ARGONNE now

A U.S. Department of Energy National Laboratory

Argonne NATIONAL LABORATORY

volume 04 / issue 01 / winter 09

an inside look at materials ▸ journey to the center of the Earth ▸ a prescription for success

Argonne's X-ray vision

Photon Sciences Light the Way to New Discoveries

ARGONNE now

volume 04 / issue 01 / winter 09

Dear friends,

As a multipurpose laboratory, Argonne is committed to addressing the many challenges that face our nation: energy, the environment and national security. To do this, we depend on our group of state-of-the-art user facilities that draw scientists from around the world to conduct groundbreaking research across a wide variety of disciplines.

On any given day, Argonne scientists and their colleagues employ these facilities to discover and develop new materials, find new ways to create and store energy, enhance our national security and address the economic, environmental and climatological questions that will shape this country in the next century.

The previous issue of *Argonne Now* focused on Argonne's new high-performance computing facilities, which have directly benefited research in all of these areas. This issue takes a similar tack; rather than focus on one avenue of study, the following four stories illustrate how Argonne researchers and their colleagues from the worlds of academia and industry employ the hard X-rays provided by the Advanced Photon Source for a myriad of different studies that strive to address the crises of today and that will shape our lives in the decades to come.

I would like to take this opportunity to again thank the Department of Energy and all of our many sponsors for providing the means and resources that allow us to carry out this vital research.

Thank you,

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news

acceleration

features

contacts

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on the cover
A silhouette of Argonne's Advanced Photon Source

news / from Argonne

This saline ice slurry could save lives by protecting organs during surgery or certain medical crises.

Putting organ failure on ice

When treating cardiac arrest victims, doctors can't call a time-out. Without the ability to obtain fresh oxygen from blood pumped through the body, brain cells start to die in just minutes. Within 10 to 20 minutes after the heart stops beating, the clock has run out. Even if doctors can get the heart restarted, the brain has died.

Recently, however, researchers in Argonne's Nuclear Engineering Division have developed a new technique that can reduce the brain's and other organs' demand for oxygen, giving doctors precious extra time to diagnose and treat critical patients in emergencies while also protecting a range of vital organs during planned surgeries.

Led by engineer Ken Kasza, the researchers have created an ice slurry — a slushy substance that somewhat resembles a 7-11 Slurpee®. This slurry, which is chemically smoothed so it does not damage fragile blood vessels, can be pumped easily into a patient's bloodstream through a small intravenous catheter.

Argonne is working with several different groups of University of Chicago surgeons to develop procedures for cooling and protecting vital organs. This research is being conducted under the newly formed University of Chicago-Argonne Bioengineering Institute for Advanced Surgery and Endoscopy.

Argonne green-lights environmental car challenge

Last fall, Argonne gave the green flag to a new environmentally conscious international sports-car racing event.

The inaugural Green Challenge took place at last year's Petit Le Mans race, the American Le Mans signature event, on Oct. 4 in Atlanta. Fourteen different manufacturers were represented by the competing cars, which were grouped into four classes and used combinations of three different renewable fuels and electricity.

The Green Challenge recognized innovations in science, technology and engineering by measuring the energy efficiency, petroleum displacement and greenhouse-gas emissions of each car during the 1,000-mile race.

Argonne's researchers have extensive experience in organizing and executing vehicle competitions. For more than 20 years, Argonne has run collegiate competitions focused on developing and demonstrating advanced propulsion technologies and renewable fuels. Many of the innovations in today's vehicles sprouted from similar contests that test and refine advanced technologies developed in the laboratory.

The Green Challenge will become a full-season feature this year, when all teams will compete for a season-long Green Challenge Championship sponsored by the U.S. Department of Energy, the Environmental Protection Agency and the Society of Automotive Engineers International.

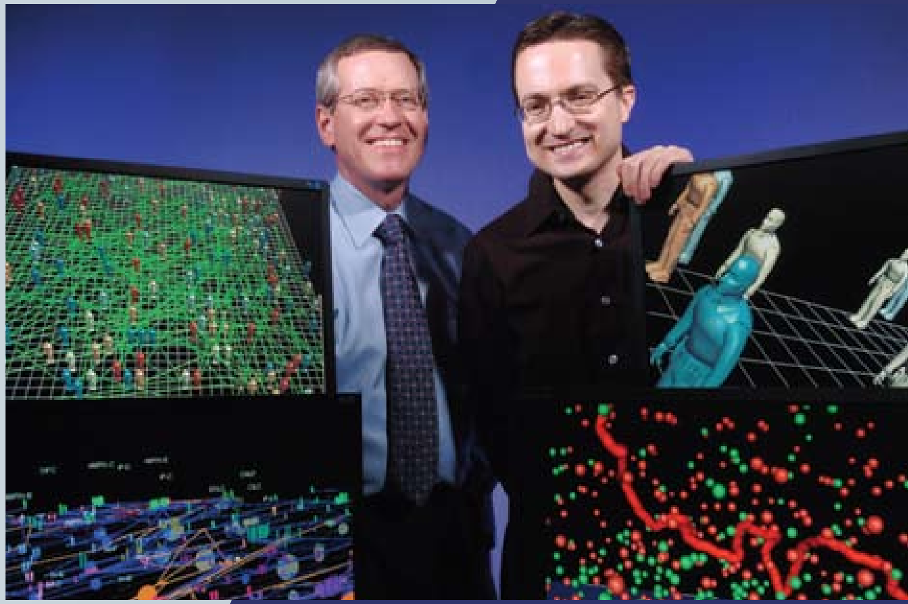
Two race cars compete in the Green Challenge at the American Le Mans Series race in Atlanta on October 4, 2008.

A model economy

Economists and business columnists have blamed many factors for the recent financial calamity. While their hindsight might be clear as day, researchers at Argonne are creating new economic models that will generate more realistic pictures of different types of markets so policymakers can better avert future economic catastrophe.

Traditional economic models rely heavily on "equilibrium theory," which holds that markets are influenced by countervailing balanced forces. Because these models assume away the decision-making processes of individual consumers or investors, they do not represent the market's true internal dynamics, said Charles Macal, an Argonne systems scientist.

