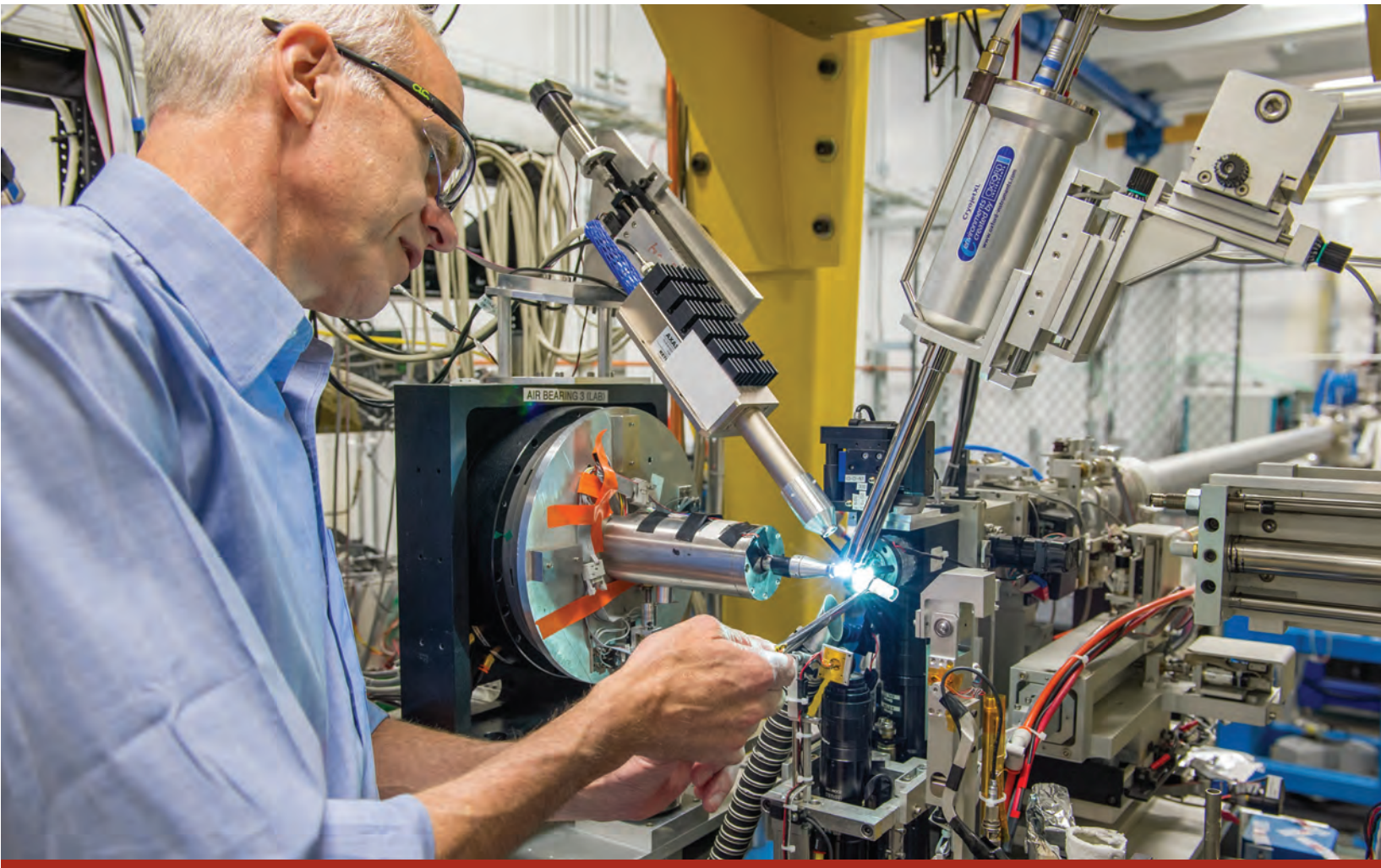
Argonne NATIONAL LABORATORY

A Bright Light for Drug Discovery



How the Advanced Photon Source at Argonne National Laboratory Powers the Fight Against Disease

The Advanced Photon Source and

Structure and function are intimately related. X-ray crystallography is the most comprehensive technique available to determine the structure of any molecule at atomic resolution. Accurate knowledge of molecular structures is a prerequisite for rational drug design and structure-based functional studies. Results from x-ray crystallographic studies provide unambiguous, accurate, and reliable 3-dimensional structural parameters at times even before complete chemical characterization is available. In addition, crystallography is the only method for determining the "absolute" configuration of a molecule.

Jeffrey R. Deschamps, "The Role of Crystallography in Drug Design"

Today's Pharmaceuticals, and Tomorrow's

Development of many critically important pharmaceuticals, existing and yet to come, grows out of macromolecular x-ray crystallography (MX)-based research carried out at sources of high-brightness x-rays such as the U.S. Department of Energy (DOE) Office of Science's Advanced Photon Source (APS) at Argonne National Laboratory and the APS Upgrade (APS-U), which will open new vistas in drug discovery.

MX is a research technique that reveals, to atomic resolution, the structure of macromolecules (proteins, protein and protein DNA complexes, and virus particles) in a crystal. The crystalline arrangement of molecules causes a beam of x-rays to diffract into many specific directions, which can be analyzed to determine structure. This technique has been at the forefront of the symbiotic relationship between sources of high-brightness x-rays such as the APS and drug discovery.

Approximately 30% of therapeutically relevant protein targets are routinely studied at the APS; the remaining 70% do not benefit from extensive structural guidance because the crystals are too small or diffract too poorly with current x-ray capabilities.

The Advanced Photon Source Facility

The high-energy, high-brightness, highly-penetrating x-rays from the APS give researchers access to a powerful, versatile light that is ideal for studying the arrangements of molecules and atoms, probing the interfaces where materials meet, watching chemical processes that happen on the nanoscale, and determining the interdependent form and function of biological proteins.

The APS facility — which is large enough to encircle a major-league baseball stadium — includes particle accelerators that produce, accelerate, and store a beam of high-energy (relativistic) electrons. As the electrons orbit through powerful electromagnets, they are deflected by permanent-magnet devices and emit synchrotron radiation, which covers a broad segment of the electromagnetic spectrum with wavelengths that are shorter than visible light. These wavelengths are invisible to the human eye and include extreme ultraviolet and x-ray radiation. They match the corresponding features of atoms, molecules, crystals, and cells — just as the longer wavelengths of visible light match the sizes of the smallest things the human eye can see.

Macromolecular X-ray Crystallography

Macromolecular x-ray crystallography has always been a major initiative for users of the APS.

- MX beamlines at the APS are highly automated, efficient, and productive.
- Of the 68 APS x-ray beamlines currently in operation, 16, or nearly one-quarter, are dedicated to MX.
- In fiscal year (FY) 2017, 1774 of 5742 APS users (31%) were biology or life sciences researchers (the majority of those carried out MX studies), making them the largest of the APS research communities.
- In FY 2017, MX researchers at the APS published 33% of the facility's peer-reviewed journal articles
- MX researchers using the APS have determined over 20,000 protein structures, more than at any other x-ray light source — nearly as many as all other U.S. light sources combined, and 20% of all structures from light sources worldwide[1].

