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Hot from the press!

7th Waedenswil Day of Chemistry Personalized Medicine: Full Speed Ahead!

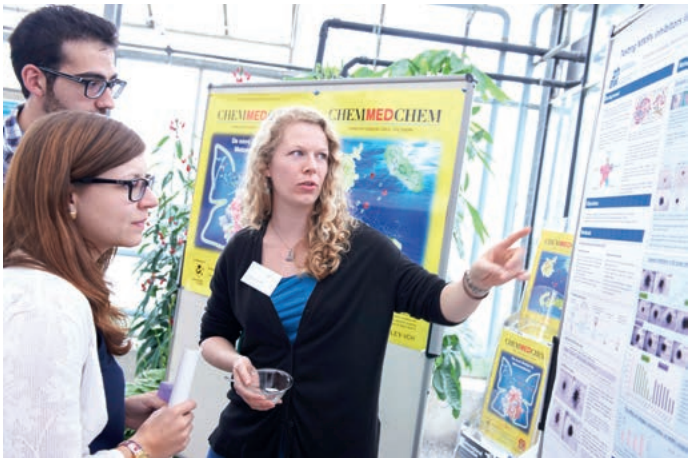
Elsbeth Heinzelmann, science + technology journalist

Abstract: The aim of Personalized Medicine in disease treatment and prevention is to take account of the individual variability in genes, environment and lifestyle for each person. This approach is applied to certain tumours but is still not common for most diseases. On June 18, 2015 the TEDD network (Tissue Engineering for Drug Development and Substance Testing) invited a total of 130 academic and industrial partners to Waedenswil to exchange ideas and discuss promising approaches.

Keywords: Personalized medicine · TEDD

Why don't we tailor medical therapies to the individual characteristics of each patient and take advantage of our knowledge about a person's unique molecular and genetic makeup that makes him or her vulnerable to certain diseases? As a result, we could better assess which medical treatments are safe and effective in a particular case of illness. In the scope of the 7th Waedenswil Day of Chemistry, the TEDD network wanted to highlight the potential of Personalized or Precision Medicine.

The TEDD conference presented the opportunity for dedicated research scientists to meet with potential partners from industrial circles all over Europe. Picture A. Schweiger.



Representatives from research institutions and industry took the opportunity at the TEDD conference to establish contacts for possible future cooperation. Picture A. Schweiger.

Swiss Tissue Culture Society partners with TEDD

Leveraging synergies and combining forces was the main reason that prompted the STCS (Swiss Tissue Culture Society) to join TEDD. The STCS unites a diverse membership from academia and pharma with a broad spectrum of interests in cell culture and in vitro models. This can even include exotic applications such as antimalarials. Professor ***Pascal Mäser***, the President of STCS and head of Parasite Chemotherapy at the Swiss Tropical and Public Health Institute (Swiss TPH), explains: "Malaria affects hundreds of millions of people each year. The sporozoites injected by an infected mosquito first enter hepatocytes. In some cases the parasites prevail in the liver, leading to malaria that only relapses after a number of years." Despite extensive research, the mechanisms responsible for hypnozoite development and re-activation in the liver are not understood to this day. "We are therefore interested to have at our disposal – thanks to networking with experts - 3D liver microtissues for infection by our parasites in order to develop reliable assays and next-generation antimalarials."

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Joint Effort Crucial to Success

Professor ***Niko Beerenwinkel***, a computational biologist trained at the Max Planck Institute for Informatics, joined the Department of Biosystems Science and Engineering of ETH Zurich in 2007. From his point of view, personalized medicine involves the integration of information about a patient's genome with clinical and pathobiological characteristics as well as environmental and lifestyle parameters. "Driven by tremendous technological advances in genomics, most notably in DNA sequencing, the goal of personalized medicine is to design individually tailored therapies and preventive measures", explains the former postdoctoral researcher at UC Berkeley. This new approach is designed to routinely take into account large-scale constitutional genomic information for an individual patient, including somatic genetic alterations and molecular signatures of pathogenic agents, in order to specifically and effectively target a molecularly defined disease while minimizing the chances of adverse events. He is convinced that "the implementation of personalized medicine represents an extraordinary challenge for scientists, engineers, health care providers and the diagnostic and pharmaceutical industry". "Research in this domain is highly interdisciplinary and includes clinical research, molecular biology and statistical

data integration." Further steps of the new Competence Center Personalized Medicine UZH/ETHZ cover collaborative research involving the development of tools and techniques for precision oncology. "We will illustrate the technical challenges associated with such research projects and present scientific, technical and organization measures to address these."

https://www1.ethz.ch/bsse/cbg/people/nikob

Professor Ursula Graf-Hausner has again succeeded in bringing together renowned experts like Dr. Bruce Jordan, International Business Leader Companion Diagnostics at Roche Professional Diagnostics in Rotkreuz, and Dr. Niko Beerenwinkel, Professor of Computational Biology ETH Zurich and Co-chair of the Competence Center for Personalized Medicine UZH/ETHZ, Hochschulmedizin Zurich. Picture A. Schweiger.

