An End to Lost Crystals?

Nearly 100 years ago Australian-born Lawrence Bragg and his father William Bragg invented a way to use X-rays to reveal crystal structures. Today in Melbourne, X-ray crystallography is one of the most important techniques being used at the Australian Synchrotron, with protein chemists and biologists lining up for access.

Proteins are the action molecules of life. As enzymes, they control all biochemical reactions, and they operate by means of their structure. That's why the bulk of research into new drugs and molecular biology nowadays involves determining the structure of proteins – typically using synchrotron X-rays for protein crystallography.

This month we talk with two of the early users of the Australian Synchrotron: Melbourne's Michael Parker and Auckland's Ted Baker.

Julian Adams at work on the protein crystallography beamline. Julian is the principal scientist for the beamline.
Photo: Colin Page

Better drugs to defend against bird flu and parasites, a way of stopping the body from attacking cancer drugs, new strategies for treating epilepsy and Alzheimer's disease – the projects of protein crystallographer Michael Parker and his colleagues link an intimate knowledge of protein structure with drug design. And they all demand access to a synchrotron.

Until the Australian Synchrotron opened for business in the middle of last year, Parker and his team at the St Vincent's Institute in Melbourne used the Advanced Photon Source in Chicago for their work. Now increasing amounts of their research can be undertaken closer to home.

And that translates into more than just convenience, says Parker, a Federation Fellow who came back to Australia from the European Molecular Biology Laboratory in Heidelberg, Germany. "If you are working at a synchrotron overseas, you have to generate your crystals here, then put in an application for time. It can take more than a year to arrange. And in the US, for instance, the time they give you will often be on a national holiday when there's no one else around.

"And then you have to get your crystals from Australia to America, which involves a trip on a plane and negotiating Customs. I know of other groups whose crystals have all been lost in the process. With the Australian Synchrotron we can get things done in weeks and months, and without the hassle of the air trip and Customs. It makes us much more competitive."

The team is impatiently awaiting the opening of a second beamline. The in-vacuum undulator will be able handle the very small crystals that much of their research generates. "The Australian Synchrotron will be one of very few places in the world to have such a facility," Parker says.

The Protein Crystallography Beamlines

The Australian Synchrotron has two beamlines devoted to protein crystallography – a high throughput bending magnet beamline and an in-vacuum undulator beamline for much finer work with smaller samples.

Both essentially fire highly focused, intense beams of X-rays at protein crystals. The X-rays interact with and are deflected by the electrons in the crystallised protein. The diffraction patterns detected after the X-rays pass through the crystal can be translated back into molecular structures with the help of sophisticated computer software.

The bending magnet beamline has been in action since the end of June. The in-vacuum beamline will open in mid 2008.

Visit www.synchrotron.org.au for more information.

Fighting an Old Enemy

There's a nasty new version of a very old enemy stalking the globe – extreme drug-resistant tuberculosis (XDR-TB). Defined less than 2 years ago, the new form is virtually untreatable by available drugs. This infectious disease is already responsible for more than two million deaths per year worldwide.

It makes Prof Ted Baker's work at the Australian Synchrotron all the more urgent as he looks for TB's Achilles' heel. Baker, director of the Maurice Wilkins Centre of Molecular Biodiscovery at the University of Auckland, and his colleagues are seeking potential leads for new drugs to treat TB. Already they have turned up several candidates.

"The Synchrotron is absolutely critical to us in all this work," Baker says. "Until recently we have been using the facility at Stanford University near San Francisco. Now we'll have much more frequent access." Baker's group is using protein crystallography to determine the three-dimensional structures of proteins necessary to the survival of *Mycobacterium tuberculosis*, the bacterium that causes TB.

The researchers are looking for ways to block, alter or otherwise inhibit the action of these proteins, thus killing the bacterium. "And if the proteins are not present in humans, so much the better," says Baker. "There's less chance of adverse side-effects from any potential drug."