MX beamlines at the APS are independently funded and operated, and they continually invest in capital equipment and other upgrades to maintain state-of-the-art capabilities for some of the most challenging problems in structural biology.

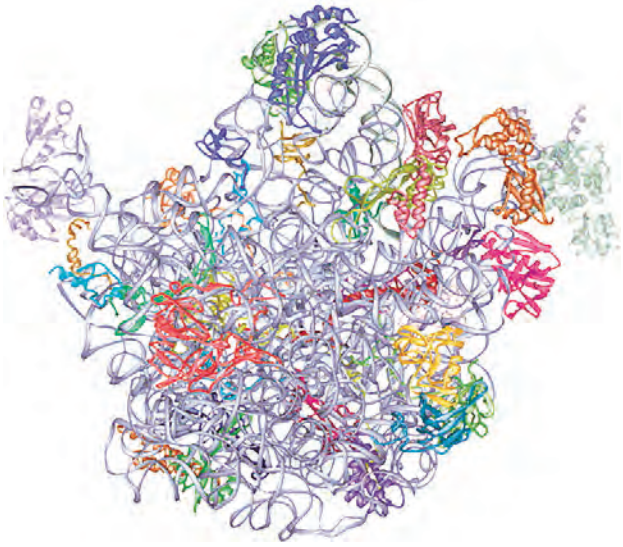
These beamlines are at the forefront of MX research techniques. Microbeam crystallography technology is an evolving research tool, and time-resolved crystallography, serial crystallography, and solution scattering are potential growth areas.

All three recipients of the 2009 Nobel Prize in Chemistry, Professors Venkatraman Ramakrishnan (Cambridge Medical Research Center), Thomas Steitz (Yale University), and Ada Yonath (Weizmann Institute) published papers on their award-winning work based on data collected at the Structural Biology Center Collaborative Access Team (SBC-CAT) MX facility at the APS, and other DOE light sources. They shared the award for their study of the structure and function of the ribosome (below left), which works as a protein factory in all organisms from humans to bacteria, and is the target of many antibiotics.

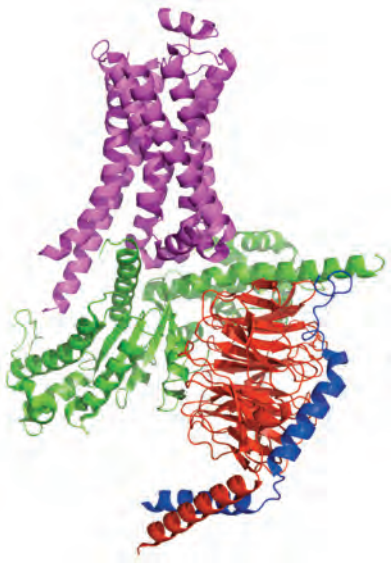
The 2012 Nobel Prize in Chemistry, awarded to Professsors Brian Kobilka (Stanford University) and Robert Lefkowitz (Howard Hughes Medical Institute and Duke University) for their work on G-protein-coupled receptors (GPCRs), was supported in large part by research performed by Kobilka at the National Institute of General Medical Sciences and National Cancer Institute structural biology facility (GM/CA-XSD) at the APS. This work determined the first structure of a human GPCR (below right), which are responsible for a number of biological responses, and are the target for 40% of all pharmaceuticals.

The following pages highlight some of today's drugs that emerged from research at the APS, a few examples of investigations that could produce tomorrow's breakthroughs, and an introduction to an upgraded APS that promises even greater success in supporting drug development.

[1]http://bit.ly/2yioV7M



Ribosome



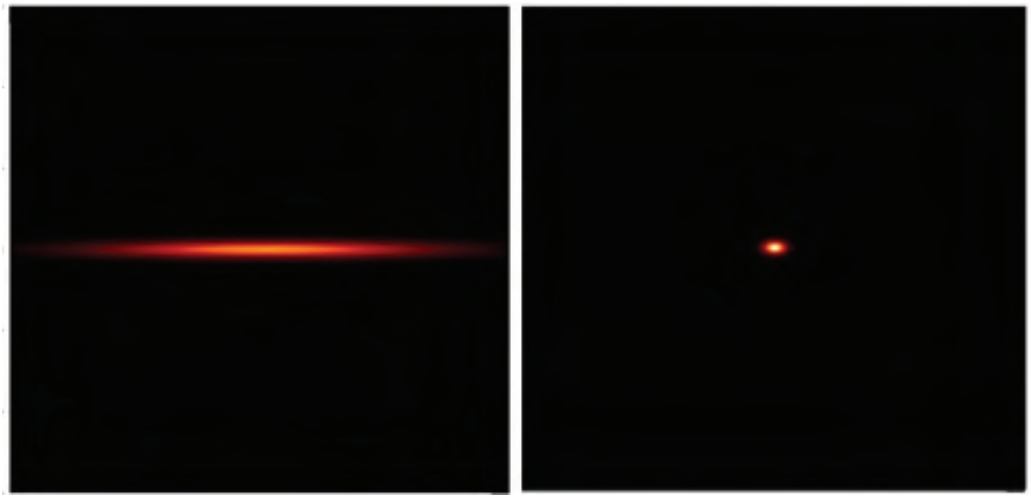
G-protein-coupled receptor

Drug Discovery and the APS Upgrade

The pharmaceutical industry has a history of using MX to enable pre-clinical drug-discovery research at storage ring x-ray light sources like the APS. Now, the APS is on the brink of a transformational advance: the multi-bend achromat (MBA) arrangement of components in a light source electron accelerator.

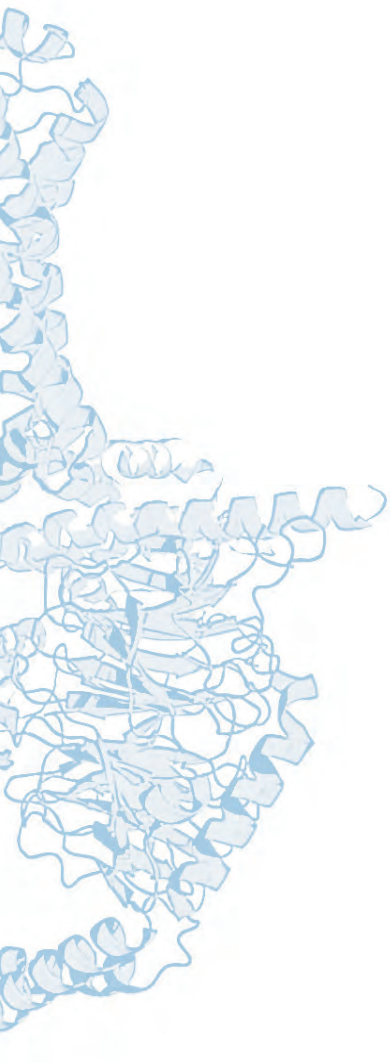
This is the centerpiece of the APS Upgrade (APS-U), which will reconfigure the APS electron storage ring (a *rendering of one upgraded sector is shown at right*), driving orders-of- magnitude increases in x-ray brightness and the number of photons that illuminate a sample being studied. The APS-U will provide high-intensity, high-energy x-rays that can be focused to sub-micron sizes to maximize the amount of data collected from a single crystal. The APS-U will revolutionize MX research by allowing thousands of potential drug-target structures to be determined in a single day. These vast improvements in photon beam properties, combined with rapid, ongoing advances in x-ray instrumentation, computing, and theory will make it possible for researchers at the upgraded APS to explore a new landscape of scientific problems that previously were completely inaccessible, including those related to MX, which is widely recognized as the most powerful tool to determine structure at the atomic level and, as noted on page 1, "a prerequisite for rational drug design and structure-based functional studies."

