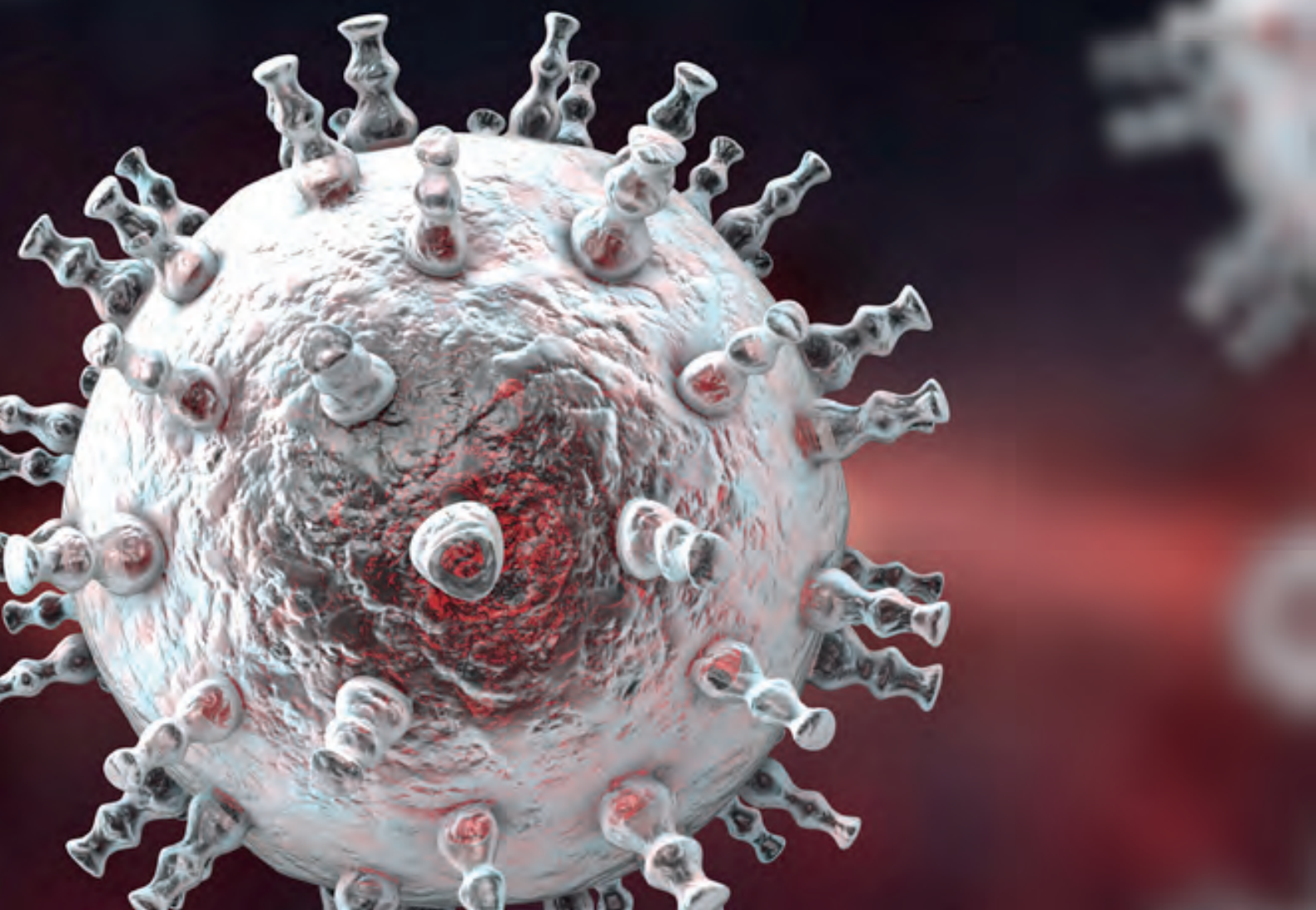
HZI HELMHOLTZ Centre for Infection Research

InFact

The magazine of the Helmholtz Centre for Infection Research | May 2019

THE SUPER STRIKER

How herpesviruses dribble out the immune system



EDITORIAL

Dear readers,

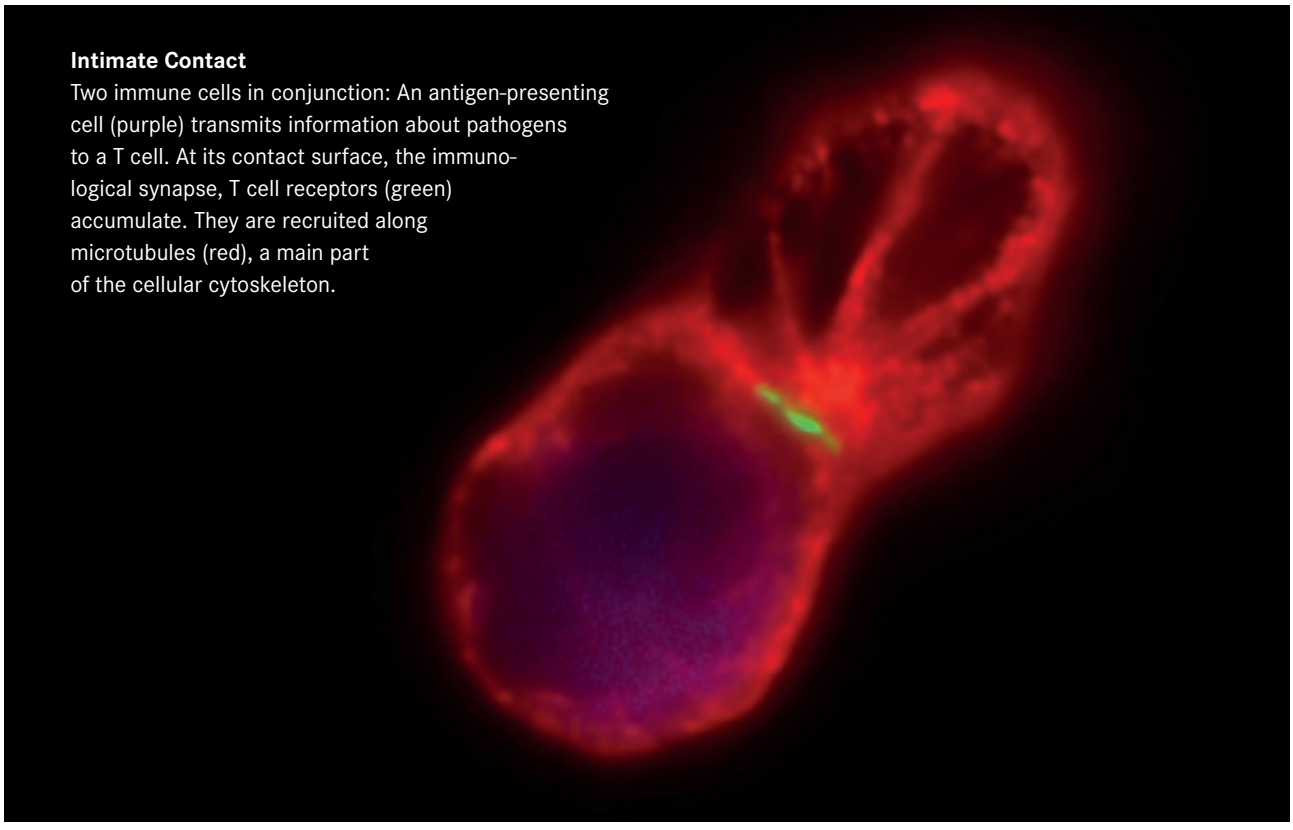
Almost everyone knows them—and almost everyone gets infected by them in the course of their lives: herpesviruses. In addition to the cold sores, they cause many different diseases, including cancer. They are responsible for chicken pox, shingles and mononucleosis, for example. They are also particularly affectionate: Once infected, they remain with us for the rest of our lives. In our cover story, you can read how these tricky viruses manage to escape the immune system and where research starts to combat them. Chronic infections with hepatitis viruses are also widespread. They do not only challenge our immune system, but also cause life-threatening long-term damage. Read more about this in the interview on page 7.

