Central COFONI Technology Platform

The structural core in the COFONI research network is a **central technology platform** that provides overarching methods and animal models as well as databases and biobanks available 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 (contact persons),
2. Research biobanks (contact persons), and
3. Research database (contact persons).

For the involvement of the central technology platform, the respective local contact persons of the facilities must be contacted in advance. In consultation with the responsible persons, it must be clarified to what extent additional costs for the services have to 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 modeling, and tuning of new data models beyond the German Corona Consensus Dataset GECCO, or performance of project-specific animal experiments) have to be included in the budget planning of the projects upon 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 great expertise and experience in dealing with corresponding pathogens such as SARS-CoV-2 make this TiHo facility a central partner in COFONI. 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. Extensive work in the BSL 3 laboratories at the RIZ is carried out by numerous renowned scientists under the coordination of Professor Maren von Köckritz-Blickwede as Head of Scientific Administration and Biosafety and Professor Albert Osterhaus as Scientific Director, a world-renowned expert in the field of coronavirus research especially regarding SARS-CoV-1 and MERS-CoV.

At the RIZ, various experimental animal models in ferrets, hamsters, and mice are also established in the BSL 3 laboratories and used for 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 Professor Asisa Volz, Professor Wolfgang Baumgärtner, Professor Maren von Köckritz-Blickwede, Professor Guus Rimmelzwaan, and

Professor Albert Osterhaus have the professional expertise and also the 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 under the leadership of Professor Volz and Professor von Köckritz-Blickwede as head of the technology platform in order to complement research results generated in patients in the best possible way. 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 or even long/post COVID pathologies. These models will be established within the central infrastructure and made available to the partners in COFONI including expertise in SARS-CoV-2-specific animal testing. As a partner, TiHo can provide the logistics and performance of animal experiments under BSL 3 conditions, including pathological examinations by the Institute of Pathology under the direction of Professor Wolfgang Baumgärtner, to all partners in COFONI within the framework of cooperation projects, thus providing a platform for regional research. This allows a fast implementation of testing of active substances and vaccines. The analysis performed in such animal models will be essential for using the data generated in COFONI 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 – Centre for Experimental and Clinical Infection Research** and represented by Professor Ulrich Kalinke. Even before the central COFONI technology platform was established, a technology platform in the field of genetically modified mice was already in place, which is jointly supported and professionally organised by the Hannover Medical School (MHH) and the Helmholtz Centre for Infection Research (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$^{fl/fl}$). Thus, the infectivity with SARS-CoV-2 of type II pneumocytes, which are an important target cell of SARS-CoV-2 in the human lung, can be further increased in mice. In this way, quality-controlled transgenic mouse models of SARS-CoV-2 infection can be made available to the partners in COFONI for various questions.

Non-human primates (NHP) are genetically, immunologically, and physiologically more closely related to humans than rodents and ferrets and better represent certain aspects of COVID-19 disease than small animal models. 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. With the help of NHP models, key insights into SARS-CoV-2 spread in the host and pathogenesis as well as its inhibition by vaccines, drugs and antibodies could already be gained at the start of the pandemic.[1,2] Today, NHP models continue to be of great importance for the analysis of, among other things, candidate vaccines and recombinant neutralizing antibodies, and are used to study virus replication and pathology after the acute phase of infection.

The Infection Biology Unit at the **German Primate Center – Leibniz Institute for Primate Research**

(DPZ) is headed by Professor Stefan Pöhlmann and has made important contributions to the study of SARS-CoV-2 infection, including the discovery of ACE2 as a receptor for SARS-CoV-2 and TMPRSS2 as an activating protease.[3] Together with the Laboratory Animal Science Unit, headed by Professor Rabea Hinkel, and partners at the TiHo, in particular Professor Albert Osterhaus, the Department of Infection Biology has established the SARS-CoV-2 infection of rhesus monkeys. This model reproduces a mild course of SARS-CoV-2 very well[4] and has been successfully used to demonstrate, among other things, the antiviral effect of a recombinant neutralizing antibody. In parallel with the TiHo, models are being established to represent pre-existing diseases and immune deficiencies. In addition, methods based on vector technologies and DPZ-licensed virus like particle (VLP) technology[5] 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 advise and assist in the submission of project applications for animal experiments.

