lifesciences plus

journal for research, laboratory and bioprocessing

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www.chemieplus.ch

"Switzerland houses an extraordinarily vital and versatile life sciences scene."

Fascinating Life Sciences

Did you know that researchers at the University Children's Hospital Zurich are developing innovative skin substitutes, which could make it possible for doctors all over the world to provide long-lasting help to seriously injured patients, such as victims of fires, requiring only one procedure? These preparations entered clinical trials this year. Would you like to "watch" fungi as they battle against bacteria on a molecular level? A microfluidic platform developed at the ETHZ allows such insights. Are you already curious about the new Campus Biotech in Geneva? In an exclusive interview, Campus Biotech Director Benoît Dubuis describes how the only centre of its kind in Europe for research and knowledge transfer is being created on the former Merck Serono site.

These are just three of the many interesting topics, which we will be highlighting in this first edition of "Lifesciences plus." Finding suitable topics is not difficult, as Switzerland houses an extraordinarily vital and versatile life sciences scene. Within Swiss universities and companies, solutions are developed, which can make a considerable contribution to improving life on this planet. This is fascinating. So what could be more obvious than dedicating a new, topical magazine to this excellent research landscape? But for me, the "life" in life sciences also means something else. It stands for a modern, forward-looking type of coexistence: scientists, engineers, contractors and employees working with great motivation towards shared objectives, succeeding, celebrating and sometimes failing together – and all this irrespective of their nationalities, genders or religions.

Granted, this is an ideal, which reality occasionally trails far behind. But I think that every step in this direction is a good move.

RALF MAYER

Editor in Chief

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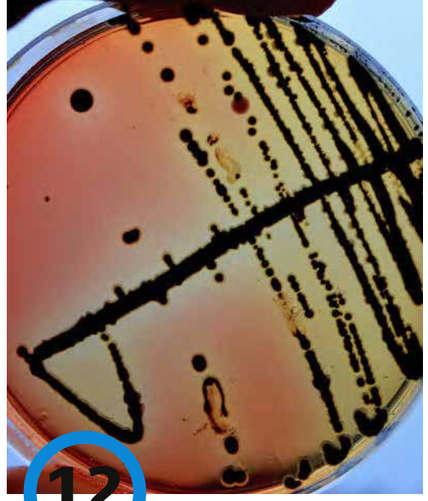
Please use the link **www.chemieplus.ch/lifesciencesplus** to pass on your reviews and suggestions about the new magazine.



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SUMMARY

MICROBIOLOGY

Salmonella diarrhea is a common infectious disease, worldwide. In Europe, a large proportion of the Salmonella diarrhea cases is caused by Salmonella Typhimurium (a close relative to Salmonella typhi, which is known for causing typhoid fever). So far, there are no effective cures or vaccines available. In order to identify new targets for intervention, researchers of the lab of Professor Hardt at the Institute of Microbiology, ETH Zurich, are analyzing the molecular basis of the disease. Investigations revealed an important and strikingly paradoxical role of the host's inflammatory defense.

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INTERVIEW

The new Campus Biotech is about to become a real jewel of science on Lake Geneva. The site where the multinational pharmaceutical and chemical corporation Merck Serono once developed and marketed innovative small molecules and biopharmaceuticals is being turned into a centre of excellence for research in biotechnology and the life sciences. In an exclusive interview, Campus Biotech Director Benoît Dubuis descirbes the projects challenges and chances.

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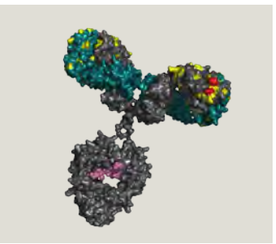
TECHNOLOGY TRANSFER

The Swiss Biotech NTN

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. A good example is the microfluidic test rig, which serves at the HES-SO Valais/Wallis as a functional model for the future point-of-care (POC) diagnostic instrument.

NEWS

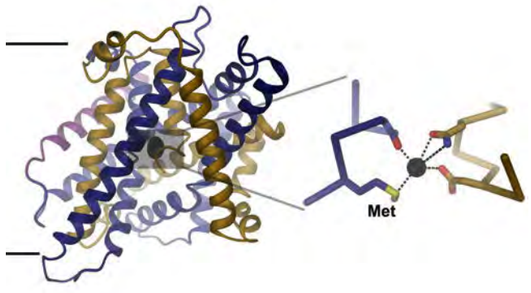
Influenza Virus Neutralizing Antibodies



A team of scientists led by Antonio Lanzavecchia (Università della Svizzera italiana) at the institute for Research in Biomedicine and Davide Corti at Humabs BioMed, in collaboration with colleagues at MedImmune and Elisa Vicenzi, Head of Unit – Viral pathogens & biosafety – San Raffaele University and Research Hospital, has been able to reconstruct the genealogy tree of a particular type of antibodies that can neutralize multiple species of influenza viruses (so-called broadly neutralizing antibodies). These antibodies bind to a conserved site on the influenza hemagglutinin that represents the Achilles' heel of the virus. There is a great interest to develop a universal influenza vaccine that can induce these types of antibodies. According to Lanzavecchia, there are plenty of precursors in the human body that can rapidly generate, with just a single mutation, potent neutralizing antibodies. This suggests that it should be possible to elicit, with an appropriate vaccine, high levels of antibodies that protect against all influenza viruses. In addition, the antibodies themselves are potential therapeutic agents for the treatment and/or prevention of influenza. The new and unexpected finding is that a single initial somatic mutation is sufficient to achieve maximal binding and neutralization of the virus, while the numerous mutations that occur at later time points are essentially redundant. The new study also shows that the making of these antibodies requires a particular gene segment (called VH1-69), which occurs in the population in two different forms, of which only one can give rise to a broadly neutralizing antibody. **# www.usi.ch**

Structure of an Iron-Transport Protein Revealed

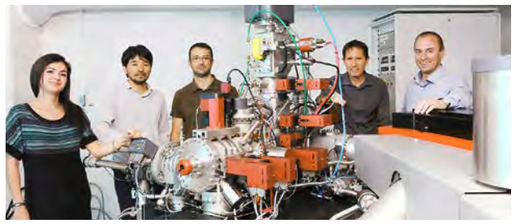
Biochemists of the University of Zurich have paved the way towards a better understanding of iron metabolism. In mammals, iron is imported into cells by the membrane transport protein DMT1. Mutations of DMT1, which affect its transport properties, lead to iron-related metabolic disorders such as anemia and the iron storage disease hemochromatosis. Ines Ehrnstorfer, a PhD student in the group of Professor Raimund Dutzler at the Department of Biochemistry of the University of Zurich, and her colleagues, have determined the first structure of an iron transport protein. Based on these results the researchers were able to explain why DMT1 binds the divalent metal ions iron and manganese (Fe^{2+} and Mn^{2+}), but not calcium (Ca^{2+}) – in spite of the latter being several orders of magnitude more abundant. To unravel the structural basis for this ion selectivity, Ines Ehrnstorfer has determined the structure of a close bacterial homologue of DMT1 by X-ray crystallography. The transport protein contains an ion binding site located at the center of the membrane that is composed of conserved amino acids. "One of these amino acids, a methionine, only interacts with transition-metal ions, but not with Ca^{2+}," explains Ehrnstorfer. The study also shows that mutations in the binding site weaken ion binding and transport in both the bacterial homologue and human DMT1. **# www.uzh.ch**



Swiss Scientists Explain Evolution of Extreme Parasites

Zoologists at the University of Basel together with scientists in Sweden and the U.S. have discovered a new parasite species that represents the missing link between fungi and an extreme group of parasites. The team of zoologists lead by Prof. Dieter Ebert has been studying the evolution of microsporidia – a large group of extreme parasites in humans and animals. Years ago, they discovered a new parasite in Daphnia (water fleas) and classified this undescribed species as a microsporidium, mostly because it possessed the unique harpoon-like infection apparatus (the polar-tube), one of the hallmarks of microsporidia. The analysis of the entire genome however revealed that the genome resembles more that of fungi than a microsporidium. In addition it has a mitochondrial genome. The new species, now named Mitosporidium daphniae, thus represents the missing link between fungi and microsporidia. The researchers showed that the new species derives from the ancestors of all known microsporidians and that the microsporidians derive from the most ancient fungi; thus its exact place in the tree of life has finally been found. Further, the scientists conclude from their work that the microsporidia adopted intracellular parasitism first and only later changed their genome significantly. Our results are of great interest to the study of parasite-specific adaptations in evolution in general," explains Prof. Ebert. **# www.unibas.ch**

A New Imaging Approach for Monitoring Cell Metabolism

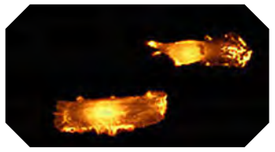


Scientists at EPFL have used a new imaging technique called NanoSIMS to monitor how glucose is used in the body. Employing NanoSIMS (SIMS stands for Secondary Ion Mass Spectrometry) they have been able to trace how glycogen is used in cells of the liver and the brain. Their findings may have great implications for diseases like diabetes. NanoSIMS images appear as colors and lines, and are not sufficient to localize molecules in a cell. For this reason, the samples were also photographed with an electron microscope, which provided an actual image of the tissue and cells. The EPFL team led by Arnaud Comment and Anders Meibom then superimposed the NanoSIMS image over the real photograph from the electron microscope, and could then obtain a complete picture of glycogen distribution in liver and brain cells. Using this method at different time intervals, the researchers were able to track how glycogen is formed over time, and in which parts of the cells. Their findings showed that liver cells store glucose into glycogen almost 25 times faster than brain cells (astrocytes). "This is the first time that this phenomenon is measured at such a small scale," says Comment. The method can be used for tracking other biological molecules, such as neurotransmitters in the brain. **# www.epfl.ch**

Flexible Flow Rates in the Kidney

A bathtub full of water and a kilo of salt make up the daily metabolic turnover of the human kidney, whose work is crucial for blood pressure stability and fluid balance. In the renal tube system, the first section reabsorbs the greatest part of water. Cells of the tubes contain Aquaporin-1 water channels, which are responsible for allowing the water to flow through the cell's lipid membranes so that it can re-enter the bloodstream. The research results of Prof. Franziska Theilig's group from the Department of Medicine of the University of Fribourg have now shown that a change in the rate of flow of the unconcentrated primary urine sends a signal to the cell which causes increased Aquaporin-1 to be built into the cell membrane. This is achieved by cellular redistribution of Aquaporin-1 from an intracellular pool into the membrane and by the channel being made more resistant through changed protein marking, thus reducing its degradation. Within a few minutes, this mechanism can bring about a short-term doubling of the flow of water through the cell and accordingly drastically increase the reabsorption into the blood. This discovery replaces the long-held hypothesis of the presence of a continually active (constitutive) movement of water via the kidney. Knowing how this regulation takes place could in future offer pharmaceutical methods of stopping the leakage or flow of liquids, thus preventing clinical complications such as the increased accumulation of water (edema and high blood or fluid pressure). **# www.unifr.ch**

Cells on the Fast Track



Cells migrate by connecting their cytoskeleton to adhesion molecules which in turn get in contact with the surrounding connective tissue. For directed movements a signal from outside is needed. In classical cell migration experiments, cells often move randomly, due to strong adhesion to the uniformly coated glass surfaces. Scientists around Prof. Olivier Pertz from the Department of Biomedicine at the University of Basel innovated the migration assay. They mimicked the connective tissue environment by using a special procedure: 20 micrometer wide lines were fabricated on glass and cells on the uneven surface were stimulated with a growth factor (PDGF), which lead to fast cell migration in only one direction for many hours – a highway for cells. The research results give novel insights into how signalling pathways are regulated in time and space in order to facilitate migration of cells only in one direction. Certain dot-like structures that are always located at the front of the cell adopt a crucial role in maintaining long term polarized cell migration. The findings are of great interest regarding the study and fight of cancer metastasis and inflammation where directed cell migration plays an important role. "The more insights we get into the mechanisms of cell migration, the more effectively and focused we will be able to intervene in certain pathological processes," first author Dr. Katrin Martin comments. **# www.unibas.ch**

Tricky Flu Virus

Viral infections always follow a similar course. The pathogen infiltrates the host cells and uses their replication and protein production machinery to multiply. The cell engulfs the virus in a bubble and transports it towards the cell nucleus. The acidic pH value inside the bubble is ultimately what causes the virus's outer shell to melt into the membrane of the bubble. However, this is only the first part of the process. Like other RNA viruses, the flu virus has to overcome a further obstacle before releasing its genetic code: the few pieces of RNA that make up the genome of the flu virus are packed into a capsid, which keeps the virus stable when moving from cell to cell. The capsid also protects the viral genes against degradation. A team of researchers from the ETH Zurich, the Friedrich Miescher Institute for Biomedical Research in Basel and the Biological Research Center in Szeged (Hungary) has now discovered exactly how the capsid of the flu virus is cracked open and how this key aspect of flu infection works: the capsid imitates a bundle of protein waste – called an aggresome – that the cell must disentangle and dispose. Deceived in such a way, the cellular waste pickup and disposal complex cracks open the capsid. The virus capsid carries cellular waste "abels" on its surface. These waste labels, called unanchored ubiquitin, call into action the enzyme histone deacetylase (HDAC6), which binds to ubiquitin. At the same time, HDAC6 also binds to scaffolding motor proteins, pulling the perceived "garbage bundle" apart so that it can be degraded. This mechanical stress causes the capsid to tear, releasing the genetic material of the virus. **# www.ethz.ch**

MICROFLUIDICS

Unprecedented Insight

into Microscopic Interactions between Fungi and Bacteria

Interactions between microorganisms are prevalent in many ecological systems and play important roles in microbial infections of humans and plants. Biomolecules modulating these processes are applied in medicine and plant protection. In order to gain insight into the interaction between living fungal filaments (hyphae) and bacteria at single cell level, a novel microfluidic platform was developed.

MARTINA STÖCKLI
MARKUS KÜNZLER

The ink cap mushroom Coprinopsis cinerea has been used as a model organism for the fungal order Agaricales (gilled mushrooms) since mid-1950 due to its easy cultivation and its capability to produce fruiting bodies under laboratory conditions. Accordingly, the genome sequence of C. cinerea was the first sequence available of this order *[1]*. Research on this organism has provided important insights into the mechanism of meiosis and the regulation of fungal fruiting body formation. Another interesting aspect of this fungus is its natural habitat, the dung of herbivores *[Figure 1]*. C. cinerea and other coprophile fungi have adapted to their nutrient-rich but short-lived substrate in that they are able to complete their lifecycles fast to disperse in time. In addition, these fungi have evolved effective strategies to successfully compete with other microorganisms e.g. bacteria living on the same substrate. ❱

01 Fruiting bodies of the inky cap mushroom Coprinopsis cinerea grown on sterilized horse dung in a glass petri dish (picture with courtesy of R. Sieber).

Vocabulary

Metagenomics
Method to capture the composition of a microbial community of an environmental sample based on high-throughput sequencing of extracted DNA.

Firmicutes
Phylum of bacteria, most of which are Gram-positive. They are found in many different environments.

Transcriptomics
Method to assess the genome-wide expression profile of organisms under a specified condition based on high-throughput sequencing of RNA extracted under this condition.

Fruiting body
Sexual reproduction structure of multicellular fungi by which meiotic spores are produced and dispersed.

Hypha
Filament formed by a linear array of fungal cells, minimal building block of the vegetative tissue of multicellular (filamentous) fungi.

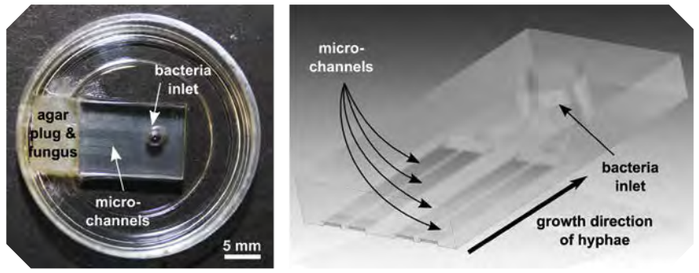
Mycelium
Three-dimensional network formed by branching and fusion (anastomosis) of all hyphae of a multicellular (filamentous) fungus; tissue.

Coprophile organism
Organism that lives on dung.

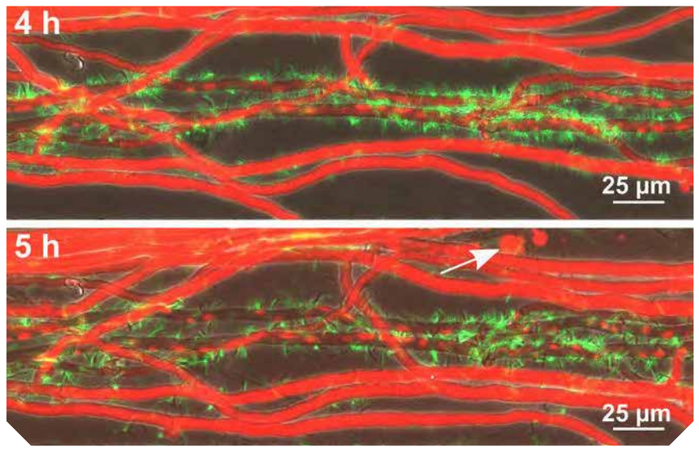
Microfluidics
Technology to control and manipulate small volumes of fluids in the pl-µl range in engineered systems.

Promoter-reporter fusion
Method to visualize the activity of the promoter of a specific gene; the region on the DNA that initiates transcription (promoter) is fused to a reporter gene which for example codes for a fluorescent protein.

An approach using microfluidic platforms was developed to study the antagonistic interaction between the dung-inhabiting mushroom Coprinopsis cinerea with the soil dwelling bacterium Bacillus subtilis.



02 Microfluidic platform for probing bacterial-fungal interactions. Left panel: Photograph illustrating the experimental setup. An agar plug with fungal mycelium is placed next to the opening of the channels. Microchannels and bacteria inlet are indicated. Right panel: 3-dimensional representation of the microfluidic platform (figure adapted from [5]).



03 Interaction between C. cinerea fungal hyphae and Bacillus subtilis bacterial cells in a microchannel of a microfluidic platform. Hyphae of C. cinerea are labeled by cytoplasmic expression of a red fluorescent protein and cells of B. subtilis are labeled by cytoplasmic expression of a green fluorescent protein. After four hours of co-inoculation bacteria are attached to certain hyphae (upper picture). After five hours of co-inoculation fungal hyphae empty and blebs are visible (arrow lower picture).

Fight for Nutrients

There is a high competition for nutrients between bacteria and fungi because these microorganisms share the same mode of nutrition. Both feed by secretion of hydrolytic enzymes into the substrate and absorption of the hydrolysis products. One strategy to succeed in this nutritional competition is to secrete molecules that inhibit the growth of the competitor. Many of these antimicrobial molecules have been identified and characterized with regard to structure and function and some of them have found applications in medicine and plant protection. The most famous fungal representative of such molecules is probably the antibiotic Penicillin. Despite all these studies, surprisingly little is known about the temporal and spatial regulation of the biosynthesis of these molecules during competition. For fungi, it has been shown that the presence of bacteria can significantly change the gene expression profile of a fungus *[2, 3]* and lead e.g. to induced expression of gene clusters encoding antibiotics *[4]*. These studies suggest that fungi are able to respond to a challenge with bacteria by the production of antibacterial molecules as part of their defense. However, the dynamics and the spatial distribution of this gene induction within a mycelium of a filamentous fungus have not been investigated so far. In addition, the signal that triggers the induction of the fungal genes and the specificity of this fungal defense response is not clear yet. In order to answer some of these questions, methods that allow the investigation of interactions between living fungal hyphae and bacterial cells in more detail are needed.

Novel Microfluidic Platform

Probing the dynamic interaction between living fungal hyphae and bacteria microscopically over longer time periods is technically challenging using existing methods because the hyphae form a three-dimensional interconnected network. Therefore it is demanding to track a single hypha or hyphal compartment over time, especially in an environment where also bacteria can be cultivated. The research groups of Prof. Markus Aebi and Prof. Andrew deMello at ETH Zurich joined forces and developed a novel microfluidic platform to tackle this challenge *[5]*. The use of microfluidic platforms in microbiology has become popular because these platforms allow the manipulation and examination of single microbial cells and of their microenvironment. An additional advantage of microfluidics over other systems is the requirement of only small amounts of compounds for an individual experiment *[6]*. The stamp of the novel microfluidic platform used to study bacterial-fungal interactions is made from the polymer polydimethylsiloxane. This material is often used for biological applications since it is non-toxic for cells, gas permeable and allows detection from 240 nm to 1100 nm. The stamp was bonded onto the glass bottom of a petri dish. This is advantageous because the petri dish can be closed and this renders the experiment sterile. The platforms designed allow cultivation of fungal hyphae in microchannels that are filled with liquid growth medium *[Figure 2]*. The height of the channels is 10 µm which constricts the growth of fungal hyphae, which have a diameter in average of 7 µm, in one direction and thus decrease the complexity of the hyphal network by transforming it from a three-dimensional to a two-dimensional one. The length of the channels allows the hyphae to grow for approximately 24 hours before they reach the end of the platform. Bacteria can be added with ease by pipetting into the bacteria inlet *[Figure 2]*. After addition, motile bacteria can freely move in the microchannels and interact with fungal hyphae. Upon contact of the two microorganisms growth speed, morphological changes of hyphae and movement of bacteria can be observed by taking a series of images over time. These platforms were used to investigate the interaction between C. cinerea and Bacillus subtilis on a single cell level. Metagenomics data of fresh horse dung, the natural habitat of the studied fungus, has revealed that Firmicutes were highly abundant and Bacillus was one of the most predominant genus found. B. subtilis is a common model organism for basic research of gram-positive bacteria and a species known to exhibit antifungal activity.

