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3.15

## Photosynthesis

### The most important chemical reaction on earth

**Prof. Dr Hartmut Michel, Director at the Max Planck Institute of Biophysics, was awarded the 1988 Nobel Prize in Chemistry jointly with Prof. Dr Johann Deisenhofer and Prof. Dr Robert Huber for the determination of the three-dimensional structure of a photosynthetic reaction centre.**

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**WHERE THE FUTURE BECOMES REALITY**

# editorial

# Hormone-related genotoxic stress at micro and nano scales

Prof. Dr Paul G. Layer

While epigenetics is certainly an exciting field, it doesn't necessarily make life any easier – not least because genetics seemed to be an exact science before its arrival. For a long time, its core message was the central dogma of molecular biology, namely that one piece of DNA, the gene, is used to manufacture one and only one corresponding protein in the cell by the processes of transcription and translation, and that each protein provides one specific function (one gene -> one protein -> one function dogma). Accordingly, if each organism were to merely possess a sufficiently large number of genes, it could be fully explained down to its last detail and would thus be strictly genetically "determined". Yet our gene count is small and our genome is anything but autonomous. It is the hormones of the endocrine system that help drive normal development during human and animal embryogenesis, for example, while hormone-mimicking substances can cause massive disruption to normal genetic programming. Members of the grimly-named family of endocrine disruptors (EDCs) include polychlorinated biphenyls (PBCs), which continue to enjoy widespread use in the form of pesticides, antimalarial agents, lubricants in aircraft oils or plasticisers in many areas of our day-to-day lives. While the anecdotes one hears in relation to these substances are often bizarre or even comic (afflicted by shrinking penis size, crocodiles can no longer copulate and hence reproduce successfully), these are drawing a veil over an ecological and social time bomb. Bodily manifestations of feminisation as a result of the effects of EDCs are not just a problem for animals, but for many male humans, too (abnormal genitalia, breast enlargement, hermaphroditism, etc.).

**Medical experts are already speculating whether men could actually "die out" altogether – following a reduction of almost 50 % in sperm counts for European men over the last 50 years. The EU has finally caught up with the USA in recognising the potential dangers posed by EDCs and is now investing heavily in EDC research.**

Such substances may not only be capable of adversely influencing the development of human foetuses in the womb or in early childhood (see article by Professor Vollmer, University of Dresden) but may even promote illnesses – such as dementia – at an advanced age. Despite the many countermeasures, the problem of EDCs is likely to persist for decades or even centuries – a scenario dramatically depicted by the gripping article from Professor Liebezeit (University of Oldenburg) on microplastics and the ways in which they permeate the world's oceans and food chains. Nor is it mere microparticles that interest us today – we've long since entered the nanoscale domain. The importance of an analytical understanding of nanoparticles and its use in creating prospective regulatory frameworks for their handling is shown by Dr Brüning (Eurofins WEJ Contaminants GmbH) in relation to their utilisation in food. As we can see, our woes and wellbeing continue to depend on research, research and yet more research. The Professor Denz lab at the University of Münster, Germany, presents a spectacular piece on the utilisation of "optical tweezers" for the non-destructive manipulation and targeted physical orchestration of living cells. One can reasonably expect this kind of laser-driven manicure to play a role in solutions to the abovementioned problems. Our readers can thus look forward to a colourful set of stories from the world of research in this issue: gripping, brand new and highly informative – and, as always with our magazine, richly illustrated. And which, taken as a whole, also work to shed copious light on a central topic of modern-day biological research: a topic commonly referred to as the nature versus nurture debate.

# content 3.15



**30**

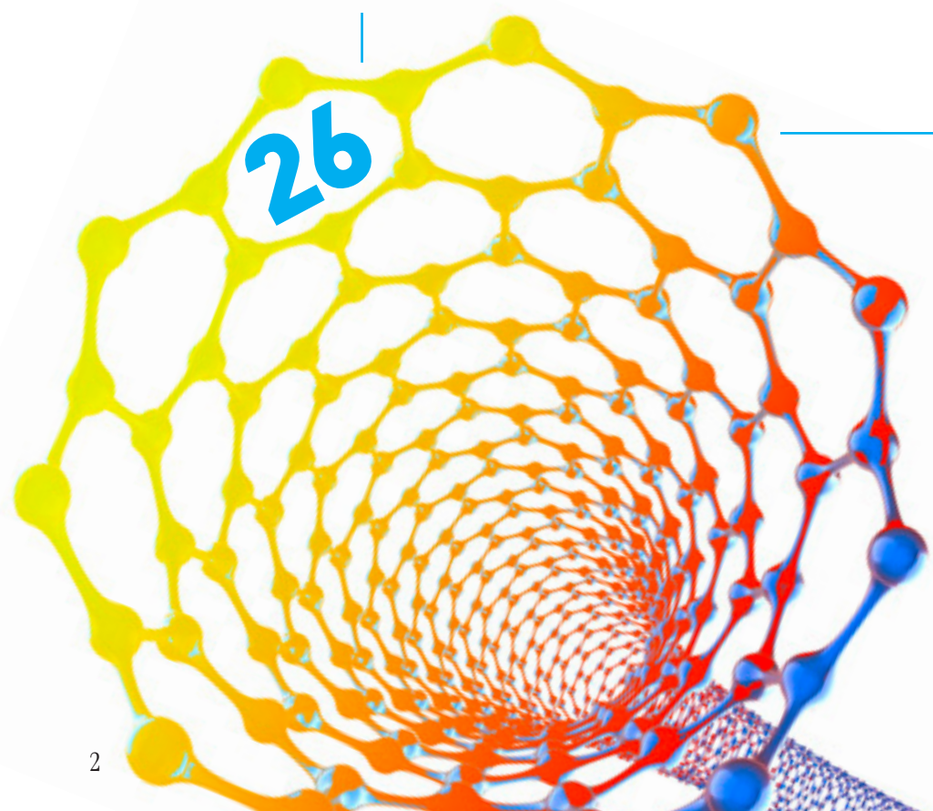
**analytics**



**environment & toxicology**



16



26

INTERNATIONAL YEAR OF LIGHT 2015

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# Photosynthesis – the most important chemical reaction on earth

This is the headline of a press release from 19 November 1988 by The Royal Swedish Academy of Sciences within the context of the joint award presentation of the 1988 Nobel Prize in chemistry to three German citizens: Dr Johann Deisenhofer (Howard Hughes Medical Institute, Dallas, Texas, USA), Professor Robert Huber (Max-Planck-Institut für Biochemie, Martinsried, Federal Republic of Germany) and Dr Hartmut Michel (Max-Planck-Institut für Biophysik, Frankfurt/Main, Federal Republic of Germany).

The arguments for this decision have been summarised as follows: "They are the first to succeed in unravelling the full details of how a membrane-bound protein is built up, revealing the structure of the molecule atom by atom. The protein is taken from a bacterium which, like green plants and algae, uses light energy from the sun to build organic substances. All our nourishment has its origin in this process, which is called photosynthesis and which is a condition for all life on earth.

The organic substances serve as nourishment for both plants and animals. Using the oxygen in the air, they consume these nutrients through what is termed cellular respiration. The conversion of energy in photosynthesis and cellular respiration takes place through transport of electrons via a series of proteins, which are bound in special membranes. These membrane-bound proteins are difficult to obtain in a crystalline form that makes it possible to determine their structure, but in 1982 Hartmut Michel succeeded in doing this. Determination of the structure was then carried out in collaboration with Johann Deisenhofer and Robert Huber between 1982 and 1985.

Photosynthesis in bacteria is simpler than in algae and higher plants, but the work now rewarded has led to increased understanding of photosynthesis in these organisms as well. Broader insights have also been achieved into the problem of how electrons can, at an enormously high speed (in the order of a picosecond = $10^{-12}$ seconds), be transferred in biological systems." (source: http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1988/press.html)

We think that the headline of the press release of 1988 is still valid today and have chosen Professor Hartmut Michel for the illustration of the cover page of this issue of lab&more. His work, the cristallization of a membrane-bound protein formed the basis of the common research of the three laureates. The determination of the structure is based on the experience of Robert Huber and Johann Deisenhofer. They had available the best possible x-ray instrumentation of that time but they did not have the computer technology which is standard today. If one realizes that the computer capacity is still growing by a factor of two every two years, one comes out with the result, that the today technology is about thirty thousand times faster that that of 1985, i.e. Deisenhofer, Huber and Michel had to work with stone age technology as far as data processing is concerned.

**Prof. Dr Jürgen Brickmann**
**Scientific Director**
**succidia AG**

*Picture: © istockphoto.com | NejroN*

# market view

## Eppendorf Group's new Chief Executive Officer is Thomas Bachmann

Picture: Eppendorf AG

Thomas Bachmann became Chief Executive Officer of the Eppendorf Group on 1 August 2015. Following the departure of Eppendorf's previous CEO, the company's Chief Financial Officer, Detmar Ammermann, had exercised the function of Spokesman of the Management Board on an interim basis in addition to his responsibilities as CFO. Bachmann, who has been a member of the Eppendorf Supervisory Board since 2013, came to Eppendorf from his position as President of the Bruker BioSpin Group. He has been active in the life science sector since 2005, when he took on the overall management of the globally active Tecan Group, which is based in Switzerland.

→ **www.eppendorf.com**

## Brain and WeissBioTech announce joint research collaboration

Biotechnology company Brain AG and enzyme specialist WeissBioTech GmbH initiated a joint research and development collaboration for the bioproduction of technical enzymes for the dairy industry. Within the collaboration the application knowhow in the growing field of enzymatic production processes in the dairy industry of WeissBioTech together with its marketing and sales intelligence will be combined with Brain's expertise in enzyme discovery, its expression technologies and enzyme development know-how. In November 2014, the two companies announced a strategic investment of Brain in WeissBioTech. During the current collaboration, new enzymes for the production of dairy products will be developed based on BRAIN's extensive range of novel enzymes and metagenome libraries, summarized in the Brain BioArchive®, and the associated technologies required for identification, development and production of enzyme products. WeissBioTech's application knowhow and market knowledge will be the essential guide for enzyme discovery, development and sales of the new products from this collaboration.

→ **www.brain-biotech.de**

Picture: Lutke Böttcher Brain AG

## Roche submits filing to FDA for companion diagnostic for non-small cell lung cancer drug therapy

Roche announced it has submitted the cobas EGFR Mutation Test v2 for Premarket Approval (PMA) to the US Food and Drug Administration (FDA), as a companion diagnostic test for AZD9291, an AstraZeneca investigational therapy for non-small cell lung cancer patients with an acquired resistant mutation. Patients with non-small cell lung cancer who have adenocarcinoma with tumour containing an EGFR sensitising mutation show significant benefit from currently available EGFR TKI therapies. However, approximately two-thirds of these patients will relapse and develop drug resistance. In many cases, this resistance is caused by an acquired mutation called T790M. The cobas EGFR v2 test can aid clinicians to appropriately select NSCLC patients who have acquired the T790M mutation and are most likely to benefit from AstraZeneca's novel form of therapy.

→ **www.roche.com**

## Allergan enters into licensing agreement with MSD

The pharmaceutical company Allergan and MSD announced that they have entered into an agreement under which Allergan will acquire the exclusive worldwide rights to MSD's investigational small molecule oral calcitonin gene-related peptide (CGRP) receptor antagonists. These are being developed for the treatment and prevention of migraine, subject to expiration or termination of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976 (HSR). Allergan will be fully responsible for development of the CGRP programs, as well as manufacturing and commercialisation upon approval and launch of the products.

→ **www.mercknewsroom.com**

## Schott to invest in China

The German technology group Schott AG is looking to extend its presence in the Asian growth market. The company has laid the cornerstone for another pharmaceutical packaging plant that will be located south of Shanghai. Starting in 2017, glass packaging for injectable drugs will be manufactured here, in particular vials and ampoules. Furthermore, the Schott Group also plans to modernize and expand its existing facilities at its integrated site in Suzhou. The Pharmaceutical Systems division of Schott will invest approx. EUR 30 million in total in China over the next three years. These measures will increase the company's production capacity by 50% over the same period. With this expansion, the company is paying tribute to the strong growth of the Chinese pharmaceutical market. Schott serves this market from two production facilities – a plant in Suzhou, and through its joint venture with Schott Xinkang. The new production facility will be built at the site of Schott Xinkang's headquarters in Jinyun.

→ **www.schott.com**

## The Science Advisory Board – Global survey results for scientific professions

The Science Advisory Board's 'Global Science 2015' survey sought scientists' feedback with a view to advising people who are interested in pursuing a scientific career. Participants from around the world shared information about how they became scientists and what it is like to be a scientific professional. Survey results coincide with the recent, controversial statements made by Tim Hunt, Nobel laureate and Royal Society fellow. His comments led to his resignation from his faculty position at University College London (UCL) after stirring controversy at the World Conference of Science on June 9th, 2015. Hunt stated that women in labs 'cry' when criticised and 'fall in love' with male colleagues. His comments have opened a global debate on the treatment of women in scientific, technical, engineering, and mathematical (STEM) careers. The survey sample includes 1478 respondents, 58% men and 42% women, from North America, Europe, Asia, and South America. The study fielded during May 2015 and has produced some interesting data on the experiences, perceptions, and differences between male and female scientists. Women are generally underrepresented in STEM. More women are pursuing scientific careers, but men still largely dominate these professions. The study results showed that some women see gender as a barrier to pursuing a career in science, whereas men did not. When asked, 'based on your experience, what do you perceive to be the biggest barrier to pursuing a career in STEM?', 15% of female respondents selected gender, compared with only 2% for their male counterparts.

