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HELMHOLTZ CENTRE FOR INFECTION RESEARCH

THE ZOO IN OUR INTESTINE

THE ZOO IN OUR INTESTINE

by Till Strowig and Niklas Hielscher

Over the past few years, public awareness of the microbial communities in our gut has grown significantly – partially thanks to Giulia Enders' book "Gut: The Inside Story Of Our Body's Most Under-Rated Organ". Scientific studies on antibiotics and the microbiota have also attracted attention: The use of these drugs is hypothesised to disrupt the sensitive inhabitants of our intestines and may cause serious damage. So how can we protect our gut flora?

The human intestine is home to around 100 trillion bacteria, which is about ten times the number of cells in our entire body. This internal menagerie, known as the microbiota, weighs at least one kilogram and contains over 500 different species of bacteria. What is more, every individual's microbiota is different – we all have our own unique zoos.

The microbiota helps its host in a number of ways, for example when digesting certain types of food, such as fibres, that the host cannot digest itself. Furthermore, the bacteria in the microbiota produce B vitamins. Although they generate these for their own use, the host is able to absorb the vitamins as well.

The microbiota also interacts with the immune system and triggers immune reactions in the intestine, as well as in the rest of the body, all the way up to the brain. However, it is very sensitive to external influences, such as certain diet ingredients and medicines. Antibiotics in particular, though they are essential for fighting life-threatening bacterial infections, affect the "good" bacteria and can kill up to a third of the inhabitants of the gut. This damage is normally short-lived and the microbiota tends to recover in two to four weeks. However, this recovery period can last longer for ill or elderly people and children. The latest studies show that multiple

▽ *Trillions of bacteria from more than 500 different species colonise the gut mucosa*

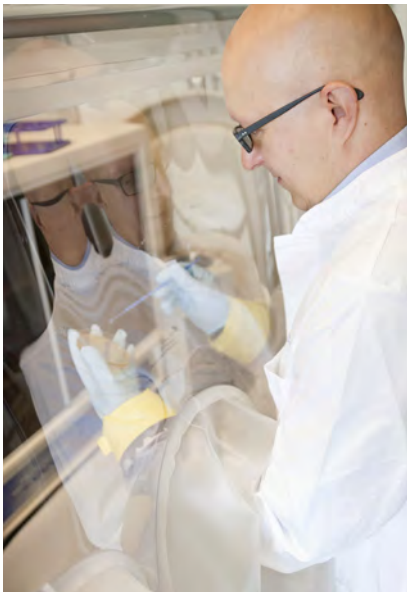
administration of antibiotics in children under the age of three can lead to long-term impairment of the microbiota – this is quite the catch 22, as doctors are more prone to rely on antibiotics during this stage of life.

In hospitals in particular, the frequent use of antibiotics goes hand-in-hand with an increased risk of acquiring pathogens. If the microbiota has been damaged, pathogens like *Clostridium difficile, Staphylococcus aureus, Klebsiella pneumoniae* or enteropathogenic *Escherichia coli* exploit this to establish themselves in the gut.

These side effects, some of which are very severe, show that antibiotics use is not without harm and alternatives would be desirable – for some areas of application at the very least. An increasing number of studies in the USA and the Netherlands are showing that stool transplants can have a similar effect to antibiotics for certain gastrointestinal bacterial infections. Populating the intestine with "good" bacteria leads to the suppression of pathogens and the prevention of new infections. However, this model is also not without risk as transferring a multitude of known and unknown bacteria can have long-term consequences for the recipient.

A decisive factor for new approaches to therapy is understanding the interaction between the microbiota, immune system and pathogens. However, it is not actually that easy to accurately study the microbiota: Sequencing, for example, provides a huge quantity of data on all bacteria, known as metagenomics. Information on the individual types of bacteria then has to be filtered out. While there may be many methods of doing so, it is often unclear which one is best for the matter at hand.

In order to solve these problems, an international team of scientists – including Alice McHardy and her HZI department "Computational Biology of Infection Research" at the BRICS in a leading role – founded the initiative "Critical Assessment of Metagenome Interpretation (CAMI)". In the first CAMI-organised benchmarking competition, scientists are able to test and evaluate their computational biology methods on a wide range of metagenomic data sets. "CAMI's aim is to test and analyse methods for metagenomic data under standardised conditions using biologically relevant metrics and to develop standards regarding which method should be used for which scientific problem," says Alice McHardy. "We invite all microbiota researchers working on the generation or evaluation of Omics data to get involved in CAMI and help us to achieve this goal."



