

FIGHTING DISEASE

WITH THE ADVANCED PHOTON SOURCE

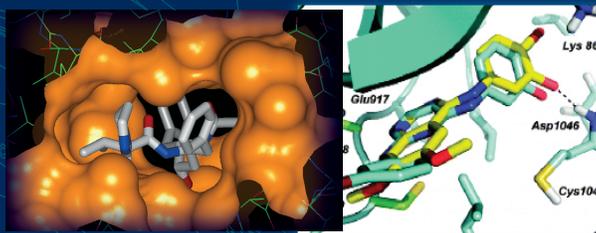
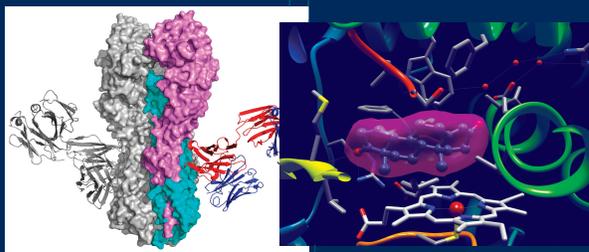
The U.S. Department of Energy Office of Science's Advanced Photon Source (APS) at Argonne provides the high-energy, high-brightness x-ray beams that scientists utilize in determining the structures of biological proteins associated with a multitude of diseases, leading to new or improved pharmaceuticals and treatments. Researchers using the APS solve more protein structures than users of any other synchrotron x-ray light source. All three recipients of the 2009 Nobel Prize in Chemistry utilized the APS (and other x-ray light sources) to reveal the atomic structure of the ribosome, the molecular factory that synthesizes thousands of proteins that make up every living cell.

The APS played a crucial role in the development of the Abbott Laboratories pharmaceutical Kaletra®, which in 2002 became the most-prescribed drug in its class for AIDS therapy; and in the development of the anti-cancer drug pazopanib, which is marketed as Votrient™ in the U.S. and Europe by its developer, GlaxoSmithKline, for the treatment of advanced renal cell carcinoma.

One biological mechanism associated with breast cancer is the inappropriate activation of cancer cell growth by naturally occurring estrogen in a woman's body. Research at the APS provided important insights that will enable researchers to seek ways of improving estrogen-binding inhibitors.

Just by changing its shape, a single protein, known as a prion, is responsible for the damage inflicted by diseases such as human Creutzfeldt-Jakob and Mad Cow. Aided by the APS, the Stanford Synchrotron Radiation Lightsource, and the Advanced Light Source, researchers have achieved a significant advance in our understanding of the infectious power of the prion.

A genetically engineered form of parathyroid hormone, approved for patients with osteoporosis who are at high risk for fracture, requires daily injections and is associated with significant risks. Research at the APS is adding to our understanding of the structure of hormone-receptor interaction, which may lead to strategies for the development of more tolerable and convenient therapies for osteoporosis and other bone disorders.



Autism, the developmental disability that affects a person's ability to communicate and interact with others, responds well to early diagnosis and intervention. But autism can and does impose hardships on those with the disability and on their families. Researchers using the APS have added to our understanding of autism's root causes by precisely mapping the locations of two neurological mutations that have been implicated in this disease.

Enzymes are essential molecules that catalyze and direct cellular reactions. Researchers utilizing the APS, the National Synchrotron Light Source, the Cornell High Energy Synchrotron Source, and the Advanced Light Source have discovered an important structure for a yeast enzyme involved in fatty acid synthesis. The research team's work constitutes immense progress in terms of our understanding of how fatty acid synthesis works and how it can lead to disease.

Research at the APS has found a neutralizing antibody with broad efficacy against multiple strains of the influenza virus. This discovery will guide ongoing research to develop a long-lasting, cross-protective flu vaccine as well as new antibody-based therapies.

The atomic structure and probable mutation mechanism of the most common cancer-causing mutant enzyme have been uncovered by research at the APS, offering direction to ongoing efforts to design targeted inhibitors that can be used for treatment.

The Advanced Photon Source at the U.S. Department of Energy's Argonne National Laboratory provides this hemisphere's brightest high-energy x-ray beams for research. Scientists and engineers using the APS help assure a bright future for our nation by carrying out research that promises to have far-reaching impact on our technological and economic competitiveness, our health, and our fundamental knowledge of the materials that make up our world.

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Kaletra® and Votrient™: Researchers from Abbott Laboratories (Kaletra®); and GlaxoSmithKline, Phenomix Corp., Medical University of South Carolina, Serenex Inc., and Takeda San Diego (Votrient™) utilized the Industrial Macromolecular Crystallography Association Collaborative Access Team (IMCA-CAT) 17-ID beamline at the U.S. Department of Energy's (DOE's) Advanced Photon Source (APS) at Argonne. **Kaletra®:** See: Vincent Stoll et al., *Bioorg. Med. Chem.* **10**, 2803 (2002). **Correspondence:** stewart@abbott.com. **Votrient™** See: Philip A. Harris et al., *J. Med. Chem.* **51**(15), 4632 (2008). **Correspondence:** philip.a.harris@gsk.com. IMCA-CAT is an organization charged by the Industrial Macromolecular Crystallography Association (IMCA) to design, build, and operate an experimental facility at the APS. IMCA is an association of pharmaceutical companies committed to the use of macromolecular crystallography as a tool in drug discovery and product development. IMCA-CAT is operated through a contract with the Hauptman-Woodward Medical Research Institute.