Does a social media account have benefits or not? Of course, we cannot answer this question comprehensively, but at least in the field of science the visibility on the net has its advantages. In her article starting on page 8, science coach Susanne Geu gives us an overview of the importance of digital science communication and tips on how to deal with social networks.

I look forward to your feedback and wish you pleasant reading!

***Andreas Fischer,** Editor-in-chief*

EYE-CATCHER



Intimate Contact
Two immune cells in conjunction: An antigen-presenting cell (purple) transmits information about pathogens to a T cell. At its contact surface, the immunological synapse, T cell receptors (green) accumulate. They are recruited along microtubules (red), a main part of the cellular cytoskeleton.

IMPRINT

Publisher:
Helmholtz Centre for Infection Research GmbH
Press and Communication
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Design: Britta Freise

Print: MAUL-DRUCK GmbH & Co. KG

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CUSTOMISED, EFFICIENT, UNIVERSAL: VACCINES 2.0

by Ulrike Schneeweiß

Carlos A. Guzmán‘s research team applies knowledge about the human immune system and its challengers to develop innovative vaccination strategies

Physicians have been using the basic principle of vaccination for centuries: They purposefully expose the body to a killed or attenuated pathogen, and the subsequently developed memory immune response prevents a more severe course of the disease following reencounter with the pathogen. Today, many vaccines consist of individual components of the pathogen, which are able to confer protective immunity, the so-called antigens. The resulting subunit vaccines display an improved safety profile; however, it is a challenge to achieve the same level of protection as with a complete pathogen. Therefore, many vaccines contain adjuvants that strengthen the vaccine response. The right adjuvant can also improve the protection provided by the vaccine for certain groups of people, because, as trivial as it sounds, “Not all humans are the same,” says Prof Carlos A. Guzmán from the Helmholtz Centre for Infection Research (HZI). For example, only a small proportion of people aged over 60 develop sufficient protection after a standard influenza vaccination. Administering the vaccine together with an adjuvant such as an emulsion of oil and water, however, significantly increases vaccine efficacy.

Emulsions or aluminium salts have proven to be efficient and safe vaccine boosters. Carlos A. Guzmán and his team are now developing a second generation of adjuvants: They are using compounds produced by microorganisms that are able to stimulate the cells of the innate immune system and activate various defence mechanisms in the body. “For a vaccine to be effective, the combination of adjuvant and antigen must be adapted to the individual characteristics of the pathogen,” says Guzmán. This is because pathogens have developed various strategies to resist human defences. Some evade the immune system, such as influenza viruses. These viruses constantly change their strongest antigens, making necessary the manufacturing of a new vaccine every season. Researchers are therefore attempting to create artificial antigens from stable components of the virus. Their vision: to develop a universal influenza vaccine based on these designer antigens.

△ Vaccinations are the most effective protection against infections

Guzmán‘s team recently constructed *in vitro* a vaccine from several parts of various stable components of the parasite *Trypanosoma cruzi*. The single-cell organism causes myocarditis and has a sophisticated way of hiding itself from the immune system, meaning that neither a vaccine nor a cure has yet been developed. “Together with colleagues from Argentina we removed all the parts of the antigens that do not trigger the proper immune response and used only those that are necessary to generate protection,” says Guzmán. The researchers combined their synthetic designer antigen with an adjuvant developed at the HZI, a second messenger substance derived from bacteria. The resulting vaccine activates the critical defence mechanisms needed to eliminate the hidden parasite. Thus, it is specifically tailored to the pathogen, thereby enabling to prevent infection by the single-cell organism. Structure-based antigen design and the use of well-defined adjuvants represent the vaccines of tomorrow: customised and efficient.

THE SUPER STRIKER

by Christian Heinrich

Herpesviruses use sneaky tricks to permanently establish themselves in our cells and to spread efficiently in the population

