Structural Biology Meets Clinic: Molecular Aspects of COVID-19

Program:

	Opening remarks and introduction
16:30	**Welcome:** Peter Schemmer, *President Scientific Soc. of Med. Doctors in Styria, Med Uni Graz &* Tobias Madl, *Speaker Integrative Structural Biology and Biophysics Initiative, Med Uni Graz, Austria*
16:35	**Keynote lecture: Molecular Aspects of SARS-CoV-2** **Sriram Subramaniam**, *Gobind Khorana Canada Excellence Research Chair in Precision Cancer Drug Design, University of British Columbia, Vancouver, CA.*
	Short talks: Structural Biology **Chair:** Tobias Madl, *Med Uni Graz, Austria*
17:05	**In situ structural analysis of SARS-CoV-2 spike reveals flexibility mediated by three hinges**. Mateusz Sikora & Martin Beck, *MPI Frankfurt, Germany*
17:20	**Selection and structural analysis of synthetic nanobodies that effectively neutralize SARS-CoV-2.** Christian Löw, *EMBL Hamburg, Germany*
17:35	**In-silico models of Spike-Ace2 interactions.** Chris Oostenbrink, *BOKU Vienna, Austria*
	17:50 5min. break
	Short talks: Medical/Clinical Research **Chair:** Peter Schemmer, *Med Uni Graz, Austria*
17:55	**Drug discovery on the Fast Track - A structural bioinformatics response to the Covid-19 pandemic through force-field and AI-based methods.** Christian Gruber & Karl Gruber, *Innophore & Uni Graz & ISB, Austria*
18:10	**Covid-19 in gastroenterology and hepatology.** Vanessa Stadlbauer, *Med Uni Graz, Austria*
18:25	**Endothelial dysfunction in Covid Pneumonia. Fact or Fiction?** Horst Olschewski, *Med Uni Graz, Austria*
18:40	**Discussion: Impact of COVID-19 on medical research and structural biology** **Chairs:** Peter Schemmer & Tobias Madl, *Med Uni Graz, Austria*
19:00	Closing remarks

Abstracts

Keynote lecture: Molecular Aspects of SARS-CoV-2

***Sriram Subramaniam**,* Gobind Khorana Canada Excellence Research Chair in Precision Cancer Drug Design, Department of Biochemistry and Molecular Biology, University of British Columbia, Vancouver, CA.

The COVID-19 pandemic is an urgent international health crisis resulting from the spread of the SARS-CoV-2 virus, the causative agent of the disease. Knowledge of the destruction caused by viruses such as the 1918 influenza pandemic and the HIV/AIDS pandemic provide a historical perspective for the havoc wreaked by diseases such as COVID-19, but few could have imagined the scale of our current predicament. Unprecedented global scientific collaborations have rapidly led to detailed insights into the origins of the virus, its molecular make-up and mechanisms underlying the infection process. In my talk, I will highlight the advances in structural biology that are laying the foundation both for the development of therapeutics to treat those who are infected, and for the design of vaccines that can protect against future infection by the SARS-CoV-2 virus.

In situ structural analysis of SARS-CoV-2 spike reveals flexibility mediated by three hinges. *Mateusz Sikora & Martin Beck,* Max-Planck-Institute of Biophysics, Frankfurt, Germany.

"Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein mediates viral entry to the host cells and initiates the infection. As the only exposed surface protein, it is a primary target for vaccine development. We combined cryo-electron tomography, subtomogram averaging, and molecular dynamics simulations to visualise and structurally characterise spike proteins on the surface of intact virions. We discover three hinges in the stalk of S protein that endow it with surprising flexibility and can be relevant in the process of binding to the surface of the host cell."

Selection and structural analysis of synthetic nanobodies that effectively neutralize SARS-CoV-2. *Christian Löw,* Structural Biology, EMBL Hamburg, Germany.

Traditional antibody generation and production are hampered by long development times and costly production. Here, I report the rapid isolation and characterization of nanobodies from a synthetic library, known as sybodies (Sb), that target the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein. Several high-affinity binders were identified of which Sb23 displayed the strongest neutralization activity. A cryo-EM structure of the spike bound to Sb23 unraveled molecular details of this interaction and explains why Sb23 is an efficient neutralizer.

