From the ESRF to the pharmacy

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The development of drugs is the ultimate aim of the pharmaceutical companies at the ESRF.

Pharmaceutical companies are increasingly turning to synchrotron light in the development of drugs.

Next time you go to the chemist with a prescription, remember synchrotron light. Maybe the drug you will be buying has its origins in structural-biology experiments carried out at one of the world's light sources.

Pharmaceutical companies are regular industrial users at the ESRF, where they study complex molecules and their binding to ligands with potential inhibitor effects. This is one of the most important steps in the design of medicines. In the process of drug design, a target protein is crystallized and its atomic structure revealed using X-ray crystallography. The structure is then used as an aid in the design of potential drug molecules. The most promising ones are then tested both *in vitro* and *in vivo*, and after successful clinical trials they appear in pharmacies and clinics.

The proof of the pudding is in the eating: a new drug to combat type 2 diabetes might be on the market soon. This form of the condition results from the body's ineffective use of insulin. It often results from excess body weight and physical inactivity, and there are an increasing number of people affected by it.

Pharmaceutical company Sanofi-Aventis is carrying out clinical trials for a new medicine for type 2 diabetes, the development of which has involved X-ray crystallographic structure solution using data collected at the ESRF. Researchers crystallized the ligand-binding domain of the nuclear receptor protein PPAR delta with agonist molecules (molecules that increase the activity of the protein). Increased PPAR delta activity is considered to have a positive effect in the treatment of the condition. X-ray diffraction data collected at the ESRF allowed the researchers to understand the structural basis of interactions between PPAR delta and the agonist molecules, and they showed that the agonist-binding pocket of the protein is large and exhibits plasticity. This information provided the key for the team to develop novel agonists with improved properties.

"We have successfully used the ESRF for the last decade," explains Magali Mathieu, head of protein crystallization at Sanofi-Aventis' Vitry site. "It has happened in the past that the results from experiments at the ESRF have made us rethink the possible composition of a product," she adds.

Mathieu is a "veteran" user, having been coming to the facility for the last 10 years. Sanofi-Aventis was the first user of the MXpress service. Mathieu's team sends frozen samples to the synchrotron, and ESRF staff analyse them. "It has been a crucial development for us, especially in routine experiments. We all monitor progress from our end: chemists, technicians, biologists, drug designers...It is a bit like *Big Brother* – we can see how the experiment is going from our lab," she says. "We still come to Grenoble twice a year to carry out experiments and catch up with beamline and software developments, but MXpress is our preferred option in general," she adds.

Multidisciplinary research

Another big fan of MXpress is Michael Schäffer, CEO of Crelux, based in Germany. This is a service company for pharmaceutical and biotech companies that outsource their crystallographic activities. Despite being a newcomer to the ESRF – 2008 is the first year that Crelux has used the facility – Schäffer claims that results are already extremely positive. "We are even considering a visit to the ESRF so that we can collect our own data and solve many structures in one go," he says.

Mathieu and Schäffer agree that a big part of the success of MxPress is the team involved at the ESRF: Elspeth Gordon and Stéphanie Monaco. "You need to trust the scientists who are collecting the data, otherwise it does not work," explains Mathieu.

The use of synchrotron light by drug companies is well established, and they represent about 25% of user activity at the ESRF's macromolecular crystallography beamlines. Mathieu explains that the capabilities of the beamlines have improved a lot: "In the past we would have considered a crystal of 100 μm just big enough; today the definition of 'big enough' is 30 μm."

Denis Zeyer, CEO of French biotech company Alix, a contract research organisation that provides services in fragment- and structure-based drug discovery, sees the future of synchrotrons as bright: "Synchrotron sources can't be detached from structural biology. At the ESRF we can test 100 samples per shift, which is huge compared with what we can do with classical sources. The idea in the Purple Book of having a dedicated beamline to test crystals and another for data collection is excellent."

Schäffer demonstrates the health of synchrotron sources with his own example: "Our company was created three years ago and we are now self-sustaining. There is an increasing trend from pharmaceutical companies to outsource because they are cutting down their discovery departments. There is also a rise in the demand for structure solution, and synchrotron sources play a significant role in that."

In terms of scientific discoveries, Mathieu, Schäffer and Zeyer agree on the next big challenge for structural biology: the routine determination of the structures of membrane proteins will be the key to discovering many new medicines. Membrane protein structure solution is a field currently dominated by academic groups, but pharmaceutical companies hope to jump on the bandwagon once recent technological advances can be implemented. Schäffer thinks that this will happen soon: "It's a matter of effort to solve this kind of structure, and in only 10 years we may be solving them systematically; I believe it will not take a long time."

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