Macal and his Argonne colleagues have created a new set of simulations called "agent-based models" to better anticipate how markets behave. By more precisely representing the behavior patterns of individual actors in a market — for example, how willing they are to accept risk, how strongly they value the future or how much time and effort they are able to spend making decisions — researchers and economists can better predict and avoid future meltdowns.



Argonne systems scientists Charles Macal (left) and Michael North showcase several of their agent-based models.

> “It’s a bit like trying to put the engine through a medical exam. It’s possible your doctor might be able to find out if there’s anything wrong with you just by looking at you, but he can tell a whole lot more by taking an X-ray.”

acceleration / at Argonne

Fueling the future

To many people, the particulars of how a car’s engine works are a mystery. From the gas tank to the exhaust pipe, the fuel we use makes a journey through injectors, cylinders and valves, transforming from a liquid to a gas along the way to combustion.

The automotive engineers who design the cars and trucks we drive can tinker with an engine to squeeze out a few extra horsepower or a slightly better gas mileage, but they lack a detailed picture of the structure and composition of fuel as it is sprayed into the combustion chamber. The composition of a fuel spray influences both how efficiently and how cleanly it combusts.

Because engines can cycle hundreds to thousands of times a second, and because the dynamics of the combustion itself are so difficult to control, researchers at Argonne have tried to understand and manipulate the structure and timing of the fuel spray, as the way that the fuel jets atomize determines how they combust later in the cycle. By adjusting the fuel spray, scientists have the potential to significantly enhance an engine’s fuel efficiency while simultaneously diminishing harmful emissions.

To do so, they need something like a high-speed camera to capture the detail of each fuel injection. With imaging tools that use visible light, however, scientists can trace only the outline of the fuel plume. Visible light cannot penetrate the dense plume, just as a high-beam headlight cannot pierce through fog. The high-energy X-rays produced by Argonne’s Advanced Photon Source, in contrast, can resolve the entire structure of the fuel spray, said Argonne researcher Jin Wang.

“It’s a bit like trying to put the engine through a medical exam,” he said. “It’s possible your doctor might be able to find out if there’s anything wrong with you just by looking at you, but he can tell a whole lot more by taking an X-ray.”

Although previous studies assumed that the outline of the fuel plume “told the whole story,” as Wang puts it, the latest research done with penetrating X-rays has found that most of the fuel contained in the spray is concentrated in a small region around its center. “You have to have a synchrotron to do this sort of work,” he said. “The highly penetrative and highly intense nature of X-rays allows us to see more than we ever could before, and allows us to take images only a nanosecond apart.”

Not all fuel sprays are the same. Even small differences in fuel droplet size, shape or structure after atomization can cause fuel to combust differently. The difference in combustion patterns not only affects the efficiency of the engine — it also generates different emission products. “For the same engine, the combustion of one type of spray might give off lots of nitrous oxides and other greenhouse gases, while a slight change to the injection parameters might greatly improve the engine’s efficiency and reduce the quantity of pollutants that it produces,” Wang said.

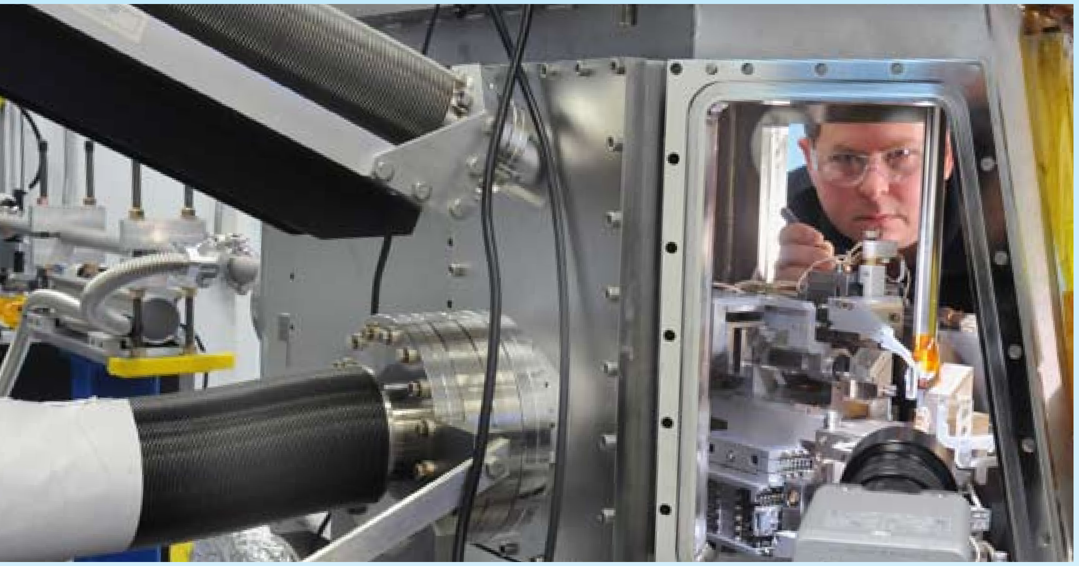
Ideally, Wang hopes to determine the mathematical and physical principles that underlie how different characteristics of fuel injection affect how the fuel spray is combusted. “The holy grail of combustion research is to come to a fundamental understanding of the entire combustion process, including the sprays. This would enable us to create a set of guiding principles to design cleaner, smarter and more efficient systems,” he said. “We’re looking for more than just a recipe that says to tweak one parameter a certain way and another one a different way. It has to be more than merely empirical.”

The deductive approach that Wang espouses has one critical advantage: with controlled modifications, researchers could likely tailor their fuel sprays to most types of engines that use any of several different fuels — including biofuels. While these new and remarkable fuels themselves have drawn much of the public’s attention in the race to meet the energy and environmental challenges facing the transportation industry, the advances scientists will make in green transportation over the course of the next several years depend on finding cleaner and more efficient ways to use them.

seeing the small picture

The unparalleled access to state-of-the-art tools and high-intensity X-rays gives researchers at Argonne's Advanced Photon Source the capability to see structural details of cells and materials at smaller scales than ever before. As these scientists push past the nanoscale to the atomic frontier, they gain new insights into the chemical and electrical processes that determine the behaviors of the cells in our body and the materials that we use in our everyday lives.

by Jared Sagoff



Beamline scientist Robert Winarski peers at a sample inside Argonne's Hard X-Ray Nanoprobe.

