Synopsis & Bibliography Speakers

Speaker: Prof. Trine H. Mogensen

Title talk: 'Inborn errors of immunity predisposing to herpesvirus infections in the CNS'

Synopsis presentation

Herpesvirus infections can lead to a number of severe diseases, particularly when involving the central nervous system. However, understanding of the factors conferring susceptibility to these diseases and their complications remains incomplete. Previous studies have uncovered that defects in the innate Toll-like receptor 3 pathway and beyond in children and adults predispose to herpes simplex encephalitis (HSE) by herpes simplex virus (HSV)1. Among these, we described IRF3 deficiency in a patient with HSE. Subsequently, our group described rare mutations in RNA polymerase III in children with varicella zoster virus (VZV) encephalitis demonstrating the importance of this innate cytosolic DNA sensor in antiviral defense against VZV. In the present talk I will provide an overview of genetic defects predisposing to HSE in children and adults. In particular I will present work on two adult patients with recurrent HSV2 lymphocytic (Mollaret's) meningitis each carrying monoallelic rare potentially disease-causing variants in autophagy genes (ATG4A and LC3). Using a neuronal cell line we found that HSV2 was captured in autophagosomes, and blockage of autophagy by disruption of the ATG5 gene resulted in enhanced viral replication and cell death. Importantly, HSV2-activated autophagy was impaired in patient fibroblasts, which also exhibited significantly increased viral replication together with enhanced cell death. We found that HSV2-induced autophagy required viral late gene expression but was independent of the signaling adaptor molecule STING. Finally, reconstitution of wt allele expression of autophagy genes in cells from both patients restored virus-activated autophagy and the ability to control HSV2 replication. Altogether, we suggest an important role for autophagy in anti-HSV2 immunity in the nervous system. This represents the first description of an autophagy defect causing a primary immunodeficiency conferring increased susceptibility to viral CNS infection in humans. Finally, some new studies on the role of autophagy in VZV infection will be presented.

Bibliography speaker

Prof. Trine H. Mogensen obtained her Medical degree from Aarhus University (AU) in 2002, a PhD degree in 2003, and a Doctor of Medical Sciences degree in 2009. International training includes studies in Biochemistry and in Medicine in Paris, Descartes University and Necker Medical Faculty, Research fellow in the laboratory of Professor Bryan Williams at the Cleveland Clinic, and a Diploma from the London School of Hygiene and Tropical Medicine. Since 2017 she is Professor in Infection Immunology at Department of Biomedicine, AU and holds a consultant position in the Department of Infectious diseases at Aarhus University Hospital. Her clinical work and research focus on the genetic and immunological basis of inborn errors of immunity and severe infectious diseases, most notably viral infections in the CNS. Through a translational approach combining WES of patient samples with functional studies in molecular immunology and virology, her group aims at delineating the pathogenesis of infectious diseases, including herpes simplex encephalitis, recurrent HSV-2 meningitis, VZV encephalitis, and most recently COVID-19, with the ultimate goal to improve diagnosis, prevention, and treatment of patients. Currently, she is the coordinator of the Horizon Europe-funded consortium UNDINE on human genetic and immunological determinants of the clinical manifestations of SARS-CoV-2 infection.

Speaker: Prof. Daniel P. Depledge

Title talk: "Making sense of VZV attenuation: the why, the how, and the way forward"

Synopsis presentation

Varicella Zoster Virus (VZV), an alphaherpesvirus that exclusively infects humans, is the only human herpesvirus for which vaccines are licensed and available. During primary infection, VZV gains access to the skin, where it causes varicella (chickenpox), and to sensory neurons, in which the virus establishes life-long latency. Reactivation of latent VZV occurs in ~ 1/3 of infected individuals and often leads to herpes zoster (shingles), a painful skin condition. Importantly, reactivation is also associated with complications such as debilitating pain (post-herpetic neuralgia), keratitis, and encephalitis. The first VZV vaccine developed contains a live-attenuated VZV strain (vOka) derived from an isolated wild-type strain (pOka). This live-attenuated vaccine is licensed in many countries for both children and adults and has been shown to prevent primary infections and also to reduce the rate and severity of reactivation in older adults. More recently, a new subunit vaccine that uses a viral glycoprotein to induce immunity was developed. While not yet suitable for children, this subunit vaccine has been shown to provide significant protection against herpes zoster and associated complications in the elderly. To understand how the live-attenuated vaccine functions to produce immunity without disease, we and many other groups have turned to viral genetic analyses to better understand the differences between wild-type and attenuated strains. Remarkably, the genomes of wild-type and attenuated strains are near-identical with just six significant single nucleotide polymorphisms (SNPs) initially identified. In my presentation, I will highlight the history of these studies and how the six candidate SNPs were identified and studied. I will further present data from a recent collaborative study in which we identified and functionally assayed a seventh candidate. Finally, I will discuss viral genetics in the wider context of disease and how mutations in VZV genomes may influence pathogenicity.

