doi:10.2533/chimia.2011.100 Chimia 65 (2011) 100–103

Conference Report

Biotech in Medicine – The Topic of the Olten Meeting 2010

Elsbeth Heinzelmann, Journalist science + technology

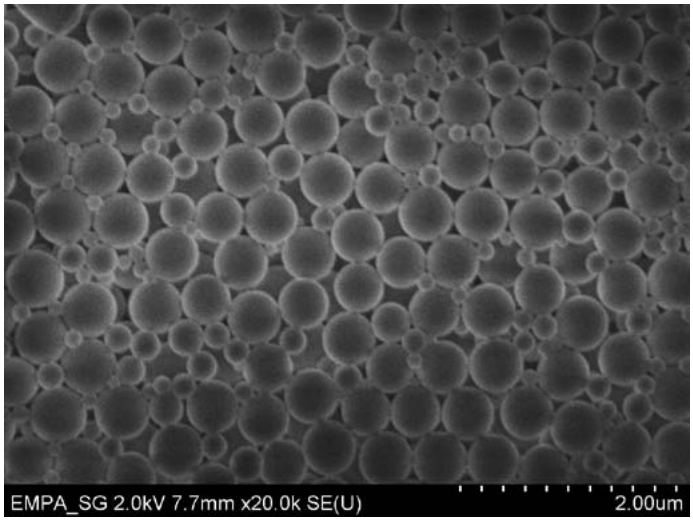
Abstract: Since 1998, the *biotechnet* – the national network of competence in biotech research – has been helping partners from industry to access excellence in R&D, giving them optimal support at low cost. Its annual 'Olten Meeting' is a dynamic hub for companies and research institutes as it highlights the latest trends in biotech. On November 24, 2010, the topical subject was biotech in medicine.

Keywords: *biotechnet* · Biotechnology · Swiss Biotech Association

The *biotechnet* looks back on a successful year. In November 2010, the Swiss Academy of Engineering Sciences (SATW) held its 'Transferkolleg' on Synthetic Biotechnology, co-organized by biotechnet, and granted 16 out of 34 biotechnet projects. *Biotechnet* has continued to support and to sponsor project ideas, up to now for a project volume of 40 Million CHF. For the Summer School 2011, *biotechnet* could gain the support of Professor Roderich Süssmuth to hold this annual training on topical biotechnologies at the Technische Universität Berlin. Thanks to financing by the Gebert Rüf Stiftung, the *biotechnet* could establish the Competence Center 'Tissues for the development of active agents' at the ZHAW in Wädenswil. For the annual 'Olten Meeting' of *biotechnet*, its President, Dr Daniel Gygax, brought together speakers experienced in biotech for medicinal purposes.

Human Placenta – Barrier for Nanoparticles?

Billions of nanoparticles surround us, including wind-borne sea salt. A forest can contain up to 50'000 particles, a city street about 100'000. But with the development of nanotechnology and engineered nanoparticles used, for instance, in medicine we really should consider what they get up to in our bodies. That is the question asked by Dr. ***Peter Wick***, Co-head for Material-Biology Interaction at Empa St. Gallen. Together with scientists at the University Hospital Zurich he investigates the human placenta. This endocrine organ acts as a barrier between the maternal and the fetal circulation and helps to exchange substances between the mother and her unborn child. The Empa biologist added fluorescent polystyrene nanoparticles ranging from 50 nm up to 500 nm in diameter to the maternal circulation and observed if they passed into the fetal circulation. Polystyrene is the perfect material for this purpose as it is easy to detect and does not cause stress to the surrounding tissue. As the study revealed, particles below 200–300 nm penetrated the fetal circulation while bigger ones could not cross the placenta barrier. "We are not really surprised by this result, but we have to further investigate and find out the mechanisms by which the particles are transported across the barrier", comments Peter Wick. "When we understand how the transplacental transfer into the human placenta works, we could probably use them as tiny vehicles to transport drugs into the circulatory system of an unborn child for therapeutic purposes." The understanding of these mechanisms could also help to administer medication for pregnant women like analgesics or anti-inflammatory drugs in a safe way, without any risk of harm for the unborn. (*www.empa.ch*)