→ **www.scienceboard.net**

## Lupin acquires Biocom in Russia

Lupin Limited announced the acquisition of 100% equity stake in ZAO Biocom in Russia subject to certain closing conditions. The acquisition marks Lupin's foray into the Russian pharmaceutical market which recorded RUB 765 billion in sales, placing it as one of the Top Ten pharmaceutical markets in the world in 2014 (IMS Health). For over a decade, the Russian pharmaceutical market has recorded double digit growth and expects to continue with this trend, projecting Russia to be one of the Top Eight pharmaceutical markets in the world by 2018 (IMS Health). Biocom is a generic pharmaceutical company with a major focus on therapies such as cardiovascular, central nervous system and antimicrobials for systemic use, and is also active in contract manufacturing and secondary packaging. The company operates a modern European GMP compliant plant and was also one of the first Russian pharmaceutical manufacturing companies to receive approved manufacturer status from the World Health Organisation (WHO) in 2013.

→ **www.lupin.com**

## Merck receives clearance from EU Regulators to acquire Sigma-Aldrich

Picture: Merck KGaA

Merck, a leading company for high-tech products in healthcare, life science and performance materials, announced that the European Commission has approved its planned acquisition of US-based life science company Sigma-Aldrich. The EU clearance, which is subject to certain conditions, follows the recent antitrust approvals in Japan (JFTC) and by the Chinese Ministry of Commerce (MOFCOM). In addition, Merck has already secured antitrust clearance from the US, Taiwan, South Africa, Russia, Serbia and Ukraine. As part of the EU commitments, Merck and Sigma-Aldrich have agreed to sell parts of Sigma-Aldrich's solvents and inorganics business in Europe. These include its manufacturing assets in Seelze, Germany, where most of the solvents and inorganics sold by Sigma-Aldrich in Europe are manufactured. In addition, the divestiture of solvents and inorganics sold by Sigma-Aldrich worldwide under the Fluka, Riedel-de-Haen and Hydranal brands as well as a temporary licence to the Sigma-Aldrich brand for the supply of solvents and inorganics in the European Economic Area have been agreed. The commitments also include the transfer of customer information, and a solution to ensure a temporary channel to the market.

→ **www.merckgroup.com**

## Pfizer's Centers for Therapeutic Innovation and Jeffrey Modell Foundation announce collaboration to help advance immunological research

Pfizer's Centers for Therapeutic Innovation (CTI) and the Jeffrey Modell Foundation (JMF) announced a collaboration agreement to conduct research in the field of immunological diseases. CTI and JMF will identify and co-fund translational research projects with leading academic medical centres within the CTI network. The goal of each research project will be to identify and validate a potential drug candidate for an immunological disease that can be moved into further clinical testing. The collaboration with CTI represents JMF's first alliance with a biopharmaceutical company. JMF is a global non-profit organisation dedicated to early diagnosis, meaningful treatments, and ultimately cures through research, physician education, public awareness, advocacy, patient support, and newborn screening.

→ **www.pfizer.com**

# researched

Cell reprogramming

## New procedure to obtain induced pluripotent stem cells

A new protocol that simplifies the process that allows induced pluripotent stem cells has been developed at the Centre for Biomedicine of the European Academy of Bolzano. While the traditional methodology requires fresh blood, the new procedure allows cells from frozen blood samples to regress to a similar state to that of embryonic stem cells. The reprogrammed cells can be used to understand how some diseases develop and to test new therapies. The new protocol reduces costs and work time in the laboratory.

*Original publication: J. Vis. Exp. (100), 2015, e52885, DOI: 10.3791/52885*
*Source: www.eurac.edu*
*Picture: EURAC/Bertolotti*

Research on IPS-cells at the EURAC laboratory

Material Sciences

## Non-stick coating to consumer goods packaging

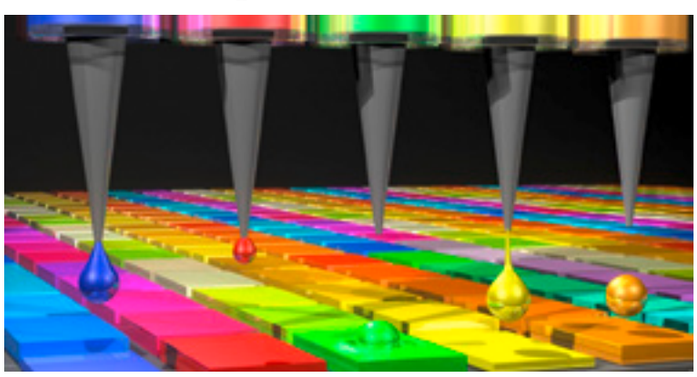
The days of wasting condiments – and other products – that stick stubbornly to the sides of their bottles may be gone, thanks to MIT spinout LiquiGlide, which has licensed its non-stick coating to a Norwegian consumer-goods producer Orkla. LiquiGlide is a liquid-impregnated coating that acts as a slippery barrier between a surface and a viscous liquid. Applied inside a condiment bottle, for instance, the coating clings permanently to its sides, while allowing the condiment to glide off completely, with no residue. The coatings consist of textured solid material that traps a liquid lubricant through capillary and intermolecular forces. Algorithms were developed that calculate how the liquid and solid coating materials, and the product, as well as the geometry of the surface structures will all interact to find the optimal 'recipe'.

Ketchup slides out of a bottle that has been coated with LiquiGlide.

*Picture: Varanasi Research Group, MIT*
*Source: web.mit.edu*

Nanomedicine

## Chemists design a quantum-dot spectrometer



MIT scientists have created spectrometers small enough to fit inside a smartphone camera, using tiny semiconductor nanoparticles called quantum dots (QDs). QDs are made by combining metals with other elements including sulphur or selenium. By controlling the ratio of these starting materials, the temperature, and the reaction time, scientists can generate a nearly unlimited number of dots with differences in an electronic property known as bandgap, which determines the wavelengths of light that each dot will absorb. The new QD spectrometer deploys hundreds of QD materials each of which filters a specific set of wavelengths of light. The QD filters are printed into a thin film and placed on top of a photodetector such as the charge-coupled devices (CCDs) found in cell phone cameras. If incorporated into small handheld devices, this type of spectrometer could for example be used to diagnose skin conditions or analyse urine samples.

*First published in: Nature, 2015, DOI: 10.1038/nature14576*
*Picture: Mary O'Reilly, Source: web.mit.edu*

Bee research

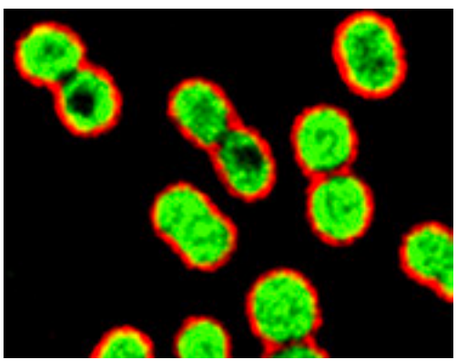
## The threat from space – or why bees are no longer coming home

In countries like the USA, Switzerland, Canada, Austria, Germany, South Tyrol, Spain, Poland and New Zealand, honey bees have been vanishing for years – without any illnesses or parasites as a detectable cause. The pollen gatherers – the adult honey bees, that is – are being lost, whereupon the queen and her brood can perish together. There have been repeated attempts to explain this phenomenon, which goes by the name of Colony Collapse Disorder (CCD). A wide range of factors have been made responsible for CCD, extending from pathogens and parasites to agricultural chemicals. Data analysis has now been carried out on readings of the HOneyBee Online Studies (HOBOS) at the University of Würzburg, under the direction of Professor Tautz. Backed up by the HOBOS data, an extraterrestrial theory has now been added to the possible explanations for the mysterious disappearance of the bees. The measurement data of the HOBOS educational platform show that losses among the pollen gatherers are also occasioned by strong solar winds. On days of high solar wind activity and in the days following, significantly higher numbers of gatherers are being lost in the field than on other days.

*First published in: Astrobiol. Outreach, 2015, DOI: 10.4172/2332-2519.1000134*
*Source: www.hobos.de*

Medicine & pharma

# Common antibiotic may be the answer to multidrug-resistant bacterial infections



Multidrug-resistant Gram-negative rod bacteria *Acinetobacter baumannii* being killed by the common antibiotic azithromycin (green) in the presence of a human antimicrobial peptide naturally present at infection sites

Contrary to current medical dogma, researchers at University of California, San Diego School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences report that the common antibiotic azithromycin kills many multidrug-resistant bacteria very effectively – when tested under conditions that closely resemble the human body and its natural antimicrobial factors. The researchers believe the finding could prompt an immediate review of the current standard of care for patients with certain so-called 'superbug' infections. Azithromycin is the most often prescribed antibiotic in the United States, where short courses can cure common bacterial infections such as strep throat and sinusitis. But azithromycin, also sold commercially as Zithromax Z-Pak, is never given to patients with some of the most nefarious multidrug-resistant bacterial infections. That is because years of testing in standard laboratory media – the nutrient broth that helps bacteria grow – concluded that azithromycin doesn't kill these types of bacteria.

*Original publication: J. EbioM., 2015, DOI: 10.1016/j.ebiom.2015.05.021*
*Source: www.health.ucsd.edu*
*Picture: UC San Diego School of Medicine*

Neurosciences

# Humans' built-in GPS is our 3-D sense of smell

Like homing pigeons, humans have a nose for navigation because our brains are wired to convert smells into spatial information, new research from UC Berkeley shows. According to the study, we can sniff our way, blindfolded, toward a location whose scent we have smelled only once before. The process of olfaction is triggered by odour molecules travelling up the nasal passage, where they are identified by receptors that send signals to the olfactory bulb and process the information. Olfactory bulbs have a strong neural link to the brain's hippocampus, which creates spatial maps of our environment.

*First published in: PLOS ONE, 2015, DOI: 10.1371/journal.pone.0129387*
*Source: www.berkeley.edu*

# New century... old challenges

Developments in analytical techniques in the academic field

Ass. Prof. Dr José C. Rodrigues
Natural Sciences and Humanities (CCNH),
Federal University of ABC, São Paulo, Brazil

**In 1897, J.J. Thomson presented the world's first particle accelerator, along with what would become, years later, the initial mass detector. Following developments in the 1940s, the equipment developed at the Cavendish Laboratory in Cambridge in 1912 was destined to, revolutionise analytical chemistry. For his discovery of 'negatively charged corpuscles', which we now call the electron, Thomson was awarded the Nobel Prize in Physics in 1906. Today, more than 100 years after this fabulous discovery, we rely on a wide variety of detection techniques for the ratio of the charge to the mass, which are applicable to various areas from the oil industry to medicine.**

**José C. Rodrigues** is an Associate Professor at the Centre for Natural Sciences and Humanities (CCNH) of the Federal University of ABC (São Paulo, Brazil), where he was Pro-Rector from 2007 to 2010 (implementation of the UFABC). He obtained his BASc degree in Chemical Engineering at the Faculty of Industrial Engineering (FEI), São Paulo, Brazil, in 1997, and his PhD in Physical Chemistry from the University of São Paulo (USP), São Paulo, Brazil, in 2002. He obtained his Postdoc in Petroleum Engineering at the State University of Campinas (UNICAMP), São Paulo, Brazil, in 2006 and 2012. He obtained a technical degree in Mechatronics in 2004 at the National Service of Industrial Training (SENAI), São Paulo, Brazil. Professor Rodrigues has more than 15 years of experience in the petrochemical industry, and has lately been involved in the fractionation of bitumen using supercritical fluids.

Unfortunately, the development of such analytical techniques and advanced equipment was not accompanied by the necessary dissemination of knowledge arising from such developments throughout the twentieth century. I do not refer here to the written materials, which exist in abundance; I am referring to the practical education and training of professionals.

Professionals with a university degree, regardless of their training in undergraduate or graduate courses, are in most cases mere readers and interpreters of graphics and data, which are provided by a computer, no matter what analytical technique is being used (GC, HPLC, MS, NMR etc.). The vast majority of users lack a critical view of the whole process involved in obtaining results. Such vision confines itself to a few members of academia and industry. This scenario is justified, in part, by the fact that at some educational institutions students do not have authorisation to handle the equipment, especially when it is very costly, for fear that they may cause damage to the equipment, which usually ends up being operated by trained technicians contracted by the universities and/or research institutes.

Such a scenario favours suppliers of analytical equipment based on low technology, because they will be able to sell their low-quality equipment to uncritical customers. For companies that invest in products of high technology the situation is a nightmare, because high-technology development involves years of investment in research and so elevated costs. However, even these companies have no interest in spreading knowledge, hiding behind patents and industrial secrets. High prices have been charged, by the standards of the emerging economies, for training courses of poor quality. These courses teach people primarily how to interpret graphs and data and push buttons. The view taken is that this is what the customer wants – just to be shown how to operate the equipment. Well, I am sure there are many customers who want more than that!

The challenge for companies developing the analytical instrumentation in the twenty-first century is to work together with academia. What is needed is a partnership with universities and research centres, with the aim of training young professionals fulfilled and active in the analytical instrumentation area, knowing not only the basics, but also aware of the factors that differentiate the equipment to be used. As a result these students and future professionals will be able not only to operate the equipment and interpret data – they will also be in a position to contribute and collaborate in the development. After all, isn't that what the big software companies have been doing over the years with much success? Why should the hardware be any different?

If we want to get out of the nineteenth century and into the twenty-first, a change of attitude and mentality in both academe and industry is needed. In the future, we hope that these two areas can really work together to project and develop new instruments.

