Issue 2 . 2020 / August

PRO LOEWE NEWS

The LOEWE Research Initiatives report

MAIN TOPIC CORONA

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Cover picture: Graduated pipettes as receptacles for cell cultures to study the envelope protein of SARS-CoV2

THE TMP LOEWE CENTRE GETS INVOLVED IN THE FIGHT AGAINST THE CORONA PANDEMIC

The Fraunhofer IME division, which has evolved from the TMP LOEWE Centre (Translational Medicine and Pharmacology), is active in various research projects related to SARS-CoV2 and provides two members of the Fraunhofer crisis team.

The SARS-CoV2 coronavirus has rapidly developed into a global challenge. Health care systems around the world are reaching their limits and the economy is struggling with the effects of the pandemic. One reason for this is not least the lack of effective drugs or vaccines. The **TMP LOEWE Centre** with its focus on **Translational Drug Development** is involved in tackling the corona crisis at various levels.

Prof. Dr Dr Gerd Geisslinger, the spokesman for the LOEWE Centre and the Managing Director of the Fraunhofer Institute for Molecular Biology and Applied Ecology (IME), has been appointed to the crisis team of the Fraunhofer Society together with PD Dr Frank Behrens (Head of the Clinical Research Department at the Fraunhofer IME) so that they can contribute their medical expertise. The crisis team is developing the necessary measures for the entire Fraunhofer Society, is responsible for compliance with the pandemic plan and maintains constant contact with local crisis teams and the responsible authorities.

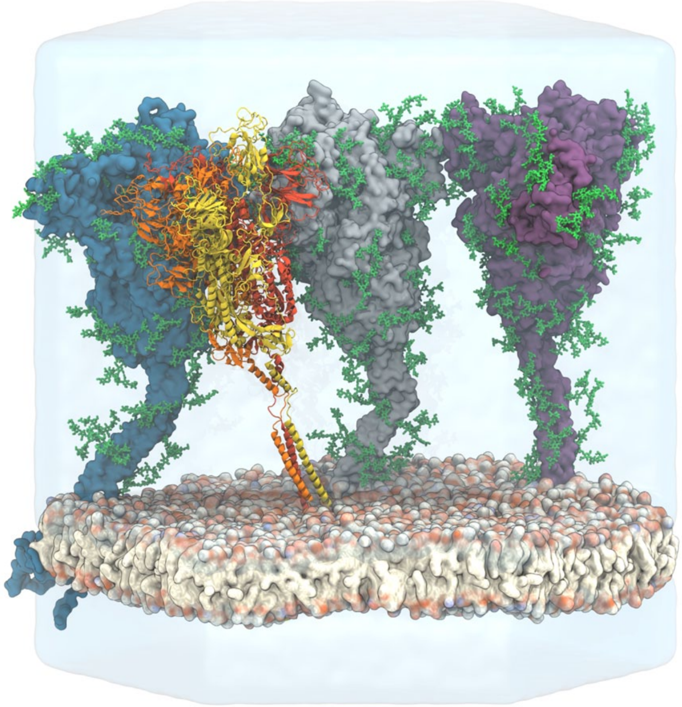
The TMP unit of the Fraunhofer IME is playing a major role in the corona task force at the University Hospital in Frankfurt/Main as part of the "National Corona Task Force" initiative. Standardising processes for collecting biospecimens, gathering data and completing clinical studies with Covid-19 patients is designed to make it possible to evaluate matters on a national scale.

The **TMP LOEWE Centre** is also involved in various research projects to combat the Covid-19 disease. These activities include the entire value-added chain from searching for an active substance to clinical development, but also clinical practice and support for the authorities in handling the corona situation. It is, for example, pursuing new approaches to blocking viral replication, testing drugs approved for other diseases to see whether they are effective against Covid-19 (drug repurposing) and conducting clinical tests on a new treatment to improve arterial gas exchange in severely ill Covid-19 patients. Other projects are focusing on the safety of blood pressure or antipyretic agents in patients with Covid-19, such as inhibitors of the renin-angiotensin system or Ibuprofen.

