AIMING FOR THE TOP AS A TEAM

Two new managing directors – one shared goal
Dear readers,

2023 saw major changes in the management of the HZI: In January, Christian Scherf took over the administrative leadership of the centre, and in July, Dirk Heinz handed over the position as Scientific Director to Josef Penninger after 13 years. The first steps taken by the new management duo include adjusting the centre’s research priorities and establishing new research groups at the Braunschweig Science Campus. Both are pursuing the goal of establishing the HZI as a world-leading centre for infection research.

In our interview, you will get to know Christian Scherf and Josef Penninger better and find out how they want to lead the HZI to the top. One of the future research topics at the HZI is personalised medicine. Therapies are to be tailored more and more precisely to patients, because every individual reacts differently to an infection or medical treatment. You can read why gender plays an important role in the development of personalised therapies from page 6 onwards. Vaccinations are frequently the subject of lively - and in many cases emotionally charged - discussions, which are often based on false expectations. We asked what a vaccination can really achieve - and what it cannot.

I wish you a pleasant read!
Andreas Fischer, Editor-in-chief
Mr Penninger, Mr Scherf, you are the new leaders at the HZI and may not have been able to meet all members of staff yet. What can we tell the staff to expect, how do you see yourself as the new leaders?

Josef Penninger: (laughs) Christian, you go ahead.

Christian Scherf: (laughs) Sure, my pleasure. I am a manager with a height of 2.04 metres, so I’m relatively tall when I enter the room. To me it’s important to listen first. I want to know what the staff’s issues are so that I can develop these topics further and contribute my leadership expertise. I’ve been doing this for 20 years and can draw on a wealth of experience. I have learnt that you can develop topics better when you cooperate instead of working by yourself.

How would you describe yourself as a leader, Mr Penninger?

Penninger: What I am certainly not is a micromanager. I am usually up in the clouds and need people to ground me and bring me back down to reality. That’s why I also need a great team, and Christian and I work really well together. I have set up an institute in Vienna and later took over an established major institute in Canada. That means I know both sides of institute development. Just like Christian said: You have to act in concert with others and take people seriously if you want them to come along with you. I believe that every person working for us is important, at every level; everyone needs to be heard and respected. And I promise: I will listen.
Your goal is to develop the Helmholtz Centre into one of the best infection research centres in the world. How far off are you on the way to becoming a world-leading centre?

Penninger: Not all that far. However, it’s like a football team in the German Bundesliga: They’re all really great, but the final efforts to get into the Champions League are essential. The HZI has been set up well by our predecessors with great scientists and a good organisation, but the final ten to 15 percent still need to be done. This will be strenuous. We need to position ourselves not only internally, but internationally as well. We have to look for talent and integrate ourselves into the global community. Whether we achieve this goal is another matter, but it is important to be confident of aiming to be among the world’s best. Only then you build the steps to get there.

The goal in administration is certainly linked to the concept of new work, i.e. a mobile working culture, flexible working time models, virtual teams, partial home office - can all of this be implemented at the HZI?

Scherf: Yes, we are working on it, or we would be very old-fashioned. We aim to be an attractive employer for researchers and administrators. This means being able to work flexibly, balancing work and family life, offering continued education opportunities and much more. Working from home is not always possible; many researchers simply have to be in the lab. There are some administrative tasks that can be done at the home office, but there are also jobs that require you to be present, such as janitorial services. We are service-oriented in administration, as in fact our DNA is a service DNA. We want to enable scientists to realise their scientific work in the way they need to.

How do you find top researchers for the HZI?

Penninger: Simply by having very, very good positions and conditions to offer. Helmholtz is one of the largest research organisations in the world. We can compete with Harvard and other institutions. But it’s not only money that attracts people to us, rather it’s the soft values, a culture. Young scientists need to be supported and promoted. I have often observed that if you really support smart people and build a biotope, a suitable playground around them, where they can work in peace and develop ideas, then very often something positive happens. In Vienna, we had people who needed five or six years to publish, but their publications changed the world and our general level of knowledge. We offer the opportunity for longer-term projects at the HZI. There is no doubt in my mind that we will be able to convince young top talents to join our institute.

