CONTACT US

Office of Science
U.S. Department of Energy
1000 Independence Ave., SW
Washington, DC 20585
P: (202) 586-5430
More Information »

03.28.11

Premier Tools of Energy Research Also Probe Secrets of Viral Disease

Advanced light sources peer into matter at the atomic and molecular scales, with applications ranging from physics, chemistry, materials science, and advanced energy research, to biology and medicine.

Print SC RSS Feeds Text Size: A A A Share / Bookmark

Enlarge Photo

Image courtesy of Peter Ginter/SLAC
Stanford's Roger Kornberg.

We all know that our DNA contains the blueprints for making our bodies run. But how are those blueprints translated into action? In the late 1990s, Stanford University's Roger Kornberg discovered an important piece of the puzzle. He used powerful X-ray beams at two DOE Office of Science national labs to probe the structure of an enzyme called RNA polymerase II and show how it translates genetic instructions in yeast, and by analogy in humans.

Enzymes are biological catalysts—materials that promote chemical reactions without being consumed in the process. This particular enzyme unzips two-stranded twists of DNA and uses the instructions from one of those strands to create messenger RNA molecules, which carry tiny pieces of the genetic blueprint over to the part of the cell where proteins are made. This fundamental discovery earned Kornberg the 2006 Nobel Prize in Chemistry.

This same process takes place in RNA viruses like the ones that cause polio, influenza, hepatitis, and Dengue fever, using an enzyme with an entirely different structure. If you could block that enzyme—gum up the works, so to speak—you could stop the virus from replicating within the cells of its victims.

A company that Kornberg co-founded two years ago, Cocrystal Discovery, is pursuing this approach using a number of DOE light sources, including the two facilities where he performed his groundbreaking research—SLAC's Stanford Synchrotron Radiation Lightsource and Lawrence Berkeley National Laboratory's Advanced Light Source—as well as Argonne National Laboratory's Advanced Photon Source.

Cocrystal is just one of a number of biopharma companies that use DOE's synchrotron light sources, which produce intense beams of light in the form of X-rays. As national user facilities, they draw scientists from all 50 states and all over the world who submit proposals for experiments in biology, medicine, chemistry, physics, and materials, earth, environmental and energy science; for scientists who publish their results in open academic journals, beam time is free.

Synchrotron light sources enable scientists to peer into matter at the atomic and molecular scales. They work on a simple principle: when charged particles accelerate around curves, they give off light, known as synchrotron radiation. The first light sources were parasites: Grafted onto particle accelerators used for high-energy experiments, they harvested the X-ray light emitted by the circling particles, which had been considered a waste and a nuisance, and put it to work.

Light sources quickly became a powerful tool, the Swiss Army knives of science. The high energies of the X-ray beams penetrate materials and interact with individual atoms in ways that reveal a great deal about their electronic properties; and their short wavelengths allow them to illuminate and image objects on a scale small enough to show atomic structures.

More than 70 light sources are at work around the world performing nearly any kind of research you can imagine, from designing new semiconductors, and ultrastrong and lightweight materials for transportation to tracking down environmental contaminants, improving the operation of batteries and fuel cells, unraveling secrets of the human body, and deciphering how plants produce energy through photosynthesis. No longer parasites, major synchrotron light sources are custom-built facilities, bigger than football fields (although round), that divert X-ray beams into dozens of experimental stations for simultaneous studies, What's more, their beams can be tuned to a variety of wavelengths, depending on the job at hand. At present, the United States, with five light sources and a sixth under construction, all supported by the DOE Office of Science, leads the world in this research technology.

In addition to synchrotrons, the latest generation of light sources includes X-ray free-electron lasers, which accelerate electrons down a linear path to nearly the speed of light, force them to wiggle through a series of magnets and gather the resulting X-ray emissions into laser beams. The newest and most powerful of these free-electron lasers, the Linac Coherent Light Source at SLAC, generates beams a billion times more intense than any previous X-ray light source. On the other end of the scale, researchers are designing small synchrotron light sources that might fit into a laboratory or doctor's office.

> **"I believe the whole future of drug development lies in synchrotrons."**
>
> Roger Kornberg
> Stanford Professor and Nobel Laureate

Light sources allow scientists to determine the atom-by-atom structures of large, complicated molecules. With the structure in hand, researchers can determine how the molecule functions and look for places where it might be vulnerable to attack. They can also determine how processes such as transcription sometimes go wrong, leading to birth defects, cancer and other conditions.

That is why one of the greatest impacts of light sources has been in the field of structural biology, where they have been the primary tool for deciphering the structures of nearly 72,000 proteins and other important biological molecules. Kornberg's Nobel Prize is one of three over the past decade—2003, 2006, and 2009, all in chemistry—based on structural biology insights from light source research. This is the path that led him to the structure of RNA Polymerase II, the insight into how it works in the cell, and the formation of a company to find therapeutic drugs that block the activities of similar enzymes in viruses.

"I believe the whole future of drug development lies in synchrotrons," said Kornberg, who heads a lab at the Stanford University School of Medicine that continues to research the basics of transcription.

Kornberg said he didn't seek out involvement in Cocrystal Discovery, which is headquartered in Bothell, Washington and has offices in Mountain View, Calif. The two other company founders, both with broad experience in the biotech industry, approached him with a request that he serve on their scientific advisory board.

"I do it primarily out of interest," Kornberg said. "It's an opportunity to bring the stuff that we've done and learned over the years to bear on a problem of great societal significance. It's almost an obligation, if we see an opportunity to do something of benefit to humanity, to do so, and here the benefit would be enormous," because the viral infections the company is targeting—hepatitis and influenza—are untreatable today.

What have they come up with so far? Kornberg said the details are proprietary, but added, "We have created extremely promising molecules in a short space of time, molecules which are much more effective than others created by our large pharma competitors."

Discovering a potential treatment is just the first step. The process of testing a drug for safety and effectiveness and bringing it to market can take more than a decade and cost hundreds of millions of dollars. Kornberg said it remains to be seen whether the company would carry out the entire process itself or hand promising drug candidates over to a larger firm for testing and development.

Both government and industry play important roles in this process, Kornberg said. "Government supports research with a very long time line, such as the development of more powerful facilities and their application to research of no apparent immediate value," he said. Then, once the value of a basic discovery becomes apparent, industry comes along and invests billions of dollars to develop it into useful products.

—Glennda Chui, SLAC National Accelerator Laboratory, glennda@slac.stanford.edu

Funding

Advanced Light Sources: DOE Office of Science, Office of Basic Energy Sciences

Light Source Beamlines: DOE Office of Science, Office of Biological and Environmental Research; National Institutes of Health

Publications

P. Cramer, D.A. Bushnell and R.D. Kornberg, "Structural basis of transcription: RNA polymerase II at 2.8 angstrom resolution, *Science* **292** 1863 (2001).

A. L. Gnatt et al. "Structural basis of transcription: an RNA polymerase II elongation complex at 3.3 A resolution," *Science* **292** 1876 (2001).

Related links

"The Nobel Prize in Chemistry 2006." Nobelprize.org. 11 Mar 2011
http://nobelprize.org/nobel_prizes/chemistry/laureates/2006/