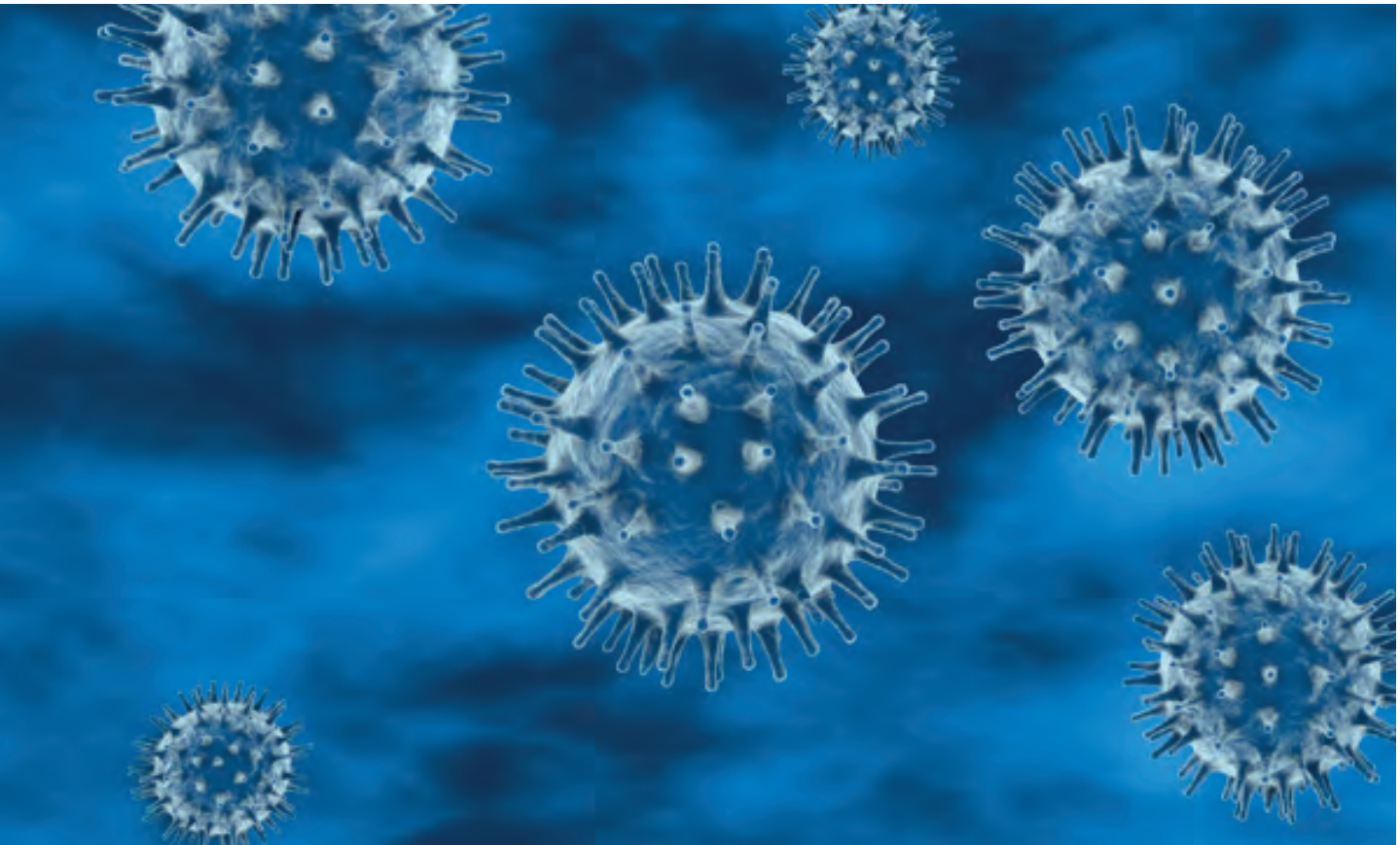
If we imagine viruses and human immune cells as opposing soccer teams, we would observe a spectacular game: The viruses have barely gained possession of the ball and they are already storming down the field towards their goal. If the defence players and goalie of the opposing team, the human immune cells, do not reach their positions quickly enough the viruses' goal cannot be prevented and a human is infected.

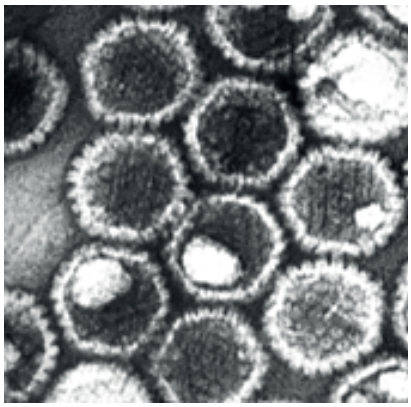
Nevertheless, the human immune system is extremely observant and a quick learner. Normally if a virus attacks a cell, this cell sounds the alarm for itself and its neighbours. It also releases messenger signals, a cry for help from additional cells—one player is calling the strikers and defenders into action. The defenders, made up of immune cells like macrophages, natural killer cells, and dendritic cells, hasten to the rescue. If a goal has been made and a cell is infected, that infected cell displays a small fragment of the virus on the cell surface. This signals to some of the strikers, the T cells, that they need to start their counterattack. Next, more strikers, the B cells, are brought into the game. The B cells produce antibodies and together with the T cells build long-term immunity; they keep watch and are well prepared for the next virus attempt on the goal. Because of the immune cell team, the virus barely has a chance to win the game, or establish itself in the body.

Herpesviruses utilise clever offensive strategies

While the host may have a good soccer team, herpesviruses are an extremely challenging opponent. They are not just any striker—they have the qualities of a super striker like Cristiano Ronaldo. They use elegant tricks to dart past their opponent: "The viruses understand the immune system extremely well and during their evolution, they have developed sophisticated countermeasures to cleverly evade the host's defences," explains the biologist Melanie Brinkmann, group leader at the Helmholtz Centre for Infection Research (HZI) and professor at the Technische Universität Braunschweig. "I would even go one step further—the

▽ Illustration of herpesviral particles





◁◁ Electron micrograph of herpes simplex viral particles

◁ Melanie Brinkmann (middle) and her team research herpesviral proteins

herpesviruses force their opponent to make an own goal." Herpesviruses deploy an entire arsenal of strategies and tools to prevent or weaken the host's defences. In fact, the viruses use their proteins to prevent the infected cell from even realising that it is infected or threatened. This gives the virus enough time to infect host cells and multiply effectively.

Melanie Brinkmann has dedicated most of her research career to herpesviruses. She sought a challenge in the extremely complex herpesviruses: Their genome, which is made up of double-stranded DNA like the human genome, contains genetic information to produce more than 200 proteins. In comparison, hepatitis C virus, which can also cause lifelong infection in humans, only encodes ten proteins. For many people, only one member of the herpesvirus family is well known—herpes simplex virus 1 (HSV-1), which leads to unpleasant cold sores. In fact, however, scientists have identified nine herpesviruses that can infect humans. They cause a variety of illnesses and pathologies ranging from chicken pox and infectious mononucleosis to cancer. One herpesvirus family member that is largely unknown and underestimated in the population is cytomegalovirus (CMV). In Germany, though, at least every second adult is infected with CMV. In most cases, the infection is mild, but in patients with a weakened immune system, CMV leads to serious complications including pneumonia and liver inflammation. CMV can also cause severe developmental disorders in children whose mothers are infected during pregnancy.

