InFact

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HELMHOLTZ CENTRE FOR INFECTION RESEARCH

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Research
knows no borders

RESEARCH KNOWS NO BORDERS

by Kathrin I. Mohr, Joachim Wink and Marc Stadler

In the search for novel medications – for example against multi-resistant pathogens – scientists look for new agents. They have to collect samples from all over the world for this purpose

A typical meal at a work meeting in Indonesia consists of rice snacks rolled up in banana leaves, whereby the leaves usually are not eaten. "But if you do eat them you can be sure of the approving glances of the locals," Joachim Wink explains after learning this lesson at the start of an international research project. Wink is the head of the "Microbial Strain Collection" at the Helmholtz Centre for Infection Research (HZI), which is closely associated with the "Microbial Drugs" department of Marc Stadler. The focus of the two scientists and their teams is on the discovery of new natural products from microorganisms and fungi. The latter organisms and the soil-dwelling myxo- and actinobacteria release a plethora of chemical substances, which they use to keep away food competitors, predators or parasites. Since these substances are directed against other bacteria or viruses, they are suitable as new candidate agents.

"To be able to get our hands on new microorganisms, we need environmental samples from all over the world and we collaborate with research institutes and universities in Indonesia, Thailand, India, Algeria, Kenya, Jordan and Iran," says Marc Stadler. Stadler's and Wink's research

▽ *Statue of Kumbhakarnas, a figure of the Indian mythology, in the botanical garden in Bali*

groups are staffed internationally as well: Scientists from all over the world come to the HZI for internships, research stays or doctoral work. In turn, researchers of the HZI travel to the partner countries for guest visits, laboratory courses, meetings or collection campaigns. “All of our work is designed on an international level, the laboratory language is English. Only this allows the expertise to be exchanged between the partner laboratories.“

One current project, abbreviated GINAICO, which stands for “German Indonesian Anti-Infectives Cooperation“, is funded by the German Ministry for Education and Research (BMBF) in the scope of a framework programme with the Indonesian government. The partners

△ *Joachim Wink giving a laboratory course*

include not only the HZI, but also the TWINCORE, the universities of Oldenburg and Bremen in Germany as well as the LIPI Institutes (Indonesian Institute of Sciences) for chemistry, biotechnology and oceanography. Indonesia is one of the countries that are richest in species and features an impressive diversity of habitats. “The high biodiversity is accompanied by a high potential for the discovery of new species,“ says Joachim Wink. In the scope of GINAICO, the scientists aim to isolate previously unknown groups of myxo- and actinobacteria as these have proven to be sure sources of novel natural products in the past.

The first collection campaign took place in April 2016: Joachim Wink and his colleague Kathrin Mohr joined their Indonesian partners to collect environmental samples on Bali and in the Bandung and Bogor regions from various habitats such as the ocean, mangroves, rainforest, rice fields, park areas and even a volcanic caldera. Wink and Mohr also organised a laboratory course at a partner institution to train Indonesian students, technical staff, doctoral students and scientists in the handling of the challenging myxobacteria. At the weekend, the researchers visited the botanical garden in Bogor – and used this opportunity for an extensive sample collection. “Not only the trees are so impressive because of their breathtaking size,“ says Wink. “Some toad species also reach impressive sizes.“

Meanwhile, supported by the DAAD and Indonesian institutions, Wink‘s team has added two Indonesian doctoral students and two more will join the team soon. The HZI researchers already isolated and tested the first myxo- and actinobacteria from the Indonesian samples. One new natural product is already being processed. “Aided by international cooperation projects, such as GINAICO, we can investigate even unusual habitats in far-away countries for microorganisms producing tomorrow’s anti-infective drugs,“ says Marc Stadler. But this can be done only if research transcending borders keeps being possible.

Dear readers,

research can be successful only if it has an international focus, if scientists are able to share their experience, results and materials beyond borders. This is exemplified by our headline story: Searching for new agents – for instance against multi-resistant pathogens – HZI scientists collect microbes in Indonesia and test them for the production of biologically active substances. They also train scientific staff on-site, which then supports them in collecting the samples.

