Human fetal organotypic brain slice cultures: a preclinical model for Zika virus infection in the human fetal brain

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

Background

Central nervous system (CNS) infections with viruses are rare, but important causes of human morbidity and mortality. Understanding the cellular and molecular details of the virus-host interactions that determine infection outcome is crucial to develop novel targets of neuroprotective therapies. Zika virus (ZIKV) belong to a group of neurotropic pathogens referred to as TORCH. TORCH stands for Toxoplasma gondii, Others (syphilis, Zika virus, etc.), Rubella virus, Cytomegalovirus, and Herpes simplex virus (HSV) and is a group of pathogens associated with different congenital diseases [2]. Infection with the flavivirus ZIKV has been linked with the development of congenital cortical malformations, such as reduction of the brain volume (microcephaly) due to thinner neocortex. Currently, it is not known to what extent microcephaly is direct cause by ZIKV infection or due to the inflammatory response in the brain or the altered placental support, which have been observed to affect brain development.

Various models have been developed to study the ZIKV-induced pathophysiology of the fetal brain, but few truly mimic human disease. Rodent models provided insight into the viral pathogenesis *in vivo*, but the interpretation of data is obscure due to species differences. Cell culture models can provide valuable information about ZIKV infection in specific human cell types, but this does not reflect the full complexity of the brain. An ideal preclinical model to investigate ZIKV neurovirulence is of (1) human origin, (2) contain all the relevant CNS cell types, including microglia (3) and maintain the complex tissue cell-to-cell interaction likewise the human brain. Recently, we developed the human fetal organotypic brain slice culture (hfOBSC) platform that meets all requirements of a good preclinical models to study the pathophysiology of TORCH pathogens in the human fetal brain. The aim of this study is to investigate the neurotropism and neurovirulence of ZIKV in our hfOBSC platform and subsequently test the efficacy and safety of various therapeutic anti-ZIKV interventions.

Research lab:

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

Research topics:

1. Investigate the neurotropism and neurovirulence of ZIKV in our hfOBSC platform and compare it patient data.
2. Determine the efficacy and safety of various therapeutic anti-ZIKV interventions in hfOBSC.

Background 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 viral infections in humans. In this project, we will investigate the neuro-

tropism/virulence of ZIKV and the efficacy/safety of promising anti-ZIKV drugs in our hfOBSC platform. These studies will be complemented by detailed histological analyses on brain tissue from ZIKV patients and controls.

Techniques and other aspects specific to this research project:
In our laboratory, we use **in-house** state-of-the-art cellular (e.g. human tissue processing, primary cell culture and human brain slicing & culture), molecular biology (e.g. (RT)-qPCR, western blotting, ELISA) and *in situ* (e.g. multiparametric immunohistochemistry and *in situ* hybridization) techniques. In this project a variability of techniques will be considered, including: hfOBSC generation and culture, virus infection, multi-color flow cytometry and multi-parametric immunohistochemistry.

Selected publications of the HerpeslabNL related to the research project:

- Rashidi AS, Tran DN, Peelen CR, Gent MV, Ouwendijk WJ, Verjans GM. Herpes Simplex Virus Induces Necroptosis in Neurons and Astrocytes of Human Organotypic Brain Slices. J Neuroinflamm. 2022. *Manuscript in progress.*
- Katzilieris-Petras G, Lai X, Rashidi AS, Verjans GMGM, Reinert LS, Paludan SR. Microglia Activate Early Antiviral Responses upon Herpes Simplex Virus 1 Entry into the Brain to Counteract Development of Encephalitis-Like Disease in Mice. J Virol. 2022;96:e0131121. doi: 10.1128/JVI.01311-21.
- Reinert LS, Rashidi AS, Tran DN, Katzilieris-Petras G, Hvidt AK, Gohr M, Fruhwürth S, Bodda C, Thomsen MK, Vendelbo MH, Khan AR, Hansen B, Bergström P, Agholme L, Mogensen TH, Christensen MH, Nyengaard JR, Sen GC, Zetterberg H, Verjans GM, Paludan SR. Brain immune cells undergo cGAS/STING-dependent apoptosis during herpes simplex virus type 1 infection to limit type I IFN production. J Clin Invest. 2021;131:e136824. doi: 10.1172/JCI136824.

Training options:
Interested and motivated students are encouraged to contact us about possibilities to do their lab internship in our team. Together with the student we will define a research plan in this ongoing project.