Herpesviruses owe their successful spread to their complexity, which has enabled them to effectively slow down the human immune system in several different ways. Understanding their success in detail will help scientists to be able to better target them. Brinkmann's team studied the impact of CMV on a host protein known as STING. Normally, when a cell is infected, STING is activated, triggering several chain reactions or signalling pathways, and resulting in multiple immune responses. One of these signalling pathways is particularly effective at raising the emergency alert level in both the infected cell as well as its neighbours. The CMV protein m152 precisely targets this emergency alert pathway. STING also activates a second signalling cascade, but CMV needs this second pathway for its own replication and leaves it unaffected. Through m152, CMV outsmarts part of the immune response while at the same time utilising a separate part of the immune response for its own purposes—leading to the aforementioned own goal of the immune system.

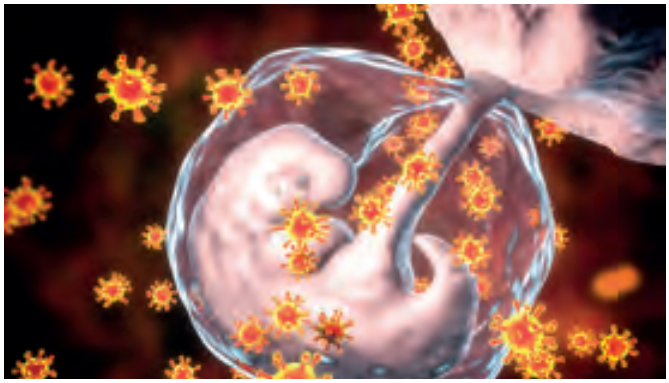
The game between these two opponents, the herpesviruses and the immune system, usually results in a draw, but it can quickly get out of control if the immune system is weakened or too active. The health of the host is at risk if it faces too much pressure from the virus. This in turn is counterproductive for the virus, which needs to establish itself in the host and spread. The virus manages this balance through a latent phase. After the immune system controls the primary infection, the virus goes into a type of dormant state from which it will only occasionally wake up to reproduce itself, a stage known as reactivation. This can be observed in the case of cold sores caused by HSV-1: The cold sores are not permanently present, but rather only appear occasionally.

△ Luka Cicin-Sain wants to use herpesvirus family members as the backbone for vaccines against other infections

"Sleeping" herpesviruses survive in the body

The balance between the latent and active proliferation phases of the virus is one of the research focuses of Prof Luka Cicin-Sain, who is the head of the "Immune Aging and Chronic Infections" research group at the HZI. He aims to understand how the virus maintains its presence during the chronic phase; in particular, how the immune system and the virus come to terms so both can coexist largely undisturbed. This is highly relevant as acquired immune deficiencies may reactivate the virus, which may cause disease or even be fatal. Infected individuals usually do not notice the latent infection, but CMV keeps the immune system very busy: "Approximately ten per cent of memory T cells specifically target CMV," says Cicin-Sain. This is a huge fraction if one considers the thousands of pathogens that humans are exposed to over the course of their lives, many of which induce immunological memory.

Considering the high prevalence of CMV in the German population and the



◁ During pregnancy, cytomegalovirus can infect the foetus and cause developmental defects

pronounced CMV immune signature, surprisingly little is known about this virus. CMV is thought to be transmitted by droplet contact, but this is not clearly established, because the clinical symptoms are often mild and always unspecific.

If a typical CMV infection is mild, is it even harmful for people with an intact immune system? Or does it impede the immune system in its fight against other pathogens, considering that more than ten per cent of its memory cells are busy with CMV? "In general, proving a negative is much more difficult than proving that something occurs," cautions Luka Cicin-Sain. In one study, he was able to show that the immune systems of CMV-positive subjects appear to work similarly to those of CMV-negative subjects in terms of recognising and controlling influenza and other pathogens. The field seems to agree with this conclusion. However, other studies have shown that atherosclerosis and related diseases, such as heart attack and stroke, are more common in CMV-positive individuals. Whether CMV is a cause of atherosclerosis or simply a bystander in these patients is an open question. Scientists are still seeking experimental proof. Research collaborations, such as the RESIST Excellence Cluster in Hannover, in which Cicin-Sain works together with clinicians and epidemiologists, are on-going.

CMV: danger for unborn infants and immunocompromised patients

In stark contrast to CMV infections in healthy patients, CMV can be extremely harmful in certain populations. For example, a new CMV infection during pregnancy can become a serious problem for the unborn child. "Infants and young children may become infected with CMV at kindergarten and take the virus home. If the pregnant mother did not have CMV previously, she may now become infected and transmit the infection to the unborn child," Brinkmann says. Approximately one per cent of all CMV-negative women become infected with CMV during pregnancy and about 30 per cent of the infections are transmitted to the unborn child, leading to symptoms in about one per cent of these children. The hearing of the unborn child may be damaged in some cases –this is one of the most frequent causes of hearing loss in infants, second only to Down syndrome. In rare cases, CMV infection of the infant may even be fatal. Strict hygiene, such as frequent hand washing and avoiding contact with urine or saliva, significantly reduces the likelihood of infection.

Immunocompromised individuals are also at risk due to CMV. To prevent organ transplant rejection or severe graft versus host disease after bone marrow transfer, transplant recipients require immuno-suppressant drugs. However, these anti-rejection medications impair the ability of the immune system to control CMV, leading to a common post-transplant complication: CMV reactivation and its associated serious tissue damage. To specifically inhibit the infection at the source, one needs to know where in the body the viruses hide during latency. While CMV has been detected in blood and bone marrow cells, its hiding place has not been identified definitively yet. "There is evidence that CMV also resides in other cells in the body, including those in transplanted organs," says Luka Cicin-Sain. While blood cells are relatively easy to obtain from a blood sample, it is not nearly as easy to obtain human liver or lung cells. Therefore, Cicin-Sain warns that latency in solid organs is underexplored. A cooperation with surgeons at the Hannover Medical School allows Cicin-Sain's research group to obtain tissue that was removed during surgeries and would otherwise be discarded. Cicin-Sain studies these samples to find the cells harbouring latent CMV. This may allow targeted and preventive treatment of infection, even before the virus becomes reactivated.