In another project, blood samples from patients, who are suffering from or have recovered from Covid-19, are being analysed in order to identify biomarkers and mechanisms associated with severe forms of the disease or the development of complications.

The **LOEWE Centre for Translational Medicine and Pharmacology** is also working to validate new kinds of rapid test methods to detect SARS-CoV2 or prove that people have recovered from the disease and develop text and data analysis methods to automate documentation processes and support public health authorities.

Numerous biomaterials for future research purposes are being stored in a biomaterials bank at the TMP LOEWE Centre so that they can also be sensibly used to answer new questions – and, among other things, conduct research into Covid-19 and the effect of a SARS-CoV2 infection on the immune system. It is absolutely essential to store the materials at temperatures of -80° C in line with the highest quality standards.



Magnification of the surface of a virion with four spike proteins embedded in the lipid bilayer. Source: Sikora et.al; Map of SARS-CoV2 spike epitopes not shielded by glycans bioRxiv 2020.07.03.186825 (Licence: CC-BY-NC-ND 4.0)

PROFESSOR DR. MATTHIAS HOLLICK, SPOKESPERSON FOR LOEWE-EMERGENCITY, APPOINTED TO THE „COUNCIL OF EXPERTS ON CYBER SECURITY"

Professor Matthias Hollick, the spokesman for the **emergenCITY LOEWE Centre** at the Technical University of Darmstadt, has been appointed to the „Council of Experts on Cyber Security". Just like the „Economics Experts", the Council of Experts on Cyber Security views itself as an committee of specialists, who express their views on cyber security issues that affect society as a whole and publish their findings in an annual report as recommendations for action by politicians and business people. The council was formed in 2019 and is coordinated by the Cyber Security Cluster Bonn e. V. It consists of six cyber security experts in all from different academic fields.

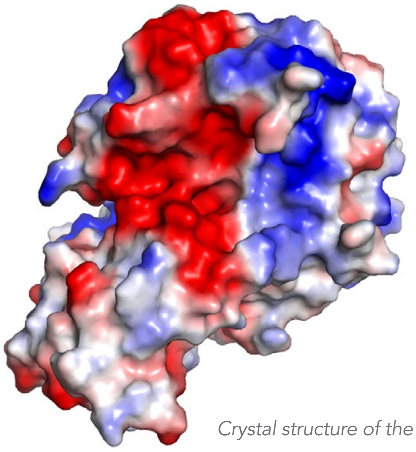
The Council's recommendations presented to the Federal Government in 2020 also involve so-called "smart cities". This is a concept for cities designed to be technologically and socially more advanced. The digitalisation of cities is a central design feature here. „Digital infrastructure in networked cities must be available, comprehensible and manageable at all times," Professor Matthias Hollick emphasises. "After all, crises such as cyberattacks, natural disasters, human and technical failure or violence and terror have threatened reliable operations of IT systems. It's therefore necessary to be able to guarantee that critical infrastructure will continue to operate, even in a crisis and when many people are using the network," he adds.

If you would like to learn more about this topic, please read the press release from the Technical University of Darmstadt entitled „Greater Security for Digital Transformation. First Report of the Panel of Experts on Cyber Security" published at https://www.tu-darmstadt.de/universitaet/aktuelles_meldungen/einzelansicht_264512.en.jsp. You will also find the link to the report there.

