

# InFact

The magazine of the Helmholtz Centre for Infection Research | May 2018

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#### **EDITORIAL**

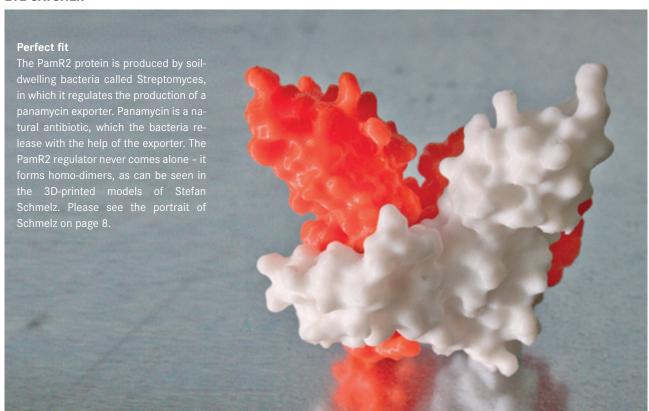


#### Dear readers,

many of us consider bacteria to be harmful pathogens - and nothing else. But, in fact, microbes do not deserve their bad image, since most species are not harmful to humans at all - quite the contrary: We now know that many species are beneficial. This changes our view of bacteria radically. No longer is our relationship to bacteria dominated by having to fight against them - as was the case in the times of the renowned microbiologist, Robert Koch. But a small number of bacterial species still manage to make us ill - e.g. Helicobacter pylori, featured on the title page: This pathogen can colonise the stomach by neutralising the gastric acid in its immediate vicinity. Read our title story to learn about the tricks used by other bacteria. To study such tricks of pathogens is one of the main topics of the HZI and - like research on the immune system and new active substances - was recently evaluated as outstanding within the programme-oriented funding of the Helmholtz Association. I hope you will enjoy reading the magazine and I look forward to your suggestions!

Andreas Fischer, Editor-in-chief

#### **EYE-CATCHER**



#### **IMPRINT**

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János Krüger; p. 9: G. Fuhrmann et al.: Engineering Extracellular Vesicles with the Tools of Enzyme Prodrug Therapy. Adv. Mater. 2018, 1706616, Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission; YUMAB GmbH; p. 10: HIPS, DZIF, János Krüger

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by Tatyana Dubich

In autumn 2017, Nigeria suspected an outbreak of human monkey pox. Immediately, epidemiologists adapted their online disease surveillance system and travelled to Nigeria to support the locals

he 2014 Ebola outbreak in West Africa revealed an urgent need of efficient disease surveillance systems, because it became evident that the outcome of an epidemic also depends on how fast disease control measures are implemented. HZI scientists from the Department of Epidemiology, led by Gérard Krause, teamed up with Nigerian scientists and developed a mobile-based application, which allows real-time data collection and application of disease control measures called Surveillance, Outbreak Response Management and Analysis System (SORMAS).

On 20 September 2017, the World Health Organization was notified of a suspected outbreak of human monkey pox in Nigeria. During that time, SORMAS could monitor nine infectious diseases occurring in Africa - monkey pox did not belong to them. "We had to develop a new disease model within two weeks - including tests and implementation," Daniel Tom-Aba from the HZI says. Since internet access is a critical issue due to limited networks during fieldwork, the scientists could also use SORMAS to collect data offline. A team from the HZI travelled to Nigeria to deploy SORMAS and train potential users. They visited cities like Abuja as well as several affected states. "Within a few weeks we had to train a vast number of specialists about 50 to 60 per state, which would not have been possible without support from the Nigerian field team," HZI researcher Kristin Schlinkmann says.

Current disease surveillance systems in Africa are paper-based. Case reports have to be transferred by personnel from one facility to another and the data is



 $\triangle$  SORMAS in action at the Nigeria Centre for Disease Control in the city of Abuja

manually typed into spread sheets. This method causes significant delay and is error-prone. "SORMAS allows medical specialists to enter the data directly and share it online between medical facilities, thus enabling to monitor the situation in real life, to follow up individual cases and to exchange the data between doctors, laboratories and epidemiology officers," HZI scientist Bernhard Silenou says. By that, the data evaluation is no longer retrospective and SORMAS makes bidirectional communication possible. "In the long-term, SORMAS will not only improve surveillance, but also reduce the daily workload of epidemiologists," Schlinkmann adds.