Viruses and novel remedies

"The extraordinary power of immune responses to CMV may also be a good thing, if they can be harnessed and redirected to make vaccines," says Luka Cicin-Sain. Accordingly, he has established a consortium of scientists to develop CMV based vaccines. In cooperation with scientists at Freie Universität Berlin, the University of Veterinary Medicine Hannover, the German Primate Center, and the Croatian Universities in Zagreb and Rijeka, Cicin-Sain is testing the utility of CMV as a vaccine vector against other viruses. Some early success has been achieved in experiments with human papilloma virus, herpes simplex virus, and Ebola viruses. Current research targets influenza and hepatitis C.

Brinkmann's insights into herpesvirus defence mechanisms may help to develop new antiviral therapies, for example drugs targeting specific viral proteins. "I want to understand Ronaldo better so that I can triumph over him," jokes Brinkmann. The reason is simple: The better we understand herpesviruses, the better we can fight against them. Although she and colleagues worldwide have made great strides in recent years, with over 200 CMV proteins, the functions of most proteins are still not well understood and there is much to be discovered.

THE HERPESVIRUS FAMILY

HSV-1 (HHV-1) Cold sores, genital herpes
HSV-2 (HHV-2) Genital herpes
HHV-3 (varicella-zoster virus, VZV) Chicken pox, shingles
HHV-4 (Epstein-Barr virus, EBV) Infectious mononucleosis ("mono") Oncovirus (causes cancer)
HHV-5 (cytomegalovirus, CMV) Pneumonia and liver infection in immunocompromised patients, hearing damage in children infected before birth
HHV-6A, HHV-6B Sixth disease (exanthema subitum or roseola infantum)
HHV-7 unknown whether it causes illness
HHV-8 (Kaposi's sarcoma-associated herpesvirus) Oncovirus

“BETTER SAFE THAN SORRY— ESPECIALLY REGARDING INFECTIOUS DISEASES”

by Helen Looney

About 70 million people worldwide are chronically infected with the hepatitis C virus (HCV). Possible consequences include hepatitis, cirrhosis and liver cancer, but the disease often remains undetected for long periods of time. Thomas Pietschmann of the TWINCORE in Hannover investigates the virus and works on the development of a vaccine that could prevent HCV infections in the future

Mr. Pietschmann, what makes hepatitis C so dangerous?
That the infection with the hepatitis C virus (HCV) often goes unnoticed for a long time. The virus is transmitted over blood, nowadays especially in the drug milieu, when people share needles. It causes a chronic infection that can cause severe liver damage over time.

And why is this virus particularly successful?
In chronic infections, the virus has years or decades replicate in a human. That means the time frame for transmission is very large. Before the discovery of the virus, medical procedures may have also aided in transmission. For if I do not know the virus, I cannot prevent it from being transmitted via blood or organ donations. But generally spoken the virus is successful because it can replicate in humans over long periods of time. And that is due to biological adaptions of the virus that help it escape the immune system.

At the TWINCORE you investigate these adaptions to develop a vaccine against HCV. How do you proceed?
We concentrate on three main areas. The first one starts in the clinic, where we cooperate with physicians at Hannover Medical School. Together we investigate which immune responses are formed by patients. This knowledge of natural immunity forms the base for our second research area where we develop and examine own vaccine candidates. Research on HCV’s specialisation forms our third focus area. We aim to learn why the virus cannot proliferate in other animals, mice for example.

△ Thomas Pietschmann heads the Experimental Virology at TWINCORE and HZI

Why is the development of a vaccine so important? Is treating existing infections not enough?
That is connected to the global prevalence of HCV. Over 70 Million people carry the virus—sometimes lifelong—and can transmit it. It is impossible to exterminate the virus with drugs overnight. Secondly, many people do not know they are infected due to the initially very unspecific progress. It would be an enormous effort to diagnose and treat all of them. The third point is the prevalence of the virus in populations that are hard to treat, drug addicts for example. The best way to control an infectious agent is to prevent infection from the beginning. Ideally, we would have a combination of treatment and a vaccine to avoid reinfection. For this must also be considered: Even after drug therapy, it is always possible to be infected again.

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

ONLINE VISIBILITY— FROM ANALOGUE RESEARCHER TO ONLINE SCIENTIST

by Susanne Geu

Scientists and science itself both profit from a social media presence, because digital science communication is far more than just self-marketing

Scientists who tweet, blog, use Instagram or produce podcasts are still a rare species—especially in Germany. According to a recent study[1], only every second junior researcher in Germany is convinced that communicating science to the public can boost his or her own career. In contrast, three-quarters of researchers from Asia and the USA agree with this statement. But how does visibility on the Internet actually work, and which advantages do Twitter and other social media platforms offer for individual scientists and research in general?

Nowadays, whoever is looking for information about a person or a topic uses search engines. This also applies to academic selection committees that review applicants for postdoc or professorial positions, but also to graduates who search the web to find a suitable lab group for their continued careers in science. Even journalists use Google to find communicative experts for articles and interviews. Scientists who do not have online profiles miss out on opportunities to be found and greatly limit the visibility of both themselves as people and their research.

Blogs and other social media expand the possibilities of scientific discourse. Between publications, research designs and theses can be discussed with peers via Twitter or in blog comments, and sharing research and thought processes can lead to new ideas for publications. In addition, informal communication via online channels can easily lead to new connections with peers or entire research cooperations that might never have existed without an initial conversation on Twitter. At conferences, the microblogging service acts as a feedback channel and organisational aid, and when you already know each other via Twitter, the ice is broken faster and networking at a symposium becomes much easier. Spending some time reading Twitter each day means staying up to date on the latest developments in your field of research, job opportunities and upcoming scientific events. A study[1] published in 2016 even confirmed that posting articles on Twitter has a positive effect on citation rates.

Melissa Terras, professor at University College in London, reported in an article, titled “Is blogging and tweeting about research papers worth it? The Verdict”[2], about how she promoted her articles via Twitter, with one exception. The articles she tweeted were downloaded between 142 and 297 times, whereas the article not tweeted was downloaded only twelve times, although it was available online at the same location.

Scientists can best showcase themselves and their dedication to their

research with their own websites. A website is the foundation of an online presence; it displaces any unfavourable Google results and is often the top search result. As opposed to a simple profile on an institute or university page, a website offers you more scope for introducing yourself and your research, and if you change jobs, your online scientific profile is retained. A personal web presence also offers sufficient space to publish videos, photos, presentations or interim results of your research.

