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Conference Report

Early Diagnosis – The Value of Knowledge

The 2014 Olten Meeting

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Abstract: The 2014 Olten Meeting of Swiss biotechnet took place under the heading of 'crystal-clear insights', referring to innovations that make prevention, diagnosis and therapy more reliable, faster and cheaper thanks to biotech breakthroughs. The balanced mixture from research and industry generates new impetus and helps to develop key strategies for the future.

Keywords: Diagnostic biomarkers · Laboratory medicine · Omics technologies · Point-of-care devices · Specific microarray detection · Therapeutic drug monitoring

Advances in diagnostics promote the welfare of patients and have to be economically profitable, whether they address early detection of chronic diseases or targeted therapies for acute illnesses. Both researchers and industry experts are working on technologies that are faster, cheaper and more precise, allow the use of portable devices, are user friendly and easily interfaced with healthcare systems. But what solutions are available in a central reference laboratory, hospital setting or at the patient's bedside?

Efficiency versus High Cost Pressure

We have to face reality. This is the message delivered by PD Dr ***Alexander B. Leichtle*** from the Center of Laboratory Medicine at the Inselspital Bern. He discusses the experience of the Klinikum Aachen. Like all university hospitals active in research, teaching and patient care, they experience a very high demand for laboratory tests and therefore operate their own central laboratory. But the laboratory market is a growth market, not least because people get older and more investigations are needed. In the face of the immense cost pressure, the Klinikum Aachen has forged new paths: The central laboratory has been transformed into a *Labordiagnostisches Zentrum* (LDZ) led by a commercial laboratory operator with the aim of achieving cost savings of up to 5 million euros per year, while dealing with more than 1000 examination methods.

"Laboratory reports influence 70–80% of all medical decisions. Laboratory medicine is a core competence", states Alexander Leichtle whose research focuses on the future of diagnostics in the face of the challenges posed by big data. "But no other medical field has been subjected in the past 30 years to such a development boost towards industrialization and marketization." One of the consequences is that chairs for laboratory diagnostics in Germany have disappeared, hence the decline of laboratory diagnostics as a scientific discipline. With the significant advances in automation and miniaturization, laboratory medicine is mutating into a factory process. One example is the nanopore-based electronic systems for the analysis of single molecules. Or just think of the often quoted lab-on-a-chip, which is capable of integrating laboratory functions on a device just a few millimetres in size. This accommodates the needs of modern healthcare, offering miniaturization and connectivity, decentralizing diagnostics and doing away with existing laboratory structures.

In order to be ready to face the future, at the Inselspital Bern the Center for Laboratory Medicine is experiencing a dynamic transition through to 2016: "We place great emphasis on omics technologies, biobanking and big data, in the sense of integrated healthcare research." Omics addresses fields of study such as the genome, proteome or metabolome. "Our planned Biobank Bern will accommodate the central control and switching systems, including plasma, serum and blood cell derivatives. And the final task is to incorporate hospital data and biobank analyses in a 'Big Data' approach for the diagnosis of diseases."

For more information: *www.ukc.insel.ch*

Acquity UPLC separation system coupled with a Xevo TQ-S (Waters) mass spectrometer at the Inselspital Bern. The UPLC separates metabolites, then the mass spectrometer ionises the molecules for the analysis. (Picture Inselspital Bern)

With the UPLC Xevo TQ-S researchers at the Inselspital Bern quantify known metabolites with a validated method. On the other hand, non-targeted metabolomics has the purpose to identify unknown metabolites. In this case, the scientists undertake a wide screening with the UPLC Synapt G2-S HDMS System in order to detect the maximum number of metabolites. (Picture Inselspital Bern)

Changing Cost Structure in Health Care

A move in a new direction is planned by Hutman Diagnostics AG in Basel with its Endocardi-Gene® Tissue, a new microarray-based molecular screening test for infective endocarditis. This is an infection of the endocardial surface of the heart, involving one or more heart valves, the mural endocardium or a septal defect. The intracardiac effects cause serious valvular insufficiency. As a result the patient suffers from intractable congestive heart failure and myocardial abscesses which, left untreated, prove fatal. All over Europe, 28'000 cases of endocarditis are reported every year. "The Endocardi-Gene® Tissue bacterial panel developed by Hutman Diagnostics covers 95% of endocarditis cases", relates Dr. ***Sabine Kressmann***, Head of the Laboratory. "It consists of a universal PCR, species-specific microarray detection and software-based readout. Sample preparation methods for guaranteeing optimal DNA extraction and sensitivity vary."

The Hutman team from right to left: Gustavo Gershuber, Dr Sabine Kressmann, Dr Bruno Golding, Michael Cernochova and Dr Nicolas Ponroy. (Copyright Kenneth Nars, bz Basellandschaftliche Zeitung)

The semi-automated test is based on the same unique technology platform employed for all Hutman products. "Besides bacterial endocarditis, we develop diagnostic test kits for pneumonia, meningitis and fever", says Sabine Kressmann. "For technical and scientific aspects of design and development we work closely together with physicians and microbiologists from hospitals all over Europe. "The advantage of the Hutman products is faster detection of the cause of infectious diseases and thus earlier treatment, a lower spend on medication, a shorter stay in hospital and generally fewer overhead expenses for the hospital", reports Sabine Kressmann. And there is a wide range of applications, not only human diseases, but also veterinary, environmental and food safety applications.

