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Spring
2020

NEWS

RESIST – Resolving Infection Susceptibility

RESIST

Our goal:
Help for people most vulnerable to infection

WE ARE VERY HAPPY TO PRESENT TO YOU THE FIRST NEWSLETTER OF OUR CLUSTER OF EXCELLENCE RESIST. FROM NOW ON, THE RESIST NEWSLETTER WILL INFORM YOU REGULARLY AND COMPREHENSIVELY ABOUT NEWS FROM OUR CLUSTER OF EXCELLENCE BY LOOKING BACK AND FORWARD – AND IN ADDITION TO OUR HOMEPAGE, WHICH YOU CAN ACCESS ONLINE UNDER THE LINK WWW.RESIST-CLUSTER.DE.

Our newsletter will inform you how RESIST grows and develops. For example, in terms of personnel, our RESIST team has been strengthened: Dr. Gisa Gerold, TWINCORE researcher and visiting professor at Umea University in Sweden, is now associated with RESIST and contributes her research on a virus that will play an increasingly important role in the future (page 2). And two new elected representatives of (post)doctoral scientists wish to support more exchange between RESIST members and are therefore even thinking about sports (from page 3). RESIST has improved its technical infrastructure – among other things, a new microscope makes it possible to diagnose more cases than before (from page 4). You can take a look at the fruits of our research in the form of publications in scientific journals on pages 6 and 7. Of course, we are also reaching out to and communicating with the public: After the successful presentation of RESIST research in October 2019 in "Schloss Herrenhausen" to the general public, we were again at the "Schloss" in January 2020 with a humerous lecture about the liver (page 8).

Our research programme is for the weakest. The current threat of the corona pandemic clearly shows how important the goals of our Cluster of Excellence RESIST are. We want to better understand the variable susceptibility of individuals to infections in order to protect vulnerable people as well as possible.

In view of the dramatic situation, we in RESIST are currently beginning work on protective antibodies against SARS-CoV2 and we have started to test potential coronavirus vaccines in preclinical trials. Further research activities related to SARS-CoV2 are also starting in RESIST institutions. For example, teams from the MHH, the TWINCORE Centre for Experimental and Clinical Infection Research and the Helmholtz Centre for Infection Research want to identify new active substances with broad activity against different corona viruses, which can serve as a basis for the development of a drug that is effective against different corona viruses. Furthermore, we want to study the response of the innate and acquired immune system against the SARS-CoV2 virus and investigate whether there is a genetic predisposition for severe courses of CoVID-19 disease. We hope that the results will lead to new approaches for antiviral therapies and their targeted, individual control.

We will keep you up to date, also via our homepage www.RESIST-cluster.de, and hope you enjoy reading this newsletter,

your RESIST speaker trio.

The RESIST speaker team: Prof. Dr. Thomas Schulz (in the middle) and the two co-speakers Prof. Dr. Gesine Hansen and Prof. Dr. Reinhold Förster.

New in our RESIST team:

Dr. Gerold researches susceptibility to infections by Chikungunya viruses

SINCE THE BEGINNING OF THE YEAR, DR. GISA GEROLD, RESEARCHER OF THE TWINCORE – CENTRE FOR EXPERIMENTAL AND CLINICAL INFECTION RESEARCH AND VISITING PROFESSOR AT UMEA UNIVERSITY IN SWEDEN, IS ASSOCIATED WITH RESIST:

Dr. Gisa Gerold

Her PhD student Lisa Laßwitz will be funded by RESIST for six months. Dr. Gerold's team investigates, within the framework of RESIST, the genetic basis for susceptibility to Chikungunya virus infections. The virus is transmitted from mosquitoes to humans and can cause arthritis-like chronic joint pain. The virus is widespread in many African and Asian countries and in Central and South America, but also occurs sporadically in Europe.