△ *Dr Till Strowig and his HZI Junior Research Group investigate microbial communities and their influence on the immune system*

A healthy diet forms the basis for a healthy microbiota. Prebiotics – substances like certain fibres that encourage beneficial bacteria – can help with this. Some companies concentrate on preparations using live bacteria that stabilise the microbiota and have a positive impact on the host's well-being – so-called probiotics. Nevertheless, probiotics remain a controversial issue as many of them have no clinically proven added value.

Finally, scientific circles are increasingly critical of the fact that so-called association studies often become the focus of public attention. These studies only show a link between certain parts of the microbiota and certain attributes in the host without verifying any causal relationship. Intensive research in labs and hospitals is therefore required in order to understand which diseases are actually linked to the microbiota and whether it can be used for diagnosis or even as a new form of therapy.

IN-DEPTH ARTICLE:

www.helmholtz-hzi.de/en/stories

Dear readers,

Most people have a negative perception of bacteria – as something that makes them ill. In fact, we could not survive without bacteria. Trillions of them live in our intestine, where they not only help us to digest our food but also support our defence against germs. The other effects that these tenants can have on our health and ways to make life easier for them in our intestine are currently in the focus of research – at the HZI of all places, as you can see from our headline story.

In our interview, Christopher Baum, President of Hannover Medical School, tells us about the hospital's new outlook and its new projects with the HZI and their shared subsidiaries.

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

Andreas Fischer

Editor-in-chief

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△ *Since April 2013, Christopher Baum has been President of Hannover Medical School*

"WE HAVE TO COLLABORATE MORE CLOSELY ON THE PROGRAMMES FOR YOUNG SCIENTISTS"

by Jo Schilling

The Hannover Medical School (MHH) has seen a great deal of change over the past few years: The school has recently undergone a phase of economic consolidation which also included a change of leadership. Prof Christopher Baum took over the role of President from Prof Dieter Bitter-Suermann four years ago – and inherited a whole host of collaboration projects with the HZI in the process. Christopher Baum spoke to *InFact* about the developments at the MHH and his plans for expanding the partnership with the HZI

The economic concerns of the MHH have attracted a great deal of attention over the past few years. This phase was very much defined by figures and the economic recovery of the MHH, while the scientific changes went on in the background. What kind of phoenix is rising from the ashes now, Professor Baum?
We managed to overcome the economic crisis, we have been economically stable for the last two years and we can now focus on substance once again. We formulated a development plan in 2014. Our core focus is to enhance the integration of research, teaching and healthcare. In parallel, we developed a structural concept in which we defined three priorities: the development of the school, outstanding teaching and excellent research. And this structural concept is now informing the development of personnel at the MHH.

How have you pursued this concept with regard to research over this period?
During the process, we focused very much on the importance of nurturing young scientists. We have established new programmes, such as the physician scientist programme, and have collaborated closely with the HZI on these matters – and in other areas as well.

And in terms of substance?
In terms of substance, we have defined our specific areas of research: infection and immunity. Transplantation and regeneration. Biomedical technology and implants. And we have identified linking elements between these three pillars – always at the interface between healthcare and its consequences for research.

Is there a weighting between these three areas – that is to say, what is the role of infection research in the context of the MHH?
Infections play a key role in daily clinical practice and are one of our domains – in close conjunction with TWINCORE and the HZI. And in daily clinical practice – which is always our mainspring, because our research is ultimately patient-focused – we see infections as a major problem. From neonatology and premature newborns to complications in critically ill patients with different underlying diseases from cancer to terminal organ failure, or transplants with immunosuppression. Infections are always key to the prognosis that the patients have. We need high levels of clinical and scientific expertise in order to manage this situation.

And the HZI contributes to this scientific expertise?
Absolutely. This is a long-standing alliance and Dirk Heinz and I are keeping it going. If you look at the whole of Germany, we probably have the highest density of infectiology experts here in the Hannover/Braunschweig region thanks to the MHH/HZI partnership. The joint institutions of TWINCORE and CIIM play a key role here, and as they expand we will be able to achieve the required level of international visibility. In all areas of the MHH, we need to do more to appreciate the opportunities created by the interaction with the HZI. We have already achieved a great deal through the work of TWINCORE. A key mechanism in this regard is the physician scientist programme.