Try to picture putting some atoms under a microscope. Even if you could pick them up, put them on a slide and get them to stay still, you still could not see them with even the most powerful optical microscope.

The reason? The wavelength of visible light measures hundreds of nanometers, the span of thousands of atoms. To zoom in all the way to the atomic level, scientists from all over the world use the high-energy X-rays produced by Argonne's Advanced Photon Source (APS).

The quest to image tiny structures and their environments presents a complex challenge and a valuable scientific opportunity. The molecular processes involved in the function of our bodies at the cellular level, as well as the chemical and physical traits that characterize materials, all depend on compositional, structural and electronic properties at the micro-, nano- and atomic scale.

The frontier of materials science has for some time pushed into the nanoscale, where objects are measured in billionths of a meter. Researchers continually strive to better understand nature at ever smaller length scales and to more precisely manipulate systems to benefit humanity and the environment. From the next generation of superconductors to solar cells to cancer treatments, the ability to image tiny structural features has the potential to make a big impact.

To enrich our understanding of the nanoscale properties of complex systems, materials and devices, scientists come to Argonne to employ the laboratory's new Hard X-ray Nanoprobe (HXRN), which is jointly operated by Argonne's Center for Nanoscale Materials and the APS. This system can currently resolve structures as small as 30 nanometers — a distance roughly equivalent to the width of 100 atoms and less than 1/1000th the diameter of an average human hair.

While other forms of imaging — electron microscopy, for example — can reveal even smaller details close to a sample's surface, the high-energy X-rays generated by the APS can penetrate into a material to reveal buried structures and interfaces. "X-ray imaging gives scientists a unique window into complex systems, allowing us to see their structure, composition and dynamics," said Argonne nanoscientist Jörg Maser, who runs the nanoprobe.

The nanoprobe works much like an optical microscope, but uses X-rays instead of visible light. These brilliant X-rays are tailored to the requirements of individual experiments by a series of X-ray mirrors and crystal optics in the nanoprobe beamline. In the final step, a Fresnel zone plate focuses this "conditioned" beam on the specimen.

Unlike refractive lenses used in an optical microscope, Fresnel zone plates focus X-rays using diffraction. In principle, this approach could allow scientists to one day focus X-rays to spot sizes smaller than 10 nanometers. "The smaller the spot to which we can focus our beam, the smaller the structures we can observe," Maser said.

In most of the scattering experiments performed to date, scientists have been able to determine only the intensity of the X-ray that hits the detector. However, by using more sophisticated X-ray techniques — such as coherent diffraction — scientists can extract not only the intensity of the X-rays, but also their phase. "The name of the game is 'how do you determine the phase of your wavefront,'" said Argonne materials scientist George Srajer. "This allows us to fully exploit the information carried from the sample by the X-rays. Amplitude and phase information go hand-in-hand."

By taking advantage of the phase information contained in coherent X-rays, Argonne's researchers can more accurately resolve the structure of their specimens, even without advanced X-ray optics like zone plates. Synchrotron radiation sources like the APS are built expressly to provide X-rays with proper coherence. "In the end, what we are really trying to create is an ultra-high-resolution image in real space, as we would see if we could just take a picture of the sample with a camera," Maser added. "That is possible if we can determine both the amplitude and the phase, which requires coherent X-rays."

By shining hard X-rays instead of visible light onto their small samples, Argonne's scientists can also study biological cells and tissues. In one experiment, Argonne researchers are using the APS's X-rays to image blood vessels as they form and branch out. This process, known as angiogenesis, occurs as one of the most important steps in the healing of wounds. However, cancerous tumors can also perform angiogenesis, which allows cancer cells to grow and spread. With the unique ability to observe angiogenesis at the subcellular level, Argonne's scientists help to discover ways to inhibit the growth of blood vessels in cancerous tissues. "It's almost like having Superman for a doctor — using hard X-rays to find cures for problems far more severe than just broken bones," Srajer said.

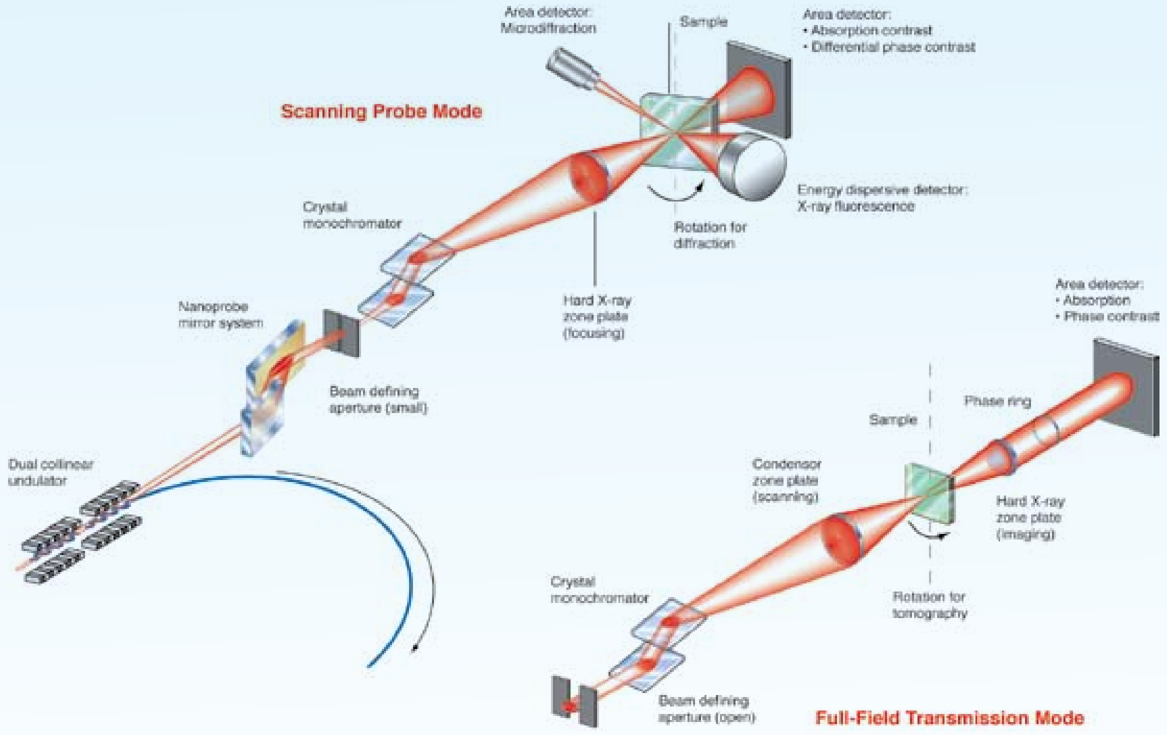
In order to do these types of biological experiments, Argonne's scientists require a device that can detect the presence of small amounts of particular compounds in highly dilute solutions. By using the HXRN or APS microprobes, researchers can study trace metal distributions in cells at ever finer spatial resolution. These high-resolution tools provide Argonne researchers with the capacity to study the cellular processes important in normal physiological function and in disease.