"In the future, the virus will play an increasingly important role here, as the virus transmitting mosquitoes will continue to spread due to global warming and the viruses within them will also multiply more rapidly," said Dr. Gerold.

Her team was recently able to discover an important human gene that promotes the reproduction of the Chikungunya virus. On this basis, the team wants find out to whether people with naturally occurring variants of the identified gene or older people have an altered risk of infection with the virus. "Being associated with RESIST allows us intellectual exchange, exciting collaborations and access to important human samples, obtained within the new RESIST study with elderly healthy individuals," she said. Dr. Gerold works besides TWINCORE at Umea University at the "Wallenberg Centre for Molecular Medicine" in the "Department of Clinical Microbiology".

More information is available online: www.twincore.de/gerold or via twitter: https://twitter.com/GeroldLab

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Five RESIST researchers elected to DFG Review Boards

Prof. Hansen, Prof. Pietschmann, Prof. Sodeik (top row from left) and Prof. Grimbacher, Prof. Stiesch (bottom row from left).

Five researchers of our Cluster of Excellence RESIST have been elected to the Review Boards of the German Research Foundation (DFG): Professor Dr. Gesine Hansen has been elected to the Review Board "Child and Youth Medicine", Professor Dr. Beate Sodeik and Professor Dr. Thomas Pietschmann to the Review Board "Microbiology, Virology and Immunology", Professor Dr. Bodo Grimbacher to the Review Board "Clinical Immunology and Allergology" and Professor Dr. Meike Stiesch to the Review Board "Dentistry; Oral and Maxillofacial Surgery".

Review Boards are responsible for scientific evaluation of proposals submitted to the DFG for financial support and for monitoring of the maintenance of uniform standards in the review process. On this basis, members of DFG Review Boards formulate funding recommendations for the DFG's decision-making bodies. In addition, they advise the DFG on issues relating to the further development and design of its funding programmes.

The approximately 600 members of the 48 Review Boards are elected by all scientists and academics who hold doctorates and work at German universities or accredited research institutions. Elections take place every four years.

Commitment to more exchange

DURING THE RESIST GENERAL ASSEMBLY ON 27 JANUARY 2020, THE POSTDOCTORAL STUDENTS ELECTED JOÃO TERENO MONTEIRO AS THEIR REPRESENTATIVE FOR RESIST. THE PHD STUDENTS CHOSE CARINA JÜRGENS.

João Tereno Monteiro

In his new position, João Monteiro's main goal is to strengthen the connection between RESIST researchers and clinician scientists. "This is of main importance – also to extend the scientific outreach of RESIST," says the 30-year-old. He knows exactly how to achieve his goal: he will contribute feedback, ideas and problems of the postdocs and clinic communities to RESIST meetings and organise regular meetings where postdocs and other clinicial scientists can exchange Information about the current status of their projects and interesting methods of their research groups.

"Social activities also improve the connection between the different members and promote the exchange of ideas and opinions," he says. Therefore, he plans to organise joint dinners and moreover to establish a RESIST running club and a RESIST sports group.

He himself works in Professor Dr. Gesine Hansen's team at the MHH Children's Hospital and is investigating in RESIST how an infection with the respiratory syncytial virus (RSV) in childhood affects immune responses and asthma development later in life. To address these issues, he uses, among other things, a cohort of RSV-infected children.

João Monteiro studied biology, obtained his master's degree in biotechnology at the University of Lisbon in Portugal, and then went on to study host immune responses against *Helicobacter pylori* and *Staphylococcus aureus* in Portugal. In 2015, he moved to Germany for his doctoral thesis in infection immunology at the University of Veterinary Medicine Hannover.