Are you planning to establish more physician scientists at the Braunschweig campus?
Most of them are at TWINCORE, and we expect that they will be primarily based here on the campus for CIIM projects too. It is still difficult to commute on a daily basis. If we expect the physician scientists not to lose touch with clinical practice, it is important that the research laboratory is as close as possible.

Do you think the collaboration between MHH and HZI will be focused on the TWINCORE and CIIM sites in the future, or do you also foresee joint research being undertaken at the HZI campus – that is to say, what role will the HZI as a campus play in the future of the MHH?
There is still a great deal of potential in direct interactions with the main campus in Braunschweig, but the new subsidiaries – as I call them – offer potential as well. We can still improve significantly in the field of active ingredient research, and we also need to rigorously develop our collaboration with the HIRI, as the field of RNA-based mechanisms and therapies features heavily in our work at the MHH.

If you take a step back and consider the partnership – what difficulties do you see?
The 70-kilometre distance remains the greatest challenge.

And do you have any requests for the HZI?
I would like us to collaborate more closely on the programmes for young scientists, and work as a single team to nurture new talent in our field. For me personally, establishing the TRAIN Academy as an interdisciplinary, interprofessional platform for translational sciences was very important. And I think we should also look at how we can improve our collaboration with regard to students, because we need to start attracting the finest talents here as early as possible.

NEW INSTITUTE IN WÜRZBURG PICKS UP SPEED

The Helmholtz Institute for RNA-based Infection Research (HIRI) was officially founded with a ceremony in Würzburg Residenz palace on 24 May 2017. The first staff have since taken up their posts

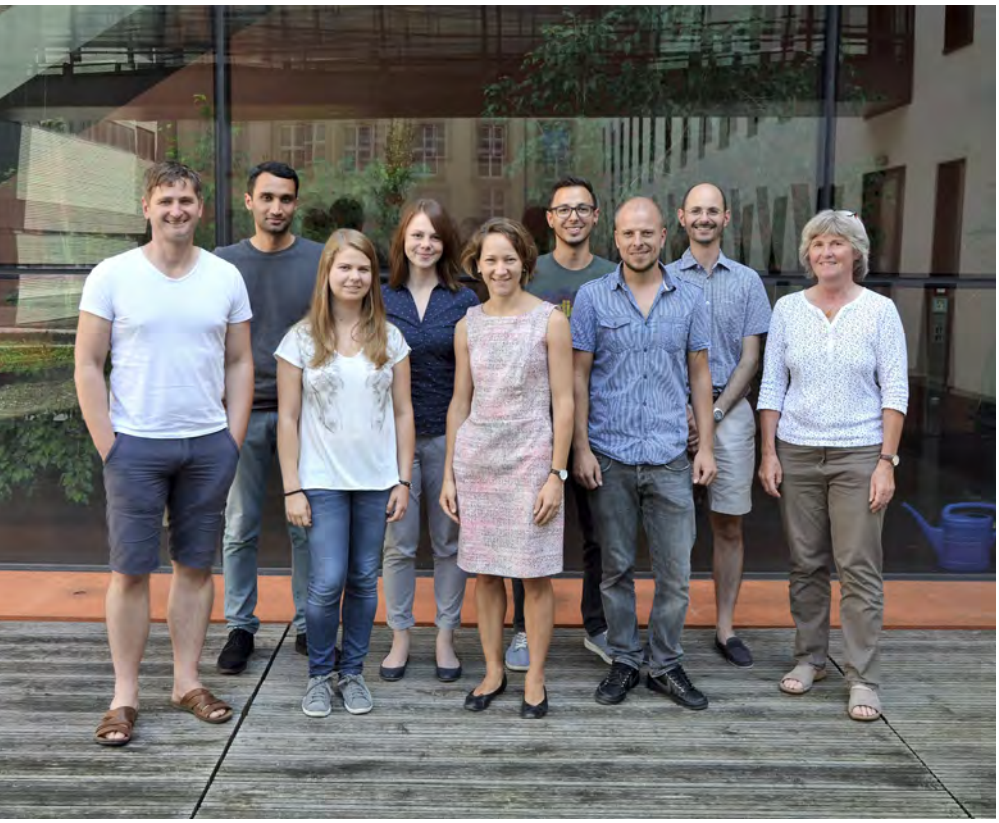
Ribonucleic acid – RNA for short – is a molecule with a wide array of functions: As a copy of the genetic information stored in DNA, it is typically used to create the proteins in an organism's cell. However, recent research work shows that RNA molecules are involved in an array of other processes. This means that there are RNAs that do not transfer genetic information and are not directly involved in the production of proteins in the cell either. Instead, many of these RNAs, known as non-coding RNAs, regulate genes.