The different types of information revealed by X-ray optics also allow researchers at the APS to investigate material processes as they occur. These experiments, known as *in situ* studies, give scientists a deeper understanding of material properties than they can glean from disconnected structures. The real benefit of *in situ* studies comes from the ability to modify materials while they are being observed.

The basic scientific explorations carried out at the APS hold the potential to spawn a new generation of products and inventions that will improve our lives and stimulate the economy. In one *in situ* experiment, researchers exposed parallel layers of silicon to a small, well-defined stress, which caused a tiny displacement of the atoms in the material.

The mismatch created regions through which electrons could pass more smoothly, like water pouring through a crack in a seal. Unlike visible light, the X-rays produced by the APS enabled the scientists to see the small displacements. This information, Maser said, could lead to the production of enhanced semiconductors for a new generation of microprocessors.

The combination of the world's finest X-ray tools and sophisticated imaging techniques has allowed scientists and engineers who use Argonne's research facilities to reach a deeper understanding of the small-scale processes and interactions that surround us. The new discoveries Argonne scientists make every day foster advances in basic knowledge and the development of breakthrough technologies that improve our health, our economy and our environment.

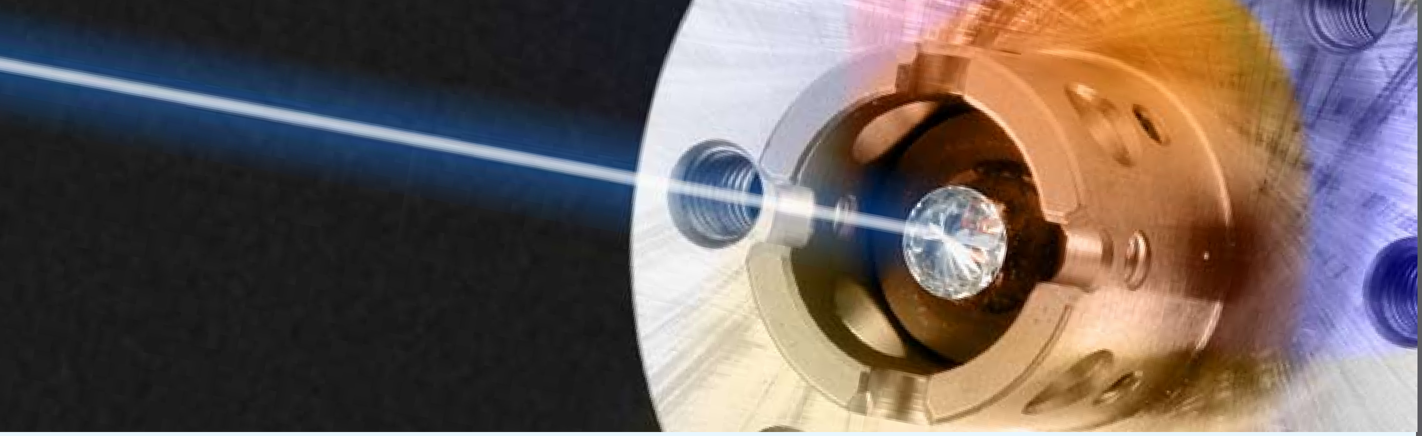


The Hard X-ray Nanoprobe (HXRN) works by focusing a bright X-ray beam onto a tiny spot through a series of mirrors and optical plates. Depending on the sample they wish to study, Argonne researchers can operate the HXRN in one of two different modes.

By combining high-power lasers, diamonds and the brilliant X-rays produced by Argonne's Advanced Photon Source, scientists from around the world can investigate materials at temperatures and pressures equal to those in the Earth's core. The knowledge they gain could illuminate Earth's distant past while revolutionizing the creation of many future materials from semiconductors to ceramics.

by Jared Sagoff

turning the world inside out



The astronomer Edmond Halley believed that it was hollow. The author Jules Verne wrote that it was home to dinosaurs and mastodons. But when it comes to determining the composition of the core of the Earth, geoscientist Mark Rivers has a few thoughts of his own.

The Core of the Matter: The Matter of the Core

"We know there's iron there for sure," said Rivers, the associate director of the GeoSoilEnviroCARS (GSECARS) beamline at Argonne's Advanced Photon Source (APS). "But until now we've really had no way of knowing exactly what state the iron is in, or what other elements or compounds might be down there."

At GSECARS — run by the University of Chicago for the U.S. Department of Energy — and at several other APS beamlines, geoscientists from around the world use tools that can dig deeper than any drill and descend farther than any mineshaft. By using powerful lasers as well as presses that range from pocket-size to several tons, these scientists can expose materials to the blazing temperatures and crushing pressures found in the Earth's outer core.

The smaller device, called a diamond anvil cell, consists of two tiny diamonds that act as a vise, squeezing together a small sample. Because pressure is the measure of a force divided by the area over which it is applied, Rivers and his colleagues need to use only a small amount of force to create an enormous amount of pressure. "With a tiny sample like this, you can create the pressure of the center of the Earth with just a small Allen wrench," Rivers said.

The pressures in the Earth's outer core are roughly two million times that of our atmosphere, strong enough to crush any known living organism and even alter the fundamental atomic arrangement of most substances. Temperatures in the outer core soar to more than 7,000 degrees Fahrenheit, but scientists do not really have a firm idea of exactly how hot it really is.