Dynamic Interactions

The results gained from these interaction studies revealed that B. subtilis cells attach in an end-on manner to only a subset of the hyphae of C. cinerea *[Figure 3, upper picture]*. No attachment of the bacteria to the tip region of the hyphae was observed. This region represents the most recently formed hyphal surface due to the apical growth pattern of fungal hyphae i.e. the cell wall of fungal hyphae is assembled at the tip and undergoes subsequent maturation processes. This result suggests that bacteria can only bind to mature cell walls of the fungal hyphae. Furthermore, the attachment of the bacteria to only a subset of hyphae within the fungal mycelium suggests that some hyphae are competent for bacterial attachment and others not. It appears that there is a significant degree of hyphal differentiation in the vegetative mycelium of a multicellular fungus that has not been recognized before.

Studies of the long-term growth characteristics of C. cinerea, using a fluorescently labelled strain, in presence and absence of B. subtilis revealed that fungal hyphae stopped growing after five hours in presence of the bacterium. This growth stop coincided with a morphological change of the fungal hyphae. Collapsed hyphal compartments which lost fluorescence and a concomitant emergence of fluorescent, membrane-enclosed cytoplasm (blebs) from these hyphal compartments were observed. This antifungal mode of action of B. subtilis has not been observed before.

Microfluidics for More Details

Taken together, interaction studies with the newly developed microfluidic platforms revealed unprecedented details of the dynamic interaction between living fungal hyphae and bacterial cells. This experimental set-up has several significant advantages over current methods and opens new perspectives for interaction studies between fungi and bacteria. It is envisaged to use this methodology to unravel the regulation of the fungal defense response towards bacteria. With the aid of transcriptomics studies candidate defense genes of C. cinerea will be selected and their temporal and spatial regulation will be studied in the microfluidic platforms using promoter-reporter fusions. These experiments will contribute to our understanding of the defense response of multicellular (filamentous) fungi against bacterial competitors. LS

AUTHORS

Martina Stöckli. *PhD student, Institute of Microbiology, ETHZ*
Dr. Markus Künzler. *Senior scientist, Institute of Microbiology, ETHZ*

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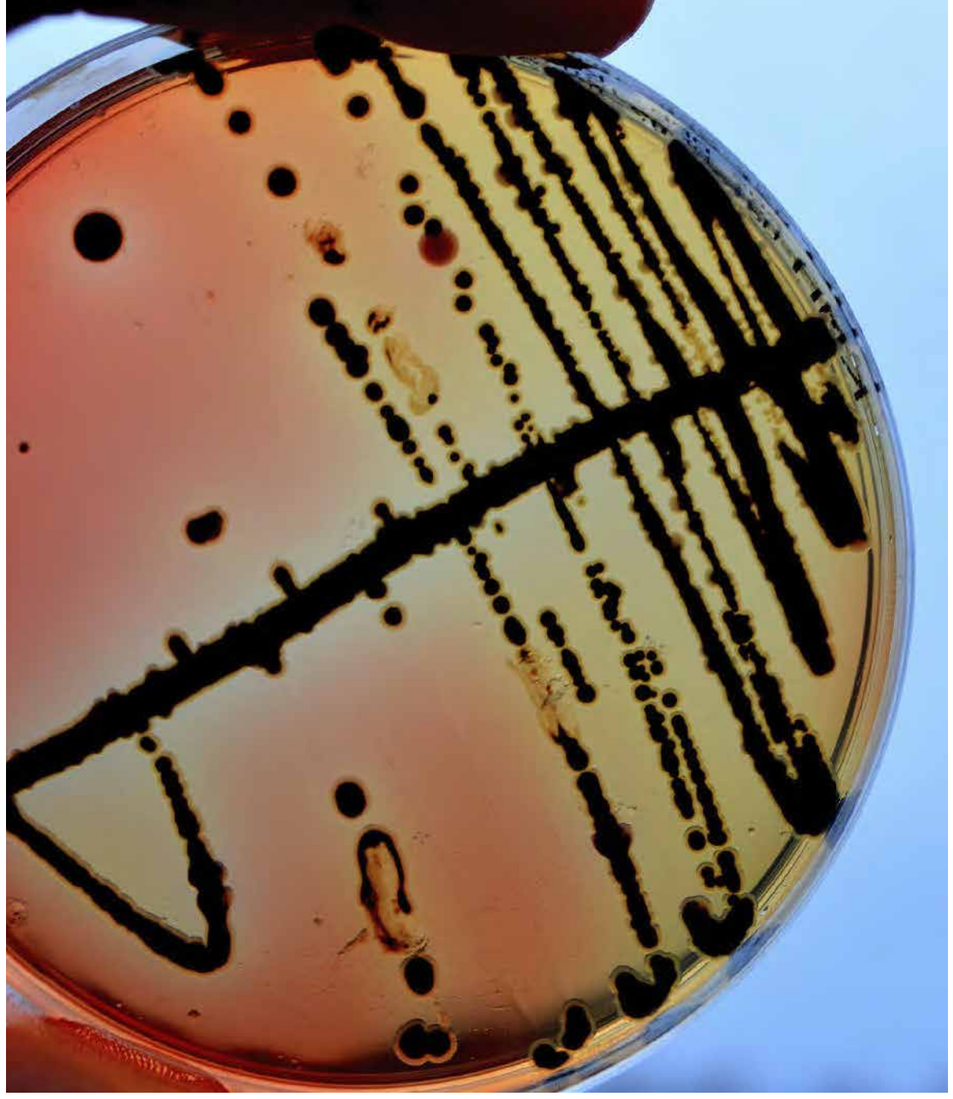
SALMONELLA

At the Interface between the Pathogen, the Microbiota and the Host

Salmonella diarrhea is a common infectious disease, worldwide. So far, there are no effective cures or vaccines available. In order to identify new targets for intervention, researchers of the lab of Professor Hardt at the Institute of Microbiology, ETH Zurich, are analyzing the molecular basis of the disease. Investigations revealed an important and strikingly paradoxical role of the host's inflammatory defense.



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WOLF-DIETRICH HARDT

In Europe, a large proportion of the Salmonella diarrhea cases is caused by Salmonella Typhimurium (a close relative to Salmonella typhi, which is known for causing typhoid fever). Salmonellosis is generally caused by consumption of contaminated food and leads to diarrhea. In the vast majority of cases, the disease is self-limiting and the patient recovers after 3–7 days. However, in immune-compromised people, the elderly and the young, the pathogen can spread and sometimes cause life-threatening systemic infections. Upon ingestion of Salmonella-contaminated food, the pathogen travels through the alimentary tract. In the intestine, the pathogen splits into two sub-populations: some bacteria remain in the gut lumen, while other bacteria invade into the gut mucosa. This tissue invasion provokes a fierce response by the mucosa's innate immune system.

Recent work has focused on the question why S. Typhimurium triggers such a strong mucosal immune response. It turns out that two quite different aspects of this host's inflammatory response are critical for the infection.

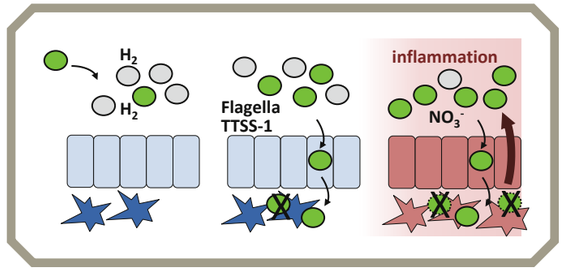
Attack and Invasion

Right after ingestion, the pathogen has to grow up in the gut lumen. Here, it faces the resident bacteria of the normal gut flora – the microbiota. These microbiota inhibit pathogen growth at least partially by using up the available nutrients, depleting oxygen levels and probably other unidentified mechanisms. In this phase, the pathogen has to use nutrients left over by the microbiota. One of these is hydrogen gas which is a typical intermediate of the microbiota metabolism. This hydrogen is used by S. Typhimurium to obtain energy *[Figure 1, Maier et al., 2013]*.

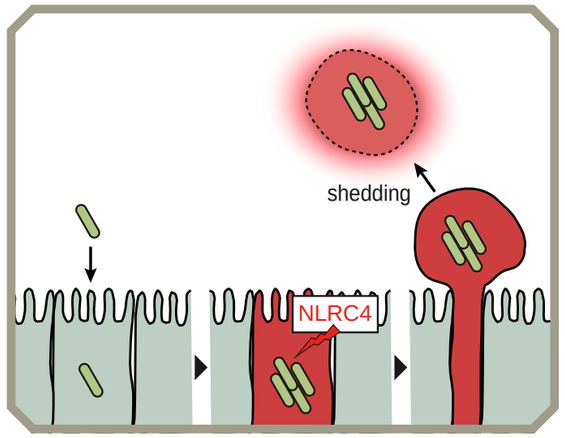
Once the pathogen has grown up to sufficient densities, it begins to invade into the gut tissue *[Figure 3]*. This tissue invasion is facilitated by several Salmonella virulence factors, such as the flagella allowing the bacterium to swim towards the gut epithelium and a so-called "Type III Secretion System" (TTSS-1), a syringe-like system which injects bacterial toxins into the infected gut epithelial cells (enterocytes). In one of this year's publications, researchers from the Hardt group were able to show that this infection is in fact recognized by the host cells. The affected epithelial cells have a particular chemosensory system, called "NLRC4-inflammasome," which constantly monitors the epithelium cell cytosol for the presence of virulence factors which are typically employed by enteropathogenic bacteria like Salmonella Typhimurium. In fact, the NLRC4 inflammasome recognizes exactly those virulence factors (flagella and the type III secretion system) employed by the S. Typhimurium to invade. Once activated, this system allows the enterocyte to respond accordingly and to mount two types of defense.

Defense with Aftermath

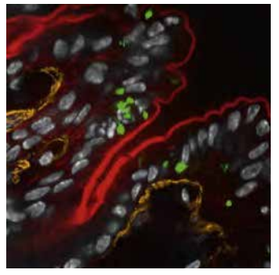
In a very fast first process, the infected enterocytes are dislodged from the epithelial layer (Sellin et al., 2014). This so-called "shedding" of the infected epithelial cells is quite effective and can reduce the pathogen loads in the gut



01 Initial steps of the gut infection by S. Typhimurium.



02 Shedding of infected enterocytes. This reduces the pathogen-loads in the gut tissue (adapted from Sellin et al., 2014).



03 Gut epithelium invaded by S. Typhimurium: The green bacteria are seen inside of gut epithelium cells (red: cytoskeleton, brush border; grey: nuclear DNA stain). The deeper gut tissue is stained in orange (Image by Mikael Sellin, ETH Zurich; adapted from Sellin et al., 2014).

Researchers of the Hardt lab use techniques ranging from biochemical analysis of virulence factor function to tissue culture assays simulating particular infection steps and animal models for deciphering the role of the host's immune response in the disease and defense against the pathogen.

tissue by as much as 100-fold. However, a few bacteria remain and can go on to invade deeper into the gut wall. The second defense that is mounted by the NLRC4 inflammasome is the release of chemical signals that call in phagocytes of the immune system and mount an inflammatory response. Again, this defense is quite effective in eliminating bacteria from the gut tissue (Felmy et al., 2013).

However, often this is not enough to clear the infection. Even worse, the mucosal defense has an important side-effect which is subverted by the pathogen: The by-products of the gut inflammation change the chemical composition of the gut lumen. This helps the pathogen to outcompete the resident intestinal microflora by a process called anaerobic respiration (Stecher et al., 2007; Winter et al., 2010). In this way, Salmonella Typhimurium can gain more energy in the gut lumen and simply grow faster than the microbiota which are mostly devoid of this trick. Thus, in the gut lumen, the pathogen can benefit from the host's response. Inhibitors targeting the Salmonella enzymes for anaerobic respiration may represent interesting targets for developing new drugs.

Tug-of-war

The immune defense appears to have multiple functions in the infection: On the one hand, this response limits pathogen invasion into the gut tissue. On the other hand, it fuels pathogen growth in the gut lumen by suppressing the normal gut flora. The infection is a tug-of-war between Salmonella and the mucosal immune defense. The mechanisms identified so far are most likely just the tip of the iceberg. Deciphering the interactions will help us to understand the complex pathogen-host interactions and might identify novel drug targets.

AUTHOR

Dr. Wolf-Dietrich Hardt. *Professor, Institute of Microbiology, ETH Zurich*

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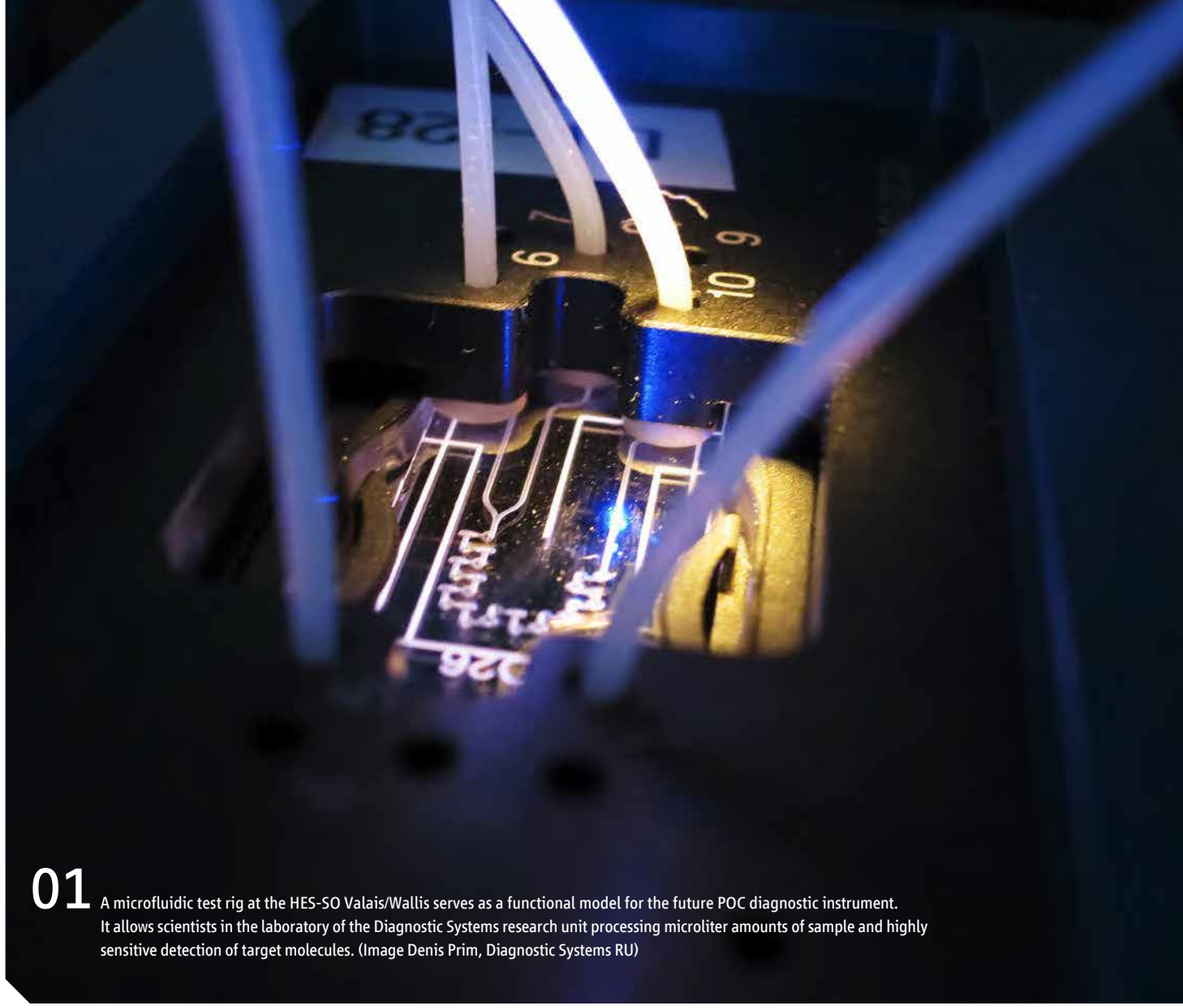


01 A microfluidic test rig at the HES-SO Valais/Wallis serves as a functional model for the future POC diagnostic instrument. It allows scientists in the laboratory of the Diagnostic Systems research unit processing microliter amounts of sample and highly sensitive detection of target molecules. (Image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

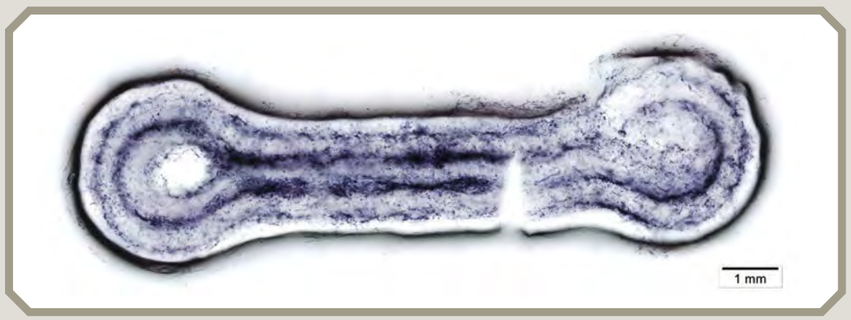
A Platform for Advanced Diagnostics

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. (ES)

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*

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ZIRP – ZURICH INTEGRATIVE RODENT PHYSIOLOGY

Bundled Competences for Research

Animal experiments are one of the key requisites for progress in medical research. Rodent models enable better insight into complex biological processes. Newly developed techniques and high-throughput phenotyping procedures – like imaging modalities, miniaturized implantable devices and laboratory analyses – enable investigations of many processes in living animals.

PETRA SEEBECK
MAGDALENA SEEBAUER

All of the animal experiment techniques have in common that the acquisition of the equipment is costly, operation and servicing are technically demanding, and downscaling to small rodents is most often challenging. Skilled staff with appropriate know-how is needed for their optimal utilization. As a consequence, the individual researcher most often does not have the ability to acquire all necessary equipment, cover its running costs and pay technical staff for operation. Zurich Integrative Rodent Physiology (ZIRP) provides infrastructure and equipment with a focus on analyses of rodent physiology on a shared resources basis, thus making complex techniques available at low cost to all researchers.

Facilitate and Improve

ZIRP pools the researchers' needs and facilitates their work by organizing and maintaining key infrastructure, providing training and support, and offering a number of basic services, such as:

- workspace, completely equipped "ready to use" or free space to build up own equipment
- sample collection
- administration of substances and
- surgical services

ZIRP offers flexible solutions and individual strategies in close cooperation with researchers by adapting procedures or combining different techniques with respect to individual requirements. ZIRP's skilled staff utilizes a broad array of standard experimental procedures, adapted to the characteristics of small rodent models.

ZIRP seeks to offer all services from one common source with all experimental work performed within the ZIRP – from transferring the animals into ZIRP's animal housing facility and performing different experiments to having the data available ready for analysis. ZIRP continuously upgrades its services and the ZIRP staff members are permanently refining existing techniques – always considering the researchers' needs.

Imaging Platform

Non-invasive imaging modalities offer numerous options for morphologic analyses and tracking of biological processes such as disease progression or metabolic pathways. The ZIRP imaging platform provides a number of state-of-the-art imaging devices as well as associated services and support.

In vivo micro-computed tomography (micro ct) is a non-invasive tool to visualize the animal's morphology. Common applications include imaging of the skeleton or bone samples, lung, cardiovascular system, soft tissue and tumours. For soft tissue imaging a multitude of contrast agents are available, e.g. for the depiction of vessels or organs *[Figure 1]*.

High-throughput imaging at low radiation doses is ideally suited for morphological phenotyping. High resolution scans are the method of choice for quantitative morphometric image analyses.