**It is time to take on this challenge...**

→ **rodrigues.jcarlos@ufabc.edu.br**

# endocrinology

# Environmental risk factors

Environmental risk factors and developmental windows of disease and disease prevention

Prof. Dr Günter Vollmer
Molecular Cell Physiology and Endocrinology, Dept. of Biology, TU Dresden, Germany

**At every stage of their life – from conception to death – organisms are exposed to a multitude of environmental factors, some of which are associated with severe health risks. Current research is now attempting to clarify the significance of particularly sensitive periods of the development of organisms, known as "developmental windows of disease". Within these windows, there is an increased chance of specific types of changes to occur which interfere with genetically-determined development processes. The resulting reprogramming can increase the risk of the development of metabolic diseases, the impairment to reproductive health, or even the occurrence of a tumour in adulthood or in its progeny.**

The development of a mammalian species from early foetal stages to adulthood is genetically determined. The precise course of this developmental programme is also subject to numerous environmental influences, with toxins, stress, behavioural factors and nutrition being the primary examples (Fig. 1). Nutrition exerts its influence on the organism via three pathways: while starvation and overeating (especially if this leads to excess weight) represent more general factors, bioactive compounds in food tend to have a highly specific effect on individual molecular structures, such as receptors or enzymes. The influence of environmental factors on the unfolding programmes of developmental biology is so potent that it may have a lifelong impact on the health of the individual. Modifications of the epigenom make some environmental influences inheritable: as a consequence, the health of subsequent generations can be influenced, a phenomenon termed the "developmental programming of disease".

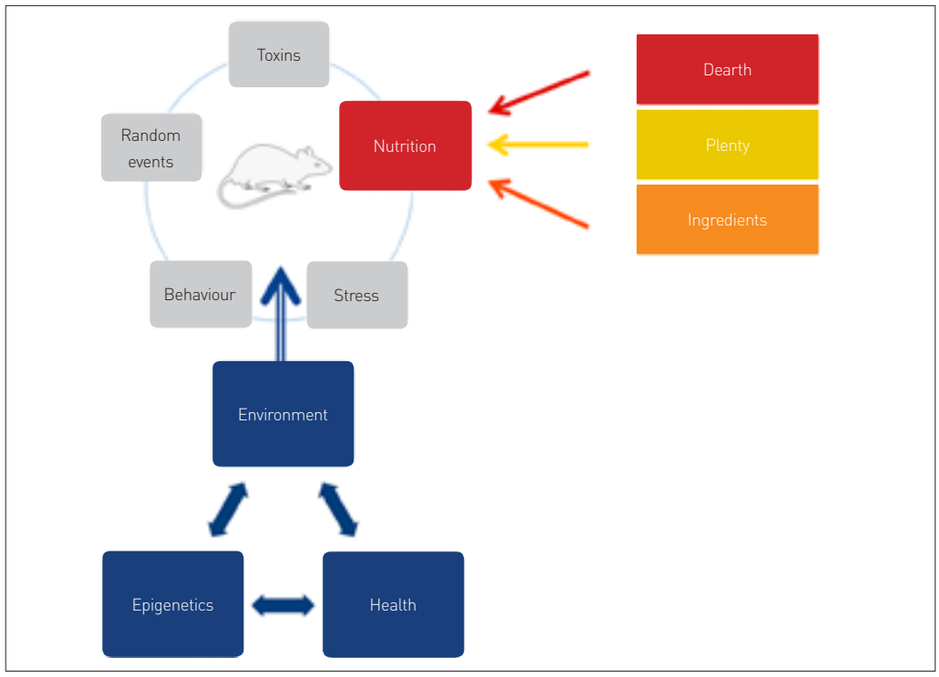



**Fig. 1** Environmental factors and health. Environmental factors such as stress, toxins and changes in behaviour and nutrition are capable of influencing health later in life or the health of subsequent generations by modulating processes in developmental biology. The modulation of epigenetic mechanisms in particular thereby appears to play an important role. The influence of nutrition is twofold: we need to distinguish between the effects that are triggered by the availability and (calorific) quality of food sources (dearth/plenty) and effects produced by individual compounds contained in food products – which, like pharmaceuticals, affect highly-specific molecular target structures such as receptors or enzymes.

## Environmental factors trigger influences over several generations

From a mechanistic perspective, environmental factors appear to reprogram processes in developmental biology primarily by means of epigenetic mechanisms (for an overview, see Gerhäuser [1]). These programming events not only influence the generations directly affected but can also impact on their progeny, even though these individuals have had no direct exposure to the environmental factor – such as a chemical. For a pregnant individual, in the worst-case scenario the exposure to an environmental factor may directly affect the mother, the fetus and the priomordial germ cells of the fetus (i.e. the F0, F1 and F2 generations). If the resulting effect are not only detectable in the mother but in the F1 and/or F2 generation it is referred to as a multigenerational effect. If the effect persists into the F3 or a later generations – i.e. into a generation without any direct (e.g. chemical) exposure – it is termed a transgenerational effect. Both types of effect (multi- and transgenerational) have been indisputably demonstrated in animal studies for materials known as "endocrine disrupting chemicals" (EDCs), in relation to impairments affecting male reproductive health. The studies showed how the epigenome of the germline cells was reprogrammed, resulting in changes of processes within development and in epigenetic alterations that were passed on to male descendants via the male germline [2, 3].

These findings raise the question of the relevance of such mechanisms for human Development. Answers are to be found by looking at the effects from the Dutch famine in the winter of 1944/45. Researchers from Leiden University followed-up both the fate of mothers pregnant at the time and their children. The results tell us that the daughters of mothers affected by starvation have significantly elevated risks of suffering from a range of health problems, including metabolic disorders (such as obesity, impaired glucose tolerance and high blood pressure), neuronal disorders or hormone-dependent tumours such as breast cancer. These effects remain in force for their grandchildren. These examples demonstrate that environmental factors (here: caloric restriction) have the capacity to impact on processes of development thereby influencing the risk of developing a disease later in life and in subsequent generations. Since these results were published, epidemiological surveys and animal studies have provided some preliminary indications that bioactive compounds in foodstuffs may also have the capacity to prevent disorders by the modulation of the developmental programming [4, 5].

## Relevant biological windows

While we know that environmental factors can reprogram the trajectory taken by processes in developmental biology, the question of timing is also of crucial importance. The question is does the organism respond to the same degree of sensitivity in all stages of development from conception to adulthood – or are some stages especially sensitive and "fragile"? In analysing the consequences of the abovementioned famine in more detail, we can see that the observed effects behave similarly to the teratogenic effects from drugs such as Thalidomide, i.e. they correlate with specific stages in pregnancy rather than being general and are strictly dependent on when the mother suffered malnutrition. An elevated risk of obesity for the child correlated with a period of starvation of the mother in the first trimester of pregnancy, while a risk of impaired glucose tolerance was associated with hunger in the second trimester. The risk for high blood pressure arose when malnutrition occurred in the last trimester [4, 5]. In summary, we can say that: a) there are a number of "fragile" windows for the programming of adverse effects on health by environmental factors in the early stages of development; and that b) these windows of fragility appear to be specific to organs or processes.

The largest risk factor for an increased risk to develop a malignant tumour of the female mammary gland appears to be the quantity of autologous oestrogens and substances that mimic oestrogens over the course of the womans lifetime. Exposure to these hormones does not seem to pose an equal level of risk for a woman at every stage of her life. In humans, particularly critical phases for oestrogen exposure discussed in the literature to date include early foetal development, development of the mammary glands at puberty and the involution of the mammary

gland following cessation of breastfeeding or involution of the breast during climacteric transition (Fig. 2 and [6]). Animal studies have also revealed an additional critical phase for exposure, namely the neonatal development of the mammary gland.

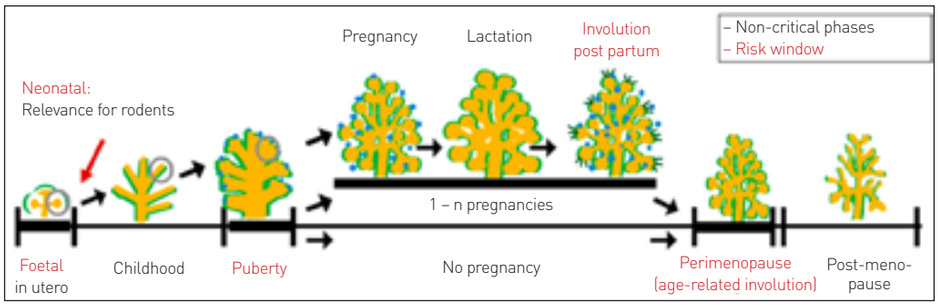



**Fig. 2** Hypothesis of developmental window for breast cancer risk. Schematic diagram of the development and lifecycle for the female mammary gland. The periods of pregnancy, lactation and post-lactational involution distinguish mothers from women who have never been pregnant. The four windows with particular relevance for the risk of breast cancer are marked in red, and include parts of foetal and pubertal development, as well as involution processes triggered by the cessation of breastfeeding or decreasing hormone production in the ovaries. Modified after [6].

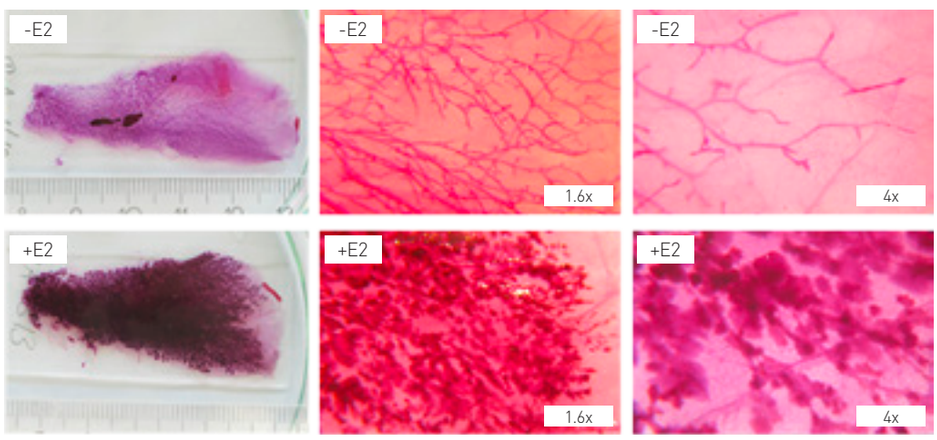



**Fig. 3** Whole-mount preparations as indicators for changes in the mammary gland. Investigations using experimental tumour models are time-consuming. In many cases, potential changes in the breast due to experimental conditions can be observed at a relatively early stage in whole-mount preparations of the organ. The figure contrasts gland ducts in preparations of the breast with and without oestradiol stimulation (+E2/-E2). The figures were supplied by Dr Frank Möller (Molecular Cell Physiology and Endocrinology, Dept. of Biology, TU Dresden, Germany).

## Xenoestrogens from the environment

Due to these influences, "environmental oestrogens" have been a particular focus of research. These xenobiotics with oestrogen-mimicking properties include both industrial chemicals and substances of plant or fungal origin (phyto/myco-oestrogens). Since plant sources are particularly rich in phyto-oestrogens, extracts are prepared from these sources and offered commercially as alternative for the treatment of climacteric/menopausal complaints. Such substances include isoflavones from soybean, red clover and kudzu, as well as hop-derived naringenins. Our lab is currently investigating these kinds of extracts – and single chemicals derived thereof – in terms of their efficacy (e.g. prevention of osteoporosis, suppression of vasomotor disorders) and safety (exclusion of any risk for breast cancer genesis or endometrial hyperplasia) in menopausal applications thereby using preclinical experimental models. As detailed above, we have been working for many years now on the hormonal effectiveness of ingredients from foodstuffs and preparations of medicinal plants – including isoflavones from legumes. Yet what is the rationale to switch from investigations of the molecular and cellular effects of soybean preparations and their bioactive principles to a topic of developmental biology namely the dietary modification of high-risk windows for mammary gland development?

The idea to deploy soybean preparations for the treatment of hormone-based symptoms – such as menopausal complaints – originated in observations made by H. Adlercreutz [7]. Adlercreutz's research compared groups of European and Asian subjects, showing that the level of isoflavones (the active ingredient in soybean) in urine was inversely correlated to the risk of breast cancer in these groups. The causal relationship between the quantity of soy products consumed and the lowering of the risk of breast cancer development was substantiated only later by epidemiological data from the period 2009 to 2014 [8]. According to these findings, a lifelong dietary consumption of soy isoflavones appears to be associated with a lower risk for the

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development of breast cancer. While clinical trials investigating the use of preparations enriched with soy isoflavones by menopausal women have up to date provided no indications of side effects – such as changes to the density of the breast tissue, a number of animal studies have produced findings that indicate soy isoflavones are nonetheless capable of promoting the growth of human breast cancer cells, which were implanted into immunodeficient nude mice [9]. If we translate the above insights into the pharmacological perspective, this means that a lifelong dietary consumption of soy isoflavones is equivalent to a chronic low-dose exposure that may exert a beneficial effect towards breast cancer risk in adulthood. The consumption of dietary supplements enriched in isoflavones at the point in time of the menopausal transition, on the other hand, would correspond to a comparatively high-dose treatment in later life. The research questions that our team has been addressing in recent years have were delineated from both the observations described above, and the hypothesis that the development of tumours of the breast is also affected by exposure during particularly sensitive and therefore critical windows of time. These questions are: a) how does a lifelong soybean-rich diet affect the potency of the female sexual hormone oestradiol as a driving force in the carcinogenesis of hormone-dependent organs in the experimental model of the rat; and b) how does a potential modulation of oestradiol effects affect the development of tumours in an oestradiol-driven, experimental breast cancer model?

