InFact

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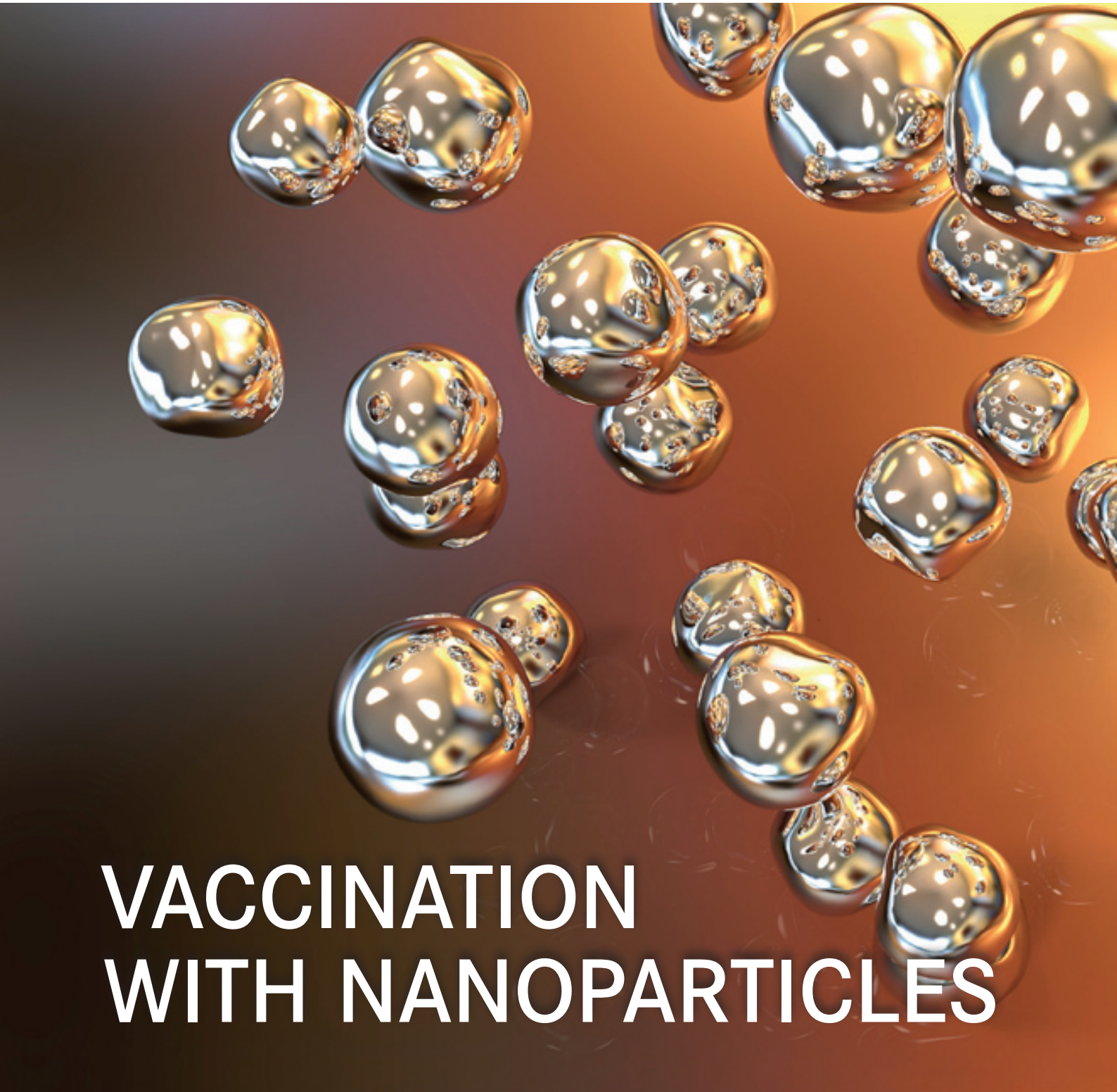
HELMHOLTZ CENTRE FOR INFECTION RESEARCH



