

# CHEMICAL

& Engineering News

SERVING THE CHEMICAL, LIFE SCIENCES, AND LABORATORY COMMUNITIES

[HOME](#) | [CURRENT ISSUE](#) | [CHEMJOBS](#) | [JOIN ACS](#)
[EMAIL ALERTS](#) | [ADVANCE](#)

- Latest News
- Business
- Government & Policy
- Science/Technology
- Career & Employment
- ACS News

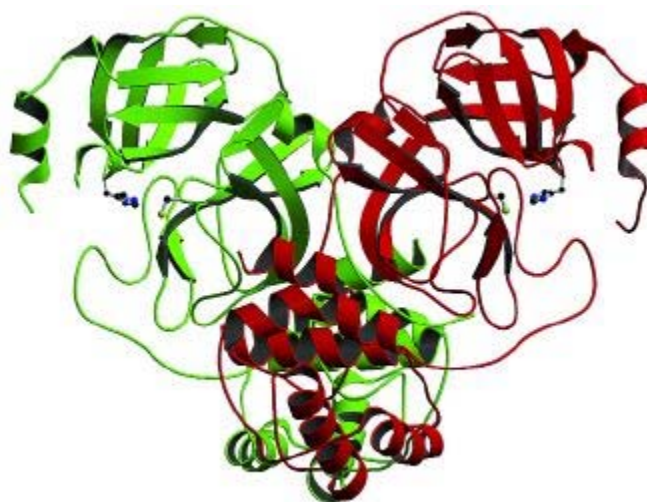
## Cover Story

September 20, 2004  
Volume 82, Number 38  
pp. 22-30

[Advertis](#)
**Active**


## STRUCTURES SPEAK UP

As structure determination becomes a high-throughput tool for optimizing drug leads, biotech companies apply it to contract research as well as their own portfolios



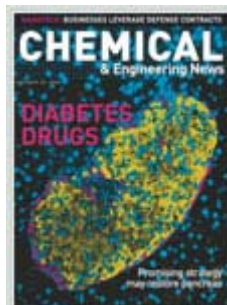
**DEADLY RIBBONS** X-ray crystal structure of the SARS coronavirus' main protease at 1.86Å resolution.

STRUCTURAL GENOMIX, ARGONNE NATIONAL LAB PHOTO

[VIVIEN MARX, C&EN NORTHEAST NEWS BUREAU](#)

There is the chicken, and there is the egg. Discussing which comes first delivers plenty of substance for late-night pondering. Transferred to the field of drug development, the question becomes whether it is more helpful to first have the small molecule and then have the three-dimensional structure involving a target, or vice versa. Far from being armchair philosophy, this decision is growing crucial to the business of lead optimization and represents a developing biotech market.

Chemist Raymond C. Stevens, who is a professor in the departments of molecular biology and chemistry at [Scripps Research Institute](#) as well as the cofounder of [Syrrx](#), a structure-guided drug development firm, argues in *Nature Structural & Molecular Biology* [11, 293 (2004)] that an estimated 50% of the cost of drug discovery would be saved if a target protein structure were used at an early stage to generate leads of high quality. Obtaining structural information is time-consuming, but efforts are under way to automate the process to quickly glean data about the looks of a target and the appearance of small molecules bound to the target.



October 25, 2004  
Vol. 82, Iss. 43  
[View Current Issue](#)

Back Issues

2004

### SUPPORT

- How to log in
- Contact Us
- Site Map

### ABOUT C&EN

- About the Magazine
- How to Subscribe
- How to Advertise



[Join ACS](#)

MORE ON STORY

[Consortia](#)

Joining Forces  
Reveal Structures

[Partnerships](#)

Building Bridges  
Between Academic and Industry

[E-mail to a friend](#)

[Print this page](#)

[E-mail](#)

Some companies--for example, [Evotec OAI](#) and [Discovery Partners International](#)--offer clients structural biology services like protein engineering and production, crystallization, and X-ray crystallography, along with numerous other services such as medicinal or computational chemistry. Others choose to focus, as [ActiveSight](#) does, on contract crystallographic services for pharmaceutical companies or, as Accelrys does, on informatics. Then there are firms such as [Structural GenomiX](#), deCode Genetics, [Astex Technology](#), Syrrx, [Vertex Pharmaceuticals](#), [Affinium Pharmaceuticals](#), and others with business models that straddle both worlds, matching structure-solving efforts for others with their own drug discovery and development efforts.

