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Conference Report

Olten Meeting – A Contact Forum for Biotech

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Abstract: The annual Olten Meeting organized by biotechnet switzerland and the Swiss Biotech Association is a place for biotech specialists from the universities and Empa to meet up with people from the private sector to network and initiate joint projects. A look at the presentations given at the event on 19 November 2008.

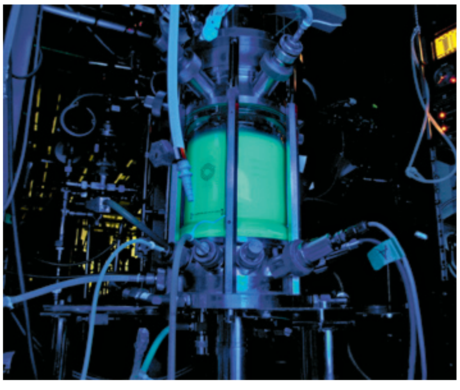
Keywords: Biotechnology · biotechnet switzerland · Swiss Biotech Association

Fluorescing Reporter Molecules

Up to now, cell-culture technicians have believed that it would be impossible to record the expression of a target protein inside a reactor because the expressed protein would have to undergo extensive processing before it could be quantified. This is now set to change thanks to a new measurement technology developed by Professor ***Bernhard Sonnleitner*** and his team.

Sonnleitner, a professor in biochemical engineering at Zurich University of Applied Sciences (ZHAW) in Wädenswil, modified optical measurement probes of the kind used to determine the turbidity of a cell suspension to make them into fluorescence probes. These can measure the fluorescence of reporter molecules inside the reactor – *i.e. in situ* – completely automatically, non-invasively and in real time. This method is based on *Green Fluorescent Protein* (GFP) from a jellyfish, which is expressed as a fusion protein at the same time as the target protein in, for example, cells of *Pichia pastoris*, a methylotropic species of yeast. The researchers stimulate GFP-expressing cells with blue light and the cells in turn emit longer-wave green light. The fluorescence is transmitted to a detector using a fibre-optic receptor probe.

In this project, which is being supported by the federal innovation promotion agency CTI, the scientists in Wädenswil are also working with their industrial partner Aquasant to investigate whether they can record other fluorescent proteins and expand the measurement method to include strains other than the conventional model organism *P. pastoris*. Sonnleitner is confident: "This measuring technique provides quantitative information about protein expression during the process and could therefore develop into a useful platform technology which would permit better control of upstream and downstream processes."



Professor Sonnleitner's team at the ZHAW has developed a non-invasive method for measuring fluorescent reporter molecules. The picture shows modified *P. pastoris* cells in a bioreactor that are being stimulated to emit light by a UV lamp. (Photo ZHAW)

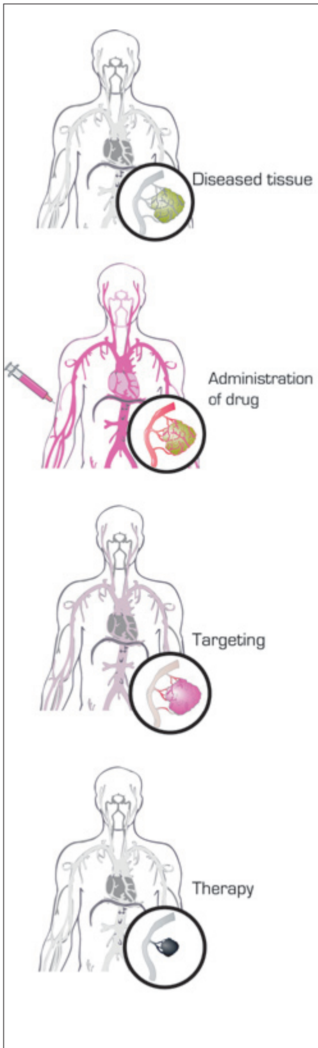
Focusing on Molecular Structure

Structure-based drug discovery is the main focus of the activities being pursued by Dr. ***Michael Hennig***, Vice-Director of Pharmaceutical Research at Hoffmann-La Roche Ltd. This involves exposing crystallized proteins to synchrotron light and determining their atomic structure from the resulting refraction pattern. The ideal tool for this is the Swiss Light Source, the synchrotron source operated by the Paul Scherrer Institute, which has a Pilatus detector capable of providing data in seconds. Knowledge of the structure of compounds makes it easier to characterize the results of high-throughput screening (HTS) and hence to select a promising lead compound. Optimization of the lead compound involves improving its binding to the target protein and its molecular properties. In this way, structural knowledge helps to optimize the active substances in existing medicinal products and to develop new active substances.

One example is the protein DPP-IV which cleaves and thus inactivates GLPS1 (glucon-like peptide), thus preventing blood glucose from normalizing. If this peptidase – dipeptidyl peptidase IV, to give it its full name – can be inhibited, it should be possible to achieve higher concentrations of GLP1 in diabetic patients and thus to lower their blood glucose levels. "Elucidation of the structure of the target molecule helped to accelerate the identification of molecules that inhibit DPP-IV and to broaden the basis of this work," is how Michael Hennig sums up the situation. "This enabled us to optimize substances that were very different in structural terms and ultimately to test them in the clinical setting."