Bibliography speaker

Dr Daniel P. Depledge career revolves around the twin pillars of molecular and computational biology. By combining these diverse disciplines, I have been able to gain unique insights into multiple aspects of host-pathogen interactions. I completed my early studies (BSc in Biological Sciences and MSc in Bioinformatics) at the University of Exeter (UK) before spending several months working on ocean genomics in Bermuda and gaining hands-on molecular microbiology experience at Montana State University (USA). Having gained an appreciation for both computational biology and the study of pathogens, I undertook a PhD in the lab of Prof. Deborah Smith at the University of York (UK) that allowed me to apply both computational and molecular approaches to the comparative study of Leishmania genomes. I subsequently spent a year working in the Parasite Genomics Unit of the Wellcome Trust Sanger Institute (UK) before switching fields to focus on viral genomics under the mentorship of Prof. Judy Breuer at University College London (UK). I subsequently obtained a three-year Medical Research Foundation award to focus my studies on alphaherpesviral latency, during which a large collaborative project Prof. Georges Verjans, Dr. Werner Ouwendijk (both Erasmus MC, NL) and Dr. Tomohiko Sadaoka (Kobe University, Japan) led to the discovery and ongoing characterisation of the varicella zoster virus (VZV) latency transcript. I later joined the lab of Prof. Ian Mohr at NYU (USA) where I furthered my studies of alphaherpesvirus latency and became fascinated by the role of RNA modifications in shaping host-virus interactions. After spending two years as an Assistant Professor at NYU, I joined the Hannover Medical School (Germany) in 2021 as an Associate Professor. Research in my lab now focuses on understanding the roles of diverse RNA modifications in shaping diverse virus-host interactions and further characterization of the VZV latency transcript.

Speaker: Dr. Ann C. Vossen

Title talk: "The disease burden of congenital CMV infection and how to reduce it"

Synopsis presentation

Congenital cytomegalovirus infection (cCMV) is the most common congenital infection worldwide, with a birth prevalence of approximately 0.6% in industrialized countries. This presentation will focus on the disease burden of cCMV, which we studied using a nationwide retrospective screening cohort, the CROCUS study. Compared to a negative control group, children with cCMV are more likely to have hearing loss, cognitive, motor and speech-language problems. These limitations lead to poorer school performance, a lower quality of life for children and their parents and higher health care costs. The significant disease burden has led to the development and implementation of various preventive and therapeutic strategies. There are multiple hurdles to overcome to really influence the burden of disease. One is the fact that a previous CMV infection does not protect against new infections and that CMV often reactivates. These non-primary CMV infections can also lead to vertical transmission and fetal infection. Primary prevention of maternal CMV infection through vaccination could result in a reduction in cCMV incidence. However, no registered vaccines are yet available and the development of a highly effective vaccine is challenging. Therefore, secondary prevention strategies using antiviral therapy or immunoglobulins for the prevention of viral transmission from mother to fetus are being evaluated. Finally, postnatal antiviral treatment is used to prevent progression of hearing loss after birth. Pitfalls and limitations of these strategies are discussed.

Bibliography speaker

Dr Ann C. Vossen studied medicine at Leiden University and then obtained her PhD in transplantation immunology at the Immunology Department of the Erasmus Medical Center. She specialized in Medical Microbiology at Erasmus MC and worked there for several years as a clinical virologist. She is currently a clinical virologist and associate professor at the Department of Medical Microbiology at the Leiden University Medical Center. Ann Vossen started her work on congenital cytomegalovirus (cCMV) infection 15 years ago and has contributed to the understanding of the epidemiology, clinical consequences, prevention and therapy of this congenital infection. She has initiated and led two major national research projects: the CROCUS study is a large retrospective study on the burden of disease from cCMV in the Netherlands and the CONCERT study is a study on the efficacy of six weeks of oral valganciclovir in children with cCMV and isolated hearing loss. As an enthusiastic teacher, she is involved in the training of both residents Clinical Microbiology and the medical students of Leiden University. Current and previous board positions include boards of the Dutch Society for Medical Microbiology, the Foundation for Quality Assessment of Medical Laboratory Diagnostics and the European Congenital CMV Initiative (ECCI).

Speaker: Prof. Ian Mohr

Title talk: 'Tuning herpesvirus reproduction to physiological cell stress responses'

Synopsis presentation

Responses to environmental and physiological stress, including latent and productive herpesvirus infections, demand swift, coordinated remodeling of the genome-wide expression landscape. Such abrupt adaptations provoked by stimuli that upset homeostasis can determine infection outcomes, by disrupting the latency program, shaping host cell intrinsic defenses, and sculpting a permissive environment that supports virus reproduction. Select examples illustrating these principles will be presented drawing upon our work on HCMV productive replication and HSV-1 latency in neurons.

Bibliography speaker

For more than 35 years, Dr. Ian Mohr's research has featured virus model systems to investigate fundamental biological regulatory mechanisms that control gene expression and replication. Following completion of his graduate research at Cold Spring Harbor Laboratory, he received his Ph.D. degree from the State University of New York at Stony Brook and was a post-doctoral fellow in the Dept. of Molecular & Cell Biology at the University of California, Berkeley. He joined the faculty in the Dept. of Microbiology at New York University School of Medicine in 1996, where he is presently a Professor and member of the Cancer Institute. He directed the NIH-funded Infectious Disease & Basic Microbiological Mechanisms Training Program at NYU School of Medicine for 10 years, served on the International Herpesvirus Workshop scientific advisory committee, was NIH Virology A study section chair, and is presently on the editorial board of Journal of Virology and Genes & Development. Discoveries made in his NIH-funded laboratory include identifying unexpected host and virus-encoded factors that control anti-viral immunity, defining new molecular mechanisms whereby viruses manipulate host translation factors, demonstrating roles for specific host mRNA translation in viral infection biology, and establishing functions for mTOR-signaling in the biology of acute and persistent infections.