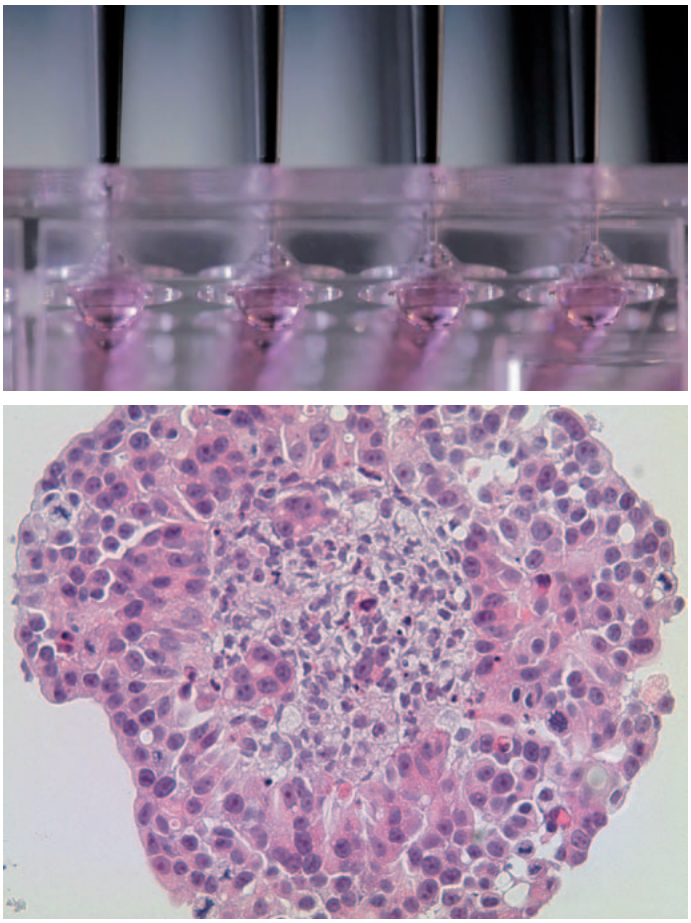
At the Empa laboratories in St. Gallen, Dr. Peter Wick and his crew investigate whether particles of polystyrene (in the picture 500 nm diameter) can cross the placental barrier and affect the fetus. Polystyrene is the ideal material for this purpose as it is easy to detect and does not cause stress to the surrounding tissue. (Source: Empa)

Pioneering Spirit in Microtissue Engineering

InSphero AG is the industrial partner of the ZHAW in the 'Kompetenzzentrum Gewebe für Wirkstoffentwicklung' and a leading supplier of organotypic, biological microtissues for biomimetic drug testing headquartered in Zurich. Although cells grow and function in three-dimensional arrangements, cell-based assays are mainly done in 2D monolayers where cells lose tissue-specific functionality. In order to develop novel 3D models, the InSphero team realized the first reliable, easy-to-use, off-the-shelf 3D microtissue for efficacy and toxicology studies. "Our 3D culturing techniques stand out due to their capacity to build their own, native extracellular matrix without any scaffold. They are immediately ready for use due to their standard 96-well format, compatible with current laboratory liquid-handling robotics and readout instruments", says Dr. ***Wolfgang Moritz***, Head of R&D at InSphero. "Besides they are highly reproducible with less than 10% in size and density variation."

The heart of the InSphero innovation is their technology for scaffold-free microtissue mass production, giving rise to various applications: For example an *in vitro* toxicology model with Liver Microtissues, based on the InSphero culture technology allowing for the first time access to a large number of identical hepatic microtissues, assembled from freshly isolated, suspended primary rat hepatocytes of one single donor. They show an excellent performance over weeks and behave similar to native liver tissues which makes them a perfect model for *in vitro* liver toxicity studies.