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Carina Jürgens

Carina Jürgens also aims to promote more exchange between junior scientists. "I am trying to improve the network of all PhD students working in the field of infection biology," she says. She is currently already actively involved in organising this year's "retreat" of the Centre for Infection Biology (ZIB). ZIB is a virtual centre hosting the PhD programmes "Infection Biology" and "Dynamics of Host-Pathogen Interactions" (DEWIN). "Most PhD students working on RESIST projects are enrolled in the ZIB PhD programme – but not all of them. During the ZIB retreat, everyone can network with each other and with external experts," she explains. Carina Jürgens works in the team of Professor Dr. Abel Viejo-Borbolla of the MHH Institute of Virology, which is involved in RESIST. The team investigates genetic factors which lead to severe disease progression after infection with varicella zoster virus, such as encephalitis (brain inflammation) and vasculitis (inflammation of blood vessels). In her project, which is funded by the German Research Foundation, Carina Jürgens works on a varicella zoster virus (VZV) protein that is important for virus replication in the skin. For her, the patient cohorts currently being established at the MHH as part of RESIST are very important.

Carina Jürgens is a veterinary medical technical assistant and biologist. In 2018, she completed her studies in Infection Biology at the University of Lübeck and is now pursuing a doctorate at MHH.

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New within Research Management Board

Professor Dr. Reinhold E. Schmidt is a new member of the RESIST Research Management Board since the Meeting on 9 December 2019.

He is now additional deputy representative of RESIST Research Unit A.

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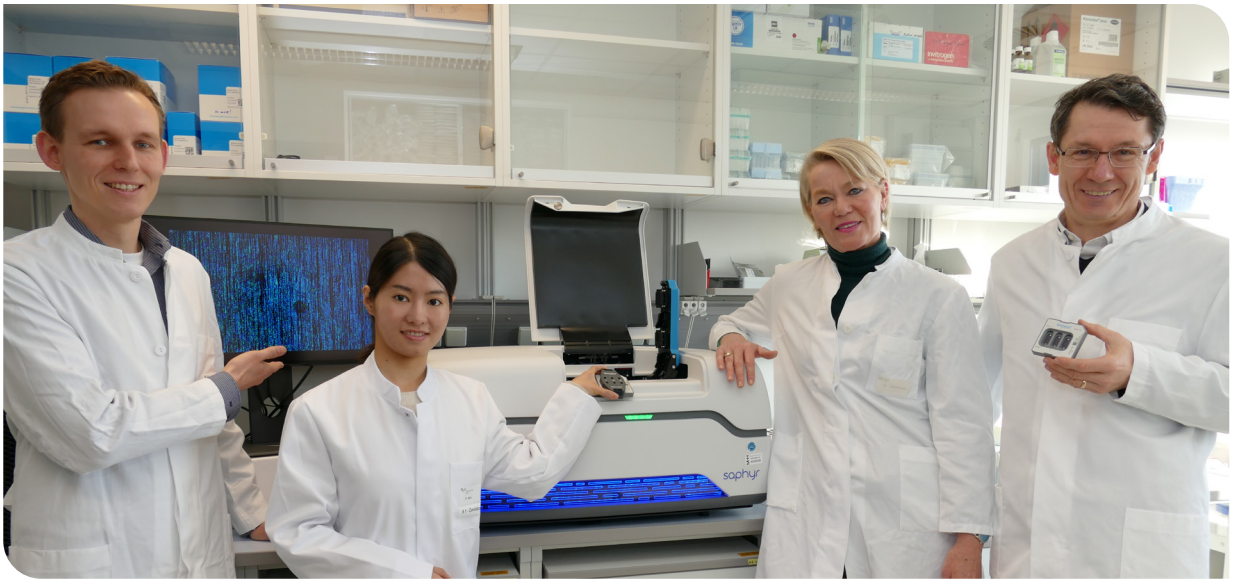
Genome analysis:
New technology established

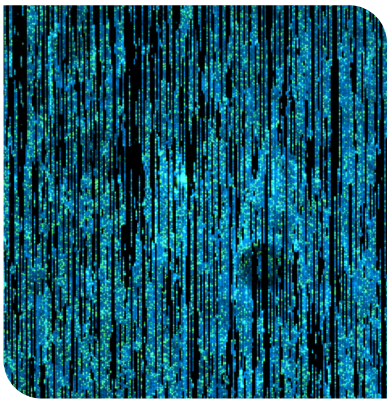


They are proud of the new large-scale genomic analysis instrument: Dr. Schieck and Rensheng Wan, Professor Dr. Steinemann and Professor Dr. Illig (from left).