Companies in this space speak of their approach as structural biology platforms that permit quicker, cheaper, and more reliable ways to let structural information guide lead development. The information--often X-ray crystallographic snapshots of a target or cocrystal structures of target plus ligand--lends support to medicinal chemists who can use this visualization in their synthetic explorations. Cocrystal structures show how the lead molecule can be tweaked for metabolic stability or solubility and reveal which parts of the molecule should not be altered at all.

**POSTER-CHILD** examples of approved drugs developed with structure-based design are HIV protease inhibitors. It took eight years to go from structure resolution to having three protease inhibitor drugs on the market--shaving several critical years off the typical drug development time frame.

Most large pharmaceutical companies have established structural biology groups, either homegrown or acquired. Agouron Pharmaceuticals, an HIV protease developer, was bought by Warner-Lambert in May 1999, and, in turn, acquired by Pfizer in March 2000. Johnson & Johnson bought structural biology firm 3D Pharmaceuticals in January 2003.

The focused service-provider approach comes in different varieties. For example, Shamrock Structures started up in Woodridge, Ill., in the fall of 2003 with venture-capital funding and a special agreement with the Department of Energy's Argonne National Laboratory that gave it access to one of the few X-ray synchrotrons in the world, the Advanced Photon Source. Last month, Shamrock signed an agreement with Intra-Cellular Therapies under which it is offering, for an undisclosed up-front fee as well as milestone payments, X-ray crystallographic data and structure determination of a protein target with bound inhibitors.

ActiveSight in San Diego, Calif., also formed last fall by Rigaku/MSO, a U.S. subsidiary of the Japanese company Rigaku, offers service crystallography of human targets as its business model. In July, the company announced an agreement with Signal Pharmaceuticals, a subsidiary of Celgene, to crystallize Signal's small molecules with a human protein produced by ActiveSight.

For companies with drug discovery in their portfolio, structural biology takes on a broader role. Medicinal chemist Daniel L. Flynn, chief executive officer and cofounder of [Deciphera Pharmaceuticals](#) in Lawrence, Kan., and chair-elect of the American Chemical Society's Division of Medicinal Chemistry, faced his own chicken-or-egg scenario. In his years at Warner-Lambert, Searle, Amgen, and Millennium Pharmaceuticals, he had seen structural information enter into projects too late, when an optimized compound was being readied for the clinic.

Not so when he started [Deciphera](#) with colleague Peter A. Petillo. "For us, it was critical that we had structures almost immediately," he says.

Deciphera, which started out in 2002 as "two guys and an idea," is devoted to finding small-molecule drug candidates for diseases caused by dysfunctionally regulated proteins. Focusing mainly on protein kinases, the firm has identified novel "shape-control" or shape-modulating pockets in these proteins. The small molecules he seeks will bind to those pockets, which are not the classic substrate-binding locations.

These pockets, however, are not just waiting to be prospected. Only when the small molecules bind are the pockets induced. It is the structure of that constellation which must be solved and used for iterations. "I can't walk up to an angel investor or institutional company and say, 'I have these neat-looking compounds that are potent against these kinases; trust me, they are binding to a novel pocket,'" Flynn says. "You have to show the proof."

Flynn picked three kinase targets in October 2002 with the goal of having structural biology data in hand a year later. It took slightly longer, until December 2003, to obtain the cocrystal structures bound to these novel pockets. "They say a picture is worth a thousand words, so having these three structures in hand enabled us to then go quickly and raise a \$15 million round," he says. This money was needed to advance the company, Flynn says. Without the money, that round might not have come to be, he says.

**THE FUNDS** have helped advance the science as well, permitting the company's medicinal chemists to iterate off the structures to make more potent and selective molecules that control shape and function in oncogenic proteins.