The InSphero's Tumor Microtissue panels exhibit morphological and functional characteristics corresponding to inter-

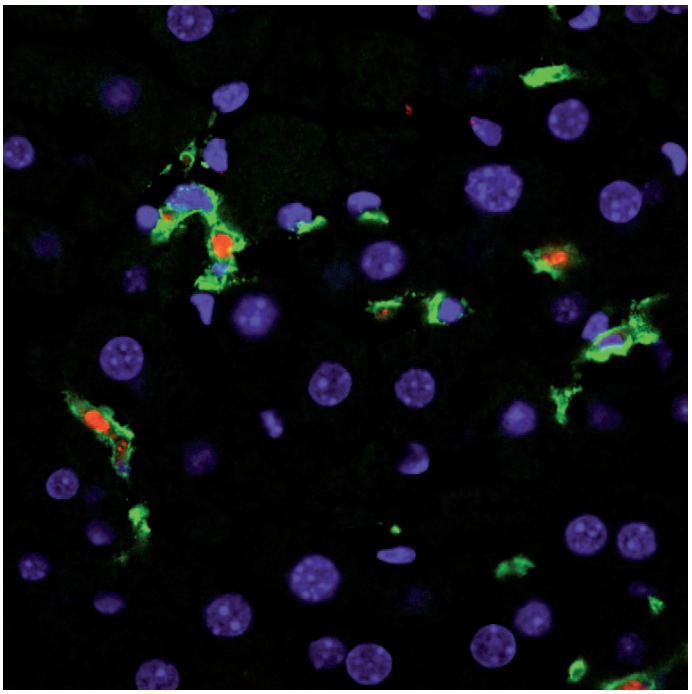


The Zurich-based InSphero offers the first reliable, easy-to-use, off-the-shelf 3D microtissues for efficacy and toxicology studies. Thanks to the 'hanging-drop technology' the microtissues are scaffold-free and build their own, native extracellular matrix, are highly reproducible with less than 10% I size and density variation. (Source: InSphero AG)

vascular regions of solid tumors. They are ideal to study tumor biology with respect to growth characteristics and drug sensitivity surpassing conventional monolayer cultures. (*www.insphero.com*)

Clinical Nano Medicine Meets the Patient

When the scanning tunneling microscope (STM) was discovered 30 years ago, no one could divine the impact nanotechnology would have on medicine. Today, thanks to nanotechnology, we see that biological cells are strongly nanostructured and possess many 'nano-machines'. "Nanotechnology gives us instruments small enough to detect damages in the complex system of our body with high precision, and they have the potential to repair them", explains Dr. ***Patrick Hunziker***, physician at the University Hospital Basel. He is exploring drug delivery systems. Packed in nanocontainers of highly biocompatible polymers, drugs are directly transported into the tissue at the place of activity. The containers recognize target cells thanks to proteins on their surface, where they bind specifically. Because of this docking, channels in the container envelope open and set free the drug. "Nanocontainers attack sick cells very precisely, sparing the surrounding tissue or other organs", states Patrick Hunziker. "Drug delivery systems therefore reduce undesirable side effects and help to intensify the effect of the medicine." This makes it possible to administer drugs which are highly efficient against certain diseases, but have side effects, *e.g.* on the liver, by 'smuggling' them past the liver.



The University Hospital Basel develops innovative drug release systems which transport medicine to sick cells, where they release the drug exactly at the place of destination. As these nanocontainers attack the sick cells very precisely, the researchers can spare all the other cells and organs – which are not involved in producing the illness – from the side-effects. (Source: University Hospital Basel)

"That means also, that we can lower the dose of medicines as they only get active at their point of destination."

Another promising domain is diagnostics. Nano diagnostics has the potential to realize diagnostics tests which are less burdensome for the patient. One vision is to measure all relevant parameters in a drop of blood at the patient's bedside within five minutes. (*www.unibas.ch*)