Bioluminescence and fluorescence imaging allow the visualization and quantification of biological processes in the living animal in real time. The method utilizes native light emission from bioluminescing organisms. The DNA encoding the luminescent protein (for example firefly luciferase) is incorporated into the laboratory animal. For light emission, the corresponding substrate (for example D-luciferin) needs to be injected into the animal prior to imaging. Bioluminescence imaging is commonly used for in vivo studies of cancer progression, development or cell migration, or infection. In addition, bioluminescence tomography allows the quantitative analysis of volumes and therefore, the precise three-dimensional follow-up of disease progression. This is useful for the growth and spread of a tumour.

Fluorescence imaging requires a specific fluorescing agent able to absorb and emit light of a certain wavelength, which needs to be injected prior to imaging. Targeted fluorescent markers actively bind to target structures, thus allowing the selective visualization of specific tissues or processes like tumour vascularization or inflammatory processes.

Telemetry Platform

Radiotelemetric transmitters enable the continuous and contact-free collection of physio-

"ZIRP's telemetry platform allows us to match *in vitro* organ chamber experiments with in vivo blood pressure measurement."

DR. ELVIRA HAAS. Research Unit, Div. of Internal Medicine, University Hospital Zurich

"This platform enables analyses of numerous parameters in small sample volumes with high accuracy."

PROF. OLIVER DEVUYST. Institute of Physiology, University of Zurich

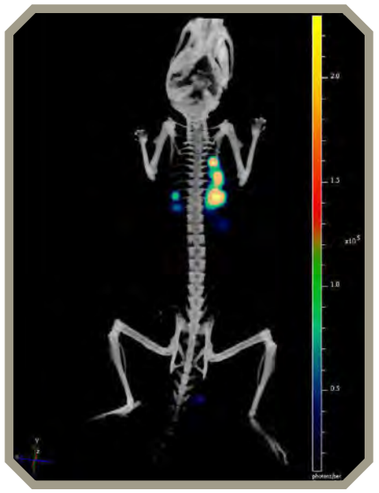
"Optical imaging of tumour cells is an invaluable tool for long term quantitative monitoring of cancer growth and spread in living mice."

PROF. IAN FREW. ZIHP Assistant Professor, Institute of Physiology, University of Zurich

About Zurich Integrative Rodent Physiology (ZIRP)

Zurich Integrative Rodent Physiology (ZIRP) is an interdisciplinary core facility at the Irchel campus of the University of Zurich. Its mission is to support and strengthen research activities in the field of integrative physiology by providing infrastructure and know-how for the advanced analysis of rodent physiology.
ZIRP is open to all researchers from the University of Zurich, the ETH, other research institutions and companies. ZIRP is currently supported by the ZIHP, the NCCR Kidney.CH and the Institute of Physiology, UZH.

Contact: Dr. Petra Seebeck
petra.seebeck@uzh.ch
www.zirp.uzh.ch



01 Bioluminescence imaging of a mouse lung tumour, co-registration of 3-D micro CT and bioluminescence data.

02 Mouse with implanted transmitter.

03 Automated analysis of serum samples.

logical data in conscious and freely moving animals. For example, respiration rate, body temperature, activity, pressure or biopotential signals can be monitored. The implanted telemetry device transmits the digitalized data via radio frequency signals to a nearby receiver plate *[Figure 2]*.

The advantages are multifaceted: Since the miniaturized transmitter and all catheters and leads are completely internalized, the risk of wound infection is eliminated, animals can be group housed in their home cage directly after implantation and handling of animals is minimized in order to avoid stress related artefacts. Telemetric measurements can be combined with other techniques like running wheels, climate chambers etc. Furthermore, instrumented animals can serve as their own controls.

The ZIRP telemetry platform offers four different types of transmitters for the acquisition of pressure and biopotential signals, body temperature and activity in mice and rats as well as the relevant hard- and software system for data acquisition and analysis. Other transmitters can be implanted on request. ZIRP's entire service includes transmitter refurbishment, surgical implantation and post-operative care with the animal handed over "ready to use."

Laboratory Platform

Biochemical analyses of biological fluids offer insight into the function of various organ systems. Animal models can be assessed by analyzing a multitude of different parameters in one sample *[Figure 3]*.

In rodents, such an evaluation is often hampered by the small volume of their body fluids – a limitation which is even more critical in case of repeated measurements during longitudinal studies or the analysis of a large number of parameters in one sample.

The ZIRP laboratory platform offers high quality analyses for a wide range of biochemical and toxicological parameters in small volumes of any biological fluid. All analyses are tailored to the researcher's specific needs. Consistency, high accuracy and technical attention to precious samples are the essential priorities.

All methods are ideally suited for the analysis in rodent models. Additionally, the laboratory platform has the capacity for high-throughput analysis of human samples from large population cohorts where small sample size could be also a limitation (e.g. genotype-phenotype correlations).

The platform utilizes liquid chemistry technologies, which allow the acquisition of a large array of reliable biochemical analyses in minimal volumes (usually < 10–15 µl) with a high throughput (> 200 analyses per hour) in combination with an automated calibration system. The platform offers a series of special protocols such as those for quantification of bicarbonate, uromodulin, cyclic AMP, vasopressin, ammonium as well as the possibility to develop new assays.

Sample collection can be challenging in small rodents. Pre-analytical errors occurring during sample collection or post-processing are a major source of missed or wrong diagnoses. Therefore, ZIRP not only offers help with any type of sample collection but also a collection of tubes suited for optimal processing of small amounts of different types of biological fluids.

AUTHORS

Dr. Petra Seebeck. *Manager of ZIRP*
(Zurich Integrative Rodent Physiology)
Dr. Magdalena Seebauer. *Manager of ZIHP*
(Zurich Center for Integrative Human Physiology)

TISSUE ENGINEERING

Joining Forces to Combat the Cause of Skin Defects

In 2001, researchers led by Prof. Ernst Reichmann and Prof. Martin Meuli established the Tissue Biology Research Unit at the University Children's Hospital Zurich as a basic science-oriented experimental research laboratory. They want clinicians and researchers working in basic science to join together to tackle hitherto unsolved tissue problems – it's proving to be a true success story.

ELSBETH HEINZELMANN

Today, large, full-thickness skin defects resulting from burns, congenital giant nevi, disfiguring scars, soft tissue trauma, tumour resection and disease leading to skin necrosis represent a significant and common clinical problem worldwide," states Prof. Ernst Reichmann, Group Head of the Tissue Biology Research Unit (TBRU) at the University Children's Hospital Zurich.

How to Exploit Available Synergies

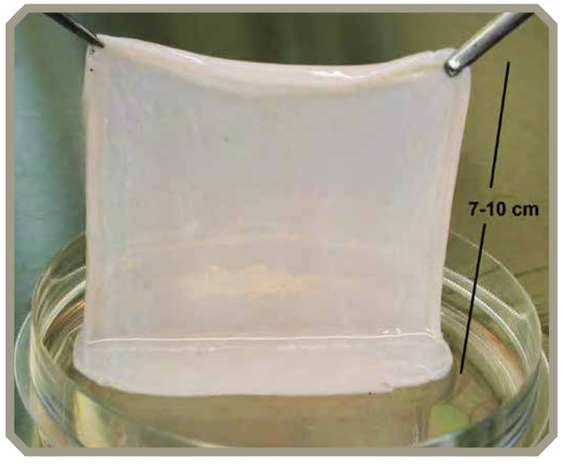
The scientist concentrates on both basic and translational research in tissue engineering and stem cell biology. He focuses on gaining insights into the factors and signals that regulate tissue renewal and histogenesis. Through the *in vitro* construction of functional skin, he and his team try to substitute lost or non-functional tissue. As part of this, he coordinates the European EuroSkinGraft project, which deals with a novel generation of skin substitutes to clinically treat a broad spectrum of severe skin defects. "The special challenge is that most autologous skin grafting techniques are based on transplanting split-thickness skin – the current Gold Standard," comments the researcher, whose group was the first in the world to engineer skin grafts containing blood and lymphatic capillaries.

"Split-thickness skin contains all of the epidermis, but only remnants of the dermis. This lack of dermal tissue frequently leads to significant scarring and thus to unsatisfying functional and cosmetic results." To get a grip on the problem, the Ernst Reichmann's team is developing strategies based on his experience with different cell types proliferating and differentiating in and on hydrogels, and – in the EuroSkinGraft project in particular – on the longstanding and fruitful collaboration between scientists and clinicians. Their priority is to improve the quality of the reconstituted dermis in order to significantly ameliorate the clinical outcome.

Visible Results to Pave the Road to Success

Clinical trials of three novel skin-reconstitution products are currently in progress and being coordinated from Zurich. One of these products is NovoMaix, an acellular dermal regeneration template. This off-the-shelf product was created for use in con-

Prof. Dr. Ernst Reichmann, Head Tissue Biology Research Unit, Department of Surgery, University Children's Hospital Zurich (Photo Kispi UZH)



Production of denovSkin & denovoDerm under GMP conditions in the Laboratories of the Tissue Biology Research Unit at the University Children's Hospital Zurich (Photo Kispi UZH)

junction with split-thickness skin to treat a certain type of skin defect.

The aim is to achieve skin regeneration with less (or no) scarring and less (or no) wound contraction in comparison with epidermal regeneration alone. "The regeneration of full-thickness skin defects after plastic reconstructive surgery or burn injury is only successful if both the epidermis and the dermis show adequate regeneration," explains Ernst Reichmann. "Skin grafting is today a clinically established procedure, either through split-skin transplantation or application of cultured keratinocytes. The healing of these wounds is still complicated by the lack of a dermal component, which results in a poor functional and cosmetic outcome due to scar formation and contraction.

Two further skin substitutes developed by the Tissue Biology Research Unit and used within the EuroSkinGraft project are denovoDerm and denovoSkin. Both products are bio-engineered autologous skin grafts. denovo-Skin and denovoDerm both entered phase 1 clinical trials in 2014. These trials are being run in close collaboration with specialized partners such as the Pediatric Burn Center in Zurich, the Dutch Burn Centre in Beverwijk and the Unfallkrankenhaus in Berlin, along with the Clinical Trial Center (CTC) and the Swiss Center for Regenerative Medicine (SCRM) in Zurich.

From the Laboratory to Practical Application

Ernst Reichmann's conclusions are positive: "Today, complex, bioengineered skin grafts reproduce the properties of normal human skin as closely as possible. Under our 'philosophy' at the TBRU, all three substitute skins only require one single surgical intervention, as they exhibit some essential structure and function of skin immediately." There is reason to expect the bioengineered skin (in particular denovSkin) to grow at the same rate as the skin of a child, which means there may be no necessity for additional surgery. Potential users of the three novel products are burn surgeons, plastic reconstructive and aesthetic surgeons and dermatologists. "Clinical application of these novel products is expected to significantly reduce a common and central clinical problem," adds the scientist. "As all three skin substitution products are applied in one surgical intervention, there are enormous potential savings."

Looking to the near future, the inventors have already filed patent applications for the skin substitutes as well as for novel devices incorporating disposable elements. They are also considering a knowledge transfer to a new company. There is much eager anticipation … LS

www.skingineering.ch
www.euroskingraft.eu

INTERVIEW WITH DR. BENOÎT DUBUIS, DIRECTOR CAMPUS BIOTECH

A Jewel of Science on Lake Geneva

In spring 2013, the Wyss Foundation and the Bertarelli family purchased the former site hosting the headquarters of the pharmaceutical giant Merck Serono with the aim of creating a centre of excellence for neurological and life sciences that is unique in Europe. The Director of the new Campus Biotech, Chemical Engineer Benoît Dubuis, is familiar with the needs of industry and research.

ELSBETH HEINZELMANN

What the Campus Biotech is setting out to achieve on the 40,000 m² site at Sécheron in Geneva is like squaring the circle. The site where the multinational pharmaceutical and chemical corporation once developed and marketed innovative small molecules and biopharmaceuticals is being turned into a centre of excellence for research in biotechnology and life sciences.

The new drivers – a consortium comprising EPFL, the University of Geneva, Hans-Jörg Wyss, and the Bertarelli family – have a clear vision: the internationally oriented platform will create new opportunities for scientists and entrepreneurs by providing a unique environment for translating ideas into products that will impact society and the world at large. The premises are shared, on the one hand, by research groups from EPFL and the University of Geneva (which occupy 26,000 m²) and, on the other hand, by the Wyss Center for Bio- and Neuroengineering, which aims to set new standards as a model for innovation, cooperation and technology translation (8,000 m²), also involving existing enterprises and start-ups (7,000 m²).

The Wyss Foundation has dug deep into its pockets and contributed 100 million Swiss francs, following the model implemented at the Wyss Institute for Biologically Inspired Engineering at Harvard University. For its part, the Bertarelli foundation is continuing to finance the two chairs it sponsors at EFPL, plus two new chairs, which will all be relocated to Campus Biotech. Campus Biotech will also accommodate small start-ups and dynamic companies, which will benefit from an on-site environment that blends science and industry.

Interview with Benoît Dubuis, Campus Biotech Director

Nowadays, research institutes with laboratories are designed specifically for their particular remit. In the case of Campus Biotech, the scientists are moving into a building where all the infrastructure needed for academic purposes has to be installed from scratch within set financial constraints, and where there are no internet or telephone connections. How are you meeting this challenge?

Dr. Benoît Dubuis: The site was planned to accommodate the headquarters of a biotech multinational, including all the necessary functions and facilities, from administration to research and development. Our first challenge has been to reallocate the available space to

Focussed on brain: The Human Brain Project will contribute to the neuroscience programme of Campus Biotech.
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meet the needs of the programme we envisaged. In the first instance, we are building this programme around two "backbones": the "neuro" initiative, which aims to create a unique ecosystem for translational neuroscience based on neurotechnology development and integrated team effort, and the "healthomics" initiative, which intends to create a multidisciplinary centre for the development of digital medicine and e-health, integrating patient information and the various omics data.

Each of these initiatives has been subject to a detailed needs analysis, leading to the drawing up of plans for adapting infrastructure and installing technological platforms, so as to provide the scientists and engineers working here with the best possible tools for the job. It is true that when the previous owners left, the installations were all decommissioned, or even dismantled, so we have had to do a lot of work to reactivate the facilities, from basic infrastructure such as the telephone system or computer network to much more complex platforms.

At present almost 400 people are working on the site (which has a capacity for over 1,000) and we should have reached 600 (half the theoretical capacity) by the end of the year. Achieving this has required the concerted efforts of the owner, the project partners and the various new arrivals, coordinated by the Campus Biotech Foundation, whose task is to manage the scientific and translational component of the Biotech Campus site. The Foundation, then, is at the heart of this effort. It is the operational driver responsible for hosting the various research groups and the Wyss Center, managing the technical platforms that will enable them to conduct cutting-edge research, promoting public outreach activities and working to integrate the site with the local and international network.

The new Campus is designed to function as an incubator offering the best possible working conditions to scientists from academic and industry backgrounds that are active in a wide variety of life-science disciplines. What do you think will be the most important factor in ensuring the necessary transdisciplinarity?

Campus Biotech is not a random grouping of individuals and scientific institutions. Rather, it aims to create a new ecosystem based on an interdisciplinary approach to the life sciences in a "translational" perspective. In this, the interdisciplinary Wyss Center for Bio- and Neuroengineering is playing a central role

- by fostering the development of groundbreaking innovations in response to new challenges in the healthcare field,
- and by speeding up the transition from discovery to clinical application and the marketing of new solutions and products.

Enterprises and start-ups will also be contributing to this new ecosystem. "Industrial" spaces have been reserved for hosting and promoting enterprises dependent on the applied research performed on Campus or which will benefit from the critical mass present on site. Finally, a space run by the Geneva Cantonal Hospitals (HUG) will complete the new arrangement and give a translational dimension to Campus Biotech. The presence of this scientific and industrial community on the Campus Biotech site will help to strengthen our world-class cluster and place our region in the vanguard of life-science research and development.

The new Campus Biotech will bring together two "research cultures" – those of EPFL and UNIGE. How do you intend to produce a coherent science programme that incorporates both interdisciplinary and translational research?

Campus Biotech creates a fantastic opportunity for close cooperation between EPFL and UNIGE in the field of applied biomedical research. It also provides a unique opportunity to boost R&D activity in the Lake Geneva region's biotechnology and neuroscience sectors and, at the same time, to create jobs in these fields. The Campus Biotech Foundation, a not-for-profit organization, has been planned as a public-private partnership involving key players in Geneva and beyond. Its strategy is founded on innovation, cooperation and a transitional emphasis.

The three key aspects of the innovation process at Campus Biotech are a specific/directed focus, the quest for excellence and an interdisciplinary approach, which plays a central role. Interconnected innovation is possible only if people from different scientific backgrounds, with complementary skills, work together to find new solutions and improvements to existing ones. Diversity is crucial. A complementary team, with distinctive ideas and points of view, is a good starting point for exploring innovative solutions to complex problems. Campus Biotech provides a unique setting in that it can draw on 20 years of research, institutional initiatives and cooperation in fields involving animal, human and IT research, and provide opportunities to pursue this work in the context of shared projects and ambitions. The cooperative dimension expressed here is vitally important.

Campus Biotech will be located at the former Merck Serono site in Geneva. (Wikimedia)

Far from trying to replace existing research institutions, and outsource neuroscience-related activities in the broadest sense, Campus Biotech is proposing a new model of integration. It draws its strength from its founding institutions (EPFL and the University of Geneva first and foremost), and from their partners, which, by their involvement in international collaborative ventures, propel it into the thick of the international dynamic.

Its translational dimension completes the picture and distinguishes Campus Biotech from its partners. In industrialized countries such as Switzerland, innovation is the key to economic growth and sustained international competitiveness. In this respect, the Wyss Center for Bio- and Neuroengineering, an essential part of this ecosystem, plays a vital role in accelerating innovation and catalyzing the transfer of technology from research to industry. By supporting the translational aspect, Campus Biotech is helping researchers to transform their results into products and, at the same time, helping companies to innovate as they benefit from the technologies and products resulting from the researchers' findings. Campus Biotech therefore provides a unique opportunity to position the Lake Geneva region and Switzerland in the forefront of innovation and development in neuroscience and bioengineering and provide a source of new products and solutions, economic progress and employment.

Campus Biotech will stand for Swiss excellence and multidisciplinarity, and set new standards in innovative research and development in Europe and internationally. But how good are Switzerland's chances after a majority of the Swiss population voted in favour of the popular initiative "Against mass immigration" on 9 February 2014?

The reason the land of opportunity that is Switzerland has been able to carve out such an enviable place and thrive in international and interregional competition is above all because it has shown openness and championed integration, two key values for Campus Biotech.

The history of Switzerland is one of successful integration. Consider integration and the dissemination of knowledge. In the 16th century, great medical researchers such as Paracelsus and André Vésale, or again Erasmus of Rotterdam, came to Basel to have their ideas and treatises published. The city was thus involved in the humanistic learning and scientific progress of the Renaissance period. Closer to home, one key to Switzerland's success has been its capacity for innovation. As a result, our universities and specialist institutions attract the brightest talents, both home-grown and foreign, in today's globalized environment. This openness is a precious asset, which can be measured, among other things, in terms of Switzerland's international competitiveness in the knowledge economy.

"Campus Biotech provides a unique opportunity to boost R&D activity in the Lake Geneva region's biotechnology and neuroscience sectors and, at the same time, to create jobs in these fields."

DR. BENOÎT DUBOIS.

DR. BENOÎT DUBUIS
DIRECTOR CAMPUS BIOTECH

Dr. Benoît Dubuis studied chemical engineering at ETH and EPFL and completed the Mastering Technology Enterprise Program (MTE) at top-ranked business school IMD. He has acquired valuable experience in industrial and research environments, holding positions of responsibility at Chemap, Ciba-Geigy/Novartis and Lonza., and as the first Dean of the School of Life Sciences at EPFL. He launched BioAlps and has founded various companies. He was a co-founder and director of the Eclosion Life Sciences Incubator and seed fund. He now heads the Campus Biotech Foundation and is Development Director of the Wyss Center for Bio- and Neuroengineering.

Take integration and the development of expertise. Our industrial progress has been aided by generations of entrepreneurs who have settled in our country. Of those who have made the greatest contributions, let us mention the Huguenots, who brought us chemical manufacturing and watchmaking. Fleeing their country following the revocation of the Edict of Nantes, silk weavers and merchants made Basel the capital of ribbon production. The need for dyes favoured the establishment of the chemical industry, which diversified into fine chemicals, then pharmaceuticals.

Then look at integration of entrepreneurs and values. Behind any great innovation is a gifted individual. Here again, the examples are legion. Remember that Nestlé was founded by the German pharmacist Henri Nestlé; that Xavier Givaudan is French; that a Swiss with dual British nationality, Charles Eugene Lancelot Brown, together with Walter Boveri, a native of Bamberg in Germany, founded the firm of Brown, Boveri & Co.; that more recently many industrialists like the Bertarellis and Mauvernays have settled in our country to set up and develop thriving companies … and this story is repeated time and again, giving Switzerland its entrepreneurial dynamism.