VACCINATION WITH NANOPARTICLES

VACCINATION WITH NANOPARTICLES

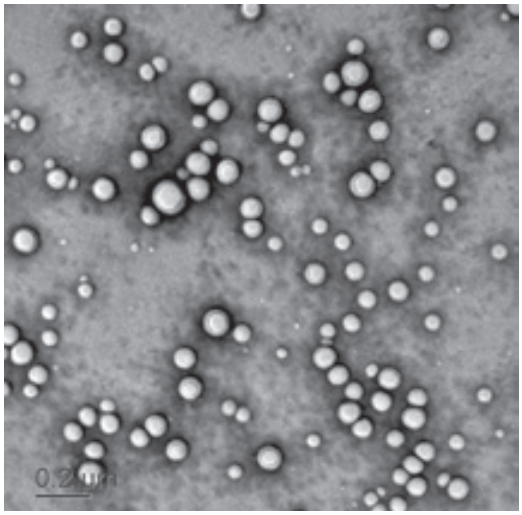
by Thomas Ebensen and Kai Schulze

Vaccination affords the best protection from many infectious diseases. Vaccines are usually administered with a syringe, but researchers are working on alternatives – like a nasal spray or a vaccination cream. These would not only avoid the unpleasant injection, but even increase the effectiveness

Vaccines usually contain killed or attenuated pathogens and are injected into the patient. This ensures that the entire vaccine truly ends up inside the body. Recognising the pathogens in the vaccine as dangerous foreign material, the immune system prepares itself for defence. The administration by injection with a syringe has its drawbacks as well: It is not the natural pathway of infection and the elicited immune response therefore does not always afford optimal protection from the pathogen. Vaccination also requires trained personnel that simply is not available everywhere and at all times, especially in less developed countries.

To be able to vaccinate significantly more people throughout the world, it would be more useful to have vaccines that can be administered in the form of a nasal spray or a cream passing through the skin. They would not only be easier to use, but also have a crucial benefit in that they mimic the natural infection process. Most pathogens penetrate into the body through the mucous membranes. If these barriers were immunised by a vaccine, they might repel the pathogen directly. They would not only provide protection from the outbreak of the disease, but even earlier, i.e. during the infection process. As a consequence, vaccinated individuals would not even be colonised by pathogens and therefore would

▽ *Thomas Ebensen administers a new vaccine in a mouse via the mucous membranes – in humans, this might be done with a nasal spray in the future*



△ *Nanoparticles produced at HIPS*

not transmit diseases to their fellow human beings. However, a disadvantage of non-invasive vaccination methods is that only small amounts of the vaccine reach the immune cells resulting in a reduced efficiency.

"We are working on making vaccines effective enough for administration via the skin or the mucous membranes," says Carlos A. Guzmán, who directs the Department of Vaccinology and Applied Microbiology at the Helmholtz Centre for Infection Research (HZI). "The safety of the patients always comes first and consequently there is a steady trend towards vaccines that contain only components of pathogens." Although this increases the safety, it reduces the efficiency because the immune system no longer considers the components to be hazardous. There is a solution to this problem: Biological nanoparticles that deliver antigens along with so-called adjuvants. These aiding substances – such as the cyclic-dimeric-adenosine monophosphate (c-di-AMP) originating from bacteria – can reinforce the vaccine, since they signal the immune system that a hazard is present.

The focus of the HZI is mainly on mucosal vaccination. Aiming at the mucous membranes, this form of vaccination can take place in the form of a nasal spray. "This form of administration targeting the nasal mucosa can activate the immune defence not only in the airways, but in the entire body, and is therefore versatile in use – e.g. against respiratory pathogens such as influenza viruses (flu) and pneumococci (pneumonia), against diarrhoeal pathogens such as salmonellae or EHEC and even against HIV or human papilloma viruses causing cervical cancer," says Guzmán.

Biological nanoparticles are detected by the immune system due to their sheer size and thereby increase the visibility of the components of the pathogen as well. In addition, they protect the vaccine from defensive biochemical responses of the body – such as enzymes or changes of pH. Suitable nanoparticles consist of e.g. lactic and glycolic acid and are already used commonly in medicine. Scientists of the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), a branch of the HZI, produce these particles in-house and are working steadily on the optimisation of these particles. Their aim: Vaccination via the skin. In this non-invasive method, the vaccine is simply applied to the untreated skin. "The nanoparticles penetrate through the hair follicles into the skin and elicit an immune reaction in the body," says HIPS researcher Hanzey Yasar. "A vaccine of this type would be very easy to administer and would certainly be well accepted by the population." Since only a small amount of vaccine actually enters the hair follicles, Yasar and her research colleagues loaded the nanoparticles with an additional reinforcing adjuvant. In initial experiments, a protein was used as the antigen, i.e. as a foreign substance, to which the immune system was to respond. Using this approach, the researchers managed to elicit an immune response against the protein by simply applying it to the skin. "In the next step, we aim to use nucleic acids bearing the information for an antigen in place of the protein. This would be advantageous since nucleic acids can be adapted more flexibly to a certain disease," explains Hanzey Yasar. However, before the new nanoparticles can be used in clinical applications, studies using various animal models are required. A vaccine of this type can therefore be expected to require another five to ten years of development before it reaches the market.