The Hutman strategy is to manage product development and portfolio management while outsourcing the production processes. The company focuses on the 300 largest hospitals in Europe with cardiology departments and a total bed capacity of more than 1000.

For more information: *www.hutman.ch*

Continuous Innovation for Breakthrough

It was in 2008 that scientist Dr. ***Ralph Schiess*** and economist ***Christian Brühlmann*** developed a first business idea. The goal was to market a blood-based test that Dr. Ralph Schiess had developed during his PhD studies at ETH Zurich. The test is capable of diagnosing prostate cancer with significantly higher accuracy than the current clinical standard. In 2010 they founded the spin-off company ProteoMediX (CHIMIA **2012**, *66*, 1-2, 61). The stakes are considerable, as – according to the NIH – prostate cancer is of increasing significance worldwide. In many industrialized nations such as the United States, it is one of the most common cancers and among the leading causes of cancer deaths. But three out of four current diagnoses are wrong and lead to unnecessary biopsies. Inadequate prognostic methods cause overtreatment, as two thirds of the prostate tumours do not need immediate treatment. Treatment procedures are unspecific, which explains why oncology drugs have no effect in up to 75% of patients. The resulting costs are enormous, as one single biopsy costs about US $ 1500, while overtreatment costs are estimated at US $ 7700 per patient in the US. Therefore, ProteoMediX wants to drive innovation forward in diagnosing the disease more accurately.

The diagnostic tools developed by ProteoMediX laboratories to enable personalized medicine will reduce overtreatment by providing urgently needed diagnostic tests that support physicians in their therapy decision making. (Picture ProteoMediX)

Today, the ProteoMediX' strategy consists of three thematic axes, as CEO Dr. Ralph Schiess explains: "On the one hand we develop diagnostic biomarkers in order to detect the cancer at an early stage and rule out false-positive results, on the other hand we produce prognostic tools that can distinguish aggressive from indolent tumours. Finally, in clinical trials our stratification biomarkers have shown considerable potential in their ability to match patients with safer and more effective therapies and thus to

enable personalized medicine." To be compatible with standard technology platforms in diagnostic laboratories, the test format was adapted accordingly and the biomarker assays transferred from the originally used mass spectrometry platform to the immunoassay format. This method allows a rapid, sensitive, reproducible, cost effective and easily manageable analysis.

The two co-founders of ProteoMediX: CEO Dr Ralph Schiess (right) developed at the ETH Zurich the biomarker discovery technology and identified the prostate cancer biomarkers. CFO Christian Brühlmann contributes his experience in business administration, finance, business development and product management. (Picture ProteMediX)

Success may not be far away: "The high specificity of our new PMX-Dx test potentially lowers the rate of unnecessary biopsies in clinical practice by more than 60%", concludes Ralph Schiess. "...and there are promising products for prognosis and patient selection in our pipeline."

For more information: *www.proteomedix.ch*

Decentralized Therapeutic Drug Monitoring (TDM)...

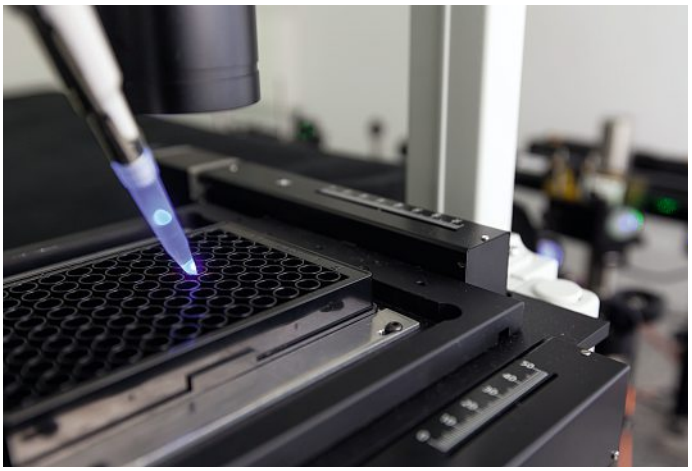
"At first glance the principle is simple to grasp", says Professor ***Marc Pfeifer***, "but reality is far more complex". In drug therapies it is crucial to maximize effectiveness and minimize toxicity; drug concentrations in the patient's blood stream above a certain level can lead to significant adverse drug reactions (ADR); a dose below an appropriate level will fail to give the expected therapeutic benefit. For instance, kidney transplant patients when treated with too high doses of immunosuppressants such as cyclosporine A (CsA) or tacrolimus can develop nephrotoxicity and other serious health issues. By contrast, concentrations below a certain threshold are associated with an increased graft rejection rate and elevated mortality.