What qualities should top researchers have?

Penninger: Creative chaos. (laughs) I mean this natural interest, this gleam in the eye - it’s hard to describe. There are a lot of smart people in the world who are well educated, but only a special few who have that sparkle, that passion. Research is not easy to do. You may have great ideas, work on them for two or three years - only for nothing to come of it. That means you also have to be resilient. It’s like a good painter, who has to learn how to paint in oils. However, that’s still not all. Gustav Klimt had two brothers who were also great painters, but nobody knows of them to date. This raises the question: How do you recognise the next Gustav Klimt or Lionel Messi of science?

You want to set up 20 new research groups, how easy or difficult will that be?

Penninger: We have launched the first call for applications. Initially, there will be four positions, and later we will continue steadily and set up 20 positions - or even more including the clinician scientists. We also need the local structures to be established to allow the researchers to work properly right away. This will be done by Christian’s team and some other people in the foreground and background, such as my deputy Thomas Pietschmann, who is doing an excellent job, and our fantastic scientific team.

Scherf: Let me add something about the locations: The HZI has grown intensively, but at the sites outside Braunschweig. The new funding also has a strategic dimension, because we are attracting young people of exceptional quality, securing the future here in Braunschweig.

Penninger: Exactly, a very important point. We are currently setting the course for the next ten to 20 years. This is, of course, a critical point that we have to approach very cleverly in order to attract the right people and establish the right structures.

You want research to produce “radically new” results. What do you mean by that?

Penninger: I am thinking of bacteria and viruses that we can learn from. They have survived four billion years of evolution, they are chemists and can do things that we know almost nothing but also as useful. This is the direction in order to learn how to decompose plastics or produce energy cheaply. Climate change is also introducing non-indigenous. They travel with mosquitoes, for example. We need to be prepared and offer solutions.

We are doing this as a hybrid interview: Christian Scherf is in Braunschweig, Mr Penninger, you are on the line. You still have a professorship in Vienna, do you have enough time for the HZI?

Penninger: Absolutely! (laughs) I have one hundred per cent of my time for the HZI. I have a 25 per cent
professorship in personalised medicine at the medical university in Vienna. So I work 125 per cent, which is what I’ve been doing for many years anyway. My job in Vienna is to develop the new Eric Kandel Institute for Precision Medicine. Eric Kandel is one of my mentors, he is now 94 years old and received the Nobel Prize for the molecular control of memory in 2000. This is also a good opportunity for the HZI to put out initial feelers to Austria and establish joint projects and synergies. Vienna is the largest university centre in the German-speaking world with around 200,000 students, so it’s a great opportunity for everyone.

You are both so qualified that you can choose your workplace: Why did you come to the HZI in Braunschweig?

Scherf: There are several incentives. After working in physics for many years, I turned to life science. I am fascinated by the question of how we can influence and understand our lives. The fact that so many partners have to be brought together here at the HZI as a multiscience centre is also very appealing to me. And finally, I’m a native of the north; it gives me incredible pleasure to work in northern Germany, and this still includes Braunschweig. (laughs)

Penninger: I am interested in the HZI because Helmholtz offers the opportunity to establish it as one of the world’s leading centres. There are very few places in the world where something like this can be realised. That’s why I came to work with Christian and Thomas in Braunschweig and the great institutes and researchers and all the staff at the HZI in Greifswald, Würzburg, Hannover, Hamburg and Saarbrücken to contribute the final ten to 15 per cent to the Champions League final.

Do you already have a club in Braunschweig that you want to play for?