ONLINE ARTICLE WITH VIDEO AND AUDIO PODCAST:

www.helmholtz-hzi.de/en/stories

Dear readers,

Vaccinations afford the safest protection from many infections. But the administration of the vaccine with a syringe has its drawbacks – not only because it is unpleasant, but also for logistical reasons: Not all places in the world have medical personnel available. A vaccine that could be used as a cream or a nasal spray without reducing the efficacy would be the perfect solution. Our title story describes how researchers from the HZI and the HIPS approach this kind of vaccine.

Silke Tannapfel has been the Administrative Director of the HZI since October of this year. In our interview, she talks about her perception of the HZI and the return to her roots.

I look forward to your feedback and hope you will enjoy reading the magazine!

Andreas Fischer
Editor-in-chief

IMPRINT

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△ *Since October 2017, Silke Tannapfel directs the administration of the HZI*

"THE HZI COULD BE MUCH MORE SELF-ASSURED IN APPEARANCE AND MANNER"

by Susanne Thiele

Silke Tannapfel has been the Administrative Director of the HZI since 1 October 2017. A lawyer with a focus on science management, she previously directed the division for extramural research support of the Bavarian State Ministry for Economy and Media, Energy and Technology in Munich

Mrs Tannapfel, how did you become aware of the HZI?
Although I grew up in Lower Saxony and spent most of my legal internship in the Hannover/Hildesheim region, I did not become aware of the HZI until 2014, when the Helmholtz Institute for RNA-based Infection Research (HIRI) was founded. After a first meeting with Jörg Vogel of the HIRI and other leaders of the University of Würzburg, who basically raved about the HZI, I quickly gathered more information and was very impressed by the positioning of the Helmholtz centre in Braunschweig.

What made you interested in becoming the administrative director?
The answer is the link of Helmholtz and infection research as well as the people. Infection research is one of the main public health challenges facing society. I perceived the Helmholtz centres to some of the more dynamic facilities in my field of responsibilities. Helmholtz is distinguished by cooperation and really is the load-bearing spine of the German science system – to phrase it in medical terminology.

What has been the largest professional challenge thus far?
In Bavaria, I was responsible for the Helmholtz, Max-Planck and Leibniz facilities in the state. One challenge was to rehabilitate a life-threatened Leibniz facility in 2016/17. I'm particularly proud

of founding a Max Planck Institute in Erlangen, which I was in a position to support – starting from a small group of researchers through the foundation of the institute and the later expansion of the centre.

Which "lessons learned" at the Ministry are you bringing along with you?

I really got a good helicopter view of the German research landscape, its strengths, key success factors and pitfalls. Moreover, the state of Bavaria invests a lot of money and time into continued education measures for the development of organisation and personnel; many of my superiors were good role models for which I am very grateful. Patience or restraint are not part of the Bavarian ministerial bureaucracy. In my view, the HZI could be much more self-assured and more resolute in appearance and manner, especially in terms of funding.

How do you perceive the HZI?

To me, the HZI seems like a powerful home with a low-key attitude. The Science Campus Braunschweig-Süd is very impressive due to its modern buildings and the cooperation of the broad range of actors. This is quite unique in Germany and we can be proud to present it to the public. Our staff restaurant is another important place. I go there regularly and can be approached there. Attentiveness to the staff is very important to me. I do not want the staff to have more problems after a conversation with me than before.

How do you like Braunschweig and Wolfenbüttel?

Braunschweig seems to have the optimal size for a science city in my mind, not too small and not too large to make it difficult to know and help each other. I have tried some of the restaurant scene in Wolfenbüttel and found some favourite places there. I buy into the slogan of the Eintracht Braunschweig fans: "Love knows no league." Being a member of the Werder Bremen club myself, I am also used to suffering. I look forward very much to the museum landscape of this region. And I can chill really well with good books and I am enthusiastic about old mechanical clocks, which I repair myself sometimes.

