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Thematic Platform *in vitro* Diagnostics Technological Progress with a Powerful Network

Elsbeth Heinzelmann, science and technology journalist

Abstract: In vitro diagnostics (IVD) has huge potential. Primary drivers in the global market are the patient's awareness of infectious diseases, the introduction of advanced molecular and tissue diagnostic tests for patient-stratified and targeted anti-cancer therapy and, last but not least, the growing geriatric population. Rapid progress in device miniaturization and information technology (IT) offers new possibilities in decentralized testing. Grand View Research Inc.[1] expects the global market for IVD to reach US $ 74.3 billion by 2020. Hence the launch in 2015 by the NTN Swiss Biotech – together with the driving forces of Biotechnet Switzerland – of the 'Thematic Platform *in vitro* Diagnostics'.

Keywords: Biosensors · Companion Diagnostics · *in vitro* Diagnostics · Personalized medicine · Point-of-care (POC) testing · Precision Medicine · Therapeutic Drug Monitoring (TDM)

Diagnostic procedures are frequently based on the quantification of biomarkers (*e.g.* proteins, DNA, metabolites) in human samples like blood, urine or tissue to identify a disease status and to obtain information on how to select the most appropriate and effective therapy. Commonly known *in vitro* diagnostic (IVD) tests include assays for infectious diseases like HIV or hepatitis, or for blood glucose and cholesterol levels. Wearable sensors and, for instance, tracer molecules employed in imaging or during an operation to precisely locate malign tissue show how – from a technological viewpoint – the *in vitro* and *in vivo* diagnostic segments have begun to coalesce.

We now know that, depending on disease area, the frequency of patients not responding to current therapies can vary between 38 and 75%.[2] One reason for this poor therapeutic benefit is that the 'one-size-fits-all' model does not really work well in many cases. Personalized medicine means that, for an increasing number of new drugs approved in the future, a companion diagnostic test needs to be in place so that these new drugs are only given to patient groups that will actually benefit with a high degree of probability. An improved benefit-risk-ratio not only positively impacts public health, but also addresses economic pressures. New bioanalytical and *in vitro* diagnostic technologies will thereby allow us to better understand disease mechanisms and obtain more accurate diagnoses, thus reducing the financial burden due to ineffective treatments or detrimental secondary effects.

How to bundle strengths and exploit synergies

In order to drive innovation in IVD, in 2015 the NTN Swiss Biotech – with the sustained support of Biotechnet Switzerland – created the *Thematic Platform in vitro Diagnostics*. This collaborative 'hub' gives access to a network of experts at internationally active universities, research centres and companies in this area, invites interested parties – industry, the medical sector and research organizations – to cooperate in clearly oriented projects. The platform brings together excellent skills from molecular biology, biochemistry, micro-/nanotechnology and bioanalytics, miniaturization, automation, data management, regulatory affairs and health economics. The initiators have set their sights firmly on national and international collaborations with renowned institutions, and support promising ideas with seed money. For this purpose they stimulate translational research and organize networking events and company visits. The focus is always on the value creation to society.

Every challenge provides an opportunity

The platform is led by Professor ***Marc Pfeifer***, Head of the Diagnostic Systems Research Unit of the Institute of Life Technologies, HES-SO in Sion, and Dr. ***Daniel Caminada***, Section Head Microdiagnostics, CSEM SA. Marc Pfeifer and his colleagues are, for instance, investigating the possibilities for improving Therapeutic Drug Monitoring (TDM), the process supporting drug dosage adjustments to maintain optimal plasma or blood drug concentrations within a target therapeutic range. "In a nutshell, personalized medicine is all about making sure the right patient receives the right drug with the right exposure", summarizes Prof. Pfeifer, who is an expert in bio-analytics and IVD product development. If a correlation is observed between dose and blood concentration on the one hand, and blood concentration and therapeutic effect of the drug on the other, then

Group photo of the Steering Committee (StCo) and Advisory Board (AdBo) of the *in vitro* Diagnostic platform. From left to right: Prof. Olaia Naveiras (EPFL – AdBo), Dr. Gesa Albert (Roche Diagnostics AG – AdBo), Dr. Manfred Schawaller (Davos Diagnostics AG – AdBo), Dr. Jakob Weber (BÜHLMANN Laboratories AG – StCo), Prof. Marc E. Pfeifer (HES-SO – StCo), Prof. Eric Kübler (FHNW – StCo), Prof. Peter Meier-Abt (SAMW – AdBo), Dr. Greta Faccio (Empa – StCo), Dr. Alexander Leichtle (Inselspital Bern – StCo), Dr. Daniel Caminada (CSEM – StCo), Dr. Thomas Stauffer (Medics Labor AG – AdBo), Prof. Bruno Schnyder (HES-SO – StCo). (Photo projektfotografie.ch)

TDM is ideal for managing dose adjustments and thus optimizing therapy.