Many drugs – immunosuppressants, antiepileptics, anti-arrhythmics and antibiotics to name a few classes – have narrow therapeutic ranges and some are situated in the low nanogram per milliliter concentration domain. What complicates maintenance of appropriate therapeutic plasma levels is the fact that intra- and inter-individual pharmacokinetic variabilities can, among other reasons (*e.g.* adherence in patients), have a major impact on concentrations observed. This is why expert clinical interpretation of measured values is important in order to factor-in aspects such as clinical (disease) state, co-medication, age, gender, anthropometric parameters and genetic polymorphisms. Individuals in the latter case with reduced CYP3A5 activity, for instance, are known to require a lower dose of tacrolimus to reach appropriate target blood concentrations. An increasingly elderly population also means aging, *i.e.* changing physiologies. In a recent publication it was reasoned that an increased number of patients aged above 65 listed for renal transplantation will require an individualized immunosuppression regimen due to their aged immune systems.

...here comes the future!

One limitation of how therapeutic drug monitoring is done today is the fact that processing and analysis of samples usually have to take place in centralized laboratories of larger hospitals. Patients have to travel to these hospitals to give blood or have to visit their family doctors who will then ship samples to be analysed with automated high-throughput instruments. Logistically this is inconvenient for the patient and associated with costs, and it means that the test results are obtained with a certain delay before therapy may have to be adjusted. Thus, a fairly complex and expensive overall workflow as well as the need to collect millilitre amounts of blood prohibits implementation of more frequent measurements to support early determination of development of inappropriate plasma concentration profiles. A reliable point-of-care (POC) device capable of measuring drug levels in a drop of blood at the family doctor's office or even at the patient's home would offer new possibilities for managing critical values and timely drug dosage adjustments. Studies with anticoagulation self-management, for instance, have actually shown that incidence and complications (thrombosis, major bleeding) can be reduced with such POC devices for home use testing.

Design model of the future POC instrument for TDM. A drop of blood is processed in a disposable sample preparation cartridge. Analyte molecules – depicted as triangles – are then quantified in the analytical module before results are sent to a remote database. (Illustration C. Guiducci, EPFL, adapted by M. Pfeifer)



A fluorescence polarization approach is currently under investigation as a candidate assay and detection format for the future point-of-care therapeutic drug monitoring device. What in future will be fully automated still requires considerable manual intervention – such as pipetting – when working with current test rig at HES-SO Valais-Wallis. (Picture photo-genic.ch)

As part of a nano-tera/SNSF funded project, the University of Applied Sciences and Arts Western Switzerland (HES-SO Valais-Wallis) is engaged in the development of a prototype POC device for TDM in close collaboration with its sister school in Yverdon (VD) and three groups at the EPFL (PI Prof. Carlotta Guiducci) as well as the University Hospital in Lausanne (CHUV). "What is remarkable about this interdisciplinary collaboration is that the team conducts fundamental and applied research while at the same time developing a prototype instrument following a process common to the medtech and *in vitro* diagnostics (IVD) industry and with a clear customer-oriented focus", says Professor Marc Pfeifer who heads the Diagnostic Systems Research Unit at the Institute of Life Technologies in Sion. He and his colleague Professor ***Jean-Manuel Segura***, an accomplished analytical chemist, work together on assay and systems development activities, knowing that the design specifications of the prototype, sample preparation and the target-specific assays are strongly interdependent. "From my experience in industry I know how long it takes to develop a new product that meets customer needs and signifies progress in healthcare," adds Marc Pfeifer. "Our goal is at least to challenge the status quo and to open the door towards a better management of variability in drug exposure and clinical outcomes. Maybe one day such portable POC multi-analyte monitoring devices can also be used during the development and clinical study of an investigational new drug (IND)?"

For more information: *www.nano-tera.ch/projects/368.php* and *www.hevs.ch/dxs-itv*

An Optimistic View of the Future

"Besides classical biotechnology, which is becoming extremely important in the fermentative production of natural substances, biochemical and recombinant proteins, as part of the automation, miniaturization and interoperability of instruments and devices, we are observing a global trend towards a new branch of biotechnology", points out Professor ***Daniel Gygax***, president of biotechnet, organizer of the 2014 Olten Meeting as part of the Biotech NTN. "Freeman Dyson called this process the domestication of biotechnology. The personalised use of smart phones, high-tech watches or glasses for the monitoring of states and functions like health monitoring of glucose levels, heart rate and prostate-specific antigen (PSA) may be an expression of what he had in mind." Just think of the versatile benefits of a cell phone, the epitome of high-tech at low cost: "With its camera of up to 40 megapixels, integrated sensors, memory capacity of up to 32 GB, amazing connectivity and apps for science, technology and health care, the cell phone is now within the reach of 7 billion subscribers worldwide. Biotechnology is currently at the threshold of a new area – and biotechnet Switzerland is playing an active role right on the front line!"

Swiss biotechnet: *www.biotechnet.ch*

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