"If you pick a point inside the Earth and tell me how deep it is, we can pretty easily figure out the pressure there. But although temperature generally increases with depth, there's never been a good way to know the exact value," said Yanbin Wang, a GSECARS researcher. "We can't exactly dig our way there."

Because the researchers could calculate the pressure at the core's boundary, they were able to use the diamond anvil cells to more accurately ascertain the temperature of the outer core. First, Argonne geophysicist Guoyin Shen squeezed a small iron sample inside the diamond anvil cell at the appropriate pressure, and then heated it with a laser. Because the outer core primarily contains liquid iron, Shen, who now runs the beamline of the High-Pressure Collaborative Access Team, could determine the minimum temperature of that iron by heating the sample until it melted.

The generation of tremendous pressures and temperatures at the APS represents only the first step in the investigation of materials under these conditions. The high-energy X-rays produced by the APS hold the key to unlocking never-before-seen chemical properties.

Making an Impact: The Birth of the Earth

By gaining the ability to see how materials respond to extreme stresses, the geoscientists using the APS can open a window not only into the Earth's interior but also into its past. "One of the biggest mysteries in earth science asks how the Earth originally formed," Rivers said. "In the early days of Earth's formation, the planet was likely entirely molten and then cooled over time. The hard X-rays produced by the APS provide us with a unique capability of understanding the effects of extreme temperatures at both the macro- and molecular scale."

The extreme temperatures and pressures produced in Earth's early history and found inside it today can radically change the arrangement of atoms in a material. Even though all the individual atoms in a material stay the same, different formations of these atoms yield exceptionally different materials. For instance, at the Earth's surface, carbon atoms frequently arrange themselves in parallel planes in the form of soft, flaky graphite. However, deep inside the Earth, the intense

"With a tiny sample like this, you can create the pressure of the center of the Earth with just a small Allen wrench."

Geoscientist Vitali Prakapenka examines a diamond anvil cell under a microscope. The cell contains a tiny sample of water that has been turned to ice by the extreme pressure generated by the diamonds. At top left, an illustration of an X-ray beam striking the diamond anvil cell.

pressure forces these atoms to rearrange themselves into strong pyramids, creating a diamond.

In these crystalline materials, the bonds between atoms act like small springs. As the initial pressure is applied to them, these “springs” compress. However, if the material experiences extreme pressure or temperature, the atoms suddenly contort themselves into a new, denser configuration.

The high-energy X-rays produced by the APS collide with the atoms in the crystal structure, which causes the X-rays to scatter. A detector on the other side of the sample captures the scattered X-rays, and the pattern that they create enables the scientists to calculate the position of individual atoms.

As the Earth cooled, its relatively uniform composition began to separate into a number of layers as different compounds solidified at different rates. Without a way to directly observe the action of those distant millennia, Wang and his GSECARS colleagues turned to a technique known for its use in diagnosing kidney stones, not looking inside rocks.

Computed axial tomography, better known as a CT or CAT scan, can separate structures of different densities inside of a given object. The scientists at GSECARS designed and built a special device that can spin the sample while it is compressed in a hydraulic press, so that CT images can be collected at extreme pressures and temperatures. Taken together, the images produced by scans of materials at different temperatures and pressures give geoscientists a glimpse into the development of the young Earth.

In order to enrich the account of the Earth’s early days, Rivers and his colleagues at GSECARS use X-rays produced by the APS to determine the composition of meteorite fragments. The hope, Rivers said, is to find analogies between the formation of meteorites and the development of the Earth.

According to Rivers, geoscientists believe that as the Earth and solar system formed between four and five billion years ago, thousands upon thousands of large meteorites collided with the surface of our infant planet. These collisions determined the composition of our planet, and scientists believe one extremely large and violent collision created Earth’s moon.

“There’s pretty much a consensus that the core contains not only iron and nickel but also light elements like oxygen or sulfur,” he said. “These meteorites contain many of the same elements and were solidifying at the same time as the Earth cooled, so they could give us clues as to what things look like thousands of kilometers down or billions of years ago.”

Under the Volcano: Sizing up Seismic Activity

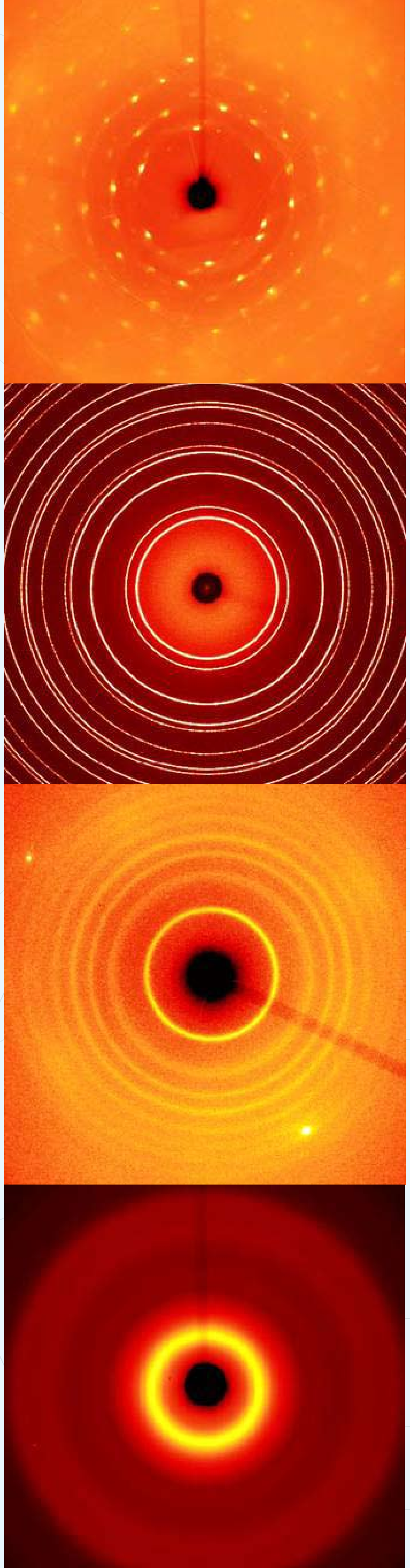
Through their attempts to glean more information about the Earth’s interior and the planet’s geologic history, the researchers at the APS slake their scientific curiosity while providing key data that could help officials predict and prepare for natural disasters.