This is the first issue of InFact in its new design and – as a reflection of our international focus – fully bilingual.

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

Andreas Fischer
Editor-in-chief

IMPRINT

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"IT IS IMPORTANT TO NOT LET BACTERIA RECOGNISE THAT WE ARE FIGHTING THEM"

by Andreas Fischer

More and more pathogens are developing resistances to antibiotics, so there is an urgent need for new anti-infectives. Eva Medina of the Helmholtz Centre for Infection Research is looking for therapeutic alternatives that will circumvent the renewed formation of antibiotic resistance

Dr Medina, which options do we have for fighting resistant pathogens?
A rational approach to combat multi-resistant bacteria would be the development of new antibiotics that do not belong to the same classes than those currently in use. But this option will only offer a temporary solution: Antibiotics kill bacteria and by doing so they apply a selection pressure. As a result, the bacteria fight for their survival and will develop resistance to any new antibiotic. In order to circumvent this problem, we are currently investigating so-called anti-virulence strategies, which aim at reducing the pathogens' virulence rather than killing them, thereby improving the capacity of the immune system to eliminate the weakened pathogen.

How does that work?
Pathogens produce a large number of factors they need for the successful colonisation of the host, the so-called virulence factors – for example, proteins the pathogens require for attaching to host cells or for defending themselves against the immune system. In the research area of anti-virulence strategies, we are looking for inhibitors that specifically block this kind of tools and render the pathogens harmless. The crucial advantage is that depriving pathogens of their virulence properties without killing them may result in reduced selection pressure and limited development of drug resistance.

◁ *Eva Medina heads the HZI research group "Infection Immunology"*

How far are you with the anti-virulence research?
This is a very new research field; we are still at the very beginning. One of the greatest challenges is to find suitable virulence factors whose production is independent of the host and whose inactivation will produce the desired attenuating effect on the pathogen.

How is this approach viewed by clinicians?
The level of interest is very high, since clinicians have to fight multi-resistant pathogens and persistent infections on a daily basis. We are engaged in an active exchange with clinicians via the German Center for Infection Research. The aim is to develop anti-virulence agents and bring them into clinical use as soon as possible, but this still needs intensive basic research.

Which research questions do you focus on?
We aim to understand the mutual interactions between host and pathogen during an infection and then use this information to identify suitable points for anti-virulence intervention. For this purpose, we need to know which genes are expressed and when. This information can be extracted from the so-called RNA profiles. We will perform some of these studies in close cooperations with the newly founded Helmholtz Institute for RNA-based Infection Research in Würzburg. In addition, we are testing various compounds in cell culture and in mice for a possible anti-virulent effect. Potential anti-virulence candidates are also available from other research groups of the HZI as well as from the Helmholtz Institute for Pharmaceutical Research Saarland. There is also an approach for personalised medicine in the anti-virulence strategy, since different patients respond differently to pathogens and treatments.

Can anti-virulence therapies help to reverse antibiotic resistances?
Well, we can be cautiously optimistic that this might be possible, since bacteria can also lose their resistances when antibiotics are not used for a long period of time. However, this will require the availability of many anti-virulence agents and extensive reduction in the use of antibiotics. Since treatment with anti-virulence agents alone might not be efficient enough to completely eliminate the pathogen within the infected tissue, it seems likely that anti-virulence drugs would be used in combination with antibiotics. This combination would require lower amounts of antibiotics to control the infection, resulting in lower levels of selection pressure on pathogens and limited damage of the commensal microbiota.

COMPLETE INTERVIEW
www.helmholtz-hzi.de/en/medina

LIVELY PARTICIPATION IN STUDY ON THE SELF-COLLECTION OF BLOOD

by Sonja Simon, Jördis J. Ott and Stefanie Castell

In January 2017, the department for Epidemiology of the Helmholtz Centre for Infection Research tested a new tool for self-sampling of blood on the HZI campus. Blood samples are indispensable for many studies investigating the incidence, prevalence and risk factors of infectious diseases in the general population. However, logistical challenges and personal constraints often make venous blood sampling difficult. A new instrument called HemaSpot™ uses filter paper to which a small amount of blood from a finger can be applied and which is then sent to a laboratory. The feasibility and implications of blood self-collection using the new device has so far not been assessed.