Consider integration of knowledge, too. Diderot, in the introduction to his celebrated encyclopaedia, said: "There are two ways to cultivate the sciences: one is to increase the

mass of knowledge through new discoveries, the other is to bring together those discoveries …" True in the 18th century, a vital necessity in the 21st. Barely appreciated by the general public and yet a real engine of change, the interdisciplinary approach is constantly opening up new avenues and is our greatest asset in maintaining our leadership position in many industrial sectors.

To sum up, we could not survive without our ecosystem. Knowledge is everywhere, and cooperation and sharing enrich it moment by moment. Switzerland has shown that it understands this by advocating integration and openness. Campus Biotech is founded on these values and has made them the cornerstone of its development.

Switzerland is involved internationally in the "Human Brain Project." This 10 year project is headed by Henry Markram at EPFL, who hopes to gain understanding of the human brain with the help of supercomputing technology. How does this contribute to the development of Campus Biotech?

This Project is a major scientific project aiming to gain understanding of the human brain by creating extremely detailed reconstructions of brain circuitry and simulations of its functioning using supercomputers. The project aims to provide insights to the biological mechanisms responsible for human thought, emotion, and learning, build revolutionary new computing technologies and develop new or more efficient medical therapies for treating the neurological disorders that affect two billion people around the world.

It is a European project with over one hundred universities and specialized institutions in 24 different countries. The Lake Geneva area is well represented, including the University Hospital of Lausanne, the University Hospital of Geneva, and the coordinating institution of the Human Brain Project is EPFL. The project has been selected as one of the European Union's two FET Flagships and brings together hundreds of researchers to work on projects with a budget of 1 billion Swiss francs. The first phase of the project began at the end of 2013 and will continue for two and a half years, until mid-2016.

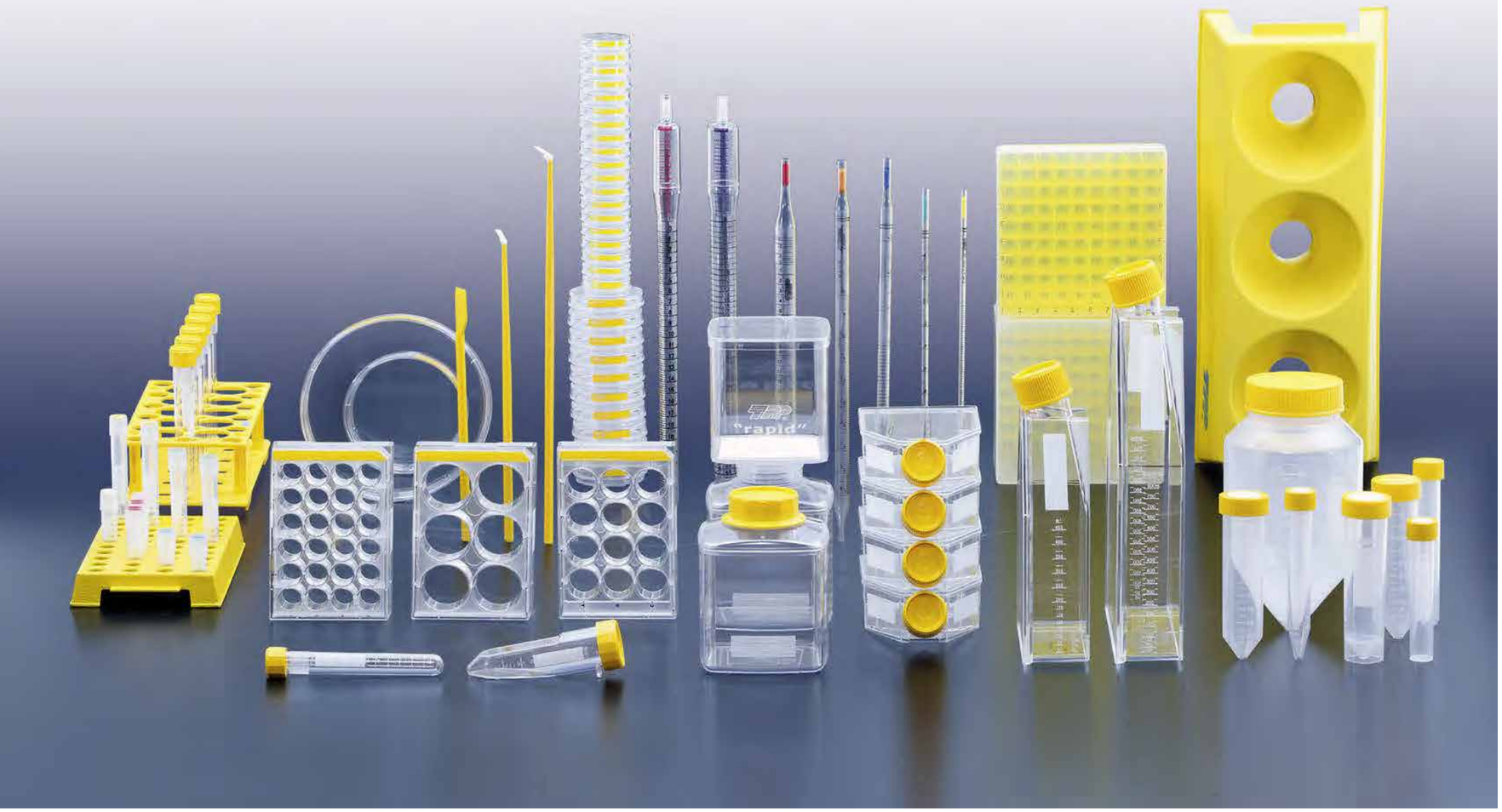
The Human Brain Project is an essential component of the new ecosystem being established on the Campus Biotech site. It will be an important contribution to the neuroscience programme of Campus Biotech.

Can you tell us more about the Wyss Center? What makes it unique? What is its strategy?

The Wyss Center has been planned to capitalize on the explosion of knowledge and technical capabilities emerging in neuroscience and to provide a novel basis for translating concepts into applications. We are at the dawn of an age of human neuroscience where knowledge of nervous system function, coupled with advances in engineering and clinical medicine, make it possible to address nervous system disorders and restore lost functions previously considered impossible to treat. Cochlear implants are a neurotechnology that has restored hearing to more than 200,000 people; vision can now be partially recovered through bionics implanted in the eye. Brain stimulation, targeting specific brain circuits, can overcome deficits produced by Parkinson's disease and, potentially, in depression. People paralyzed by a stroke can move devices with their thoughts, as a first step to recovery of movement. Neurons can be modified so they can be restored to normal function, or adjusted by rendering them sensitive to light.

These advances, most of which are in the very early stages of development, require exceptional teams of scientists, engineers and clinicians to progress them from concept through to real-world applications. New ways of treating brain disorders, such as reading out millions of brain signals to detect a seizure, or restoring brain circuit function in depression, are often so risky that they cannot benefit from the funding needed to see them through from idea to final product. But the rewards of such treatments can be immense, as millions of people will face dementia, paralysis, or devastating mood disorders, which take a great personal toll and entail unsustainable costs of care. Advances of this kind are, however, hindered by a lack of support for the most adventurous projects and a lack of reliable cutting-edge technology and technical support to bring them to fruition. Under the scientific leadership of Prof. John Donoghue and gifted scientists from various institutions, such as EPFL and its world renowned Center for Neuroprosthesis, the Wyss Center is creating an extraordinary environment in which it is possible to catalyze and accelerate progress from innovation to commercialization by providing access to a highly integrated set of engineering, neuroscience, clinical, and business platforms, as well as substantial research support. This unique endeavour, housed on the unique Campus Biotech site, is made possible by funding from the Wyss and Bertarelli foundations and by our academic partnerships with EPFL and UNIGE.

www.bertarelli-foundation.org
www.epfl.ch
www.unige.ch
www.wyssfoundation.org



TPP – HOME OF TISSUE CULTURE

Yellow High Tech for Single Use

In the last decades, requirements in respect to quality and user friendliness on sterile, single-use labware changed tremendously. Where classic test tubes and microreactors used to be re-usable and made of glass and stainless steel, today they are designed for single use and made of high-quality plastics. Yet, standards for these disposable goods are extremely high: They must be user-friendly, of high quality but innovative at the same time. TPP, Swiss manufacturer of plastic labware, knows how this works.

SONJA BICHSEL-KÄSER

Working in the lab made easy! Wishful thinking of every researcher, while spending days and often also spare time in the lab, cultivating, pampering and harvesting cells and tissue cultures. In Switzerland and worldwide, labware of the label TPP has proven to be the brand of choice for working with cell cultures: Cultivation, incubation, centrifugation, filtration, transfer of suspensions, and storage – for every operation in culture handling, there is a tool with the characteristic yellow colour available. "The yellow colour was chosen by me when I was young," remembers CEO Rolf Tanner in an interview. Then, the company was run by his father Max Tanner, founder of the enterprise. Today, TPP is an established brand and strongly active in the international market. As a first product, the polymer specialist TPP launched the square tissue culture flask, which is still one of the most sold products out of the whole product portfolio. There were other similar flasks available on the market at that time. But TPP added small but useful innovations to the available design, such as for example the canted neck, the highly visible bilateral marking area and the convenient stacking ring. In addition, the company developed the cell scraper with rotating blades for the end-user to be able to accurately harvest each cell, even in the corners of the flask. According to the principle "clean even in the remotest corners," the idea for a rotating scraper-blade turned up "while watching mother doing the vacuum cleaning with the movable nozzle," Tanner says with a smile.

Besides cell culture flasks TPPs variety of goods also comprise Tissue Culture Flat Tubes and the TubeSpin Bioreactors. The first ones are an efficient all-in-one system, since cultivation, microscoping and harvesting can be done in the same tube without the need of transferring the cells. Cells in a TubeSpin Bioreactor, however, may be incubated by placing them on an orbital shaker in an incubator. The three sizes of the reactors (15, 50 and 600 ml) allow an up-scaling by running several assays in parallel. TubeSpin Bioreactors have either a round or a conical bottom and are suitable for centrifugation – a particularly quick harvesting procedure. The TubeSpin Bioreactors are growing to be popular on the market and hence have been copied by competitors already three times, as mentioned by Kirsten Braehler, Sales and Marketing Manager at TPP. "If your product is copied by others, you know that you have developed the right thing," she says.

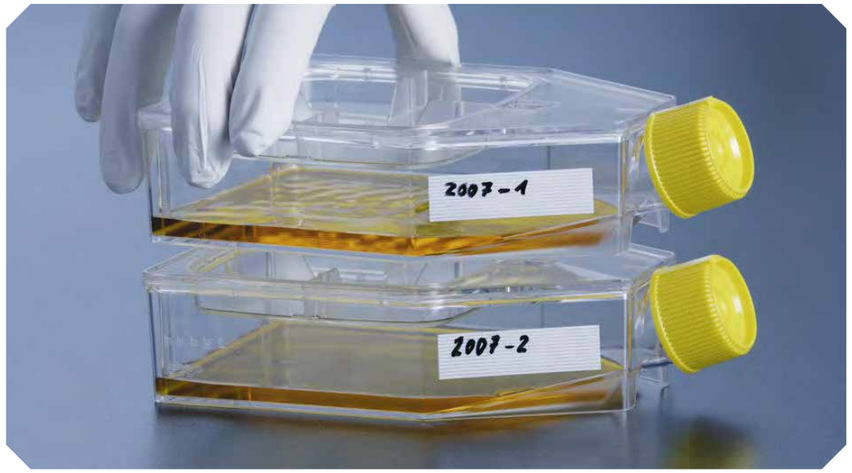
For Liquid Handling, TPP offers serological pipettes and compatible electric pipetting aids. The elaborate Vacuum Filtration System "Rapid-Filtermax" – filter top mounted on a sterile flask – is also worth mentioning. Due to its square shape, the system is more stable than comparable round products. The filtrate passes the large filter surface rapidly and gets collected in the sterile flask. The filter-top may be detached and discarded while the filtered good can be stored in the container, sealed with an accessory sterile – yellow of course.

About TPP

TPP, the colour yellow is the Swiss brand that belongs to the international circle of brands for high-quality plastic disposable products for tissue culture and laboratory technology. TPP is constantly active in the research and development of new products as well as improvements on treatment of the cell growth areas. For more than 50 years, TPP has been a successful manufacturer for high-quality disposable plastic products. The company is headquartered in Trasadingen (SH), close to the border to Germany, and employs 130 persons.
TPP is run as a family business by CEO Rolf Tanner, son of the founder. Injection molds for plastic production is supplied by the associated company Tanner Formenbau, managed by Felix Tanner, Rolf Tanner's brother.

"Disposables of high technology standard at reasonable prices are in demand."

ROLF TANNER. CEO TPP Techno Plastic Products



Staple and slip-free stacking of multiple-tissue culture flasks.

Quality Meets Innovation

In 1966, when the company was found, plastics was about to become more and more en vogue. First plastic products were launched by TPP during this time and the competitive situation was still calm. "However, the actual market is saturated and much more competitive," CEO Tanner says. Today, a company is only successful by being innovative and ensuring reliable quality at the same time. While manufacturing procedures and product features are optimized and developed, product quality should remain as it is, for the user needs to rely on established values. For unpredictable changes in cell culture equipment would lead to problems in every lab – whether research or GLP accredited quality control. "In past and present times, conditions of the TPP products are still the same," assures Tanner, "which is not easy, since many factors such as temperature, humidity, material, man and machine influence the production of goods. Technical parameters must be followed strictly in order to produce reliable quality."

Innovation at TPP is fast and straightforward thanks to synergies of tool construction and plastic production. Plastic products are manufactured by injection molding, by melting plastic granulate at 250 °C in an extruder and molding under high pressure (2000 bas). Development of new techniques is fast, since the tool design company "Tanner Formenbau," which is managed by TPP CEO's brother, and TPP work in close cooperation. Thus, reactions to requests from market are accelerated. Distributers and users appreciate this proximity to the manufacturer and the resulting prompt support if problems or questions occur, remarks Kirsten Braehler: "Customers and distributers know that service at TPP goes beyond production and selling and that they can rely on us."

Not only shape but also the characteristics of plastic are constantly innovated. In order to make cells feel at ease in their artificial plastic homes, polymer surface needs to be treated to create ideal growth conditions for cells. TPP has developed a proprietary procedure of surface treatment – the company's secret. Further innovation, reveals Tanner, is going on in the field of stem cell and cancer research. TPP coordinates a project of the European EUREKAs Eurostars Programme, which is dedicated to innovative surface treatment simultaneous to production. Aim of the project is to develop labware with a highly sophisticated coating that provides cells a nearly natural, reproducible and sterile environment. In a plastic culture container, properties of the synthetic itself and the coating with protein layers strongly influence cell adhesion. Today, most coated labware is prepared manually by the researcher, by incubating a sterile protein solution in the culture dish. In the future, these layers should be applied online during production of the dishes and flasks. The obvious advantage of immobilized proteins is that they do not enter the medium of the cell and tissue culture but stay attached to the culture dish.

Disposable High Tech

In order to create the right conditions for cultivation and examination of cell cultures, the plastic surfaces need to meet certain requirements: Production of TPP labware is carried out under strict hygiene and clean room conditions and all products are sterilized when leaving the company. The plastic products must be free of RNA and DNA contamination from other sources than the cultivated cells. Otherwise analysis of genotype could be strongly impaired. Equally, labware has to be free of DNAse and RNAse, to avoid enzymatic degradation of extracted genetic material. TPP products are free of these enzymes as well as free of endotoxins, which play an important role as pyrogenes. Furthermore, it has to be guaranteed that no cytotoxic substances or other components are eluted from the plastic material during incubation of cultures. This so-called leaching is circumvented by processing only highly purified and certified raw material for plastic production, free of plasticizers or other undesired additives. Therefore, supplier qualification is a must. In addition, TPP plastic production does without mold-lubricant, which could contaminate the product. Quality control of all TPP products is carried out in house or by accredited laboratories.

One for All

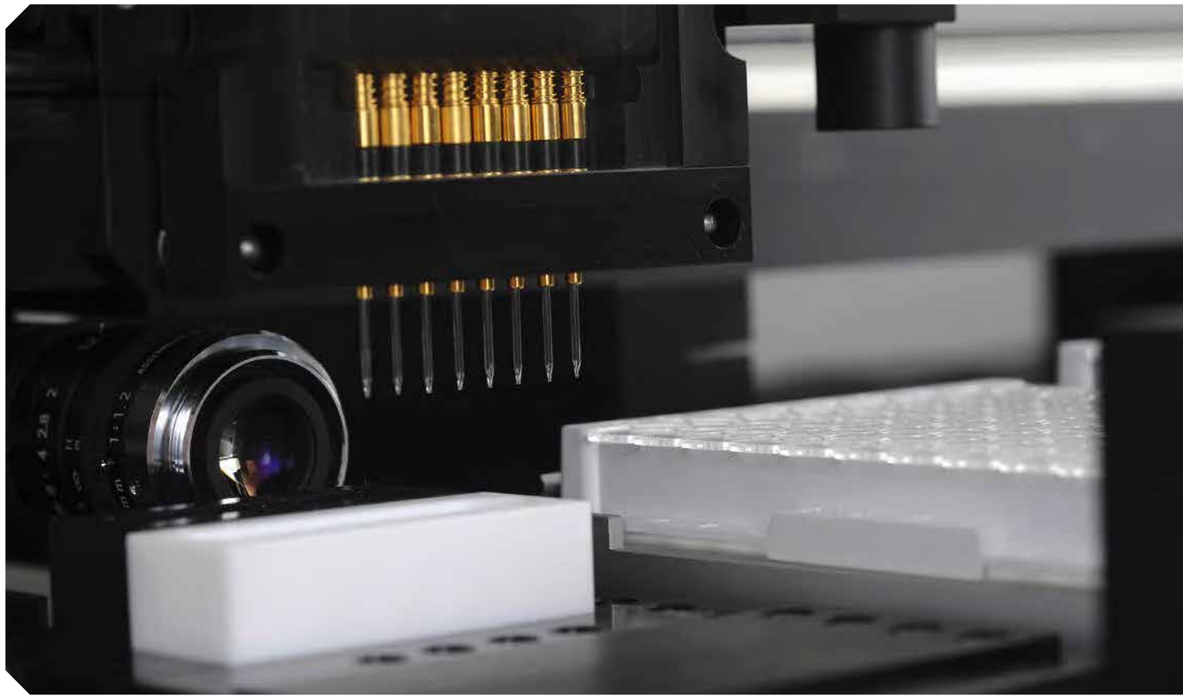
Considering all these quality properties, TPP products are suitable for successful works of every lab. They meet requirements of industrial and regulatory standards and guidelines (such as GMP, GLP, MDD, pharmacopoeia), they facilitate lab work by being highly developed, fast and disposable systems, and they create optimum growth and reproduction conditions for cells as well. "Disposables of high technology standard at reasonable prices are in demand," Tanner says. In addition products should be available on short notice. TPP makes it all possible and with that satisfies many customer requirements worldwide. However, not only customers but also employees satisfaction represents a constant concern to the management. The company employs a variety of professionals such as plastic technologists, engineers, storekeepers or sales representatives, just to name some. Automatic production is important but would not be successful without the staff. «Our employees should take pleasure in their work,» emphasizes Tanner. Thus, personal commitment and team work along with technical know-how ensure the company's success. TPP products are well established and their further development is welcome by specialists. In Switzerland, TPP products are exclusively distributed by Faust Labor Bedarf AG. (FS)

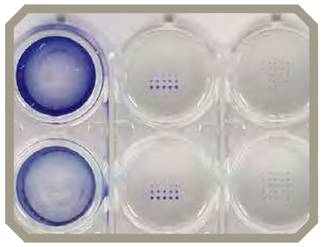
www.tpp.ch
www.faust.ch

APPLICATIONS, DOSING TECHNOLOGIES AND QUALITY CONTROL

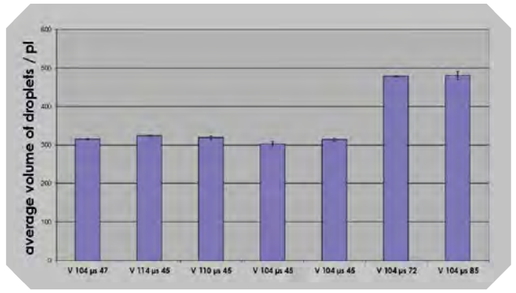
Dispensing Picoliter: What is Feasible Today?

The precise dosage of picoliters plays a central role, particularly in the production of biochips, the placement of biosensors, lab-on-a-chip substrates and the production of point-of-care diagnostics. We are talking about very small droplets, but it is a common misconception that you cannot see a drop this small. Liquid volumes in the 50 picoliter to a nanoliter range, less than one millionth of a milliliter, can be seen by eye and also well characterized with modern analytical methods.