Aromatase Inhibitors to Treat Breast Cancer

Professor ***Ajay S. Bhatnagar***, former head of endocrine research at what was Ciba-Geigy and is now Novartis, is working on the impact of laboratory developments on patients' lives. His special field is aromatase inhibitors in the therapy of breast cancer. Aromatase plays a critical role in oestrogen synthesis, and the enzyme is therefore regarded by experts as a good target for selective inhibition. It was on this basis that the drug Letrozol was developed, in the expectation that maximum suppression of oestrogen would lead to maximum suppression of the tumour. The first and second-generation aromatase inhibitors were not satisfactory because they were not selective enough, but the third-generation compounds are now inhibiting oestrogen production effectively, reducing circulating oestrogens by more than 95% in some cases without affecting other steroid signalling pathways. Modern aromatase inhibitors combine a low rate of side effects with high selectivity and efficiency, and this prevents the hormone-sensitive tumour from growing. "The extent to which aromatase is inhibited determines the clinical success of treatment," Ajay Bhatnagar explains. "This is why the development of aromatase inhibitors represents a paradigm shift compared with



Dario Neri, Professor of Biomacromolecules at ETH Zurich, is researching antibodies which, when loaded with a cancer treatment, seek out cancer cells and kill them. (Picture ETHZ)

the previous therapeutic standard with antioestrogens."

Antibodies Armed with Active Substances

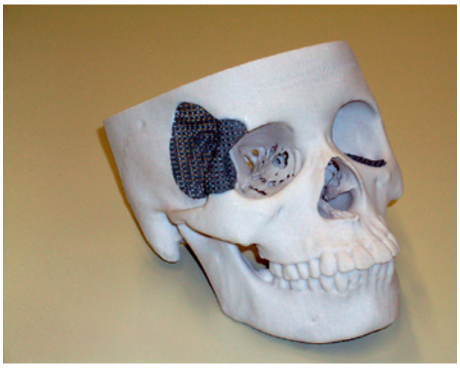
Dario Neri, Professor of Biomacromolecules at the Institute of Pharmaceutical Sciences at ETH Zurich, is working on the binding and catalytic properties of proteins as a new approach to cancer therapy. One of the main focuses of his work is monoclonal antibodies as tumour killers. "Cancer cells form new blood vessels in a process known as angiogenesis, and this supplies the tumour with oxygen and nutrients *via* the circulation," Neri explains. "What we need to do is stop this process which is vital for the tumour's survival, and this will stop its growth." His team is therefore loading active substances into monoclonal antibodies. The antibodies make straight for the blood vessels that supply the tumour and destroy them. No harm is done to blood vessels that are not associated with the tumour.

Neri and his team are producing their first successful results with three monoclonal antibodies that are being tested clinically in the therapy of kidney and pancreatic cancer. Dario Neri won the SWISS BRIDGE Award in October 2008 for his work. The award is conferred on scientists pursuing outstanding research in the fight against cancer.

Individual Structures Made from Titanium

The annual incidence of craniocerebral trauma is around 8,000 per million inhabitants. If malformations, bone degeneration and the removal of tumours are added to this figure, the need for individual implants becomes clear. Researchers at the Institute of Medical and Analytical Technology (IMA) at the University of Applied Sciences of Northwest Switzerland (FHNW) in Muttenz are tackling the problem using layer-building processes similar to the rapid prototyping method that has been used in technical applications for over 20 years. They derive three-dimensional data sets from the computed tomograms of a patient, for example, and use the data to produce anatomical models. The overriding considerations here are biocompatibility and biofunctionality. The success of integrating a titanium implant into the bone depends on its surface topography and surface chemistry. A rough surface on the implant ensures that it will be anchored well in the bone and thus have excellent biomechanical stability. This is why the team at the IMA is modifying the surfaces of patient-specific implants by sandblasting, spark anodization, electropolishing, anodization or etching so that they can be used in trials. Implant materials used for clinical applications have to be capable of dealing with considerable mechanical stress, so their structural properties are systematically investigated using metallographic structural analysis and dynamic mechanical testing under simulated real-life conditions. A technique known as *Selective Laser Melting* is used particularly for implants required in surgery of the mouth, jaw and face.

The advantages of the method over established manufacturing methods are obvious. Medical rapid prototyping provides flexibility, enables complex implants with an internal structure to be created, is fast, and enables individual pieces to be produced without tools straight from CAD or medical imaging data. It is also economical, ideal for small numbers of parts since it involves no programming or tooling costs, and also makes efficient use of expensive materials. "Work is still at the research stage," comments Professor ***Michael de Wild*** from the IMA. He believes that custom-made implants have a bright future. "Market studies are forecasting double-digit growth rates!"



Professor Michael de Wild's group at the FHNW is producing individualized structures made of titanium using layer-building processes. The picture shows a skull implant produced using rapid prototyping. (Photo FHNW)

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biotechnet – Networking Knowledge in Biotechnology

biotechnet is the expert network of the Swiss Universities of Applied Sciences in the field of biotechnology and brings together expertise in research and development and initial and continuing training. Its main focus is on bioanalytics, the production of biomolecules and tissue engineering. Biotechnet offers companies one-stop customized support to enable them to move into new markets with their innovations. This includes research collaborations, consultancy on bioprocesses and product development, and access to state-of-the-art knowledge. The network is also the ideal partner for initial and continuing training activities, and organizes highly specialized courses tailored to the individual needs of the company.

For further information, please contact Dr. Daniel Gygax, Professor of Bioanalytics at the FHNW School of Life Sciences and President of biotechnet.

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