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Conference Report

Biotech Research: Bringing Better Therapies to the People

The Olten Meeting 2009

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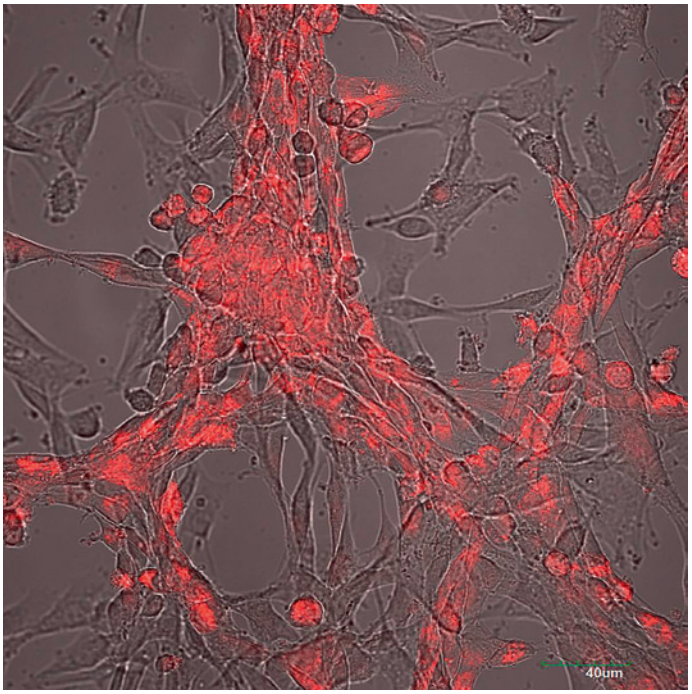
Abstract: Biotech specialists met on November 19, 2009 for their traditional 'Olten Meeting'. On their agenda: to orientate biotech research to more efficient diagnostic instruments and therapies to lead the fight against incurable diseases. A look behind the scenes of current research in Swiss biotechnology.

Keywords: *biotechnet* · Biotechnology · Swiss Biotech Association

Biotechnology has the potential to provide powerful tools to develop new vaccines and therapies and to improve the availability and quality of diagnosis, treatment and care. That is the message we can take along from the Olten Meeting 2009, the traditional exchange of ideas organized by the Swiss Biotech Association and *biotechnet*, which connects partners from industry and science in challenging projects.

Protoporphyrin Reveals Malignant Cells

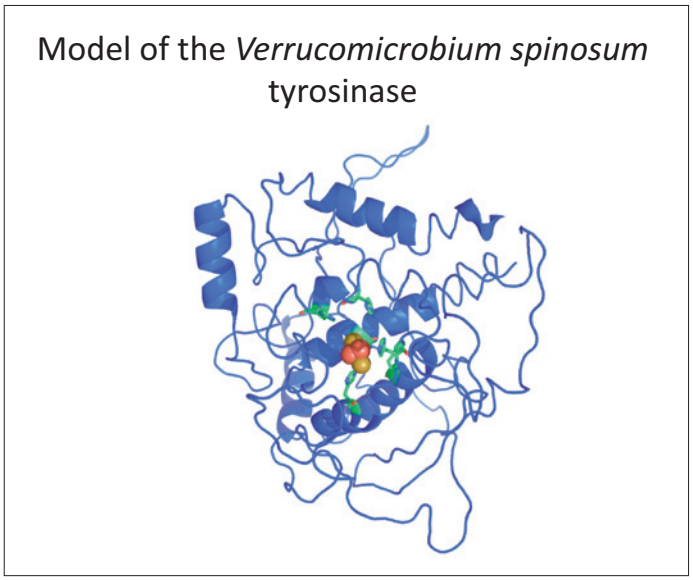
A good example of an innovative way to treat brain tumours is shown in a cooperation between neurosurgeons, cell biologists at the Zurich University of Applied Sciences (ZHAW), physicists at the University of Applied Sciences Northwestern Switzerland (FHNW) and the surgical division of Leica Microsystems AG. Malignant gliomas are one of the most aggressive brain tumours. Generally, they are surgically resected and patients are treated by a combinatory radio- and chemotherapy. Nevertheless, survival rates remain very low. The use of aminolevulinic acid (ALA) is a promising approach to achieving better clinical results due to the ability of ALA to be metabolized into the fluorescent product protoporphyrin IX. "PplX accumulates in tumour cells and can be visualized during the operation by a special microscope with a fluorescence filter. It also can be irradiated with visible light for photoactivation. This leads to the generation of reactive oxygen species and therefore the induction of cell apoptosis", explains Professor ***Vera Luginbühl***, head of the pharmaceutical technology at the ZHAW. She has been working together with Dr. ***Martin Hefti***, neuro surgeon at the University Hospital Schleswig Holstein, for a few years and establishes cell culture models to evaluate *in vitro* effects of ALA on human glioblastoma cells. In 2007, the research group received the *Synthes Award* for the *in vitro* studies of effects of the 5-aminolevulinic acid on five different glioblastoma cell lines. Aim of the new project is the development of an imaging system, integrated in the surgeon's microscope, which quantifies the fluorescence intensity, visualizes the results cartographically and offers the possibility of superimposing this view with a 'live' microscope image. By this means, the surgeon obtains a rational decision support, which increases precision and sensitivity and helps to avoid interpretation mistakes. "Not only does the new method improve the clinical results substantially, but – thanks to a better treatment method – the hospital can realize considerable cost savings." For the industrial partner the measuring system offers a good chance of consolidating his or her leading market position and opens promising perspectives on a future application in the photodynamic therapy (PDT).