Despite of the fact that many people in Nigeria speak English, explaining technical details turned out to be challenging: Especially in the remote regions, where people mainly speak local languages like Hausa, the HZI scientists had to rely on translation by Nigerian

colleagues. Travelling to those regions was a challenge itself. Tom-Aba says: "We had to use local planes every other day and often experienced turbulences or engine smoke. I almost got into an accident twice."

SORMAS already covers 15 federal states with 36 million people, but the HZI scientists aim to further implement it and collect data on other infectious diseases, such as SCM meningitis. Silenou shares his vision: "The idea of SORMAS is so elegant that I hope to bring it one day to my home country, Cameroon, and, eventually, to all Africa."

#### **MORE ABOUT SORMAS:**

www.sormas.org



△ Enteropathogenic Escherichia coli (EPEC; red) bacteria inducing a human intestinal cell to produce pedestals

# CLEVERLY INFECTED – THE TRICKS OF BACTERIA by Andreas Fischer

To most people, bacteria are pathogens that cause complicated infections, although the majority of bacteria are harmless. In fact, many of them are quite useful, especially in the process of digestion. In the times of Robert Koch, they were seen as being equal to cholera, plague and tuberculosis. But hazardous pathogens are the exception rather than the rule and they use clever tricks to seize human cells

volution has provided the human body with a sophisticated immune system that recognises invaders immediately, eliminates them and recognises them again later on. This is to protect the body from infections – at least in theory. Usually, this works fairly well, but pathogenic bacteria often manage to find a loophole. The ability to proliferate rapidly is their major strength. Under optimal conditions, some species

produce a new generation every 15 minutes and each of the new generations is adapted to the host a little better than the previous one. The caries pathogen, *Streptococcus mutans*, has taken this to the extreme in that it kills other bacteria in the tooth pocket to be able to take up their genetic material in order to obtain new strategies for adaptation. By this means, bacteria have developed a surprising repertoire of tricks over

millions of years that allow them to be one step ahead of the human immune system.

Salmonellae, which usually cause diarrhoea in humans, are one prominent example. They often enter the body via food, like eggs, meat or soft ice cream, and usually end up in the intestines. This is where they stick to the epithelial cells and produce tiny molecular syringes. They use this so-called type 3 secretion

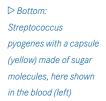
system to inject various substances into the intestinal cells and to initiate a surprising mechanism: Using signalling substances, they cause the intestinal cells to bulge out membranes and encapsulate the bacteria. The manipulated cells finally take in the Salmonellae, i.e. the host is basically triggered to ask the enemy in. The Salmonella bacteria can then proliferate with impunity within the intestinal cells. If they are subjected to stress by an antibiotic, Salmonellae can reduce their cell division and enter into a kind of resting state. Since many antibiotics kill only actively dividing bacteria, this strategy allows the Salmonellae to survive the attack as sleeper cells or persisters as they are called by experts.

Similar tricks have been detected in pathogenic strains of the intestinal bacterium Escherichia coli: "They induce their host cells to produce pedestals on the surface," says Manfred Rohde, who directs the Central Microscopy Unit at the Helmholtz Centre for Infection Research (HZI). "The misled cell then uses these structures to contact the bacteria - this is the first step of infection."

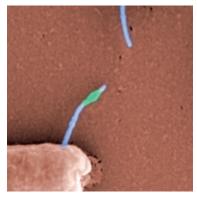
In order to get comfortable in the intestines, E. coli possesses small pumps in its membranes that transport toxic substances, such as the bile salts of the intestine, out of the bacterial cell. Since the efflux pumps can also remove antibiotics, some infections by pathogenic E. coli strains are difficult to treat. And they also are capable of surviving as so-called persisters.

Bacteria from the Yersinia genus are also well-armed pathogens aiming for the human intestines. They use RNA molecules, i.e. copies of the genetic information, to measure the ambient temperature and to find out whether they are outside or inside the host. "At 37 °C, the RNA thermometers unfold and make their information accessible," says Petra Dersch, who is the head of the "Molecular Infection Biology" department at the HZI. "This tells the Yersinia cells that they are inside the host and, if they meet defence cells, they multiply their virulence plasmids. These special DNA molecules bear the genetic information that makes the bacteria pathogenic." Yersinia uses this to switch into an attack mode and then injects toxic substances into the

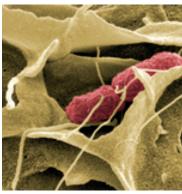
▶ Top: Salmonella bacteria use syringelike secretion systems (left) to inject toxins and signalling substances, for example into intestinal cells and to make them evaginate membranes (right).