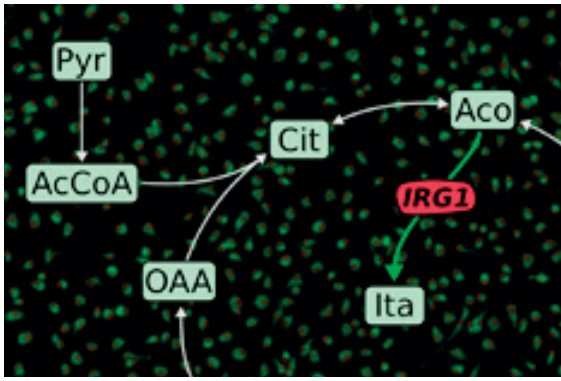
COMPLETE INTERVIEW:
www.helmholtz-hzi.de/en/interview

HOW METABOLISM IMPACTS THE IMMUNE SYSTEM

by Yannic Nonnenmacher, Karsten Hiller and Ida Retter

For decades, immunology and metabolism were separate fields of research. In recent years, these fields have moved toward each other and the metabolism of the immune system has become a highly active research field. One typical example are the studies of Karsten Hiller's team investigating the metabolism of macrophages, which are the scavenger cells of the immune system.

The so-called metabolome analysis captures all small molecules of a cell at a certain point in time. Karsten Hiller, metabolome specialist, investigated the metabolism of macrophages already during his stay at the Luxembourg Centre for Systems Biomedicine. His research group in Luxembourg discovered that these immune cells contain unusually high concentrations of itaconic acid, a previously poorly studied molecule. Collaborating with Eva Medina from the HZI and other partners, the researchers determined the enzyme that is responsible for the production of itaconic acid. Further studies showed that itaconic acid acts as an endogenous antibiotic in that it kills the bacteria that are taken up by the macrophages. In July 2016, Karsten Hiller accepted an appointment at the Technische Universität Braunschweig. In addition to this position, he is also a department head at the HZI working in the Braunschweig Integrated Centre of Systems Biology. Meanwhile, his doctoral student, Yannic Nonnenmacher, developed and applied a special procedure to observe that itaconic acid inhibits an enzyme of the citrate cycle directly in mitochondria – i.e. the power plants – of macrophages. This inhibition leads to an increase in the amounts of succinate – a metabolite, which plays a crucial role in the re-programming of macrophage metabolism. Therefore, itaconic acid is obviously an important link between metabolism and the immune system.



△ *Macrophages with mitochondria (green) and nuclei (red). The scheme shows the part of the citrate cycle, in which the enzyme IRG1 converts aconitate to itaconic acid (Pyr=pyruvate, AcCoA=acetyl coenzyme A, OAA=oxaloacetate, Cit=citrate, Aco=(cis-) aconitate, IRG1=immunoresponsive gene 1 proteine, Ita=itaconic acid)*

AN EYE FOR THE SMALLEST STRUCTURES

by Tatyana Dubich

Michael Kolbe investigates the tools used by bacteria to infect their hosts down to the single atom. His findings help to understand bacterial evasion strategies and to find new targets for rational therapies

For millions of years eukaryotic cells have built up defence systems against pathogens. But the pathogens did not sleep either: In parallel, Gram negative bacteria, such as *Salmonella* or *Shigella* that cause food-borne illnesses, developed a system to outsmart those defence strategies: They possess a molecular syringe, called type three secretion system, which allows them to inject proteins directly into target cells, bypassing host defence and facilitating infection. Michael Kolbe wants to unravel the structure and function of these sophisticated tools literally down to the smallest detail. He leads the department "Structural Infection Biology" of the Helmholtz Centre for Infection Research, but his research group is located at the Centre for Structural Systems Biology (CSSB) in Hamburg. Kolbe also holds a professorship at Hamburg University.

Physicists, biologists and pharmacologists work together in Kolbe's group to elucidate molecular mechanisms of bacteria-host interaction on every magnification level possible going from tissue to sub-nanometre level. The CSSB provides unique facilities having high level biosafety laboratories just a dozens of metres away from the beamlines of the storage ring PETRA III. "Experiments that used to require elaborated logistics for samples transfer can be done just across the hall. This empowers us to collect enormous amounts of data," says Kolbe, "but it also leads to the greatest challenge of our research: integrating different approaches to create meaningful data."