Vera Luginbühl: Protoporphyrin IX enrichment in human glioma cells. Confocal laser scanning microscopy, magnification 600x. (Source: ZHAW)

Keep it a Secret – and Make Money

It is known that the enzyme tyrosinase catalyses the production of melanin pigments from tyrosine and contributes to the browning of fruit and hyperpigmentation in skin. New tyrosinases for biocatalysis and biomaterials are the domain of Dr. ***Linda Thöny***, head of the biomaterials group at Empa. "Tyrosinases catalyse in nature the bio synthesis of the black pigment melanin from the amino acid tyrosine", explains Linda Thöny. "But they can also use other phenolic substrates and are therefore interesting candidates for depollution or as biosensors for phenols." Tyrosinase is also able to associate tyrosin residuals in polypeptides with other polypeptides or material in free amino groups, for instance chitosan. But Linda Thöny, who has also worked as a patent attorney, reminds her colleagues to be careful with the publication of scientific results. "Clarify precisely which part of your work you want to make public; don't hesitate to consult a patent attorney – and remember that scientific research is not only related to winning laurels but also to earning a lot of money!"



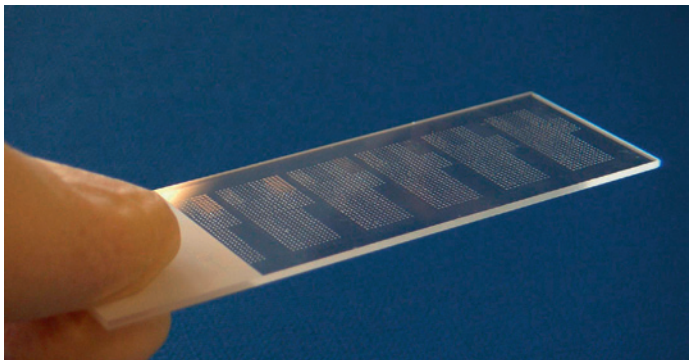
Linda Thöny: Tyrosinases are bi-copper oxygenases, which in nature catalyze the biosynthesis of the black pigment melanin from the amino acid tyrosine. However, they can also oxidize other phenolic substrates, which is why they are interesting enzymes for decontamination of toxic substances or as biosensors for phenols. (Source: Empa)

Enzymes – Efficient Catalysts for Biochemical Reactions

One of the research topics of Professor ***Jean-Louis Reymond*** at the Department of Chemistry and Biochemistry of the University of Bern concerns high-throughput screening (HTS) enzyme assays. Such assays are essential to identify catalytically active species libraries of catalytic antibodies, enzyme mutants and synthetic catalysts. His group is working on fluorogenic substrates and product sensor systems for enzymes of industrial relevance such as hydrolytic, redox and C–C-bond forming enzymes. Of particular industrial interest is the development of methods for enzyme activity fingerprinting. "Fingerprinting consists of measuring the activity of an enzyme with several substrates simultaneously to obtain an activity pattern", explains Jean-Louis Reymond. "This pattern can be used as a fingerprint as different enzyme product different patterns." The realized microarrays for fingerprinting are useful for classifying enzymes by their function as well as for quality control and identification. The studies on enzymes make sense as they constitute more than one third of all naturally occurring proteins. They catalyze chemical reactions with exquisite specificity and rate acceleration. Enzymes are useful in manufacturing and medical care, serve as targets for drugs where they act as their inhibitors. "Enzyme assays are key analytical tools for discovering and using any enzyme or inhibitor", sums up the biochemist, who worked at the Californian Scripps Research Institute. "With such HTS assays we can test thousands of samples per day in a miniaturized and economic format at reduced cost."