The APS Upgrade, with its greatly expanded throughput of excellent crystallographic data, promises to drive explosive growth in structure-guided drug discovery and transform the pharmaceutical industry's search for and optimization of new and improved drugs for the all-important fight against disease.



Simulated x-ray beam source profiles, comparing the beam from the APS today (left) to the beam from an upgraded APS storage ring (right), which will exceed the capabilities of today's hard x-ray storage rings by 2 to 3 orders of magnitude in brightness and coherent flux. Narrowing the APS x-ray beam to a spot as opposed to a "pancake" will deliver more photons to the sample being studied, which will greatly increase the amount of information obtained and the speed at which that information is collected.

A Drug That Fights AIDS



Kaletra®

Kaletra®, one of the most successful drugs used to stop the progression of the human immunodeficiency virus (HIV) into AIDS, got its start at the APS when scientists from Abbott Laboratories used the Industrial Macromolecular Crystallography Association Collaborative Access Team (IMCA-CAT) x-ray beamline at the APS to discover a way to stop HIV from replicating in the body through the use of a protease inhibitor that blocks the breakdown of proteins.

They pinpointed how the atoms of Kaletra® interact with the viral protein and where the drug should target the virus.

The drug was designed to fit into a hole in the HIV protease protein, lock into position there, and prevent HIV from replicating.

Out of that work came the drug Kaletra®.

In 2002, Kaletra® became the most prescribed drug in its class for AIDS therapy, and it remains widely used today, prolonging the lives of thousands of AIDS patients.

A Drug That Fights Skin Cancer

Zelboraf®

To help design the drug Zelboraf®, which can halt the progression of malignant and inoperable skin cancer, researchers from Plexxikon, Inc., and Genentech, the drug discovery and manufacturing companies, respectively, that developed the melanoma treatment, used the x-ray light sources at three DOE national laboratories—SLAC National Accelerator Laboratory, Lawrence Berkeley National Laboratory, and the Structural Biology Center (SBC) CAT x-ray beamlines at the Argonne APS.

Zelboraf® is the first drug to treat advanced melanoma by targeting a specific gene mutation.

Zelboraf® was extremely successful during clinical trials in disrupting the disease and extending the lives of those who were diagnosed with it.

A Drug That Fights
Type 2 Diabetes

Januvia®

Early research that led to the development of Januvia®, a type 2 diabetes medication manufactured by Merck & Co., was done on the IMCA-CAT beamline at the APS. Januvia® helps lower blood sugar levels in adults with type 2 diabetes, and Januvia® is the top-selling brand in its class.

The drug was approved by the U.S. Food and Drug Administration (FDA) in 2006 and is one of the most popular type 2 diabetes drugs on the market. In 2007, the FDA approved a variation of Januvia® called Janumet®, which is a combination of sitagliptin and metformin, and is also made by Merck.

Type 2 diabetes, once known as adult-onset or non-insulin-dependent diabetes, is a chronic condition that affects the way the body metabolizes sugar (glucose). The body either resists the effects of insulin — a hormone that regulates the movement of sugar into cells — or doesn't produce enough insulin to maintain a normal glucose level.

More common in adults, type 2 diabetes increasingly affects children as childhood obesity increases. There is no cure.

A Drug That Fights Kidney Cancer

Votrient®

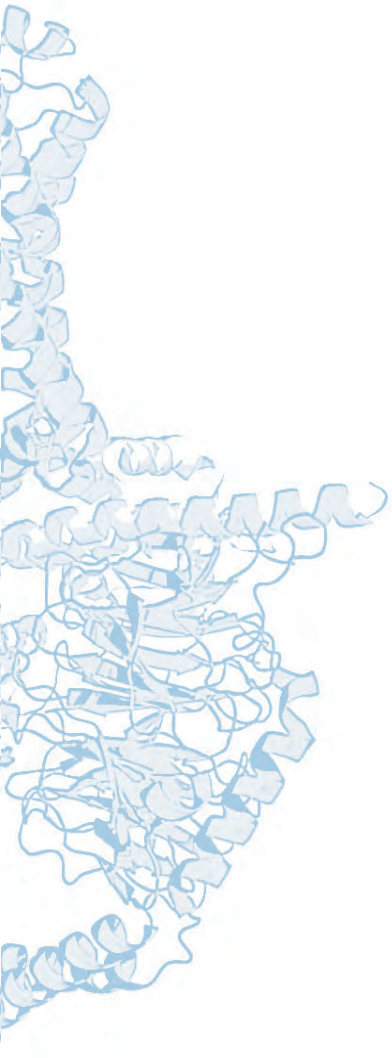
The research that led to the development of Votrient®, a successful drug for fighting advanced kidney cancer, was carried out by scientists from GlaxoSmithKline using the IMCA-CAT x-ray beamline at the APS.

The American Cancer Society's most recent estimates for kidney cancer in the United States in 2017 noted 63,990 new cases of kidney cancer (40,610 in men and 23,380 in women), with about 14,400 fatalities (9470 men and 4930 women) from this disease. These numbers include all types of kidney and renal pelvis cancers.

Votrient® is an angiogenesis inhibitor, which interferes with the growth of new blood vessels needed for solid cancer tumors to survive.

Votrient® is used to treat advanced renal cell carcinoma (kidney cancer). Votrient® is also used to treat soft tissue sarcoma, a tumor that can develop in or around muscles, tendons, joints, organs, or blood vessels.