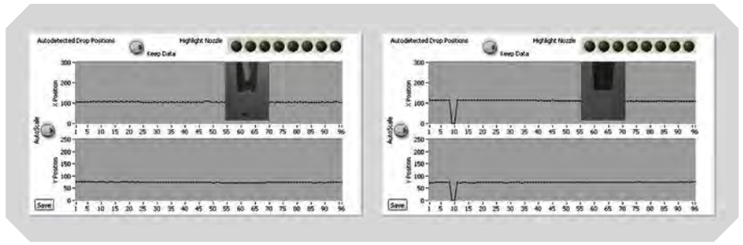




01 Illustrative comparison of a conventional microtiter plates based ELISA using coated wells (left column), using a 5 × 5 array format with different volumes in a single well (middle column, from top to bottom per spot applied volumes are 100, 200, 400, picoliter 1000 and 2000), and using a 5 × 5 array with a fixed volume of 100 picoliters per spot (right column). Microtiter plate used: sciPLEXPLATE, Scienion.



02 Output of about 300 picoliter drops of a dispenser, with the various printing parameters for pulse height (volts / V) and pulse width (microseconds/us) is operated. 10,000 drops per bar were recorded with a CCD camera and determined volumetrically and gravimetrically driven.



03 Presentation of droplet velocity and deflection to the inclusion of different samples (drop graph). Horizontal gradients indicate a flawless system performance. Deviations are detected as "pip" immediately and preventive measures can be taken.

04 Directly connected to the dispensing head mounted camera for real-time viewing of the drop deposition on a biochip substrate (right).

HOLGER EICKHOFF

The miniaturization of reaction systems has an increasing importance where small quantities of valuable substances and reagents can be saved. If it is possible to develop an assay that uses 100 picoliters instead of a microliter of a particular reagent, the reagent costs can be reduced by up to four orders of magnitude. Even allowing for dead volumes, existing in the various picoliter liquid handling systems, which may include a few microliters; this still represents a considerable savings. The conventional coating of ELISA microtiter plates with capture proteins or antibodies as compared to using a "spotted" plate makes the differences very clear.

In standard ELISA protocols about 200 microliters of a solution of antigen or antibody-capture molecules are used in a single test. The capture reagents are typically used at a concentration of 1 µg/ml. With a price per milliliter of coating solution of about 0.3 euros, this corresponds to 0.06 euros per well. For a 96-well plate where coating reagents are consumed, this represents a cost of about 6 euros per plate. In comparison, a "spotted plate," containing for example a 5 × 5 array of capture reagent(s), offers several advantages. The costs are significanthy reduced because the amount of dispensed reagent is only 25 × 100 picoliter = 2.5 nanoliter = 0.0025 microliter or according to the above model calculation 0.0000007 EUR/well (or less than a penny per plate). As a bonus, the test gives not only one, but 25 measurements per sample, which can be a good basis for further statistical analyzes.

The miniaturization of the above described ELISA assay also allows for the application of serial dilutions in a single well. Thus, by varying the volume dispensed, for example, one, two, four, ten and twenty drops per spot, data can be generated and evaluated with an increased dynamic range for an analyte. The various spots may further comprise from different capture molecules (multiplex ELISA), with then theoretically (technically) make it easy to determine up to 144 analytes in parallel. Practice, however, shows that the establishment of such systems is often associated with a significant development effort. The main reason for this is cross-reactivity of the capture and detection reagents used, which are, of course mercilessly exposed in such a highly parallel multiplex method. Practical experience, however, shows that 4 to 12× multiplex reactions can be developed relatively quickly.

In addition, it is possible to determine simultaneously the background signal for measurement in a spotted plate. The signal between the individual spots in a well is used in most cases. In conventional ELISA plates on the other hand an additional plate well is required for the measurement of the background signal. If several assays were performed in one plate, one well per assay is needed for background and this usually leads to an entire "background" column in an ELISA microplate *[Figure 1]*.

Technical Progress in the Preparation of Arrays

The technique for the preparation of these arrays has progressed significantly in recent years. While initially needles or other Contact printing methods were used for the production of arrays of antibodies or proteins as capture molecules, contactless dispensing methods have now been established. In non-contact dispensing capture molecules can be applied in a more gentle, reproducible manner, and without mechanical damage to the target surfaces of choice (polymer, glass, silicon, metal …). For the use of this technology in research and development, as well as in manufacturing scale production, SCIENION has developed several methods that can monitor and analyze the process of droplet deposition and deposition on a surface very accurately.

The necessary volume per emitted droplets can be finely adjusted by varying the applied electrical pulse signals. Measurements show that the reproducibility of the drop release is excellent and standard deviations amount to less than 3 % or less than 10 picoliters per 300 picoliter drops *[Figure 2]*.

In addition to the on-line determination of droplet volume, the droplet velocity and deviation of the drop direction from the ideal line can be determined. For this, the dispenser tip is moved in front of a combination of strobe flash and CCD camera. Then, typically after a short delay following drop ejection, the flash allows the recording of the image of a stationary droplet moving at a speed of between 2.5 to 3 m/s. The coordinates and direction of this drop can be automatically recorded. With this data, automatically recorded after each sample spotting, a very good process control is possible. Changes in the sample liquid (such as an aging solution can lead to a higher viscosity and a slower drop, or different batches of identical scavenger solutions) or changes in the dispensing process (such as deposits on the nozzle tip leading to a drop deflection) can be immediately detected and countermeasures such as washing and rinsing processes can be initiated before the system produces defective products *[Figure 3]*.

Another on-line process control step can be done during droplet deposition on the substrate. This is possible through a dispensing camera mounted at an angle of 45 degrees. Equipped with appropriate optics, droplet deposition on a substrate surface, e.g. biosensors or biochips can be monitored in real-time *[Figure 4]*.

Summary

In summary it can be said that the development of control mechanisms for the central process step in the deposition of expensive biochemical reagents on biochips, biosensors, miniaturized test systems or Point of Care Diagnostics, now offers an excellent basis for the quality control of these products. In contrast to classical methods, such as those offered for conventional liquid-handling systems, the technologies described here operate in real time and therefore allow fast process intervention. This results in a significant increase in productivity and a good basis for the increased demands in the quality control of modern diagnostic products.

www.huberlab.ch

AUTHOR

Dr. Holger Eickhoff. *CEO Scienion AG, Berlin*

WITEC AG

Your Partner for Complete Western Blot Solutions

Witec AG distributes instruments and reagents to the Swiss life science market. The product range includes electrophoresis instruments, reagents and consumables as well as high-end Western blot imaging systems.

PATRICK MEYER

For more than 26 years, Witec AG acts as the local Swiss partner of numerous manufacturers of instruments and reagents from all over the globe. Besides exciting technologies in the field of single cell genomics and proteomics, Witec AG has established itself as a leading provider of complete solutions for Western blotting. Witec's electrophoresis & Western blot portfolio ranges from standard electrophoresis equipment to very complex imaging systems of outstanding performance from Vilber Lourmat. With an installed base of over 20,000 systems worldwide, Vilber Lourmat is the European market leader for gel and blot imaging solutions in the life science research and drug discovery sectors. The company has pioneered the post electrophoresis market and introduced breakthrough products such as integrated stand-alone gel-documentation systems, the Super-Bright UV transillumination technology as well as dedicated chemiluminescence imaging systems.

New Solution for high sensitive Imaging of Western Blots and Gels

Vilber Lourmat recently launched the FUSION SOLO S, the latest member of the FUSION family of premium performance Western blot imaging systems. Designed to take advantage of the burgeoning global market for personal laboratory instruments, the SOLO S personal gel imager combines an extremely sensitive camera with the innovative new Application Pad container principle for maximum flexibility in applications – all in a very compact format. FUSION SOLO S's scientific-grade sensor and its unique optical design are key to critical imaging of low signal chemiluminescent Western blots. The imagers' integrated illumination sources combined with a four position emission filter wheel are designed for imaging a wide variety of fluorescent visible and IR labels, providing maximum flexibility regarding the growing list of fluorescent labels used in laboratories. The FUSION SOLO S also excels at white light imaging using classical, non-fluorescent methods such as Coomassie or silver stains.
The new FUSION SOLO S offers:

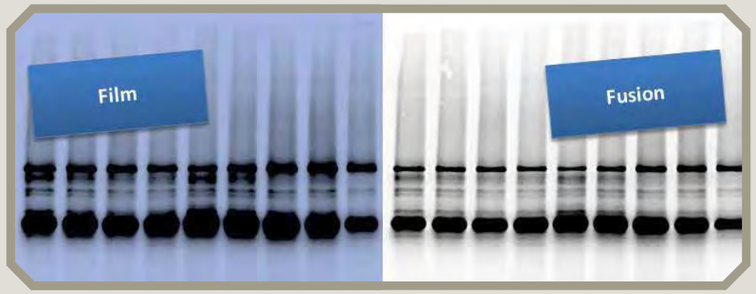
- Compact design: Industry leading dimension requires minimal bench space.
- Scientific grade camera: Super sensitivity and extremely high level of resolution – up to 10 MP.
- High Dynamic range enables quantitative analysis and the detection of slightest signal variations.
- Pre-calibrated focus for all sample positions – no additional focussing needed
- Four position filter wheel: Flexibility in fluorescent dye selection.
- New Application Pad container principle: Exchangeable UV, blue, white light and IR/NIR Application Pads for trans- and epi-illumination can be integrated into the system.
- Application Pads can be used outside the instrument as stand-alone transilluminators.
- White light imaging: Bright Epi-LEDs for marker images of blots and optional white light Application Pad for conventionally stained protein gels.
- Intuitive software workflow, ideal for multi-user environments. (ZS)

www.witec.ch

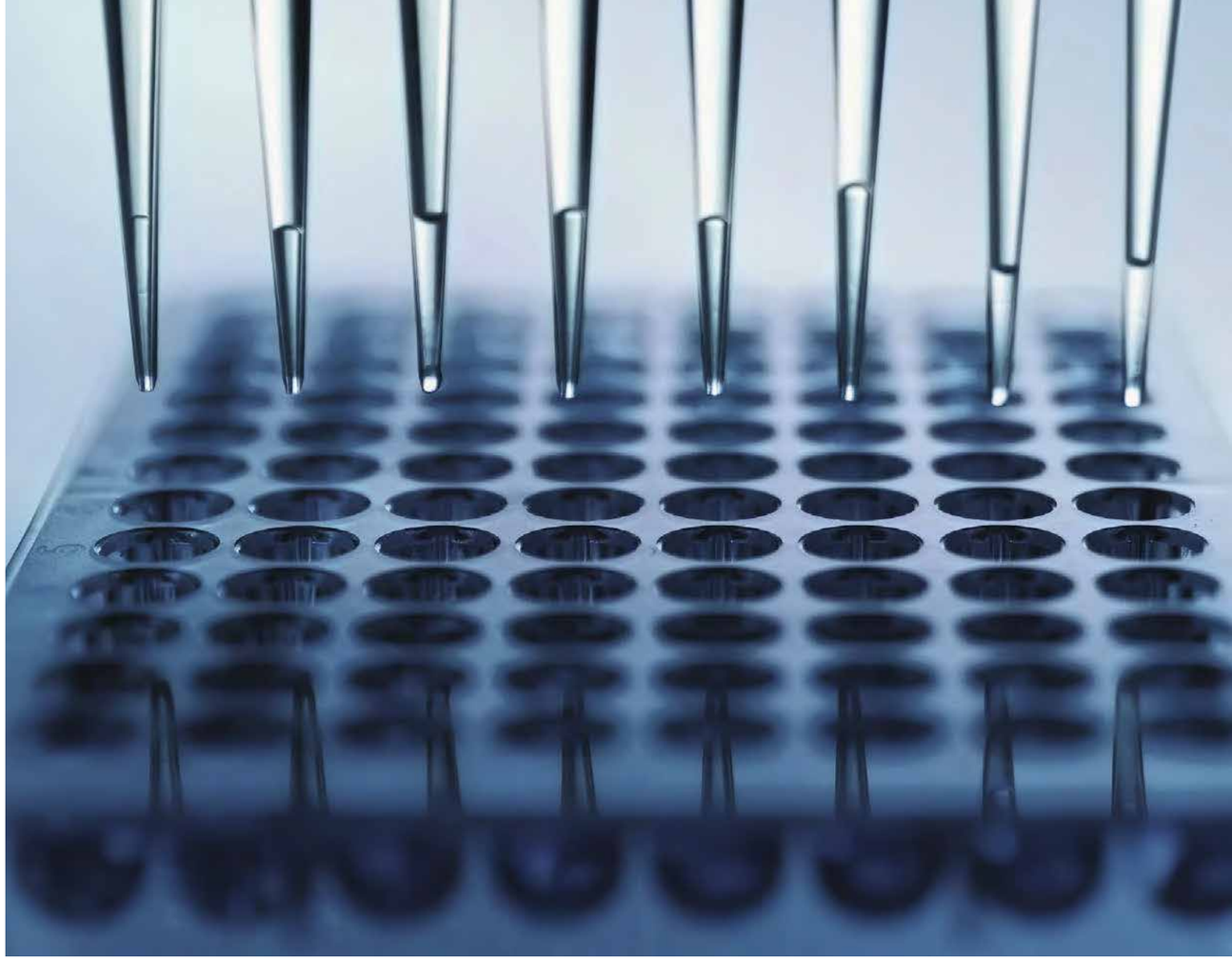
AUTHOR

Patrick Meyer. *Managing Director, Witec AG*

Fusion Solo S Western blot and gel imaging system.



Comparison of Western blot exposures on film and the Fusion FUSION SOLO S imager.



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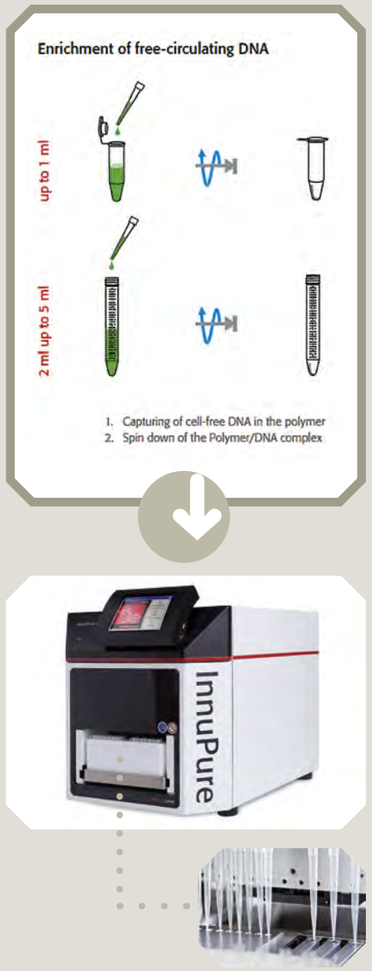
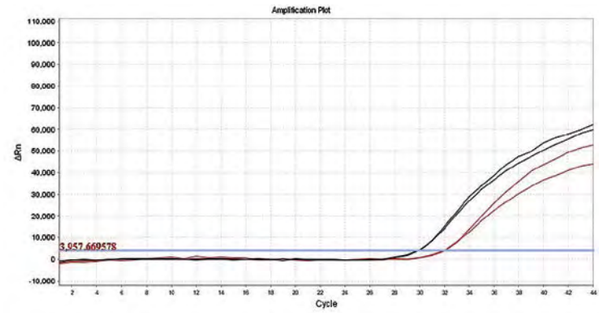
CELL-FREE CIRCULATING DNA

Novel Technology for Enrichment and Subsequent Automated Extraction

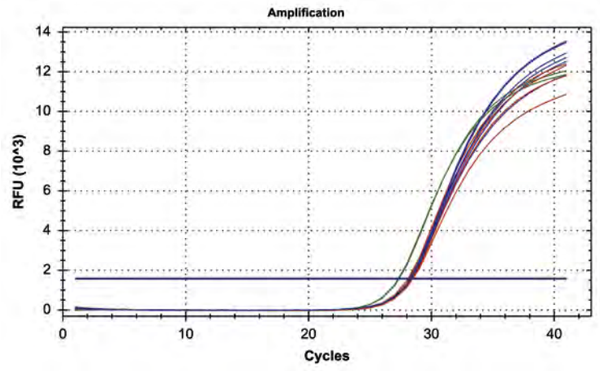
Cell-free circulating DNA is gaining importance in diagnostics. However, due to the molecule's naturally low concentration in body fluids, extraction and enrichment is necessary prior to analysis. Whereas common techniques are time-consuming and need high sample volume, novel Polymer Mediated Enrichment technology is more efficient and works with a reduced sample volume.



01 Enrichment of cell-free circulating DNA and subsequent automated extraction by InnuPure C16.



02 Cell-free circulating DNA extracted from 1 ml (red graphs) and from 5 ml (black graphs) of human plasma. The cfDNA has been firstly captured by using PME technology and afterwards automatically extracted in the InnuPure C16. cfDNA was analyzed by real-time PCR for amplification of human specific gen.



03 Real-time PCR analysis after bisulfite conversion of cell-free circulating DNA from human plasma. cfDNA has been captured using PME technology and subsequently automatically extracted by the InnuPure C16.

a) Unconverted cfDNA (green graphs)
b) Bisulfite-converted cfDNA desulfonated and purified automatically in InnuPure C16 (blue graphs)
c) Bisulfite-converted cfDNA desulfonated and purified manually by spin column method (red graphs)

M. GRUNT, A. BERKA, T. HILLEBRAND, V. PATEL

Cell-free circulating DNA (cfDNA) is present in many different kinds of body fluids, for example plasma, serum, urine, etc. The analysis of cfDNA is gaining more and more importance in medicine. Application fields of the cfDNA are most of all the diagnostics and monitoring of tumour diseases[1]), the noninvasive pre-natal diagnostics[2]), the diagnostics in metabolism diseases and in sports medicine.

Improved cfDNA Isolation

cfDNA is present as short DNA fragments and it often occurs in very small concentration[3]). Because of that, the isolation of this DNA is more difficult and complicated. Due to small concentration of cfDNA, higher volume of initial sample must be processed in order to get sufficient amount of DNA for reliable diagnostic result.

Common technologies are based on sample lysis, binding nucleic acids on a solid material, washing and elution of nucleic acids. Because of the high sample volume, these procedures are very time-consuming, laborious and require large quantities of reagents. However, Analytik Jena AG developed new technology (patent pending) called Polymer Mediated Enrichment (PME). PME is a technology based on the new innovative principle allowing for efficient cfDNA isolation. High sample volume is greatly reduced by addition of a reagent mixture, which forms the polymer complex. During this process the cfDNA is captured inside the polymer and the cfDNA is enriched *[Figure 1]*.

After dissolving of cell-free circulating DNA/Polymer complex in a special buffer, it is transferred into the Reagent Strips or Reagent Plate, which are already prefilled with all reagents needed for the extraction process. Subsequently, the cfDNA is automatically extracted by the InnuPure C16. The InnuPure C16 extraction process is based on binding of the cfDNA on specially modified surface of magnetic particles.

After washing steps, the cfDNA is eluted from the magnetic particles with the use of low salt buffer and is then ready for further applications. The extraction chemistry in combination with the InnuPure C16 protocol are optimized to get the maximum of yield and quality *[Figure 2]*.

As the cell-free circulating DNA finds vast applications in different areas, one of the most important of them is tumour diagnostics. Analysis of cfDNA methylation pattern, due to its lasting heredity and reversibility, is in a great interest as a tumor marker, patient outcome indicator and possible treatment target.

Purification of Bisulfite Converted DNA

Besides automated cell-free circulating DNA extraction kit, Analytik Jena AG developed also the first automated kit to purify bisulfite converted DNA and introduced it into the market for the bisulfite conversion of all kinds of DNA sample, e.g. cell-free circulating DNA. In this product, the external bisulfite conversion of the DNA is followed by the desulfonation and purification processes run automatically in InnuPure C16.The combination of automated extraction of cfDNA followed by automated purification of bisulfite converted cell-free circulating DNA, run both in the InnuPure C16, serve as a perfect tool for methylation pattern analysis *[Figure 3]*.

www.bio.analytik-jena.com
www.huberlab.com

AUTHORS

Analytik Jena AG, Jena
AJ Innnuscreen GmbH, Berlin
Magdalena Grunt, *PhD Student*
Dr. Timo Hillebrand, *CEO and Head of R&D*
Vipulkumar Patel, *Application Specialist Enrichment Technologies*
Alexander Berka, *General Manager Life Science, Analytik Jena AG*

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[3] *Dennin RH. (1979): DNA of free and complexed origin in human plasma: concentration and length distribution, Klin. Wochenschr. 57, Issue 9, pages 451-456*

FLUORESCENT CELL-BASED MICROPLATE ASSAYS

Direct Optic Bottom Reading Improves Detection

Since the isolation of GFP from the Aequorea victoria jelly fish in the early 1960s and its cloning in the early 1990s, scientific research has developed several hundred different fluorescent proteins or dyes for biological, biochemical and life science applications. Besides fluorophores, highly developed detection systems are crucial for excellent results.

