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NEWS

RESIST – Resolving Infection Susceptibility

Research concerning **SARS-CoV-2**

WELL-KNOWN VIRUSES, FIT ANTIBODIES AND EVEN DRUG BANKS WILL HELP TO IDENTIFY NEW TESTING METHODS, THERAPIES AND VACCINES

Corona research in the S3 laboratory

Numerous RESIST scientists from various RESIST institutions have started their research on SARS-CoV-2 for several months now, and they have already been able to gain very interesting and important findings and publish them in renowned scientific journals. We are pleased to report on a large number of these projects, current activities and research results. Some of the projects are generously supported by the State of Lower Saxony and, of course, there are also other subsidies. In the following article, you can learn for example how well-known viruses, fit antibodies and even drug banks are helping to find new test methods, therapies and vaccines against SARS-CoV-2. In addition, we also report about an antibody test, a coronavirus module and an infinite loop.

With smallpox vaccination vector against SARS-CoV-2

In his search for a suitable vaccine against the coronavirus SARS-CoV-2, Professor Dr. Reinhold Förster relies on old friends. In cooperation with the Ludwig-Maximilians-University Munich (LMU), the co-speaker of RESIST and head of the Institute of Immunology, Hannover Medical School (MHH), is testing a promising vaccine based on the smallpox virus: He uses the Modified Vaccinia Virus Ankara (MVA) as a gene shuttle and additionally inserts the construction instructions for the so-called spike or S protein of the surface of SARS-CoV-2. The S protein enables the viral infection of host cells. The viral fragment is intended to stimulate the body's immune system to produce protective antibodies against the corona virus. ▶

To understand

why some people are more susceptible to infections than others, in order to protect each individual as well as possible – with this RESIST goal in mind, our researchers have been able to gain numerous new insights during the last months and publish them in scientific journals. Of course, a lot of attention was focused on SARS-CoV-2. But even beyond that, the thread of exciting research results did not break.

For example, our experts discovered the "gold" in breast milk (page 8), extended our knowledge about the immune system at the time of birth (page 6) and established a new liver cell model helping to expand the knowledge of the hepatitis C virus infection (page 7).

We are also particularly pleased to welcome new associated scientists as members of our Cluster of Excellence RESIST (page 10) and we congratulate Professor Dr. Yang Li on receiving an ERC Starting Grant and Gisa Gerold on her professorship (page 9).

Please remember to attend the (virtual) RESIST seminar on Thursdays (page 11). We would also like to invite you to the new RESIST Methods Seminar, which is mainly directed at RESIST postdocs and PhD students (page 12).

These and other articles about what is happening in our Cluster of Excellence can be found on the following pages of this newsletter and at our homepage www.RESIST-cluster.de. We are happy to keep you up to date,

your RESIST speaker team

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

> WE ARE LOOKING FOR ANTIBODIES THAT PREVENT THE VIRUSES FROM BINDING TO THE HUMAN CELLS
>
> Professor Dr. Thomas Schulz

Professor Dr. Reinhold Förster

"A genetically modified MVA has already been developed by my Munich colleague Professor Dr. Gerd Suttner against the related MERS virus and successfully tested on dromedaries," explains Professor Förster. The smallpox vaccine against SARS-CoV-2 will now be used and initially tested on mice. Unlike in Munich, the MHH scientists administer the vaccine via the respiratory tract. "In our opinion, vaccination via inhalation has the advantage that it triggers a particularly strong immune response exactly where the virus hits most aggressively – namely in the lungs," says the immunologist.

If the vaccination is successful in animal experiments, it will also be tested on humans. Additionally, Professor Förster wants to develop a new test for detection of SARS-CoV-2. This test will not only detect antibodies against the virus, but also show how well these antibodies protect against re-infection. "This is important to identify all those people who have gone through an infection without symptoms and are now immune without knowing it". The Ministry of Science and Culture of Lower Saxony (MWK) is supporting this project with 1.7 million euros.

Fit antibodies should help

People who recovered from the infection with SARS-CoV-2 have protective antibodies in their blood, some of those are particularly effective. Detecting these highly potent antibodies, producing them genetically in the laboratory and then using them for protection against infection and therapy – this is the goal of the team led by RESIST speaker Professor Dr. Thomas Schulz, MHH Institute of Virology, RESIST researcher Professor Dr. Thomas Krey, Institute of Biochemistry, University of Lübeck, as well as Professor Dr. Rainer Blasczyk, MHH Institute of Transfusion Medicine and Transplant Engineering, and Professor Dr. Axel Haverich, MHH Clinic for Cardiac, Thoracic, Transplant and Vascular Surgery.