Penninger: No, I am still looking. If someone needs a player my age, I’m ready to go. I get to play for the Austrian physician’s national team, which is great. We also play in the world championships. We came in last in Cancun, but it’s the Olympic spirit that counts. (laughs)

Scherf: My day at work is that of a research manager with lots of meetings and appointments. It’s important to make a decision in life regarding priorities. For me, it’s important to strike a balance between being able to contribute and develop as a managing director and having a private life, a marriage and seven children. I have to be able to combine both and so far I have found: It is doable.

Where do you see yourself in five years’ time?

Scherf: Is this a job interview? (laughs)
DO WOMEN AND MEN REACT DIFFERENTLY TO INFECTIONS? 
by Christian Heinrich

Men are more susceptible to a number of chronic infections, while women, in turn, are more likely to overreact to infections. The underlying reason and why it needs to be taken into account more in clinical practice in the future

Am I more likely to have a mild case of pneumonia or is it more likely to be life-threatening? What is my risk of side effects from COVID-19 vaccination? Do I belong to a group of people who are more likely to contract chronic viral hepatitis than others? The answers to these questions vary – depending on your sex and gender. Hospitalised for pneumonia, males are twice as likely as females to need to be transferred to intensive care1. Females, in turn, are more than twice as likely as males to suffer side effects from the COVID-19 vaccine. And chronic hepatitis B is more common among males than among females.

“Aside from other factors, the immune system and its effectiveness differ considerably between the sexes. Which has far-reaching consequences: for the vast majority of infectious diseases, for vaccinations, for autoimmune diseases,” says Dr Henning Jacobsen from the department Viral Immunology at the Helmholtz Centre for Infection Research (HZI).

Hormones and genes bear the primary responsibility for these biological differences. Put simply, the male sex hormone testosterone slows down the immune system a little. In turn, other than in pregnancy, which is an exception, the female sex hormones of women – the oestrogens and progesterone – tend to have a promoting effect on the reaction of the immune system. “In particular, interferon gamma can be activated by oestrogens, and that, in turn, activates numerous processes that are associated with an inflammatory reaction,” says Jacobsen.

In addition to hormones, the genes also play a role. “For example, many genes that are essential for the immune system, are located on the X chromosome. And unlike men, women are known to have two X chromosomes

instead of one,” says Prof Markus Cornberg, Deputy Director of the Clinic for Gastroenterology, Hepatology, infectiology and Endocrinology at the Hannover Medical School (MHH) and Director of the Centre for Individualised Infection Medicine (CiIM), a joint facility of the MHH and the HZI. “Likewise, Toll-like receptor 7, TLR7 for short, is also encoded on the X chromosome. The receptor is important for early detection of invading viruses,” says Cornberg, who is also Clinical Director of the HZI.

All these differences in hormones and genes mean that autoimmune diseases are more frequent in females because the immune system tends to overreact. However, upon exposure to a pathogen, a female’s immune system also often reacts more quickly and effectively to the hazard than that of a male.

“In clinical settings, we see chronic viral infections in males significantly more often than in females,” says Cornberg, whose work includes hepatitis research. Whether chronic hepatitis B, C, D or HIV – males are more frequently afflicted by many chronic viral infections.

Then there are the sociological differences, which may add to the biology. “The English language distinguishes between sex – the biological sex – and gender – the non-binary gender identity and the influence of the gender role in society,” Jacobsen explains. Even though there has been some convergence in gender roles in many areas in recent years, there are still enough differences, with gender-specific consequences for infectiology. To put it in simple terms – as mentioned, gender can be non-binary – on average, women go to the doctor more often than men, talk more honestly about their symptoms, which, in turn, has an impact on the treatment strategy for infections as well. Another example: Women work in hospitals more often than men and have a correspondingly higher risk of contracting pathogens that are common in hospitals.