TOBIAS PUSTERLA

Fluorescence is probably the most widely-used detection mode in biological research. Thousands of different applications specifically designed for a variety of cellular processes can be measured using fluorescent proteins. Intracellular transport, protein signaling, receptor desensitization, cell movement, migration, division, apoptosis, metabolism, differentiation and chemotaxis are just a few examples of such applications. Parallel to the development of fluorophores, the instrumentation for detection and quantification of fluorescence for analytical purposes also evolved considerably. Microscopes, flow cytometers (FACS) and microplate readers are the three main instruments available on the market today for fluorescence detection in cellular assays.

A microscope easily displays live, real-time pictures and movies of cellular processes highlighted by different fluorescent proteins at micrometer scale. Microscopes allow researchers to obtain fantastic snapshots of biological processes using fluorescent proteins. However, since only one single cell or cell cluster can be analyzed at a time, collection of reproducible data is time-consuming. Moreover, data can only be quantified partially.

Another popular method is flow cytometry. Specialized types of flow cytometers can perform Fluorescence-Activated Cell Sorting (FACS), which is often used in high-throughput screening (HTS) and high-content screening (HCS) labs. FACS provides a way to separate a mixed cell population into homogeneous subgroups, thereby counting and separating cells with or without different fluorescent labels from each other. Compared to microscopy, FACS has a higher throughput as it provides an automated and quantitative method that reliably counts specific cell populations. However, like the microscope, flow cytometers are still limited in the time it takes to obtain data from different activating compounds at different concentrations. Depending on the quality and amount of samples, FACS experiments can take hours. This, in turn, may affect the obtained results. For time may cause cells to cease or exhaust the specific cellular process the researchers are analyzing, whereas upcoming stress responses may affect the accuracy of the readout.

Microplate Readers and Fluorescent Protein Cell-Based Assays

Nowadays, fluorometry in microplate readers is a means that most biological and biochemical laboratories have access to. Used mainly in life science laboratories or in high-throughput screening (HTS) facilities to study simple, homogeneous fluorescence experiments, microplate readers have become multifunctional instruments that can perform complex, heterogeneous, cell-based assays. Formats up to 3456-wells have allowed to significantly miniaturize samples to nl volumes, positively influencing throughput and costs. Finally, microplate readers allow for all manner of reproducible, cell-based assays to be measured in seconds or minutes, depending on the density of the microplate format.

In live, real-time cell-based experiments, it is beneficial to read from the bottom of the microplate and not from the top. Bottom reading offers several advantages for cell-based detection. The light collector can be placed closer to the sample, decreasing light dissipation. Moreover, the interfering effect of the cell culture medium is significantly reduced. Both factors improve sensitivity. In addition, bottom reading allows for a cover or lid to be placed on top of the microplate to prevent cell contamination and liquid evaporation. This is particularly important in time-lapse experiments.

Despite these advantages, a measurement from the top of the microplate without lid will always give higher signal-to-blank ratios than measurements from the bottom. This is mainly due to the fact that the plastic of the bottom of the microplate impairs the light transmission, both for excitation and emission, resulting in lower overall signals. Light reflection caused by the plastic surface and the plastic type also increase blank values. Another factor is the longer fiber optics required in most microplate readers to reach the bottom of the microplate, since correlation between the length and the loss of transmitted light is proportional. Hence, much of the signal is lost when measuring fluorescent proteins from the microplate bottom. This obviously has negative implications with regard to performance. While the first two drawbacks intrinsically depend on the chemical and physical properties of the plastic of which microplates are made, the latter is open to improvement.

Direct, Free-Air Optical Path to the Bottom of the Microplate

In an effort to perfect cell-based assays in microplate readers, German company BMG Labtech has eliminated the need for fiber optics both in top and bottom reading. BMG Labtech proprietary direct optic bottom reading system, found in the Pherastar FS HTS reader and the Clariostar LVF Monochromator reader, has set the standard in bottom reading for microplate instruments. Just like a microscope, the readers take advantage of a free-air optical path to direct and focus light onto either the bottom or top of the microplate. No fiber optics are used. This is achieved by a series of software-controlled, motor-driven mirrors. This advanced reading system displayed a significant improvement in signal-to-blank ratios when compared to readers with fiber optics, where the transit through two different mediums (air and usually quartz) is the major cause of the loss of light *[Figure 1]*. A significant part of the light does not enter the fiber path because of reflection and diffraction. Further limiting factors are the width of the fiber and the amplitude angle of light collection. All these limitations are absent in free air optical paths as the mirrors allow up to 97 % light transmission.

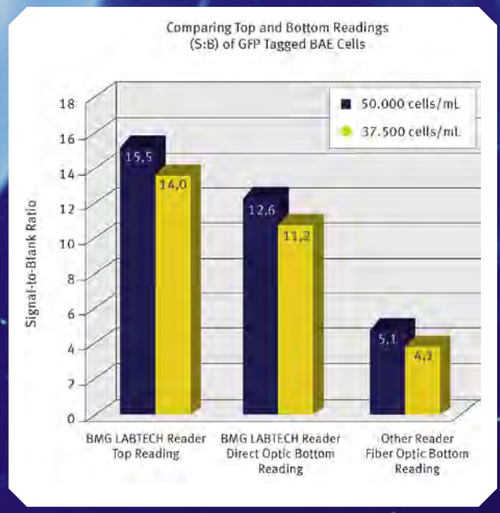
In the Clariostar and Pherastar FS, direct optic bottom reading is fully integrated into the reader's optical system. The switch between top and bottom reading modes is achieved with a simple mouse click in the control software. No manual intervention by the customer, such as displacement or installation of any additional hardware is required.

Further features can enhance the capabilities of bottom reading in cell-based assays: microplate readers usually detect the light at the center of the well at a height specifically optimized for top measurements of liquid (homogeneous) samples. However, adherent cells usually have a different focus height and heterogeneously distribute on the bottom of the well. Consequently, the ability of directly focusing on the cell layer and of scanning the bottom of the well dramatically affect the efficiency and sensitivity of bottom readings in cell-based assays. On the Clariostar and Pherastar FS, direct optic bottom reading can be coupled with an automatic optical focusing system that precisely focuses light onto the cell monolayer at the bottom of the well with a 0.1 mm resolution and with the capability to scan the bottom of the well with resolution of 900 points/well *[Figure 2 and 3]*. All these features taken together make the two readers a good choice for the measurement of fluorescent-based cellular assays.

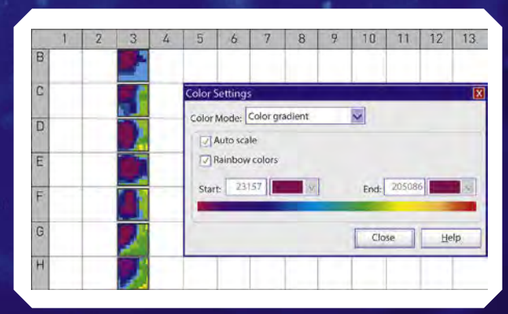
www.bmglabtech.com

AUTHOR

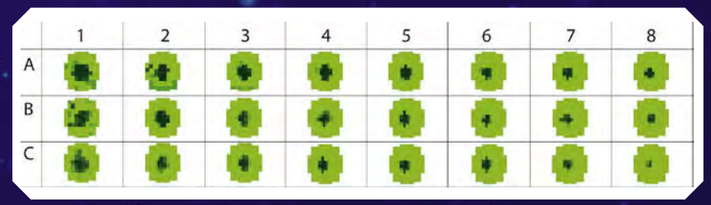
Dr. Tobias Pusterla. *International Marketing Manager at BMG LABTECH*



01 Comparison of signal-to-blank ratios for top and bottom reading: GFP-tagged BAE cells were measured with a BMG LABTECH reader with direct optic bottom reading and with a reader with fiber optics.



03 Bottom reading high resolution cell layer scanning (100 points/well): shows the uneven distribution of HEK cells in each well. Samples with higher cell density in the middle of the well gave a more robust calcium response than lower density wells.



02 Cell migration assay: Oris cell migration assay performed with U2OS cells on a BMG LABTECH reader with direct optic bottom reading and well scanning.

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EXACT AND DISPOSABLE DOSING FOR BIOTECHNOLOGY

Downscaling as a Trend

There are several cost driven trends on the R&D side of biotechnology. One of those is the downscaling of single-use bioreactors to milliliter and even microliter volumes. Since dosing of smallest amounts of liquid under controlled condition is a challenge, an innovative single-use micro dosing system has been developed.

PH. HASLEBACHER, D. EIBL, S. ZUMBRUNNEN, S. BERGER, N. STEIGER, K-H. SELBMANN

An efficient research setup requires a large number of cultures running in parallel under identical, controlled conditions. In the next stage of scale-up, the process needs to be optimized and made as cost and time efficient as possible (DOE experiments). At this step, a large number of cultures need to be run in parallel under different conditions to select the optimal growth- and production parameters for the selected strains or cell lines. Typically, this work was carried out in 3-liter bioreactors on the laboratory bench with the explanatory statement that the 3-liter scale is the smallest volume that would still allow an equal mixing regime and the use of the same sensor and actuator technology as on the larger scales.

Sensors and Actuators

Recent developments in sensor and actuator technology enable downscaling of bioreactors, while maintaining the required scalability to production volumes. Non-invasive measurements of pH and dissolved oxygen are standard today and have successfully been applied in biopharmaceutical production processes. This was a good first step to enable measurement in small bio-reactors, but the control field including processes like liquid- and gas addition still lacks tools. The challenge is to add and measure smallest amounts of liquid under controlled conditions (continuous, discontinuous, exponential, etc.). Adding a 50-µl-droplet of concentrated medium on a 3-liter scale does not influence the culture much, but the same droplet on a 50-ml volume makes a significant change to the concentration of the culture media. Therefore, a special sterilizable injection valve was developed by ReseaChem GmbH to add continuously or periodically nanoliter droplets of liquid to a cell culture broth. It was introduced to the market in 2011 by Applikon Biotechnology BV and allows smooth additions of (highly concentrated) liquids into the bioreactor. However, it has to be calibrated and run under controlled conditions (pressure and temperature). ReseaChem GmbH went a step further and developed a single-use (disposable) micro dosing system with an integrated flow controller.

Disposable Dosing Unit

The electromagnetically actuated micro valve and the sensor are integrated in a compact disposable unit *[Figure 1 and Table 1]*. The flow measurement is done by a pressure loss generated by a restrictor. Thanks to the sensors unique restrictor setup, it is capable of measuring flow as well as the viscosity of the fluid. The Dosing Unit does not need to be calibrated before use, no matter what kind of fluid is used.

Dosing System

The dosing system consists of a micro valve with an in line flow sensor and a control unit. As shown *[Figure 2]*, the dosing rate is defined via user interface or a superior control. While the valve is pulsed (e.g. 10 ms) the flow sensor is continuously sampled by the control unit in order to acquire the exact volume of each droplet. With both the desired flow rate and the last drop volume, the delay to the next injection is computed. With this dosing strategy, the system can react to changes of the drop size caused by pressure, temperature or viscosity and maintain the desired flow rate.

The control unit can be used to define linear and exponential feed rates, to purge the valve, to fill the tube and to pause the dosing process. It is also capable of adding a certain amount to the reactor or stopping the feed process after a defined time.

Successful Applications

First tests with mammalian cells have been performed in an ApplikonMiniBio reactor setup system *[Figure 3]* at the Institute of Biotechnology of the ZHAW in Wädenswil. The Dosing Unit was delivered gamma radiated and mounted directly on the bioreactor in a laminar flow cabinet. Media connections are done by Luer connectors. The handling of the new Dosing Unit is much easier compared to the existing micro valve and the micro peristaltic pump since it does not need to be calibrated. Compared to micro peristaltic pumps, also lower feeds are possible.

For the test, the culture was fed with a constant flow of 2.7 ml/h over three days. A control has been performed as batch system and as system in which the feed was given as daily bolus.

Courses of cell density and viability for the cultivations with the Dosing Unit *[Figure 4]* were comparable to those of the control fed-batch cultivation in shake flasks. Manipulation during the process was not required. Consequently, the risk for contamination during the process performed with the disposable Dosing Unit was lower. The system is very easy to operate since a calibration of a valve or pump is no longer required. In addition, the system is independent from pressure drops or temperature changes in the media tank. (LS)

The trend to downscaling includes obtaining more data in an earlier stage of process development, which leads to more efficient decisions in selecting specific strains or cell lines and optimizing media for further development steps or production.

TABLE 1: DEVICE SPECIFICATIONS

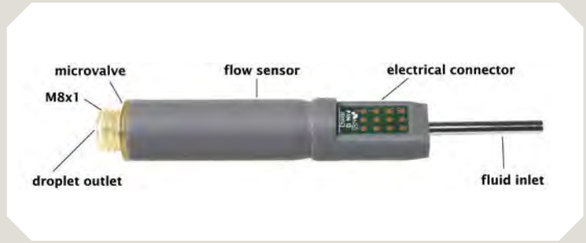
Parameter	Value
Range of pulsed flow rate	0.01–10 ml/h
Accuracy of flow rate	±5 %
Continuous flow rate (flow sensor range)	2–12 ml/min
Droplet size	< 1 µl
Valve switching cycles	> 1 million
Fluid pressure	0.5–1 bar
Fluid viscosity range	0.5–10 mPas
Materials in contact with fluid chemical resistant to	2-molarHCl, 2-molar NaOH
Sterilization treatment	gamma radiation

AUTHORS

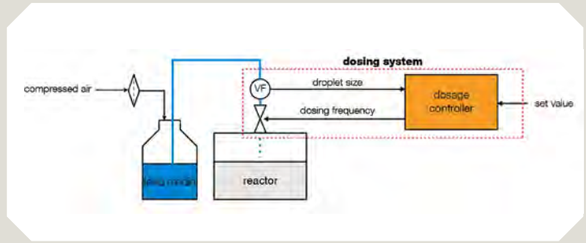
Institute for Print Technology
Bern University of Applied Sciences (BUAS), Burgdorf
• Philipp Haslebacher. *Head of project electronics*
• Simon Zumbrunnen. *Head of project mechanics*
• Karl-Heinz Selbmann. *Head of Institute for Print Technology*
www.drucktechnologie.ch

ReseaChem GmbH, Burgdorf
• Stefan Berger. *CEO*
www.reseachem.ch

Institute of Biotechnology
Zurich University of Applied Sciences, Wädenswil
• Dr. Dieter Eibl. *Professor, Head Biochemical Engineering*
• Nina Steiger. *Scientific assistant*
www.zhaw.ch

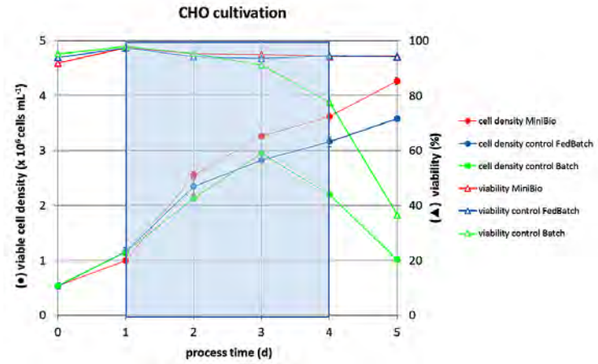


01 The disposable Dosing Unit containing valve and flow sensor.



02 The controlled dosing system.

03 The disposable Dosing Unit mounted on an ApplikonMiniBio bioreactor system.



04 Comparison of cell densities and viabilties during the CHO cultivation in the MiniBio bioreactor system with the Dosing Unit (fed-batch) and shake flasks (controls in batch and fed-batch mode). The blue marking shows the phase in which medium was added in fed-batch cultivations.

INFECTIOLOGY

Ebola, the Looming Threat

Not only Africa but the entire world is threatened by an epidemic of the Zaïre Ebola Virus. Professor Andreas Widmer, from the University Hospital Basel, informed about the possibilities and issues regarding treatment of Ebola patients in Switzerland. The fight against Ebola is not easy to win.

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SONJA BICHSEL-KÄSER

The situation is becoming more and more critical: Thousands of African people got infected with Ebola during the last months. But among the patients were also Europeans and Americans, people who were involved in nursing Ebola patients. The disease is apparently coming closer. Hospitals in Switzerland are doing their best in order to prepare for the care of patients with a suspected Ebola infection.

Protective Garment and Caution

Ebola virus is transmitted via bodily fluids. Therefore, medical staff nursing patients have to take a series of precautions. In order not to get in direct contact with contaminated fluids, they wear a protective suit with a respiratory protection mask. But even while wearing a protective suit, one has to follow the strict guidelines for working on a quarantine ward. "Working in a protective suit is one thing, but taking it off correctly is very complicated and has to be exercised as well," says Professor Andreas Widmer, Head of Hospital Epidemiology at University Hospital Basel (USB). He emphasizes that training of staff is one of the key issues. For only one imprudence may have fatal consequences: "Touching of the own skin with a contaminated glove, like rubbing ones' eye or nose can open the door for virus particles."

About 250 protective suits are on stock in the hospital. In addition, gloves, face masks, filters for respiratory protection masks and other protective equipment is required in large amounts. "Single use protective equipment might run low. But not only a gap in provision but also a gap in disposal might occur," says Widmer. At USB, used equipment is collected in a sealable and autoclavable bin and autoclaved before disposal via regular garbage.

The limiting factor in treating Ebola patients in Switzerland is the lack of infrastructure: University Hospital Basel for example could medicate only one patient after the other in a quarantine room. Equipment, space and above all, staff, would run low in case of a widespread epidemic.

Nevertheless, equipment at USB is high-tech: The isolation chamber is kept under controlled, negative air pressure and is only accessible through an air lock. Doors of the quarantine chamber can't be opened by the patient (anxiety and confusion can be symptoms of a later state of Ebola infection, isolated patients might feel threatened and want to escape). Communication with the patient is possible via video transmission to the room next door. After use, rooms are decontaminated via hydrogen peroxide vaporisation (HPV), which is extremely effective against a wide range of biological agents and even category III and IV pathogens.

Decontamination of personnel and surfaces is carried out by mechanical cleaning and disinfection with a common disinfectant, such as Chlorhexidine and Polyhexanide or Ethanol. Fortunately, Ebola virus can be inactivated with established disinfectants (Unlike for example the unpleasant Noro virus, which

"Ebola is spreading avalanche-like. We cannot ignore it and simply proceed with our daily business."

PROF. DR. ANDREAS WIDMER. Head Hospital Epidemiology, University Hospital Basel

Hydrogen peroxide vaporisator for decontamination of isolation chambers.

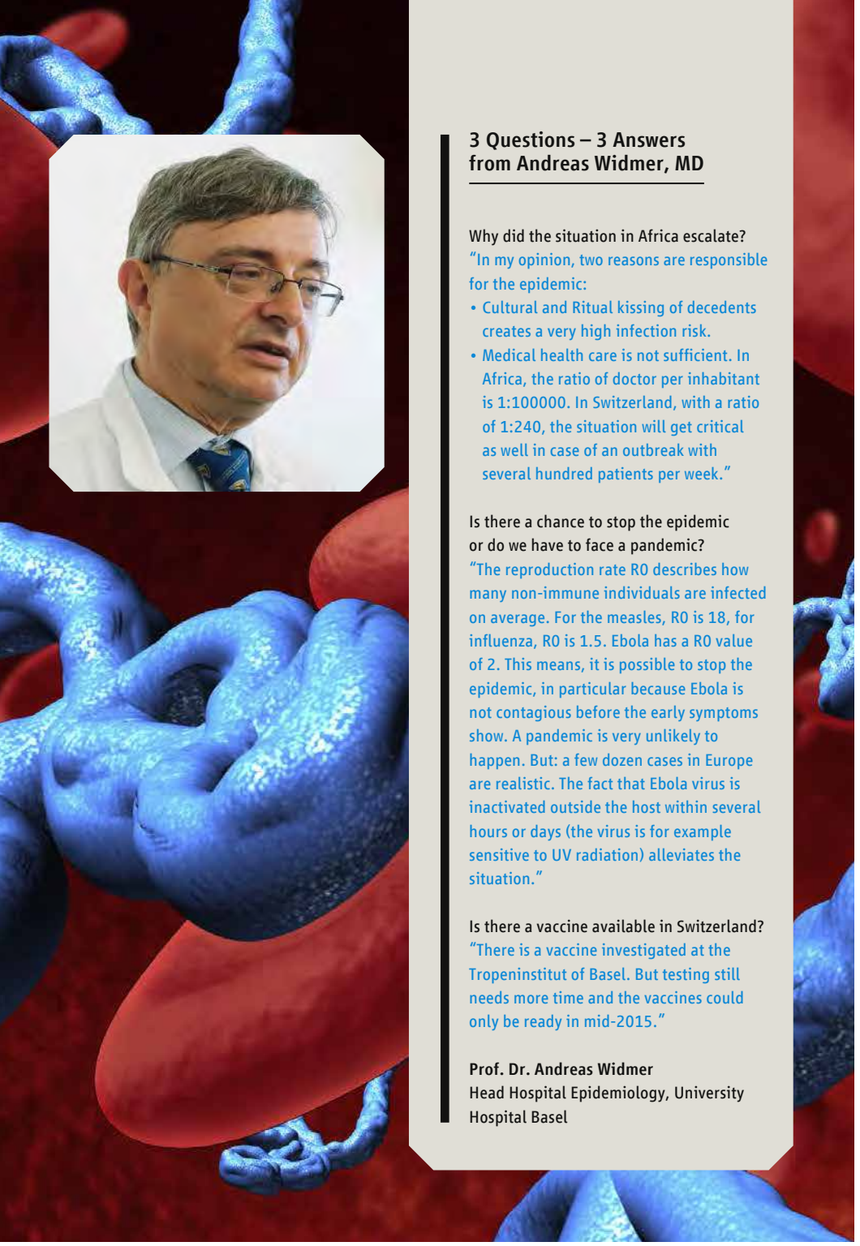
Ebola Virus and Disease

Virus

Five species of Ebola virus are known, which belong to the genus of Filoviridae. The virus particles contain a negative sense single strand RNA genome. The virus is filamentous or bacillus shaped or may be bent in u-shape with a length from 0.8 of up to 14 µm and a diameter of 80 nm. Thus, the virus is quite large and its size is comparable to the related Marburg virus. Ebola virus infects almost all kinds of cells of the host. Most often, mucosa cells of the mouth, respiratory passages or cells of the eye are highly exposed to virus contact.
In order to enter the host cell, cholesterol-transporter protein NPC1 is assumed to be necessary. Cells of patients with a mutation in NPC1 (Morbus Niemann-Pick) are found to be immune.
The virus is transmitted to people from wild animals and spreads in the human population through human-to-human transmission. The average fatality rate is around 50 %. Case fatality rates have varied from 25 % to 90 % in past outbreaks.