In addition to the diamond anvil cell, the GSECARS scientists use a device called a large volume press — which essentially combines many different anvils — to investigate the viscosity of a variety of melted minerals and compounds. The viscosity of a material measures how much it resists flow.

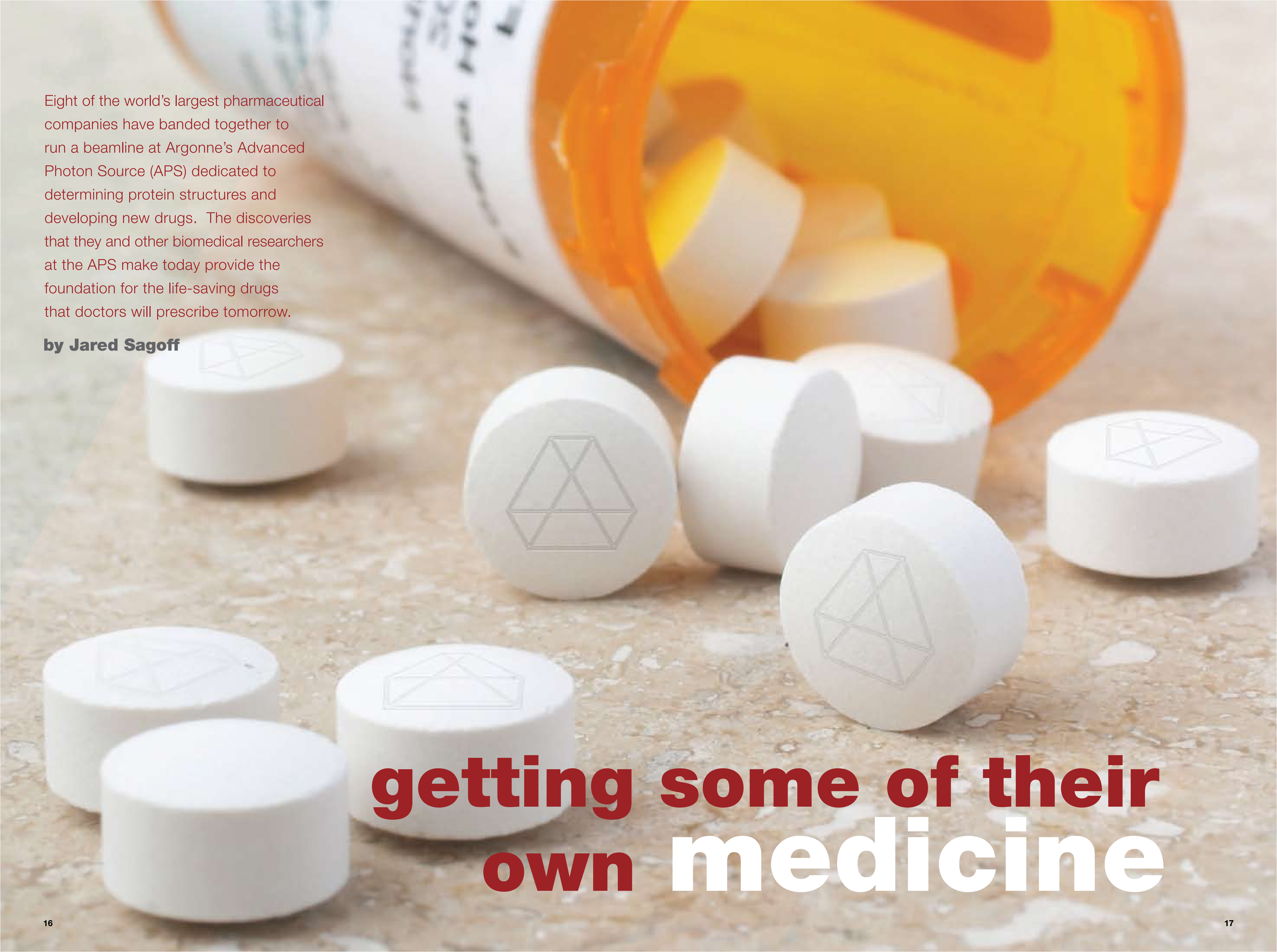
The effects of high pressure and temperature on viscosity determine the structure of volcanoes and how the seismic waves of earthquakes propagate through the Earth’s interior, Wang said. “Volcanoes form when the liquid magma is less dense than the surrounding rock, but since liquids are more compressible than solid rock, the density and viscosity of the magma typically increases the lower you go. The style of the eruption depends primarily on the viscosity.”

Although scientists have already mapped out the major fault lines along which earthquakes occur, that knowledge provides them with only a limited ability to predict and understand the mechanisms that produce potentially catastrophic earthquakes. The viscosity research “gives us a three-dimensional view of an earthquake’s path,” Rivers said. “The research we’re doing on these tiny samples of iron and rock could eventually end up saving lives.”

By exposing materials to extreme conditions, scientists do not merely seek to appease their geological inquisitiveness. Under these stresses, materials show novel and unexpected properties that help scientists and engineers understand why certain substances act in the way that they do. The creation of new generations of electronics, textiles, ceramics, catalysts and fuels requires an understanding of the entire spectrum of material properties.



The patterns created by the X-rays as they diffract off very hot and highly pressurized materials reveal their molecular structures. The four images at left are diffraction patterns generated by the same type of silica with different grain sizes that range from the macroscopic (top) to only several nanometers (bottom).



getting some of their own medicine

Eight of the world's largest pharmaceutical companies have banded together to run a beamline at Argonne's Advanced Photon Source (APS) dedicated to determining protein structures and developing new drugs. The discoveries that they and other biomedical researchers at the APS make today provide the foundation for the life-saving drugs that doctors will prescribe tomorrow.

by Jared Sagoff

Imagine Mozart and Salieri teaming up to write a symphony, or Hemingway and Fitzgerald collaborating on the Great American Novel. Now imagine the most famous names in drug discovery joining forces to find new cures for the world's most widespread and serious diseases.