The RESIST team of Professor Dr. Doris Steinemann and Professor Dr. Thomas Illig (right) is proud of a new large-scale genomic analysis instrument: the BioNano Saphyr. This technology can be used to investigate genetic changes that underlie diseases and are difficult to detect with conventional sequencing technologies. The new instrument was financed half by RESIST (i.e. by the German Research Foundation, DFG) and half by the MHH. "We are now one of six locations in Germany where such genetic analyses can be performed. We invite all researchers working in RESIST to cooperate with us," says Professor Steinemann. Initially, the team will focus on congenital immunodeficiencies. An important goal is to diagnose as many people as possible with a congenital immunodeficiency at an early stage and to better understand the genetic causes.

The first twelve patients have already been analysed and different structural variants identified. Which of these variants are related to the observed disease has now to be further explored. The technique has great potential for future research projects. "It is now possible to clarify a large number of previously diagnostically unsolved cases from various disease areas. The analysis is not limited to human DNA, for example bacterial samples can also be examined," explains Professor Illig.

"Basically, BioNano is a highly specialised microscope for observing extremely long fragments of chromosomal DNA. We use it



Analysis result of the new technology: The basic DNA framework is blue and the specific recognition sequences are coloured in green.

to look at every part of the genome up to 200 times," explains Dr. Maximilian Schieck. The new technique is an alternative analysis method for cases that could not be clarified with the currently widely used next generation sequencing technologies (NGS).

Conventional next generation sequencing (NGS), which is mostly done using the Illumina technology, can be used to detect pathogenic gene variants. However, this is only possible for certain gene variants occurring in a proportion of patients and is highly dependet on the disease. Conventional NGS techniques may fail to detect structural gene variants that are responsible for the disease. With the aid of the new BioNano technique, it is for example possible to determine, whether a gene is present twice or located at the correct position in the genome. Therefore long-chain DNA molecules with an average length of 275,000 base pairs are first isolated from patient samples, labelled with a dye at specific sequences, visualised on the BioNano Saphyr and then assembled by specific software into longer genome segments. This newly assembled genome is in the next step compared to reference genomes to identify structural variants.

If you are interested in cooperation, please contact Dr. Schieck and Professor Dr. Steinemann at the MHH Institute of Human Genetics.

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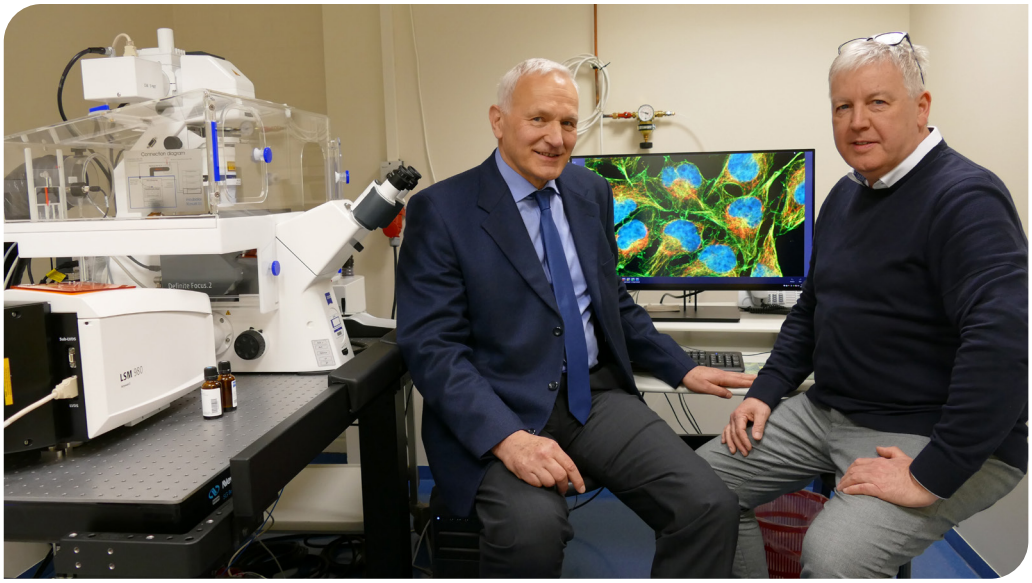
New equipment in Laser Microscopy and Structural Biochemistry