A Drug That Fights Leukemia



Venclexta™

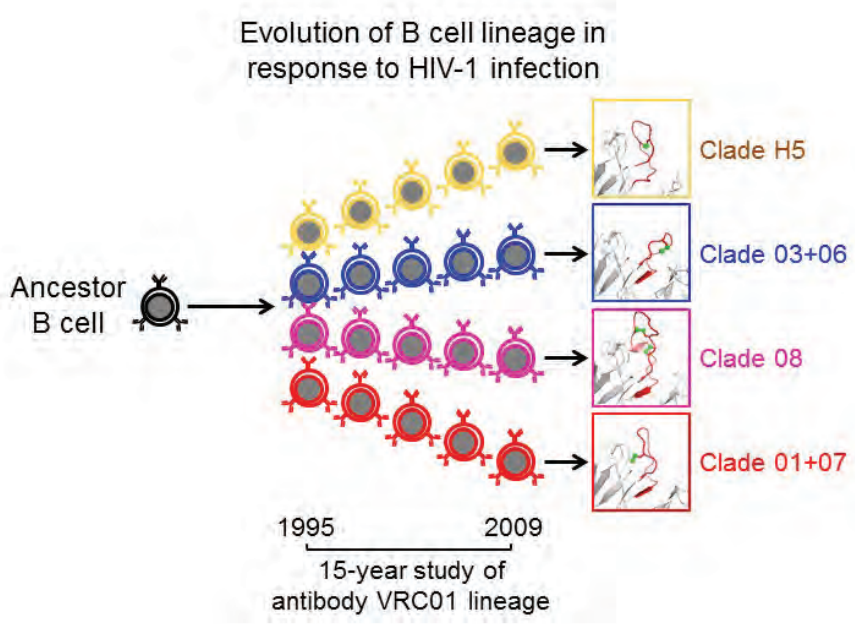
Venetoclax™, from AbbVie, a small-molecule drug that treats chronic lymphocytic leukemia in those with a specific chromosomal abnormality, emerged from research at the IMCA-CAT x-ray beamline at the APS. The researchers studied the structure of a particular protein and how it interacted with potential inhibitors.

In April 2016, Venclexta™ was approved by the FDA to treat chronic lymphocytic leukemia (CLL), one of the most common types of leukemia in adults with about 15,000 cases diagnosed each year. 10% to 20% of patients with CLL have a chromosomal abnormality in which a portion of the chromosome that inhibits cancer growth is missing.

Patients with that abnormality comprise 30% to 50% of relapses after CLL treatment and often have a life expectancy of two to three years.

Venclexta™ is the first FDA-approved treatment that targets a protein that blocks programmed cell death and can promote the growth of CLL cells.

Closer to an Effective HIV Vaccine



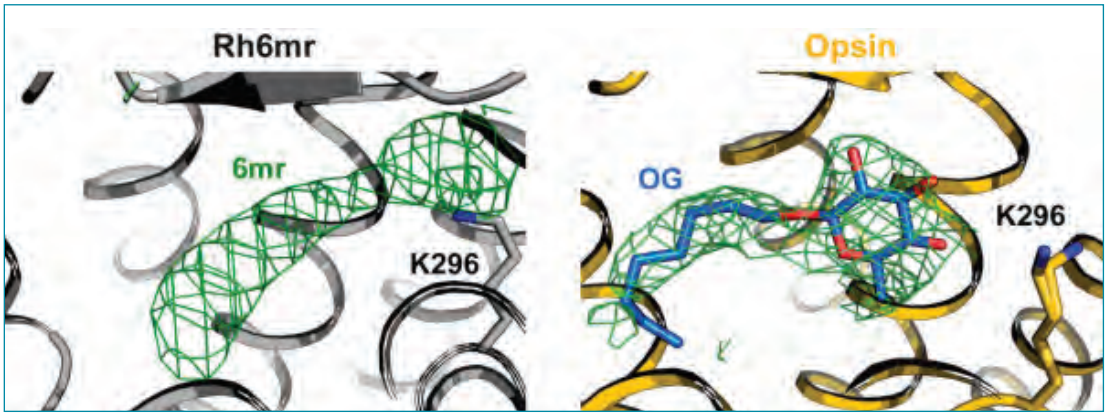
Crystal structures (insets) of several diverse antibodies from the VRC01 lineage. Ribbon representations highlight the third complementarity determining regions (red) and disulfides (green).

Macromolecular x-ray crystallography data collected at the Southeast Regional (SER) CAT beamlines at the APS were employed to investigate the development of VRC01, extraordinary antibodies that can neutralize about 90% of all strains of HIV. An understanding of how VRC01 antibodies are generated might ultimately lead to the ability to induce similar antibodies in HIV-infected people.

The researchers examined the crystal structures of several antibodies from the VRC01 lineage and identified significant differences in their amino acid sequences. They also tracked the development of the VRC01 B cell lineage and found that it involved hundreds of generations of B cells that evolve faster than HIV-1 (the predominant strain of the virus), allowing the development of VRC01 antibodies that can neutralize the virus effectively. However, during natural HIV infection, VRC01 does not develop into its mature form quickly enough to protect people from the virus.

The results of this study, therefore, have important implications in the development of a long-awaited HIV vaccine.

A Therapy for Improved Vision



Comparison of two rhodopsin binding pockets based on x-ray diffraction data obtained at NE-CAT at the APS. From S. Gulati et al., Proc. Natl. Acad. Sci. USA ***114****(13), E2608 (Published online March 13, 2017). © 2017 National Academy of Sciences.*

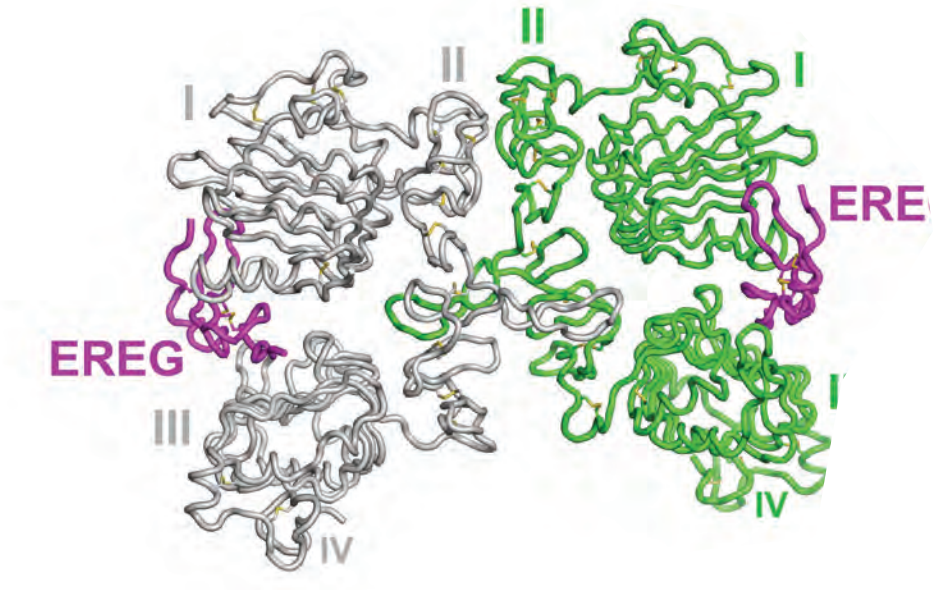
A new therapeutic opportunity for modified retinals that helps improve vision, and offers a major improvement over current therapeutics designed to perturb cell signaling in the eye, was aided by research at a Northeastern (NE) CAT x-ray beamline at the APS.

A light-sensing pigment found in everything from bacteria to vertebrates can be biochemically manipulated to reset itself, an important therapeutic advantage.

Researchers used a modified form of vitamin A, called "locked retinal," to induce the recycling mechanism and engage proteins central to human vision.

The targeted proteins include light-sensing rhodopsin, which belongs to the family of proteins — GPCRs — that sit in cell membranes and transmit external cellular cues into internal cell signaling pathways.

A Key Target for Cancer Drugs



The structure of the EGFR protein.