However, regardless of where the differences originated, experts like Cornberg and Jacobsen are certain: So far, they have not been taken into account in clinical practice to a sufficient extent. Just one example: side effects of COVID-19 vaccinations, which occur significantly more often in females than in males. At the same time, though, the control of antibody titres shows that females gain better vaccination protection after the vaccination. “As a scientist, I naturally ask myself whether females could be given lower doses of the vaccine to reduce the side effects, since the effect of the vaccine appears to be stronger in them. Or, in turn, whether you can give higher vaccine doses to males to increase the effectiveness of the vaccination,” says Cornberg. But so far none of this is being seriously considered. Even with drugs for the treatment of infections, the dose is usually made to depend on age or other factors, but almost never on gender, although there are many cases, in which demonstrable differences in the extent of the effect have been shown.

At first glance, this seems sobering. The era of personalised medicine has arrived and highly individualised treatments tailored to a single patient are being developed, such as gene therapy. But at the simplest level, it is not implemented to a sufficient extent: subdividing all people into just two groups, males and females, and treating them accordingly. Why is this so?

One reason is that it involves additional effort and expense in research to differentiate by gender. Of course, the biological sex is always determined and stated in clinical studies. “But in order for sex differences to be as meaningful as the overall results of all test subjects, you would need twice the number of test subjects – and that can make clinical studies more time-consuming and expensive,” says Jacobsen. It also rarely pays off for the companies: Instead of one dosage, they would have to produce two different dosages, and there is always a risk that the efficacy may be too low in one group.

Perhaps it is simply because the magnitude of the gender differences in vaccination against and therapy of infectious diseases has not yet trickled through to the wider medical community. After all, many findings in this highly dynamic field have only been made in recent years. Jacobsen is hopeful that this will soon change: “With every relevant finding that is made on sex differences in infectious diseases, this issue should be recognised in clinical practice to a broader extent.”
WHAT CAN WE EXPECT FROM VACCINATIONS – AND WHAT NOT?

by Nicole Silbermann

Vaccinations do not always live up to what we would want them to do – so far, anyway. But they are still invaluable for our health and life in our communities.
When the COVID-19 pandemic struck in 2020, vaccines against the SARS-CoV-2 virus, which was spreading all around the world, were developed in record time. There was widespread anxiety—and the expectations of many people regarding the effect of the vaccines were just as high: The vaccines should not only protect against severe illness, but also prevent both infection and the transmission of the virus. “That would certainly have been very desirable. But expecting the COVID-19 vaccines to achieve all this was clearly too ambitious and in some ways even illusory,” says Prof Carlos A. Guzmán, who is the head of the department Vaccinology and Applied Microbiology at the HZI. “Because vaccines administered through an injection are not generally designed to be able to do that at all, as they cannot reach and activate the immune system in the right location and activate the required immune effector mechanisms.”

Yet, injection-based vaccinations are highly effective and can achieve the most important goal of vaccination: protection against severe courses of the disease. Stimulated by the vaccination, the immune system produces antibodies, effector cells and the so-called memory cells that remember certain features of the pathogen for use in the long term. In the future, when the vaccinated subject enters in contact with the pathogen, the immune system is activated very quickly and produces suitable antibodies and effector cells to ward off or at least contain the illness. “For a certain period of time other people can catch the disease-causing pathogen from an infected vaccinated person,” says Guzmán. “But different studies showed that this time window is usually shorter and the pathogen load is reduced as well after vaccination.”

**EFFECTIVE PROTECTION AT THE POINT OF ENTRY**

However, what is the proper location for a vaccination to act in order to provide protection against the infection and significantly reduce the risk of transmission? “At the mucous membranes,” says Guzmán. “Vaccines administered via the mucosa stimulate the formation of mucosa-specific memory cells right in the mucosa, which injected vaccines cannot do.” Some mucosal vaccines against influenza and polio (poliomyelitis) are already available. They are applied via the nasal mucosa in the form of a spray, or via the oral mucosa in the form of an oral vaccine to be swallowed. This means that they are administered right at the point of entry at which the pathogens causing these diseases enter the body. The vaccination builds up an effective defence barrier at this site that, ideally, blocks the pathogens completely or interferes with the infection process.

