screening.

SGX, Burley claims, has bought a computer platform that "rivals the one that Celera has." It has also built a set of four beamline stations for crystal analysis at the Advanced Photon Source at Argonne National Laboratory in Illinois, the first of which will start operating this month. The company had already invested in protein structure modeling experts and software. The chance to coordinate all of this was an "unparalleled scientific opportunity," Burley said.

It is "a very good time for structural biologists," says Rockefeller colleague Andrej Sali, who understands how friends like Burley can be lured into companies. But he still doesn't understand how they will make a profit. That's an entirely new puzzle that Burley and others will be trying to solve.

–ELIOT MARSHALL

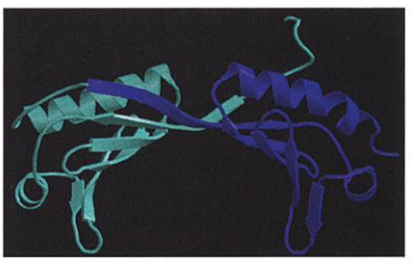


X-ray vision. Burley stands behind a generator for x-ray crystallography.

CREDITS: (TOP TO BOTTOM) COURTESY OF BURLEY LAB; ANTONIO MARI

A Physicist-Turned-Biologist

Stephen Burley's switch from Rockefeller University to a start-up company (see main text) is not the first strategic shift in his career. After beginning in science as an undergraduate student of theoretical physics at the University of Western Ontario, he saw that biology held better prospects, and "crystallography looked like the obvious place to go." He went to Oxford as a Rhodes Scholar, earning a D.Phil. in molecular biophysics under David Phillips in 1983. Then he enrolled in a Harvard–Massachusetts Institute of Technology health sciences and technology program, earning a Harvard M.D. in 1987. He quit the clinic but not his interest in medicine, returning to crystallography as a postdoc at Harvard until 1990, when Rockefeller hired him.



TATA box–binding protein.

His best known work may be the research with Robert G. Roeder and other colleagues at Rockefeller determining the structure of a molecule critical in DNA transcription called the TATA box–binding protein (see image). Lawrence Shapiro of Mount Sinai School of Medicine also credits Burley with pioneering two widely used techniques to analyze proteins that are hard to crystallize.

Recently, Burley has worked with computational biologist Andrej Sali at Rockefeller to apply modeling techniques to protein structures. Sali has developed a program called ModBase that predicts the structure of any protein based on sequence data; he makes it available free on his Web site. With Burley, he formed a company 2 years ago to exploit the technology; in 2001 it merged with Structural GenomiX.

–E.M.