A total of 155 persons at the HZI campus participated in the self-sampling of blood. In addition, medical staff collected venous blood samples from 57 persons to allow the quality of HemaSpot blood sampling to be evaluated.

The analysis of the questionnaires and feedback sheets and the laboratory analyses of the blood samples are ongoing. The presence of antibodies against hepatitis A and tetanus in the two available samples is being compared in the laboratory analyses. The principal investigators Jördis J. Ott and Stefanie Castell concluded on the usefulness of the study regarding the further use and the need for adaptation of the device in order to make it an alternative to venous blood sampling.

HemaSpot™ as an alternative to venous blood sampling?

The department for Epidemiology is grateful for the lively participation, the sophisticated remarks and the detailed testimonies. The results are intended to be published in a scientific journal after completion of the analyses to make them available to all interested parties.

△ *The HemaSpot device for blood self-collection*

NANO-RESEARCHER, BUT WELL-EARTHED

by Kathrin Fuhrmann

Gregor Fuhrmann wants to use tiny membrane vesicles to transport active substances to where they are needed in the body. He started a junior research group at the HIPS to pursue this project

Gregor Fuhrmann basically inherited his interest in science from his parents, who are both graduate chemists. The native of Berlin decided to take up a course of study in pharmacy in Germany's capital. For his internship year, he visited the laboratory of Jean-Christophe Leroux in Montréal. "Since the chemistry between us was so good, we kept contact after my visit," Fuhrmann explains. After he received his license as a pharmacist, he commenced his doctoral work at the ETH Zürich in 2008 – again with Leroux, who had just transferred to Zürich.

Months before receiving his doctoral degree, which he completed with honours, Fuhrmann secured a position as a post-doctoral fellow with Molly Stevens, a materials researcher in London. There he studied extracellular vesicles, i.e. vesicles released by body cells for purposes of communication with other cells or for defence against pathogens. It was obvious to Fuhrmann that vesicles can be used as targeted transporters to navigate active substances through the body to the site of disease: "As a messenger material the body is familiar with, vesicles are perfectly suited for this purpose," he says. He received no less than two stipends to pursue his idea.

His next goal was to set up his own research group to work on the control of infections. Especially the fate of cystic fibrosis patients, who suffer from persistent lung infections, drew his attention. And he went to look for help for his undertaking. In Germany, one person stood out in particular: Claus-Michael Lehr, who develops *in vitro* lung models at the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS). Ultimately, Fuhrmann approached Lehr at a conference in 2014. "It was also helpful that both Molly and Jean-Christophe were present at the conference to put in a word for me," he explains. Since December 2016, Fuhrmann and his "Biogenic Nanotherapeutics" junior research group at the HIPS have been isolating and characterising vesicles from mammalian cells and bacteria, testing them on bacterial cultures either without modification or laden with active substances. "Within the next five years, we want to establish a method for the preparation and loading of vesicles with active substances that has the potential to be developed further for the market," he says.

In his career, from studies in Berlin to the junior research group in Saarbrücken, the 35 year-old has seen much of the world, while his focus always was on research. And this is no different in Saarbrücken: "The city is really nice and down-to-earth, not as aloof as London," he says. "But the good research conditions are the crucial difference." The HIPS is fascinating because of its modern looks and the local research groups are very experienced and very well networked.

Smalltalk not being his thing, Gregor Fuhrmann may sometimes seem a little standoffish because of his reticence. But he has managed to establish friendships from Jena to Québec and from Stockholm to Verona. The father of two children is also an enthusiastic amateur bio-gardener and fan of the Hertha BSC football club – two passions that are successful rarely enough but keep the professional high-flyer well-earthed.