Further criteria for TDM are intra- and inter-individual pharmacokinetic variability and a narrow therapeutic index. Several of the most common immunosuppressive drugs (ISD) administered at regular intervals following organ transplantation require detection limits in whole blood in the lower µg/L ranges. "For instance, the therapeutic range of the calcineurin inhibitor (CI) tacrolimus is 5–20 µg/L with a necessary limit of quantification (LOQ) of 1 µg/L", says the scientist. "This does not pose a problem for the analytical chemist working in the central laboratory of a hospital with a sophisticated LC-MS system or clinical analyzer with several millilitres of specimen. However, it is a formidable task for scientists and engineers to develop a robust and sensitive assay with all the critical reagent components and incorporating a reliable sample preparation process, everything integrated in a small device adapted for point-of-care (POC) testing and requiring just a single drop of blood as input for analysis."

"It was something of a reality check for the team of scientists from the University of Applied Sciences and Arts Western Switzerland (HES-SO), the EPFL and the University Hospital in Lausanne (CHUV) when they recently concluded system performance verification with their first ISyPeM2 project demonstrator. It is always a special moment when you conduct a formal assessment of the performance of your prototype assay with preliminary hardware and software components. You always encounter interface performance issues and deficiencies. Fortunately, our colleagues of the nano-tera/SNSF project and I had planned development iterations in order to come up with improved and more advanced 2nd and 3rd generation demonstrators paving the way towards a future innovative medical device enabling a decentralized and personalized optimization of drug exposure."

Focusing on human cell culture systems

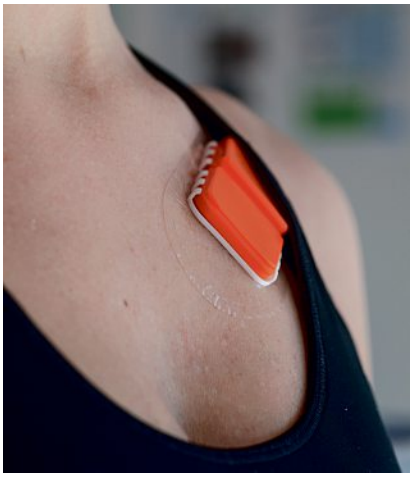
Professor ***Bruno Schnyder*** and his coworkers at the HES-SO in Sion are investigating different aspects of human cell culture systems as part of diagnostics systems. Their cell culture facility offers theoretical and practical know-how in a wide array of applications, ranging from microbial to human cell-based assays. This includes the design and development of custom-made assays, as well as applications of known test methods. The latter include intestinal bioavailability tests using Caco2 cells or cellular enzyme activity tests (*e.g.* beta-galactosidase). Such cell-based tests using patient's derived cells versus healthy cells serve to predict and compare the treatments in groups of patients. With this approach they provide a link to so-called personalized healthcare.

"Our designed three-dimensional cell systems come close to the *in vivo* situation. They allow the co-culturing of different cell types which can combine, for example, mucosal barrier cells with cells of the immune system", explains Bruno Schnyder. When exposed to conditions representing inflammatory, infectious, or other diseases, the cells are analyzed by monitoring a selection of standard inflammatory parameters (cytokine systems) and novel biomarkers. "With this approach we apply proteomics-type diagnostics to cellular systems."

The scientists have recently combined several of the above-mentioned modules in an approach that monitors the effect of anti-microbial plant extracts on infectious diseases. The promising results have been filed in a patent and prompted the initiation of the CTI-founded project 'Swiss alpine plants for the control of infectious disease' involving HES-SO Valais-Wallis in Sion and the academic partners at Mediplant Valais, Conthey and Basel University, as well as the industrial partner Pharmalp at the Phytoark Valais, Conthey.

