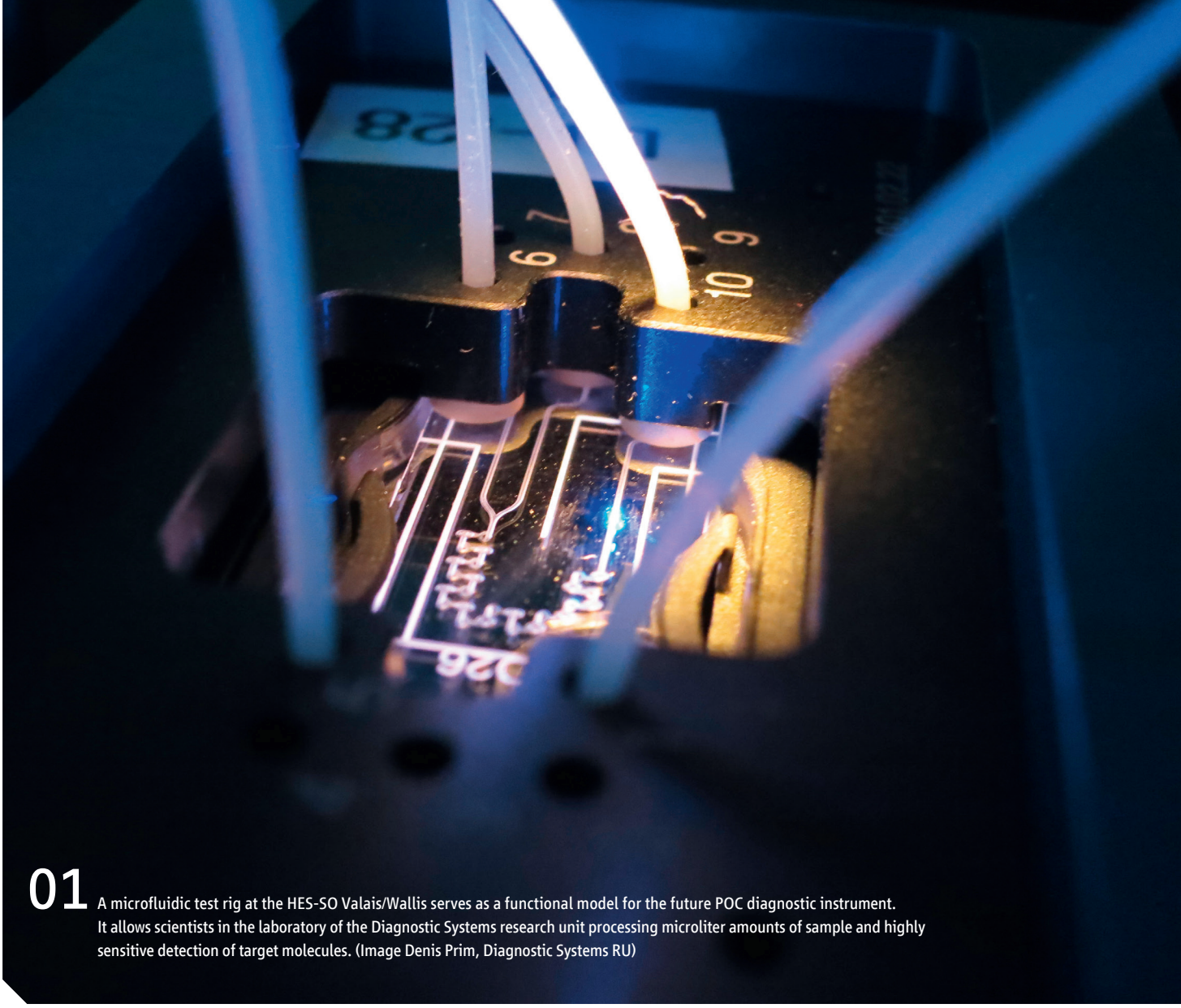


01 A microfluidic test rig at the HES-SO Valais/Wallis serves as a functional model for the future POC diagnostic instrument. It allows scientists in the laboratory of the Diagnostic Systems research unit processing microliter amounts of sample and highly sensitive detection of target molecules. (Image Denis Prim, Diagnostic Systems RU)

SWISS BIOTECH PLATFORM

NTN Swiss Biotech – Competences across the Entire Value Chain

The National Thematic Networks (NTN) created and supported by the Commission for Technology and Innovation CTI in 2013 are a step towards a more efficient transfer of knowledge and technologies. The NTN Swiss Biotech provides a powerful link between research & development and technology transfer for the Swiss Biotech Association and for biotechnet Switzerland, serving as a basis to promote world-class innovation.