Deciphera had in-house expertise in medicinal chemistry, enzymology, and biophysics but decided to shop for outside help with X-ray crystallography and structural biology. The companies Flynn approached--six in total and which he declines to name--were ready for the task. But, one after another, the firms came back saying they also wanted to share intellectual property (IP) and revenue from any resulting products.

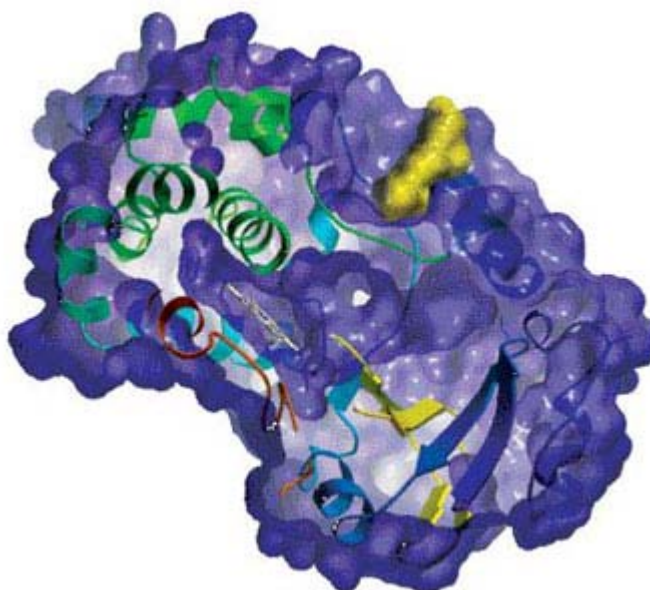
"For a start-up company right out of the gate, that, of course, was a nonstarter," Flynn says. Only one company offered to work with Deciphera as a contract research organization with no IP strings attached: deCode Biostructures in Bainbridge Island, Wash.

DeCode has since solved more than 10 crystal structures of kinases with small molecules bound to them for Deciphera. "The structures are for us not an add-on; they are critical," Flynn says. The structures cost Deciphera less than \$100,000 per piece, Flynn says. This, in his words, "affordable" price cannot be generalized across the protein universe, since willingness to crystallize varies greatly among proteins.

Lance Stewart oversees the Structural Biology Group at [deCode Biostructures](#), a subsidiary of deCode Genetics. He had started out with his own structural biology firm, Emerald BioStructures, in 1997. To pool expertise, he collaborated with MediChem Research, based, like Shamrock Structures, in Woodridge.

MediChem then decided to go public, as Stewart says, "with a business model that connected the chemistry back toward the gene" and offer an integrated service package to customers. Emerald went along for the initial public offering ride in October 2000 to become part of MediChem Life Sciences. The following years were rocky for chemistry, Stewart says, although a bit less so for structural biology. MediChem caught the eye of deCode Genetics, and deCode acquired the company in March 2002.

"The demand for structures is growing very rapidly, and it is being enabled by automation," Stewart says. "Having a crystal structure of an important molecule can save chemists many, many hours in the lab." At deCode, part of the structural determination work involves toolmaking and developing option plans when roadblocks pop up. In April 2003, AstraZeneca bought deCode's automated protein crystallography platform for its drug discovery sites in Alderley Park, England, and Mölndal, Sweden. The system includes robotics and informatics that help with generating, storing, and analyzing crystals of target proteins as well as protein-ligand complexes.



**PEEK INSIDE** Cross section of the CYP3A4 enzyme reveals the active-site cavity in the middle. Progesterone (yellow) binds peripherally in a shallow pocket of the enzyme.

ASTEX TECHNOLOGY PHOTO, © SCIENCE 2004

**STRUCTURAL BIOLOGY** tasks reach across disciplines. First, in the gene/protein engineering steps, so-called protein constructs are created in the recombinant expression system of choice. These protein variants are in turn tested, purified, and crystallized. X-ray diffraction data must be collected at 3 Å or, preferably, below 2 Å. The data must then be assembled into an electron density map from which models can be built. "Getting below 2 Å adds a whole other beneficial dimension--that is where you can see water molecules really clearly," Stewart says. Chemists can then better anticipate movements in interactions between a target and a small molecule, he says.