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 particular, the identification of good low molecular lead structures requires the profiling of a large number of compounds. The **Helmholtz Centre for Infection Research (HZI)** is a specialised centre for infection-related assays under S2 and S3 conditions within the European infrastructure EU OPENSCREEN. The existing infrastructure and technology were expanded as part of the COFONI project to profile active substances against SARS-CoV-2 in a cellular assay cascade. A plaque-based secondary assay is used in addition to a high-throughput primary assay in 384 microtiter plate format. Several cell lines and viruses are available. The infrastructure will profile compounds from the COFONI network and from other national and international partners. If larger numbers of active substances are found, these will be filtered and prioritised in accordance with industry standards based on chemical and biological data. In addition, bioanalytical capacity will be provided to determine drug concentrations and pharmacokinetic parameters from the animal models described above via high sensitivity quadrupole mass spectrometry.

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[1] Baum *et al* (2020), Science, https://pubmed.ncbi.nlm.nih.gov/33037066
[2] Munster *et al* (2020), Nature, https://pubmed.ncbi.nlm.nih.gov/32396922
[3] Hoffmann *et al* (2020), Cell, https://pubmed.ncbi.nlm.nih.gov/32142651
[4] Rockx *et al* (2020), Science, https://pubmed.ncbi.nlm.nih.gov/32303590
[5] Hoffmann *et al* (2016), Mol Ther Nucleic Acids, https://pubmed.ncbi.nlm.nih.gov/27003757

2. Research biobanks

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 within COFONI.

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 biospecimens and associated data. Over the years, the biobank has expanded and now supports many Germany-wide multicentre studies. Headed by Professor Thomas Illig, the HUB has developed into one of the largest state-of-the-art biobanks in Germany and today manages approximately 3.22 million diverse biospecimens for a range of diseases.

The **Central Biobank of the University Medical Centre Göttingen (UMG)** was founded in 2015 as a central service facility of the UMG to support medical research. 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. To enrich the biospecimens with clinical data from patients, the Central Biobank exchanges information closely with the Medical Data Integration Center. It supports national as well as international multicenter studies while providing 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 excellence network funded by the Federal Ministry of Education and Research. Today, more than 30 biobanks of university hospitals and an IT expert centre are members of the GBA. The members have established uniform quality standards and provide biospecimens for various national and international research projects. Since 2017, Professor 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 (NUM) 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.

As part of the Network of University Medicine, the National Pandemic Cohort Network (NAPKON) was funded, which recruits patients for COVID-19 research at 36 sites across Germany and stores the collected biospecimens locally. Patients are enrolled in three cohort platforms, the high-resolution platform (HAP), the cross-sector platform (SÜP), or the population-based platform (POP), and followed longitudinally until three years after infection. NAPKON makes the collected data and biospecimens available to research projects through a use and access process. The various NAPKON infrastructure cores subsequently process approved applications and provide the required data and biospecimens. The HUB is part of the infrastructure and, as a biospecimen core, is responsible for requesting the requested biospecimens from the individual sites and sending the biospecimens collectively to the applicants. The UMG participates in the biospecimen collection of the SÜP for the Göttingen site with 118 patients included so far (5th place of the university sites recruiting for SÜP), and the HUB participates in the biospecimen collection for the Hannover site in the HAP. Professor Thomas Illig is one of the five principal investigators in NAPKON, spokesperson for the biospecimen core, and serves on the Steering Committee and Use & Access Committee.

The NAPKON cohort currently includes a total of 6,715 patients with over 500,000 biospecimens. A comprehensive data set will be collected on the collected biospecimens in accordance with the "German Corona Consensus" (GECCO) with clinical data, diagnostics, interventions, demographic data, treatments, imaging data, and, as needed, specific data sets (pediatrics, neurology, etc.). A total of 2,520 patients in the cohort were systematically characterized for baseline, acute course, and a three-month follow-up. Ongoing analyses of this characterization include genotyping with GSA chips, transcriptomics and epigenetic profiling with EPIC array, ATAC-seq and ChIP-seq, proteomics, metabolomics, and a cytokine panel as well as viral typing, serum PCR, and serological spike, nucleocapsid, and neutralizing antibody assays. Subsequently, 600 patients of the analyzed collective will be selected on the basis of a post-COVID syndrome score and their 12-month follow-up will also be molecularly characterized. The planned analyses include transcriptomics and epigenetic profiling with EPIC array, ATAC-seq and ChIP-seq, proteomics, metabolomics, and a cytokine panel. All generated results of these analyses can be submitted to the Use & Access procedure in NAPKON.

Through funding from the Lower Saxony Ministry of Science and Culture (MWK), a longitudinal COVID-19 cohort with broad clinical data and diverse biospecimens has additionally been established at the HUB since 2020 under the direction of Professor Thomas Illig. In addition, data and biosamples are included from the Göttingen site (PD Dr. Sara Nußbeck, Central Biobank UMG). Together, data and biosamples from more than 400 patients are thus available. The cohort at the Hannover site will be continued by existing study personnel depending on the number of infected patients and will be continuously enlarged.