ELSBETH HEINZELMANN

There are good reasons why Switzerland has – in relation to its population – the world's densest concentration of biotech companies: the financial power of investors, well-trained and highly qualified employees, a high quality and precision awareness and the presence of pharma giants who are among the three largest around the globe in terms of revenues. The success is founded on top-level research and clever networking of research and industry.

A Platform for Advanced Diagnostics

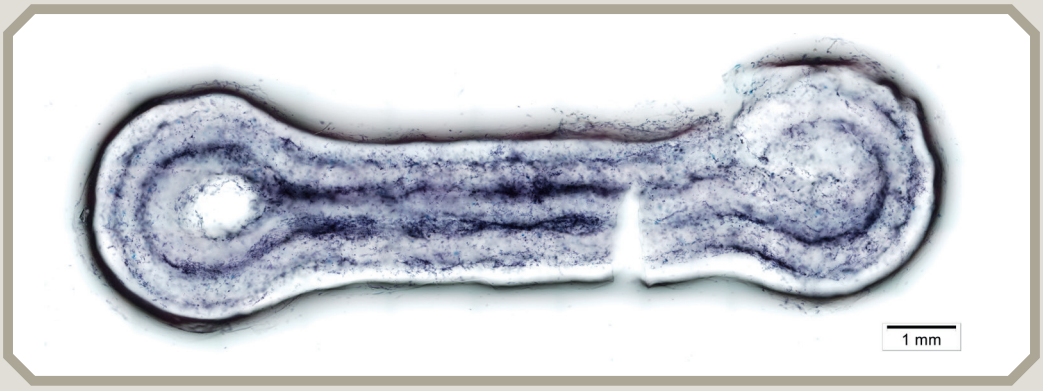
The market for diagnostics has been rapidly evolving over recent years. The demand for reliable diagnostics is growing worldwide; dependability and speed is vital. At the School of Life Sciences at the University of Applied Sciences Northwestern Switzerland (FHNW), the group led by Professor Daniel Gygax – president of NTN Swiss Biotech and biotechnet – is developing an innovative platform for sophisticated and practice-oriented diagnostic systems together with the University Hospital Base, Bühlmann Laboratories AG and Dorner Health IT Solutions. The focus is on new test kits in the domain of bioanalysis for use in *in vitro* diagnostics. "The platform can be used to design integrated processes, from the gene to the gene product and for realizing test systems," explains Prof Dr Daniel Gygax. "All disease-related molecules – DNAs, RNAs, proteins and metabolites – are available as potential markers for *in vitro* diagnostics."

A good example is Bühlmann's Quantum Blue Calprotectin rapid test for quantitative calprotectin analysis. It's a point-of-care (POC) test for the treatment of Inflammatory Bowel Disease (IBD), and it is the only one of its kind in the world. IBD is a chronic inflammation of the digestive tract. It includes ulcerative colitis and Crohn's disease. Patients suffer from severe diarrhea, pain, fatigue and weight loss, all of which may lead to life-threatening complications. Together with forteq Ltd. in Nidau, the researchers developed the CALEX device, a complex plastic tube filled with a buffer solution. "It enables the patient to take a small sample of stool rapidly and hygienically," comments Dr. Jakob Weber, Corporate Scientific Officer at Bühlmann. "The tube is then used to homogenize the sample and apply an accurately metered drop of the resulting mixture to a calprotectin test cassette, managed by an app and measured using a smartphone camera." In no time at all, the result appears on the screen in the form of a traffic light (normal, moderate, high). Then it is sent over the Internet to the treating physician, who saves it in a web-based patient dossier.