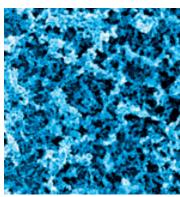


mutans biofilm (right)









intestinal cells. In an effort to survive their host cells, Yersiniae dissolve their colonies. They then hide, for example, in the appendix as individual cells and shutdown the production of a toxin called CNF<sub>v</sub>. This makes them invisible to the immune system.

The scarlet fever pathogen Streptococcus pyogenes, which often elicits inflammations of the throat and skin as well, has a direct effect on the human immune response: Infected host cells release a messenger substance called interleukin-8 and use it to attract defence cells to fight the bacteria. But streptococci possess the SpyCEP enzyme, which cleaves interleukin-8 and silences the call for help of their host cells. This is not the only protective mechanism used by streptococci: "Like the hospital pathogen Staphylococcus aureus, streptococci can encapsulate themselves in a thick shell of sugar molecules and prevent defence cells from disintegrating them," says Manfred Rohde.

Any infection, in which the pathogens agglomerate into a biofilm, is particularly difficult to subject to treatment. To this end, the pathogens cross-link sugar molecules outside the cells to produce a matrix, in which they then form a dense colony. This protects the bacteria from attacks of the immune system and allows them to withstand the effect of antibiotics for long periods of time.

Like streptococci, the hospital pathogen Pseudomonas aeruginosa is feared mainly because of this property. It can infect all organs of the body even implants - and can cause recurrent pneumonia, sepsis or chronic wound infections. In addition, Pseudomonas bacteria possess efflux pumps that allow them to pump antibiotics out of the bacterial cells. These mechanisms have led to many types of antibiotic resistance. For this reason, HZI scientists are searching for alternative agents that weaken bacteria without killing them, giving them no reason for the development of resistance. This anti-virulence strategy is aimed, for example, at signalling pathways or molecules, which the bacteria use to induce the production of a biofilm. Other approaches aim to inhibit molecular syringes, colonisation factors or the flagella that is used for motion by some bacterial species. "This type of agent would weaken the pathogens sufficiently such that the immune system - maybe in combination with a low-dose antibiotic - can eliminate them," Petra Dersch says.



 $\triangle$  Dieter Jahn is the speaker of the Braunschweig Integrated Centre of Systems Biology (BRICS)

# "WE NEED TO DEFINE TOPICS, IN WHICH WE COMPLEMENT EACH OTHER PERFECTLY" by Ida Retter

"Infections and Therapeutics" is one of four research foci of the Technische Universität Braunschweig. This positions TU Braunschweig as a close partner of the HZI. Their cooperation was the basis of the systems biology centre BRICS that was established jointly in 2011. In an *InFact* interview, BRICS speaker Dieter Jahn, who is a professor of microbiology, explains how the TU Braunschweig and the HZI may benefit from each other in the long term

cepted an appointment at the Institute for Microbiology in 2000, the HZI was still named German Research Centre for Biotechnology (Gesellschaft für Biotechnologische Forschung - GBF). What was the relationship between the TU Braunschweig and the GBF like at the time? When I moved into the Biozentrum, on each floor there were signs reading "GBF" pointing to research groups that had been working there originally. It was the original vision of the Biozentrum to have TU and GBF research groups work collaboratively on important topics in biotechnology. But this was basically obsolete by the year 2000 and the last GBF groups moved out soon thereafter. The relationship of some colleagues from the TU to the GBF was reduced to some kind of friendly ignoring.

rofessor Jahn, when you ac-

#### Rudi Balling arrived in Braunschweig almost at the same time as you to serve as the scientific director of the GBF and there was a major change in topics when the GBF became the HZI. How did the TU Braunschweig respond to these changes?

We were undergoing some major changes ourselves at the time. The Bologna process, i.e. the switch to the bachelor and master system, forced us to revamp all our teaching. And the universities were exposed to increasing competitive pressure. We needed to establish a clear profile in order to generate national and international recognition. Therefore, we initiated a profile development process, in which the new HZI focus was taken into consideration appropriately.

#### Why has the TU moved so much towards the focus of the HZI?

Compared to other universities, our biology department is relatively small. If we want to be recognised internationally, we need to do this in a partnership with the HZI. Not to forget the DSMZ, another important partner of our institution. We need to define joint topics, in which we can complement each other perfectly. We see these topics mainly in the basic research on infections and therapeutics, since there can be no translation of research into applications without basic research.