The path between gene and protein-ligand cocrystal structure is replete with pitfalls and bottlenecks that companies address in different ways. Stewart likens the steps to a game board with numerous "go back"

squares. Automated and parallel approaches help to avert dead ends. "Sample prep is a key bottleneck," he says. Stewart and his colleagues are also always looking to reduce the amount of sample needed.

For the protein engineering step, deCode has developed software, called Gene Builder, to design oligonucleotides and synthesize gene variants for protein constructs. The software aids, for example, in identifying domains that help or hinder crystallization. These constructs in turn are purified in a specially devised chromatography robot called Protein Maker, an automated liquid-handling system that delivers protein solutions, wash buffers, and elution buffers. Stewart and his colleagues built it when they could not find one commercially available.

Determining the 3-D structure of a protein is similar to climbing a mountain. As Stewart and colleague Peter Nollert point out, when it comes to membrane proteins, that mountain becomes the Himalayan range. About half of all current drug discovery targets--ion channels and G-protein-coupled receptors (GPCRs), for example--are proteins in cell membranes. "Fifty percent of all drug revenues come from compounds that target GPCRs," Stewart says. Yet these compounds were not developed with structural information. Membrane proteins, embedded in their lipid bilayer, cannot be coaxed with common tricks of the crystallization trade, such as using detergent solubilization.

One crystallization technique deCode is applying to these proteins is lipidic cubic phase (LCP), developed at the University of Basel, in Switzerland. In LCP, the protein is mixed with lipid and a phosphate salt or solution as a crystallization agent. The protein is thus kept in a matrix, a kind of quasi-solid environment, during crystal growth. The company has developed a prototype liquid handler geared to dispense viscous fluids like those involved in LCP. The technique has worked for bacterial membrane proteins, and the company hopes it will work, eventually, for human GPCRs.

**BESIDES SOLVING** structures for deCode's own drug development, part of the firm's business model is to provide structural biology work on a fee-for-service basis. As Stewart explains, customers range from large pharmaceutical companies to biotechs with multiple targets that lack internal capacity. In both cases, deCode faces intense pressure to quickly obtain structures, Stewart says. After all, there are other companies offering similar services.

One such competitor is Structural GenomiX (SGX), a biotech company in San Diego. In 2001, to the surprise of his colleagues, structural biologist Stephen K. Burley abandoned an endowed professorship at Rockefeller University and resigned his position as Howard Hughes Medical Institute investigator to become chief scientific officer at SGX.

Prior to his arrival, SGX had raised more than \$84 million in venture capital. The company put part of the money into building its own dual undulator beamline facility at the Advanced Photon Source. The company is one of a few, if not the only, drug discovery companies with a dedicated beamline. "There was a very large capital investment required to build the beamline," Burley says. "We have monetized that asset by providing beamline access to strategic partners, one of which is [Eli Lilly](#)." SGX has achieved two milestones since linking up with Lilly in 2003 while producing "large numbers of cocrystal structures" to help guide medicinal chemistry efforts there.

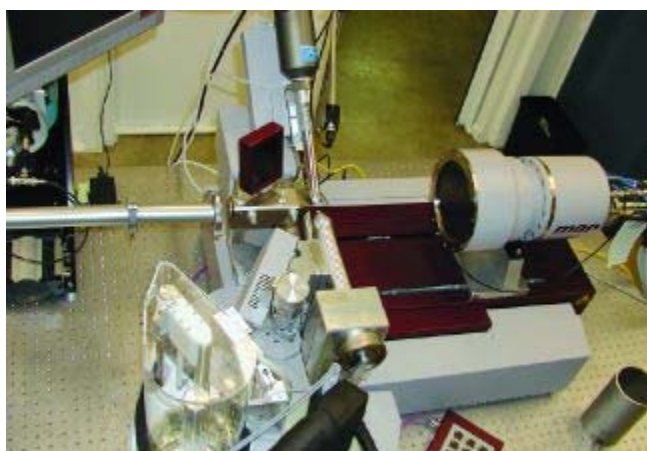
"The other thing we have done with Lilly is to create a clone of our

target structure platform for them," Burley says. Handing over a high-throughput structural biology facility may seem like a quick way to lose a customer. But Burley explains that it makes sense as this partnership and others expand to include a new fragment-based lead discovery technique called FAST, for fragments of active structures. FAST is geared toward finding small-molecule inhibitors of drug targets within a six-month time frame and uses crystallography as the primary screen.