There is virtually no limit to the creative use of social media. Twitter can be used as a teaching tool[3] or a way to retell events from history[4]. Sometimes, however, it is a way to reassure yourself that other scientists are also facing similar challenges. For example, researchers around the world share their everyday research life on Twitter and Instagram using the hashtags #phdchat, #phdlife and #showusyourscience.

Being successful on social media requires some clear goals. What do I want to achieve with my online activities? Establish a network of scientific colleagues? Or communicate scientific concepts to a non-scientific audience? Only once you have decided on this you can choose which platform is most suitable.

Using your full name on social media means these profiles can also be found by search engines. If you would rather stay anonymous during your initial forays online, you can register using a pseudonym or start off by just reading other peoples' posts, rather than posting yourself. Every social network functions differently and it takes time to get to know the conventions of each platform. You can also use your offline contacts to help build your online network: simply enter the name of an institute colleague into Twitter and see who they are connected to.

A study completed in 2011[5] found that scientists retweet more often than other user groups. However, if you want to use social media effectively, you will need to interact with others. This means being confident in speaking up and participating in online discussions. Scientists with a large number of followers understand how to show their personality and their ability to engage in conversations; their posts focus on scientific topics, they curate content from other scientists or they enthusiastically provide help online. Jule Specht[6], Professor of Psychology at Humboldt-Universität zu Berlin, is also outspoken about scientific policy and has over 1500 followers on Twitter.

Although writing a regular science blog takes a lot of time, good blog posts can be disseminated widely and linked via social media. Each blog post is another opportunity to be found online as an expert. An analysis of 126 science blogs[7] showed that 72 per cent of bloggers also have a Twitter account, which is considered the most important social network in science. There is also a growing scientific community on Instagram; female scientists in particular, such as neuroscience student Stina Börchers[8], use the platform to explain science visually or show what everyday life in the lab is like. Inspiration and motivation tend to be the focus here, whereas Twitter is used more for news and events. Facebook is the least-used professional network, but it is used by scientists to stay connected with colleagues and university friends. Deciding on which channel is most appropriate depends not only on your personal goal, but also just as much on where you feel most comfortable and where you can best communicate the benefits of your own field of science.

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"MY GOAL IS TO BE ABLE TO MAKE AN INDIVIDUAL TREATMENT DECISION FOR EACH PATIENT"

by Andreas Fischer

Markus Cornberg, a medical doctor by training, is the new Clinical Director of the Helmholtz Centre for Infection Research (HZI) and heads the Centre for Individualised Infection Medicine (CiiM) in Hannover. He took up this role on 1 January 2019, succeeding Michael Manns, who has taken over the presidency at Hannover Medical School (MHH). In an interview, Cornberg talks about the initial steps towards individualised infection medicine that takes into account the specific characteristics of individual patients or patient groups

Mr Cornberg, how would you describe your first 100 days as Director of the CiiM?
Very positive and exciting! This role combines everything that I have wanted to do for quite some time. I have always wanted to advance infection medicine in the area of individualised treatment, following the example of cancer medicine. The combination of research, medicine and clinical work with patients is ideal for this purpose, and this is exactly what the HZI and the MHH as parent institutions of the CiiM offer. I have been involved ever since the idea of the CiiM came into being and had made it my goal to get my own research group at this centre.

You are also the Clinical Director at the HZI. What does that role entail?
It is not so easy to separate the tasks in that role from those of the CiiM Director. For both, I have to find out the relevant infection topics for which we can bring together research groups from the MHH and the HZI in order to investigate certain aspects of infection medicine. Currently, I am having a lot of conversations about this, discussing with HZI researchers the possibilities offered by the large amount of patient data from the MHH, and which ongoing patient studies can be elevated to a higher level by integrating the HZI.

Do you have any concrete examples?
Yes, we have gathered a few ideas and have already implemented some initial very interesting projects. For example, we have integrated a scientist from Michael Meyer-Hermann's department at the HZI into a project with hepatitis B patients. There is no cure for hepatitis B, but it can be controlled with medical treatment. In some patients, the viral relapses after discontinuing treatment, but in others it does not. With the help of the Meyer-Hermann lab that uses machine learning with our data, we have identified a set of signal substances that can predict with over 90 per cent certainty what will happen to each patient after discontinuing hepatitis B treatment. In another collaboration with Karsten Hiller's research group at the BRICS, we are planning a programme to investigate the effects of hepatitis C treatment on metabolomics. And together with Carlos Guzmán from the HZI we are currently developing a project with an individualised approach: Data from cohort studies have shown that patients with liver cirrhosis respond worse to influenza vaccinations than healthy patients. Together, we want to explore this correlation. In addition to my collaborations, there are, of course, numerous other collaborations between research groups at the MHH and the HZI.

The CiiM is still a virtual centre. What challenges does that present?
Quite simply, there is no central building in which vital interdisciplinary approaches can be actively pursued, a space where colleagues can exchange ideas while standing at the coffee machine. To me, such virtual centre currently means: a lot of travel to visit partners and a lot of organisational work to implement collaborations. Having our own building will also be important for implementing new technological standards—and as a sign of the importance of the research field in the region. However, the projects that we have already started, and are currently initiating, are far more important to me. Ongoing projects are always better than an empty building without projects.

When do you anticipate the virtual centre to become a physical centre?

△ Markus Cornberg has been heading the CiiM in Hannover since January and is the Clinical Director at the HZI

The first steps are now being taken and the building could be ready by the early 2020s. This will give us space for around 150 employees.

How would you describe the long-term goals of the CiiM?
Individualised approaches are about being able to choose the most suitable prophylaxis or treatment for an individual patient. We use patient data to search for characteristics—specific marker molecules—that we can use to divide patients into different groups and thus make appropriate treatment decisions for each group. Our goal is to determine before starting a treatment which patients would not respond to it, which antibiotic would be most suitable, or whether a vaccine would trigger the desired immune response.

Do you intend to work with patients at the CiiM?
I can see that happening. For example, I see an opportunity for the CiiM to offer a clinical consulting service: If a clinic is not making progress with a particular patient, because he or she is not responding to any treatment—or the exact opposite, has an extraordinarily good response—then we could continue to support the patient and test for different markers. Maybe we can use our methods to find out more about this patient's special case. Of course, the patients would have to agree to this, for privacy reasons.