Although those masterpieces of music and literature will have to remain in the realm of fantasy, a consortium of the biggest of the big drug companies has taken root at Argonne's Advanced Photon Source (APS). At the APS, eight of the 16 largest pharmaceutical giants — Abbott, Bristol Myers Squibb, Eli Lilly, Johnson and Johnson, Merck, Novartis, Pfizer and Schering Plough — currently team up to form the Industrial Macromolecular Crystallography Association (IMCA).

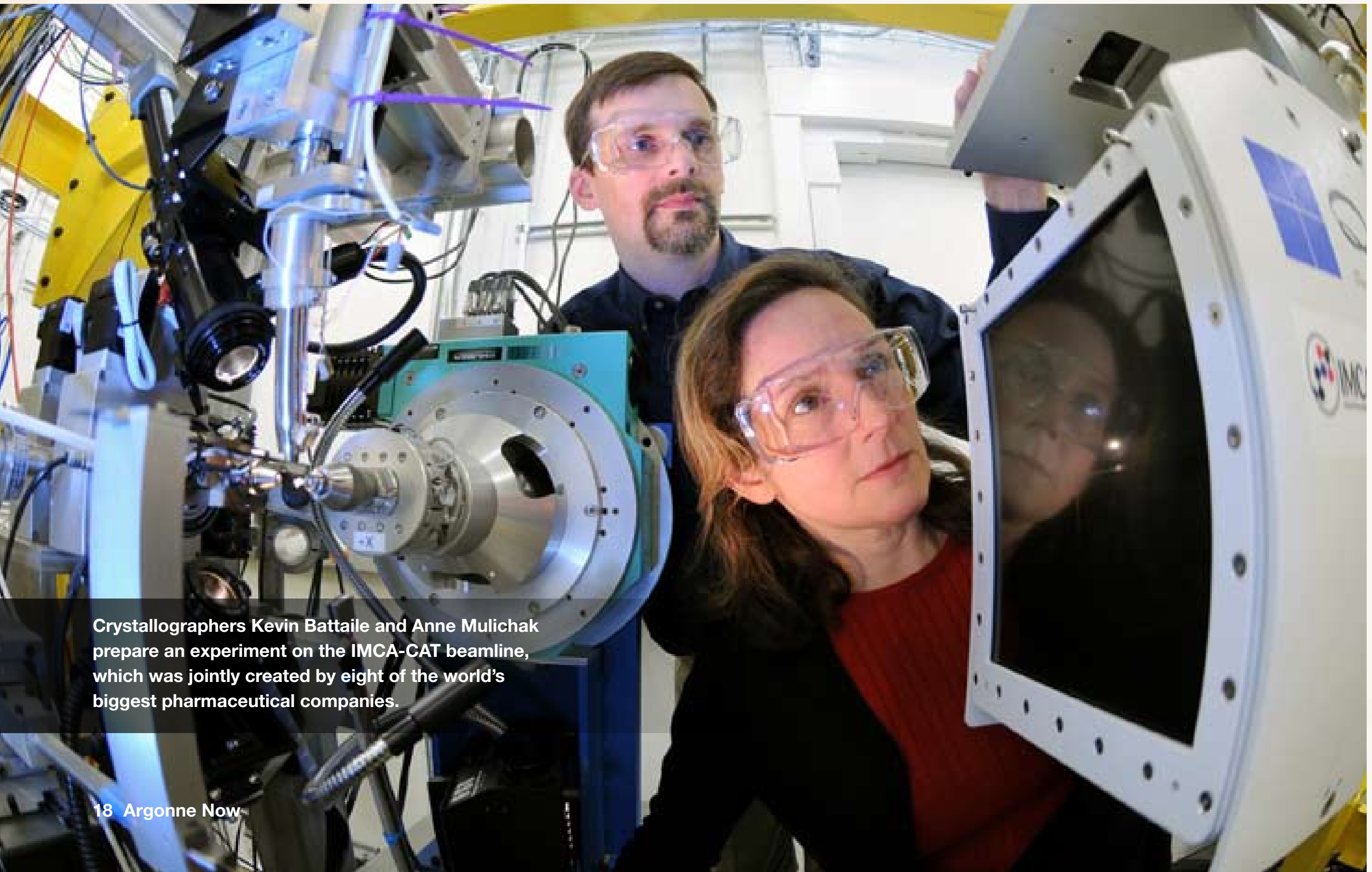
The creation of IMCA allowed all of these companies together to own what none of them could separately afford: two beamlines at Argonne's Advanced Photon Source. The X-rays produced by the APS synchrotron and shot through IMCA's beamlines allow the researchers at these companies to scan thousands of proteins and inhibitor molecules for the next wonder drug.

The road of drug discovery is long and arduous. Once a drug company identifies what disease it wants to treat, it has to determine the protein responsible for causing its symptoms. Then, the company's chemists fashion scores of inhibitors, tiny molecules that can bind to the protein's surface and prevent it from carrying out its function.

Not every inhibitor, however, can form the core of a new drug. A molecule that binds to the target protein might also inhibit several others, wreaking havoc in other biological pathways. It can take years for the examination of thousands of potential candidates to yield a single ideal inhibitor. "Finding the right inhibitor is like trying to find a jigsaw puzzle piece in a 10,000-piece puzzle with two dozen sides," said Lisa Keefe, who directs the IMCA-Collaborative Access Team (IMCA-CAT) beamlines for the University of Chicago. "It has to fit exactly right, and you almost always have to make it yourself."

To determine protein structures — their grooves, curves, nooks and kinks — scientists use a process called X-ray crystallography. In this method, researchers at the drug companies manufacture small crystals of the pure protein-inhibitor combinations they want to study and take or ship them to the APS for analysis. The crystals are then robotically loaded onto a small arm and exposed to the APS's brilliant X-rays. IMCA-CAT provides pharmaceutical reasearchers with on-site, mail-in and remote Internet access to the beamline.

When the X-rays hit the protein crystal, the electrons in the atoms of the protein's structure scatter, or "diffract," them in all different directions. These diffracted X-rays then hit a detector on the other side of the crystal. By looking at the position and intensity of the scattered X-rays on the detector, biophysicists can calculate the positions of the atoms in the structure of a protein and its inhibitors.



