Neutron crystallography aids drug design

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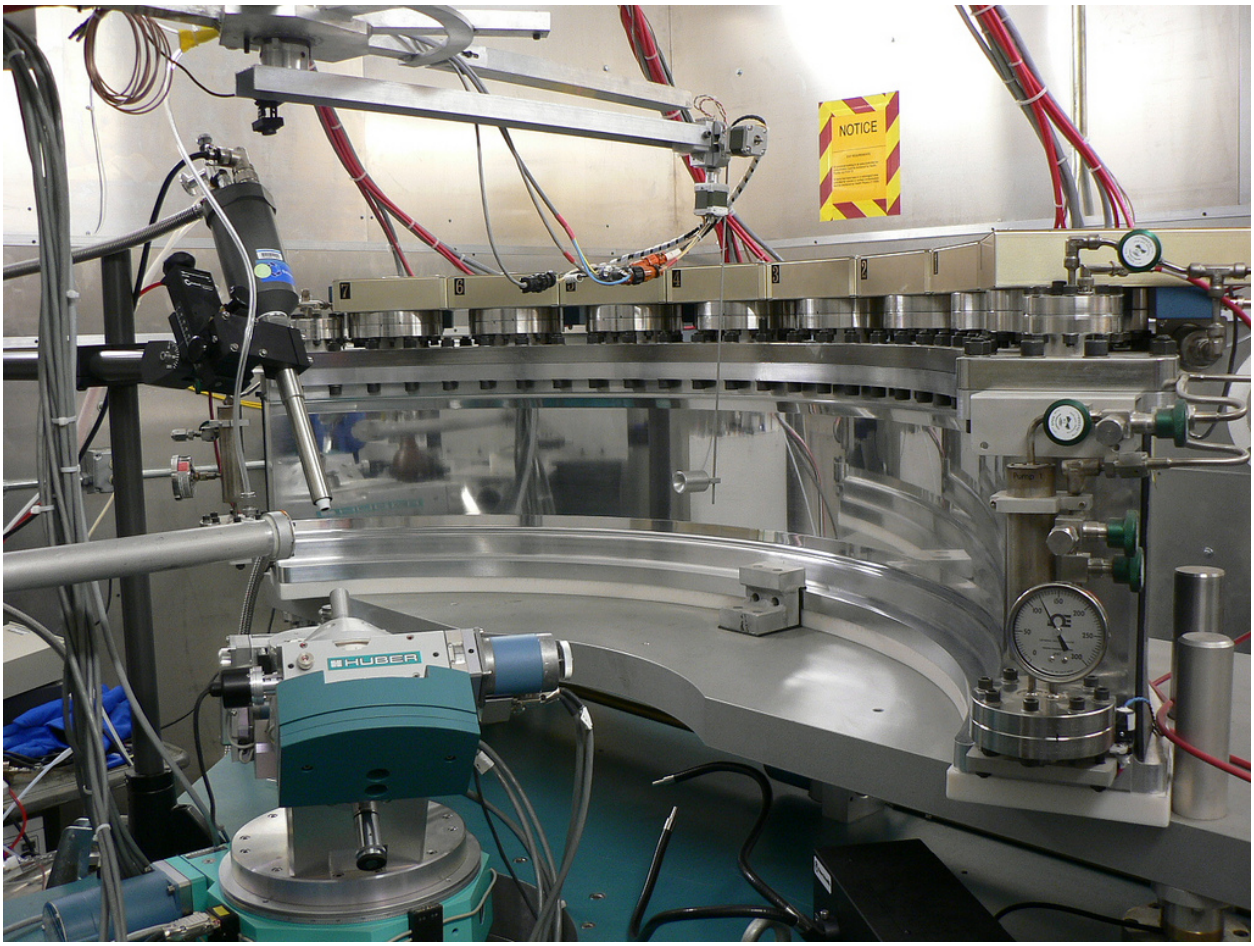

Precisely tailored pharmaceuticals could reduce medical side effects

LOS ALAMOS, N.M., October 9, 2012—Researchers at Los Alamos National Laboratory have used neutron crystallography for the first time to determine the structure of a clinical drug in complex with its human target enzyme. Seeing the detailed structure of the bonded components provides insights into developing more effective drugs with fewer side effects for patients.

The atomic details of drug binding have been largely unknown due to the lack of key information on specific hydrogen atom positions and hydrogen bonding between the drug and its target enzyme. In this research, scientists used the drug acetazolamide (AZM) -- a sulfonamide drug that has been used for decades to treat a variety of diseases such as glaucoma, altitude sickness, and epilepsy. But when the drug binds with the wrong form (called an isoform) of the target enzyme for the disease, it can produce unpleasant side effects in patients (so called “off-target” drug binding).

Enter neutron crystallography – the use of neutron scattering to paint a picture of these bonds.

By providing precise information on hydrogen bonding between target enzymes and the treatment drugs (carbon anhydrase II targeted by AZM in this study), the research enables improvements in targeted binding with fewer side effects. Neutron crystallography offers a new and unique insight into these details, providing imagery of the exact structures involved.

Scientists from Los Alamos National Laboratory collected the data at the Protein Crystallography Station using neutrons from the accelerator at the Los Alamos Neutron Science Center, LANSCE. The Journal of the American Chemical Society published the research, “Neutron Diffraction of Acetazolamide-Bound Human Carbonic Anhydrase II Reveals Atomic Details of Drug Binding” available online at http://pubs.acs.org/doi/abs/10.1021/ja3068098.

Researchers include Zoë Fisher and Mary Jo Waltman of the Los Alamos Bioenergy and Environmental Science group, Andrey Kovalevsky formerly of Los Alamos and currently at Oak Ridge National Laboratory, and Robert McKenna, David Silverman and Mayank Aggarwal of the University of Florida.

The U.S. Department of Energy Office of Science funds the Protein Crystallography Station at LANSCE. Zoë Fisher received partial support through a Laboratory Directed Research and Development (LDRD) Early Career Award.

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