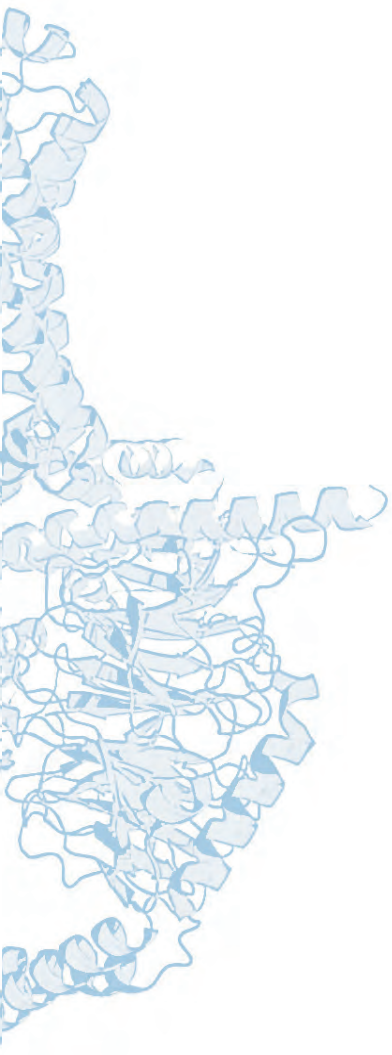
Many approved cancer therapies target a protein called "epidermal growth factor receptor" (EGFR) that regulates many crucial cellular processes and — when mutated — can promote the proliferation of tumor cells. Scientists, carrying out research at a GM/CA-XSD x-ray beamline at the APS, made a fundamental discovery about EGFR signaling that may open the potential for new types of cancer drugs.

Science has long known that growth factors activate EGFR by "stitching" two receptor molecules together. This paradigm has always suggested that the receptor has to be either "off" or "on," so all EGFR drugs have been designed to shut off the receptor and thus shut off proliferation. But a longstanding puzzle was that the EGFR is regulated by a total of seven growth factors, which can make the cell take different actions. How can those different actions be driven by a single binding (and activation) scenario?

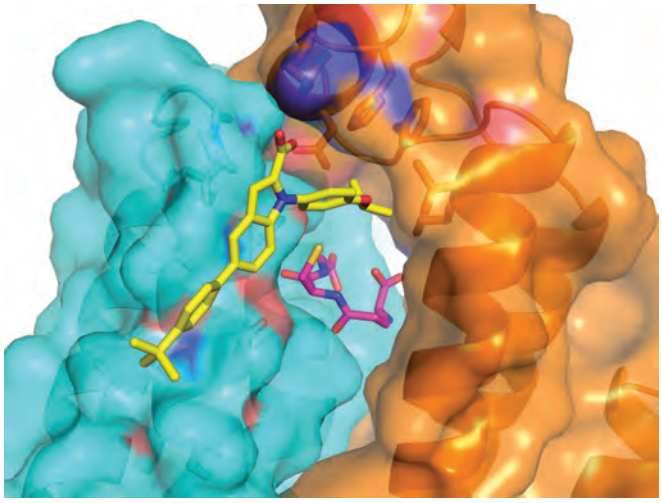
The researchers found that EGFR signaling is not just an on/off process controlled by stitching two receptors together. Rather, the growth factors can turn on the receptor in a spectrum of different ways, depending on the strength of the stitch and the timing of this binding. Instead of therapeutics that just shut off EGFR, new ones might be designed that encourage it to give a beneficial signal.

The spectrum of effects from different EGFR binding mechanisms also might help shed light on other biological mysteries such as the causes of liver cancer, where pathways that work in similar ways to EGFR signaling play major roles that have not been well explained.

Building a Better Aspirin



Science has been working for decades to improve upon the first non-steroidal anti-inflammatory drug (NSAID), commonly known as aspirin. Newer versions of NSAIDs such as ibuprofen, naproxen, and celecoxib are the mainstay of treatment for pain, from minor bumps and bruises to more serious chronic pain and inflammatory conditions such as arthritis and cancer, but these drugs also have gastrointestinal side effects and are associated with rare fatal adverse reactions.



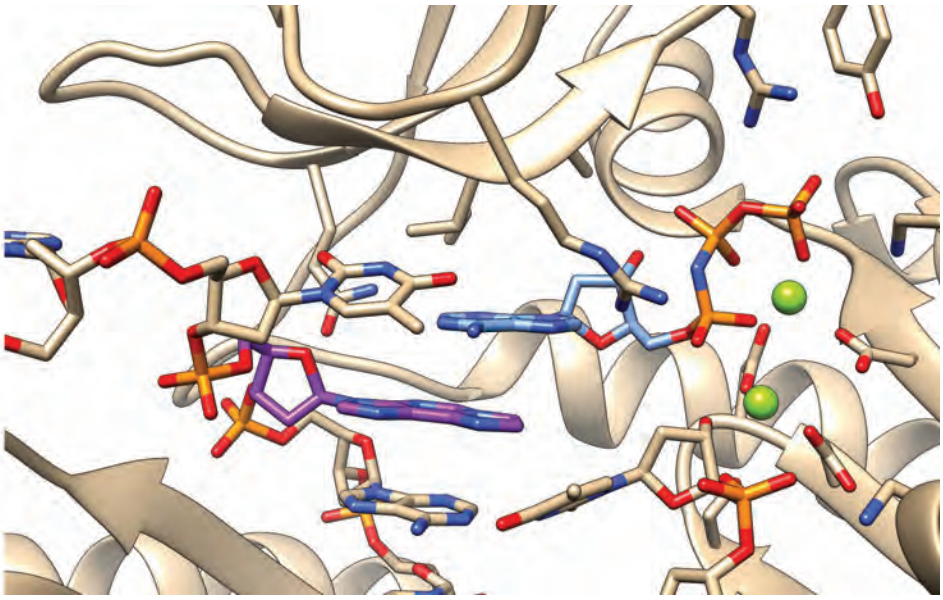
Representation of the mPGES-1 active site with an inhibitor shown in a yellow stick model and glutathione shown in a magenta stick model. Two of the three mPGES monomers that form the active site are shown in cyan and orange.

Researchers utilized the Lilly Research Laboratories (LRL) CAT x-ray beamline at the APS to study the structure of the microsomal prostaglandin synthase 1 (mPGES-1 enzyme) with the aim of providing a framework for the rational design of new molecules that can control inflammation and pain without troublesome side effects.

Their approach was to selectively inhibit an enzyme that generates a specific inflammatory lipid compound without blocking other lipids that are important in the regulation of blood clotting, blood pressure, and control of gastrointestinal integrity, thus eliminating the associated side effects that those lipids control.

These findings offer an opportunity for optimizing the interaction between the inhibitors and mPGES-1 to improve the action of potential drugs.

Bypassing DNA Damage



Structural basis of error-prone bypass of the etheno-dA DNA adduct by human polymerase revealed by the crystal structure of the ternary polymerase•DNA•dNTP complex trapped at the insertion stage.