"We are looking for antibodies that prevent the viruses from binding to the human cells – i.e. that have a neutralising effect – and that are also able to recognise dangerous corona viruses that may already be known or that may be transferred to humans in the future," says Professor Schulz.

The team will initially detect highly potent antibodies in blood samples from recovered patients. "We primarily need samples from people who have produced a particularly high number of protective antibodies after overcoming COVID disease. This is the case in ten to 15 percent of all patients," says Professor Schulz. Antibody-producing cells as B-lymphocytes are isolated from donated samples.

Then the most effective antibodies are cloned in the laboratory using genetic engineering techniques – building on the expertise of Professor Krey. The generated antibodies will also be tested in animal models by the team of Professor Dr. Albert Osterhaus, University of Veterinary Medicine Hannover, Foundation (TiHo). "A therapeutic agent made from genetically engineered antibodies might be available next year at the earliest," says Professor Schulz.

Professor Dr. Thomas Schulz

The team also receives blood samples from patients from Professor Dr. Markus Cornberg, MHH Clinic for Gastroenterology, Hepatology and Endocrinology, and Professor Dr. Marius Hoeper, MHH Clinic for Pneumology. Lower Saxony Ministry of Science and Culture is supporting this project with around 1.2 million euros.

Professor Dr. Thomas Pietschmann

Search in the substance collection

In order to find a drug for the treatment of COVID-19, an international consortium of scientists is searching for substances that act against SARS-CoV-2 in the world's largest substance repurposing bank "ReFrame". The collection comprises around 14,000 approved drugs as well as active ingredients for which extensive safety data are already available with regard to their use in humans. Several laboratories in the USA, four in the UK and one each in China and Germany are involved in the search.

MHH Professor Dr. Thomas Pietschmann, researcher of the Excellence Cluster RESIST and TWINCORE, is head of the work taking place in Germany. He is working with Professor Dr. Thomas Schulz, RESIST speaker and Director of the MHH Institute of Virology, to determine whether the reproduction of the virus is inhibited. For their analysis, they are using a robot that is operated within the framework of the German Center for Infection Research (DZIF) and a genetically modified"common cold" coronavirus developed by Professor Dr. Volker Thiel from the Institute of Virology and Immunology at the University of Bern. "ReFrame" was established by Scripps Research, California, in 2018 with the support of the Bill & Melinda Gates Foundation.

"The entire bank has already gone through the primary screen and we have found 140 primary candidates and confirmed them with dose titrations. Currently, the confirmation of these compounds with tests against the SARS-CoV-2 virus is underway," explains Professor Pietschmann. "Once we have found substances that can inhibit replication of this virus, we will look at how they work in the human lung cell, why they inhibit replication and what dose is required to do so." Chemical-biological properties of selected active substances are investigated in cooperation with Professor Dr. Mark Brönstrup, Helmholtz Centre for Infection Research in Braunschweig and DZIF. In the future, clinical studies can then be carried out. "I am very hopeful that our orientation study, which we are making publicly available, will provide starting points for drug development against COVID-19," says Professor Pietschmann. The MWK is supporting this project with around one million euros.

Biobank collects COVID-19 samples

In the Hannover Unified Biobank (HUB), headed by RESIST researcher Professor Dr. Thomas Illig, a COVID-19 cohort is currently under development: a collection of biosamples and data of 1,000 patients suffering from SARS-CoV-2 as well as control samples of people with other respiratory diseases from various clinics of the MHH and the Klinikum Region Hannover (KRH). The samples include blood cells, plasma, saliva, urine and cells from the respiratory tract and have already been made available to numerous researchers at the MHH and the HZI for molecular analyses. The team of RESIST researcher Professor Dr. Markus Cornberg, MHH Clinic for Gastroenterology, Hepatology and Endocrinology, is responsible for the processing of living blood cells. The analyses of the biosamples as well as precise information on the individual patients, such as age, sex, course of the disease, laboratory values, drug intake or nicotine consumption, should help to solve the mystery of COVID-19. "We suspect that a mixture of an overreacting immune system, individual genetic features and metabolic processes is responsible for the very different degrees of disease severity," explains Professor Cornberg. The Ministry of Science and Culture of Lower Saxony (MWK) is supporting this project with more than two million euros.