In-silico models of Spike-Ace2 interactions. *Chris Oostenbrink,* Inst. of Molecular Modeling and Simulation, University of Natural Resources and Life Sciences, Vienna, Austria.

Infection and viral entry of SARS-CoV-2 crucially depends on the binding of its Spike protein to angiotensin converting enzyme 2 (ACE2) presented on host cells. Glycosylation of both proteins is critical for this interaction. Recombinant soluble human (rsh) ACE2 can neutralize SARS-CoV-2 and is currently undergoing clinical trials for the treatment of COVID-19. We generated 3D structural models and performed molecular dynamics simulations defining the critical glycans that influence Spike-ACE2 complex formation. Engineering of ACE2 N-glycosylation by site-directed mutagenesis resulted in enhanced binding affinities and improved virus neutralization.

Drug discovery on the Fast Track - A structural bioinformatics response to the Covid-19 pandemic through force-field and AI-based methods. *Christian Gruber* & *Karl Gruber,* Innophore & Inst. of Molecular Biology & Integrative Structural Biology and Biophysics Initiative, University of Graz, Austria.

The development of drugs targeting multiple check points in the viral life cycle of SARS-CoV-2 could serve as a strategy to combat the current Covid-19 and future coronavirus pandemics. Here, we report on a large-scale virtual drug screening that combined the identification of potential binding sites employing the Catalophore pipeline with molecular docking performed by VirtualFlow to identify inhibitors targeting SARS-CoV-2. In this structure-based virtual multi-target screening campaign, we analyzed an average of approximately 1 billion molecules against 40 different targets on 17 different potential virus and host targets in the Google Cloud. While analyzing potential drug targets in the viral cavitome, we found that specific amino acids in peripheral loops in the binding domain of the SARS-CoV-2 viral spike protein are frequently mutated in emerging SARS-CoV-2 genomes. Using steered molecular dynamics simulations and normal mode analysis, it was shown that several of these mutations increase local flexibility and improve the binding of the spike protein to the human receptor ACE2. This information is fed into ongoing development pipelines to generate recombinant ACE2 variants that bind more strongly to the spike and relevant variants and might yield a starting point for the second generation of anti-spike biologics.

Covid-19 in gastroenterology and hepatology. *Vanessa Stadlbauer,* Division of Gastroenterology and Hepatology, Medical University of Graz, Austria.

Infection with the SARS-CoV-2 virus can affect the gastrointestinal system. ACE2 Receptor expression can be found in several parts of the gastrointestinal tract. Nausea, diarrhea and anorexia were frequently reported in the early phase of the pandemic by Asian countries and associated with worse outcome. Also increased transaminases have been observed. Effects of SARS-CoV-2 infection on the gut microbiome are still unknown. The gut microbiome may be an interesting target to treat or prevent viral infection. In this talk the implications of Covid-19 disease in gastroenterology and potential therapeutic approaches as well as potential connections to structural biology will be discussed.

Endothelial dysfunction in Covid Pneumonia. Fact or Fiction? *Horst Olschewski,* Division of Pulmonology, Medical University of Graz, Austria.

Covid-19 pneumonia has a high lethality, particularly in patients with old age, male gender, hypertension, and morbid obesity. The same risk factors are associated with endothelial dysfunction, causing hypertension, venous thromboembolism, myocardial infarction and other vascular diseases. In COVID-19 pneumonia, oxygenation may decrease in parallel with a decrease in pCO_2, indicating a predominant failure of pulmonary diffusion capacity with no decrease in lung ventilation capacity. This is a typical feature of a pulmonary „leakage", which is characterized by a fluid leak from the pulmonary capillaries into the interstitial lung tissue and eventually into the alveolar space. In parallel, COVID-19 causes thrombosis of the small pulmonary arteries. This is the second typical feature of endothelial dysfunction. Although there are some morphologic findings at autopsy suggesting „endothelialitis" of the pulmonary vessels, the cellular and molecular mechanisms remain largely unknown.

Online Co-hosts: *Andreas Winkler & Gustav Oberdorfer,* Inst. of Biochemistry & Integrative Structural Biology and Biophysics Initiative, Technical University of Graz, Austria.