The biospecimen collection with MWK funding currently comprises more than 30,000 samples in Hannover alone, and more than 10 % of these were already assigned for analysis to a large number of research groups. The molecular characterization of the cohort was partly performed by the institutes themselves as well as in the context of COFONI projects. (i) Genome sequencing was performed from 140 patients and transcriptome sequencing from 210 clinically relevant time points. The generated omics data were already published within the German COVID-19 OMICS Initiative (Decoi) as well as the Host Genetics Initiative (HGI), and currently three additional research groups are working on the analysis of the data. (ii) The epigenome of 227 clinically relevant time points was longitudinally characterized and will be analyzed integratively together with the genome and transcriptome data as well as the clinical data. (iii) Furthermore, structural variants in 60 patients were investigated by optical genome mapping and preliminary results were already published. (iv) Genomic variants were investigated and published in an international Genome Wide Association Study (GWAS). (v) The immune response of the cohort was characterized using cytokines and leukocyte populations from plasma samples, and (vi) the heterologous immunity of the cohort was examined using B and T cell populations using Peripheral Blood Mononuclear Cells (PBMCs) from 128 time points. (vii) The transcriptome of specific cell types was analyzed using single-cell sequencing. (viii) Other projects include studying circulating non-coding RNAs and analyzing the metabolome profiles of long-COVID patients compared to convalescent patients. The projects can draw on an extensive set of clinical data, which was additionally collected for all severe and moderately severe visits following the German Corona Consensus (GECCO) dataset and the WHO clinical progression scale as well as a detailed post-COVID dataset established by the Pneumology Department of the MHH. Remaining gaps in the characterization of the cohort, especially in the study of post-COVID visits, can continue to be filled within the research network COFONI. In this context, the analyses will be performed at the Hannover and Göttingen sites according to their

expertise. The data collection will be continuously expanded.

Thus, with the close ties of the biobanks in Göttingen and Hannover to the German Biobank Alliance (GBA), expertise in quality management and harmonization in accordance with national and international standards is provided. The two biobanks prepare the samples appropriately (e.g., extraction of DNA and RNA or preparation of 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 the Department of Medical informatics and the computation centers of the participating institutions.

3. Research database

All research data collected and processed within the framework of projects funded by COFONI that are relevant for reuse are modeled 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 all researchers in the COFONI research network. For this purpose, a database infrastructure that can be used jointly within COFONI was set up by the two university hospitals involved, **UMG and MHH**. Further expansion will take place on a demand-oriented basis and in close coordination with the "Zukunftslabor Gesundheit" of the Centre for Digital Innovations Lower Saxony (ZDIN). The models of the national GECCO data set are the basis for this. Information and data models that go beyond the GECCO data set will be jointly adapted.

Applicant researchers must seek advice in advance from the contact persons at the research database regarding the necessary data and analysis infrastructure and, if they have wishes and requirements that go beyond the basic infrastructure, they must include appropriate funding in their project applications. The close coordination with the research database ensures a harmonisation of data sets and enables widespread further use within the COFONI network. Existing data can be used for new application projects. The research database offers to create appropriate tools (digital questionnaires, apps) for standardized data collection from study participants. The expenses for this are to be budgeted for in the applications in coordination with the contact persons of the research database.

Wherever possible, existing standards are used to describe the data (metadata). In close coordination with the researchers, data models will be agreed upon, implemented, and maintained in accordance with the HiGHmed data governance model.[6] In this context, the researchers are responsible for providing the content and checking the technical aspects of new 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, existing high-performance computers will be used as needed, or existing systems will be upgraded, operated, and made available. In the spirit of good scientific practice, the FAIR criteria will also be applied to analyses and their execution environments. For this purpose, in addition to common version control systems with internal and public domains, virtualisation options will also be provided and managed via container technologies.

Research Data Platform

The COFONI Research Data Platform is a secure, extensible, and interoperable platform for providing COVID-19 research data.

With this platform, the COFONI network promotes the translational idea of the network by providing researchers with a tool for reuse of structured COVID-19 research datasets from funded projects. These include clinical data (e.g., laboratory values, medical history/therapy data, and findings) as well as non-identifiable personal and interview data, e.g., social status, occupational status, and biography.

The data are available in anonymized form and can be requested by researchers for subsequent use. A graphical user interface can be used to compile cohorts and identify the number of cases. Hereafter, the created cohorts can be linked to a data use application. The data use application is then reviewed by a Use & Access Committee and, once approved, the requested data can be exported directly via the user portal in common file formats (.csv/ .json).

[6] Wulff *et al* (2018), Stud Health Technol Inform, https://pubmed.ncbi.nlm.nih.gov/29726437

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