Novel Therapy for Spiral Cord Injury

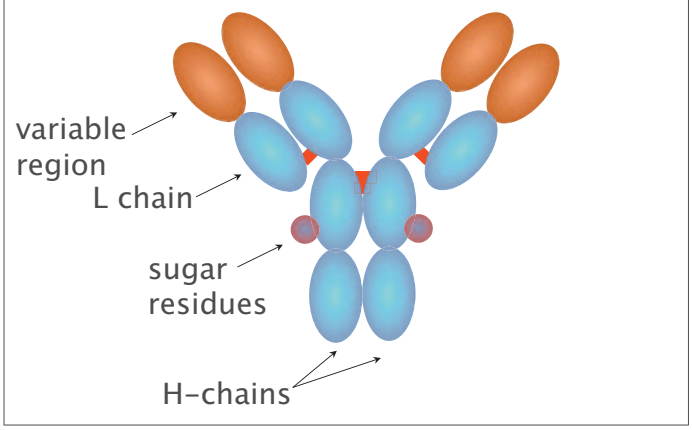
Millions of people suffer each year from spinal cord injury (SCI) and often the damage results in a loss of function such as mobility or feeling. The spinal cord contains many bundles of nerves that carry impulses to and from the brain to the rest of the body. It constitutes with the brain the central nervous system (CNS). Treatment of spinal cord injuries involves mostly physiotherapy; regeneration-promoting treatments do not exist yet. The problem of an efficient regenerative therapy is that after SCI nerve fibers of the spinal cord are disrupted and new outgrowth is very limited. The group of Professor ***Martin E. Schwab*** at the Brain Research Institute of the University and ETH Zurich is investigating the molecular mechanisms responsible for the incapacity of CNS nerve fibers to regenerate after the damage. In their search for cellular and molecular interactions the scientists could characterize a protein, called 'Nogo-A', that inhibits nerve outgrowth specifically in the CNS. They found out that Nogo proteins, which interact with receptor components, act as negative regulators of neuronal growth, leading to stabilization of the CNS wiring at the expense of extensive plastic rearrangements and regeneration after injury.

As the Nogo family of membrane proteins shows a 80% identity between rat, bovine and human, the team of Martin Schwab produced monoclonal function blocking antibodies and applied them *in vivo* after spinal cord injury in rats. "In doing so, we

could observe the outgrowth and regeneration of injured nerve fibers, and the return of lost functions to a high degree", outlines Martin Schwab. "Even nerve fiber tracts not directly affected by the injury sprout after treatment with inhibitor-neutralizing antibodies". A novel therapy for paraplegics consisting of the injection of antibodies in the cerebrospinal fluid is now under development in collaboration with Novartis. (*www.neuroscience.ethz.ch*)

Engineering B Cells for Therapeutic Antibodies

They are perfect defense molecules of our immune system, protect our body from viruses and bacterial infections. When used as therapeutics, they can enable us to combat diseases, like autoimmunity and cancer, against which we are usually not able to produce protective antibodies. Antibodies are produced by specialized immune cells known as B lymphocytes or B cells. They feature a specific and unique target binding region which results in a diversity of target binding specificities in a given collection of antibodies. This means that almost any antigen entering the body is recognized by an antibody. Unsurprisingly, scientists intended to develop and produce antibodies for the use as therapeutic drugs. However, it is not that simple as antibodies developed in laboratory animals like mice and rats are not suitable to treat human diseases: the human immune system recognizes them immediately as foreign invaders, and neutralizes them.

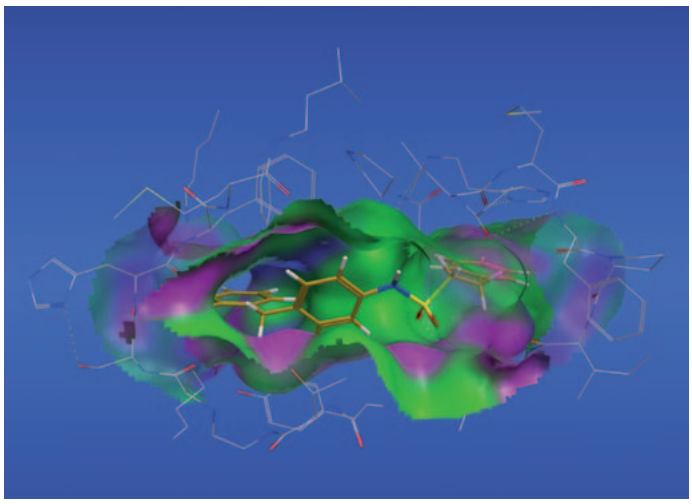


The researchers of 4-Antibody have developed a technology platform, by which they can genetically modify mouse precursor B-cells so that they will produce fully human antibodies. The technology allows 4-Antibody to produce single antibodies as well as libraries of antibodies with highest affinity. (Source: 4-Antibody AG)