## Isoflavones modulate the activity of oestradiol

Since the activity of oestradiol has a decisive role in the carcinogenesis of hormone-dependent organs, we performed an initial multi-generational feeding study with animal feed containing predefined quantities of soybean-derived isoflavones. Control animals received a control feed containing no phyto-oestrogens. Feeding with these diets began in the parent generation prior to mating and was sustained in the first generation of progeny throughout all critical windows of development (foetal, neonatal and pubertal phases). From the 97th day of life after birth, we used a procedure known as a "uterotrophic assay" to assess the extent to which the isoflavones in feed affected oestradiol responsiveness in the target organs of uterus and mammary gland. Key findings here were as follows: the sensitivity of the tissue of the uterus to oestradiol treatment was increased significantly [10], while the oestradiol-dependent stimulation of prolifer-

ation of the mammary gland epithelium was clearly attenuated by isoflavones [11]. The latter finding is clearly relevant when assessing the impact of soy isoflavones on the risk of breast cancer. Since values for bone mass and density were also elevated in the animals that received feed enriched with isoflavones, we may summarise the findings from these investigations as follows: a) continuous exposure to soy isoflavones reprograms the responsiveness of hormone-dependent organs to the female sexual hormone oestradiol; and b) the extent and the direction of the effect triggered by environmental factors on developmental programs is organ-selective – as is shown by the opposite nature of the effects manifested in the two primary target organs for oestradiol, namely uterus and mammary gland.

## Do isoflavones also modulate carcinogenesis of the mammary gland?

In the human mammary gland, carcinogenesis is an oestradiol-dependent process in about 70% of cases. This holds for both the initiation of carcinogenesis by genotoxic oestradiol metabolites and for the promotion of carcinogenesis of the mammary gland by oestradiol in a receptor-mediated mechanism. For this reason, our finding that isoflavones modulate the sensitivity of breast tissue to oestradiol is of particular relevance. The goal of our current work is to investigate whether and how isoflavones are also able to influence oestrogen-dependent carcinogenesis of the mammary gland. To answer this question, we require a suitable model in which development of breast cancer is dependent on oestradiol. Female ACI rats are especially suitable for this purpose. Artificial elevation of endogenous oestradiol levels in these animals greatly increases the incidence of breast tumours [12]. This protracted tumour experiment was carried out jointly by Dr Frank Möller and Dr Oliver Zierau in our research team. In technical terms, adapted the experiment on our feeding study described above with isoflavone-rich feed compared to isoflavone-free placebo feed. At the onset of puberty, an oestradiol releasing device was implanted and the experiment was conducted until postnatal day 285.Whole-mount preparations of the mammary gland (Fig. 3) were used to allow the authors to follow the progression of the process.

Results from this promising experiment have yet to be completed and therefore final, detailed data are not available yet. We can already report one extremely important and unambiguous finding, however: exposure to soy isoflavones throughout all of the sensitive phases of mammary gland development does modulate oestradiol-dependent carcinogenesis!

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# Environmental microplastics

## A danger to human health?

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**Humans create their own environment and since the 1950s, this has increasingly included products made from synthetic polymers, commonly referred to as "plastics". Plastic waste in the environment is probably here to stay for decades – if not centuries. But can we actually remove plastics – and microplastics in particular – from the environment?**

While such compounds were known of before the establishment of polymer science (Fig. 1), the decisive structural propositions were put forward by Hermann Staudinger in 1920 [1]. From a paltry 1.7 million tonnes in 1950, global plastic production has risen by an average of 0.9% annually to reach 299 million tonnes in 2013, with 57 million tonnes being produced in Europe (EU except Croatia, plus Switzerland and Norway; source: www.plasticseurope.de). Polyethylene (PE), polyethylene terephthalate (PET), polypropylene (PP), polyvinylchloride (PVC), polystyrene (PS) and polyurethane (PU) make up the bulk of this production volume.

A considerable percentage of global polymer production is destined for use in disposable products, primarily packaging (about 40% in the EU). While the European average for plastic waste in landfill sites is only 38%, there is a marked North-South and East-West gradient. Accordingly, some 37% to 87% of this waste ends up in official landfill sites in countries that still allow this disposal route to be used for plastics. While figures on illegal tipping are naturally not available, appearances suggest that this disposal route can make a major contribution to the eyesore of countryside littering in several European countries. Of the 275 million tonnes of plastic waste generated by the 192 coastal states, figures from Jambeck et al. [2] suggest that annually between 4.8 and 12.7 million tonnes end up in the ocean (data for 2010).

The greatest advantage of products made from synthetic polymers is at the same time their most problematic feature in environmental terms – namely their durability. And the resistance of plastics to microbial degradation is indeed one of their most critical attributes in both an aquatic and terrestrial context. It can take up to 600 years for some types of plastics to disappear from the environment (Table 1).

The actual rate of degradation will depend on the formulation of the polymer and actual environmental conditions, however. In interpreting these values, we must also bear in mind that they have generally been obtained by determining the loss of mechanical properties as a result of ageing: end-stage degradation to water and carbon dioxide has been infrequently studied to date.

## Where do microplastics come from?

The first stage in the process always involves the fragmentation of environmental macroplastics into smaller-scale particles – i.e. to mesoplastics, microplastics and nanoplastics (Table 2, Fig. 2). According to figures from the Federal Environment

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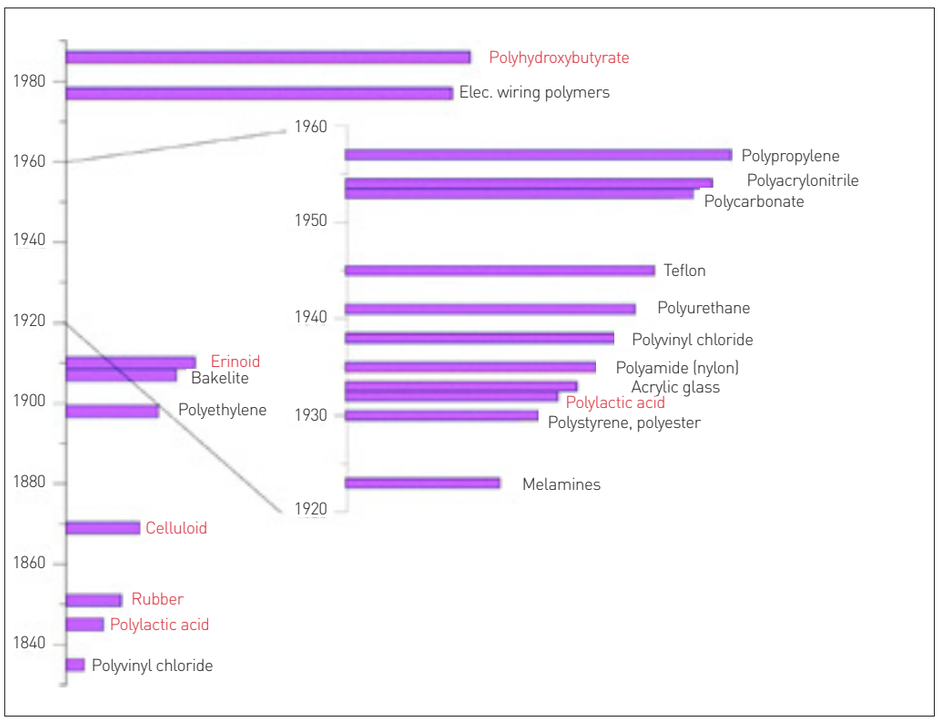


**Fig. 1** Developments in polymers – red: some synthetics based on biological polymers


**Fig. 2** From macro- to microplastics

**Fig. 3** Polystyrene waste "scum" from a 7 cm flower pot

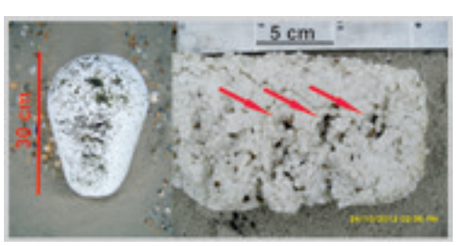


**Fig. 4** Expanded polystyrene float ball (left) and block (right) with peck marks made by large gulls – Kachelotplate sandbar, East Frisian Islands, and Mellum, German Bight – 2012

Agency, 65 plastic bags are used per person per year in Germany. This equates to an annual consumption of 5.3 billion plastic bags – or 10,000 bags a minute. Alongside Spain and the UK, Germany leads the rest of the EU in terms of plastic bag consumption.

These figures not only include the illegal littering of plastic bags, beverage bottles or fast food packaging: mulch film from the agricultural and horticultural sectors is also a contributor to particle pollution. Mulching films are typically made from polyethylene, which is naturally resistant to degradation. Accordingly, metal salts (such as cobalt compounds) are added to ensure the product breaks down when exposed to ultraviolet radiation and oxygen.

Recycled polystyrene (expanded polystyrene) and urea formaldehyde resin waste is

**Tab. 1** Estimated degradation times for various polymers in an aquatic environment, from the literature

| Material | Degradation time |
|---|---|
| Paper bus ticket | 2–4 weeks |
| Cotton fabric | 1–5 weeks |
| Cotton rope | 1 month |
| Hemp rope | 3–13 months |
| Wood (untreated) | 1-3 years |
| Woollen fabric | 1 year |
| Cigarette butt | 1–5 years |
| Plastic bag | 10–30 years |
| Wood (treated) | 13 years |
| Fishing net | 30–40 years |
| Beer can | 100 years |
| Aluminium can | 80–500 years |
| Plastic bottle | 450 years |
| Monofilament fishing line | 600 years |
| Glass bottle | 1 million years |

**Tab. 2** Size classes for various categories of plastic waste:

| | Size |
|---|---|
| Macroplastic | > 5 cm |
| Mesoplastic | 5 cm – 5 mm |
| Microplastic (MP) | 5 mm – 0.1 µm |
| Large MP (LMP) | 5 mm – 1 mm |
| Small MP (SMP) | 1 mm – 0.1 µm |
| Nanoplastic | < 0.1 µm |

used as a soil additive with particle sizes of only a few millimetres. While the solid PS improves soil air circulation, the porous resin increases the capacity for water retention. Polystyrene is (intentionally) very light (density 15 to 90 mg/cm³), however, and can be easily scattered into the environment by the wind (Fig. 3).

Biological processes can also lead to microplastic pollution. Marine isopods can gnaw holes into polystyrene floats to create burrows or havens from predators; marine birds also increase microplastic pollution by pecking at macroplastic waste [3]. The focus of such activities will often be a piece of expanded polystyrene (Fig. 4).

While these degradation processes occur within the environment, microplastics can also enter the environment directly. Sources here include cosmetics and detergents containing particles (typically made from polyethylene but polypropylene or polyamide polishing agents are also found) and metalworking abrasives, used as a substitute for the traditional sand in surface finishing treatments.

Every piece of clothing sheds fibres during wearing, washing and drying. Wearing is clearly responsible for the largest proportion of this shedding, even if exact figures are not available. When an article of polyester or polyacrylic clothing is washed, it sheds around 0.01–0.06% (by weight) of its fibres. Carried in waste water to treatment plants, these fibres are not fully filtered out and so end up being released with the treated water into the environment [4]. If the sewage sludge – which initial measurements tell us contains the bulk of the fibres – is then used as an agricultural fertiliser, the retained fibres can be released into the atmosphere and be distributed very widely indeed. Airborne fibres can be deposited on any surface, including flower petals – and thus end up in honey, for example [5].

Thermoplastic synthetics are shipped as raw materials in a form known as “pre-production pellets”. A few millimetres in size, these granular particles can be lost during loading and thus end up in the environment (www.pelletwatch.org).

Microplastics can thus be found everywhere: in the air, in the water, in soils and in aquatic sediments. From here, they can enter food and potable water and be taken up by organisms.

## What risks are posed by microplastics?

While synthetic polymers are generally harmless in their pure form, two other factors turn them into an environmental hazard. First, plastics can contain traces of monomers such as bisphenol A (used as starting material for polycarbonates, for example) and di-/tri-styrene or styrene. Second, almost all synthetic polymers will contain one or more additives. Obvious candidates here include brominated flame retardants and plasticisers – especially phthalates, which in PVC products can make up as much as 60% of the product's weight. Many of these additives have hormonal effects. In aqueous media, they leach out of plastics and thus end up in the environment (see www.lfu.bayern.de/umweltwissen/doc/uw_120_phthalate.pdf, for example). Some compounds can also outgas, especially when exposed to strong solar radiation.

Generally, plastic is hydrophobic. This allows e.g. polyethylene films to be used as long-term collectors of lipophilic organic contaminants such as PCBs, PAHs or DDT, DDE and DDD. Since microplastics also have a high surface-to-volume ratio, they can also adsorb very large quantities of such pollutants [5]. If these kinds of contaminated particles are ingested by organisms, the pollutants (and additives) can be released into the stomach or digestive tract, become stored in the animal's tissue and trigger health problems [6].

And, as various lab studies have shown, even uncontaminated microplastics are problematic: when small enough – roughly < 5 µm – they can be taken up by zooplankton, common mussels or lugworms and become incorporated in tissue, where they can cause inflammatory reactions [7]. Even larger-sized, microplastics can still be ingested by organisms and passed up the food chain. In the first stage, microplastics are eaten by zooplankton. From here, they are passed on to mussels, fish, marine birds or marine mammals such as harbour seals, grey seals or porpoises. Microplastics have also been discovered in sediment-dwelling or -ingesting animals such as lugworms and sea cucumbers [8]. While data for humans are not yet available, the negative effects of tiny particles taken up via the airways (for example) have been known for a long time (asbestosis, silicosis).