Phases and progression of the disease

2 to 21 days after infection (in general 6 to 10 days) fever, headache, malaise, myalgia, and sore throat are the first symptoms. In 50 % of the cases, diarrhea and nausea with vomiting follows. In later stages, blood coagulopathy with hemorrhage occurs, which can lead to multi-organ failure and death.
In every phase, the number of released virus particles increases dramatically. Recovery from Ebola depends on supportive care and the patient's immune response. People who recover from Ebola infection develop antibodies that last for at least 10 years, possibly longer. It is not known if people who recover are immune for life or if they can become infected with a different species of Ebola. Some people who have recovered from Ebola have developed long-term complications, such as joint and vision problems.



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3 Questions – 3 Answers from Andreas Widmer, MD

Why did the situation in Africa escalate?
"In my opinion, two reasons are responsible for the epidemic:
- Cultural and Ritual kissing of decedents creates a very high infection risk.
- Medical health care is not sufficient. In Africa, the ratio of doctor per inhabitant is 1:100000. In Switzerland, with a ratio of 1:240, the situation will get critical as well in case of an outbreak with several hundred patients per week."

Is there a chance to stop the epidemic or do we have to face a pandemic?
"The reproduction rate R0 describes how many non-immune individuals are infected on average. For the measles, R0 is 18, for influenza, R0 is 1.5. Ebola has a R0 value of 2. This means, it is possible to stop the epidemic, in particular because Ebola is not contagious before the early symptoms show. A pandemic is very unlikely to happen. But: a few dozen cases in Europe are realistic. The fact that Ebola virus is inactivated outside the host within several hours or days (the virus is for example sensitive to UV radiation) alleviates the situation."

Is there a vaccine available in Switzerland?
"There is a vaccine investigated at the Tropeninstitut of Basel. But testing still needs more time and the vaccines could only be ready in mid-2015."

Prof. Dr. Andreas Widmer
Head Hospital Epidemiology, University Hospital Basel

causes severe gastro enteritis and is inactivated only by specific chemical agents). At least disinfectants seem to be sufficiently available and effective – provided, that virus particles are accessible for the chemical agent. In body fluids, such as vomited matter, viruses might be protected from disinfectants by liquids and enzymes. Therefore, mechanical cleaning of contaminated surfaces prior to disinfection is crucial.

Laboratory Assays for Diagnosis

Early symptoms of Ebola infection are very unspecific. Therefore, differential diagnosis is necessary. Persons who are showing the early symptoms and might have had or have had contact with the virus, should be isolated and public health professionals notified. Samples from the patient can then be collected and tested to confirm infection. The following laboratory tests can be used.

Within a few days after symptoms begin:
- Antigen-capture enzyme-linked immunosorbent assay (ELISA) testing
- IgM ELISA
- Polymerase chain reaction (PCR)
- Virus isolation

Within a few days after symptoms begin:
- IgM and IgG antibodies

Or retrospectively in deceased patients:
- Immunohistochemistry testing
- PCR
- Virus isolation

A quick result can be obtained with the "(EZ1) rRT-PCR Assay," which is highly sensitive but could lead to false negative results in early infection stage. However, the test is not FDA approved but has an Emergency Use Authorization (EUA).

According to Professor Widmer, the isolation room at USB could be provided with laboratory equipment for analysis of blood or other samples. Currently, samples of infected patients have to be analysed in biosafety level 4 laboratories. In Switzerland only the Labor Spiez and the Laboratory of the Geneva University Hospital are licensed. For this reason, diagnosis of a suspected Ebola infection lasts up to 36 hours. During this time, the isolation chamber would be blocked for other patients.

Medical Treatment

Providing intravenous fluids (IV) and balancing electrolytes (body salts), maintaining oxygen status and blood pressure, treating other infections if they occur can significantly improve the chances of survival when used early. Experimental vaccines and treatments for Ebola are under development, but they have not yet been fully tested for safety or effectiveness.

However, in animal models the following approaches were successful:
- Antisense therapy (such as AVI-600) was tested in Rhesus monkeys and has been showed to be effective in 60 % of the cases
- Monoclonal antibodies (Zmapp) was tested in Rhesus monkeys and has been showed to be effective in 100 % of the cases
- Antiviral substances (such as Favipiravir) was tested in mice and has been showed to be effective in 100 % of the cases
- Adenosin analogue (such as BCX4430) was tested in rodents and Java monkeys and has been showed to be effective in 100 % of the cases.

The WHO has announced two vaccines, based on chimpanzee adenovirus and the vesicular stomatitis virus. The vaccines could be ready in November, if their safety is proven by then.

Since possibilities for treatment are limited, precaution is still the safest way to avoid infection and to stop the epidemic. LS

GPP GOOD PIPETTING PRACTICE

Efficiently Minimizing Costs, Errors and Health risks

It happens every day in laboratories: qPCR data cannot be reproduced, sequenced peaks prove to be artifacts, or the 96-well plate enzyme assay has to be repeated due to a pipetting error. In the long term this results in significant expense. However, most of these costly events can be avoided if pipetting is understood as a holistic process with several components. GPP (Good Pipetting Practice) presents a comprehensive and systematic approach to optimizing pipetting accuracy and repeatability.

MARIA ZWEIG

Each measurement, no matter how carefully it is taken, is always based on an inherent probability of error; no one can ever exactly measure the true value of a variable. The frequency of error is dependent on the precision of the measuring device, as well as the correct calibration and appropriate use of the tool.

The most important dosing instrument in any laboratory is the pipette to which, unfortunately, is often paid too little attention. Studies show that over 30 % of all pipettes in use do not work within the expected tolerances. Accentuated by error propagation in multistage measurement protocols, enormous deviations in the measured data occur. Inconsistent, or even erroneous, pipetting is not only a fundamental risk factor which can lead to inaccurate data or non-reproducible results, it is also a cost factor that should not be underestimated: For example, a single ELISA involves more than 1000 pipetting processes, and every microliter of reagent costs an average of 1 US dollar. If the pipette dispenses 1.2 µl instead of 1 µl, a single experiment will cost 20 % more than originally thought. Regular pipette testing and professional maintenance are essential in order to ensure that the pipettes work inside the specified tolerances.

Pipetting – a Holistic Process

Pipetting is much more than the transfer of small quantities of fluid from A to B, it is a holistic process which cannot be oversimplified. It requires successful interaction between the tool and correctly chosen accessories, and the right technique. A thorough evaluation of the operational procedure and an informed choice of liquid handling tools are equally as important as experienced, trained users and the careful maintenance that tools require in order to work reliably over time. Although the pipette is a universal tool, it must not be forgotten that every application and every sample have specific properties that must be taken into account. Only tips that have been tested and certified for absolute purity should be used for molecular genetics studies. Plasticizers found in some polypropylene laboratory consumables might interfere with enzyme reactions or cause false-positive spectrometer values at 260/280 nm.

For reliable data, it is crucial that strict standards are applied in manufacturing and quality control. Testing for potential biological contamination, including traces of DNA, DNAse, pyrogens and ATP, is indispensable and, for this reason, tips like Rainin BioClean from Mettler Toledo, for example, are supplied with a certificate guaranteeing absolute cleanliness and purity.

Application Dictates the Pipette-tip Combination

The individual application type dictates which pipette should be selected in order to achieve the most accurate results possible, and the highest possible productivity. The properties of the particular fluid can strongly influence pipetting performance and results. At room temperature and average air pressure, the majority of aqueous samples can be pipetted most accurately with air displacement pipettes, whereas problematic fluids (viscous, high density, volatile, hot, cold) can be pipetted more precisely with positive displacement pipettes.

Optimal productivity of operational procedures is dependent on the tool. Electronic pipetting is gradually replacing manual models for several reasons: the growing use of 96-well plates, the increasing complexity of modern pipetting tasks, and strict regulatory requirements. While manual pipettes are cost effective, robust and simple to use, their performance is dependent on the pipetting ability of the user. In addition, results are less easy to reproduce compared to electronic pipettes.

The high resolution stepper motors of electronic pipettes, however, rule out any user-related irregularity, ensuring a measurably greater level of accuracy and repeatability.

The most important dosing instrument in any laboratory is the pipette to which, unfortunately, is often paid too little attention.

Reliable Compliance with Regulatory Requirements

Laboratories that are subject to strict regulatory requirements must frequently check many factors, such as compliance with service intervals. The latest generation pipettes have an embedded RFID (radio-frequency identification) chip. This technology enables automatic identification of pipettes, and significantly facilitates the collection of data such as serial number, date of manufacture and date of next calibration.

In areas subject to regulation, each operational procedure takes place according to a predefined standard operating procedure (SOP). In order to ensure that employees work exactly in accordance with the prescribed protocol and do not deviate from it, the newest electronic pipettes, such as Rainin E4 XLS+ from Mettler Toledo, have advanced administrative and security functions: They help laboratories fulfill regulatory requirements and ensure proper pipette management procedures. The password-protected “admin mode” defines pipette settings, reports and maintenance intervals, and thus ensures conformity with GLP and GMP. GLP data, relating to pipetting cycles, pipette status or maintenance records, are also tamper-proof.

Ergonomic Pipetting Solutions for Lasting Success

Pipetting results are strongly dependent on technique, particularly when working with small volumes. When performing repeated pipetting cycles, any change can have a noticeable effect on accuracy and precision. Tiredness or pain, for example, can cause users to vary their pipetting rhythm. Ergonomic pipetting affects well-being as well as accuracy and precision and subsequently, the reproducibility of experiments.

Pipet-Lite XLS+ Single Channels.

Electronic XLS+ Multichannel Pipette.

Ergonomically advanced pipettes are characteristically lightweight and well balanced, with intuitive operation requiring minimal expenditure of energy, which is noticeable when, after many hours of pipetting series, the user continues to expend minimal energy. It is important to work with pipettes with pipetting forces reduced to a minimum and minimal expenditure of energy required when mounting and removing tips. Most pipettes work with two springs, the first of which is used to aspirate and dispense the sample, the second to eject the pipette tip. The second spring has significantly higher resistance so that the user can reliably detect the first stop point between the aspiration and ejection positions. A reduction in this spring force would make the first stop point more difficult for the user to detect, and also lead to significantly lower precision and accuracy of pipetting. Mettler Toledo offers an innovative solution in the shape of Magnetic-Assist technology, which enables a significant reduction in spring forces for aspirating, dispensing and the ejection process, without reducing accuracy.

When pipetting, the most energy-intensive work steps include mounting and removing tips. Comparative investigations of conventional and LTS (LiteTouch) tip ejector system from Mettler Toledo pipettes have shown that only 1 kg of force is required to mount and remove LTS tips, whereas conventional tips require significantly more force up to several kilograms. The LTS features a cylindrical shaft and pipette tip instead of the conventional conical design, which significantly reduces the contact surface between shaft and pipette and guarantees a secure seal.

Optimal productivity of operational procedures is dependent on the tool.

Every newly produced pipette is calibrated by the manufacturer before delivery, and thus meets all requirements in terms of volume, accuracy and precision. The calibration is performed using tips from the same manufacturer, as the pipette and tip together form a unit and only the optimal tip fit guarantees the best possible performance. For measured data of the highest possible reliability, it is advisable to use tips and pipettes from the same manufacturer, and to have pipettes calibrated directly in a reliable, accredited calibration laboratory. Further improvement of the quality of data can be achieved by Good Pipetting Practice (GPP), the comprehensive and systematic approach from Mettler Toledo. LS

www.mt.com

AUTHOR

Dr. Maria Zweig. *Mettler Toledo*

DRUG DESIGN

SWISS START-UPs

Antibody-Drug Conjugates Made by NBE

The newly founded Basel based company NBE Therapeutics has developed novel technologies allowing the development of second generation antibody-cytotoxin conjugates for the treatment of oncological diseases. The company's patent-pending *in vitro* mammalian cell based antibody expression and screening technology allows development of fully human antibodies against any target of choice.

BEATE PEISELER-SUTTER

Technological advances and substantial biological understanding have recently enabled the development of highly potent and effective second generation antibody-drug conjugates (ADC), such as Adcetris for lymphoma and Kadcyla for HER2-positive breast cancer. ADCs are composed of a monoclonal antibody linked to a cytotoxic drug by a chemical linker with labile bonds. The antibody is designed to bind only to a specific target, such as certain molecules expressed on the surface of tumour cells. After binding, the whole ADC is internalized within the target cell and the drug is released upon degradation of the linker. This innovative concept promises minimal side effects on healthy cells, but the devil is in the detail and diverse hurdles remain.

Biologist Ulf Grawunder, CEO of (new biological entities) NBE-Therapeutics resumes: "There are significant challenges involved in developing a potent and safe ADC with the optimal combination of an internalizing antibody to a relevant tumour target, a linker with desired functionality, and a cytotoxic payload with optimal potency on the targeted tumour cells. The first generation ADCs suffered from suboptimal linker structures and a first ADC, Mylotarg, developed by Wyeth and Pfizer, had to be taken off the market after ten years, due to strong side effects caused by too loose coupling of the payload to the antibody. The recently approved second-generation ADCs are much better in this respect, but consist in heterogeneous mixtures with variable potency. NBE-Therapeutics is working on homogeneous third-generation ADCs with most stable, but functional linker structures." Grawunder founded NBE in 2012, after leaving 4-Antibody, a Swiss therapeutic antibody engineering company that he had co-founded in 2004. NBE receives financial support from the Boehringer Ingelheim Venture Fund, five private investors and the Swiss Commission for Technology and Innovation (CTI). The funds were used to develop two proprietary technology platforms in house. NBE-Therapeutics is managed by Ulf Grawunder, CEO, and biologist Roger Beerli, Vice President Research and Development. The company currently has ten employees.

Fully Human Antibodies

NBE's fully validated Transpo-mAb technology is a discovery platform for monoclonal antibodies, allowing screening of antibody libraries in mammalian cells (e.g. murine pre-B cells). The technology allows stable integration of antibody constructs into any mammalian host cell type, thereby enabling perfect genotype to phenotype, without the need to use viral vector systems. The antibody libraries may be derived from different sources (tumor-immunized patients, immunized animals, artificial genes produced by means of synthetic biology, etc.). In order to permanently integrate the genes into the mammalian cells' genome, transposable elements are used as vectors. The transfer is carried out by the enzyme transposase. "Transposable elements are well known tools used in molecular biology, but have never been used for antibody production so far," states Grawunder. The mammalian cells produce complete antibodies and can be manipulated in order to secrete these into the culture medium permitting early functional tests. "NBE produces its own antibodies and does not rely on external technologies. Our long-term objective is to develop fully human antibodies as a basis for ADCs. This research is conducted in close collaboration with Christoph Rader, Associate Professor at the Scripps Research Institute in Jupiter, Florida," Grawunder informs.

Advanced Linking

NBE's SMAC-technology allows the development of site-specifically conjugated ADCs under physiologic conditions via stable peptide linkers. "Many ADCs on the market are based upon unstable Maleimide linker chemistry," explains Grawunder. NBE does not apply chemistry in the linking process but uses bacterial Sortase. The enzyme usually catalyzes the exchange of virulence factors on the surface of pathogens such as Staphylococcus aureus and is used in molecular biology as a tool for protein-protein ligation. By means of synthetic biology, NBE scientists produce antibodies with specific leucine-proline-any-threo-

"Our long-term objective is to develop fully human antibodies as a basis for ADCs."

DR. ULF GRAWUNDER. CEO, NBE Therapeutics

NBE Founder and CEO Dr. Ulf Grawunder (middle) and his research associates Dr. Nikolas Stefan (left) and Dr. Lorenz Waldmeier (right).

nine-glycine (LPXTG) sequences, a sorting sequence recognized by sortase enzymes. When toxins are provided with a short stretch built up of glycines, sortases are able to covalently link both up. "This method works with over 95 % efficiency in our hands and enables us to produce highly homogeneous ADCs. It was applied for creating an enzymatically-conjugated version of Kadcyla, using the same monoclonal antibody Trastuzumab and the cytotoxic agent Mertansine. We could show that our enzymatic version has comparable potency for tumour killing in cell culture and in tumour bearing mice, relative to Kadcyla. It may be that our stable peptide linker even has a therapeutic advantage over the original drug. With this experiment, we succeeded to demonstrate the feasibility of our technology in only two years," Grawunder is pleased.

In cooperation with Georg Lipps, Professor at the Institute for Chemistry and Bioanalytics of the University of Applied Sciences and Arts Northwestern Switzerland (FHNW), NBE is evaluating further Sortase classes. The objective is to specifically attach two synergistically acting cytotoxins to one anti-tumour antibody. NBE focuses on validated cytotoxic compounds like Maytansines and Auristatins, but is also evaluating other toxins with different modes of action, e.g. DNA modifying properties.

www.nbe-therapeutics.ch

Technical requirements for ADC

Antibody Drug Conjugates (ADCs): are composed of a tumour-specific antibody coupled to a cytotoxic small molecule. The antibody is designed to target a specific receptor or other target, which should exclusively be expressed on the surface of a specific type of cancer cell. The ADC must be specific for binding sites on these targets and has to be taken up by the cancer cells and discharge the cytotoxin inside in order to effect cancer cell death.

Antibody
Ideally, the chosen antibody must not only demonstrate high selectivity and affinity for the tumor-specific target, but also show low immunogenicity. It has to bind to a target binding site (epitope) that leads to internalization of the antibody. Chimeric antibodies are created by fusion of variable domains of mouse antibodies to constant domains of human antibodies, but due to the mouse-derived antibody binding domains a certain level of immunogenicity remains. Immunogenicity can be further reduced by replacing the mouse hypervariable loops by those of the human counterpart (CDR grafting). Unfortunately, humanizing antibodies may result in loss of activity. Fully human antibodies can efficiently be developed using phage-, bacterial or eukaryotic display libraries, with eukaryotic systems having the advantage to do post-translational modifications. Alternatively, transgenic animal platforms may be used, which produce antibodies from human genes. Until 2010, seven human monoclonal antibodies (mAb) have been approved for marketing, about thirty more being under clinical investigation.

Linker
Linkers are a key component of ADCs. These short molecular spacers covalently couple the cytotoxic drug to the antibody protein. Linkers must ensure stability of the ADC during its circulation in the blood stream, but subsequently need to deliver the cytotoxic payload upon internalization into the target cell. There are linkers that are cleaved by reduction in the cytoplasm, in the acidic environment of the lysosome, or by proteases, as well as by catabolic degradation. Traditionally, cytotoxic payloads are attached to antibodies by chemical linkers either via amino groups of lysine residues or via thiol groups of cysteine residues. The outcome of such chemical conjugations are heterogeneous mixtures containing from free antibody up to multiply modified molecules, a long way from the original objective of creating homogeneous chemical species.