#### Systems biology is another common topic of the TU and HZI. How exactly does the collaboration within BRICS work?

The systems biology centre BRICS is the "concrete" legacy of Rudi Balling at the HZI and the TU. It is the institutional basis of our common research and ensures our continuing collaboration. This can work only based on reciprocity: HZI research groups work in the BRICS building on the TU campus and TU research groups work on the Science Campus Braunschweig-Süd. But BRICS is more than just the building. It now encompasses 24 research groups of the TU, HZI, DSMZ and TWINCORE in Hannover. BRICS is therefore a platform for coordinated research on joint projects such as the CDiff consortium on the Clostridium difficile pathogen or the cooperation on the metabolism of the immune system. Further, it is a technology platform that covers the OMICS technologies required by all partners in a complementary and integrated manner.

#### The co-appointment of senior scientists of the HZI is another link between the HZI and the TU. How do you see this?

The co-appointments allow us to integrate the HZI colleagues into the teaching and research structures of the TU. This comes with certain rights, such as the right to bear the title of Professor and to hold doctoral examinations. In return, they have to teach a small number of courses at the TU. It is obviously attractive to our students to be able to incorporate the expertise of the HZI into their studies. And the HZI gets well trained students in return. Again, the principle of reciprocity. It is very important to us that this allows us to ensure a very high level of quality in the teaching of our institutions.

#### In addition, the TU is involved in the Science Campus Braunschweig-Süd. What is the significance of this campus beyond the fact that it houses the TU research groups?

The Science Campus provides the integrated infrastructure required for our common research and development. It brings people and topics together that belong together. One typical example is our joint proteomics unit. In addition to



the HZI and the DSMZ, the Fraunhofer ITEM located there is another important partner of the TU. I think we need more companies that translate our findings into products. There is still sufficient space available.

#### And finally a look to the future: What do you think is important for the success of this partnership to continue?

Any sustainable partnership needs to be based on a deliberate culture of giving and taking. In order to produce welltrained infection biologists and natural product researchers, the TU needs the deliberate and substantial contribution of the co-appointees of the HZI to the teaching of the TU. Reliability is of the essence here, especially when times are difficult. In research, it is important to fully explore the extensive overall potential of the BRICS, the Pharmaverfahrenstechnikzentrum PVZ (Pharmaceutical Process Engineering Centre) and the HZI including HIPS and HIRI - there is a new level of collaboration emerging.

#### COMPLETE INTERVIEW:

www.helmholtz-hzi.de/en/interview

## "JUST BE CREATIVE"

by Christine Bentz

Stefan Schmelz prints his world the way he likes it: The structural biologist sees no problems, only challenges

t outside temperatures of -10 °C, Stefan Schmelz, wearing a shortsleeved shirt, seems to have discovered an alternative energy source for himself. The postdoctoral fellow in the "Structure and Function of Proteins" department at the HZI would seem to need one to master all the tasks in his workday. He calls it a challenge - rather than a problem - to be working to capacity both at work and at home. The father of three small children knows exactly how important it is to be organised and to address tasks with an aim. "Time management is everything," he says. The large range of tasks entrusted to him in the department is impressive: He is responsible for the entire computer infrastructure and the major equipment as well as the X-ray room, the imagers and the crystallography units.

Having to change his agenda is his everyday routine - and he is happy with it: He likes his work at the HZI and does not want the routine of an assembly line job.

He discovered structural biology rather by coincidence. Even early on in his studies of physical biochemistry in Darmstadt, he had a strong desire to spend some time abroad - a dream he made come true when he worked as a doctoral student with lames. Naismith at the University of St Andrews in Scotland. The research group focused on structural biology and Schmelz kept to this focus later on. A guest lecture of a German scientist named Dirk Heinz was his first contact to the HZI, followed by an appointment after his unsolicited application in 2010 - first with Dirk Heinz for three years, then with Andrea Scrima and presently with Wulf Blankenfeldt.

"I never regretted embarking on this path," Schmelz says.

Stefan Schmelz has published 15 protein structures since 2010 - and there are some more in his pipeline. And he is well connected: Working with Rolf Hartmann of the HIPS, he studies proteins that contribute to the production of biofilms by Pseudomonas aeruginosa, whereas his work with Melanie Brinkmann of the HZI solved the structure of a tegumental protein of herpes viruses. A protease that destroys lung tissue in Legionnaires' disease is the research topic of a collaboration with the TU Braunschweig, whereas he and Andriy Luzhetskyy of the HIPS develop biosensors for effective screening of new antibiotics.