Creating the products for future markets

Also on board is CSEM, for instance with a brilliant idea in the domain of wearable sensor technologies. "Wearables are predicted to play an important role in sports and healthcare as they continuously monitor body parameters in sweat or other secreted body fluids", explains Dr. Daniel Caminada, Section Head Microdiagnostics at CSEM. "This allows an immediate intervention in the event of a change in a parameter. For example, signs of dehydration can be detected at an early stage, and detrimental effects on human health and reduced physical and mental performance can be avoided." For years, CSEM has been active in accurate, real-time and on-body measurement of various health indicators like heart rate, heart rate variability and blood oxygenation. Today, they are looking into more specific non-vital biomarkers such as the lactate level, an indicator of tissue oxygenation.



Wearable patches: The patch is placed directly on the body and is designed to measure various parameters in parallel in sweat (*e.g.* pH, sodium, potassium, lactate, impedance). It consists of a disposable part containing the sensors and the tape and a reusable part containing the electronics. The information is transferred wirelessly to external devices such as a smartphone. (Image CSEM SA)

Based on these body parameters, the CSEM researchers focused their activities on biocompatible, disposable sensing solutions for monitoring skin pH, conductivity, ion content, sweat rate and lactate levels. The result of their efforts is a smart patch capable of collecting data from the sensors and transmitting them wirelessly to a device such as a smartphone. The sensors are based on screen printing technology. They are integrated in an adhesive patch that is placed directly on a person's body. The concentrations of the parameters in sweat are read out in real-time. For example, the continuous monitoring of lactate will alert an athlete of any sub-optimal use of resources during physical effort. "Wearable sensor devices are on an upward trend as they give feedback to their wearers about their physical activity and, in the future, about their health", concludes Daniel Caminada. "They are point-of-care devices in all but name as they bring the laboratory directly to the person. This opens up completely new perspectives to the healthcare system as it allows better prevention and monitoring of the population, thereby reducing expensive treatment costs."

How to tackle the problem of wound healing

Under the lead of Professor ***Bradley Nelson*** at the Multi-Scale Robotics Lab at ETHZ, Dr. ***Stefano Cattaneo*** at CSEM, Dr. ***Brigitte von Rechenberg*** at the Tierspital, University of Zurich and Dr. ***Greta Faccio*** (Empa) are joining efforts in the development of molecular sensing strategies for the monitoring

of metabolites involved in wound healing. This proceeds within the nano-tera-funded FlusiTex project 'Developing a wound dressing with an integrated sensing layer for non-invasive wound monitoring using fluorescence lifetime detection'.

"FlusiTex will develop a wound dressing with an integrated sensing layer for non-invasive wound monitoring using fluorescence lifetime detection", explains Greta Faccio. "Functionalization comprises modified polymer hydrogels with embedded enzymes and fluorescent protein-based sensors." These sensing layers provide information on biochemically and physically relevant wound characteristics. A dedicated camera with fluorescence lifetime capability will be developed for periodically monitoring the response of the layers non-invasively, thus providing immediate feedback on the progression of wound healing at various points in time. "Since the wound healing process is not yet fully understood, studies on factors relevant for the process will be conducted by a medical team in parallel with the development of the sensor-pad."

The sensing elements will be integrated within a commercially available wound pad, and fabrication techniques will be developed to enable reliable large-scale production. The data from the embedded sensing elements will be collected by a specially developed CMOS lock-in fluorescence lifetime imager and optimized to match the sensing needs, thus dispensing with the need for the expensive integration of the electronics within the wound pad. At the end of the project, a prototype of the system will be tested *in vivo* in an animal study. "A variety of companies have indicated strong interest in this project", concludes Greta Faccio. "They will provide industrial expertise with the goal of joining the project at a later stage for the subsequent technology transfer, *e.g.* in the form of projects supported by the Commission for Technology and Innovation CTI."