LINK

www.helmholtz-hzi.de/en/bion

PREPARING FOR THE UNKNOWN

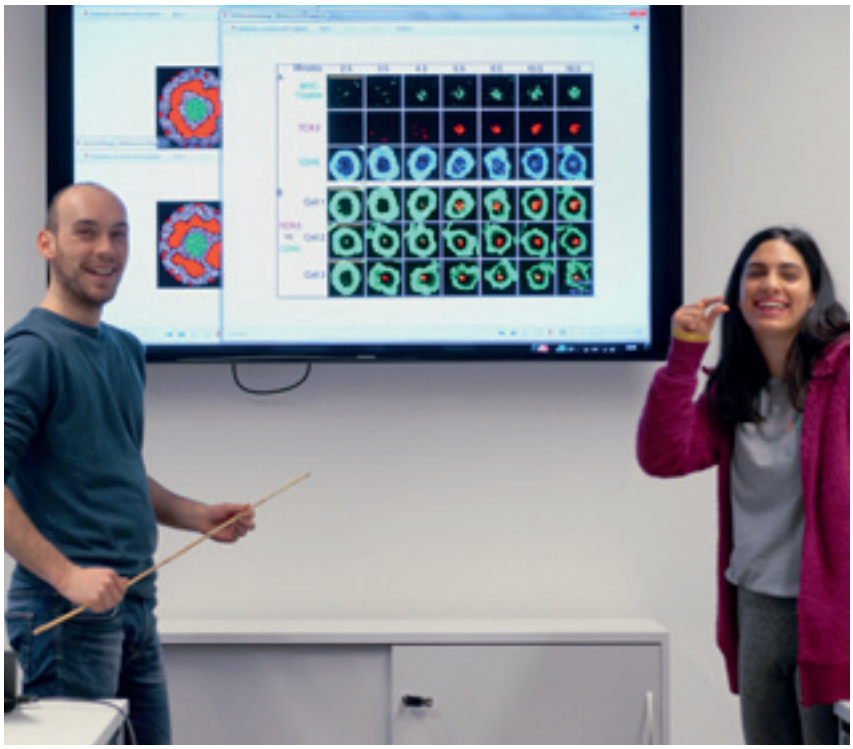
by Sebastian Binder

How the mutation of B cells makes a difference in the body's fight against pathogens

Once a B cell – i.e. a specific white blood cell – starts producing antibodies, they become one of the most efficient means against pathogens. However, the adaptive immune system first has to learn how to produce the antibodies in a process called "affinity maturation" which takes around two weeks.

The goal in this process is to develop B cells that produce antibodies efficiently recognising a pathogen. The key to it is the ability of B cells to mutate within so-called germinal centres. In these structures, B cells with a high affinity to the target prevail in an evolutionary process of mutation, division and selection. This makes B cells respond efficiently to previously encountered pathogens, but can this process prepare the immune system for unknown challenges?

One possible answer comes from mathematical models. At the Braunschweig Integrated Centre of Systems Biology (BRICS), a joint research centre of HZI and TU Braunschweig, individual B cells are simulated in a virtual germinal centre. Cells survive based on how good they are at recognising the target. One might expect a clear winner in this competition: The B cell with the highest affinity divides more and survives with a higher probability. In a recent study in collaboration with partners from Cambridge and New York, the descent of B cells in germinal centres was analysed. This is easy to track in the computer model and can be validated by innovative experiments exploiting the brainbow allele, which allows to permanently stain a B cell lineage. A high dominance of a single B cell lineage was found only in a part of the germinal centres. Others displayed a remarkable diversity of B cells from different descents. While this means that there are less copies of the optimal B cell, the suboptimal B cells might be what prepares the immune system for fast mutating pathogens likely to be encountered in the near future.



◁ *BRICS scientists present simulations of the interactions between antigen presenting cells and lymphocytes*

NEW PROJECT ON ANTIBIOTIC RESISTANCE

The computational biologists in Alice McHardy's research group (BIFO) start a new DFG funded project at the BRICS: They will develop a method for tracking CRISPR dynamics in complex bacterial communities. CRISPR is a bacterial adaptive immune system that is able to restrict horizontal gene transfer. Together with Bärbel Stecher (LMU Munich), McHardy and her team will analyse the transfer of CRISPR elements within the microbiome of the gut of mice. Philipp Münch: "We will test the hypothesis that CRISPR elements limit the transfer of antibiotic resistance genes. When we understand the role of CRISPR in preventing the spread of antibiotic resistance, this will eventually open up new strategies against emerging resistant pathogens." (pcm)

