COVID-19
FORSCHUNGSNETZWERK
NIEDERSACHSEN

Central COFONI Technology Platforms

The COFONI research network is based on a content-related and a structural pillar. In terms of content, the existing scientific core competencies in the Lower Saxony metropolitan region of Göttingen-Hannover-Braunschweig are being brought together to form four key areas that are of crucial relevance to pandemic response:

1. Epidemiological modelling: pandemic intervention.

2. Antiviral strategies: active agents and vaccines

3. Digital infectious medicine: individualised patient care

4. Pathophysiology: immune modulation and control

The exact funding goals of the four key areas are explained in more detail on COFONI's homepage.

The logistical core for the four thematic research directions is a central technology platform that provides overarching methods and animal models as well as data and biobanks with maximum efficiency for all participants to share. The following parts of the technology platform are presented individually below: 1) Animal models and test systems, (2) Research biobank, and (3) Research databases.

For the integration of the central technology platforms, the respective local contact persons of the institutions are to be contacted in advance (see page 7-8). In consultation with the persons responsible for the central technology platform, it must be clarified to what extent additional costs for the services must be included in the project application. Extensive services of the technology platforms beyond consulting and provision of basic infrastructure (e.g. use of high performance/ GPU clusters for data analyses, FAIR-compliant modelling and tuning of new data models beyond the German Corona Consensus Dataset GECCO or performance of project-specific animal experiments) must be included in the budget planning of the projects after consultation.

1. Animal models and test systems

For the interdisciplinary treatment of the SARS-CoV-2 research questions addressed in the various key areas, the University of Veterinary Medicine Hannover, Foundation (TiHo) provides all project partners within the network with state-of-the-art laboratories and animal housing for Biosafety Level 3 (BSL 3) experiments at the Research Centre for Emerging Infections and

Zoonoses (RIZ) within the framework of cooperation projects. The extensive logistical equipment for BSL 3 animal husbandry and the expertise-rich experience in dealing with corresponding pathogens, such as SARS-CoV-2, make this TiHo facility a central partner in this initiative. The RIZ with its BSL 3 laboratories has a multi-level safety system including a thermal wastewater system and double HEPA filtration of individual laboratory tracts, which prevent the pathogens from escaping into the air. The technical systems and equipment were checked in a lengthy test phase, and workflows, maintenance and emergency processes were intensively validated and trained. Since January 2020, the BSL 3 laboratory and also the Animal Biosafety Level 3 (ABSL 3) Facilities have started operations in handling human pathogenic aerosol transmissible pathogens. Initial work in the BSL 3 laboratories at the RIZ has already started under the leadership of Professor Maren von Köckritz-Blickwede as Head of Scientific Administration and Biosafety and Professor Ab Osterhaus as Scientific Director, a world-renowned expert in the field of coronavirus research especially regarding SARS-CoV-1 and MERS.

At RIZ, various experimental animal models in ferrets, hamsters and mice are currently being established in the BSL 3 laboratories and used for initial studies for testing vaccines and new antiviral strategies. The highest possible standards in terms of animal welfare and biosafety are required for performing these animal experiments. The scientists involved like Prof. Guus Rimmelzwaan, Professor Asisa Volz, Professor Wolfgang Baumgärtner, Professor Maren von Köckritz-Blickwede and Professor Ab Osterhaus have the professional expertise and also institutional requirements with state-of-the-art building technologies to meet these standards.

To support the questions addressed in the COFONI research network, the previously established SARS-CoV-2 animal models will be further optimised for project-specific conditions to best complement the research results generated in patients. This includes the additional development of SARS-CoV-2 animal models that reflect particular pathophysiological conditions in humans, such as (1) specific pre-existing disease/immunosuppression and (2) age. These models will be established within the central infrastructure and made available to the partners in the consortium including expertise in SARS-CoV-2-specific animal testing. As a partner, TiHo can offer the logistics and execution of animal experiments under BSL 3 conditions including pathological examinations to the overall consortium within the framework of cooperation projects, thus providing a platform for regional research to implement testing of active substances and vaccines as quickly as possible. The analysis in such animal models will be essential to use the data generated in this consortium for establishing new diagnostic methods as well as for developing new therapeutics and vaccines in humans.

Another essential part of this cross-site central project "Animal Models" is located at TWINCORE and represented by Professor Ulrich Kalinke. A technology platform in the field of genetically modified mice is already available, which is jointly supported and professionally organised by Hannover Medical School (MHH) and HZI. Mouse models of SARS-CoV-2 infection developed at TWINCORE are of particular importance for COFONI. Previously produced transgenic mice expressing the human receptor of SARS-CoV-2, angiotensin converting enzyme 2 (ACE2), which is an important enzyme in blood pressure regulation and the renin-angiotensin system (RAS), will be combined with a tamoxifen-inducible deletion of the type I interferon receptor (IFNAR) on type II pneumocytes of the lung (Sftpc-Cre^{ER}IFNAR$^{fl/fl}$). In this way, the infectivity with SARS-CoV-2 of type II pneumocytes, which are an important target cell of SARS-CoV-2 in the human lung, should be further increased in mice. In addition, other ACE2 transgenic mice are currently being produced worldwide, some of which differ greatly in susceptibility to SARS-CoV-2 infection. Therefore, the various ACE2 transgenic mice will be brought into the region, studied and modified as necessary. In this way, quality-controlled transgenic mouse models of SARS-CoV-2 infection can be made available to the partners of the consortium for the various questions.