Estrogen-binding inhibitors and breast cancer: The structure of the enzyme aromatase was solved to 2.9-Å resolution by researchers from the Hauptman-Woodward Medical Research Institute and the Roswell Park Cancer Institute utilizing the Structural Biology Center (SBC) CAT beamline 19-ID at the APS. See: Debashis Ghosh et al., *Nature* **457**, 219 (8 January 2009). **Correspondence:** ghosh@hwi.buffalo.edu. This research was supported in part by grants GM62794 and GM59450 (to D.G.) from the National Institutes of Health. See also: "Inhibiting Estrogen-Dependent Breast Cancer," *APS Science 2009*, p. 90, ANL10/-06 (Argonne National Laboratory, May 2010).

Prions: Researchers from the University of California, San Francisco, and Vanderbilt University utilized the BioCARS beamline 14-ID at the APS, beamline 4-2 at the Stanford Synchrotron Radiation Laboratory, and beamline 12.3.1 at the Advanced Light Source to obtain diffraction patterns from infectious prions, compared them with diffraction patterns from genetically engineered prions, and discovered important differences, both in structure (as determined by diffraction studies) and in heterogeneity (as determined by electron microscopy). See: Holger Wille et al., *Proc. Nat. Acad. Sci. USA* **106**(40), 16990 (2009). **Correspondence:** gerald.stubbs@vanderbilt.edu. This work was supported by National Institutes of Health grants NS064, AG010770, and AG02132; the Fairchild Foundation; the G. Harold and Leila Y. Mathers Foundation; and a Jane Coffin Childs postdoctoral fellowship (to D.W.C). See also: "The Power of Proteins: Prion Diseases Demystified," *APS Science 2009*, p. 60, ANL10/-06 (Argonne National Laboratory, May 2010).

Osteoporosis: Researchers from the Van Andel Research Institute utilized the Life Sciences (LS) CAT beamline 21-ID-D beamline to solve the structure of the binding domain of the parathyroid hormone-receptor complex to a resolution of 1.95 Å. See: Augen A. Pioszak and H. Eric Xu, *Proc. Nat. Acad. Sci. USA* **105**, 5034 (1 April 2008). **Correspondence:** eric.xu@vai.org. This work was supported by the Jay and Betty Van Andel Foundation; Department of Defense Grant W81XWH0510043; Michigan Economic Development Corporation Grant 085P1000817; and National Institutes of Health Grants DK071662, DK066202, and HL089301. See also: "Hot Dogs and Healthy Bones: The Parathyroid Hormone-Receptor Complex," *APS Science 2008*, p. 103, ANL-08/24 (Argonne National Laboratory, May 2009).

Autism: Utilizing the Southeast Regional CAT 22-BM-D and LS-CAT 21-ID-D beamlines at the APS, researchers from the Northwestern University Feinberg School of Medicine have succeeded in visualizing the extracellular portions of a murine neuroligin-neurexin complex to a resolution of 2.4 Å. See: Xiaoyan Chen et al., *Nat. Struct. Mol. Biol.* **15**(1), 50 (January 2008). **Correspondence:** x-he@northwestern.edu. Partial support for this research was provided by the Brain Tumor Society and National Institutes of Health Grant 1R01GM078055. See also: "How the Brain Makes Connections," *APS Science 2008*, p. 72, ANL-08/24 (Argonne National Laboratory, May 2009).

Yeast enzyme: A research team from Yale University utilized the Northeastern CAT beamline 24-ID-C and the SBC-CAT beamline 19-ID at the APS, and beamlines X25 at the National Synchrotron Light Source, A1 at the Cornell High Energy Synchrotron Source, and 8.2.1 and 8.2.2 at the Advanced Light Source to take a close look at the structure of fatty acid synthase, an extremely complicated enzyme. See: Ivan B. Lomakin et al., *Cell* **129**, 319 (April 20, 2007). **Correspondence:** yong.xiong@yale.edu, eatherton@csb.yale.edu. This work was supported in part by the U.S. National Science Foundation with grant No. DMR-0453804 and by an award from the Research Corporation, the DOE-BES under contract No. DE-FG02-05ER46202 and a Grant-in-Aid for Science provided by the Japan Society for the Promotion of Science. See also: "Architecture of a Vital Cellular Machine," *APS Science 2007*, p. 100, ANL-07/25 (Argonne National Laboratory, May 2008).

Antibody therapies: Antibody-antigen crystals imaged by researchers from The Scripps Research Institute and the Crucell Holland BV using the General Medicine and Cancer Institutes CAT 23-ID-B beamline at the APS demonstrated that the antibody targets a highly conserved portion of the influenza A virus. See: Damian C. Ekiert et al., *Science* **324**, 246 (10 April 2009). **Correspondence:** wilson@scripps.edu. This work was supported in part by National Institutes of Health grant AI-058113 (I.A.W.) and a predoctoral fellowship from the Achievement Rewards for College Scientists Foundation (D.C.E.) and the Skaggs Institute. See also: "A Potent Antibody against Influenza," *APS Science 2009*, p. 74, ANL10/-06 (Argonne National Laboratory, May 2010).

Mutant enzyme: Using data collected at the Lilly Research Laboratories (LRL) CAT 31-ID beamline at the APS, researchers from The Johns Hopkins University uncovered the atomic structure and probable mechanism of the most common oncogenic mutant of signal transduction enzyme *PIK3CA*. See: Diana Mandelker et al., *Proc. Nat. Acad. Sci. USA* **106**, 16996 (October 6, 2009). **Correspondence:** gabelli@jhmi.edu. Use of the LRL-CAT beamline was provided by Eli Lilly & Company, which operates the facility. Support for this research was provided by the Virginia and D.K. Ludwig Fund for Cancer Research and National Institutes of Health Grants CA43460, GM07309, and GM07184. See also: "Closing in on a Common Cancer Mutation," *APS Science 2009*, p. 78, ANL10/-06 (Argonne National Laboratory, May 2010).