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Conference Report

Olten Meeting 2011 – Where Benign Cells Meet

November 23, 2011

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Abstract: This year's Olten Meeting – the annual get-together of the biotech experts from the Universities of Applied Sciences, Empa, the Swiss Biotech Association and industry – was held on November 23, 2011 under the motto Personalized Medicine and Cleantech by Biotech. Speakers from academia and the business world gave an insight into cutting-edge research and the chances for the industrial application of pioneering scientific results.

Keywords: Biotechnology · Swiss Biotech Association

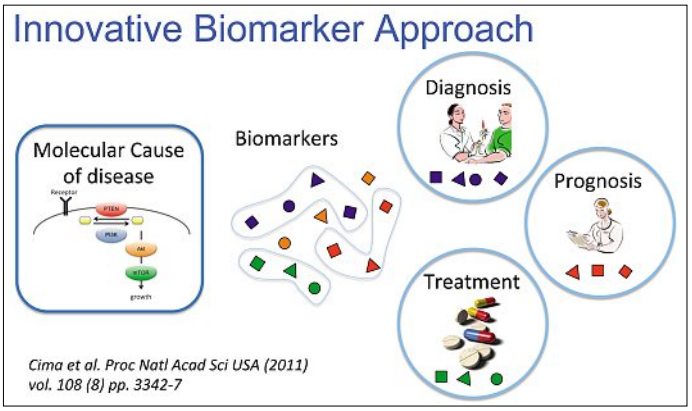
Do we all have the same shoe and clothing size, standard lenses for everybody, a 'one size fits all' dental implant? Of course not, since we are not chocolate bunnies straight off the assembly line, but individuals with customized needs.

Tailor-made Therapies

What goes without saying in different spheres of life is still an alien concept in medicine. The number of incompatible drugs and side effects with often fatal consequences is alarming. Experts estimate for example that the rate of ineffectiveness among cancer patients is about 75%. As we do not fully understand the genetic and environmental factors that cause major diseases like cancer and Alzheimer's, our methods of treatment are all too often imprecise, unpredictable and ineffective.

The time is ripe for *Personalized Medicine,* which will revolutionize our way of seeing sick human beings, as it takes account of a person's genetic code in determining a diagnosis or tailoring a specific treatment. This approach is based on the approximately 25'000 different genes in the genetic code of humans, which was mapped as part of the Human Genome project completed in 2003, enabling us to determine how to treat a medical problem. One of the leading specialists in Personalized Medicine is ProteoMediX, a company founded by a multi-disciplinary group of renowned scientists and clinicians. The group develops non-invasive diagnostic tests for detecting and assessing disease prognosis and also for matching patients with safer and more effective therapies. "Our strategy builds on the latest proteomics technology, enabling us to realize novel diagnostic tools with competitive advantages", states Dr. ***Ralph Schiess***, CEO and co-founder of ProteoMediX. "Our non-invasive diagnostics are directly linked to the origin of the disease at the molecular level tested in model systems. We combine multiple biomarkers to capture the complexity of the disease and attain fast cycles through biomarker detection and targeted validation."

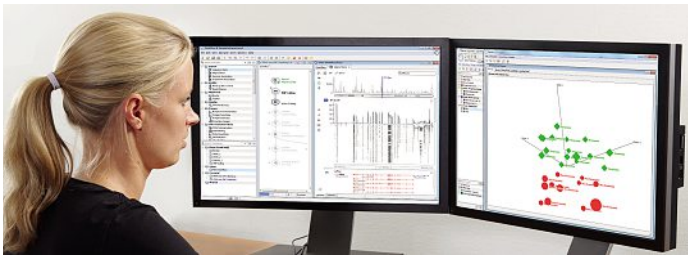
The first product being developed is a diagnostic test for the early detection of prostate cancer, the most frequently diagnosed cancer in men and the second leading cause of male cancer-related deaths. "The clinical tests based on a proprietary protein signature are very promising, as they prove to be superior to the current standard Prostate Specific Antigen (PSA) test", says the developer of the biomarker discovery technology. "They reduce considerably the high false-positive rate, as 3 out of 4 men are still being misdiagnosed due to the PSA test." As a result, the ProteoMediX method reduces the number of unnecessary biopsies, which cause anxiety, discomfort and complications, saving costs for the healthcare system, which amount to over $ 2 billion annually in the United States. (*www.proteomedix.com*)