02 PuraLev 200SU: Single-Use Pump System for gentle conveyance of sensitive media. 1200 l/h consistent flowstream and no noise at 11 cm². (Image Levitronix)

03 Research assistants Katharina Blaschczok (right) and Ina Dittler are working at the ZHAW on the project with Levitronix for the development of magnetically levitated bearingless motor technology for low-shear pump systems. (Image ZHAW Wädenswil)

04 Viability staining (MTT) of human myoblasts printed with bio-ink in a layer-by-layer mode and differentiated for 7 days. Scale bar: 1 mm. (Image ZHAW Wädenswil)



Point-of-care Diagnostics on the Rise

Laborious sample preparation as well as data management constraints are two reasons why the number of marketed POC diagnostic devices has remained limited. Hospital bedside testing and family doctor's office requirements are not or only poorly compatible with the need to collect blood in milliliter instead of microliter, quantities making it necessary to perform centrifugation or complicated analyte extraction procedures. "Imagine an instrument that is capable of processing just one drop of blood to give you a reliable result in just a few minutes," says Professor Marc Pfeifer, Head of the Diagnostic Systems Research Unit (DxS RU) at the Institute of Life Technologies. "It goes without saying that the device envisioned was able to support a broad test menu via dedicated analyte-specific cartridges," adds his colleague Professor Jean-Manuel Segura, an expert in the field of fluorescence detection. Significant technological advances have been made in recent years in areas such as microfluidics, sensors, molecular capture probes and systems integration.

As far as data management is concerned, the boundaries of the interconnection and interoperability of devices are gradually vanishing with the advent of cloud computing and the Internet of Things (IoT). Test results can be instantaneously transferred to a central database and interpreted by the treating physician and, if necessary, the specialist involved. "Ground-breaking progress in healthcare can be made if we are able to combine these powerful new eHealth applications with highly sophisticated molecular assays and smart hardware design solutions," explains Michael Schumacher, Professor at the Institute of Information Systems and coordinator of the Health Technology Innovation Center (HTIC). To exploit the potential, several institutes of the University of Applied Sciences Western Switzerland of the canton of Valais (HES-SO Valais/Wallis) started to collaborate more closely together at the beginning of this year under a common umbrella organization termed HTIC to foster large interdisciplinary R&D projects. "The value chain is based on us being able to bring together the necessary experts to conceive and develop innovative and comprehensive solutions to unmet healthcare needs," concludes Marc Pfeifer, HTIC vice-coordinator.

POC tests are one of the most rapidly growing segments of the *in vitro* diagnostics (IVD) market. "This is another good reason why we would like to organize a Swiss Symposium for POC Diagnostics in 2015," Professor Segura and Professor Pfeifer both agree. It will be a nice way to show how new technological developments can translate into future products for healthcare. Of course, inter- or multidisciplinarity also means that the team in Valais is completely open to collaborations with research groups across Switzerland.

Cost-effective Manufacturing with single-use Technology

Today, single-use technologies are – together with continuous processing – the key drivers in the bioprocessing industry. They are the ideal approach for small biotech firms for initial scale-up and late-stage trials, but also so that big manufacturers are able to meet increased demand for new products more rapidly. One pioneer is Lonza, who has been investing in single-use technology and facility upgrades for clinical antibody drug conjugate (ADC) manufacturing since summer 2014 and has therewith expanded its ADC production area.

Internationally renowned experts in the domain of single-use technology are Professor Regine Eibl, head of the Section for Cell Cultivation Technique, and Professor Dieter Eibl, head of the Centre for Biotechnical Engineering at Zurich University of Applied Sciences in Wädenswil. Together with Levitronix GmbH, specialists in the development of magnetically levitated centrifugal pumps, the

"All disease-related molecules – DNAs, RNAs, proteins and metabolites – are available as potential markers for *in vitro* diagnostics."

PROF. DR. DANIEL GYGAX. Professor at the Institute for Chemistry and Bioanalytics at FHNW

"Imagine an instrument that is capable of processing just one drop of blood to give you a reliable result in just a few minutes."