In Laser Microscopy: Professor Dr. Dietmar Manstein (left) and Dr. Rudolf Bauerfeind.

New equipment is available at the Central Research Facilities Laser Microscopy and Structural Biochemistry of MHH: a laser microscope, an analytical ultracentrifuge and a "high-throughput incubation and imaging system" for crystal growth. The German Research Foundation (DFG) has approved the acquisition of the large-scale research equipment within the framework of the "large-scale research equipment" programme and, together with the state of Lower Saxony, has provided more than 1.7 million euros in funding. Being able to use the techniques are: RESIST scientists, all researchers at the MHH and other interested parties.

The new microscope is the "inverse laser scanning microscope Zeiss LSM 980 with Airyscan 2 and multiplex mode". Laser microscopy can be used to observe dynamic changes in living cells in three dimensions – for example processes of immune defense or interactions between disease-causing organisms and host cells. "The new microscope allows fast imaging of large fields of view with high resolution – and with increased quality due to a better signal-to-noise ratio and a lower photon load in comparison to previous methods" says Professor Dr. Dietmar Manstein, who as head of the Institute of Biophysical Chemistry has acquired all the new large-scale research equipment. The central research facilities Laser Microscopy and Structural Biochemistry are affiliated to his institute.

Dr. Rudolf Bauerfeind is in charge of Laser Microscopy. This research facility supports scientists by providing access to a wide range of microscope systems and services. The new microscope is currently in test operation. Scientists can register for a training course and use it independently after instruction.

The two other new large-scale facilities are located in the Research Facility Structural Biochemistry: The new analytical ultracentrifuge enables the qualitative and quantitative characterization of interactions of proteins, nucleic acids and ligands in solution. Among other things, quantitative interaction studies of spectroscopically distinguishable molecules and investigations of large complexes and unstable proteins can be carried out more effectively than before. With the help of the new "high-throughput incubation and imaging system" for crystal growth, the crystallization of proteins can be optimized, which is necessary to determine the spatial structure of these proteins.

Further information can be found on the Internet via the links:
www.mhh.de/institute-zentren-forschungseinrichtungen/lasermikroskopie
and
www.mhh.de/structural-biochemistry.

Impressum

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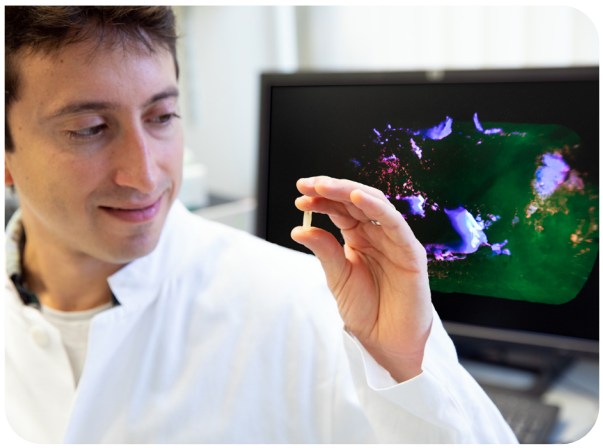
Immune system enhances the formation of biofilms