ProteoMediX: Protein biomarkers linked to molecular cause of disease for either diagnosis, prognosis or treatment selection. (Picture by ProteoMediX)

How to Target the Interactions between Genes

Dr. ***Timo Wittenberger***, Head of Professional Services at Genedata AG, believes that Personalized Medicine will serve as a tool for classifying individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. "We can then concentrate preventive or therapeutic interventions on those who will benefit, sparing expense and side effects for those who will not." He cites chemotherapy, where only 25 out of 100 patients benefit from the treatment. Most cytotoxic agents are not really effective against specific cancers, focusing their activity on all particularly fast-growing tissues. Also the cells for hemopoiesis in the bone marrow divide much more frequently than other tissues and can therefore be affected by cytotoxic drugs. "The intensity of the greatly feared side effects depends on the individual genetic makeup", according to the scientist, who goes on to refer to the well-known list of non-responders published in *Clinical Trends in Molecular Medicine*: 38% for anti-depressants, 40% for asthma drugs, 43% for diabetes drugs, 50% for arthritis drugs, 70% for Alzheimer drugs and 75% for cancer drugs. Can such a waste of resources be tolerated nowadays?



High-throughput processing of genomic data by Genedata: Understanding how genetic and epigenetic factors influence phenotype and treatment response. (Picture by Genedata)

The experts at Genedata say not. They developed a software system called Genedata Expressionist®, which uses biostatistical methods and algorithms to analyze the interactions between genes, proteins and metabolites to find out if these molecules function as useful biomarkers. Using sophisticated technologies it is possible to screen tens of thousands of biological molecules per

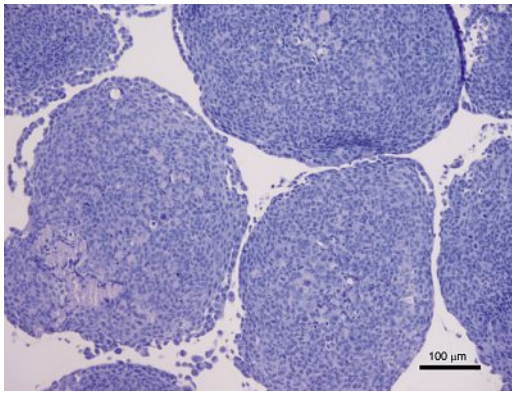
sample and to process thousands of samples with high throughput in a quick and reliable way. "It is possible to outline the genetic makeup of a patient thanks to terabytes of raw data, which can be read and processed using innovative mathematical and statistical methods", explains Timo Wittenberger. Genedata Expressionist® generates lists of genes, proteins and metabolites that could potentially serve as biomarkers and help predict whether a drug is effective or identify those patients who would be more likely to respond to a specific drug. By doing so, it provides a basis for the development of Personalized Medicine. (*www.genedata.com*)

Tissues for Drug Development

The *Tissue Engineering for Drug Development (TEDD) Competence Centre,* launched in June 2011 at the Zurich University of Applied Sciences (ZHAW) in Wädenswil, is tipped for success. "Organ-like human tissue models play an increasingly important role in the evaluation of active substances and in drug development, as conventional tests involving animal experiments are no longer socially accepted and will be completely forbidden for cosmetics by 2013", says Professor ***Ursula Graf-Hausner***, Head of Tissue Engineering and Cell Culture Technology. For years her group has been developing tissue models with functions and structures of healthy and diseased tissues and organs with relevant biological and physiological characteristics. In light of the growing importance of 3D cell and tissue culture, TEDD was formed to bring together basic and applied research with industrial aspects of pharmaceutical, biotech-related and medical companies. TEDD aims to implement this emerging technology using the combined efforts of different disciplines, such as biology, chemistry, biomaterial sciences and engineering. Strong partners are already on board, including ETH Zurich, university hospitals, CSEM, Empa, universities of applied sciences, industrial partners from biotech and enabling technologies and the end-users from pharmaceutical and cosmetic companies.

