COMMUTE
Quarterly Bulletin
July 2024

Prof. Dr. Martin Hofmann-Apitius, Coordinator and Colleague

The COMMUTE project started in December 2023, and now – after six months of operation – it is time to communicate the first bulletin on the progress we made within the first two quarters of the project.

What is COMMUTE all about?

COMMUTE aims at systematically collecting evidence for the co-morbidity between COVID-19 and Neurodegenerative Diseases (such as Alzheimer's and Parkinsonism). One key goal of COMMUTE is to unravel the mechanisms underlying the possible link between SARS-CoV-2 and neurodegeneration and to generate models that allow for personalized risk assessment for COVID-induced cognitive decline. The other major goal of COMMUTE is to develop cellular assay systems that identify drug-repurposing candidates that prevent or reduce COVID-induced neurodegeneration risk. Finally, the ethical and legal Work Package (WP) will come up with recommendations for handling ethical and legal aspects of virus-induced neurodegenerative disease risk.

After the kickoff on December 14, 2023, the project team started building a team and organizing regular meetings in the different WPs.

COMMUTE is organized in a rather straightforward and simple way, which makes management easier. We have only five WPs, of which WP 1 covers all management, dissemination, and communication, and WP 5 deals with all ethical and legal aspects of the project.

That leaves three WPs for the core objective of identifying the mechanisms underlying the presumed co-morbidity between SARS-CoV-2 and Alzheimer's Disease or Parkinsonism. We do that in a dual strategy: WP 3 follows a *hypotheses-free, data-driven* approach. The partners in this WP have access to many relevant data sets, including observational data, population data, and clinical study data. WP 4 comprises all experimental biology, (incl. assays) and clinical research and that is where the translational clinical expertise resides. WP 2 organizes all data and knowledge and bridges between the hypotheses-free and hypotheses-driven approaches.

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The following figure illustrates the **Integrative COMMUTE Strategy** that combines hypotheses-free and hypotheses-driven approaches:

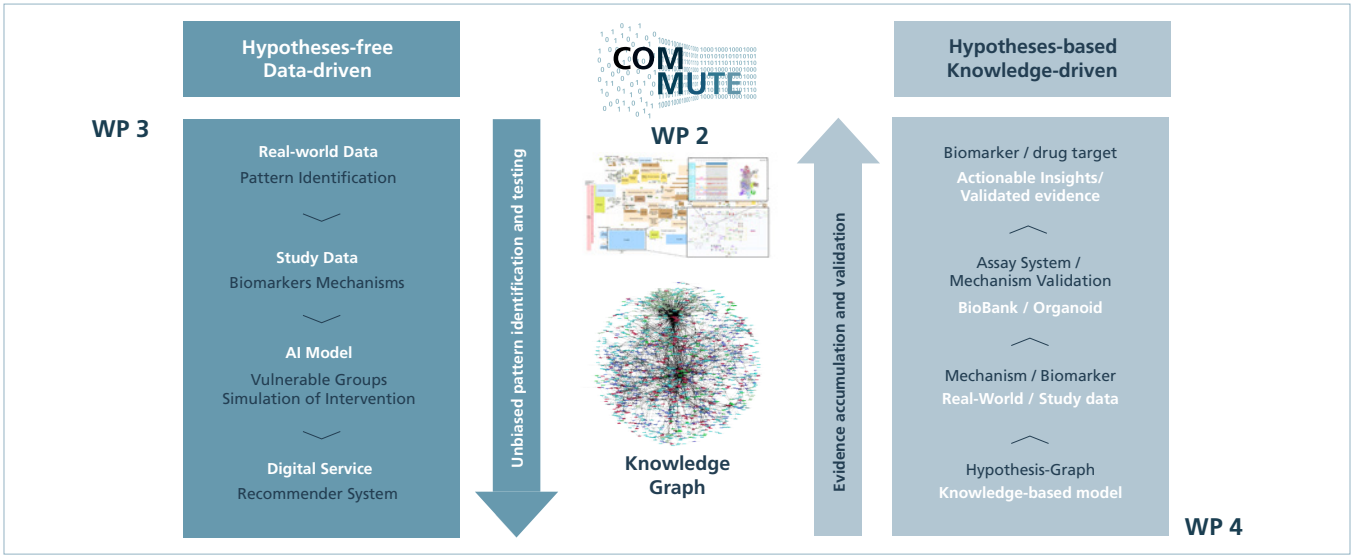

Fig. 1: High-level strategy for the integration of hypotheses-free, data-driven approaches and hypotheses-based, knowledge-driven strategies in the COMMUTE project.