"It is a very elegant application of structural studies of protein-ligand complexes, combined with very sophisticated combinatorial chemistry, to make choices about what syntheses to do in the lab as opposed to what syntheses you can contemplate in silico," Burley says. The company has developed a library of small, leadlike fragments. In a screen of this library, electron density maps are automatically compared to find the best fragment hit. The fragment hits then feed into chemical syntheses that are guided by structural considerations.

Lilly is one FAST partner, and [Serono](#) is another. The Lilly deal, of undisclosed financial dimensions, began in 2003. The Serono partnership was struck in March and could yield up to \$68 million for SGX. Earlier this month, a FAST alliance with Roche was announced to develop antiviral drugs.

SGX is also applying the crystallographic screening method for its own drug discovery efforts. One project is focused on Gleevec-resistant Bcr-Abl. Work in animal models for the company's lead compound is slated for early 2005. The overproduction of white blood cells in the body that accompanies chronic myelogenous leukemia is caused by an overactive tyrosine kinase enzyme called Bcr-Abl. Gleevec, which is made by [Novartis](#), works by binding to the enzyme, but when the enzyme mutates, that effect is lost.



**BEAM IT** At Structural GenomiX' beamline at the Advanced Photon Source, a detector, cryostream, and sample changer robot are sitting on an optical table with the beam pipe entering from the left of the photograph.

STRUCTURAL GENOMIX, ARGONNE NATIONAL LAB PHOTO

**IT WAS A** different era in the early 1990s, Burley says, when he laboriously managed to solve the structure of the TATA-box binding protein, which plays an important role in DNA replication. At that time, data were collected on a conventional X-ray source, not today's high-brilliance synchrotrons. In X-ray crystallography, the crystal is rotated in small increments, and its lattice atoms scatter the X-rays. The resulting 3-D pattern of diffraction is characteristic for that crystal. The pattern

reveals the intensities of the diffracted beams. Their phases, however, are missing. Protein crystallographers use so-called anomalous scatters to help out with this phase problem. Electron-density maps are then calculated from the collected X-ray diffraction data using Fourier syntheses.

Today, resolving the TATA-box binding protein would be much quicker, Burley says, although protein-nucleic acid complexes still remain a challenge. Last year, the company solved the crystal structure of the main protease from the coronavirus that causes severe acute respiratory syndrome. The data were put in the public Protein Data Bank.

"It took on the order of a month to go from gene cloning all the way to completion," Burley says. "This example gives you an idea of the speed with which we can move in providing initial structural information for drug discovery targets." Moreover, a single cocrystal structure can be determined at the beamline in 15 minutes, he says. Novel structures of protein kinases have required less than a month, in some cases. Crucial to the work is the "very tight integration of the entire process," he says, between gene cloning, protein expression, purification, automated crystallization, and data handling. "Every step is highly automated," he explains.

Unlike other companies applying high-throughput X-ray crystallography, [Astex Technology](#) in Cambridge, England, picked fragment-based drug discovery as its core concept when it was founded in 1999, says Harren Jhoti, founder and chief scientific officer. "There is a lot more interest in this space now than previously," he says. While much structural proteomics begins with a gene and leads to crystals of proteins and potentially therapeutic targets, Astex decided to leave out the genetic part.

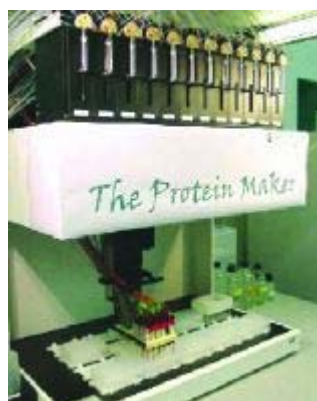
"Most of us came out of larger drug companies; in my case, it was Glaxo Wellcome," Jhoti says. "We never figured the problem was getting more targets but [rather] better drug candidates against a target we already have." The business model at Astex is to take the targets the industry is working on and, in a high-throughput way, use X-ray crystallography to screen fragments against these protein targets. Then medicinal chemistry starts. "This is protein-ligand crystallography, rather than novel structure determination," he says.