Several projects are running on the TEDD platform. To standardize 3D *in vitro* tissue models, the scientists evaluated eight different marketable systems, both with and without scaffolds. Microtissues of human colon cancer cells (HCT-116) were treated after 8 days' cultivation with an anti-cancer drug (Taxol). The systems were compared in respect of different criteria such as cell behavior, biological relevance, potential to apply suitable analyses and gain predictable read-outs, troublesome influence of scaffolds, ability for automation, costs, *etc*.

In another project, a team is testing different freezing media for the cryopreservation of microtissues using spheroids from the industrial partner InSphero AG. In contrast with single cells, microtissues encounter new obstacles during the freezing process due to their 3D structure. Successful freezing experiments have been completed, and dose-dependent compound testing to investigate the biological behavior of frozen microtissues is under way.



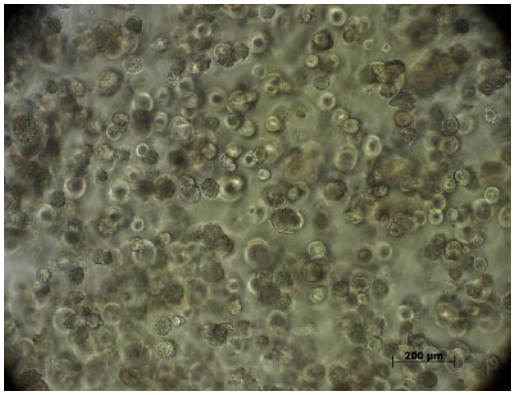
TEDD/ZHAW: Microtissues produced without scaffold in hanging drops after cryopreservation (HE staining). (Picture by ZHAW Wädenswil)

"Our goal is to establish a platform on which new technologies for drug development in pharmaceutical industry and personalized medicine can progress" summarizes the scientist. The Tissue Engineering for Drug Development(TEDD) competence centre receives start-up funding from the Gebert-Rüf Foundation, Switzerland (GRS-040/10). (*www.icbc.zhaw.ch/tedd*)

Personalized Oncology – A Political Problem?

Personalized treatments based on the understanding of cancer biology can offer millions of cancer patients around the globe targeted and effective therapies, but for this to become reality governments, pharmaceutical companies and the medical profession need to adapt the way drugs are developed. By way of example, Professor ***Thomas Cerny***, Head Physician Kantonsspital St. Gallen, cites advanced lung cancer, where modern predictive diagnostic tests subdivide the disease into several new entities so that each now has a much higher chance of responding to the initial treatment. On the other hand, even highly curative treatments such as the cisplatin combinations available for advanced testicular cancer patients since the 1980s took almost 30 years before the 90% chance of cure was eventually realized. This means that we not only have to focus on innovation, but also on faster translation into complex medical systems.