Non-human primates (NHP) are genetically, immunologically and physiologically more closely related to humans than rodents and ferrets and are thought to better represent certain aspects of COVID-19 disease. Therefore, important hypotheses developed in cell culture and/or small animal models need to be tested in NHP models. In particular, the immune systems of NHP and humans show strong similarities. NHP are therefore particularly suited to elucidate which processes are important for the establishment of a protective immune response against SARS-CoV-2 and how these processes are disrupted by the virus. They are also central to ruling out unwanted antibody-mediated enhancement of disease by vaccination. Such an enhancement was first demonstrated for feline coronavirus (FCoV), but it has also been observed in the use of SARS vaccine and SARS infection models. [1]

The German Primate Centre - Leibniz Institute for Primate Research (DPZ) will establish and continuously improve NHP models for COVID-19 to optimally represent COVID-19 disease. One focus will be on African green monkeys, which are particularly susceptible to SARS-CoV-2 infection. [2] In addition, macaques will be used, which, after experimental SARS-CoV-2 infection, at least represent essential aspects of COVID-19 [3] and are more readily available. In parallel with the TiHo, models will be established to represent pre-existing diseases and immune deficiencies. In addition, methods based on vector technologies and DPZ-licensed virus-like particle (VLP) technology [4] will be established that allow targeted modulation of host cell factor expression in the respiratory tract. This approach can significantly contribute to identifying cellular factors as targets for COVID-19 therapy. The corresponding animal models will be established within the infrastructure and made available to partners in the consortium as part of a collaboration. In this context, the DPZ will take over the planning and execution of the NHP work, including the virological and immunological analysis of the animals, and will provide advice and support in the submission of applications for animal experiments. The availability of the NHP models outlined above will greatly enhance the establishment of effective and safe vaccines and therapeutics.

Prior to testing in animal models, the efficacy of small molecule compounds and biotherapeutics must be demonstrated in target-based and cellular assays. Likewise, sufficient pharmacokinetic properties must be proven. In many cases, the identification of good small molecule hits requires the profiling of a large number of compounds. The HZI is a specialised centre for infection-related assays under S2 conditions within the European infrastructure EU OPENSCREEN. The existing infrastructure and technology will be expanded within COFONI and operated under S3 conditions to profile active substances against SARS-CoV-2 in a cellular assay cascade. This will involve the use of a high-throughput primary assay in 384 microtiter plate format and an imaging-based secondary assay. The infrastructure will profile compounds from the COFONI network and from other national and international partners. If larger numbers of active substances are found, they will be filtered and prioritised in accordance with industry standards based on chemical and biological data. In addition, bioanalytical capacity

[1] Liu *et al* (2019), JCI Insight, https://pubmed.ncbi.nlm.nih.gov/30830861
Czub *et al* (2005), Vaccine, https://pubmed.ncbi.nlm.nih.gov/15755610
[2] Liu *et al* (2019), JCI Insight, https://pubmed.ncbi.nlm.nih.gov/30830861
Czub *et al* (2005), Vaccine, https://pubmed.ncbi.nlm.nih.gov/15755610
[3] Liu *et al* (2019), JCI Insight, https://pubmed.ncbi.nlm.nih.gov/30830861
Czub *et al* (2005), Vaccine, https://pubmed.ncbi.nlm.nih.gov/15755610
[4] Liu *et al* (2019), JCI Insight, https://pubmed.ncbi.nlm.nih.gov/30830861
Czub *et al* (2005), Vaccine, https://pubmed.ncbi.nlm.nih.gov/15755610

will be provided to determine drug concentrations and pharmacokinetic parameters from the animal models described above via high sensitivity quadrupole mass spectrometry.

2. Research biobank

Biobanks are responsible for the collection, processing, storage and release of biospecimens and thus form the basis of a large part of medical research. Decisive for future analyses is the quality and standardisation of the processes. Biobanks form the basis for different research projects of the Infection Network Lower Saxony, Germany and are especially central for the key area "Digital Infection Medicine".

The Hannover Unified Biobank (HUB) is the central biobank of Hannover Medical School (MHH). It was established in 2012 to provide an infrastructure for the standardised collection and storage of high-quality biomaterial and associated data. Over the years, the biobank has expanded and now supports many Germany-wide multicentre studies. Led by Prof. Thomas Illig, the HUB has developed into one of the largest state-of-the-art biobanks in Germany and today manages approximately 2.88 million diverse biospecimens for a range of diseases.