Infection monitoring

RESIST researcher Dr. Stefanie Castell at the HZI records how often immunocompromised patients, who for example have a previous infection such as HIV, are infected by SARS-CoV-2 or become seriously ill after an infection. The study is funded by the Ministry of Science and Culture of Lower Saxony. This so-called infection monitoring is carried out with usage of an application named PIA (Prospective Monitoring of Acute Infection Application) developed by the HZI Department of Epidemiology. PIA is used as a symptom diary in the context of COVID-19 and was already applied in the NAKO Health Study to investigate acute respiratory diseases. Project partner at MHH is Professor Dr. Georg Behrens. More information about PIA can be found online at: https://info-pia.de/pia-english-2/

From the left: Professor Dr. Thomas Illig and Professor Dr. Markus Cornberg

Strong together

NUMEROUS RESIST SCIENTISTS PROVIDE IMPORTANT INFORMATION ON SARS-CoV-2

Professor Dr. Luka Čičin-Šain has developed an antibody test for SARS-CoV-2 at the HZI. This is a so-called neutralisation test, which can be used to measure the antiviral capacity of antibodies in blood samples in response to an infection or of monoclonal antibodies developed as immunotherapeutics against SARS-CoV-2. A sensitive high-throughput test developed in his lab is used therefor. Antibodies already identified in this process are now undergoing safety testing before they can be applied therapeutically in clinical trials. Furthermore, his lab is developing technologies for the identification of infected cells by fluorescent reporter genes. These technologies should help to better diagnose the viruses in the blood, develop vaccines and identify antiviral molecules against SARS-CoV-2. His group has already posted several findings on virus inhibition, tropism – the ability of the virus to penetrate and multiply in a particular cell type – and viral evolution on preprint servers and is currently working on the development of animal models to study SARS-CoV-2 infection.

Professor Dr. Kay Grünewald, Heinrich-Pette-Institute, Leibniz Institute of Experimental Virology and University of Hamburg at the Centre for Structural Systems Biology (CSSB) in Hamburg, and his colleague, RESIST researcher Dr. Ulrike Laugks, helped to clarify how corona viruses "rebuild" infected cells in the course of their replication. As part of an international team, coordinated by researchers at the University Hospital Leiden, they were able to contribute structural data revealing the mechanism by which newly formed viral genomes can leave their double-membrane enveloped "niches". The work was published in the journal "Science". The discovered pore-like protein structure is a possible new approach for the development of antiviral drugs.

Professor Dr. Ulrich Kalinke is developing a preclinical mouse model for SARS-CoV-2 infection at TWINCORE, which can be used as a basis for the development of vaccines and antiviral agents. Another mouse model will also be established to investigate the questions why some patients lose their sense of smell as a result of COVID-19 disease. He is also interested in the B-cell responses of patients recovered from COVID-19 disease with the aim to isolate monoclonal antibodies from B memory cells for therapy. These antibodies will be tested for binding and neutralisation of the virus. Promising candidates will be transferred into clinical trials as soon as possible. Prof. Kalinke cooperates with the RESIST researcher Professor Dr. Torsten Witte, MHH Clinic for Immunology and Rheumatology, and Professor Dr. Rainer Blasczyk, MHH Institute for Transfusion Medicine and Transplant Engineering, among others.

Professor Dr. Gérard Krause at the HZI is investigating the dynamics of infection spread of the novel coronavirus in the population. His team has added the "coronavirus module" to the App SORMAS developed at the HZI. With this module, even in peripheral regions, individual cases of COVID-19 patients can be recorded at an early stage, clinical details and laboratory confirmations documented and all contact persons accompanied. In cooperation with the Natural and Medical Science Institute at the University of Tübingen in Reutlingen his department has developed a test that is more sensitive than other tests to detect antibodies against different coronaviruses in a differentiated manner. Professor Krause also coordinates the EU project CORESMA, which is supporting the management of the COVID-19 pandemic in Africa, Asia and Europe with the help of serological studies, modelling and digital health.

Professor Dr. Immo Prinz and Professor Dr. Reinhold Förster are investigating at the MHH how the immune system reacts to SARS-CoV-2 in a study led by Dr. Christian Schultze-Florey and Professor Dr. Christian Könecke, in which Professor Dr. Markus Cornberg is also involved. For example, the team already found out that in severe courses of COVID-19, all lymphocyte subtypes were reduced compared to healthy controls. This was significantly less pronounced in mild disease courses. In addition, the team observed that in COVID-19 patients with mild diseases, the number of effector cells increased significantly in parallel with disease improvement. The dynamics of lymphocyte subtypes and effector T cells could therefore serve as biomarkers to assess the severity of the disease at an early stage by measuring the immune status.

