Meeting report of the 23rd workshop "Cell Biology of Viral Infections" of the German Society for Virology (GfV) in Schöntal

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For its 23rd edition, the „Cell Biology of Viral Infections" Workshop of the German Society of Virology (GfV) took place at Kloster Schöntal, in Baden-Württemberg, between October 8 and 10. Altogether 32 participants - PhD students, postdocs or group leaders - gathered to exchange their newest research at the interface of Virology and Cell Biology. While the contributions of the participants covered the breadth of this topic, three of the four keynote speakers focused on neurotropic viral infections, a topic of high medical relevance across various virus families.

The first keynote lecture was given by Prof. Konstantin Sparrer, from the University of Ulm and the DZNE (German Center for Neurodegenerative Diseases). Prof. Sparrer shared his most recent work to identify new causes for the onset of neurodegenerative diseases, focusing on amyotrophic lateral sclerosis (ALS), a type of motor neurodegenerative disease. Only 5% of patients with ALS have known genetic predispositions for such diseases. Studying cohorts of matched patients and healthy individuals, Prof. Sparrer showed that ALS was strongly associated with a history of severe HSV-1 reactivations. At the molecular level, he demonstrated that the herpesviral protein ICP0, an E3 ubiquitin ligase, led to the degradation of PML bodies and, in turn, to the aggregation of the transcription and splicing factor TDP-43, a hallmark of ALS.

Prof. Anna Överby-Wernstedt from Umeå University, Sweden, also responded to her invitation by sharing her insights on tick-borne encephalitis virus (TBEV) infection in the mouse brain. TBEV is an emerging pathogen whose spread towards western Europe is well documented. Using antibody labelling in cleared brain tissue and overlaying light sheet microscopy tomograms with a standard brain topology obtained by MRI, Prof. Överby was able to image the tropism and spread of TBEV as well as a low-pathogenic relative, Langat virus, in the whole organ. Using interferon receptor knockout mice, her team showed the importance of the interferon defense system in restricting infection tropism and containing brain damage. Single nucleus RNA sequencing was used to verify the nature of the infected cells. At the same time, Prof. Överby´s work illustrated the limitations of cell culture systems to study brain infections since infection rates in cell culture did not reflect viral tropism *in vivo*. Interestingly, swapping the envelope glycoproteins between Langat virus and TBEV did not confer TBEV tropism to chimeric LGTV, illustrating that tropism and pathogenesis cannot be reduced solely to virus-receptor interactions.

Later in the day, Prof. Giuseppe Balistreri, from the University of Helsinki, Finland, highlighted the potential of combination therapy targeting simultaneously both entry routes of SARS-CoV2: the fusion at the plasma membrane (dependent on the TMPRSS2 protease) and endosomal entry (PI5 kinase-dependent). While inhibiting independently the TMPRSS2 protease with Camostat or the PI5 kinase with apilimod had no or only mild effects on SARS-CoV2 infection, simultaneous inhibition of both entry routes completely blocked infection in vitro and in mice, when applied during or shortly after infection. Prof. Balistreri also shared his innovative approaches to detecting viral infection of the brain. In collaboration with engineers and physicists, Prof. Balistreri is currently testing multiparametric noninvasive measurements in mice, including pupillometry (eye response to weak light patterns) to diagnose viral brain invasion at an early stage.

The last keynote lecture was given by Prof. Urs Greber, from the University of Zürich. Prof. Geber took the audience on a fascinating journey along the routes taken by adenoviruses to infect their target cells, from entry to morphogenesis and spread. Particularly impressive was the innovative use of click chemistry to track viral components during these processes, and identify for instance the host E3 ubiquitin ligase Mib1, which destabilizes the virus capsid during uncoating. Prof. Greber explained how the host interferon system promotes viral persistence by inhibiting adenoviral IE5 transcription, while the unfolded protein response (UPR) is harnessed by the virus in a transcriptional feedback loop to maintain the viral genome. The final part of the lecture focused on viral assembly, with imaging of viral replication and assembly compartments reorganizing the nuclear space and the use of pulse-chase click chemistry to distinguish the fates of early and late viral RNAs. The lecture also nicely illustrated how basic research advances our understanding of an important human pathogen but also an important gene therapy and vaccine vector.

The remaining sessions were devoted to the different steps of the viral replication cycle and their intricate interplay with the host cell biology. The first session was dedicated to early events in viral infection featured presentations that shed light on the entry routes of human papillomavirus and explored the function of host proteases in the proteolytic activation of highly pathogenic human viruses. The topic of HIV-1 reactivation and its potential use to clear proviral reservoirs in patients undergoing antiretroviral therapy was addressed in two talks in the virus-host interaction session. Meanwhile, liquid-liquid phase separation remained a subject of significant interest, as illustrated by several short talks on herpesviruses. Presentations on the mathematical modeling of influenza A virus entry and on the endogenous expression of the IFITM2/3 restriction factors in endothelial cells emphasized the benefit of interdisciplinary research approaches. Last but not least, the audience awarded Yasmin Roeder form the University of Lübeck the best oral presentation prize for her demonstration of the use of proximity labeling to identify protein complexes that specifically regulate pestivirus replication and morphogenesis.

We wish to express our sincere gratitude to all workshop participants for their excellent presentations, stimulating discussions, and the friendly atmosphere maintained throughout the three days. In addition, we thank the German Society for Virology (GfV) for its generous financial support. Having organized the workshop for the past three years, we are delighted to announce that Prof. Petr Chlanda (Heidelberg University) and Prof. Linda Brunotte (University of Giessen) have volunteered and been selected to organize the next “Cell Biology of Viral

Infection” workshop. We are happy to see the tradition continue and look forward to another engaging and memorable meeting!

For updates, please visit our website at https://cellviro.g-f-v.org/.

The 23rd edition of the “Cell Virology of Viral Infections” Workshop of the GfV took place from October 8th to October 10th at the Kloster Schöntal.

Yasmin Roeder, PhD student at the University of Lübeck and winner of the best presentation award, surrounded by the organizers Christian Sieben and Gabrielle Vieyres. Yasmin Roeder was awarded the prize for her presentation on the characterization of pestiviral replication and assembly machineries.