Diagnostic Tools Reveal Molecular Origin

The medical need for a more patient-tailored approach has resulted in a greater number of targeted therapies focused on better defined patient groups. Within the past few years Roche has embarked on a systematic approach for the development of medicines, interweaving diagnostic and pharmaceutical expertise to pave the way for Personalized Healthcare (PHC). "We have already begun to provide healthcare professionals with more powerful diagnostic tools and targeted treatments that are based upon new insights into how disease arises at the molecular level", explains Dr. ***Bruce W. M. Jordan***, Business Development Manager at Roche Diagnostics International Ltd. "Up until now, this has happened mostly in the fields of oncology and virology, and new developments will address equally high areas of unmet medical need such as asthma and Alzheimer's disease." One focus is on advancing our understanding of the molecular basis of asthma. This may, at least in part, explain the heterogeneity observed in the response to medication. For patients with this disease – in whom exacerbations can still be life-threatening – laboratory testing also has the potential to allow the tailoring of treatment based on individual characteristics, and to improve overall treatment success.

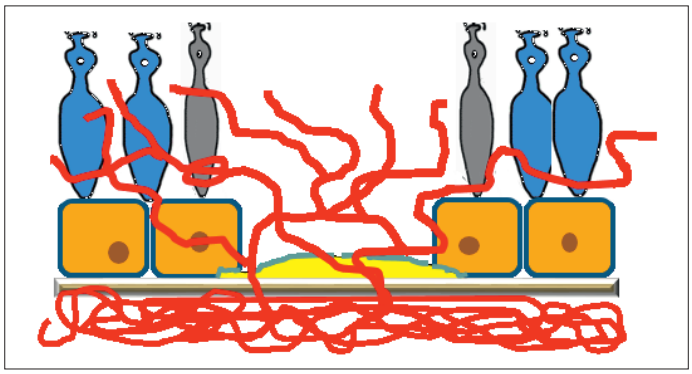
Alzheimer's disease is a serious burden on patients and society as the overall population ages. The identification of reliable biomarkers of AD has, therefore, become increasingly important, not only for risk prediction and diagnosis in order to provide appropriate care, but also to identify those patients who could be eligible for inclusion in clinical trials of novel therapies being tested at the early stages of the disease when treatments may potentially yield the greatest benefits.

"It is clear that the growing number of game-changing targeted therapies in development will require ever more innovative diagnostic tools to guide their use", points out Bruce Jordan. "Their limited number of PHC approaches suggests that there are still many challenges, as well as opportunities in this emerging field of medicine. "

www.roche-diagnostics.ch

Gene Therapy for the Eye: The Target AMD Project

Eye diseases are particularly suitable targets for gene therapy because the eye is easily accessible and treatment effectiveness is readily measurable. Moreover the eye is immune privileged. During the last few years, using virally mediated gene delivery, gene therapy has been successfully applied to the treatment of inherited Retinitis Pigmentosa, for example. One report has also shown that the virally-mediated delivery of the *PEDF* (pigment-epithelium derived factor) gene intravitreally inhibits choroidal neovascularization (CNV) in neovascular Age-Related Macular Degeneration (AMD) patients. PEDF is a potent inhibitor of VEGF (vascular endothelium growth factor), which is responsible for CNV.



In neovascular AMD, major cause of blindness in elderly, an imbalance between pro-angiogenic factors (*e.g.* VEGF) and anti-angiogenic factors (*e.g.* PEDF) provokes a choroidal neovascularization (CNV) leading to blindness. Instead of elaborating monthly injections with anti-VEGF antibodies to stop CNV, the consortium of the TargetAMD project develops a non-viral gene-therapeutical approach as safe and efficient alternative. Picture Department of Ophthalmology, University Hospitals of Geneva.

With the EU-funded Target AMD project (AMD = age related macular degeneration), involving 13 partners and seven countries, the consortium plans to transplant PEDF-transfected cells to the subretinal space of neovascular AMD patients. To safely transfect pigment epithelial cells, Target AMD will use transposon-mediated gene delivery using pFAR4 plasmids. "Specifically, retinal and iris pigment epithelial cells will be transfected with the *PEDF* gene using the enhanced *Sleeping-Beauty* (*SB100X*) transposon system", explains biologist Dr. ***Martina Kropp*** of the Department of Ophthalmology of the University Hospitals of Geneva, and a participant in this EU project. "The latter integrates the gene into the host cell's genome and provides a safe and efficient alternative to viral systems." The use of pFAR4 miniplasmids will further increase the safety and quality of gene integration. With the proposed Phase Ib/IIa clinical trials in Target AMD with the harvesting, transfection and transplantation of autologous cells during a single surgical session, the consortium would implement the first European clinical trials using the *SB100X* transposon system in humans. "*In vitro* studies in our laboratories have demonstrated long-term *PEDF* gene expression and protein secretion by *SB100X*-mediated transfection and, during *in vivo* studies with animal models of neovascularization, the transplantation of PEDF-transfected cells reduced neovascularization significantly", concludes Martina Kropp.