Professor Dr. Yang Li, Centre for Individualised Infection Medicine (CiiM) in Hannover and Helmholtz Centre for Infection Research (HZI) in Braunschweig, contributed her expertise in computational biology on the study of gene activity of individual cells during SARS-CoV infection within the national consortium "German COVID-19 OMICS Initiative" (DeCOI)". A study conducted by this consortium showed that during a severe COVID-19 disease, not only does a strong immune response occur, but also the immune response is trapped in a continuous loop of activation and inhibition.

Professor Dr. Michael Meyer-Hermann at the HZI dedicates himself to mathematical modelling in order to gain insights into the risk assessment of the coronavirus pandemic. Together with the Forschungszentrum Jülich, he simulated the effects of various conditions on the development of the COVID-19 pandemic in Germany and was able to predict that the restrictions in social life would allow a further slowing down of the spread. His team described a method for the daily situation assessment in which the basic reproduction rate plays a major role. The basic reproduction rate indicates the average number of people infected by an infected person and is therefore an important indicator for the speed of pandemic spreading.

Professor Dr. Rolf Müller carries out diagnostic studies on COVID-19 at the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) in Saarbrücken in cooperation with the Saarland University Medical Center in Homburg. Data and blood samples are collected and analysed in order to better predict the course of disease of COVID-19 patients, identify high-risk patients at an early stage and develop new therapeutic procedures. He is also participating in a study on the prevalence of COVID-19 in nursing homes and care facilities. The aim of this study is to identify diseases as early as possible and support the affected institutions in this way.

Professor Dr. Guus Rimmelzwaan is working at the TiHo on vaccine development of candidates against the SARS-CoV-2 virus. In addition, his research aims at obtaining a better understanding of cell-mediated immunity to SARS-CoV-2 in humans.

Professor Dr. Albert Osterhaus works at the TiHo on candidate therapeutic antibodies that act against a certain protein on the viral envelope of SARS-CoV-2. The antibodies are intended to block the protein, thus neutralising and rendering harmless the corona virus SARS-CoV-2. In addition he works on the development of vaccine candidates that mimic parts of the same protein and therefore should induce protective antibodies.

Professor Dr. Till Strowig is analysing susceptibility of children to the coronavirus SARS-CoV-2 at HZI with the help of the LöwenKIDS cohort – among others in collaboration with Professor Dr. Gisa Gerold. This is a project of the German Centre for Infection Research (DZIF). They are studying the spread of the pathogen and also want to carry out antibody tests. The results will help to define the role of children in the viral spread.

Professors Rita Gerardy-Schahn, Françoise Routier, Gisa Gerold, Ulrich Kalinke and Thomas Pietschmann are partners in a project of the international research consortium iCAIR®. In this project, different drug banks are analysed with the aim of drug development against SARS-CoV-2. Good candidates of the drug library are chemically modified if necessary. In addition, the consortium is developing analytical concepts to investigate why older people show increased susceptibility to this virus.

Elected

RESIST Co-Speaker Professor Dr. Gesine Hansen, Director of the Clinic for Paediatric Pneumology, Allergology and Neonatology at Hannover Medical School (MHH), was appointed to the selection committee for the awarding of Alexander von Humboldt Professorships.

An Alexander von Humboldt Professorship is endowed with up to five million euros. It is awarded by the Alexander von Humboldt Foundation and financed by the Federal Ministry of Education and Research. Established researchers from abroad can receive this award for a research stay in Germany.

For example, RESIST researcher Professor Dr. Guus Rimmelzwaan, virologist at the University of Veterinary Medicine Hannover, Foundation (TiHo), is an Alexander von Humboldt Professor since 2018.

Professor Dr. Gesine Hansen

Starting signal birth – Immune earlier than expected

At the MHH Institute of Immunology: Professor Viemann, Dr. Fichtner, Professor Ravens and Professor Prinz (from the left) with reagents for the sequencing of T cell receptors

PROTECTION FROM THE BEGINNING: RESIST RESEARCH TEAM FOUND OUT THAT CERTAIN T CELLS EXPAND IMMEDIATELY AFTER BIRTH

They play an important role in the recognition of "danger" from invading pathogens and spread quickly and intensively during acute infections – we are talking about certain immune cells, which belong to the so-called gamma-delta T cells. These specialised white blood cells, known as Vγ9Vδ2 T cells are highly functional. Until now, it was assumed that they multiply slowly over the course of a lifetime, depending on bacterial and certain environmental factors, and that they continue with development of their necessary functions as defense cells.