Innovative Diagnostic Tests for a Better Life

More than six million people around the world have to live with anticoagulation. Reasons therefore are cardiac valve replacement, atrial fibrillation, thrombosis or inherited coagulopathy. Although a regular self test of blood coagulation is for these patients of vital importance, it should not affect their living conditions too much. With the CoaguChek S system, a new generation of a handheld meter to test the coagulation status, the Diagnostics Division of F. Hoffmann-La Roche AG created a simple, fast and convenient way



Jean-Louis Reymond: A microarray for fingerprinting lipases. (Source: DCB Uni BE)

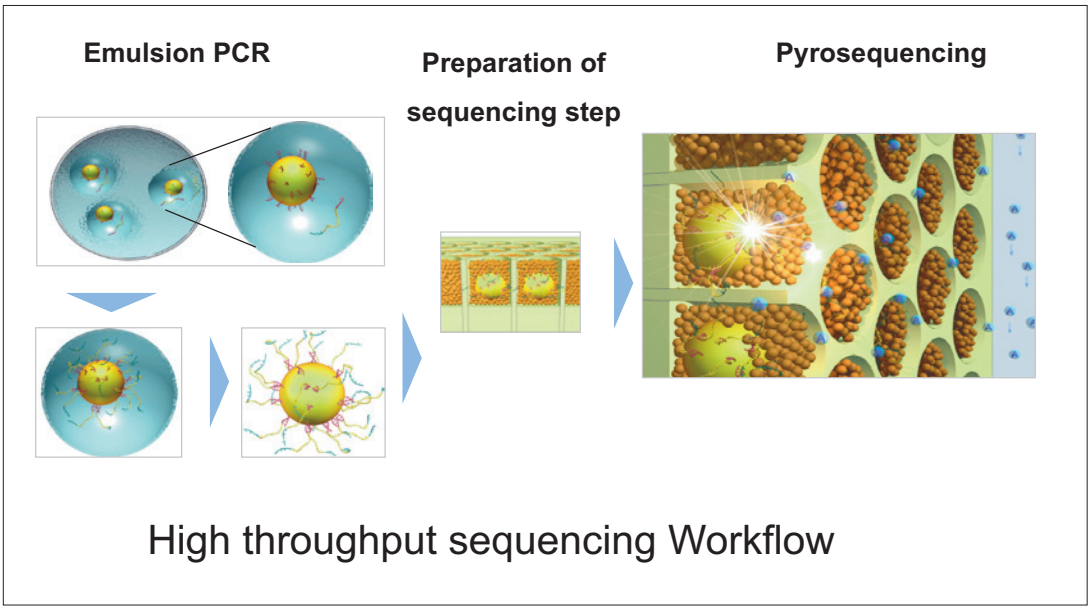
for patients to directly monitor their INR result. They only need a fingerpick, a drop of capillary blood and in one minute the INR result is available to help the physician to successfully monitor the therapy. "This self test reduces mortality by two-thirds", explains Dr. ***Gerd Grenner***, Chief Technology Officer at Roche Diagnostics. "Efficient diagnostic tools are today crucial to detect diseases in an early state, to identify possible risks and to determine the adequate therapy. But they have to be adaptable to everyday life: The personalized diagnostics are trendsetting."

We note a particular need for early diagnosis in oncology. The sooner a tumor can be detected, the better are the chances of healing. Particularly promising are new diagnostics tests that combine different tumor markers. As experience shows, one biomarker is often not capable, in case of complex diseases like rheumatoid arthritis, of detecting the disturbance. However, combinations of different markers can describe a large part of disease factors. "For the time being we are developing a highly sensitive blood test combining six different markers, which enhances the sensitivity from 30% for a single marker to 70% for the combinatory tests. Crucial is not the 'fitness' of one single marker, but the question of how much information they can all give. The best combination of markers needs not imperatively contain the best single marker."