http://www.hug-ge.ch/ophtalmologie

www.targetamd.eu

How to Model Cancer Progression

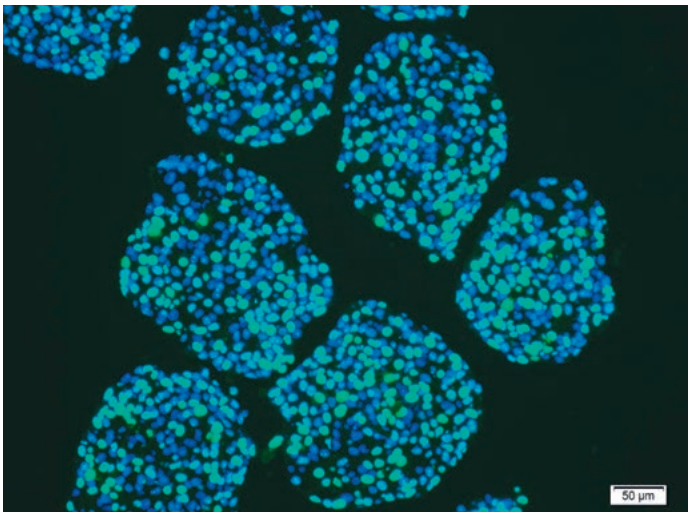
Professor ***Gerald Schwank*** of the Institute for Molecular Health Sciences of the ETH Zurich, ranks as a pioneer in stem cell research and was the first person to repair a genetic defect present in the lung disease cystic fibrosis. He focuses on diseases where regulatory mechanisms are disturbed. In a research study with the University of Cambridge and the University Medical Center Utrecht he is developing a method to expand human intestinal stem cells in culture over long periods as genetically and phenotypically stable three-dimensional epithelial organoids. These so-called 'miniguts' comprise nearly intact physiology and consist of all major intestinal cell types, including Lgr5 positive stem cells. "We used the CRISPR/Cas9 system for genome editing in organoids", he explains. "The system allowed us to introduce tumour driver mutations into organoids to model cancer progression and to functionally repair disease-causing alleles such as CFTR mutations in organoids derived from disease modelling and gene therapy by CRISPR/Cas9 genome-editing in stem cell organoids." This research work contributes to the advancement of regenerative and personalized medicine and its use in the three-dimensional reconstruction of cellular structures, especially in the field of embryonic and tumour stem cell research.

http://www.mhs.biol.ethz.ch/research/schwank.html

The Swiss Platform for Personalized Medicine

"Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes – and to give all of us access to the personalized information we need to keep ourselves and our families healthier." This was the statement issued by President Barack Obama in his State of the Union Address on January 20, 2015. The project is backed up with passion by Francis S. Collins, Director of the National Institutes of Health (NIH). It is currently funded to the tune of US$ 215 million. Europe is also preparing for the future with Horizon 2020, the biggest EU Research and Innovation programme ever, with nearly EUR 80 billion of funding available from 2014 to 2020 – in addition to the private investment that this money will attract. From introducing safe and effective innovative treatments in multidisciplinary standard care, we expect more breakthroughs, discoveries and world-firsts by taking great ideas from the lab to the market.

Professor Ursula Graf-Hausner, initiator and head of the TEDD network, and Professor Pascal Mäser, President of the Swiss Tissue Culture Society (STCS) announced at the meeting that they will work together in the future in order to exploit resulting synergies. Picture A. Schweiger.



Human 3D tissue models to foster personalized medicine. Immunostaining of SaOS-2 microtissues cultured for 12 days and stained for Ki-67 (green, proliferating cells) and cell nuclei (blue, DAPI) (part of this work is published in Rimann *et al.* **2014**,. doi: 10.1016 / j.jbiotec.2014.09.005). Picture TEDD/ZHAW.

In Switzerland, the international Competence Centre TEDD – Tissue Engineering for Drug Development and Substance Testing – provides the ideal platform where innovative technologies for personalized medicine can be developed and translated into pioneering technology leaps on the international markets. As an example, close cooperation exists between the applied and pre-clinical research of Professor Dr. ***Ursula Graf-Hausner***, Head of the TEDD network at the Zurich University of Applied Sciences (ZHAW), and Professor Dr. ***Bruno Fuchs***, Head of Tumor Surgery and Research at the University Hospital Balgrist and Head of the Sarcoma Center Zurich (*www.sarkomzentrum.ch/*). The common objective is to develop reliable and robust *in vitro* 3D micro-tissue models to improve the current standard treatment of osteosarcoma patients, based on the drug sensitivity of patient-derived material obtained at initial diagnostic biopsy. Osteosarcoma is a severe, but rare, bone cancer that is still associated with poor outcome in the event of metastasis formation. The search for new drugs that efficiently disrupt metastasis is therefore essential. Both research institutions evaluate scaffold-free 3D cell culture platforms to produce reliable and reproducible micro-tissues from osteosarcoma cell lines for drug assessment. Potential *in vitro* evaluated drugs will be tested in orthotopic osteosarcoma mouse models to assess their *in vivo* efficacy. The use of primary patient-derived material for micro-tissue production will further foster personalized medicine.

www.icbc.zhaw.ch/tedd

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