However, a RESIST team has now discovered that these cells proliferate expansively in premature babies directly after birth and remain until childhood. Another research group has been able to gain similar findings during investigation of mature babies. "We assume that these gamma-delta T cells play an important role in early childhood immune defense and homeostasis and may even persist for a lifetime," says Professor Dr. Sarina Ravens. Together with Dr. Alina Fichtner, Professor Dr. Dorothee Viemann and Professor Dr. Immo Prinz, she has published these findings in the scientific journal "Proceedings of the National Academy of Sciences of the United States of America" (PNAS).

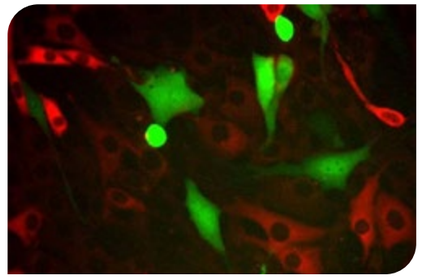
The RESIST scientists work in the Institute of Immunology as well as in the Clinic for Paediatric Pneumology, Allergology and Neonatology at Hannover Medical School (MHH). The blood samples required for this work come from cohorts led by Professor Viemann – among others from the PRIMAL study, which focuses on the immune development of premature babies. Now the research team wants to investigate the exact role of these gamma-delta T cells in the immune defense of newborns and children. The long-term goal is to develop better prevention, diagnosis and therapy options based on a more comprehensive understanding of the formation and regulation of the immune system of newborns.

Gamma-delta T cells have characteristics of the innate immune system with its rapid, beneficial response to many foreign substances and are produced in the fetal thymus around the eighth week of pregnancy. But they also have properties of the acquired immune system, which with its slower, very specific immune response leads to a long-lasting memory against subsequent challenges such as infections. They thus form a bridge between the innate and the acquired immune system. They are named after their T cell receptors – the protein complex on their surface that is responsible for the recognition of antigens. In order to investigate how these cells react to microbial exposure in newborns, infants and toddlers, the research team used the method next generation T cell receptor sequencing.

The defiance of viruses

PROFESSOR ČIČIN-ŠAIN HAS IDENTIFIED THE KEY FACTOR THAT VIRUSES USE TO PARALYSE IMMUNE DEFENSE MECHANISMS

Defense cells constantly patrol our tissues to detect pathogens. If they find body cells invaded by a virus, they instruct the infected to destroy themselves by a range of mechanisms that share a central switch. Viruses can block this important switch and thus prevent the cellular self-destruction. This discovery was made by the team around RESIST researcher Professor Dr. Luka Čičin-Šain at the Helmholtz Centre for Infection Research (HZI) in Braunschweig.



Human cells infected with cytomegalovirus (green) and those protected by interferons (red).

"Our findings lead to a paradigm shift in viral research and the interaction of viruses with the immune system," says the virologist, who is dedicated to cytomegalovirus (CMV) research. Professor Čičin-Šain described the observed mechanism at the molecular level, in animal models and during the infection of human cells. Previously, it was assumed that the viruses suppressed antigen presentation. Professor Čičin-Šain is certain that the survival mechanism described now will be identified in the same or similar way in the context of other viral infections.

The article is based on a press release of the HZI by Ulrike Schneeweiß. The original publication "Cytomegalovirus inhibition of extrinsic apoptosis determines fitness and resistance to cytotoxic CD8 T cells" can be found in "Proceedings of the National Academy of Sciences".

RESIST team develops a cell model for **host-HCV interactions**

The RESIST team led by Professor Dr. Thomas Pietschmann at TWINCORE – Centre for Experimental and Clinical Infection Research has improved a liver cell model to investigate the life cycle of the hepatitis C virus (HCV) and also the disease development caused by this virus in more detail.

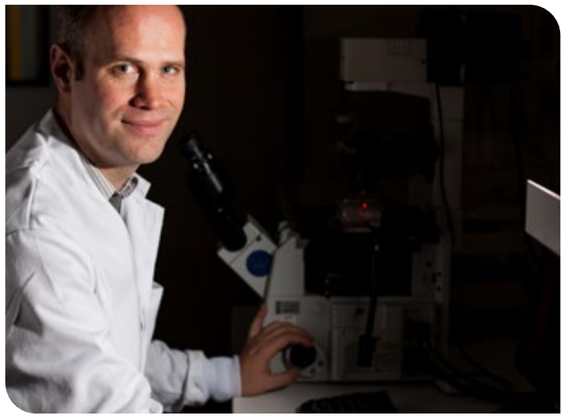
HCV and the human host cell interaction and their impact on both acute and chronic infections as well as the mechanisms of innate immune control can be studied using the adapted cell model.