By focusing on the molecular biological level of cell development, scientists can increase their understanding of cell growth and help save more human lives by increasing the cure rate and length of survival. Today, some 75% of breast cancer patients survive the first five years after surgical intervention. Many forms of malignant lymphoma can be cured in 70–90% of cases. Medicine is also making progress in intestinal cancer, especially colon cancer. "We can spare every third patient from suffering a relapse", says Cerny, who is also President of Cancer Research Switzerland. New active agents intervene precisely in the molecular mechanisms responsible for the transformation of



TEDD/ZHAW: Scaffold-based microtissue: colon carcinoma cells HCT-116 were cultivated in 3-D-Life PVA Hydrogel (Cellendes, Germany). (Picture by ZHAW Wädenswil)

a once normal cell into a proliferative malignant cancer cell. The example par excellence is Glivec (Gleevec) from Novartis for the successful treatment of Chronic Myelogenous Leukemia (CML), Gastrointestinal Stromal Tumors (GIST) and other diseases. This drug inhibits the enzyme tyrosine kinase, which is produced in excessive quantities because of a unique genetic defect, leading to uncontrolled growth. On the other hand, Avastin from Genentech/Roche, a humanized monoclonal antibody, is effective in fighting metastatic intestinal cancer, usually in combination with chemotherapy. Avastin starves the tumor by neutralizing a vascular growth factor, thereby inhibiting the formation of the blood vessels required for supplying the cancer with nutrients. (*www.krebsforschung.ch*)

The Point of Departure for 'Cleantech by Biotech'

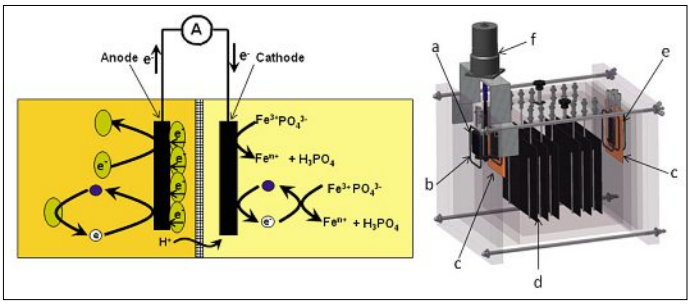
The afternoon session on the industrial biotechnology *Cleantech by Biotech* was opened by Dr. ***Anna Bozzi Nising*** from *scienceindustries*, formerly SGCI. Cleantech defines those technologies, manufacturing processes and services that contribute to the protection and conservation of natural resources and systems. In Switzerland, products and services provided by cleantech companies generate a gross value added of approximately CHF 20 billion and create 160,000 jobs (2008). Swiss cleantech companies are well positioned globally, having applied for around 8000 cleantech patents between 1991 and 2007. The Swiss cleantech companies are export-oriented, selling 38% of their products and services abroad. 1.5% of all sold cleantech goods and services around the globe are 'made in Switzerland'.

Switzerland is also well-positioned in cleantech research and production. However, in order to fully prepare the country for the future global challenges, a Cleantech Masterplan was worked out as the Federal Government's strategy for improving resource efficiency and promoting renewable energies. The vision for Switzerland is to reduce its resource consumption to an ecologically acceptable level and to take a leading position in cleantech business and innovation. Science industries and the Swiss Biotech Association (SBA) have joined forces to create awareness of, and develop supporting measures for, 'Cleantech by Biotech' in industrial production. A proposal for a new national research program: 'Industrial Biotechnology: *Cleantech by Biotech*' was submitted to the Swiss National Science Foundation (SNSF) in June 2011. Although the project has now been put on the back burner due to the political decision to focus the NRP 2011 on energy research, science industries and SBA are confident that the SNSF will return to the subject without any further delay in 2012. (*www.scienceindustries.ch, www.cleantech.admin.ch*)

Phosphate Made in Switzerland

Professor ***Fabian Fischer*** at the University of Applied Sciences Western Switzerland (HES-SO) in Sion focuses on the recovery of phosphate. In order to prevent eutrophication of waters, phosphate is currently precipitated in purification plants with $FeCl_3$ as an insoluble salt and embedded in sewage sludge. The spreading of sewage sludge on farm land as a fertilizer is the most convenient way of reusing phosphate. However, since digested sewage sludge contains toxic contaminants such as As, Pb, Cd, Cr, Cu and Zn, it cannot be used as a fertilizer but has to be incinerated and deposited without any further treatment. For this reason the phosphate cannot be exploited as a precious raw material for the fertilization of agricultural soils.