THE IMMUNE SYSTEM FIGHTS AGAINST THE FORMATION OF BIOFILMS. OR AT LEAST THAT IS WHAT SCIENTIST HAD ASSUMED. BUT NOW RESIST RESEARCHERS, LED BY PROFESSOR DR. REINHOLD FÖRSTER, HAVE DISCOVERED THAT THE IMMUNE SYSTEM CAN ENHANCE THE FORMATION OF BIOFILMS. THEY DEVELOPED A NEW MOUSE MODEL FOR THEIR RESEARCH.

Biofilms – an important topic in the RESIST Cluster of Excellence – are well-organised microbial communities that can, among other things, colonise implants and are often neither affected by the immune system nor by antibiotics. Professor Förster, head of the MHH Institute of Immunology, and his research group have now established the first mouse model that can be used to investigate the formation and combating of biofilms. As part of a RESIST project, Dr. Rodrigo Gutierrez Jauregui was able to gain initial insights and publish them in the journal "Frontiers in Immunology". "In contrast to the previous assumption that the immune system counteracts the formation of biofilms, it has been shown that the defense mechanisms promote the formation of biofilms," said Professor Förster. The mouse model enables subsequent research and the development of new therapies. The team implanted osmotic pumps into mice. Biofilms grew on the pumps, which were used to supply immune-cell-activating substances such as cytokines. Thus, the effect of immunological responses on biofilm formation could be studied *in vivo*.



Dr. Rodrigo Gutierrez Jauregui: He holds an osmotic pump in his hand with which the formation and control of biofilms (seen in the background) can be investigated.

You can find the original publication "IL-1ß Promotes *Staphylococcus aureus* Biofilms on Implants *in vivo*" in "Frontiers in Immunology" 2019.

Immunodeficiencies:
Towards better diagnoses and treatments

Collecting data from patients in registers is an important basis for subsequent research.

How many people in Germany have an inherited congenital immunodeficiency that makes them particularly susceptible to infectious diseases? And which of the approximately 200 known forms do they have? In order to be able to answer questions like these, data on patients have been collected since 2009 in the German National Register for Primary Immunodeficiencies (PID-NET). Professor Dr. Bodo Grimbacher, Centre for Chronic Immunodeficiency at the University Hospital of Freiburg and his team have now analysed the data of the approximately 2,400 patients and published their findings in the scientific journal "Frontiers in Immunology". The results of this study form an important basis for research of the Cluster of Excellence RESIST.

On average, 2.7 of every 100,000 inhabitants have a congenital immune deficiency. More than half of them have not enough functional antibodies. A further 22 percent show immune dysregulation – often an autoimmune disease. The first symptoms, mainly infections, can occur at any time in the course of a lifetime – from birth to late adulthood. "The results will ultimately lead to faster diagnoses and better treatments," says Professor Grimbacher.

You can find the original publication "The German National Registry of Primary Immunodeficiencies (2012-2017)" in "Frontiers in Immunology" 2019.

RESIST cohort

Why does one patient suffer only mildly from an infection, but the other severely? What role do the immune system and genes play? In order to be able to answer questions like these, it would be ideal to examine healthy and sick people in the same way and compare the results. Our Cluster of Excellence RESIST will make it possible in the future. Since mid-December 2019, RESIST clinicians and scientists have begun to recruit a group of healthy citizens from Hanover. These volunteers will be examined clinically, will donate a comprehensive set of samples and make their data available for research. In total, 650 individuals will be recruited in the new RESIST cohort by 2023. By March 2020 we will have recruited and examined about 100 participants. The cohort is organised and implemented by the teams around Dr. Yvonne Kemmling, and Professor Dr. Gérard Krause, Helmholtz Centre for Infection Research (HZI), Professor Dr. Thomas Werfel, MHH Department of Dermatology, Allergology and Venereology, Professor Dr. Martin Stangel, MHH Department of Neurology, Professor Dr. Thomas Schulz, Speaker of the Cluster of Excellence RESIST, MHH Institute of Virology, and Professor Dr. Thomas Illig, MHH Institute for Human Genetics, Hannover Unified Biobank (HUB).