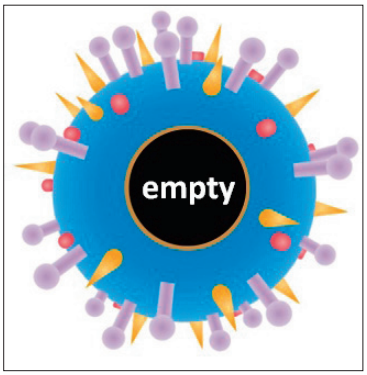
Pioneer work is also done by the Roche scientists with a protein microarray chip operated with 'nano-spheres', tiny polymeric balls with only 100 nm in diameter. Each one contains several thousand molecules of fluorescent dyestuff, which can be excited with near infrared. The chip could open up new applications in oncology, cardiology, allergy and diabetes. "The testing of different markers on the same tissue would simplify the test, increase the consistency of the results and reduce cost." Nanotechnology-based high-throughput sequencing enables new diagnostic tests in organ transplantation, AIDS therapy and predisposition testing in cancer (see Figure).

How to 'Outwit' a Protective Barrier

Why do we have to torture ourselves by swallowing or painfully injecting medications? A question asked by many chronic patients compelled to take medicine regularly. It is also a fact that our liver, a very powerful detoxification system, degrades a part of our orally taken drugs and therewith reduces their efficiency. Certainly, the skin, our most important organ, could be an attractive alternative for drug transport. However, it has the function of a protective barrier, difficult to break through. Dr. ***Martin Fussenegger***, Professor for Biotechnology and Bioengineering at the Department of Biosystems at the ETH concocted a sophisticated plan. His trick is to embed living transgenic CHO cells, which contain a specially designed genetic network, in a gel capsule and to implant it into the skin. The network generates the SEAP protein. When deploying a



Gerd Grenner: High-throughput sequencing workflow. (Source: Roche Diagnostics)



Corinne John: Virus simulator with different proteins on its surface, but without any dangerous genetic information inside. (Source: Redbiotec)

special cream on the skin, a commercially available milking grease blended with phloretin, the transgenic cells begin to produce the desired active agent inside. The activator phloretin, found in the flesh and skin of apples, is particularly good at getting through the skin barrier. It belongs to the polyphenol group and acts as an antioxidant, protecting cells and body chemicals against damage caused by free radicals. "The phloretin binds in the transgenic CHO cells on a modified *Pseudomonas putida* transporter system and controls the formation of a phosphatise", explains Martin Fussenegger, who named the System PEACE (synthetic mammalian phloretin-adjustable control element). When developing the system, the scientist had no particular disease in his sights. But one thing is sure: "The PEACE-controlled target gene expression could foster advances in biopharmaceutical manufacturing as well as gene- and cell-based therapies."

The Art of Quickly Creating a New Vaccine

The swine influenza A (H1N1) was a new virus, which is why no swine flu vaccine was immediately available to prevent infection. Within only seven months a vaccine was developed, tested and approved, in November 2009 the first doses arrived at doctor's office and clinics. "That's amazingly rapid, but much too late to prevent a pandemia", states Dr. ***Corinne John***, CTO at Redbiotec AG. The Zurich-based company is specialized in the fast-track production of high quality protein complexes and multi-protein virus simulators in unprecedented short time. The origin of the Redbiotec core competencies is the MultiBac Technology, a reliable baculovirus system developed at the ETH Zurich and licensed exclusively for Redbiotec. With this protein complex production platform the company realizes Virus-Like Particles (VLP) in a very quick and extremely powerful way. These complex empty virus 'shells' are composed of different special proteins and serve as biological virus simulators. They look like natural viruses but are not infectious. That means, researchers can use them instead of real viral pathogens and make experiments or simple drug testing without protective suits and outside the high security laboratory. The Redbiotec crew also uses the virus simulators as their own vaccine candidates. For the time being their pipeline comprises simulators for seasonal influenza viruses, avian flu viruses H5N1 and the human papillomavirus (HPV), which infects the epidermis and mucous membranes of humans, and can lead to cancers of the cervix. "The pressure on the price and the time to market is very high", states Corinne John. "But with this new generation of protein-based pharmaceuticals the odds are in our favour to treat most different cancer and viral diseases in a much more targeted, rapid and efficient way."

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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