Many marine birds look for food on the surface of the water and will try to consume anything they find there, including plastic. As omnivores, seagulls not only eat fish, crustaceans or mussels but will also hunt for food on land – often visiting rubbish dumps, for example. This type of scavenging leads to the consumption of both macro- and microplastics, which they regurgitate [9] and which become especially concentrated in bird colonies. Fulmars grind up plastic they consume with their gizzards, thereby contributing to the production of microplastics.

## Outlook

Plastic waste in the environment is probably here to stay for decades – if not centuries. But can we actually remove plastics – and microplastics in particular – from the environment? Unlike the macroplastic problem, the collection of tiny pieces of plastic is an untenable alternative, and filtering microplastics out of rivers, seas or oceans with small-mesh nets would mean wholesale interference in aquatic ecosystems, since the technique would also remove zooplankton and thus the base of the food chain.

Pressure from environmental groups and consumers has led to the banning of microplastic polishing agents from toothpastes in Germany, and almost all large cosmetic producers have stated – after huge pressure from environmental groups and consumers – that they will soon be phasing out microplastics in exfoliants and similar products. The option of banning plastic bags now being discussed by many local authorities is also certainly helping to raise public awareness about the problem of plastic waste of all sizes. Operators of water treatment plants must also be required by law to install facilities capable of removing microscopic fibres from waste water. Despite all of the above, the long lifetimes estimated for environmental plastic will also require political decision-making to reduce the tidal wave of plastics, e.g. by bans on disposable packaging (and plastic bags in particular) – as currently being discussed within the EU. As consumers, we can all take action to reduce plastic waste, however. There are plenty of alternatives for cosmetics, clothing, packaging and other consumer goods.

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# biophotonic

**International Year of Light**

# Tweezing without touching

Cell experiments with optical tweezers are revolutionising biomedicine

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**Ultramodern imaging techniques such as the Nobel Prize-winning STED microscopy enable the investigation of organisms, cells, bacteria and even viruses, DNA or individual molecules at very high spatial and temporal resolution. Active intervention in these tiniest of biological structures has been largely limited to indirect methods, however. While new developments such as microtweezers and micromechanical clamps are promising, these devices generally tend to alter the properties of the objects to be investigated, making meaningful measurements difficult – especially in vivo. Focused laser beams, on the other hand – known as "optical tweezers" – permit the contactless manipulation of cells and bacteria in three three dimension of space.**

## Viscoelasticity: an essential feature of both health and disease

Many of life's processes depend on the spatial and temporal interaction of proteins or cells as fundamental building blocks. Studying these interactions is an essential part of almost all areas of disease research – especially for work on infectious diseases and cancer – and is closely related to the question of the cell's biomechanical properties. Many cellular processes depend on the viscoelasticity of cells and their environment. An object is said to be "viscoelastic" if it exhibits both the elasticity found in solid objects (such as rubber) as well as the viscosity found in liquids (such as honey). During different cellular processes, as .e.g cell division, infection or cell death, the viscoelasticity of cells can undergo significant modifications. In coronary heart disease, for example – easily the most prevalent cause of death worldwide – the build-up of deposits on the inner wall of blood vessels causes these vessels to lose their elasticity [1, 2].

The relationship between cellular processes and biomechanical properties therefore holds the keys to many questions in biomedical research. Knowledge of the changes to viscoelasticity occurring between and within cellular processes can improve our understanding of important modern diseases – including Alzheimer's and tumour growth – and help us to develop medications to treat them. Any investigation of cell viscoelasticity requires us to deform these cells and take measurements that quantify the force required for this deformation. Accordingly, we need to develop a technique with which we can repeatedly deform a cell with a predefined force. In 1970, Arthur Ashkin showed that light can be used to exert a force on objects [3].

## Holographic optical tweezers

As early as the 1600s, Johannes Kepler had already hypothesised that the tail of a comet was caused by light pressure accelerating the comet's

dust particles to form the tail. The tail points away from the sun, i.e. in the same direction as the propagation of light. The force moving objects in the light's direction of propagation is termed "scattering force" and is proportional to light intensity. For transparent objects and inhomogeneous intensity distributions, an effect termed the "gradient force" also applies. This force is directed towards the point of highest light intensity. A large gradient must be present in order to move objects towards this point. This can be achieved by focusing the light beam, typically using strongly focusing microscope objectives with a high numerical aperture. The numerical aperture defines one half of the aperture angle of the light cone exiting the objective. This angle – and thus the gradient force – increases proportionally with the numerical aperture. If light intensity is sufficiently high, the gradient force exceeds the scattering force, pulling transparent objects towards the focal point and trapping them stably there in three three dimension of space.

In 1986 Arthur Ashkin worked with subsequent Nobel Prize winner Steven Chu to develop the first gradient light trap based on this principle [4], later to become more widely known as "optical tweezers". This approach not only lets us trap transparent objects with the aid of a focused laser beam but also allows us to move them in three three dimension of space. Objects with a size of several microns can be trapped in this way, that process is ideal for cells and bacteria. Optical tweezers are typically integrated into existing microscopy techniques thus enabling the objects to be manipulated and observed simultaneously. Since the manipulation of the trapped objects is also both contactless and sterile, this offers biological and medical applications a key advantage when compared to conventional methods for micromanipulation.

To characterise the manipulation appropriately, it is necessary to determine the forces actually created by the optical tweezers. To do so, the position of the trapped object is compared with the focal position of the optical tweezers. If no additional force is acting on the object, the object is at the focal point. If a bacterium (for example) attempts to move with the aid of its flagellum, then the bacterium itself exerts a force countering the optical force exerted by the optical tweezers. This enables the bacterium to remove itself slightly from the focal point while still being confined in the optical trap. The distance from the focus to the bacterium is proportional to the force generated by the bacterium and can thus be determined by positional measurements. Optical tweezers are especially useful for measuring minute forces at the piconewton (pN) scale within cells and between single biological cells. These forces are at the same scale as those acting on and within a cell. As an example, intracellular nutrient transport is achieved by molecular motors with a force of about 5 pN.

Optical tweezers make it possible to trap just one object at a time. To characterise viscoelasticity, it is necessary to immobilise and then deform a cell. Multiple traps are therefore required and it must be possible to move them dynamically. We achieve this by making use of holographic methods. Holograms contain three-dimensional information describing the position of the traps in the focal plane. We use spatial light modulators (SLMs) to impose the hologram onto the laser. A light modulator is a liquid-crystal display that performs per-pixel modulation of the laser beam to enable the presentation of an arbitrary image. This approach transforms the optical tweezers into holographic optical tweezers (HOT). HOT can manipulate a large number of traps by modulating a single laser beam. Figure 1 presents a schematic overview of a HOT system integrated into a microscope. Examples of typical holograms

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**Christina Alpmann** studied physics at the University of Münster and is currently working as a research assistant in the Institute of Applied Physics. Her research focuses on the holographic modulation and analysis of complex light fields in terms of amplitude, phase and polarisation for use in optical micromanipulation applications, which is the subject of her doctoral studies in Cornelia Denz's "Nonlinear Photonics" lab.

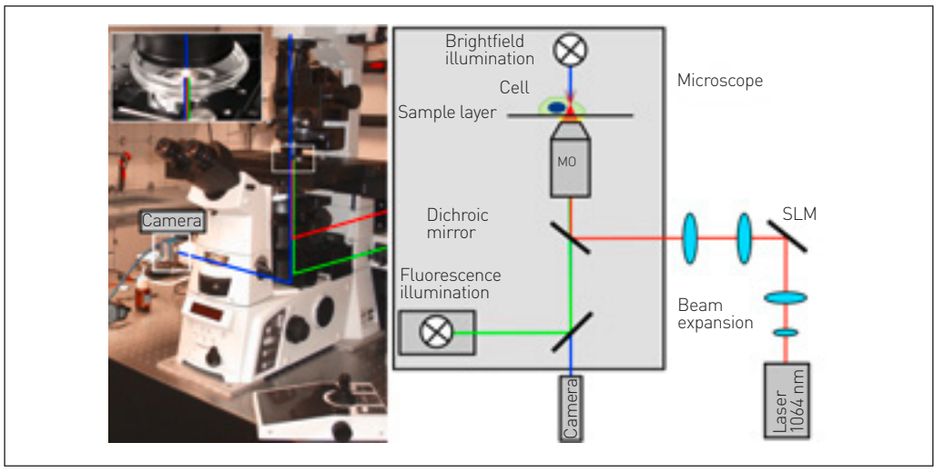



**Fig. 1** Optical tweezers, integrated into a microscope (left). The detail shows the sample layer. In the microscope, the optical tweezers can be combined with various modern high-resolution microscopic techniques, such as dark-/bright-field microscopy, fluorescence or confocal microscopy and quantitative phase-contrast microscopy. Two lenses are used to widen the laser beam, which then illuminates the light modulator. Two further lenses are then used to guide and focus the beam onto the microscope objective.

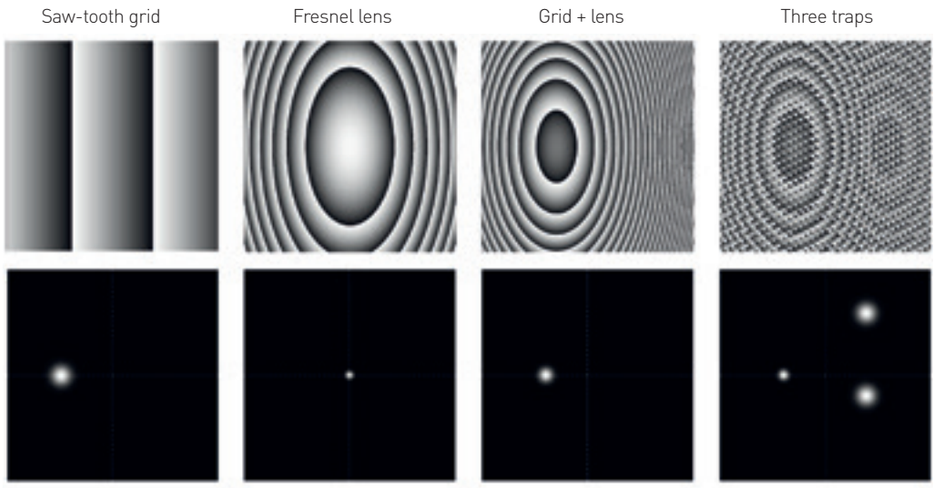



**Fig. 2** The specific hologram used (shown in the upper row) determines both the layout and number of traps (shown in the bottom row). A grating-like pattern displaces the traps laterally, while a lens-type pattern displaces the traps axially. By combining multiple gratings and lenses, a single laser beam can be used to generate multiple traps, which we can arrange three-dimensionally and vary dynamically over time. These traps can be manipulated independently of one another and simultaneously.

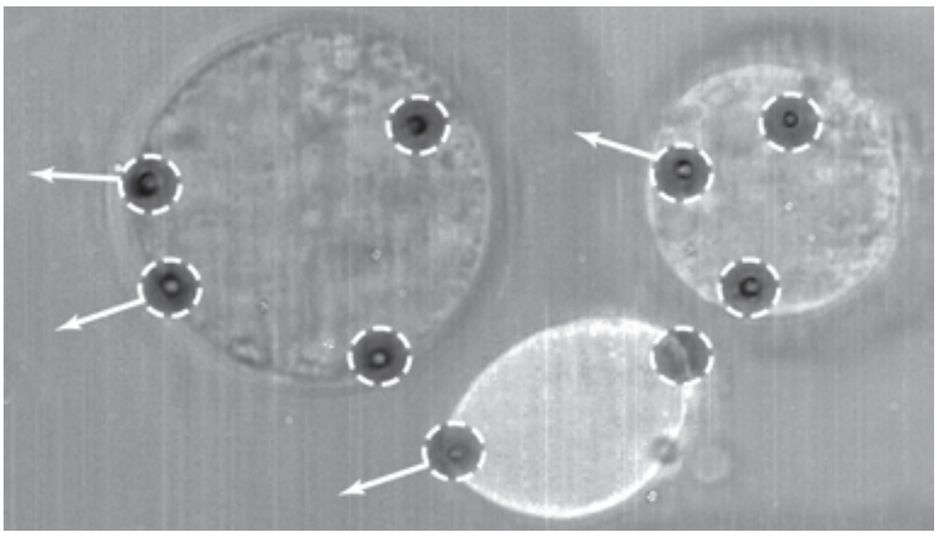
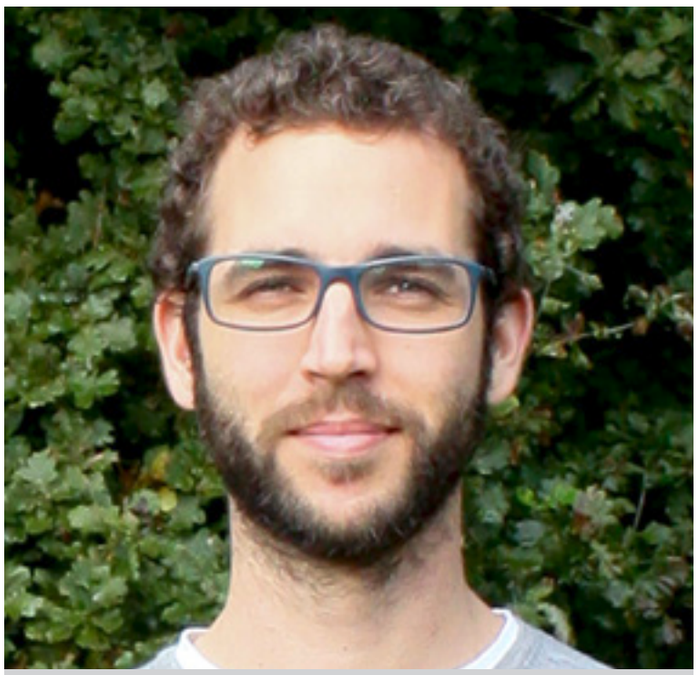


**Fig. 3** Deformation of multiple living cells. Multiple traps (white circles) are deployed with the aim of deforming the membranes at multiple locations in different directions (shown by arrows), so as to determine local viscoelasticity. Cell elasticity is proportional to the degree of deformation. Many diseases cause cells to lose their elasticity. Here, we typically see major differences in cell deformability.