WP 1 – Project Management

(incl. Coordination, Communication and Dissemination)

WP 1 started with the basics of any collaborative EU project, namely contractual work, the implementation of a project website, and the organization of regular meetings of WPs and between WPs. The first version of essential dissemination material was generated, and the first dissemination events (including a talk at a Keystone Symposium) have already taken place.

Vanessa is a biologist by training and has specialized in neuropharmacology. For the past four years, she has combined the roles of a project manager and a scientist in various projects coordinated by Fraunhofer SCAI.

Meet the Head of the Project Management Office of COMMUTE, Dr. Vanessa Lage-Rupprecht.

WP 2 – Data and Knowledge Graphs

(incl. Data & Knowledge Management and -Integration)

COMMUTE partners in WP 2 already brought essential resources to the project. Both Fraunhofer SCAI and the University of Luxembourg have generated large knowledge graphs ("disease maps") for COVID-19 and Alzheimer´s or Parkinsonism. Within WP 2, we have identified three core working areas: Knowledge Graphs, Shared Semantics, and Technical Coordination.

In a dedicated curation approach, we have extracted helpful information from a corpus of literature covering the co-morbidity between COVID and Alzheimer's / Parkinsonism. In a complementary approach, we started to extract useful information from even larger co-morbidity corpora using NLP workflows provided by our partner, KAIRNTECH.

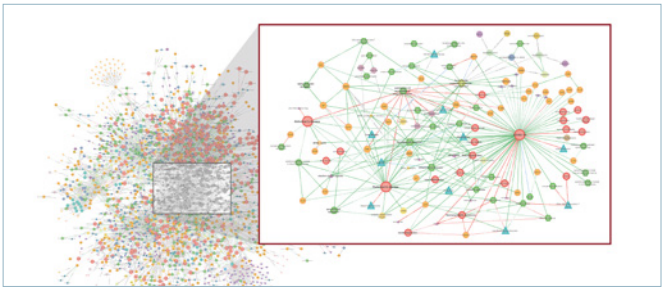

Fig. 2: Cause-and-Effect Graph representing essential information from 63 publications (primary papers and reviews) on the COVID – Neurodegeneration Co-Morbidity. The graph was generated by Heval Atas Güvenilir and Alpha Tom Kodamullil (Applied Semantics, Business Area Bioinformatics, Fraunhofer SCAI).

WP 3 – Data Science, Machine Learning and Artificial Intelligence

WP 3 harnesses the capabilities of Data Science, Artificial Intelligence (AI), and Machine Learning (ML) to address significant challenges in the understanding and prediction of Neurodegenerative Diseases (NDDs) and their association with COVID-19. The primary focus of this WP is to develop AI-driven tools and models that can predict the risk of NDDs and unravel the molecular interactions between these conditions and COVID-19, aiding in the early diagnosis and tailored therapeutic strategies.

WP 3 meetings started in January 2024 with a **workshop on causal inference** led by FRAUNHOFER, which emphasized the critical methodological frameworks that will underpin the modeling efforts in WP 3. Furthermore, the WP 3 team developed a **Modeling Plan** that details the strategic approaches and architectures for the AI/ML models under development. This dynamic document is regularly updated to reflect new insights and adjustments. A proposal was made to create a **Data Dictionary** to further enhance data management and consistency. This tool is designed to streamline and standardize data usage across various datasets.

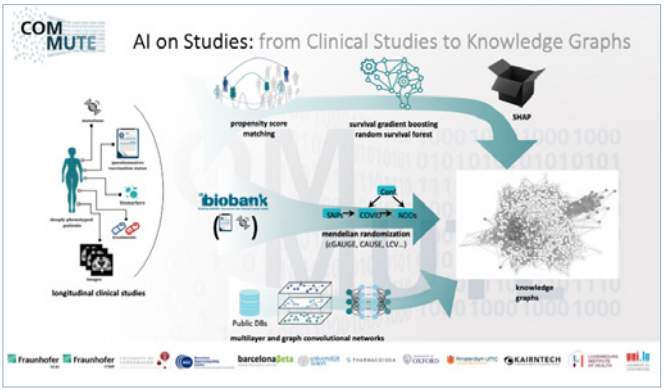

Fig. 3: Overall strategy for modeling of clinical study data and observational data in the Data Science / AI Work Package. Workflow schema developed and provided by Davide Cirillo and Jon Sánchez Valle (Barcelona Supercomputing Center, BSC).