The team published the findings in the high-ranking journal GUT. The first author is Dr. Arnaud Carpentier.

This liver cell model is based on "hepatocyte-like cells" (HLC) derived from human stem cells. The HLCs resemble authentic liver cells and function in a similar way.

Until now, this model has allowed the hepatitis C virus to replicate only to a limited extent. By using a highly replicating virus, the scientists could significantly improve the efficiency of this model.

They were able to show that the HLC's innate immune response is comparable to that of the primary adult liver cells, a critical feature missing in the widely used cell culture models based on transformed cell lines. "Cell models like these may help to discover new principles that govern the highly variable outcomes of HCV infection, thereby instructing personalised infection medicine," says Dr. Carpentier.



Dr. Arnaud Carpentier

The gold of **breast milk**

RESIST TEAM FOUND OUT: ALARMINS POSITIVELY INFLUENCE THE DEVELOPMENT OF THE INTESTINAL FLORA AND THE IMMUNE SYSTEM AFTER BIRTH. FOOD SUPPLEMENTS COULD PREVENT SEVERE INFECTIONS IN NEWBORNS AND LONG-TERM OBESITY.

Breast milk stimulates the child's immune system and strengthens the intestinal flora. This is well known. But why is that so and what are the underlying molecular mechanisms? And why can't bottled baby milk do that? A team of the Cluster of Excellence RESIST has now discovered that this happens through alarmins. "Alarmins are the gold of breast milk. These proteins prevent disturbances in the intestinal colonisation, which can lead to life-threatening blood sepsis and intestinal inflammation", says team leader Professor Dr. Dorothee Viemann from the Clinic for Paediatric Pneumology, Allergology and Neonatology at Hannover Medical School (MHH). The results were published in the high-ranking scientific journal Gastroenterology. The first authors are Maike Willers, MHH, and Dr. Thomas Ulas, University of Bonn.

After birth, the intestinal immune system – the intestinal flora and mucosa – largely evolves through interactions with bacteria from the environment: This creates a high bacterial diversity that is maintained throughout life and protects against many diseases. "At the same time, alarmins control this adaptation process," says Professor Viemann. Her research has shown that alarmins are formed by the breast milk, but are also developed in the child's intestines. The contractions are also responsible for this: Babies born by cesarean section have fewer alarmins than those born vaginally. Furthermore, premature babies produce fewer alarmins by themselves in comparison to mature babies. This can be the reason why people often suffer from chronic inflammatory diseases. For this research work, which was supported by the VolkswagenStiftung within the framework of "Offen – Für Außergewöhnliches" and by the Cluster of Excellence RESIST, the team measured the alarmin concentration in stool samples in children during the first year of life and investigated its effects on the development of the intestinal flora and mucosa.

Intensive care unit for premature and newborn babies at the MHH: Professor Dr. Dorothee Viemann (right) and Dr. Sabine Pirr with a premature baby. The photo was taken before the corona pandemic.

"If newborns do not produce enough alarmins or receive them through breast milk, a dietary supplement containing these proteins could support the development of newborns. It could also prevent numerous long-term diseases associated with intestinal colonisation disorders, for example chronic intestinal inflammation and obesity," says Professor Viemann. Her statements are based, amongst other things, on the fact that the single administration of alarmins in the mouse model could protect against poor intestinal colonisation and the associated diseases. The RESIST researchers now intend to carry out further preclinical and later clinical work based on their results.

Scientific writing:

Great participation in the "Nature" course

15 young RESIST researchers are currently taking part in the online course "Scientific Writing and Publishing". There they learn how to write and publish their research or review papers – from editors who work for one of the prestigious "Nature" journals. This course teaches scientific writing skills and confidence in writing for journals.

Moreover, participants learn about editorial processes, submission and peer review procedures directly from experienced colleagues. The course will be offered again next year if required. Interested RESIST scientists are welcome to contact us by e-mail from January 2021: RESIST@mh-hannover.de. More information about the course "Scientific Writing and Publishing" can be found on the homepage https://masterclasses.nature.com/. Further measures for promotion of young scientists by RESIS are described on the RESIST homepage.