LOEWE-CMMS USES STATE-OF-THE-ART COMPUTER SIMULATION AND MATHEMATICAL MODELS TO CONDUCT RESEARCH INTO VACCINES AND STRATEGIES TO CURB THE COVID-19 PANDEMIC

It is necessary to consider many factors when conducting research into a new type of virus or epidemic. The biological and physical properties of SARS-CoV2 itself are interesting, for example, but also the way that the disease progresses and the dynamics related to its spread in the population. This is precisely the starting point for Maria Barbarossa's research. Maria Barbarossa is a scientist at the **CMMS LOEWE Cluster (Centre for Multiscale Modelling in Life Sciences)** and at the FIAS (Frankfurt Institute for Advanced Studies). She heads the CMMS sub-project entitled "Mathematical Immunoepidemiology" and she has been working on the dynamics of infectious diseases for several years. The mathematical models, which she has helped develop, made it possible to study the spread of COVID-19 in the German population during the first few weeks of the pandemic and therefore assess the introduction and impact of different control measures. The models that have been developed take into consideration various factors, such as age structure and the geographical distribution of the population; they can influence the probability of the virus spreading, but also the contact dynamics of people in different areas of life. In order to minimise the risk of possible future outbreaks of COVID-19, the models can be used to simulate strategies to curb the current pandemic on a computer and propose appropriate control measures.

The **CMMS LOEWE Cluster** is bringing together researchers from different disciplines to gain a comprehensive understanding of fundamental molecular biological processes. This broad-based expertise enables scientists to not only examine the question of propagation dynamics, but also other aspects of the corona epidemic. The search for a suitable vaccine is also a central topic for CMMS, for example, and the group is working on this with scientists from other research projects. One protein, the SARS-CoV2 spike (S) protein, is the central focus here. It is located on the virus surface and "opens the door" to ensure that the virus can enter the host cell. CMMS scientists Gerhard Hummer and Roberto Covino (Max Planck Institute for Biophysics and FIAS) are using state-of-the-art computer simulation processes to facilitate the development of a protective vaccine. They hope to use them to identify weak points on the surface of the S protein, which could be attacked by antibodies. This work is being consolidated in a fairly large cooperation arrangement with the EMBL (European Molecular Biology Laboratory), the Paul Ehrlich Institute and other research bodies.



Crystal structure of the human furin protein. (Graphic: Kornelia Hardes, Fraunhofer IME)

FIGHTING SARS-COV2 WITH INHIBITORS FROM THE PROTEIN SCISSORS FURIN – LOEWE-DRUID AND ZIB CONDUCT RESEARCH ON THIS ISSUE

Scientists around the world are working to find out how SARS-CoV2 enters the human body and what conditions it needs to do so. The envelope protein of coronaviruses, also known as the spike protein, plays an essential role in virus replication. It acts as a kind of key that enables the virus to enter the cell by binding to specific receptors. The virus can then channel the genetic information into the cell and multiply. Before the protein can take over these functions, it must be activated by cell enzymes called proteases. Analyses of the viral genome show that the structure of the spike protein in SARS-CoV2 is different in some areas to that of its close relation, SARS-CoV, which triggered a global pandemic with around 8,000 infected people in 2002/2003. The spike protein of SARS-CoV2 carries an activation sequence at the so-called s1/s2 cleavage site, which is well-known from dangerous bird flu viruses, but is not found in the similar SARS-CoV, for example.

Scientists working at the **DRUID LOEWE Centre**, led by Prof. Dr Eva Friebertshäuser and Prof. Dr Torsten Steinmetzer from the Philipps University in Marburg, have been able to show that an enzyme called furin is largely responsible for this activation process. Furin might be described as protein scissors that occur throughout the body. The enzyme cuts and activates numerous precursor proteins, including many hormones and receptors, but is also exploited by a broad range of pathogens such as Ebola or yellow fever viruses to activate their proteins. The use of furin inhibitors has been shown to significantly reduce the spread of SARS-CoV2 in human lung cells, making it an interesting target for antiviral therapy to treat Covid-19 infections. In addition to SARS-CoV2, furin inhibitors have already been successfully used in cell cultures against numerous other pathogens such as dangerous avian flu or dengue viruses.

However, furin is not only found in human cells, but also in many other species such as mosquitoes. Researchers at the **ZIB LOEWE Centre**, headed by Prof. Dr Andreas Vilcinskas, are working to develop strategies to combat mosquitoes and the infectious diseases that they transmit. The aim is to shed light on both the physiological functions of furin and its role in the insects themselves in the reproduction of different viruses that are transmitted by mosquitoes.