WP 4 – Validation & Mechanistic Understanding

The "hypotheses-driven" WP in COMMUTE pursues multiple research approaches. One of the main pillars of WP 4 is clinical research based on cohorts managed by several of our COMMUTE partners. Notably, amongst our members, we lead a total of 5 longitudinal cohorts defining multiple aspects of neurodegenerative disorders, such as Alzheimer's disease and Parkinson's Disease, and/or SARS-CoV-2 infections. These cohorts are central to framing comorbidities' impact between SARS-CoV-2 and neurodegeneration. On the other hand, we have a resourceful list of in vitro tools, mostly based on advanced tissue cultures such as brain organoids and a dedicated, multicellular blood-brain-barrier (BBB) model to tackle the molecular events of the comorbidities. In the first months of our COMMUTE project, we established the direction of this endeavor:

1. we have identified the commonalities amongst labs for ***in vitro* resources and protocols,** and
2. we have reviewed the literature and **updated into common knowledge the state-of-the-art in COVID-19 and neurodegeneration.**

The first of our points is central to defining the best experimental strategy and facilitating the interaction and legal aspects involving sensitive material amongst different labs in different EU countries. This task is especially intertwined with the advances from the legal Work Package 5. The second task aims at the most comprehensive review of evidence and mechanistic foundations of the COVID-19 – neurodegeneration co-morbidity. We are working on preparing a publishable report involving this information for the scientific community in the form of a review manuscript that will be submitted to a high-impact journal to target the right audience.

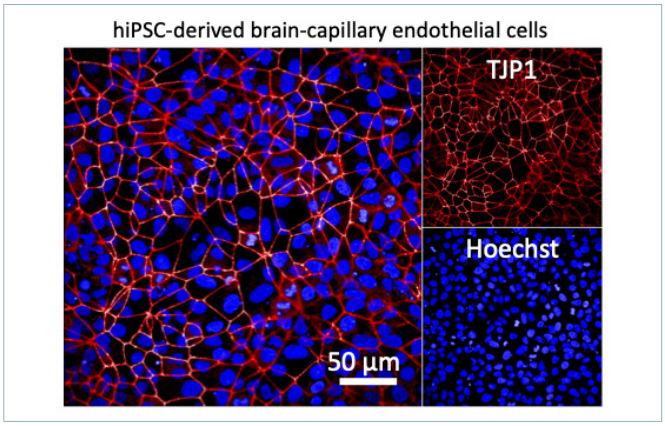

Fig. 4: Blood-Brain-Barrier model based on human inducible Pluripotent Stem Cells (hiPSC). Endothelial cells with their Tight Junctions (connectors between cells) stained. The picture was provided by Undine Haferkamp and Ole Pless (partner Fraunhofer ITMP Hamburg).

WP 5 – Ethics & Legal

To further ensure an ongoing exchange between the project consortium and representatives of end-users and to foster understanding of end-user needs and concerns, UNIVIE, in coordination with Fraunhofer and input from partners, established a Legal and Ethical Advisory Board (LEAB). The LEAB includes the following distinguished experts:

- Dr. Andrea Jelinek, Chair of the European Data Protection Board; former head of the Austrian Data Protection Authority (DPA)
- Dipak Kalra, President of The European Institute for Innovation through Health Data (i~HD)
- Joachim Maurice Mielert, Network Patient Safety, LEAB of REPO4EU
- Prof. Dr. Louisa Specht-Riemenschneider, University of Bonn
- Dr. Marco Straccia, Co-Founder and CEO of Fresci

Fig. 5: The Department of Innovation and Digitalization in Law of partner Universität Wien (University of Vienna). If you are a computational or biomedical scientist, you may feel envious. But that´s okay …

UNIVIE will coordinate the regular meetings of the LEAB, who will be involved in consortium discussions, review deliverables, and advise partners to guide the project process and outcomes.

The UNIVIE team analyzes and identifies legal and ethical requirements and addresses emerging issues relating to the COMMUTE project. The current focus is assessing the need for a Data Protection Impact Assessment (DPIA) for the COMMUTE project and further compliance with the General Data Protection Regulation (EU GDPR).

What comes next?

The next COMMUTE bulletin (due at the end of September 2024) will focus on our project's main challenge: the time constants of short-term processes linked to SARS-CoV-2 infections and their long-term consequences in the human brain. We will discuss the implications for modeling and endpoints and the reasons why we have chosen to follow a dual strategy with data-driven and knowledge-driven approaches.

Contact

Fraunhofer Institute for Algorithms
and Scientific Computing SCAI
Schloss Birlinghoven 1
53757 Sankt Augustin

Prof. Dr. Martin Hofmann-Apitius
Phone +49 2241 14-4103
martin.hofmann-apitius@
scai.fraunhofer.de

www.commute-project.eu