The Central Biobank of the University Medical Centre Göttingen (UMG) was officially established in 2015 as a central service facility of the UMG to support medical research, following the establishment of campus-wide software for biospecimen management in 2012. Through close collaboration with the UMG Laboratory (Central Laboratory) and the Institutes of Pathology and Neuropathology, processes for the collection and processing of liquid and solid biospecimens and parallel data acquisition have been standardised. The Central Biobank UMG is also in constant exchange with the Data Integration Centre at the Institute of Medical Informatics in order to enrich the biospecimens with clinical data from patients. It supports independent national as well as international studies and at the same time provides a prospective collection of biospecimens and data that researchers can access.

Since 2017, the Central Biobank UMG and the HUB have been members of the German Biobank Alliance (GBA), a German biobank network funded by the Federal Ministry of Education and Research. Today, 20 biobanks of university hospitals and two IT expert centres are members of the GBA. The members have established uniform quality standards and provide biospecimens for various national and international research projects. Since 2017, Prof. Thomas Illig has been the deputy spokesperson of the GBA. Furthermore, he is one of five coordinators of the National Research Network of University Medicine in the field of "Cohorts and Biobanking" (NAPKON). PD Dr. Sara Nußbeck is a member of the GBA Steering Committee and leads the GBA subproject Education and Training. In the European Biobanking Society ESBB, she is also head of the working group Education and Training.

With funding from the Ministry of Science and Culture of the State of Lower Saxony (MWK), a longitudinal COVID-19 cohort with broad clinical data and diverse biospecimens is already being established at the HUB under the leadership of Prof. Thomas Illig. In addition, data and biosamples from Göttingen (PD Dr. Sara Nußbeck, Central Biobank UMG) will be incorporated. Together, data and biosamples from more than 265 patients are thus available. The cohorts will be continued at the two sites by existing study personnel depending on the number of infected patients and will be continuously enlarged.

In the region of Lower Saxony there are already a number of research groups working on molecular (omics), especially immunological characterisation of the cohort. Part of the planned molecular characterisation could already be realised by funds from different institutes on their own or is planned: (i) the genome and transcriptome sequencing is performed by the DFG sequencing centre at the University Hospital Tübingen, (ii) the epigenome is characterised by

the Professor Jörn Walter's group (Saarland University), (iii) Professor Karsten Hiller (TU Braunschweig) is studying the metabolome in plasma, urine and saliva samples of the cohort, (iv) Professor Christine Falk (MHH) is characterising the immune response of the cohort using cytokines and leukocyte populations, and (v) Professor Markus Cornberg and Professor Reinhold Förster (MHH) are studying the heterologous immunity of the cohort using the B and T cell population. Remaining gaps in the characterisation of the cohort could be filled within the research network COFONI and thus support a comprehensive picture. In this context, the analyses will be performed at the sites in Braunschweig, Hannover and Göttingen according to their expertise. The Institute of Diagnostic and Interventional Radiology of the MHH, under the direction of Professor Frank Wacker, generated approximately 200 X-ray thorax images and 17 CT thorax images of COVID-19 patients by 01.06.2020, which can be used for image marker analysis. The data collection will be continuously expanded.

With the close ties of the biobanks in Göttingen and Hannover to the GBA, expertise in quality management and harmonisation in accordance with national and international standards is thus provided. The two biobanks prepare the samples appropriately (e.g. extraction of DNA and RNA or cell cultures) and send the samples to scientists for characterisation. The molecular data can be stored in the HUB in a systematic manner in the BIMS (Biobank Information Management System). This is done in close coordination with medical informatics and the computer centres of the participating institutions.

3. Research databanks

All research data collected and processed within the framework of this project will be modelled and provided with metadata according to the common FAIR criteria (findable, accessible, interoperable and reusable) for research data management in accordance with good scientific practice, so that they are available to researchers in the COFONI research network regardless of location. To this end, a database infrastructure that can be used jointly by the four institutions is being set up by the two university hospitals involved. This will be done according to demands and in close coordination with the future laboratory "Health" of the Centre for Digital Innovations Lower Saxony (ZDIN) in distributed data storage with jointly agreed information and data models for all data beyond the national GECCO data set.

Applicant researchers must seek advice in advance from the contact persons at the university hospitals regarding the necessary data and analysis infrastructure and must provide for corresponding funds in their applications if they have further requirements that go beyond the basic infrastructure. This ensures a harmonisation of data pools and enables widespread further use within the COFONI network. Existing data can be used for new application projects.

Whereever possible, existing standards are used to describe the data (metadata), e.g. a specific DICOM database for image data and biosignal data. In close coordination with the researchers, data models will be agreed upon, implemented and maintained according to the HiGHmed data governance model. The applicants are readily available for supporting data modeling with regards to the content and for reviewing data models. In the further course of the project, query and filter tools will be developed and made available to researchers on the basis of the standardised data models, as will the export into common data formats for analyses and the import of results. For the execution of computationally intensive data analyses, additional high-performance computers will be procured as needed, or existing systems will be strengthened, operated and made available. In the spirit of good scientific practice, the FAIR

criteria are also applied to analyses and their execution environments. For this purpose, in addition to common version control systems with internal and public domains, virtualisation options are also provided and managed via container technologies.

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