For a comparison of healthy volunteers with patients, two parallel patient cohorts on herpes diseases are currently created: The "Zoster Cohort" for people suffering from severe shingles, caused by the varicella zoster virus and the "Herpes Cohort" for people which suffer from severe skin diseases such as eczema herpeticatum, caused by herpes simplex infections and which usually occurs in connection with atopic dermatitis. The central question for each cohort is: Which mechanisms lead to a severe course of disease? Viral DNA is also analysed in order to link individual virus strains with clinical courses and experimental data.

The patients will be admitted to the cohorts via the MHH Clinic for Dermatology, Venerology and Allergology or the Clinic for Neurology. Each of the two cohort should include 150 patients in the course of the RESIST funding period. First patients should be recruited from mid-March 2020. Potential volunteers can be reported by other MHH-clinics: Phone: 17-9859.

You can find more information at:
www.RESIST-studie.de

New strategy for vaccine development

RESIST SCIENTIST PROFESSOR DR. MICHAEL MEYER-HERMANN HAS USED COMPUTER SIMULATIONS TO INVESTIGATE HOW THE NATURAL FORMATION OF RARE ANTIBODIES WITH SPECIAL PROPERTIES IS PROMOTED: THESE SO-CALLED BROADLY NEUTRALISING ANTIBODIES CAN BIND TO VIRUS COMPONENTS THAT DO NOT CHANGE SIGNIFICANTLY AND ARE THEREFORE VERY EFFICIENT IN INHIBITING THE ENTRY OF THE VIRUSES INTO CELLS.

Vaccination situation: New, adapted vaccines against influenza viruses must be used every year.

Most components of HIV, influenza or hepatitis viruses can change rapidly. This means, that new, adapted vaccines must be used against influenza virus every year, so that people – in particular with a weak immune system – can be protected. A common influenza infection can be life-threatening for immunosuppressed individuals. The results of Professor Meyer-Hermann's computer simulation suggest that it is possible to promote a natural formation of broadly neutralising antibodies by injection of antibodies against dominant viral components. The newly gained knowledge provides a basis for the development of new innovative vaccines and therapies. The research results were published in the prestigious journal "Cell Reports".
More information can be found on the homepage of Professor Meyer-Hermann's research group "System Immunology" at the Helmholtz Centre for Infection Research (HZI) in Braunschweig.

The original publication "Injection of Antibodies against Immunodominant Epitopes Tunes Germinal Centers to Generate Broadly Neutralizing Antibodies" can be found in "Cell Reports" 2019.

DFG Acknowledgements

The German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) is funding RESIST with approximately 32 million euros between 2019 and 2025. Without their support our scientific work in RESIST would not be possible. RESIST is also evaluated by the DFG, not least on the basis of published work. Therefore, it is important to acknowledge the DFG correctly within RESIST publications and mention the DFG and the identification number (ID) of the cluster. The following wording is important: "... funded by the Deutsche Forschungsgemeinschaft (DFG) as part of the German Strategy for Excellence - EXC 2155 "RESIST" - Project ID 39087428.

RESIST live on stage

COFFEE IS GOOD FOR THE LIVER! THIS IS ONE OF THE MANY INTERESTING MESSAGES THAT RESIST RESEARCHER PROFESSOR DR. MARKUS CORNBERG AND PD DR. BENJAMIN MAASOUMY GAVE TO THE APPROXIMATELY 320 GUESTS WHO HAD COME TO "SCHLOSS HERRENHAUSEN" FOR THEIR PRESENTATION ON THE EVENING OF JANUARY 22ND.