The brainwave of ***4-Antibody AG*** was to genetically modify precursor B cells of mice so that they produce fully human antibodies, instead of mouse ones. The human antibody producing precursor B cells can be screened *in vitro* for specific antibodies by high throughput cell sorting (up to 60'000 cells per second). Highest affinity fully human antibodies can further be generated *in vivo*, after human antibody producing precursor B cells are transferred into mice. The hereby obtained antibodies have a defined, high affinity against a specific antigen for the treatment of serious medical diseases with minor secondary effects and a high selectivity of the products. "The innovative centerpiece of our technology is a suite of worldwide patent protected preB cell based antibody engineering platforms", says Dr. ***Ulf Grawunder***, CSO and co-founder of 4-Antibody. "They are, for instance, the basis for the Retrocyte Display and Hu-PAC technologies, both technologies based on the retroviral expression of fully human antibodies in mouse precursor B cells for the purpose for identifying and optimizing fully human therapeutic antibodies." Human antibodies are the basis for the development of efficient antibody drugs to attack and neutralize specifically tumor cells, infecting agents and soluble pathologic messengers, respecting entire compatibility with the human immune system.

The Perfect Fit in Drug Discovery

About 20 years ago, pharmaceutical researchers began – thanks to increasing computer capacity – to develop structure-based drug design (SBDD) tools for the discovery of new drugs. In SBDD the three-dimensional structure of a drug target interacting with small molecules is used to guide drug discovery, as you can see exactly how your molecule interacts with its target protein. At the starting point we have the target, an enzyme, causing problems in the human body. It is assumed that the molecules of a drug are effective if they bind optimally to the target in order to inhibit the activity of the problematic enzyme. Using the crystal structure of the enzyme as a template allows us to produce molecules which fit perfectly into the geometric and chemical characteristics of the target protein. At the ZHAW Wädenswil the group of Dr. ***Rainer Riedl*** is investigating proteases, enzymes



Structure-based drug design is in the focus of the ZHAW Wädenswil. In order to improve the potency and selectivity of inhibitors of validated drug targets, Dr. Rainer Riedl and his crew rationally design and synthesize novel scaffolds based on X-ray data of co-crystal structures. The iterative process of computational design, organic synthesis and biological testing leads to detailed structure activity relationships for therapeutically validated drug targets. This allows for the development of novel drug candidates for the treatment of diseases. (Source: ZHAW Wädenswil)

playing a central role in metastasis of tumors. In a first step the scientists are searching crystal structures of proteins in a protein database, for which a drug has to be developed. The computer places the potential small molecule drugs in the active site of the target. The researchers perceive from the high resolution 3D structures, which molecules fit best into the target. In a second step, the appropriate molecules have to be synthesized and optimized in the laboratory. The synthesized compounds will be tested on the target to evaluate whether they really inhibit the target. Finally, the *in vivo* and clinical tests will follow in order to develop the small molecule to a marketed drug.

"It's hard work as only five of about 10'000 synthesized compounds continue their way to the clinic and will be tested on human beings", states Rainer Riedl. "And only one compound will in the end reach the market. From the initial idea until the drug hits the market it takes about 10 years." In order to improve the potency and selectivity of inhibitors of validated drug targets, his team rationally designs and synthesizes novel scaffolds based on X-ray data of co-crystal structure. The iterative process of computational design, organic synthesis and biological testing leads to detailed structure activity relationships for therapeutically validated drug targets. "Ultimately, this allows for the development of novel drug candidates for the treatment of diseases", the scientist summarizes. "Our focus is on the design and synthesis part of the drug discovery process."

He has set himself the goal of pushing the molecules in the Wädenswil laboratories to the extent that they can be sold to the pharmaceutical industry. Pharmaceutical companies will then perform the *in vivo* tests and the clinical trials. The odds are in his favor: "We have a very solid process for the design and discovery of novel scaffolds based on our unique databases and are open for cooperation with industry." (*www.icbc.zhaw.ch/organischechemie*)

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

www.biotechnet.ch

Received: December 19, 2010