Cytotoxic
At last, the modified antibody must be bound with a potent cytotoxic molecule. There are only a few major chemical classes of toxins being explored. Duocarmycins and calicheamicins lead to DNA damage by targeting DNA. Amatoxin analogs disrupt cell metabolism by inhibiting messenger-RNA synthesis. And maytansinoids and dolastin analogs stop cell division by inhibiting polymerization of tubulin, a protein, which makes up the cytoskeleton's microtubules.

Roland Studer, managing director of Faust Laborbedarf AG.

FAUST LABORBEDARF AG

Competent and Ready to Deliver at Every Time

RALF MAYER

Excellent research demands a specific, state-of-the-art laboratory environment. Instruments and consumable supplies, including many single-use products, must be kept constantly available in perfect quality. As a result, the increasing importance of the life sciences sector presents laboratory suppliers with big challenges. "LifeSciences plus" spoke to Roland Studer, managing director of Faust Laborbedarf AG.

Faust Laborbedarf offers a full range of products to the laboratory industry. What role does the life sciences sector play in this?
Roland Studer: Year by year, life sciences products are becoming more important to us. Almost 50 % of Faust Laborbedarf AG's range today comprise articles that will be utilised by the life sciences sector.

Who are your main customers in the life sciences sector?
We deliver to a wide spectrum of companies and institutes that are active in life sciences. There is a strong focus on industrial research laboratories as well as universities in Switzerland.

In relation to your overall business, has the life sciences sector grown at a disproportionate rate in the past few years? If so, why is that the case?
The growth in this sector was massively disproportionate. It is because life sciences activities have developed dynamically in Switzerland. We are participating in this growth by constantly adjusting our range according to the requirements of the customer.

What special challenges does a trader in the life sciences sector have to face, for example regarding shipping, warehousing, etc.?
The ability to deliver in time is generally a central theme in our business, but it is particularly important in the life sciences segment. Cell culture products for example: Faust Laborbedarf is an exclusive representative of the TPP company in Switzerland. That means that we always have all TPP products in stock at our warehouse in Schaffhausen. Furthermore, we must always pay attention to certain products that have expiry dates. This is very demanding in terms of warehouse management.

Working in a microbiological laboratory requires specialist knowledge. How do you make sure that your employees can bring this knowledge into the service of customers?
Even during recruiting we ensure that our future employees are carrying a great deal of knowledge with them. This is the reason why our field and office sales teams only employ people with a background in laboratories. But that alone is not enough – continuous further training in cooperation with manufacturers is a must.

Is your life sciences business always growing or do you also notice fluctuations – perhaps caused by changes in the market such as the departure of Merck-Serono for example?
Of course we notice the departure of a large firm. But in the past 10 years we have always been able to record growth.

Could you please say a few words about why customers from the life sciences sector should order at Faust Laborbedarf AG?
Thanks to our competent employees we are in a position to advise customers. We know what our customers are talking about and we communicate with them on an equal footing. Our competencies do not just extend to sales and service, we also employ highly qualified experts in logistics. In this way we guarantee fast delivery in the highest quality. Not least do we have an extensive range at our disposal which is documented in our catalogue or on our online shop. A further important point is the close collaboration with our suppliers: we have been maintaining contact with them for over 20 years. This ensures that decisions can be made in the required short space of time.

www.faust.ch

TOOLS

Conductometer: Robust, Reliable, and Simple to Use

The new Metrohm meters are "two in one": precision instruments for the laboratory and robust companions for mobile use in the field and the process. During field use the new meters are powered by batteries which can be recharged after use, on the road on the cigarette lighter with the use of an adapter. "Two-in-one" applies to the performance of the new meters, too: parallel measurement of pH and conductivity with the 914 pH/conductometer; parallel recording of two pH values with the 913 pH meter. Both versions indicate the temperatures of the samples. The 912 Conductometer measures the conductivity, salinity and temperature of the sample. Ergonomic design makes sure the new meters fit comfortably in one hand. Each key on the clearly organized user interface comes with a secure pressure point. Hence, the meters can be operated intuitively with one's left or right thumb while the other hand remains free to hold the electrodes in the medium in which the measurement is done. The new Metrohm meters wouldn't be Metrohm if they weren't extremely robust: all three versions meet the requirements of IP67. Back in the office, the meter is simply plugged in the USB port of the PC and the collected data is exported straight to the LIMS or Excel or can be managed in tiBase, the Metrohm titration software.
Metrohm Schweiz AG | www.metrohm.ch

To Protect or not to Protect – Plungers of Bottle Top Dispensers

Bottle top dispensers are widely used for repeated dosing of reagents straight from the bottle. Since liquids come in direct contact with plunger and barrel during dispensing, it is crucial to choose the appropriate plunger model either with or without protection layer. Protection layers are mostly made of fluoropolymers, such as PFTE, FEP and PFA which have a smooth surface that prevent building of biofilms and crystals. Oleophobicity, hydrophobicity and low binding capacity for aqueous solutions as well as chemical resistance and reduced friction are further material characteristic. In addition, protection layers are in compliance with FDA regulations. A known limitation however is their mechanical fragility. Without sufficient coating thickness, scratches may occur and impair proper working of the dispenser. Moreover, some solvents and strong acids in high concentration might react with the coating and lead to swelling or peeling. For these classes of chemicals, plungers without protection layers made of glass or ceramic are more suitable, since these materials are chemically inert. However, when using ground glass it is difficult to guarantee a smooth glide of plunger in the barrel. Further limitations are: high friction with some liquids, higher sensitivity to freezing when dispenser not used, scratch of barrel wall (if force is applied, or if the plunger got stuck), increased capillary effects and "sticky feeling" during plunger activation. Ceramic (like Al_2O_3) shows excellent chemical resistance and a better mechanical shock resistance compared to glass, but is a highly expensive material and thus increasing the price of the instrument. Most suppliers offer models with and without protection layer. They know best about the recommended use and limitations and must remain available anytime to provide necessary technical support when needed. **Socorex Isba S.A. | www.socorex.com**

Single-Use Hybrid Purifier for Cell Culture Clarification

With the Emphaze AEX Hybrid Purifier, 3M presents a new product for the purification during biopharmaceutical manufacturing. The all-synthetic, multifunctional system clarifies cell cultures and contains both a Q-functional anion exchange media as well as an integrated 0.2 µm membrane for the retention of fine particles and bioburden reduction. The high binding capacity for negatively charged impurities of the anion exchange media provides a substantial reduction of DNA and HCP. At the same time the defined 0.2 µm membrane delivers a strong reduction of fine particles and bioburden load. Therefore the hybrid structure of the novel product provides maximum product purity after clarification when using a single unit operation. The Emphaze AEX Hybrid Purifier not only produces a reduction of impurities such as turbidity, DNA, HCP and bioburden, but also offers a loading capacity similar to fine grades of highly charged conventional depth filters, and can easily be incorporated into existing manufacturing processes where such a depth filter would be used. Moreover, it enhances the performance and protection of the subsequent chromatographic steps, such as the protein A column. The single-use Emphaze AEX Hybrid Purifier is easy to use and improves process economics, as the early, highest possible product purity protects valuable downstream processes and facilitates a reduction of the total cost of ownership.
3M Schweiz GmbH | www.3M.com

Let it Glow

BD Biosciences, a segment of Becton, Dickinson and Company, is one of the world's leading businesses focused on bringing innovative tools to life science researchers and clinicians. The company's portfolio includes a wide range of cell analyzers and sorters for flow cytometry and related software and reagents. BD Biosciences is focused on continually advancing the science and applications associated with cellular analysis. The release of extremely bright fluorochromes with a minimum spillover in adjacent channels offers completely new perspectives for the daily work on the flow cytometer. The new BD Horizon Brilliant dyes, such as BD Horizon Brilliant Violet, Ultraviolet or Blue reagents, facilitate the creation of multicolor panels and ensure the reliability, reproducibility and standardization of flow cytometry data. Advantages are:

- High sensitivity to resolve dim populations
- Stability to fixation
- High lot to lot stability also for the tandem formulations avoid to obtain wrong results
- Low spectral overlap into other channels leading to lower background signals and optimized resolution for all channels
- Increase the flexibility for your panel design

BD dyes expand the choice of bright colors and maximize flexibility in multicolor panel design.
BD Biosciences | www.bdbiosciences.com

FCX Oxygen Sensor Module

Pewatron's new oxygen sensor module FCX-MC can be used in many different applications and in several configurations. Key element is the oxygen sensor from Fujikura – an amperometric solid-state sensor with high output accuracy, short response time to gas concentration changes and ruggedness against pressure change, humidity and other gases. The non-amplified signal from the oxygen sensor is in the range of micro amps and non-linear. The FCX-MC sensor module is a signal-conditioning unit with the option of different sensor output modes, e. g. analogous linearised current output (0–20 mA), analogous linearised voltage output (0–10 V) or a digital output using the RS485 communication protocol. Total power consumption is low (< 3 W), making the FCX-MC suitable for mobile applications. The oxygen sensor is configured in a flow configuration with connectors for housing or in a diffusion configuration. In the flow configuration, the sensor encapsulation is an aluminum flow housing, for analysis of oxygen concentrations from small sample extracts. The sensor can be placed on the sensor module PCB board for integration into transmitters or connected to the sensor module PCB board via cables (of up to 10 meters length) in either configuration. The FCX-MC can withstand gas temperatures as high as 250 °C. Output oxygen concentration is highly linear and accuracy is better than 1 % FS with a response time for gas concentration changes of below 10 s. Concentration ranges are from 0–25 vol % and 0–5 vol % O_2.
Pewatron AG | www.pewatron.com

The New ViscTool

Traditionally liquid handling systems reach their limits when it comes to dispensing viscous samples. Standard pipetting tools cannot handle highly viscous materials with the required precision. Many applications including the pipetting of oils, the preparation of samples of healthcare products, the development of formulations of lubricants and the distribution of polymers demand the precise pipetting of highly viscous materials. Our new positive displacement ViscTool has been developed in house to meet all the technical requirements needed to dispense highly viscous solutions:

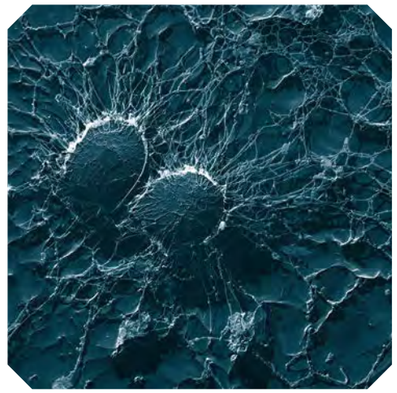
- It can be operated using disposable syringes from various suppliers or precision glass syringes
- Volume range is from 100 µl to 50 ml
- Dispensing volumes start from 1 µl
- Very high resolution (> 80.000 steps/cm)
- Under full WinLissy Software control for optimum accuracy and precision
- Melted solids
- Prefilled tips with grease/pastes

The new ViscTool can be upgraded onto all of our previously installed automatic workbench systems.
Zinsser Analytic GmbH | www.zinsser-analytic.com

Biotech and Laboratory Technology Business made in Hannover

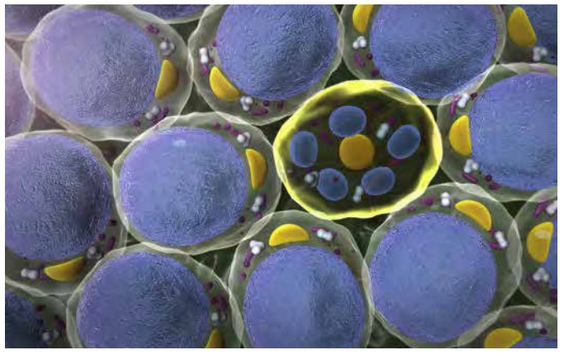
Preparations for Europe's No. 1 meeting place for biotechnology, the life sciences and lab technology are in full swing. The next BIOTECHNICA will be staged from 6 to 8 October 2015 and feature two special marketplaces dedicated to the topics of "bio-economy" and "personalized medicine technologies." Another major emphasis at BIOTECHNICA is on helping the biotech industry get down to business, with tailored matchmaking offerings designed to maximize the number of promising leads and partnerships generated at the show. "When it comes to successful networking, Hannover offers all the right formats for the scientific and R&D communities as well as providers of biotech goods and services," said Dr. Jochen Köckler, member of the Managing Board at Deutsche Messe. "This makes BIOTECHNICA stand out as Europe's best business and knowledge-sharing platform." BIOTECHNICA's impact will also be enhanced when Deutsche Messe launches its brand new LABVOLUTION laboratory technology trade fair in 2015, at the same time and place. The new fair spotlights laboratory technology also as used in other fields besides biotechnology and the life sciences. LABVOLUTION hosts the key chemical, pharmaceutical, plastics, materials development and materials testing, cosmetics, medical technology, environmental engineering and nutrition sectors. A single ticket price covers admission to both exhibitions.
Deutsche Messe AG | www.messe.de

NEWS



A Possible Alternative to Antibiotics

Scientists from the University of Bern have developed a novel substance for the treatment of severe bacterial infections without antibiotics, which would prevent the development of antibiotic resistance. The scientists engineered artificial nanoparticles made of lipids, "liposomes" that closely resemble the membrane of host cells. These liposomes act as decoys for bacterial toxins and so are able to sequester and neutralize them. Without toxins, the bacteria are rendered defenseless and can be eliminated by the cells of the host's own immune system. In clinical medicine, liposomes are used to deliver specific medication into the body of patients. Here, the Bernese scientists have created liposomes which attract bacterial toxins and so protect host cells from a dangerous toxin attack. "We have made an irresistible bait for bacterial toxins. The toxins are fatally attracted to the liposomes, and once they are attached, they can be eliminated easily without danger for the host cells," says Eduard Babiychuk who directed the study. "Since the bacteria are not targeted directly, the liposomes do not promote the development of bacterial resistance," adds Annette Draeger. Mice which were treated with the liposomes after experimental, fatal septicemia survived without additional antibiotic therapy. The Technology transfer organisation of the Universities of Bern, Basel and Zurich "Unitectra" has filed a patent for this compound. The liposomal treatment is being developed as a new medicine named "CAL02" by LASCCO SA, a Geneva-based biomedical company specialized in innovative technologies for diagnostics and therapeutics. The first clinical study, conducted on patients suffering from severe streptococcal pneumonia, is scheduled for 2015.
 # www.unibe.ch

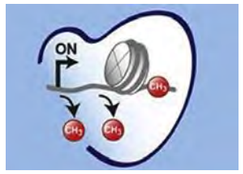


How Bile Acids Could Fight Diabetes

EPFL scientists, working with researchers from Italy and the Netherlands, have shown that bile acids activate a little-known receptor to overcome the loss of insulin sensitivity, forming the basis for a new class of drug against type-2 diabetes. One of the major problems of type-2 diabetes is that it often coincides with chronic inflammation in the body's fat tissue. This inflammation arises from the activity of immune cells called macrophages within the fat tissue, which recruit even more macrophages through chemical signals. The accumulation of macrophages interferes with the ability of fat cells to respond appropriately to insulin; this condition is known as "insulin resistance." Consequently, pharmaceutical companies are urgently searching for treatments that minimize the accumulation of macrophages in fat tissue. A research team led by Kristina Schoonjans at EPFL has discovered that a receptor called TGR5, which is located on macrophages, can inhibit the inflammation of type-2 diabetes. TGR5 is activated by chemicals in our bile, collectively referred to as "bile acids". Bile acids have traditionally been thought to be restricted to the small intestine, helping with the digestion of lipids. But recent studies – many led by Schoonjans – have shown that bile acids also enter the bloodstream and behave like hormones, acting on receptors like TGR5, and affecting the behavior of different types of cells. **# www.epfl.ch**

Epigenome of Cardiac Muscle Cell

Pharmacologists at the University of Freiburg (Breisgau) have succeeded in mapping the epigenome of cardiac muscle cells. The epigenome is the totality of epigenetic mechanisms that decide which genes are active in a cell and which are not. Changes in internal or environmental conditions, such as nutrition, stress, or drugs, can leave behind epigenetic patterns. The heart accomplishes enormous feats during development and in the growth process after birth. It is the first organ to be formed in the growing embryo, and it continuously supplies the entire body with oxygen and nutrients. The nucleus of cardiac muscle cells assumes the central function to control the gene expression program. A team led by Dr. Ralf Gilsbach and Prof. Dr. Lutz Hein has now developed a novel method for isolating nuclei of cardiac muscle cells from heart tissue consisting of various types of cells. The scientists applied the method of next generation DNA sequencing to the isolated nuclei to create high-resolution maps of DNA methylation – one of the most important epigenetic mechanisms for the regulation of gene activity – as well as further epigenetic markers of all of the genes. This enabled them to identify the epigenetic switches that trigger the switching of the cardiac gene program during birth and in the case of chronic cardiac failure.



 # www.uni-freiburg.de

European Amphibians Suffer from "Asian Disease"

A Skin-Eating fungal disease brought to Europe by humans now poses a major threat to native salamanders and newts, scientists of the University of Zurich and Ghent University have warned. They say nations need to urgently consider appropriate biosecurity measures to stop the further spread of this pathogen. The previously unknown fungus Batrachochytrium salamandrivorans was discovered last year by researchers investigating a huge crash in the population of fire salamanders in the Netherlands. Now the same team have screened over 5000 amphibians from four continents to ascertain the threat the new disease presents to other species.The results show that B. salamandrivorans is very dangerous to salamanders and newts. The fungus was found to be present in amphibians from Thailand, Vietnam and Japan as early as 1894 without causing disease, suggesting it originates from Southeast Asia. The fungus probably arrived in Europe recently, and its presence in traded amphibians suggests that the intercontinental movement of amphibians explains its introduction. The great crested newt, a protected and threatened species in Switzerland, is among the species that rapidly die once infected. "Globalisation has resulted in the movement of humans and animals all across the world, bringing pathogens into contact with hosts that haven't had the opportunity to establish resistance. As a consequence, pathogens like B. salamandrivorans that are brought to a new environment can very rapidly threaten many species with extinction," said co-author Dr. Benedikt Schmidt from the Institute of Evolutionary Biology and Environmental Studies at the UHZ. **# www.uhz.ch**

New antibiotic in mushroom that grows on horse dung

Microbiologists and molecular biologists at ETH Zurich and the University of Bonn have discovered a new agent in fungi that kills bacteria. The substance, known as copsin, has the same effect as traditional antibiotics, but belongs to a different class of biochemical substances. Copsin is a protein, whereas traditional antibiotics are often non-protein organic compounds. Copsin belongs to the group of defensins, a class of small proteins produced by many organisms to combat microorganisms that cause disease. The human body also produces defensins to protect itself against infections. They have been found, for example, on the skin and in the mucous membranes. The researchers led by Markus Aebi, Professor of Mycology (ETHZ), discovered the substance in the common inky cap mushroom Coprinopsis cinerea that grows on horse dung while studying the fungus' ability to kill bacteria in general. Andreas Essig, postdoc in Aebi's group and lead author of the study, is currently exploring potential applications for copsin that has been registered for patent approval. It was the biochemical properties of the substance that led the scientist to do so. According to Essig, Copsin is an exceptionally stable protein. In general, proteins are susceptible to protein-degrading enzymes and high temperatures. Copsin however, remains stable when heated to a temperature of 100 degrees Celsius for several hours or when subjected to protein-degrading enzymes. The researchers believe that the protein has these properties because of its extremely compact three-dimensional structure, as NMR spectroscopy has shown. The ETH researchers were also able to unravel the exact mechanism of action, discovering that copsin can bind to lipid II, an essential building block for the cell wall of bacteria. If copsin binds to lipid II, the bacteria die because they are unable to build new cell wall. In addition to being used as an antibiotic in medicine, it may also be possible to use copsin in the food industry as well: Copsin kills many pathogens including Listeria, a type of bacteria that can cause severe food poisoning. **# www.ethz.ch**

People in this Edition

"Everyone is a genius. But if you judge a fish on its ability to climb a tree, it will live its whole life believing that it is stupid."

A. Einstein

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Managing Director: Roland Kühne
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Editors
LifeSciences Plus
Neumattstrasse 1, Postfach, CH-5001 Aarau,
Telefon +41 (0)58 200 56 88
Ralf Mayer (Editor in Chief)
Telefon +41 (0)58 200 56 88,
ralf.mayer@azmedien.ch
Sonja Bichsel-Käser
Telefon +41 (0)58 200 56 86,
sonja.bichsel@azmedien.ch

Sales director
Jürg Rykart
Telefon +41 (0)58 200 56 04
juerg.rykart@azmedien.ch

Sales
Thomas Kolbeck
Telefon +41 (0)58 200 56 31
thomas.kolbeck@azmedien.ch
Advertisement Prices: www.chemieplus.ch

Head of Marketing
Valentin Kälin

Subscription
abo@chemieplus.ch, Telefon +41 (0)58 200 56 93

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Contact
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