**Álvaro Barroso** studied physics at the University of Seville before then completing an M.Sc. at the University of Münster (WWU). He has been working on his doctorate in optical manipulation/biophotonics since 2012 in the WWU's Institute of Applied Physics.

**Cornelia Denz** completed her undergraduate and doctoral studies in nonlinear optics at TU Darmstadt. Following periods of research in France (Paris), the USA and Australia, she has been a professor in the WWU's Institute of Applied Physics since 2001 and became its Director in 2003. She has been Vice-Rector for International Affairs and Junior Academics at WWU since 2010. Her research interests cover various aspects of photonics, including optical information processing, nano-photonics and biophotonics. She has published over 190 articles in peer-reviewed journals, and is the author of 3 books and numerous book chapters. She was awarded the State of Hesse's Lise Meitner Prize in 1993 and the Adolf-Messer Prize in 1999. She was voted Professor of the Year by the Unicum student magazine in 2012. She is a Fellow of the European (EOS) and American (OSA) Optical Societies and a Board member of the German Branch of the European Optical Society (DGAO).


## Thanks

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for generating a variety of trap configurations can be seen in Figure 2. This offers us a technique satisfying all of the requirements for the characterisation of viscoelasticity in the context of disease research.

## Intracellular viscoelasticity and mobility

To investigate the viscoelasticity of cells, tissue and blood vessels, we need to understand the involvement of individual cell components and organelles in this process. Considering the cell as a whole, viscoelasticity is a product of several effects stemming primarily from the cell membrane, cytoplasma and cytoskeleton, but also involving other cellular components. Since most of the cell's biomechanical properties are determined by its cytoskeleton, this structure is of particular interest [5]. To characterise the viscoelasticity of the cytoskeleton, the dense network of filaments in the cell needs to be stretched and deformed. Deformation also results from the natural movements of cell organelles such as vesicles, for example. We also introduce particles into the cell plasma of living cells. By using HOT to move the particles within the cell, we can draw conclusions about the cytoskeleton and thus characterise the interior of the cell itself [5]. The same experiment can also be used to determine the viscoelasticity of the cell membrane. To do so, we need to guide the particles within the cell plasma towards the cell membrane. Figure 3 shows three cells in which particles have been pressed against the cell membrane from the inside, resulting in obvious stretching. In these cases, HOT are used as a holographic optical "stretcher". With the help of HOT, we can deform a large number of cells. This technique also stretches the cytoskeleton, enabling us to examine its influence. This makes it possible to examine cells specifically and locally at multiple locations, and to identify differences in viscoelasticity within a cell or a group of cells. The interplay between cellular processes and cell viscoelasticity can also be investigated. This enables us to take a systematic approach to study the biomechanical mechanisms of disease.

## Conclusions: interventional options for biomedicine

The use of HOT lets us trap and manipulate cells or bacteria with light. Two fundamental forces – scattering force and gradient force – are responsible for the action of light as an optical trap into which transparent objects can be pulled and captured. A spatial light modulator can be used to generate multiple optical traps dynamically and simultaneously, so as to move and investigate cells in three dimensions in a minimal invasive way. This makes it possible for us to analyse or artificially initiate biomechanical processes, observe such processes in their natural environment and intervene in a way that enables us to gain new insights into disease progression. Current research in this field is now focusing on applying these techniques to larger living organisms consisting of several thousands of cells – an achievement that will revolutionise disease research.


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*Picture: © istockphoto.com | Rich Legg*

# Microscopy Conference 2015 – Interview with Conference Chairman Prof. Dr Michael Seibt

**Around 800 to 1000 microscopy experts are expected to attend the Microscopy Conference which is being held in Göttingen from 6 to 11 September. They will be presenting the latest results of their research, and discussing current trends and discoveries in different subject areas. The Conference Chairman this year is Prof. Dr Michael Seibt of the Physics Institute of the University of Göttingen. In an interview ahead of the event he talks about main areas of emphasis and highlights of the forthcoming congress.**

As has been the case at successful microscopy conferences in the past, highly regarded experts will be presenting their discoveries and research findings. What are the main areas of emphasis of this year's conference? What new impulses do you expect? What is likely to be spectacular?

Prof. Seibt: In the nature of the things, the principal focus will be on the latest developments and applications in the field of electron microscopy. At the same time it is clear that in practically all areas of research the combination of multiple microscopy techniques and the use of spatial and spectral high resolution methods are increasingly favoured. This can be seen just in the variety of microscopies represented in the plenary and prizewinners' lectures. A spectacular start to the Microscopy Conference 2015 will be the opening lecture by Nobel Prize winner Stefan Hell, who will be talking about his revolutionary work in the field of light microscopy.

What is the special orientation of the conference, and what main themes have you dictated this year? What particular wishes and goals do you have, as Conference Chairman of MC 2015?

Prof. Seibt: Like past conferences, MC2015 will give an overview of recent developments in microscopy. This will not just cast light on the scientific aspects – current technology will also be presented, not least as a result of the trade exhibition, where all important suppliers in the field of microscopy will be represented. I am particularly concerned that the conference should encourage a younger generation of scientists. MC2015 offers young scientists the opportunity of presenting their own work to a wide international public.

One major emphasis of the conference is on the field of life sciences. What will be the main focus here? To what extent do new and recent microscopy techniques open up new research perspectives in the life sciences?

Prof. Seibt: Different areas of application for microscopy in the life sciences will be intensively discussed at special meetings. These include neurobiology, medicine and classic cellular biology. Alongside this, new applications of microscopy techniques will be presented which could recommend themselves for use in various working areas. Here the following trends are ongoing – the use of different microscopy techniques to address a specific complex of questions (ideally using one and the same preparation), and the extension of the scope of investigation to large areas and the third dimension.

Distinguished national and international experts will be presenting a wide variety of topical aspects of microscopy, among them Prof. Stefan W. Hell, winner of the 2014 Nobel Prize for Chemistry, who researches in Göttingen. What particularly interesting lectures can conference participants look forward to?

Prof. Seibt: In fact the conference will be starting with Stefan Hell's contribution, which will undoubtedly be a highlight of MC2015. But there will be further very interesting lectures in the following days.

With the Ernst Ruska prizewinners, the focus will be on the three-dimensional determination of structure: Jian-Min Zuo of the University of Illinois will present his work with electron nanodiffraction, while John Briggs (EMBL, Heidelberg) and Jürgen Plitzko (MPIB, Munich) will report on electronic tomography in the field of the life sciences. The determination of electron wave phase will find a place in the lectures of the Harald Rose prizewinner Angus Kirkland, of the University of Oxford, and Hannes Lichte (TU Dresden), who will cast light on this topic from different points of view. Exciting cellular biology will be the subject of the lecture by Paul Walther of the University of Ulm, who will show how the loophole between light microscopy and electron microscopy can be closed.

The interview was conducted by Kerstin Aldenhoff of Conventus.

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**Michael Seibt** Prof. Dr Michael Seibt, Professor at the Physics Institute of the University of Göttingen. Spokesperson of the High Resolution Transmission Electron Microscopy (HRTEM) Working Group of Deutsche Gesellschaft für Elektronenmikroskopie e.V. [the German Electron Microscopy Society, Regd. Assn.], Chairman of the Microscopy Conference 2015.

# Switchable nanochannels

Using functional polymers in porous structures for transport control

Ass. Prof. Dr Annette Andrieu-Brunsen
Ernst Berl Institute of Technical and Macromolecular Chemistry, TU Darmstadt, Germany

**Can molecular transport be controlled by nanoscale pores? In both human technology and Nature, many transport and separation processes are based on pores and porous materials. If transport needs to be time-controlled and separation based not merely on size, it becomes necessary to combine pores of a certain size with switchable chemical functions or polymers.**

In Nature, molecular transport processes are based on the interplay of structure and function at the nanoscopic scale (1 nm = 1 x 10-9 m). Examples include ion transport through membranes with the help of ion channels and water transport through pores such as aquaporin. Transport processes can also be selective, switched or unidirectional. From a technological perspective, porous structures are important in separation processes or sensor systems, for example. Here, there is increasing interest in miniaturizing sensors and isolating them from outside factors such as pressure. Such work depends on the ability to understand and control transport processes at the micro- and nanoscale. One fascinating approach to understanding and controlling transport processes is offered by the combination of relatively stable, porous ceramic structures and switchable functional polymers.

## Porous films

Mesoporous materials have pores with a diameter of 2 to 50 nm and can be made from materials such as silica – i.e. glass (Fig. 1). Methods of manufacturing such mesoporous films include the sol-gel process and evaporation-induced self-assembly, for example [1, 2]. In another procedure, block copolymer micelles are used as a template: these are burnt out following membrane separation, leaving behind an ordered, porous silica structure with a smooth surface (Fig. 1). This procedure for manufacturing mesoporous films has been known of since 1999 [2] and permits the configuration of pore diameter, pore arrangement and pore connectivity. To date, these kinds of films have been produced from a variety of materials and for a wide range of potential applications. Examples include porous semiconductors for solar cells, porous glass for separation methods and porous support materials for catalysts [3]. The functionalization of mesoporous walls can be achieved either by binding organic functions after film manufacture (post-grafting) or by the addition of functionalized educts during the film production process (co-condensation). An advantage of this in-situ functionalization is the homogenous distribution of organic functions. The disadvantage is that the porous structure obtained may also be influenced. The organic functions so introduced can subsequently be used for the binding of switchable polymers.

## Polymer functionalization of nanopores

The polymer functionalization of these porous membranes is particularly interesting: due to the monomers from which their chains are con-

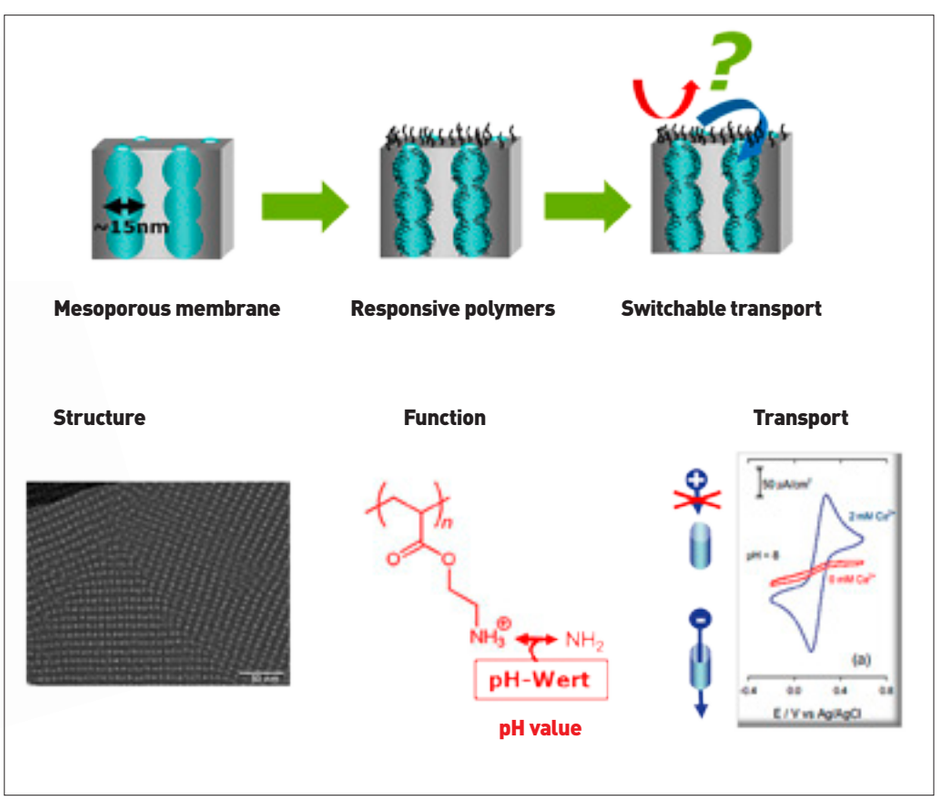


**Fig. 1** Schematic diagram of the combination of a mesoporous structure with functional polymers for the switching of transport processes. An electron micrograph of a mesoporous film is shown below (left), as well as a cyclic voltammogram, that illustrates the switching of ionic pore accessibility by way of example (right).

# smart membranes

structed, polymers possess a specific chemical function plus additional characteristics determined by their chain structure. One example is a stimulus-response behavior, for example. There are polymers that vary their degree of swelling (their expansion in a solvent) dramatically in response to slight changes in temperature. The binding of polymers to a surface also changes the properties of that surface – such as wettability and the surface charge, for example.