"In a project supported by the Federal Department of the Environment, Transport, Energy and Communications (DETEC) we intend to reclaim the phosphate from the sewage sludge by means of a microbial fuel cell", explains Fabian Fischer. "Since the cell should also gather up the heavy metals, the remaining biomass can be directly used as a fertilizer in agriculture." The applied technology works at ambient temperature with protons and electrons supplied by the metabolic activity of microbes. The microbial fuel cell serves as a power source by supplying not only the electrons, but also the protons needed to reduce electrochemically insoluble $FePO_4$. In the fuel cell's cathode, stoichiometric amounts of electrons and protons are shuttled as hydrogen equivalents by methylene blue. Electrons reduce the iron cations, and charges are replaced by protons, resulting in orthophosphate mobilization into the aqueous supernatant solution. "The realized system constitutes an advanced sewage treatment system and, in addition to clarifying sewage, it also produces energy, phosphate and other primary products." (*www.itv.hevs.ch*)



HES-SO Sion: Phosphate recovery: Microbial fuel cell for the mobilization of orthophosphate from $FePO_4$ the cultivation chamber are transferred to the anode. The reduction in the cathode follows two mechanisms: (i) $FePO_4$ containing sludge particles collide with the RVC electrode, (ii) are reached by methylene blue mediation. Right: 2.5 l microbial fuel cell: (a) mobilization cathode, (b) reticulated vitreous carbon electrode, (c) proton exchange membrane, (d) cultivation chamber with six carbon felt electrodes, (e) reference cathode for online monitoring, (f) stirring motor. (Picture from 'Microbial fuel cell enables phosphate recovery from digested sewage sludge as struvite', *Bioresource Technology* **2011**, *102*, 5824–5830, Copyright Elsevier Ltd.)

Tapping the Full Potential of Microalgae

The Institute of Biotechnology at the ZHAW in Wädenswil currently possesses unique know-how on the cultivation of microalgae up to very high cell densities. The research builds on the expertise of a team within the Bioprocess Technology section led by Professor ***Karin Kovar***, and concentrates particularly on the design, optimization, control and simulation of microbial processes. "Although microalgae exhibit considerable metabolic versatility and flexibility, they are currently underexploited in the biotechnological manufacture of known plant-derived compounds, novel biomolecules and enriched biomass", states Professor Kovar, the ZHAW's specialist in microbial physiology. "Recent research provides a good deal of information about the cultivation of microalgae under photoautotrophic conditions, *i.e.* with light and carbon dioxide. However, the production of high-value compounds with microalgae in conventional, stainless steel, stirred bioreactors remains largely unexplored. With such bioreactors, microalgal biomass is produced under heterotrophic conditions, with an organic carbon source but without light."

Until now, investigations of microalgae have been limited, as the required quantities of biomass could not be collected directly from nature. The novel process strategy of Karin Kovar's group paves the way for the economically feasible production of microalgal biomass of the required quality using the existing facilities. Advanced control of a fedbatch process enables up to 160 grams per liter of biomass (cell) dry weight of green microalgae to be obtained within 50–70 hours (F. Bumbak, S. Cook, V. Zachleder, S. Hauser, K. Kovar, *Appl. Microbiol. Biotechnol.* **2011**, *91*, 31–46). Moreover, the ability of microalgae to adapt their metabolism to various culture conditions provides opportunities to modify, control and thereby maximize the formation of targeted compounds with non-recombinant microalgae. In this way biomass can also be specifically enriched with lipids and organically bound microelements.

The new approach enables a plant-like material to be produced whose quality is independent of weather conditions or seasons. The natural active substances that can be extracted from microalgal biomass have wide potential for use in the pharmaceutical, food, animal feed and cosmetics industries. (*www.ibt.zhaw.ch*)

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

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