Crystallographers Kevin Battaile and Anne Mulichak prepare an experiment on the IMCA-CAT beamline, which was jointly created by eight of the world's biggest pharmaceutical companies.

The X-rays produced by the APS synchrotron and shot through IMCA's beamlines allow the researchers at these companies to scan thousands of proteins and inhibitor molecules for the next wonder drug.

Because of the enormous resources these companies invest in each new drug they create and the vast number of possible inhibitors they have to sort through, they need a fast machine to characterize and evaluate them. "To these companies, time truly is money," said Keefe. "Our mission is to take their hundreds and hundreds of crystals and analyze them as quickly as possible. By having an X-ray beamline dedicated to this work, these companies can radically reduce the time they need to plan and execute their research."

The best-known drug to emerge from research at the APS, Kaletra®, has already saved thousands of lives by helping to prevent HIV-positive patients from developing full-blown AIDS.

In the mid-to-late 1990s, Abbott Laboratories, one of the founding partners of IMCA, used the APS's X-rays to examine a protein called HIV protease. Abbott's researchers hoped to find an inhibitor that would block the action of HIV protease, effectively thwarting the virus by preventing it from replicating.

After an exhaustive search, Abbott's scientists found an inhibitor that shut down the virus without harming other bodily functions. After months of animal and human testing, Kaletra gained FDA approval in 2000 and is now the most prescribed drug in its class for AIDS therapy.

More recently, another IMCA member has taken up the fight against another notoriously deadly disease. Merck scientists used the IMCA beamline to determine the structure of platensimycin, a member of a previously unknown class of antibiotics that scientists have successfully synthesized within only the past two years. According to Keefe, Merck hopes to use the information gained from the APS to tailor platensimycin to treat infections against which conventional antibiotics have little effect. The most infamous of these, Multidrug-Resistant *Staphylococcus aureus* (MRSA), killed more than 18,000 nationwide in 2005. Merck also used its time on IMCA-CAT to determine the structure of proteins involved in Type II Diabetes, which aided their development of the drug Januvia®.

The idea of a dedicated beamline attracted the IMCA consortium because the companies themselves would retain the rights to all of the discoveries made by scientists at IMCA-CAT. Under this kind of arrangement, called proprietary research, the drug companies pay for all the costs of construction and operation of the beamline, as well as a proprietary fee to the APS, and in return are able to develop their research for an eventual patent instead of making their results public. Without proprietary research, Keefe said, few if any medications would ever reach the hands of those who need them the most.

Proprietary research, however, is not the only method by which scientists can work towards new cures and treatments. At least a quarter of the beamtime at IMCA-CAT and the other APS beamlines is reserved for use by unaffiliated researchers at universities, laboratories and other scientific agencies from around the world. The collected structural knowledge that these general users gain goes into a shared protein "library," to which researchers constantly add new knowledge about disease chemistry. This "Protein Data Bank" is available to the public and can be accessed online at www.rcsb.org.

Aside from IMCA-CAT, Argonne offers several other beamlines that produce groundbreaking medical discoveries. One of these, SGX-CAT, is operated by SGX Pharmaceuticals, Inc., a company recently acquired by Eli Lilly. Another beamline represents part of Argonne's Structural Biology Center (SBC), where researchers have determined more protein structures than at any other facility in the world, according to SBC Director Andrzej Joachimiak. Thirteen other beamlines at the APS also house X-ray crystallography experiments.

Work at the SGX-CAT beamline focuses on the discovery, development and commercialization of innovative cancer drug therapies. In one experiment, scientists at SGX-CAT are targeting abnormal proteins that result from a genetic abnormality known as the "Philadelphia translocation," a molecular mistake in which two different chromosomes inadvertently swap small segments of DNA.

These wells contain samples of proteins and inhibitors that are taken or shipped to IMCA-CAT for analysis. In order to protect the samples from being damaged by the high-energy X-rays, crystallographers need to cool them in liquid nitrogen, which causes a coat of frost to form on the wells.

Scientists have ascertained that these anomalous proteins trigger uncontrolled cell growth that results in a bone-marrow cancer called chronic myelogenous leukemia. "The most effective treatment of this disease relies on finding inhibitors for these rogue proteins," Joachimiak said.

SGX-CAT offers a number of non-profit and for-profit crystallography services to the biology community. In addition to a mail-in crystallography service, SGX developed several new approaches and technologies for drug discovery.

One of these new approaches, an algorithm called Fragments of Active Structures (FAST), draws on a diverse library of approximately 1,000 small molecular fragments. By using FAST, scientists increase the likelihood of developing a successful drug candidate by focusing their research on a small number of fragments that can then form the backbone of a range of novel and potent pharmaceutical candidates.

Unlike the users of IMCA-CAT and SGX-CAT, the majority of users of the SBC's beamline come from academic institutions. Although they do not have as large a financial stake in their discoveries as IMCA's scientists, these researchers also tackle some of medicine's biggest challenges.

In one project currently underway, SBC biologists are trying to determine the structure of the aldose reductase enzyme, a protein that breaks down glucose into a sugar alcohol called sorbitol. In diabetics, an accumulation of sorbitol in the bloodstream often causes nerve and eye damage. A successful inhibitor of aldose reductase could form the core of a new drug that would dramatically improve the lives of more than 20 million American diabetics.

"Drug discovery is an incredibly expensive and time-consuming process," Joachimiak said. "The facilities we have here at Argonne speed it up considerably, allowing these drugs to get to the people who need them more quickly, cheaply and safely." ▲

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did you know...

...that Argonne's Advanced Photon Source produces the brightest X-ray beams in the Western Hemisphere? The APS currently comprises 34 different sectors, each of which can operate several different beamlines simultaneously. The facility drew 3,412 unique users to Argonne in 2007 to work on cutting-edge research in materials science, biochemistry, environmental science and basic physics.

The knowledge gained from these experiments can impact the evolution of combustion engines and microcircuits, aid in the development of new pharmaceuticals, and pioneer technologies whose scale is measured in billionths of a meter, to name just a few examples. These studies promise to have a far-reaching impact on our technology, economy and health as well as on our fundamental knowledge of the materials that make up our world.

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