The combination of both building blocks – nanoscale pores and functional polymers – results in the creation of a new field of research, which has recorded a huge growth in popularity over the last few years [4, 5]. Another aspect of polymer functionalization is the choice of "grafting onto" or "grafting from" – i.e. a polymerization reaction that is initiated on the surface itself. In the case of grafting onto, an entire polymer chain must diffuse onto its later support site: for large polymers and small pores, this permits the targeted functionalization of the external surface, for example. Since surfaces in mesoporous materials (pore walls) are juxtaposed at distances of only a few nanometers, surface forces and mesopore accessibility play a decisive role in polymer functionalization, in determining polymer properties in pores and for the control of transport processes by such pores. One example is the effect of pore size on chain growth during a polymerization reaction. If pores are smaller than 10 nm in diameter, then the probability increases that radical polymerization reactions break off relatively quickly. One reason for this happening is that the radicals responsible for chain growth react with one another and not with a new monomer [6, 7]. Alongside the polymer functionalization itself, polymer behavior is another aspect influenced by the confined spaces available in nanoscale pores: as one example, we know that the pKa value of polymers can be shifted to more extreme pH values [8]. Theoretical calculations have also shown that, as a function of chain length and pore size, polymers can collapse either towards the pore wall or even to the pore center, depending on whether an increase in polymer-polymer association or the entropic losses of chain stretching are favored. Polymer distribution also has a role to play [9]. Understanding this polymer behavior is a basic precondition for the targeted control of molecular transport processes by pores of this kind.

**Annette Andrieu-Brunsen** studied chemistry in Marburg and completed her doctoral studies from 2007 to 2010 at the Max Planck Institute for Polymer Research in Mainz. During her doctoral research, she worked on designing swellable polymer networks for biosensors. This was followed by a period of research in Buenos Aires (Argentina), where she first worked on the functionalization of porous materials. This resulted in her burgeoning interest in polymerization reactions at the nanoscopic scale and the control of pore accessibility. In 2011, Dr. Andrieu-Brunsen accepted the post of Associate Professor of Chemistry at TU Darmstadt, where she now heads the "Smart Membranes" research group. In December last year, Dr. Andrieu-Brunsen also received the Adolf Messer Prize – TU Darmstadt's most highly-endowed prize for science – for her research project investigating the nanoscale control of chemical reactions on ceramic membranes.

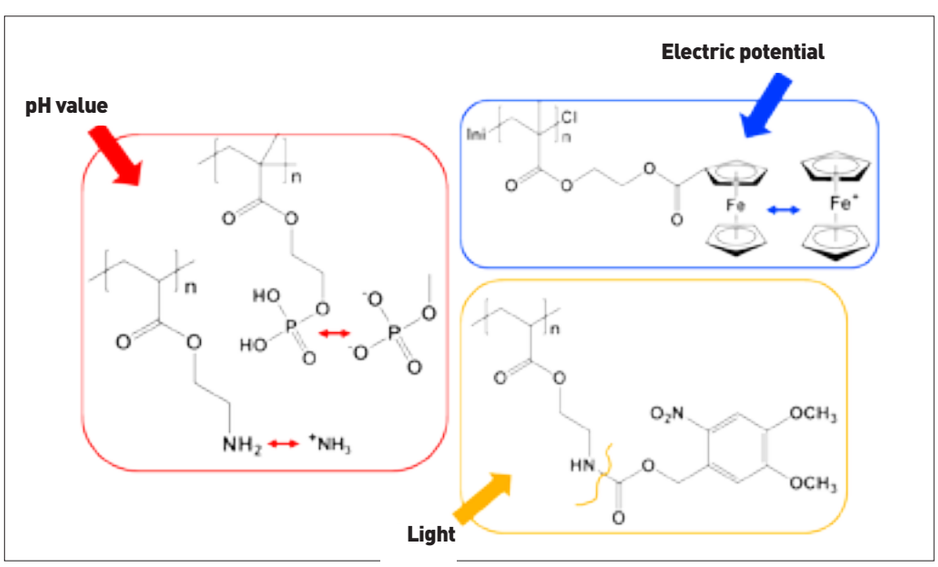


**Fig. 2** Potential stimuli-responsive polymers for transport control in combination with ceramic mesopores.

## Controlling molecular transport in nanopores

In this field of research, many examples over the last few years have demonstrated that switchable mesopore accessibility is possible for charged molecules [4, 10]. This research has investigated a range of polymers and switching stimuli (fig. 2). A switching of the polymer charge – and thus of mesopore accessibility – has been achieved by altering the pH value from acidic to basic, by complexation reactions involving multivalent ions, by light, by temperature and, just recently, by redox reactions (Fig. 2) [4, 13]. The common principle remains the combination of pore size and polymer chain length. If the polymer is charged using a stimulus, the sphere of influence for its electrostatic charge is described by the Debye screening length. If pore size is on the nanoscopic scale, then Debye screening length and pore size are comparable – even for relatively high concentrations of ions. Accordingly, the polymer bound to the pore wall acts as a "bouncer" for small charged molecules: the pore will now no longer filter just by size but also by charge. Molecules with the same charge cannot force their way into the pores, while molecules carrying an opposite charge can be concentrated. While the control of molecular transport by charge-switchable polymers is now possible, many challenges remain to be solved in this field. Questions have

still to be answered not only regarding the control of polymerization reactions and thus pore charge, but also in relation to the opportunities and limits to local control in nanoscale functionalization. Initial studies show that an incremental configuration of polymer quantity and thus charge leads to an incremental control of the ionic transport [7, 11]. Within certain limits, the quantity of a permanently-charged polymer can be controlled via the polymerization reaction time, leading to a variation in the ionic pore accessibility – from molecule exclusion through to molecule concentration.

Knowledge of such transport processes can also be deployed in a synthetic context: as one example, catalysts can be bound to these pores and starting materials for nanoparticles concentrated via surface charging, thus creating catalytically or optically active nanoparticles in porous membranes. The enclosure of metallic nanoparticles of gold or platinum leads to catalytically active pores, for example. The ability to make such mesopore transport processes switchable is also being investigated in medical applications. One example is the use of porous nanoparticles as carrier systems for the local release of drugs within tumor cells [12]. The combination of ceramic mesoporous materials with functional, switchable polymers is therefore not confined to the investigation and clarification of molecular transport processes. Instead, it may well prove useful in the long term for other areas of research and potential applications in fields such as catalysis, separation, sensors and medicine.

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## ISSAID, 30 September – 3 October 2015 in Dresden

### 8th International Congress of Familial Mediterranean Fever and Systemic Autoinflammatory Diseases

The 8th Congress of ISSAID, International Society of Systemic Auto-Inflammatory Diseases will offer numerous opportunities to convene with experts on FMF and other auto-inflammatory diseases. More than 400 participants will be welcomed from all over the world to discuss the latest scientific and clinical developments, including new treatment options. The congress will be held at the Dresden Hilton in the historic city center, ideally located on the Elbe River, steps away from attractions such as the famous Frauenkirche, Semperoper, the Zwinger and Royal Palace museum complexes. Starting with a pre-congress satellite meeting on Nonbacterial Osteitis, the program will be followed by a Young Investigators Meeting and the Opening Ceremony. On the following three days the organisers will offer "Meet the Expert" sessions, plenary educational lectures, and oral and poster abstract presentations.

→ **www.issaid2015-congress.de**

## LABComplEX, 20 –22 October 2015 in Kiev, Ukraine

### VIII International exhibition - the main event of laboratory industry in Ukraine

LABComplEX will be held in EC "Kyiv-ExpoPlaza" and is the main event of laboratory industry in Ukraine which covers the whole range of equipment and tools, furniture and supplies as well as services for creation, equipping, modernization of all types of laboratories in various industries, research field and medicine. The purpose of the Exhibition is to contribute to the professional development of industry experts, exchange of experience with international colleagues, making long-term business relations and the introduction of innovative scientific and technological solutions in most industries in Ukraine in the context of a rapid European integration processes. Our visitors are heads and experts of field-oriented institutions and control-inspection bodies, enterprises of different industries and research institutes, laboratories working in quality control, manufacturing, testing, clinical diagnostic and other types of laboratories.

→ **www.labcomplex.com**

# Nanoparticles in food

## What can analytics tell us?

Dr Philipp Brüning
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**Over the last few years, legislation specifically governing the handling of nanomaterials (NMs) has been steadily expanded within the EU (Fig. 1). One example is the Food Information Regulation, which requires that food ingredients in the form of "engineered nanomaterials" must be clearly indicated in the list of ingredients. To produce accurate labelling – and to inspect and assess this labelling – clear definitions are required, alongside valid analytical methods.**

Basic orientation is provided by the broad definition for a NM given in Commission Recommendation 2011/696/EU. This Recommendation 2011/696/EU and the definitions given in specific legislation contain measurable aspects. One criterion listed is the size of the particles or the particle size distribution. A material is a NM if 50% or more of the particles in the number size distribution lie in the size range 1 to 100 nm.

Many challenges must still be overcome in the analysis and assessment of NMs – some of which result from the measurable aspects of these definitions. While the various measurement techniques that are suitable for determining sizes in the 1–100 nm range are known, they have strengths and weaknesses depending on the measurement task involved and need to be further improved or made more specific to such tasks. These end results need to facilitate answers to the following questions:

**I Is a material a NM?**
**II Does a product contain a NM?**

- Qualitative: Which nanoparticles does the sample contain? Here, a distinction may need to be made in terms of naturally-occurring particles, and the material formulation needs to be investigated.
- Quan titative: How many particles does the sample contain? This requires a classification into size fractions, and a distinction between primary particles, agglomerates and aggregates.

### Requirements for the methods used to analyse nanomaterials

The taking of samples is itself a potential source of error. As of this writing, there is no published research that focuses specifically on NM sampling and assesses whether the typical methods result in representative lab samples. In addition, little is known about the behaviour of NMs in industrial batches (for example) or in complex matrices such as foodstuffs.

For lab work, it is generally necessary to adapt the methods to the respective materials: where manufacturers use additives or modify surface properties, materials can behave very differently even though the same declaration has been made for the "base" particle. This leads to a situation where labs create solutions specific to each sample, resulting in high labour costs per sample. The problem is aggravated by the fact that food contains many natural substances at nanoscale dimensions (globular proteins, carbohydrates) that must be separated out before measurement (especially if detection is non-specific). This places extra demands on sample pre-processing work. It is important not to disturb the particle distribution, for example. Once the materials have been successfully

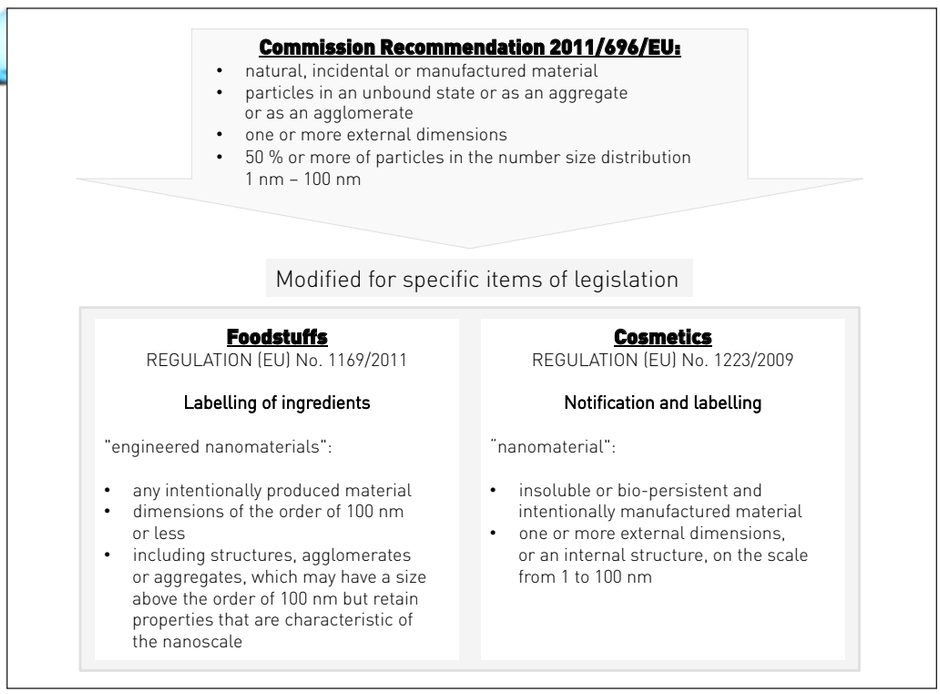


**Fig. 1** Recommendation 2011/696/EU and its modification for specific items of legislation

**Philipp Brüning** studied food chemistry at the University of Hamburg. After receiving his doctorate from the Institute of Food Chemistry at the University of Hamburg he then completed his Second State Examination at the Institute of Hygiene and the Environment. He joined Eurofins WEJ Contaminants GmbH in 2011 and has been head of the Nanotechnology Dept. since 2013. He also chairs the "Nanomaterials" working group in the German Food Chemistry Society (LChG).

extracted from the matrix, analysis methods such as Dynamic Light Scattering (DLS) or Field-Flow Fractionation require the production of dispersions for measurement. Such dispersions must remain stable at least until measurement is complete. One must also remember that ultrasound treatments or the addition of stabilisers can have a major impact on the results.

Standards or generally defined and accepted performance requirements have not been established in this field to date. In-house validations are also made more problematic by the lack of standard/reference materials covering multiple size ranges. One validated method was recently published for the detection of silver nanoparticles in meat. As a rule, results must be valid for three parameters with reference to the respective matrix and NM, namely: identification of the material, size and size distribution [2]. For further details of requirements, the reader is referred to the reports published by the Joint Research Centre [3, 4, 5].

The kind of routine analyses familiar to us from established processes cannot yet be performed, for the reasons discussed above: in each case, the methods need to be modified to suit the specific analysis task (matrix and analyte). Interpreting the results to produce a final assessment is also problematic.

