Synchrotron lights the path for Canadian pharmaceutical development

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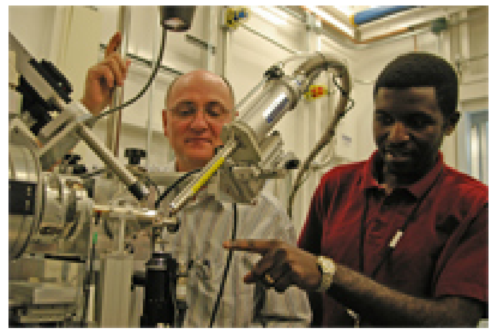
All life is an intricate dance of molecules, a subtle choreography that is slowly yielding its secrets for new medicines and environmentally-friendly products thanks to a powerful new research tool at the Canadian Light Source (CLS) at the University of Saskatchewan.

The Canadian Macromolecular Crystallography Facility – CMCF for short – is the only place in the country where researchers can use synchrotron light to determine the shapes of molecules.



Beamline scientists Pawel Grochulski and Michel Fodje explain the business end of CMCF-I at the Canadian Light Source synchrotron. Protein crystals are loaded into a holder and precisely aligned with a microscope before being exposed to X-rays to determine their structure. *Photo by Angela Hill.*

“The drugs in the anti-AIDS cocktail were all developed by this method,” says U of S biochemistry professor and CMCF team leader Louis Delbaere.

Australian researchers used synchrotron light to develop the anti-flu drug Relenza; other teams are targeting proteins associated with glaucoma and diabetes in search of treatments.

To understand how protein crystallography works, hold up a crystal in a sunbeam and watch the pattern as the light is diffracted onto a wall. With the proper computer software, this pattern could tell you the shape of the original crystal.

At CMCF, immensely bright and precise synchrotron X-rays shine through tiny protein crystals, creating diffraction patterns that tell researchers the shape of the molecule and even the location of the atoms within it.

It’s a powerful tool. For example, one of Delbaere’s projects is aimed at creating a new type of herbicide designed to inhibit plant enzymes. Because these enzymes don’t exist in humans, it would be non-toxic. Biotechnology companies, particularly those in pharmaceuticals, use synchrotron light extensively in their research. This fact motivated German pharmaceutical multinational Boehringer Ingleheim to be among the first to sign on with funding for the CLS project when it was launched in 1999.

So far, use of CMCF is limited to the beamline design team members: so-called “friendly users” who are helping to test the beamline in its early startup phase in exchange for access to the powerful research tool.

“We’re commissioning it right now,” Delbaere says, “There are always bugs to fix, but we’re getting more good data off the line all the time.”

The first successful research results from CMCF have already been obtained, and Delbaere estimates that by January 2007 they’ll be accepting routine applications for beam time.

Beamline scientists Pawel Grochulski and Michel Fodje are hard at work to make this happen. There are actually two CMCF beamlines, known in the acronym-rich language of the synchrotron floor as CMCF-I and CMCF-II. Grochulski is in charge of CMCF-I, while Fodje leads CMCF-II, which will begin construction in April 2007.

Grochulski says CMCF offers several advantages. Canadian scientists don’t have to cross international borders with their delicate crystals. Coaxing reluctant proteins into crystal form is an art unto itself, requiring advanced knowledge, experience, and even luck. Even with the right “recipe” a crystal can take weeks to grow.

Another advantage is precision. CMCF is among the best: down to about 20 microns – about one fifth the thickness of a human hair.

CMCF-II will be a complementary facility, with essentially the same capabilities, but with the ability to test many more samples in the same amount of time. Fodje uses the analogy of auto manufacturing: CMCF-I is like a Rolls Royce factory – it operates more slowly with lots of hand-tweaking, but is precise and delivers very high quality results. CMCF-II is like a Toyota factory – more automated, with higher throughput, but also producing high quality results.

Fodje joined the CLS in April 2006 from Sweden’s MAX-lab national synchrotron, drawn by the chance to get in on the ground floor of Canada’s largest science project in a generation.

“It’s a good opportunity to be part of bringing this facility to a world-class level,” he says. “This was the main incentive that brought me here.”

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