Grown up in a family of teachers, young Michael Kolbe has been interested in chemistry, biology and physics since school years. "How molecules that create life interact with each other has fascinated me from the very beginning," recalls Kolbe. "One of the things that intrigued me the most was photosynthesis. I wanted to know how plants work on the molecular level." Driven by his interest, he went on to study chemistry at the University of Paderborn and continued with his master studies having a focus on biochemistry at Hamburg University. "My biggest inspiration was my PhD advisor Dieter Oesterhelt from the Max Planck Institute of Biochemistry in Munich," says Kolbe. "He was applying physical methods in order to study biological molecules and that was something I always wanted to do as well. Going to his lab was a key step in my career."

Now that Michael Kolbe has his own research group he serves as an inspiration for young scientists himself. Research is not always a straightforward success story, says Kolbe. On a way to discovery scientists face multiple obstacles: Experiments do not work as expected, hypotheses need to be reconsidered, manuscripts get rejected. Kolbe sees just one way to deal with frustration: Optimism. Although he hesitates to elucidate one formula for success, he says: "If I could give advice to young scientists, I would say 'Don't be afraid of making mistakes or asking stupid questions. Stay optimistic and believe in what you are doing!'"

Moving from Berlin to Hamburg and establishing laboratories there is another challenge that Michael Kolbe is facing. But he likes to discover the new city by bike with his wife and three children. "As scientists we sometimes lose the count of hours in the lab. But it is important to take a step back and recharge by spending time with family and friends," he says.

INITIAL RESULTS OF THE INFLUENZA STUDY AT THE HZI

by Andreas Fischer

The course of influenza can vary widely and is currently not predictable. Subjects from the HZI contributed to a study searching for markers indicating the severity of influenza diseases

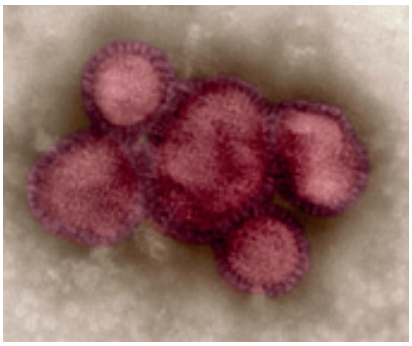
According to estimates of the World Health Organization WHO, each year about three to five million people are afflicted by influenza throughout the world. This infection can take a moderate course, or a severe one that leads to fatality in ten to 15 percent of the afflicted individuals. While early antiviral treatment might alleviate the course of the disease, there is no solid evidence known that allows for reliable prognosis early in the infection process. Instead, patients are often given antibiotics that are ineffective against influenza viruses and therefore fail to contain the infection.

A researcher team directed by Klaus Schughart from the Helmholtz Centre for Infection Research (HZI), Benjamin Tang from the University of Sydney and Jens Schreiber from the Otto von Guericke University Magdeburg tested blood samples of influenza patients for markers that might be indicative of the course of the disease. The majority of the control samples from healthy individuals was taken at the HZI. "We selected blood samples from influenza patients with a moderate versus severe course of the disease and from healthy individuals as well, and produced transcription profiles of the three groups," says Klaus Schughart. "This analysis shows us which genes are active in the patients and which are not. Without the contribution of the volunteers from the HZI, it would not have been possible to complete the study the way it was done and I'm very grateful to everybody who volunteered to participate in our study."

The study aimed to find genes that distinguish the three test groups from each other. Patients who were hospitalized for influenza and released early were considered to have a moderate course of the disease. Severe courses included patients who needed to be artificially ventilated. "In the first step, we were able to show that the *IFI27* gene is upregulated in all influenza patients. This makes *IFI27* a unique biomarker for differentiation of an influenza infection from a bacterial respiratory infection," says Schughart. In the next step, the researchers searched for a marker of the severity of the course of the disease – and they found a gene that is particularly active in all patients suffering from a severe course. "The result has not been published yet. This new marker is now being tested in larger studies to determine the point in time at which it is upregulated," says Schughart.

The study also showed neutrophils – a type of immune cells – to be activated. Neutrophils can be seen as the first line of defence at the site of infection, where they shoot oxygen radicals at infected cells or capture the pathogens with DNA nets. This reaction seems to overshoot in influenza cases with a severe course though and possibly increase the fatality. "The activity of neutrophils can be controlled and this may be a potential new approach for future therapies," says Schughart.