PROF. DR. MARC PFEIFER. Head of the Diagnostic Systems Research Unit, Institute of Life Technologies HES-SO Valais/Wallis

"Our models should reduce animal experiments and save time and costs."

URSULA GRAF-HAUSNER. Professor at the Institute of Chemistry and Biological Chemistry at the ZHAW

group led by Dieter Eibl qualified and improved the single-use prototypes of the company's PuraLev series. Even though pumps can increase process safety and efficiency, they can damage shear sensitive fluids such as culture broths containing mammalian cells, which have to be conveyed in the majority of biopharmaceutical production processes.

The Levitronix novel single-use pumps are pulsation and seal-free with a pump head made of plastic to be discarded after one use and do not have the drawbacks of shafts, seals and leaks, which are typical of traditional pumps. In a CTI-funded project, researchers evaluated the mechanical stress that was caused by the Levitronix single-use pumps to CHO suspension cells, lysozyme solutions and a model emulsion. In addition, numerical simulations and comparative investigations were carried out using multi-use versions of the pump series and two pumps made by competitors (a peristaltic and 4-piston diaphragm pump).

As the results confirm, the Levitronix pumps cause significantly lower cell death rates (up to 41 %) in CHO suspension cells than their counterparts. This finding was also confirmed by the Sauter diameter determined in dependence on energy dissipation rate. Furthermore, no protein activity and structure changes were found for the PuraLev 200 SU and 600 SU pumps.

Generating new knowledge about the bioengineering characteristics of single-use equipment helps this promising technology to find its way into the biotech industry and to become an even more significant value-added factor.

Human Tissues for Drug Development

A breeding ground for innovative ideas in tissue engineering is the TEDD network (Tissue Engineering and Drug Development).
The network is the brainchild of Ursula Graf-Hausner, Professor at the Institute of Chemistry and Biological Chemistry at the ZHAW. The partners from public and industrial research institutions cover the entire development and value chain. Their focus is on the realization of 3D tissue cultures using human primary cells for different types of tissue such as bone, cartilage and intervertebral discs, connective tissue and skin, liver, kidney and tumor tissue. Besides production with or without scaffolds, 3D bioprinting technology is one emphasis made possible by industrial partner regenHU. Bio-ink, a biomaterial supporting cellular growth, in combination with the 3D Discovery bio-printer – both developed within CTI projects by ZHAW and regenHU (CEO Marc Thurner) – generate 3D constructs of cells, proteins and extracellular matrix components for tissues and organ models. Pioneering work has been accomplished in a CTI-project with Novartis, regenHU and Weidmann Medical Technology AG. Their *in vitro* test device comprises a microstructured multiwell culture plate with stimulation and readout for bioprinted muscle and tendon tissues. The system replaces animal based *ex vivo* test arrangements which have insufficient throughput and poor reproducibility. The application of 3D bioprinting processes enables the mimicking of complex *in vivo* muscle and tendon tissue. This fulfills a long-standing need, as there were no pharmaceutical therapies for muscle and tendon-related diseases until now. "The huge advantage of the printing technology is the exact positioning of cells, matrix component and signalling factors," says Ursula Graf-Hausner. "Our models should reduce animal experiments and save time and costs." Bioprinting is a technology with enormous potential to produce living organ-like tissue models with high complexity and functional structures. "Now we are ready to go for complex tissue models and further applications, not only in drug development but also in the area of regenerative medicine," concludes Graf-Hausner. LS

MENTIONED PARTNERS AND PROJECTS OF THE SWISS BIOTECH NTN

- FHNW. *www.fhnw.ch/lifesciences*
- HTIC. *http://htic.hevs.ch*
- HES-SO (DxS RU). *www.hevs.ch/dxs-itv*
- ZHAW. *www.lsfm.zhaw.ch/de/science/ibt-bvt.html*
- ZHAW. *http://project.zhaw.ch/en/science/tissue-engineering-for-drug-development.html*
- Swiss Biotech NTN. *www.swissbiotech.org/ntn_swiss_biotech*
- Biotechnet. *www.biotechnet.ch*
- Swiss Biotech Association. *www.swissbiotech.org/industry_association_sba*