They reported interesting messages about the liver: PD Dr. Benjamin Maasoumy (left) and Professor Dr. Markus Cornberg (right) in "Schloss Herrenhausen".

The RESIST researcher from the MHH Department of Gastroenterology, Hepatology and Endocrinology, and his colleague fascinated their audience in an entertaining and really funny way with a humorous stage dialogue as part of the "Herrenhausen Late" event series of the Volkswagen Foundation.

Based on a fictitious medical history of the patient Gisela, who came to MHH with jaundice, they explained diverse functions of our central metabolic organ and gave insights how liver diseases can be detected, especially jaundice. During their talk both speakers constantly involved the audience, who became increasingly enthusiastic about this organ. They illustrated that being overweight or obese can lead to fatty liver and consequently to cirrhosis of the liver, as can the excessive consumption of sugar, especially fruit sugar. "Moderate alcohol consumption – up to 125 millilitres of wine a day for women, five evenings a week at most – is something the liver can cope with quite well. For men it is twice as much," says Professor Cornberg. "But smoking is definitely bad," adds PD Dr. Maasoumy. Of course, our genes also play a role: "Some gene mutations lead to the fact that you can drink more without getting a fatty liver. But there are also mutations where the opposite is the case," explains Dr. Maasoumy.

Viruses can also cause liver inflammation. There are 5 hepatitis viruses, numbered as A, B, C, D and E. "In the 1980s, the hepatitis C virus was not yet known, but today, hepatitis C can even be cured. The MHH has played a major role in this success story," Professor Cornberg summarises. As part of RESIST, which is mainly located at MHH, he is working on a Hepatitis C vaccine in a team with other experts such as Professor Dr. Thomas Pietschmann. The speaker of the Cluster of Excellence RESIST, Professor Dr. Thomas Schulz, was also among the guests. He addressed a short greeting to the audience and explained the research that goes on in the Excellence Cluster: "Some people become only mildly ill when they "catch" viral or bacterial infections, whereas others are affected much more severely. But what are the reasons for these differences? And how can the course of a disease be predicted and personalised treatments developed? These questions are being addressed by the RESIST Cluster of Excellence teams", he said.

When Professor Cornberg asked "Who eats ground pork?" many member of the audience replied that they did. "Consumption of raw pork can lead to hepatitis E infections. Up to one in five people may have had one. This is not a huge drama for healthy people, but people with a weak immune system should rather avoid ground pork," said Dr. Maasoumy. "I really liked the dynamic between the two and enjoyed listening to their dialogue," says 30-year-old student Ben. "The two doctors addressed many exciting topics and explained everything very clearly. I particularly liked the fact that the common thread was a patient story," says 26-year-old PhD student Anna. 30-year-old Björn found the lecture very entertaining, amusing and vivid. He was particularly interested in RESIST research and the fact that coffee is healthy for the liver. Why can't you go wrong with three or four cups of coffee a day? "The beneficial effect of coffee on the liver probably depends on the mix it contains – for example, its polyphenols play a role," explains Professor Cornberg.

After the lecture, some guests considered having their liver values checked while enjoying a glass of water or wine – or the alcohol-free cocktail "Gisela".

The clinicians and scientists working in the Cluster of Excellence RESIST (Resolving Infection Susceptibility) aim to offer scientific excellence for the people most vulnerable to infections. RESIST researchers work at **Hannover Medical School** (MHH), **TWINCORE** Centre for Experimental and Clinical Infection Research, **Helmholtz Centre for Infection Research** (HZI) in Braunschweig, **Center for Structural Systems Biology** (CSSB) in Hamburg, **Centre for Chronic Immunodeficiency** in Freiburg and the **University of Veterinary Medicine Hannover, Foundation**. The work of the Cluster of Excellence RESIST is funded by the **German Research Foundation** (DFG).