"The significance of RNA molecules in infection processes has been underestimated until recently," says Professor Jörg Vogel, Director of the HIRI. "We now know that RNAs interact with many molecules in the host cell and the pathogens. Here at the HIRI, our aim is to tap into these mechanisms."

The HIRI is a joint institute set up by the HZI and Julius-Maximilians-Universität Würzburg (JMU). Jörg Vogel has been Chair of Molecular Infection Biology at JMU for many years. In June, he began working as the head of his own research department at HIRI known as "RNA Biology of Bacterial Infections". One of his goals is to research bacterial RNA molecules and better harness possible agents against infections. One employee already working on this subject in Vogel's department is PhD student Annika Schulz, who studied chemistry at Heriot-Watt University in Edinburgh, Scotland. She would like to change specific parts of small RNA molecules so that they can curb infection processes. Over the long term, they could be used as antimicrobials but, to achieve this, Schulz first has to find suitable target structures and transportation paths to the source of infection.

The new working group "Single Cell Analysis" is being managed by Dr Antoine-Emmanuel Saliba, who studied biotechnology and biochemistry at the Institut National des Sciences Appliquées in Toulouse and completed his PhD at the Institut Curie in Paris. His most recent post was as a scientist at the University of Strasbourg. With his HIRI group, he is keen to study infection processes in individual cells and, as a result, decode them on a molecular level. Dr Saliba is receiving support from PhD student, Ehsan Vafardanejad, who is analysing the genome data in individual cells using computer-based mathematical methods. Vafardanejad studied microbial biotechnology at the University of Teheran.

The remaining HIRI team consists of admin manager Alice Hohn, scientific coordinator Dr Nina Littwin, assistant to the director Hilde Merkert, secretary Christoph Kosche, and in-house technician Sebastian Stockmann. The recruitment process for the continued expansion of the HIRI is currently underway. Based on current information, further research groups are set to expand the HIRI from January 2018, including the group "Synthetic RNA Biology" chaired by Dr Chase Beisel. (afi, asc, ehv, nli)



◁ *The new HIRI team (from left): Jörg Vogel, Ehsan Vafardanejad, Annika Schulz, Nina Littwin, Alice Hohn, Christoph Kosche, Sebastian Stockmann, Antoine-Emmanuel Saliba and Hilde Merkert*

THE TISSUE ARTIST

by Tatyana Dubich

Marina Pils knows how to prepare and visualise fine tissue structures. By creatively developing histological methods she helps scientists to investigate infectious diseases on tissue level

If we could take a look under our skin, what would we see? Cells, of course. If you ask Marina Pils, she will answer: "Tissues. A living body is more than just a pile of cells. Cells organise themselves into functional units and often fitness of the unit, rather than fitness of particular cells, is what separates health from disease." The veterinarian leads the "Mouse Pathology Platform" at the HZI and looks under the skin on a daily basis. Together with her team she develops histological methods to figure out the relationship between infectious diseases and changes in tissues. "Histology is a scientific study of tissue structure and, based on that, of disease development," she says.

Marina Pils studied veterinary medicine in Hannover and Lyon, France. Grown up on a small farm, her love for animals motivated her to become a veterinarian. Later, her passion for science made her continue her research career at the HZI. While working on her doctoral thesis she established histological stainings for her own project. Soon she started to help her color-blind colleague with the preparation and evaluation of samples. "Finally I ended up doing histological analyses for the whole department," Pils says.

After completing her PhD project she worked as a researcher at Hannover Medical School. In 2009 she returned to the HZI as deputy head of the animal facility and implemented the CAT system: This software registers every laboratory mouse and is used regularly by everyone working with animals at the HZI.

When her first child was born, Marina Pils had to work out the balance between child-care, house chores and staying scientifically up-to-date. "Although I enjoyed the time with my daughter it was important to stay in touch with my colleagues and to keep solving research problems," she says. Soon after returning from parental leave, she was offered a position as leader of the mouse pathology unit. In that position she now helps HZI researchers with establishing histological methods. "That's what I always wanted to do," she recalls.

Today Marina Pils and her husband have two children – and a horse: Twice a week Pils goes riding to get the fresh air she does not get in the lab. But the most challenging part of her work is not the lab air: It is to match scientific questions with technical possibilities. "It is a bit like in chess, you have to think a few steps ahead: which fixation technique will work with which staining and which evaluation strategy would fit best." Although methods might be described in literature, they often have to be adapted to a specific question. After the strategy is developed, application requires hours of scrupulous work for sample preparation and evaluation by microscopy.