In addition to your responsibilities at the CiiM and the HZI, you are also a senior consultant at the MHH and professor for clinical infectiology with your own research group at the German Center for Infection Research. Do you sometimes wonder exactly which hat you're wearing at any given moment?
True, it is not always easy. *(laughs)* There is a lot of overlap. My boss always said, a day lasts 24 hours and then there's the night. I have excellent colleagues who do a lot of work for me in the clinic. They are key to it all. But my diverse range of tasks is exactly what I have always wanted to do. I have been interested in infection medicine since my doctoral thesis, and I have pursued individualised research approaches since my postdoc at the University of Massachusetts Medical School in the USA. But it is also important to me that I am not just doing research. Working with patients, such as through daily rounds at the clinic, is what makes medicine so varied.

You are a new face for many of the staff at the HZI—so tell us, who is Markus Cornberg?
Yes, who is Markus Cornberg … *(laughs)* I am married and we have two sons, 13 and nine years old. Our eldest son is an enthusiastic swimmer and the younger plays basketball—so we spend a lot of our weekends travelling. I used to play handball myself, but now I do not have the time. Unusually for someone from northern Germany, I go to Cologne for the carnival every year, which I have been doing regularly since 1999. I am from Hessisch Oldendorf in the Weser Uplands which was the former heartland of carnival in northern Germany—so I grew up attending carnival celebrations.

A SERVICE PROVIDER WITH PASSION

by Christine Bentz

The Purchasing Department at the HZI is headed by a strong woman: Anja Anfang. The business economist gives us an insight into her work

Anja Anfang is a woman with a lot of energy. You notice this in her firm handshake and the way she is constantly on the move. This kind of momentum is necessary as head of a department with such a wide range of tasks as the Purchasing Department at the Helmholtz Centre for Infection Research (HZI). Her team processes around 22,000 requests each year; with a workload of this magnitude, the unit must function perfectly –and, according to Anja Anfang, her 14-strong team does exactly that. Without staff who have a passion for their jobs, this work would not be possible, she says.

She sees the Purchasing Department as a service provider for the HZI, with the scientists as her customers, and close collaboration with the specialist departments is very important to her. Without their expertise, for example when ordering large-scale equipment, the Purchasing Department would face real problems: "We're not scientists, after all." Anyone may request information on the cost of a specific product, whether they are a scientist or an administrative employee—ultimately, however, the Purchasing Department is always responsible for controlling the awarding process and ensuring compliance with statutory regulations. Ideally, the specific request is put out for tender, in order to find the most economical supplier. From an economic point of view, it is not always the cheapest price that counts, but rather the best supplier in terms of the required quality. The reason for this is to ensure the appropriate use of the taxpayers' money that the HZI receives, says Anfang.

So that is her department, but who is Anja Anfang? A woman with a lot of energy—not only in her job, but also in her personal life. Even after spending long days in the office, she still finds time to be active after work: She regularly goes to the gym, enjoys spending time outdoors on her bicycle and, lately, also on skis. "I go skiing once a year, and each time I learn a little more," she tells us.

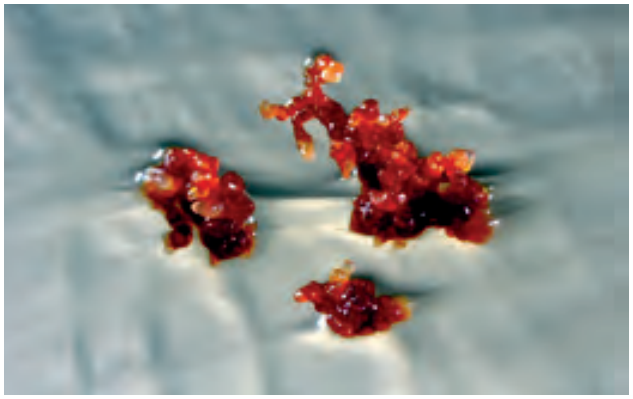
Her willingness to try something new and constantly improve her skills is something that brought her to the HZI. In 2016, she changed industries and left her long-standing position with a power supplier to take up a new challenge at the HZI. Previously, she worked her way from the bottom up in procurement, holding her own in male-dominated fields such as vehicle fleets and tool purchasing. The Purchasing Department at the HZI fulfills the needs of the entire centre, from ballpoint pens and marketing services to highly complex scientific equipment and construction services. "It's the major projects that are particularly interesting, such as the architectural competition for the new Helmholtz Institute for RNA-based Infection Research (HIRI) building in Würzburg," says Anfang. The process took one and a half years from the idea to awarding the contract, and was carried out in close collaboration with a Berlin service provider, which brought new perspectives to her work.

She is also in close contact with the other 18 Helmholtz centres: The Purchasing managers from all the centres meet twice a year. "On a specialist group level, there are collaborative projects; for example, at the moment we're procuring occupational safety software for six centres," says Anfang. At the HZI, the Purchasing Department is closely connected to other units, such as Technical Services and the Finance Department. Staying well connected, both inside and outside the HZI, makes a big difference. "The Purchasing Department isn't an island," says Anja Anfang with a smile. On the contrary: She and her team represent one central department that exists to support everyone. A service provider with passion, indeed.

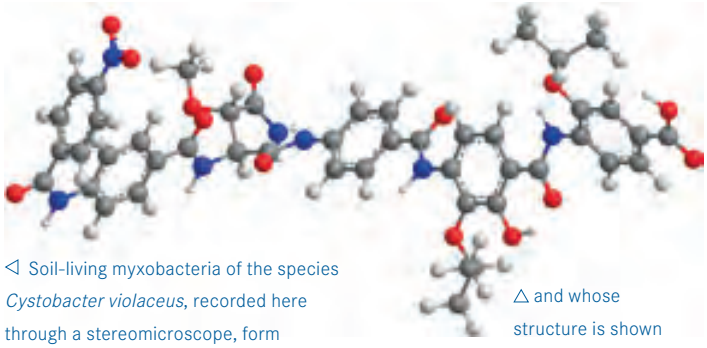
ANTIBIOTICS OF THE FUTURE?

by Manfred Braun

Among the hospital germs, Gram-negative bacteria are particularly difficult to treat: Their double membrane envelope effectively keeps antibiotics from reaching their target. Remarkably, substances from the extensive collection of bacteria held by the HZI are now raising hopes for a remedy. The class of cystobactamids will be further developed into drugs in a partnership with the pharmaceutical company Evotec



◁ Soil-living myxobacteria of the species *Cystobacter violaceus*, recorded here through a stereomicroscope, form substances known as cystobactamids, which kill other bacteria ...