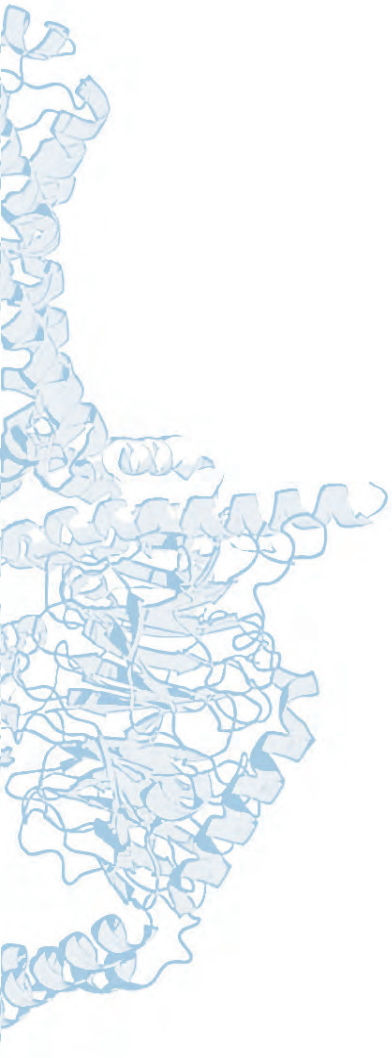
Cancer, aging, and a host of other diseases are linked to damage or "lesions" in DNA, the molecular blueprint for a cell. The body has developed a sophisticated machinery to deal with DNA damage. For example, a certain human translesion polymerase can bypass DNA damage caused by ultraviolet radiation.

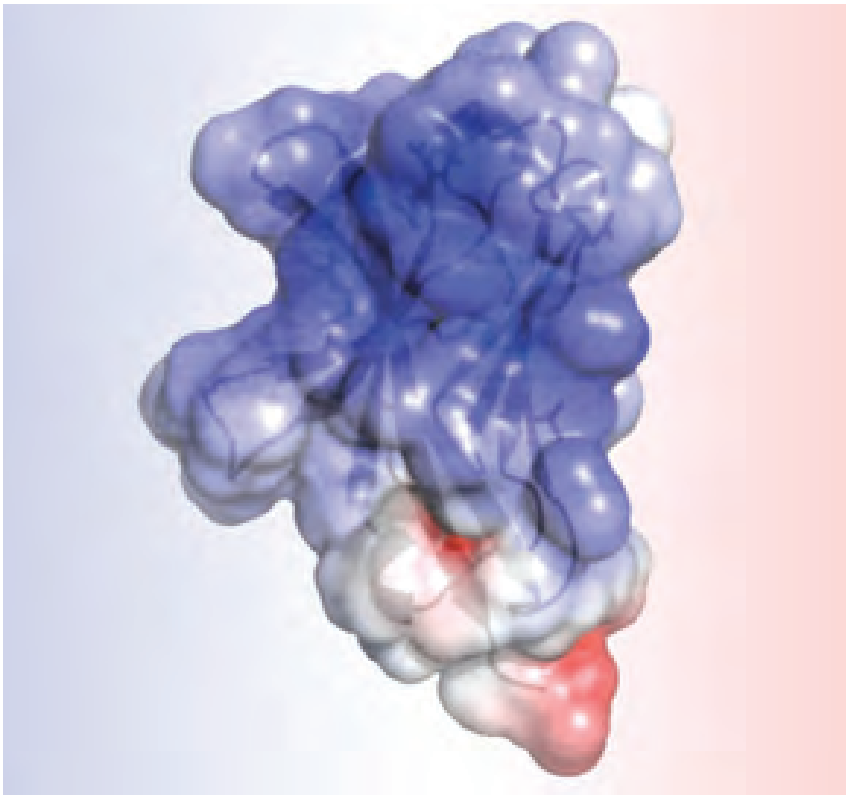
The polymerase can also bypass intentional damage inflicted by the anticancer drug cisplatin, leading to chemoresistance.

Sometimes the polymerase can get it wrong, leading to errors in the replicated DNA. Damage that takes the form of a segment of DNA bound to the cancer-causing chemical 1,N6-ethenodeoxyadenosine ("etheno") triggers error-prone bypass by polymerase.

To learn why the polymerase makes miscoded DNA in this case, researchers solved the structure of polymerase in complex with etheno-damaged DNA using x-ray data collected at the Life Sciences (LS) CAT x-ray facility at the APS. Their insights into how polymerases bypass DNA damage may pave the way to the discovery of inhibitors of translesion synthesis, helping chemotherapeautics such as cisplatin remain effective.

The Molecular Roots of Alzheimer's Disease





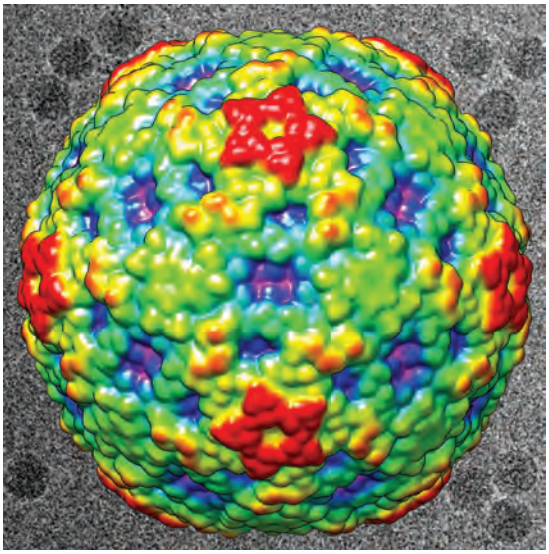
The structure of TREM2.

Scientists utilized the high-brightness x-rays from the APS at a SBC-CAT x-ray beamline to detail the structure of a molecule, TREM2, that has been implicated in Alzheimer's disease.

TREM2 also has been implicated in other inflammatory conditions, including chronic obstructive pulmonary disease and stroke, making the structure of TREM2 important for understanding chronic and degenerative diseases throughout the body.

Knowing the shape of the molecule — and how that shape may be disrupted by certain genetic mutations — can help in understanding how Alzheimer's and the other neurodegenerative diseases develop and how to prevent and treat them.

Treatments for Respiratory Disease



This color-coded image shows the surface view of enterovirus D68. The virus has stricken children with serious respiratory infections and might be associated with polio-like symptoms. Red regions are the highest peaks, and the lowest portions are blue. In the black-and-white background are actual electron microscopy images of the EV-D68 virus. Image: Yue Liu and Michael G. Rossmann (Purdue University)

Research at a BioCARS-CAT x-ray beamline at the APS showed that small modifications to the anti-viral drug pleconaril may make it an effective treatment against modern versions of enterovirus D68, which causes a severe respiratory disease.

Most enteroviruses are stabilized by a molecule that occupies a binding pocket found in the protective shell of the virus. When the virus binds to a human cell, this molecule is squeezed out of its pocket, destabilizing the virus. The virus then disintegrates and releases its genetic material into the cell, where it replicates and, ultimately, causes infection.

Researchers used the APS to determine the crystal structure of EV-D68 by itself and when bound to the anti-viral drug pleconaril, which they discovered was effective against the 1962 strain of the virus.