Single-particle ICP-MS (SP-ICP-MS) can be performed rapidly and is therefore a method with the potential for routine application. Unlike standard ICP-MS measurements, SP-ICP-MS utilises a time-resolved analysis mode with short dwell times. With the sample appropriately diluted, individual signal events can therefore be detected, which correspond to single nanoparticles. By applying a spherical model together with a known particle density, number-based size distributions can be calculated. The method has the advantages of being highly specific and matrix-tolerant while being able to count a multitude of particles in a short analysis time (approx. 1 min.) As a "counting method", no conversions are needed for an assessment of the number size distribution in the sense of the definition. The problem of interferences places size detection limits on this measurement method, however. That said, SP-ICP-MS is ideal for use as an initial screening step before the application of more complex methods (examples are given below). To confirm results and perform complete characterisation of the NMs, suitable methods include electron microscopy techniques such as transmission electron microscopy. These kinds of imaging techniques make it possible to detect nano-objects such as agglomerates and distinguish these from primary particles. Automated image analysis and cheaper equipment are making such methods more suitable for use in routine practice.

Asymmetrical Flow Field-Flow Fractionation (or AF4) uses a parabolic flow in a separation channel to separate particles by their size. The separation force is generated by cross flow perpendicular to the channel. This produces a vertical force field in opposition to the particles' natural diffusion. Smaller particles thus enter areas of the channel with faster flow profiles and are therefore detected first. When combined with various online detectors, this non-destructive separation technique can enable the acquisition of important characterisation parameters. Particle size distribution can be determined with a suitable size calibration via the elution time or by using light scattering detectors (MALS or DLS). Detectors using mass spectrometry (ICP-MS) provide further details of the composition of inorganic NMs, offering both sensitivity and specificity. Quantitative analyses are also possible. As described, the multi-detector setup therefore enables the identification of the particles while also determining particle size/particle size distribution. When evaluating the results, however, one must bear in mind that the particle size distributions obtained are based on mass or intensity. Conversions to number-based distributions are currently subject to errors, however.

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# Starting a new era of bioprocess development – smaller, smarter, controlled

A new generation of microfluidic microbioreactors paves the way for accelerated R&D

## Research based on parallel fermentation

Reducing costs while developing efficient bioprocesses is the market need. Intensive screening including a vast number of different experiments regarding strains, media composition and process conditions has to be conducted in order to create high yields and product titers. High-throughput fermentation in microliter scale is the method of choice as it generates high data output while cutting costs due to savings on time and workforce, automation and low material input. Whereas different solutions for milliliter scale fermentation already exist, the market still lacks powerful tools for full process control in microliter scale.

Already established in academia and industry the BioLector® system offers highly paralleled fermentations in a 48 well microtiter plate with standard SBS footprint. Utilizing the unique FlowerPlate® the system provides full online measurements of biomass, DO and pH-value, as well as up to three additional fluorescences for each individual well in 800–1500 µL working volume. Due to its special shape the FlowerPlate® can reach oxygen transfer rates (OTR) of up to 120 mmol/L/h, comparable to bench-top stirred-tank reactors. The disposable plates are delivered pre-calibrated, sterile and ready-to-use.

## The microfluidic principle

The next generation tool, BioLector Pro®, pushes the capabilities of microscale fermentation forward to individual full bioprocess control. The advanced system offers individually and fully controlled reactor wells with liquid pH-regulation and fed-batch possibilities. A microfluidic chip replaces the usual plate bottom allowing to pump nanoliter-amounts of liquid independently into the individual wells without losing the online-monitoring capabilities of the basic system. As the first two well rows are used as reservoirs for the desired feeding solutions, the remaining 32 wells work as distinct bioreactors. The task for each reservoir row can be chosen independently, enabling the system to deliver two different feeding solutions, one feed and one pH-value up- or down-regulation, or full pH-control for each well column. Constant, linear or exponential feeding can be chosen while a PI-controller derivate ensures proper pH-control. The microfluidic technology utilizes pressurized air to actuate membrane valves at the bottom of the microfluidic chip. The liquids are pumped through the chip via micro channels directly into the wells. The complete plate remains a closed system and can still be purchased as a disposable item.

→ **www.m2p-labs.com**

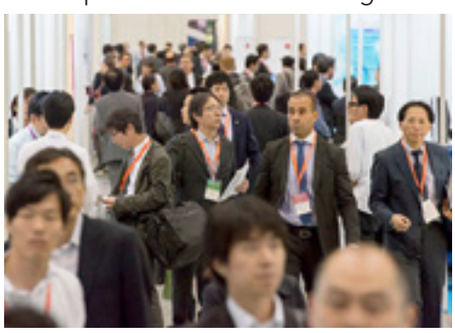

**Fig. 1 BioLector® Pro microbioreactor**

**Fig. 2 FlowerPlate® with microfluidic chip**

## BioJapan from October 14 –16 October 2015 in Yokohama

BioJapan 2015 YOKOHAMA

One of this year's main focuses of BioJapan will be about regenerative medicine.



In October, 2012 the Japanese stem cell researcher Professor Shinya Yamanaka was awarded the Nobel Prize in Physiology or Medicine jointly with Sir John B. Gurdon for the discovery that mature cells can be converted to stem cells. Only a few days later, Prof. Yamanaka gave a lecture at Japan's annual Biotechnology event BioJapan which was hopelessly overcrowded. 3 years later Prof. Yamanaka will again speak at BioJapan about his work on induced pluripotent stem cells (iPS cells). In the meantime, his Nobel Prize has given a big push to regenerative medicine in his home country. Japanese companies see huge opportunities in regenerative medicine and have increased activities in this field and will attend BioJapan in Yokohama from October 14 –16 October to further advance their strategies for regenerative medicines and to discuss new deals in the Partnering.

→ **www.ics-expo.jp/biojapan**

Advertorial


The future of the German biotech sector was discussed during the "Biotech made in Germany" Congress in Martinsried, Germany: (LTR) Dr Marion Jung (Chromotek), Sandra Wirsching (Biocom AG), Stefan Höfer (Deutsche Börse AG), D. Georg Ried (Bayern Kapital GmbH), Dr Simon Moroney (Morphosys AG).

# Biotech investors are back

**The "Biotech made in Germany" Congress at the IZB in Martinsried showed that the sector is picking up momentum again. Things are looking up – this was the mood at the international congress with financial experts on 16 and 17 July 2015 in Martinsried near Munich. The Innovation and Startup Center for Biotechnology (IZB) on the Martinsried Campus, in co-operation with the Member of Parliament Florian Hahn, organised the congress with top-ranking international financial experts.**

Venture capitalists and the CEOs of the globally successful biotech companies Morphosys and Evotec had some positive news for the approx. 100 participants: after a long pause, the venture capital financers TVM are investing in Germany once again. The US early-stage funder is opening an office in Munich, and the German Accelerator Program as well as the German Stock Exchange Venture Network are also slowly gaining momentum in life sciences. A conclusion derived from the two podium rounds: the German biotech sector should benefit over the coming months from the ongoing global biotech boom.

A sign of the upward trend: Hubert Birner from TVM Capital, whose last investment in Germany was made in 2009, stated at the congress that the company will announce an investment in Munich of around 22 million Euro within the next few weeks. The money stems from the TVM Life Science Ventures VII which won significant funders in Canada. Altogether, a total volume of around 250 million dollars is available, some of which will now flow towards Europe.

Simon Moroney from Morphosys compared Germany with the USA: 400 million dollars were invested in the biotech sector here while it was 40 billion dollars in the USA – 100 times more. According to him, investors are not prepared to invest large sums in small business models. What is needed are more ambitious businesses that aim to develop their own medications. And in the USA in particular, there are enough investors who would be prepared to give a lot of money for a good idea.

IZB CEO Peter Hanns Zobel, who jointly celebrated the IZB 20th anniversary this year, took a brief look at the successful years of the IZB. According to Zobel, the heads, location and capital stand for success. There are enough clever minds at the IZB and especially on the Martinsried Campus. 12,000 people work here, 650 at the IZB alone. The location is impressively set up with institutes, a Chemistry College, kindergarten and the new IZB Residence CAMPUS AT HOME for overnight guests of the Martinsried Campus. The new Faculty Club serves as a communication centre for the Campus with its modern design and view of the Alps.

## From Micromet via Amgen to investor

Dr Patrick Bäuerle also reported on new financing options for German biotech enterprises. The former SEO for the Munich antibody specialists Micromet, acquired by Amgen for 1.16 billion Euro in 2012, moved to the US early-stage investor MPM Capital, located in Cambridge and San Francisco, three months ago. He explained that MPM Capital is actively involved in the initial spin-off phase from the academic environment and assumes direct management responsibilities for financial entry. Within the first three months, he has already launched two US biotech companies. MPM therefore seeks to take on the initial management of its portfolio companies itself. This will allow a rapid and highly professional start. A total of 400 million dollars are available in current funds at MPM Capital.

Andy Goldstein, Executive Director of the LMU Entrepreneurship Center in Munich, was pleased to announce that the first 18 life sciences companies from Germany will go to Boston through the German Accelerator Program in order to access both the US market und US investors. The American co-ordinates this programme initiated by the Federal Ministry of Economics and has supervised it for three years for the IT sector. Now it is also being developed for the life sciences. Also involved is Johannes Frühauf from Cambridge Biolabs who supports incubators in Boston. There are currently plans to raise such incubators in Germany, too.

→ **www.izb-online.de**

*Picture: IZB*

# products

## CombiFlash® EZ Prep of Axel Semrau®

The CombiFlash® EZ Prep streamlines the purification process, quickly switching from Flash to high-pressure preparative chomatography in just two clicks. Pre-purify on Flash followed by Prep for submission quality compounds. User-friendly PeakTrak® software controls both Flash and Prep HPLC chromatographic conditions.

→ www.axel-semrau.de

## BÜCHI introduces Rotavapor® R-300

BÜCHI Labortechnik introduces a ground-breaking, commercial laboratory system with the launch of the Rotavapor® R-300. The innovative, modular platform with a plug & play concept enables seamless combinations of components to provide tailor-made solutions, from a basic rotary evaporator to a fully-automated system.

→ www.buchi.com/rotavapor

## RoboLector® of m2p-labs

RoboLector®, an automated cultivation platform combines the high-throughput fermentation and online monitoring capability of the BioLector® with the accurate and reproducible pipetting of a liquid handling robot for media preparations, automated sampling and dosing steps, inductions and fed-batch processing.

→ www.m2p-labs.com

## Easy handling with larger capacities

The LyoCube with useable shelf area of up to 0.6 m² provides user-friendly operation with front door and rectangular shelves. Flask drying in up to 2 x 3 glasflasks is available as an option. The LyoCube is available for the latest LSCplus laboratory freeze dryer product line or as a retrofit of existing freeze dryers with LSC controller.

**www.martinchrist.de**

## Multimode microplate reader with LVF monochromatorsTM and Atmospheric Control Unit

The CLARIOstar® multimode microplate reader is equipped with unique LVF monochromatorTM technology, filters, and an UV/Vis spectrometer. The triple technology offers high performance for a variety of applications in all detection modes. With its outstanding LOD specifications for Fluorescence Polarization and Fluorescence Intensity the CLARIOstar® has again been proven to be the most sensitive monochromator-based microplate reader on the market. With the new Atmospheric Control Unit (ACU) the reader is able to provide the physiological environment for any cell type, making cell-based assays more biologically relevant.

**www.bmglabtech.com**

## A Trailblaizer – Shimadzu's new RF-6000 spectrofluorophotometer

Shimadzu's new RF-6000 spectrofluorophotometer provides stable analyses at a level of sensitivity unrivaled by other instruments in its class. Combined with new LabSolutions RF software, the RF-6000 covers excellent measurement accuracy and easy operation for a diverse range of customers' measurement needs. The RF-6000 provides features which contribute to even more precise analysis results and reduced running costs. Outstanding sensitivity and high-speed 3D measurement extend the comprehensive range of applications.

**www.shimadzu.eu/rf-6000**

# products

## Memmert IVF Module for in Vitro Fertilisation

The IVF module minimises recovery times of $CO_2$ content, $O_2$ content and humidity after the door has been opened. The breeding unit with separate slide-in units is inserted in a Memmert $CO_2$ incubator INCOmed. The module has eight slide-in units and can be used an INCO108med $CO_2$ incubator which has been certified as a class IIa medical device for in vitro fertilisation.

→ www.memmert.com

## Light Flash Apparatus for Determining Thermal Diffusivity and Conductivity

The flash method is a precise, reliable and efficient method for determining the thermophysical properties of a variety of materials. Netzsch had already set a new benchmark in this sector back in 2013 with its introduction of the now-established LFA 467 HyperFlash with ZoomOptics. Barely two years later, Netzsch is again showcasing its strength with the new LFA 467 HT HyperFlash.

→ www.netzsch.com

## Improved Membrane Chromatography Performance

For the more effective recovery of large molecular weight proteins, such as blood factors and conjugated proteins or viruses and virus-like particles, Sartorius Stedim Biotech has reconfigured its Sartobind® membrane chromatography capsules. A range of capsule sizes with a 4 mm bed height is now available from the 1 mL nano unit up to the new 2.5 L jumbo version.

→ www.sartorius.com

## Siemens Healthcare Diagnostics Launches Xprecia Stride Coagulation Analyser

Siemens Healthcare Diagnostics is introducing a first-of-its-kind, hand-held portable coagulation analyser. The Xprecia Stride Coagulation Analyser delivers fast, reliable Prothrombin time testing (PT/INR) for point-of-care monitoring and management of oral anticoagulation therapy (OAT) with warfarin, a vitamin K antagonist.

→ www.siemens.com

## The ViMix – a New Development from Zinsser Analytic

Zinsser Analytic has developed a multi-position vertical shaker that can mix several samples in parallel using a 15 mm vertical movement at up to 1200 cycles per minute. The vertical shaker can be adapted to accept customer-specific labware vessels.

→ www.zinsser-analytic.com

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