One of his private passions is also very future-oriented: 3D printers and their virtually limitless opportunities. Schmelz designed the second of his two printers himself and implemented it with printed components, then optimised it. He uses a range of different materials, from biologically degradable plastics to coppercontaining filament, which looks like shiny metal when polished. He can make functional or decorative things such as an inside-illuminated model of the moon, a reproduction of a sculpture from the Easter Islands - or an InFact sign.

He utilises his private technology for the purposes of the HZI as well: Structurally complex proteins with matching binding partners can be well represented as a computer model, "but to be able to hold them in your hand as three-dimensional components and to assemble them easily just opens up very different opportunities," he says. His technology is also useful for immediate help at work: When he found an old fraction collector whose orifices were too large for the sample vessels, he simply constructed a new attachment with smaller holes, and the find from the basement became a useful item again. It is easier to just purchase new equipment, Schmelz says. But often a small repair might save you money - "you just need to be creative."



#### COMPLETE PORTRAIT:

www.helmholtz-hzi.de/en/portrait

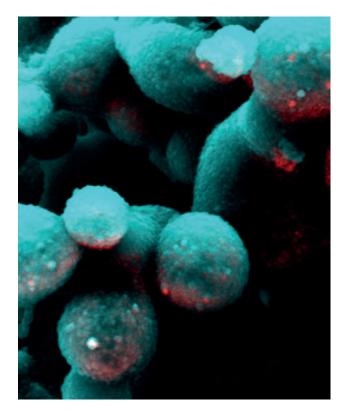
### USING A NANOGEL AS A DRUG TAXI

by Andreas Fischer

hen a patient swallows a tablet, the drug in the tablet gets into the blood and is distributed throughout the body even if the substance is needed in a small place only. For this reason, researchers throughout the world are looking for methods that allow them to deliver drugs specifically to the site of a disease in order to be able to reduce the side effects. Gregor Fuhrmann of the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) also pursues this kind of approach: He uses tiny membrane vesicles, which are naturally released by cells, to transport drugs. Body cells and bacteria alike utilise these so-called extracellular vesicles for communication with each other: They exchange various signalling molecules by means of these vesicles - and Fuhrmann aims to extend this to drugs.

He recently combined his vesicles with another drug transport approach: He embedded them in hydrogels. These aqueous, gel-like structures are also being tested as medical transporters which, loaded with a drug, are transported to the desired site in the body to release their freight. "One current drawback of these gels is that they exert their effect immediately and for a short period of time only. The vesicles can be utilised for a longer period of time, but it has not been possible to keep them permanently in one place - as they become diluted in the body," Fuhrmann says. "We wanted to combine the two approaches in order to eliminate their shortcomings."

And it worked: In cooperation with a research team from the London Imperial College, Fuhrmann isolated vesicles from mesenchymal stem cells, loaded an enzyme -  $\beta$ -glucuronidase - into them and embedded them in a hydrogel of the size of a 1-cent coin. Then he tested these gels in a cell model for inflammatory reactions: Immune cells in culture activated macrophages - received first a gel coin and then an anti-inflammatory agent that was coupled to a sugar. The enzyme contained in the vesicles cleaved



of a gel loaded with extracellular vesicles. The large beads are gel structures, whereas the embedded vesicles show up as small red

off the sugar and released the drug. For comparison, Fuhrmann also tested gels loaded with synthetically produced transport vesicles - so-called liposomes - as well as gels loaded with free enzyme.

"We used certain markers to show that the inflammatory reaction was reduced in these approaches," Gregor Fuhrmann says. "It was even possible to use the gels with encapsulated enzymes repeatedly since their activity persisted significantly longer than that of the gels with free enzyme." Stem cell vesicles possess a crucial advantage as compared to liposomes: They exert an antiinflammatory effect even in the absence of enzyme, as has been shown in control experiments. "Hydrogels with these vesicles can therefore be developed as drugs against skin infections or inflamed wounds," Fuhrmann says.