But why aren’t many more vaccines administered via the mucous membranes then? “The problem has been the mucosa itself,” says Guzmán. “Because the mucosa possesses a sophisticated barrier function that is supposed to ensure that pathogens or other dangerous entities are effectively warded off, as well as to prevent overreactions of the local mucosal immune system.” This means that vaccines have to trick the mucosa in some way to be able to both get inside and promote an effective response. The toolbox with the right tricks for achieving that needs to be expanded. This is what Guzmán’s and his team’s research focusses on. He is searching for mucosal immune response enhancers (adjuvants) that promote an effective activation of the immune system post vaccination. “Mucosal vaccination is an extremely effective form of immunisation. We hope that research will continue making progress in this aspect in the next few years so that this type of vaccination can be routinely used against a broad spectrum of pathogens in the future,” says Guzmán.

**ERADICATED – AN UNPRECEDENTED SUCCESS**

Besides protection against disease, infection and transmission, there is another – albeit quite ambitious – goal that can be pursued through vaccination: the complete eradication of a pathogen. This was achieved for the first and so far only time in 1980. Since then, the smallpox virus has been considered to have been eradicated. Poliovirus and measles virus are two candidate pathogens on the current eradication list as they are quite dangerous and meet all prerequisites for possible eradication. “The most important requirement is that the pathogen is able to infect exclusively humans and has no animal reservoirs available to it,” Guzmán explains. “It is also crucial that the pathogen cannot change greatly in a short period of time or give rise to many subtypes. And: The vaccine used for eradication must achieve efficient and long-lasting immunity through, ideally, a small number of vaccinations providing a robust defence in case of renewed contact with the pathogen.”

Polio vaccines today provide effective protection against all three existing types of poliovirus based on three vaccinations and a subsequent booster. Only two doses of vaccine are needed for lifelong protection against measles.
So far, it has not been possible to eradicate polio and measles. This is because it requires a comprehensive vaccination concept working on a global scale, which is associated with enormous effort and high costs. “There are a number of pitfalls in the process, for example the access to the vaccine and trained health care personnel must be guaranteed in every corner of the globe, but the level of public acceptance and compliance of the vaccination, together with a robust infrastructure for vaccine storage are crucial as well. For example, uninterrupted cold storage cannot be reliably provided in every region of the world. With regard to smallpox, we were lucky at the time that the vaccine did not require a very strict cold chain, as e.g. mRNA vaccines do,” says Guzmán. A vaccine against polio has been available since 1955. There have been no new polio infections reported in Germany since 1992. The African continent was declared polio-free in August 2020. However, occasional cases of polio continue to pop up in various crisis regions around the world. Complete eradication is not yet in sight, similar to measles.

TRUST CAN ONLY COME FROM CLARIFYING INFORMATION

“Some 25 years ago, a study linking measles vaccination to autism was published. The results of the study turned out to be wrong, though. But many people still remain unconvinced,” says Guzmán. “Good clarifying information is enormously important to gain the public’s trust in vaccinations that protect them against dangerous infectious diseases. And this also benefits vulnerable groups of people who cannot be vaccinated such as newborns or people with suppressed immune systems.”

The measles virus is one of the most contagious viruses and therefore requires a high vaccination rate among the population. To eradicate it, 95 per cent of the world’s population would have to be vaccinated. “Regrettably, we are still a long way from that,” says Dr Berit Lange, who is the acting head of the Epidemiology department and the Clinical Epidemiology at the HZI. “The vaccination gaps are still too extensive, and outbreaks continue to occur in many regions of the world, even in Germany.” Currently, there is even an upward trend year-on-year: As early as in February of this year the number of measles cases worldwide surpassed the number for all of 2022. “And this was caused by the Corona pandemic. Nearly 40 million children missed one of the two measles vaccinations during this time,” explains Lange. “This is where countermeasures must be taken at full speed.”