△ *The study of the course of influenza diseases was based on blood samples*



△ *Electron micrograph showing influenza viruses (H1N1)*

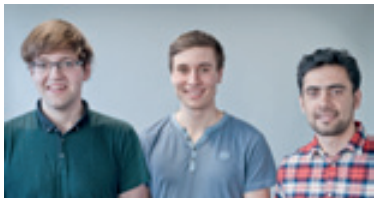
NEWS

GRAND OPENING OF THE SCIENCE CAMPUS

△ *Dirk Heinz (HZI), Timo Jäger (DZIF), Anke Kaysser-Pyzalla (TU Braunschweig), Iris Eisenbeiser (BioS), Norbert Krug (ITEM) and Jörg Overmann (DSMZ; f.l.). Image: HZI/Verena Meier*

On 6 October 2017 the "Science Campus Braunschweig-Süd" was officially inaugurated by Lower-Saxony's Minister for Science and Culture, Gabriele Heinen-Kljajić, and Braunschweig's Mayor, Ulrich Markurth. The Stöckheim campus now has its own name that is also used in a new street signage concept of the city of Braunschweig. The campus partners, still independent organisations, include the Helmholtz Centre for Infection Research (HZI), the German Center for Infection Research (DZIF), the Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures, the Technische Universität Braunschweig, the Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM) and the Biotechnologische Schülerlabor Braunschweig (BioS). The aim of the joint umbrella brand is to expand the visibility – e.g. with a view to the new round of the Excellence Initiative, attract new cooperation partners and cross-link the partners even more closely.

NEW PHD REPRESENTATIVES



△ *Daniel Meston, Kevin Becker and Sami Ullah (f.l.). Image: János Krüger*

Daniel Meston, Kevin Becker and **Sami Ullah** are the new speakers of the PhD council "DO IT". Joining forces with the Graduate School, they support the maintenance of quality standards in doctoral student training and tutoring and the continued improvement of the working conditions at the HZI. The DO IT initiative was established in 2002, and the term of the speakers is one year.

AWARD-WINNING WORK

△ *Gregor Fuhrmann (5th from the right) at the Galenus Award ceremony. Image: Galenus-Privatstiftung*

Gregor Fuhrmann of the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) was awarded the Galenus Technology Award endowed with €5000. The award recognises his research on extracellular vesicles leading to the development of new therapeutic approaches. In addition, Fuhrmann receives funding from the Volkswagen Foundation's programme titled "Experiment! – Searching for daring research ideas". In the scope of the funded project, he will use extracellular vesicles to generate a bacteria-like surface on microparticles and test if this can be used to regulate overshooting immune reactions.

The biology laboratory assistant, **Kira Baumann**, was one of the best examinees of the Chamber of Industry and Commerce Braunschweig. She completed her training at the HZI half a year early with flying colours (mark: A). The Helmholtz Association also honours special performance of non-academic trainees: This marks the third time trainees from all fields at all Helmholtz centres can be nominated for the **Helmholtz Trainee Award**. The nominations can be submitted by the corresponding trainers or the trainees themselves (along with a statement from the trainers). Any support by the tutors from the scientific departments is welcome. HZI projects came in in second and third place in the past. The deadline for entries is 31 January 2018.

NEW BOOK

Jesko Köhnke, junior group leader at HIPS, and partners edited a book entitled "Cyclic Peptides – From bioorganic synthesis to applications" that will be published by the Royal Society of Chemistry at the end of 2017. Cyclic peptides are very common in natural products and tend to be more stable and resistant to degradation compared to their linear counterparts. This is reflected by the over 100 macrocyclic therapeutics in use today. The book contains a detailed overview of biosynthetic routes to cyclic peptides and examples of classical chemistry approaches, as well as examples of how synthesis and biological methods can be combined. In addition, it also features a section on the use of cyclic peptides in drug discovery. (afi)

NEW PERSONNEL

HIPS, Saarbrücken: Kathrin Andres, MINS | Ravindra Jumde, DDOP | Matthias Köck, MINS | Emilia Oueis, MINS | Teresa Röhrig, DDOP
HIRI, Würzburg: Tobias Krammer, SIGA | Julia Mendorff
HZI, Braunschweig: Sebastian Goy, DZIF | Jana Niemz, EXIM | Doris Pester, NIND | Urmi Roy, MIKI | Tim Trojahn, BCO | Grazyna Wittek, DMC
TWINCORE, Hannover: Moritz Redlich, EXPI | Damaris Werner, BIOM

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