DR.-ING. ANDREAS NAU-GREDE NEW MANAGING COORDINATOR AT ALLEGRO

Dr.-Ing. Andreas Nau-Grede has been working as the coordinator responsible for management tasks for the **ALLEGRO LOEWE Cluster** at the Department of Separating and Joining Manufacturing Processes (tff) at the University of Kassel since August 2020. He replaced Dr.-Ing. Ghazal Moeini, who has accepted an appointment as professor for materials and joining technology at the Department of Mechanical, Environmental and Building Technology at the Westfälische Hochschule (Westphalian University of Applied Sciences) in Gelsenkirchen.

After spending more than four years in the automobile industry, to be precise, at Schaeffler Automotive Bühl GmbH und Co. KG, where he worked in the field of „quality assurance, damage analysis and material development", Andreas Nau-Grede has now returned to the University of Kassel. After studying mechanical engineering, he had already completed his doctorate there at the Institute for Materials Technology (IfW) in the field of residual stress analysis. His research work focused on extending the application thresholds for the borehole and toroidal core method. This topic was then addressed in a project backed by the Federal Ministry for Economic Affairs and Energy (BMWi) with the Gesellschaft für Reaktorsicherheit (GRS) as the project sponsor and the MPA Stuttgart (Materials Testing Institute) as the project partner.

Parallel to his doctorate, he completed a course in welding engineering. „The practical work that I enjoyed during my doctorate was the perfect balance to long days at my desk. I'm now looking forward to my new tasks at my ‚home university' in Kassel", says Nau-Grede. With his scientific and industrial expertise, the engineer has the ideal qualifications to actively contribute to the successful continuation of **ALLEGRO** (High-performance Components Made of Aluminium Alloys through Resource-Optimised Process Technologies).

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ProLOEWE. LOEWE Research Initiatives Network
Phone: +49 561.804-2348
kontakt-proloewe@uni-kassel.de
www.proloewe.de

Postal address:
Pro LOEWE
c/o Universität Kassel
Mönchebergstrasse 19
34125 Kassel
Germany

Person in charge: Tanja Desch
Design: designstübchen, Osnabrück
Printing: Grunewald GmbH, Kassel
Picture credits: Fotografie MD2020/Mathias Daum (title, iNAPO and ProLOEWE faces), Fraunhofer CIMD, copyright: Uli Planz (TMP), Kathrin Maurer (ALLEGRO)

LOEWE-INAPO: THE ION CHANNEL FORMING ENVELOPE PROTEIN OF SARS-CoV2 IS A PROMISING TARGET FOR DEVELOPING VIROSTATIC AGENTS

The scientists – including Dominique Tandl shown here – are not working with the virus itself, but produce the E protein in human cells for their microscopic and electrophysiological experiments. The work with these cells must be carried out in extremely clean conditions to prevent any contamination.

The researchers in the Thiel and Bertl working groups at the Technical University of Darmstadt are working on the structure and function of viral ion channels as part of the **iNAPO LOEWE project**. Shortly after the outbreak of the CoVID-19 pandemic, the scientists became aware of a protein in the SARS-CoV2 virus, which could possibly act as an ion channel: this is the envelope (E) protein. Just like a protein that is already well-known from SARS-CoV1, the so-called envelope (E) protein from SARS-CoV2 is also suspected of channelling ions across membranes and therefore intervening in the ion balance in the host cell. Since this protein is involved in the formation of virus particles and the budding of mature virus particles from the host cells, the E protein is a promising target for developing antiviral drugs.

Thanks to the experience gained with **LOEWE-iNAPO** and a wide range of techniques that are absolutely suitable for investigating the function of ion channels from viruses, the researchers have gained extremely promising insights within a very short time: Dr Oliver Rauh and Tobias Schulze (M.Sc.) have been able to show by using electrophysiological methods that the E protein alters the electrical properties of the membrane of cells. The complementary fluorescence-optical measurements performed by Tobias Schulze and Dominique Tandl (M.Sc.) for this purpose suggest that this leads to an increase in the Ca^{2+} concentration in the cells. This is very interesting, because Ca^{2+} plays an important role in the signal processing of cells.