After developing Pyramid, Astex's proprietary method of growing lead compounds using fragments, Jhoti and his colleagues wondered how structural biology might help with drug metabolism issues. "Could we get a competitive edge by, say, solving a problem of metabolic liability of our compounds?" Jhoti asks. He picked cytochrome P450s, a family of important metabolizers in the body that are also a major cause of lead compound failure, he says.

Honing in on P450s, Jhoti recruited a number of scientists from Scripps Research Institute, including Pamela A. Williams and Jose Cosme. Cosme had devoted his career to getting a crystal structure of a P450. "Membrane proteins did not scare him, but they did cause him plenty of heartache," Jhoti says. Work on P450 started late in 1999.

Partners began approaching the company, some of whom were interested in the P450 program, Jhoti explains, and collaborations ensued with AstraZeneca, Aventis, Mitsubishi Pharma, and Fujisawa. Other partners, notably Schering, Boehringer Ingelheim, and Johnson & Johnson, were keener on the fragment-based approach. These

collaborations are not fee-for-service, but rather arrangements based on royalties and milestones.



**AUTOMATED**  
Protein Maker is a parallel liquid chromatography system delivering protein solutions, wash buffers, and elution buffers to as many as 24 columns.

DECODE  
BIOSTRUCTURES  
PHOTO

**SOME PARTNERS** wish to be involved more closely than others. In this vein, Astex has regular meetings with AstraZeneca chemists about an Alzheimer's target,  $\beta$ -secretase. "This is a tough target that had not yielded to conventional high-throughput screens," he says. "We have been able to deliver several lead series against this target, which has triggered milestones for us." As a biotech company, Jhoti says, it is important to be able to point to method successes of this kind.

In the Schering and Boehringer collaborations, Astex develops compounds against the company's targets according to criteria that the partners have drawn up. The companies retain the right to in-license those compounds. "That is a more 'over the wall' type approach," Jhoti says. Some of these targets have not yielded to conventional approaches to high-throughput screening, but, as he says, they are too important for the companies to walk away from.

Astex made a bit of a splash recently with a paper in *Science* documenting crystal structures of human cytochrome P450 3A4 (CYP3A4) and crystals of it bound to metyrapone and separately to progesterone [*Science*, **305**, 683, (2004); [C&EN, July 19, page 7](#)]. The active site itself turned out to be smaller than expected, and binding did not appear to markedly change the enzyme's conformation. The structural surprise of the work came in the form of an unexpected peripheral binding site, which is currently being explored for its relevance for drug-drug interactions.

Alongside its multitarget drug discovery efforts with partners, Astex views as its core activity its drug discovery portfolio based on Pyramid. "We have selected key targets in oncology and are developing our own lead compounds against them," Jhoti says. The company expects to begin clinical trials in the first half of next year with the most advanced of the leads, a compound that inhibits the cell cycle process. "It's our own homegrown molecule, and it is nice, after building the technology, to actually apply it," he says.

Structural proteomics, particularly the high-throughput version, covers a wide bio-chemico-physical landscape: the engineering of genes and proteins, purification techniques, crystallization, biophysical methods, instrumentation, and automation. As Stewart of deCode says, "We have to be jacks-of-all-trades."

#### **MORE ON THIS STORY**

##### [Consortia](#)

Joining Forces To Reveal Structures

[Partnerships](#)

Building Bridges Between Academia And Industry

Chemical & Engineering News

ISSN 0009-2347

Copyright © 2004

[Home](#) | [Latest News](#) | [Current Issue](#) | [ChemJobs](#)

[Pubs Page](#) / [chemistry.org](#) / [ChemPort](#) / [CAS](#)

[Copyright © 2004 American Chemical Society](#)