Pils shares that the most rewarding part of her work is when after all the hours in front of a microscope the result helps to answer the initial question. "When a car stops working," she says, "one can easily fix it, because it was built by man and we know exactly how it works. When something breaks in the body it is not always clear how to fix it." As to Marina Pils, the ultimate goal of natural scientists is to figure out mechanisms of pathology and ways to treat it. And the only way it can be done, she says, is through carefully designed experimental work.

NEWS

AWARD-WINNING WORK

△ *Helma Wennemers. © ETH Zürich*

The 2017 Inhoffen Medal has been awarded to **Helma Wennemers**, Professor of Organic Chemistry at ETH Zurich. She and her research group are working on the chemical production of tiny molecules that could be used in new materials, for instance. Wennemers has been honoured for her outstanding research work in the field of synthetic chemistry. She will be presented with her award at the Inhoffen Lecture on 7 November.

△ *Tobias Bock (l.) und Islam El-Awaad. © privat*

This year's PhD Awards will also be presented during the Inhoffen Lecture: The winners are **Dr Tobias Bock** from the HZI and **Dr Islam El-Awaad** from Technische Universität Braunschweig. The Inhoffen Medal (€ 5000) and the PhD Awards (€1000 each) are awarded jointly by the Friends of the HZI and Technische Universität Braunschweig.

△ *Christine Goffinet. © privat*

Junior Professor Christine Goffinet from TWINCORE and her colleagues **Dr Shuting Xu** and **Dr Aurélie Ducroux** have received the 2017 German AIDS Award. The scientists received the award for a publication in the journal *Cell Host & Microbe*. The award comes with a prize money of €10,000 and is presented every two years by the German AIDS Society.

△ *Claus-Michael Lehr (l.) and Maike Windbergs. © Jörg Pütz; HIPS*

Professor Claus-Michael Lehr from HIPS has been selected as one of the top 100 most influential experts in drug development by the British trade journal "*the Medicine Maker*". The list is compiled on the basis of reader votes and an assessment by a jury. The goal of Lehr's research is to be able to transport drugs through the body's biological barriers to precisely where they are due to take effect. In conjunction with **Professor Maike Windbergs**, Lehr has also received the CRS T. Nagai Postdoctoral Research Achievement Award from the Controlled Release Society. The prize honours outstanding research work performed during a post-doctoral placement. Windbergs worked as a post-doc under Lehr's supervision, and both will receive a prize of $3000.

△ *Rolf Müller. © Hallbauer & Fioretti*

In May, Leopoldina National Academy of Sciences welcomed new members into Class II – Life Sciences. The new additions included **Professor Rolf Müller** from HIPS. Leopoldina was founded in 1652 and, as Germany's national academy, represents German academia on international committees. (afi)

SCHEDULE

14 September:
A Day on Career Opportunities; Forum of the HZI
15-27 September:
Anniversary celebrations for "10 Years of the City of Science"; Burgplatz in Braunschweig
6 October:
Opening of the "Science Campus Braunschweig-Süd" with guests from politics and business
7 November:
Inhoffen Lecture; from 3 p.m. in the HZI Forum

NEW PERSONNEL

CRC, Hannover: Ulrike Lawrenz, EPID
HIPS, Saarbrücken: Ahmed Saad Abdelsamie Ahmed, DDOP | Mostafa Hamed, DDOP | Marcus Miethke, MINS | Julia Mohr, DDOP
HIRI, Würzburg: Alice Hohn, RABI | Christoph Kosche, RABI | Nina-Vanessa Littwin, RABI | Antoine-Emmanuel Saliba, SIGA | Sebastian Stockmann, RABI
HZI, Braunschweig: Kai Antweiler, EPID | Nanaji Arisetti, MCH | Kevin Becker, MWIS | Franziska Faber, MIBI | Lamiaa Kabary Hassan, ESME | Jörn Hoßmann, MINP | Sarah Kirstein, TEE | Mustafa Krause-Turkic, TB | Christian Leitner, CBIO | Jessada Mahatthananchai, MCH | Vanessa Melhorn, EPID | Christian Schinkowski, NBSC | Nathalie Scholz, DMC | Corinna Schünke, GFA | Erik Stempel, MCH
TWINCORE, Hannover: Carina Elsner, AIVE

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