△ and whose structure is shown here as a 3D model

The collection of myxobacteria at the Helmholtz Centre for Infection Research (HZI) has proven time and again to be a real treasure trove. The soil bacteria, which were initially regarded as uncultivable, have been grown and analysed on a large scale by the HZI and its predecessor institution since the 1970s. Since then, the main collection has been continuously expanded. At HZI and its Saarbrücken branch, the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), myxobacterial extracts have been examined for interesting natural substances—and they are always up for a surprise.

"We first identified a compound that is active against Gram-negative bacteria in an extract from the myxobacterial species *Cystobacter* back in 2011," remembers Rolf Müller, myxobacteria researcher and Managing Director of the HIPS. Looking at other myxobacterial species, Müller and his colleagues later found other variants of the substance, which have since been termed "cystobactamids". It turned out that some of these variants act much more effectively and against a wider range of germs than the compound they found first. It is assumed that with substances such as cystobactamids myxobacteria are able to keep unwanted competitors for food at bay.

The mode of action is promising: Cystobactamids are so-called gyrase blockers. They prevent bacteria from unwinding their DNA in a way that is required for reproduction. "Gyrase blockers already exist and have been successfully used as antibiotics in clinical settings," says Müller, "but many bacteria have become resistant to them." Cystobactamids, on the other hand, are still effective against such germs.

Together with the teams lead by Mark Brönstrup (HZI), Marc Stadler (HZI), Rolf Hartmann and Anna Hirsch (both from HIPS) and Andreas Kirschning (Leibniz Universität Hannover), Müller and his colleagues further improved the properties of cystobactamids, tested them in mice and developed methods for producing them in larger quantities in the laboratory.

In order to develop these promising substances into drugs used in hospitals, the HZI has secured a high-profile partner for the next stages: the Hamburg-based pharmaceutical company Evotec. "There's still a lot to be improved in terms of chemistry: The efficiency of the synthesis needs to be increased and the pharmaceutical properties must be optimised," says Müller. "This would take us years on our own."

HZI has concluded a cooperation agreement with Evotec as an industry partner for an initial period of three years—but how fast will things progress? Müller is optimistic: "The risks in drug development are always high. But I hope that it'll be possible to carry out clinical trials in humans within three to four years —and ideally, obtain market approval two to four years after that."

NEWS

AWARD WINNING WORK

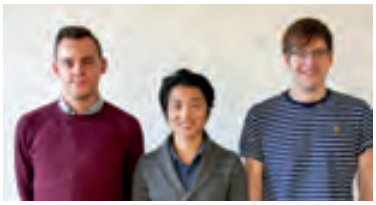
Katharina Borst, Phil Baran & Michael Kany (f.l.)

Phil Baran of the Scripps Research Institute in La Jolla, USA, is the holder of the 25th Inhoffen Medal. He is a leading natural product scientist of our time, who synthesised highly complex natural products with unsurpassed efficiency. His methods and reagents are widely applied in basic chemical research, in the synthesis of pharmaceutical drugs, and have been commercialised successfully. During the Inhoffen lecture **Dr Katharina Borst** from TWINCORE and **Dr Michael Kany** from HIPS were awarded their outstanding doctoral theses. Borst investigated the behaviour of myeloid liver cells during infection with viral hepatitis; Kany researched patho-blocker target structures in pathogenic bacteria.

Dr Clara Chepkirui received the award "DECHEMA-Doktorandenpreis für Naturstoff-Forschung". While doing her doctorate in the HZI department "Microbial Drugs", headed by Prof Marc Stadler, Chepkirui discovered the microporenic acids, which proved effective against bacterial biofilms. In addition, Chepkirui isolated more than 50 other active substances.

Olga Kalinina is the new endowed professor for active substance bioinformatics at HIPS. Kalinina works at the interface between natural products and drug research at HIPS with a focus on antibiotic development and the bioinformatic modelling of drug molecules at the Centre for Bioinformatics at Saarland University. The Klaus Faber Foundation in Saarbrücken will support her research with a total of 1.6 million euros until 2022.

NEW PHD REPRESENTATIVES



Carsten Peukert, Lianxu Hao and **Daniel Meston** (f.l.) are the new speakers of the PhD council "DO IT". Together with the HZI Graduate School, they are committed to maintaining quality standards in doctoral student training and to further improving working conditions.

SAVED RESOURCES

Recycling saves resources and thus protects the environment and climate. The HZI is also striving for greater sustainability—with great success. The Braunschweig site saved 1023 kg of materials and 35,520 kg of greenhouse gases in 2017 alone. The figures are based on calculations by the Fraunhofer Institute for Environmental, Safety and Energy Technology. The recycled materials included steel, old electrical devices, copper, wood and paper.

NEW BOOK

Susanne Thiele, head of the Press and Communications department, published the book „Zu Risiken und Nebenwirkungen fragen Sie Ihre Türklinke", which was released by HEYNE in 2019. On a journey through our home, the book offers insights into the world of microorganisms and gives tips on how to deal with our smallest roommates on a daily basis. Well-founded and easy to understand, it is especially aimed at interested non-professionals who want to deepen their knowledge of microbial relationships. (hlo)

SCHEDULE

27-28 June: HIPS Symposium 2019 on 10 years of HIPS, Aula of Saarland University
4 July: Day on "Alumnis´ professional life", HZI forum
5 September: HZI Summer Fête
20 September: 14th Mini-Herpesvirus Workshop, HZI forum
25 October: Day on "Different communication cultures", HZI Gründerzentrum

NEW PERSONNEL

BRICS, Braunschweig: Zhi-Luo Deng, BIFO | Yen Lee Loh-Bode, BIFO
CRC, Hannover: Isabella Bauer, EPID| Annemarie Gwildies, EPID
CSSB, Hamburg: Maike Eiben, STIB
HIPS, Saarbrücken: Annette Herkströter, DDEL | Alberto Hidalgo, DDEL | Lena Keller, MINS | Jelena Konstantinovic, DDOP | Yannic Nonnenmacher, MINS | Pascal Paul, DDEL
HIRI, Würzburg: Oleg Dmytrenko, RSYN
HZI, Braunschweig: Bianca Fleig, TB | Aida Iljazovic, MIKI | Vadim Korotkov, CBIO | Christian Lentz, CBIO | Magdalena Mietkowska, ZBIO | Christine Morgan, PA | Stephanie Stahnke, ZBIO
TWINCORE, Hannover: Angela Bortenreuter, ADMIN | Carolina Skowronek, ADMIN