Based on these results, Sebastian Höler (M.Sc.), one of the scientists involved with a background in yeast membrane biophysics, is developing a yeast-based test system to test the reaction of the E protein to possible inhibitors for high-throughput processes.

This is creating a foundation for a targeted search for active substances that can inhibit the channel function of the E protein and therefore combat the spread of CoVID-19.

Researchers Oliver Rauh, Tobias Schulze, Sebastian Höler and Dominique Tandl (from left to right) are investigating the tasks and functions of the E protein.

Junior Professor Ulrike Kramm in front of her workplace at the Technical University of Darmstadt, where she is conducting research into the local environment of tin in the FLAME LOEWE project. Behind her is a fuel cell, which is one of the main topics of her working group: to develop catalysts that do not contain any precious metals.

Junior Professor Dr. Ulrike Kramm
Looking for resource-friendly solutions for energy applications

Professor Kramm, you're working in the FLAME LOEWE cluster with the Department of Catalysts and Electrocatalysts. What exactly is the major focus of your research work? *The description of my field of expertise may be misleading at first in terms of my connection with the FLAME LOEWE cluster (Fermi Level Engineering of Antiferroelectric Materials for Energy Storage and Insulators). In fact, I did not join FLAME because of my expertise in catalysts, but because of my specialist knowledge of Mössbauer spectroscopy. Mössbauer spectroscopy is a method for examining specific elements and allows us to make statements about the environment of certain ones. For example, you can see whether an element is present in metallic or oxidised form. Our work focuses on the local environment to determine, for example, how many binding partners are present and which ones. By using this method, we want to find out how small changes in the composition of the structures being investigated affect the local and electronic environment of individual metals – and to what extent or whether this relates to their antiferromagnetic properties. Within the FLAME programme, we're mainly analysing the environment of tin in antiferroelectrics containing lead to see the effect of this element on the desired properties. We need this information to develop new, lead-free antiferroelectrics, which can then be used, for example, for energy storage purposes.*

Physics and mathematics, your main courses at your grammar school, were certainly helpful for your current work in this field of research. Why were you so interested in science as a teenager? *I never thought it was unusual for me to be interested in mathematics and physics. In my opinion, both subjects have an advantage over arts or humanities subjects: they have a clear structure and there is a clear categorisation of what is right and wrong - at least, related to what you learn at school.*

My teachers always emphasised very strongly that it's important to realise what simple tools were used to make a large number of major scientific discoveries. This has certainly helped to promote my interest in the history of science and the natural sciences as such. A certain sense of pragmatism also played a role at the beginning of the sixth form, because I was able to achieve better results in both subjects with less effort than I probably would have had to make in other subjects.

What do you believe makes the Hesse research promotion programme entitled LOEWE (Landes-Offensive zur Entwicklung Wissenschaftlich-ökonomischer Exzellenz or State Offensive to Develop Academic/Economic Excellence) special or what opportunities does it provide for your work that you wouldn't have had otherwise? *As regards the volume of applications, the application process for LOEWE research funding is relatively straightforward and fast; as a result, not much time elapses between defining the research subject and the actual project. This can be the crucial time advantage, particularly for current topics where a great deal of research is taking place, and enable you to launch a topic at a university in Hesse and therefore strengthen Hesse as an academic economic centre too.*

The FLAME LOEWE cluster also provides strong cross-links between the research disciplines that are involved. I believe this interdisciplinary approach is very beneficial for training Ph.D. students; it makes specialist knowledge generally comprehensible at an early stage or the "languages" of the different disciplines are adapted. This helps people later at larger conferences or meetings at companies where an interdisciplinary approach is necessary.

Read the whole interview at proloewe.de