Intrinsic immune control of neurotropic virus infections

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Duration	Yes/No	Available per (date)
6 months	Yes	January 2023 (flexible)
12 months	Yes	January 2023 (flexible)
18 months	To be discussed	Only after further contact

Background
Humans are continuously exposed to a variety of viruses that can infect the nervous system. Among these are the neurotropic human alphaherpesviruses herpes simplex virus 1 (HSV-1), HSV-2, and varicella zoster virus (VZV) as well as several (re-)emerging RNA viruses including Zika virus, Dengue virus, and West-Nile virus. Following virus invasion, either the infection process itself or the antiviral immune response can lead to severe, chronic, and debilitating morbidity and mortality, posing a significant threat to human health. Currently, the development of improved therapeutic approaches and vaccines is hindered by our incomplete understanding of the virus-host interactions that dictate the outcome of infection. In particular, the intrinsic antiviral mechanisms that protect neurons against virus infection as well as the viral evasion strategies interfering with these processes are poorly understood.

Recent studies revealed an important role for the cellular RNA degradation pathway 'nonsense-mediated decay' (NMD) in controlling infection by a variety of viruses, including human herpesviruses. However, besides a few recently reported mechanisms by which RNA viruses perturb NMD, interference strategies by DNA viruses, including human herpesviruses, are completely unknown. In this project, herpesvirus proteins that interfere with the host NMD pathway will be identified, followed by the detailed molecular characterization of their role and mechanism of action during virus infection of human cells including neurons.

Research lab:
This research project will be performed at the HerpeslabNL (www.herpeslab.nl) at the Department of Viroscience (Erasmus MC).

Research topics:
1. Identify herpes simplex virus proteins that modulate NMD activity.
2. Characterize the mechanism-of-action of the identified protein(s) in molecular detail.

Background of the research project at HerpeslabNL:
The aim of the Herpesvirus lab is to elucidate the virus-host interactions involved in the immune control and pathogenesis of herpesvirus infections in humans, in particular in the human nervous system. Historically focusing on adaptive, T-cell mediated control of infection, the laboratory has now expanded to also study innate and intrinsic host immune mechanisms that combat (herpes-)virus infections. The current project is part of a newly established research line that focuses on NMD-mediated intrinsic control of neurotropic virus infections in the human nervous system.

Techniques and other aspects specific to this research project:
In our laboratory, we use a unique combination of clinically relevant human tissues (*ex vivo* and *in situ*), (primary) human cell and infection systems (*in vitro*), and computational methods (*in silico*) in combination with a large variety of in-house state-of-the-art molecular, biochemical, immunological, and virological assays to study virus-host interactions. This includes CRISPR-mediated genome editing and (single cell) RNAseq, human tissue processing and primary cell culture, multiparametric flow cytometry, mass spectrometry, qRT-PCR, Sanger and next-generation sequencing (NGS), luciferase and fluorescence reporter assays, immunofluorescence staining and confocal microscopy, Western blotting, immunoprecipitation, cloning, protein expression by transfection and transduction, cell sorting, multiparametric immunohistochemistry, and *in situ* hybridization techniques.

Selected publications related to the research project:

- van Gent, M., Reich, A., Velu, S.E., Gack, M.U. (2021). Nonsense-mediated decay controls the reactivation of the oncogenic herpesviruses EBV and KSHV. *PLoS Biology* 19(2): e3001097.
- May, J.P., and Simon, A.E. (2021). Targeting of viral RNAs by Upf1-mediated RNA decay pathways. *Curr. Opin. Virol.* 47, 1–8.
- Leon, K. & Ott, M. (2021) An 'Arms Race' between the Nonsense-mediated mRNA Decay Pathway and Viral Infections. *Seminars in Cell & Developmental Biology* 111:101-107.
- Kurosaki, T., Popp, M.W. & Maquat, L.E. (2019) Quality and quantity control of gene expression by nonsense-mediated mRNA decay. *Nature Reviews Molecular Cell Biollogy* 20, 406–420.
- Balistreri, G.; Bognanni, C.; Mühlemann, O. (2017) Virus Escape and Manipulation of Cellular Nonsense-Mediated mRNA Decay. *Viruses* 9, 24.

Training options:
Interested and motivated students are encouraged to contact us about the possibility to perform their lab internship in our team. Together with the student a specific research plan will be defined that fits in this ongoing project.