Comparing the crystal structures with and without pleconaril indicated that the drug displaces a fatty acid contained within the hydrophobic pocket of the 1962 strain. The results may suggest potential alterations to the drug to make it effective against current strains of the virus.

Today's Research for Tomorrow's Pharmaceuticals

- Bacterial cell survival depends on the integrity of its genetic information and the stability of replicated chromosomes during cell division. Bacteria that package genomic DNA as linear chromosomes face a special challenge: their ends are prone to damage from DNA degradation or aberrant repair reactions. The ends of the chromosomes fold into tight hairpins that protect the DNA while permitting accurate replication of genetic material at the chromosome ends. Research at BioCARS-CAT produced a clearer understanding of the process, which is important for the development of protelomerase inhibitors that may be useful in treating certain bacterial infections.
- Data collected at GM/CA-XSD showed how receptor-binding site (RBS)-directed antibodies bind to the viral protein hemagglutinin (HA) — the key target of antibodies that protect against the influenza virus, revealing important implications for understanding the mechanisms involved in the binding of RBS-directed antibodies with HA, as well as their application to the development of improved vaccine design.
- Studies at IMCA-CAT elucidating the interactions of enzymes that are central to ubiquitination (the addition of ubiquitin to a substrate target protein) are critical to understanding how the complex ubiquitin system works and to the rational design of drugs that target an ever-widening array of ubiquitin-related diseases.
- Researchers working at LRL-CAT have created the first atomic-level structural models of the protein Rumi in complex with a major signaling protein called Notch, which controls the expression of genes that help determine which cells should develop into specific cell types like skin, heart, or neurons. These models reveal the details of Rumi's interactions with Notch, paving the way for potential anti-cancer medications that target Rumi.
- Researchers using LS-CAT revealed the inner workings of the hepatitis C virus (HCV) RNA replication, and the way in which sofosbuvir (brand name Sovaldi®), a remarkably effective drug against HCV, interacts with an active site on HCV, potentially providing an avenue for the rational design of additional therapeutics against HCV.
- The structure of the human serotonin transporter in complex with serotonin-specific reuptake inhibitors, determined at NE-CAT, provides important new information about how antidepressants block serotonin binding and transporter activity, the possible role of known disease mutations, and allosteric regulation of the transporter, thus aiding in the design of small molecules capable of more-precise activity against a variety of neurological disorders.
- Research conducted at SER-CAT solved the structure of an enzyme (the laforin glucan phosphatase) responsible for the formation of insoluble glucan inclusion bodies that cause neuronal death, thus providing important insights into both the basis of Lafora disease and normal glycogen metabolism.
- Molecular x-ray crystallography experiments at SBC-CAT determined the first three-dimensional structure of the two-pore channel (TPC) voltage-gated ion channel protein in a closed conformation, providing an avenue for treatments that target TCPs in lysosomal diseases and Ebola.

MX Sectors at the APS

Sector 14: BioCARS-CAT is mainly supported by the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health (NIH) and is dedicated to the development of resources and facilities to foster frontier research in time-resolved macromolecular x-ray crystallography and time-resolved biological small-angle and wide-angle scattering. Watching macromolecules in action furthers our understanding of how macromolecules function, ultimately leading to advances in the cause, prevention, and treatment of diseases.

Sector 17 (beamline 17-ID): IMCA-CAT, dedicated to accelerating drug discovery research, operates a state-of-the-art structural biology synchrotron beamline for the pharmaceutical industry. The facility is optimized for high-quality, high-throughput macromolecular crystallography experiments, producing essential data for determining the structures of key components in structure-based drug design. The facility is funded by the pharmaceutical members of IMCA (Industrial Macromolecular Crystallography Association): AbbVie, Bristol-Myers Squibb, Merck, Novartis, and Pfizer, and operated through a contract with the Hauptman-Woodward Medical Research Institute. Data from IMCA-CAT have been crucial to the development of a significant number of therapeutics for the prevention and treatment of disease.

Sector 19: SBC-CAT, which is funded by the DOE Office of Biological and Environmental Research, operates a national user facility for macromolecular x-ray crystallography at the APS in order to advance and promote scientific and technological innovation in support of the DOE mission by providing world-class scientific research and advancing scientific knowledge. SBC-CAT is an important component of integrated biosciences and contributes to the expansion of existing programs and exploration of new opportunities in structural biology, proteomics, and genomics research with a major focus on medicine, bio-nanomachines, and biocatalysis that are highly relevant to health, energy resources, a clean environment, and national security.

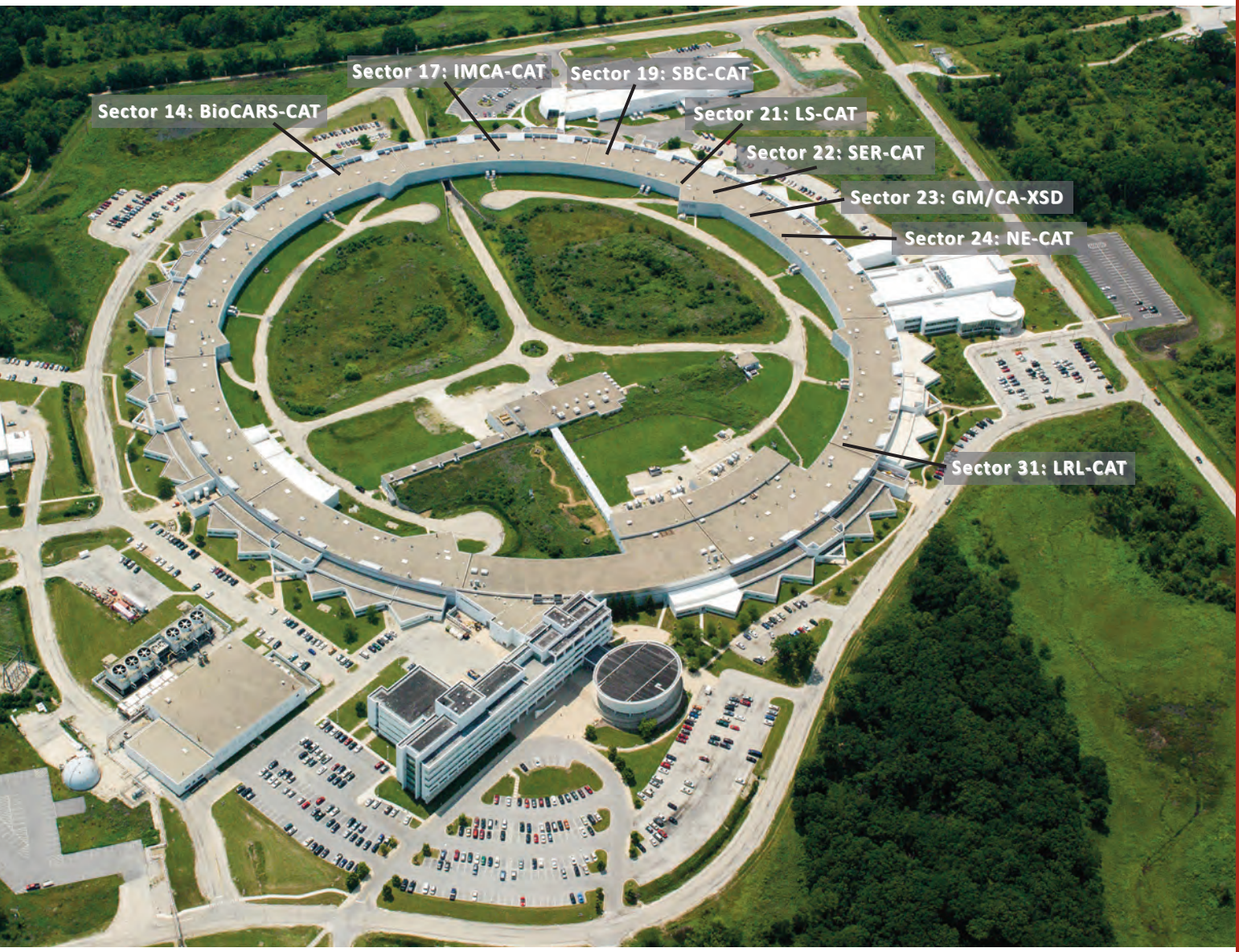
Sector 21: LS-CAT, which is supported by the Michigan Economic Development Corporation and the Michigan Technology Tri-Corridor, provides macromolecular x-ray crystallography resources for those with a need to determine the structure of proteins via access to state-of-the-art x-ray diffraction facilities.