Personalised vaccination strategies for improved effectiveness

ERC Starting Grant for Professor Dr. Yang Li

The European Research Council (ERC) has awarded RESIST researcher Professor Dr. Yang Li with an ERC Starting Grant – a funding of up to 1.5 million euros over a period of five years. The scientist is director of the Centre for Individualised Infection Medicine (CiiM), a joint institution of the Helmholtz Centre for Infection Research (HZI) and the Hannover Medical School (MHH). Professor Li analyses why the effectiveness of vaccines differs from person to person.

With the ERC-funded project "ModVaccine" she now wants to find out to what extent the effectiveness of a vaccine depends on genetic and non-genetic characteristics of a person as well as on environmental influences. In addition, the individual response to vaccinations will be investigated systematically.

Professor Dr. Yang Li

"The results of our research will enable to create reliable models for efficacy prediction of vaccines and to develop adapted personalised vaccination strategies against infections," says Professor Li. Contact: Yang.Li@helmholtz-hzi.de

Professor Dr. Gisa Gerold

Gisa Gerold is now **professor at the TiHo**

Since September 1st, RESIST scientist Dr. Gisa Gerold is Professor of Biochemistry – Molecular and Clinical Infectiology at the University of Veterinary Medicine Hannover, Foundation (TiHo). With her research group "Virus Interaction Proteomics", she will pursue to investigate zoonotic viral pathogens, which are viruses transmitted from animals to humans. She wants to understand the factors that determine which host is infected by a virus.

Moreover, she is analysing molecular mechanisms of infection with zoonotic pathogens to pave the way towards the development of novel effective drugs. She wants to discover how zoonotic agents cause disease, which tissues they affect and whether they can cause long-term consequential damage in the host organism. Pathogens in focus are SARS-CoV-2, mosquito-borne viruses such as chikungunya virus and virus causing encephalitis. Contact: Gisa.Gerold@tiho-hannover.de

Impressum

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WE ARE VERY PLEASED TO WELCOME OUR NEW RESIST SCIENTISTS

Welcome!

Professor Dr. Heiner Wedemeyer, Director of the Clinic for Gastroenterology, Hepatology and Endocrinology at MHH, has been working for many years on chronic viral infections of the liver, which can lead to liver cirrhosis and hepatocellular cancer. His team was able to demonstrate the importance of various immune cells such as T cells and natural killer cells (NK cells) for the control of hepatitis B, C and D. "The findings are particularly important for the use and control of antiviral therapies. A special focus in RESIST will be studies on hepatitis D, which is the most severe hepatitis infection," declares Professor Wedemeyer. Contact: Wedemeyer.Heiner@mh-hannover.de

Professorin Dr. Françoise Routier, Institute for Clinical Biochemistry, dedicates her research to biofilms – a matrix consisting of proteins, extracellular DNA and polysaccharides embedding microbial communities. Biofilms not only shield the microorganisms from the host immune system but also limit the efficacy of antimicrobials. "Our aim in the RESIST project C3 is to develop molecules preventing biofilm formation to facilitate clearance of the microbes by the host immune system and to enhance the efficacy of existing drugs", says Professor Routier. She characterises with her team bacterial and fungal enzymes involved in the biosynthesis of the polysaccharide component of the biofilm, defines the structure of these enzymes and searches for inhibitors. Contact: Routier.Francoise@mh-hannover.de

PD Dr. Roman Fedorov, Institute for Biophysical Chemistry of the MHH, focuses in his research on innate immunity – the ancient defense mechanism that was already protecting living organisms for half a billion years ago. In the course of evolution, pathogens have developed ways to evade innate immunity allowing spreading of the infection. However, in some cases the activation of the innate immune response can cause an intense inflammation leading to tissue damage. "Our team of the RESIST project D4 is developing molecular switches that can activate or inactivate this ancient mechanism, as an antimicrobial or anti-inflammatory therapy", PD Dr. Fedorov explains. Contact: Fedorov.Roman@mh-hannover.de

Dr. Stefanie Castell, Department of Epidemiology at the Helmholtz Centre for Infection Research (HZI) in Braunschweig, is infection epidemiologist and is interested in risk factors and predictors of acute infectious diseases that have a major impact on public health, especially for particularly vulnerable groups. These factors can be further investigated with the help of RESIST and the RESIST cohort. "The eHealth tool PIA, which we have developed, allows prospective data collection by performing survey of infection symptoms already during the disease" she says. Contact: Stefanie.Castell@helmholtz-hzi.de

Our new RESIST professors will be presented in the next issue of the RESIST Newsletter.