In Germany, the number of measles cases has dropped significantly from 516 in 2019 to 15 in 2022. Might this possibly be an indication of the effectiveness of the compulsory measles vaccination, which was introduced in 2020 for children in day-care centres and schools as well as for the staff of community facilities and medical institutions? “That is difficult to say at this stage,” says Lange. “The decrease in the measles incidence in Germany could also be related to the Corona pandemic, in that a reduced number of personal contacts may also lead to a reduced incidence of measles. Whether, and how well, compulsory vaccination works will only become clear in the next few years.”
Hortense Slevogt investigates the immune response in the lungs - as a physician and as a researcher

Professor Hortense Slevogt is an expert in the field of respiratory and lung infections and immunology. Both as a renowned researcher and a doctor. If you ask her for a catchy name for what she does, she doesn’t hesitate: “I build bridges.” Bridges between research and clinical practice.

Slevogt has been a W3 professor at Hannover Medical School since 2022 and is a senior physician for clinical infectiology with the Department of Pneumology and Infectiology. She is also the head of the “Dynamics of respiratory infections” research group at the HZI in Braunschweig. In her role as a clinical scientist, she finds it extremely fulfilling to translate discoveries from the laboratory and clinical studies into direct benefits for patients.

Chronic obstructive pulmonary disease (COPD) is a very common respiratory disease. Slevogt has mainly focused her research on the host immune response to airway colonisation by potential lung pathogens in this lung disease and others. It has only been recognised in the past ten years that the respiratory tract and lungs are also colonised by a microbiome that is generally not pathogenic but plays an important role in maintaining lung ecology and preventing infections by lung pathogens. This is where the research of Slevogt and her team starts. The goal is to develop therapeutic strategies for many respiratory diseases by better understanding the interactions of these microbes.

However, filing for third-party funding precedes every research project. Looking at the positive side, the project has to be carefully worded, which makes it more concrete in the mind’s eye and often initiates yet another perusal of the existing literature on the subject. With an approval rate of one in three or one in four, one must tolerate frustration rather well. But that is more of an incentive to Hortense Slevogt: “If we produce good data, that is promising for a new application.” Her guiding principle: be curious, unwavering and passionate about science.

For seventeen years, Slevogt treated patients with severe infectious diseases such as pneumonia, HIV, tuberculosis and malaria in the Charité’s infectious diseases department. During this time she also researched the immunological host-pathogen interactions of potential pathogens in the lung. Her habilitation followed in 2009. In 2011, she successfully expanded her research in molecular biology in Jena to include the field of immunology of sepsis. She was involved from the very beginning and quite significantly in setting up the Host Septomics research group of the ZIK Septomics at the University Hospital Jena. Her research has linked immunological sepsis and infection research to clinical research - which takes us back to the bridge metaphor.

Since 2016, she has also taken on clinical tasks again in the clinical pneumology department in Jena.

Hortense Slevogt’s family resides in Berlin. She is a “successful commuter” thanks to her “supportive husband” and the help of nannies and housekeepers. She appreciates her husband’s great interest in her work. He is a paediatrician and runs a large medical care centre in Berlin-Kreuzberg. Her daughter is studying medicine, “but with a focus on neurology,” while her son is currently working on his German equivalent of the A levels. She finds horseback riding through Brandenburg or Lower Saxony with her family to be the best way to relax.

You can find further portraits on our homepage: https://www.helmholtz-hzi.de/en/news-events/portrait/
A ftter thirteen years, Dirk Heinz has resigned from his position as Scientific Director and is now devoting himself to research again in his new department “Molecular Structural Biology”. We are delighted that he will be staying with the HZI and would like to take this opportunity to say a big “Thank you” for all his hard work. Perhaps the next milestone will be a call from Stockholm? Think big! (chb)

THANK YOU, DIRK HEINZ!

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