NEWS

A BUSY ANNIVERSARY "10 YEARS CITY OF SCIENCE"

10 Jahre Stadt der Wissenschaft Braunschweig 2017

Back in 2007, Braunschweig was elected "City of Science" by the Stifterverband (Donors' Association). Ten years later, we are looking back not only on a successful year 2007: Since then, more than 800 events have familiarised the citizens of Braunschweig more closely with science in their everyday life. We also managed to establish a House of Science in Braunschweig. This is where the lecture series "Tatsachen – Forschung unter der Lupe" together with HZI and the Science Slam originated, which has attracted an enthusiastic audience ever since. In the fall, the city of Braunschweig will join the scientific institutions, museums and government authorities of this research region (ForschungRegion Braunschweig e.V.) and set up a large net at Burgplatz to symbolise the joint networking in this region. Science can be experienced there each day from 13 - 27 September. The HZI will be one of the participants.

And we will be active in Stöckheim as well: The campus partners HZI, DSMZ, Fraunhofer ITEM, TU Braunschweig and DZIF are working on a new signage concept titled "Campus-Süd" aimed at presenting us jointly as an innovative life science campus and part of ForschungRegion Braunschweig. (sti)

AWARD-WINNING DOCTORAL THESES AT THE HZI

The "Arbeitskreis für Biomedizinische Forschung e. V." awarded its Advancement Awards 2015 and 2016, endowed with €1000, for special contributions to biomedical research:

Molecular biologist Sebastian Schulz received the Advancement Award 2015 for deciphering the regulatory networks of the most important sigma factors in *Pseudomonas aeruginosa*. Schulz's work contributes to a better understanding of the adaptability of this dangerous hospital pathogen. Meanwhile, Schulz has become a postdoctoral fellow in the "Structural Infection Biology" department of Prof Michael Kolbe at the CSSB.

△ *Siegfried Weiß presenting the Advancement Award 2015 to Sebastian Schulz*

Molecular immunologist Sebastian Felgner received the Advancement Award 2016 for establishing a strain of salmonella that elicits a strain of counter-reaction of the immune system when it colonises tumours, but is controlled well by the body. Felgner is now a postdoctoral fellow in the "Infection Biology of Salmonella" junior research group of Dr Marc Erhardt. (nhi)

△ *Sebastian Felgner receiving the Advancement Award 2016*

PLAYING SOCCER FOR HZI

The HZI soccer team is looking for some reinforcements. The team is built of players of different nationalities, genders and age groups and meets up routinely on Wednesdays. Additionally, the team participates in the League System organised by Betriebssportverband Braunschweig, where it takes on other local company teams in six to eight games per year. Beginners and experts are welcome. If you're interested please contact Björn Bulitta. (nhi)

SCHEDULE

22 April: March for Science, *www.marchforscience.de*
14 May: Open House: German Aerospace Center (DLR); Braunschweig
18 May: Tatsachen – Forschung unter der Lupe: "Antibiotics"; Haus der Wissenschaft Braunschweig
17 June: TU-Night; TU Braunschweig
18 July: Inhoffen lecture and presentation of the Inhoffen Medal; Forum of the HZI
14 September: A Day on Career Opportunities; Forum of the HZI

NEW PERSONNEL

BRICS, Braunschweig: Philippe Robert, SIMM
CRC, Hannover: Patricia Gliewe, EPID | Tatjana Kröschel, EPID | Isabell Nitzel, EPID | Friedrich Schmidt-Martens, EPID | Marcel Seidensticker, EPID
CSSB, Hamburg: Michele Lunelli, STIB
HIPS, Saarbrücken: Hans Eisenbrand, MINS | Katja Gemperlein, MINS | Xabier Murgia, DDEL | Stefanie Schmidt, BION | Tabea-Catharina Schramm, DDOP | Francisco Torres, MINS | Fu Yan, MINS
HZI, Braunschweig: Roland Böttcher, TB | Vladimir Goncalves Magalhaes, VIMM | Katarzyna Sitnik, IMCI | Michael Wegener, MCH

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