RESIST cohort extended

Due to the corona pandemic, recruitment of participants to the RESIST cohort had to be paused from mid-March to mid-June. Since then it has continued – of course under strict hygiene conditions. All participants have been or will now be asked about their experiences with symptoms and tests connected to the corona pandemic, social contacts and possible effects of the imposed restrictions. Those recruited since mid-June will be tested for SARS-CoV-2 antibodies in addition to all previously planned examinations.

The cohort currently being established by RESIST will help to better understand the relationship between the ageing process and changes in the immune system. It will include 650 randomly selected citisens from Hanover. The aim is to compare the obtained data with those of diseased patients in order to better understand and treat infections in the future.

"We are now also performing specific cellular tests with SARS-CoV-2 antigens in order to better understand the age-dependent immune mechanisms involved in the defense against this virus in comparison to other viral infections," says Professor Werfel, head of this study. The data of people who become infected over time will be compared with data of non-infected. Dr. Yvonne Kemmling is in charge of conducting this study. More information about the RESIST cohort can be found online at www.RESIST-cluster.de.

Professor Werfel (left) and Dr. Kemmling (right)

RESIST Seminars

Every Thursday (except during school holidays) two RESIST scientists or top-class researchers from external institutions present their work at the RESIST seminar series. The dates and titles of the presentations are published on the homepage www.RESIST-cluster.de as soon as they are known.

The seminars are taking place from 5 to 6 pm in lecture hall Q or lecture hall R (MHH building J6), unless otherwise stated. Due to coronavirus pandemic, lecture hall Q can hold 17 people and lecture hall R 46 people at the moment. Please wear a face mask when entering and leaving the lecture hall and keep the first four rows free.

Everybody has to follow the 1,5 m distance rules to another person, also during the lectures. We will transmit the talks via video.

If you are interested in participating via video (online) and not receiving the seminar announcements, please contact RESIST@mh-hannover.de.

08 October:
PD Dr. Jens Bohne and Dr. Adrian Kordes (Working Group Professor Häußler)

29 October:
Professor Dr. Rolf Müller and Professor Dr. Till Strowig

12 November:
Dr. Stefanie Castell and Professor Dr. Thomas Krey

19 November:
Professor Dr. Benjamin Willcox (Guest Lecture)

26 November:
Dr. Martin Empting and Dr. Szymon Piotr Szafrański (Working Group Professor Stiesch)

10 December:
Dr. Yvonne Kemmling and Professor Dr. Gérard Krause

17 December:
Professor Dr. Gisa Gerold and PD Dr. Roman Fedorov

On a visit: **Robert Habeck**

Robert Habeck (to see on the photo on the left), Federal Chairman of Bündnis 90/Die Grünen, visited the Hannover Medical School (MHH) on 31st of July. He was informed about patient care during the corona pandemic, about research activities on the SARS-CoV-2 virus, the COVID-19 disease and about the financial implications for the university hospital.

During his visit, Habeck was accompanied by Belit Onay (second from the right), Lord Mayor of the City of Hanover, and MHH President Professor Dr. Michael Manns (right). During his visit, he exchanged information in the central laboratory with RESIST spokesperson Professor Schulz (second from the left), among others. In the middle of the photo is Marlies Wehrhane, MHH-Institute of Virology.

Virtual Fair: **Research in Germany**

RESIST took part at the virtual career fair "Research in Germany" on July 7th, where numerous international students and postdoctoral researchers interested in doing research in Germany have been looking for the offered options. Professor Ravens and Professor Tümmler answered questions on research opportunities, which were mainly asked by (prospective) doctoral students and postdocs. More than 25 German universities and research institutions took part in this online meeting (a screenshot of the RESIST stand is shown on the right). "Research in Germany" is the central information platform of the initiative "Advertising Germany as a location for innovation and research" of the Federal Ministry of Education and Research (BMBF). The portal is edited by the German Academic Exchange Service (DAAD).

First **RESIST Methodological Seminar Series**

Postdocs and PhD students of the Cluster of Excellence RESIST apply excellent techniques in their laboratories, which they now present in the RESIST Methodological seminar: The seminar took place for the first time on 24th of September and the next date is 14th of October from 13.30 to 14.30 in the lecture hall S, MHH building J6. Coffee and cake are provided after each seminar. "The idea for the presentation and discussion is to create a more informal environment to better promote interactions within the groups," says the seminar organiser João Monteiro, PhD. For the other dates and titles of the presentations, please visit www.RESIST-cluster.de. Contact: TerenoMonteiro.Joao@mh-hannover.de

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, **Centre for Structural Systems Biology** (CSSB) Hamburg, Centre for Chronic Immunodeficiency 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).