The Biobank Bern gives a helping hand

The Inselspital Bern is the largest healthcare provider in the canton of Bern and is the teaching hospital of the University of Bern. In numerous projects it fosters the evolution of precision medicine and its translation to patients:

"The hospital-integrated Biobank Bern Liquids was recently inaugurated and, together with the Institute of Pathology of the University of Bern, forms the Biobank Bern, offering exceptional sample quality, fully automated pre-analytical processes, and robotized storage at –80 °C and < –130 °C", explains ***Alexander B. Leichtle***, MD, Consultant for Sample and Report Management and Clinical Trials. "It will be connected to a clinical data warehouse combining the respective clinical information and rendering the institutional sample collection a perfect mirror of the Inselspital's patient population for future research."

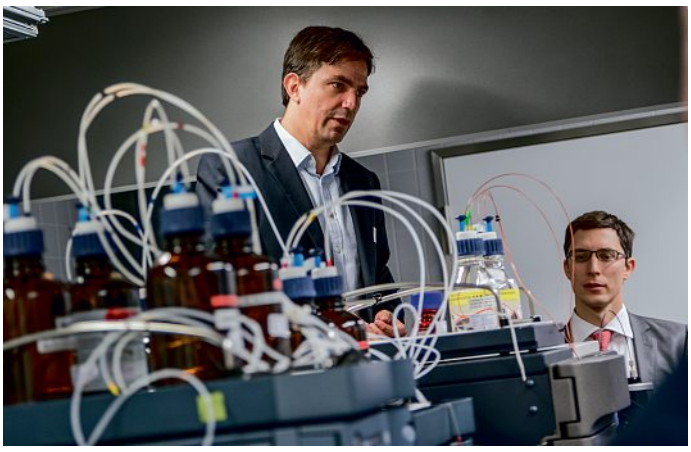
During the reconstructions, the Institute of Pharmacology of the University of Bern moved into the building directly next to intensive care units, emergency medicine, surgery and, in particular, the newly founded Center of Laboratory Medicine, sharing a common floor and enabling close collaboration, platform sharing and exchange of ideas, *e.g.* for the development and testing of companion diagnostics. The Center of Laboratory Medicine has been completely rebuilt and now combines the latest analytical technology and sample logistics, as well as a Clinical Metabolomics Facility in a high-throughput environment. It also has facilities for the pre-market testing of new analytical instruments, which are in great demand by the industry partners.

How to stimulate a pioneering spirit

To ensure excellent scientific quality and a broad base of experience, an expert advisory board – consisting of seasoned professionals from industry and academia – monitors the activities of the steering committee of the Thematic Platform and contributes with know-how and guidance in the development and implementation of the strategy. The Thematic Platform's mission is to promote technological innovation in *in vitro* Diagnostics (IVD) and to enable translational research from academia to

Laboratory tour of Clinical Chemistry at the Inselspital Bern during the Thematic Platform IVD event on the 25th of April 2016. Sample automation at the Inselspital in Bern. Blood samples of patients are tracked and transported, in a fully automated process, to the respective locations for analysis. (Photo projektfotografie.ch)

The Hamilton BIOS system installed at the Inselspital in Bern allows biological samples to be stored at –80 °C. The system fully automates the handling of the sample, including its storage, retrieval and inventory. (Photo projektfotografie.ch)



Laboratory tour of Clinical Chemistry at the Inselspital Bern during the Thematic Platform IVD event on the 25th of April 2016. Alexander Leichtle of the Inselspital displays the laboratory's analytical equipment. (Photo projektfotografie.ch)

industry. It offers a platform to all players in the IVD market to gain access to the most recent trends and technologies and to find the best partners to realize their next-generation products. However, success depends on the creativity and innovative spirit of the platform members. That's why interested parties are cordially invited to contact the IVD platform for an informal exchange of ideas on potential collaborations. The next chance to meet the Thematic Platform IVD is at the scientific forum 'Molecular Diagnostics (22 September 2016) during the Basel Life Science Week.

Thematic Platform IVD at a glance

Network Projects: To get access to companies, medical and academic institutions

Seed Money: To advance smart ideas and perform proof-of-concept studies

Company Visits: To deepen your understanding on the challenges in industry and to learn from others

Workshops & Symposia: To extend your network, exchange ideas and discuss new trends

For further information please contact:
Website: *http://www.biotechnet.ch/content/vitro-diagnostics-0*

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[1] Grand View Research Inc. is a US-based market research and consulting company in San Francisco.

[2] B. B. Spear, M. Heath-Chiozzi, J. Huff, *Clinical Trends in Molecular Medicine* **2001**, 7, 201–204.