Sector 22: SER-CAT, which is operated by the University of Georgia and funded by supporting institutions (www.ser-cat.org/members.html), provides third-generation x-ray capabilities to macromolecular x-ray crystallographers and structural biologists in the southeastern region of the U.S. Emphasis is placed on structure determination, high-resolution structural analyses, large unit cells, drug design, structural genomics, soft x-ray data collection, and next-generation beamline automation.

Sector 23: GM/CA-XSD, which is located organizationally within the APS, operates a user facility for structural biology with synchrotron beamlines specializing in intense, tunable micro-beams for crystallography to determine the structure of proteins and other macromolecules at the forefront of biological research, with an emphasis on problems in structural genomics and structure-based drug design. The scientific and technical goals of GM/CA-XSD emphasize streamlined, efficient throughput for a variety of sample types, sizes, and qualities representing the cutting edge of structural biology research. GM/CA-XSD is funded in whole or in part with federal funds from the National Cancer Institute and NIGMS of the NIH.

Sector 24: NE-CAT is managed by Cornell University for its seven member institutions (http://necat.chem.cornell.edu/aboutus/Organization/Members.htm). NE-CAT, which is supported primarily by a grant from NIGMS of the NIH with additional financial support from the member institutions, operates an x-ray crystallographic research facility designed to address the most demanding and complex diffraction problems in structural biology and is organized to allow its operation to be driven by the requirements of its users.

Sector 31: LRL-CAT, which is operated by Eli Lilly and Company, is dedicated to the determination of protein structures and the analysis of the interactions between potential pharmaceutical compounds and a protein of interest to further research into the causes, prevention, and treatment of disease.



The APS facility at Argonne National Laboratory. Sectors comprise one or more x-ray beamlines. Locations of the macromolecular x-ray crystallography sectors (see facing page) are indicated in the photo above.

Access to Beam Time at the APS

All beam time at the APS (either non-proprietary or proprietary) can be requested each cycle through the web-based Beam Time Access System. A proposal describes an experiment and identifies the experimental team. A beam time request on a proposal identifies where and when the researchers want beam time. A proposal can have several beam time requests. For information and inquiries about accessing beam time at the APS, contact Dr. Dennis Mills, Argonne Deputy Associate Laboratory Director for X-ray Science • dmm@aps.anl.gov • (630) 252-5680

For more information about the APS, please contact Dr. Stephen Streiffer, Argonne Associate Laboratory Director for Photon Sciences and Director, Advanced Photon Source • aps-director@anl.gov • (630) 252-7990

On the front cover: Advanced Photon Source user Prof. Brian Kobilka (Stanford University) preparing a protein crystal for study in one of the x-ray beamlines operated by the National Institute of General Medical Sciences and National Cancer Institute structural biology facility at the Advanced Photon Source. Kobilka and his colleague Prof. Robert Lefkowitz (Duke University) were awarded the 2012 Nobel Prize in Chemistry for research largely carried out at this facility.

Fast Facts about the APS

Scientific disciplines investigated at the APS:

Pharmaceutical research; materials and chemical science; environmental, geological, and planetary science; physics; polymer science; biological and life science; atomic, molecular, and optical physics; and the properties of nanoscale materials.

Some benefits accruing from research at the APS:

Clues to the causes of and treatments for a multitude of diseases including AIDS, and toxic threats such as anthrax.

Better materials for lithium-ion batteries and other energy-related technologies.

The path to more efficient designs for fuel-injection systems.

A greater understanding of human physiology.

Ways of eliminating and remediating environmental depredations.

Insights about conditions at the center of the Earth, the causes of earthquakes and volcanoes, and the composition of cosmic dust.

A nearly endless array of new information about materials that support the development of practical applications such as advanced digital storage media, more efficient lighting, environmentally friendly refrigerants, methods for increasing the durability of man-made structures, and the characterization of nanostructures whose sizes are measured in atoms, to name but a few.

The APS facility:

Electrons cannot go faster than the speed of light, but getting them close to it produces some amazing effects, one of which is length contraction: The electrons in the APS storage ring have an energy of 7 billion electron volts), so they are traveling at over 99.99999999% the speed of light.

There are over 2000 conventional electromagnets and 16 pulsed electromagnets in the APS electron accelerators.

Over 700 beam-position monitors, 600 corrector magnets, and 80 computer systems monitor and correct the electron orbit, steering x-ray beams to within a fraction of the width of a human hair.

More than 120 programmable logic controllers monitoring over 25,000 signals comprise radiation interlock systems protecting personnel and equipment.

The APS has five 1-megawatt radio frequency (rf) power systems (the equivalent of 5000 microwave ovens) that are used to accelerate and maintain high-energy electron beams in the storage ring.

The storage ring rf systems contribute to a combined accelerating voltage equal to a 16-million-volt power supply.

APS rf systems produce more rf power than the combined output of every radio and television station in the city of Chicago.

The superconducting detectors that collect data from the interaction of high-brightness APS x-rays and the sample being studied operate at temperatures colder than outer space.

The outer diameter of the APS experiment hall is 1225 feet; slightly less than the height of the Willis (Sears) Tower in Chicago (1454 feet).

Experiment hall construction required 56,000 cubic yards of concrete (equal to a football-field-sized block 30 feet high); 5000 tons of structural steel (enough for 3500 mid-size cars); 2,000,000 linear feet (380 miles) of electrical wire; and 190,000 feet of pipe for water, steam, drainage, and HVAC.

Total floor space of all APS buildings is 1,042,811 feet2.

Facility construction started in spring 1990; research started in the fall of 1996.

Total APS construction and project cost at completion in 1995 was $812 million (1995 dollars).

The number of APS employees is approximately 450.

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