#### **IN-DEPTH ARTICLE:**

www.helmholtz-hzi.de/en/stories



#### New on Science Campus

YUMAB, a German biotechnology company that started out five years ago as a spin-off from the Technische Universität Braunschweig, has moved its headquarter to the Science Campus Braunschweig-Süd, where it is located in the building A of the HZI. The team of more than 20 employees around the company founders Stefan Dübel, André Frenzel, Michael Hust and Thomas Schirrmann provides i. a. rapid, large-scale discovery and optimisation of fully human monoclonal antibodies, custom libraries, antibody engineering and custom-made antibodies to difficult targets. (afi)

### **NEWS**

#### AWARD WINNING WORK



Anna Hirsch has received a Starting Grant from the European Research Council (ERC) to establish innovative methods for identifying target structures for new drugs. At the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Hirsch leads the department "Drug Design and Optimization" and investigates lead structures for the development of new antibiotics and anti-infectives with her team. The ERC funding covers 1.5 million euros over a period of five years.



Alexander Titz was awarded the Innovationspreis in Medizinisch/Pharmazeutischer Chemie der Gesellschaft Deutscher Chemiker (Innovation Prize in Medical/Pharmaceutical Chemistry of the German Chemical Society, GDCh). The prize is worth 5000 euros and will be shared this year. Titz heads the Junior Research Group "Chemical Biology of Carbohydrates" at the HIPS. Last year, the Innovation Prize of the GDCh went to his HIPS colleague Anna Hirsch. (afi)

#### **NEW BOOKS**

Joachim Wink, head of the HZI research group "Microbial Strain Collection", has published the book "Biology and Biotechnology Actinobacteria", together with two Iranian colleagues. The book has appeared in 2017 in the Springer printing house. Members of the class Actinobacteria are well known for their variety in the secondary metabolism and as producers of antibiotics. The book treats the cellular structure, the life cycle, genetics, ecology and physiology of Actinobacteria. Other chapters contain the regulation of secondary metabolism und the role of Actinobacteria in biotechnology, especially as producers of antibiotics. In addition, the book contains one chapter on the practical aspects of working with these bacteria. (jwi)

Thomas Böldicke, senior scientist at the HZI department "Structure and Function of Proteins", has edited two books: "Protein Targeting Compounds", published by Springer in 2016, and "Antibody Engineering", published by INTECH in 2018. Both books describe antibodies for therapy, diagnosis and research. The first one focusses on examples of recombinant inhibitory antibodies and current alternative knockdown techniques. The second book describes in detail the in-vitro selection and modification of human antibodies. The power and tasks of antibody engineering are to generate and modify human antibodies against virtually every protein and desired epitope or conformation. (tbo)

#### **FANCY PLAYING IN A BAND?**



Did you know the HZI has its own music band? You may have seen a gig of the HZI band at a centre party (summer fête, Christmas or ID party). The band connects staff from all areas of the centre coming together to play their favourite music as well as selfcomposed pieces and to enjoy jamming. Band members have been fluctuating since the project started and it thereby benefitted from lots of different ideas and performances. Currently, the band is left with only

three musicians - Axel (bass), Steffi (vocals) and Ulfert (guitar) - and is actively searching for new members. Every instrument and voice will be welcome; meeting times are very flexible. The band will have a brandnew room for rehearsals very soon (building Y, HZI campus), and meetings typically happen once per week for an hour (after working hours). Are you interested? Get in touch with Axel (axel.plaehn@helmholtz-hzi.de). (ura)

#### **SCHEDULE**

April - July: RNA Seminar with focus on RNA-centric science and technologies, the structure and function of RNA in eukaryotic, prokaryotic and viral systems; HIRI, Room 01.002-004; upcoming dates: 8.5., 22.5., 19.6., 3.7. 17 May: Inhoffen Lecture with award of the Inhoffen Medal to Rolf Müller (HIPS) and presentation of the PhD Awards by the Friends of the HZI; 3 pm at "Aula" of the TU Braunschweig, Haus der Wissenschaft 30 May: Visitor's Day for registered groups; HZI

**16 June:** TU Night with HZI booth;

TU Braunschweig

23 August: HZI Summer Fête; HZI

#### **NEW PERSONNEL**

HZI, Braunschweig: Pietro Mascheroni, SIMM

CRC, Hannover: Svenja Rothe, EPID HIPS, Saarbrücken: Dennis-Thomas Jener, DDOP | Varsha Ravindra Jumde, DDOP | Besnik Quallaku, MINS HIRI, Würzburg: Tatjana Achmedov, RSYN | Lars Barquist, IIIB | Neva Caliskan, REMI | Verena Hasselbacher, RABI | Laura Jenniches, IIIB | Tatyana Kisseleva, REMI | Sarah Reichardt, HOPI

HZI, Braunschweig: Andreas Holz, NIND | Martina Klünemann, CBIO | Christin Walter, EPID

TWINCORE, Hannover: Moritz

Winterhoff, BIOM