Antiviral immunity in Alzheimer's disease

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

Background
Alzheimer's disease (AD) is a progressive brain disease characterized by memory loss, decline in brain function and ultimately death. AD pathogenesis involves the deposition of amyloid-β plaques, activation of the brain's resident innate immune cells (microglia) and formation of neurofibrillary tangles. Besides aging, genetic predisposition and environmental risk factors contribute to AD. Herpesvirus infections are an important AD risk factor. However, how these viruses contribute to AD is poorly understood.

The neurotropic herpesvirus herpes simplex virus 1 (HSV-1) is most often associated with AD. Most individuals acquire HSV-1 during childhood, after which the virus establishes lifelong latency in neurons of the trigeminal ganglion (TG). The TG projects to both the orofacial epithelia and the central nervous system. Therefore, reactivation of latent HSV-1 can cause cold sores (herpes labialis) and in rare cases encephalitis. My preliminary data indicate that low frequencies of HSV-1 infected neurons are often detected in multiple brain regions of AD patients, but not control subjects. Interestingly, these observations could explain the recently identified AD-specific microglia subpopulation that expresses a network of antiviral response genes. These antiviral microglia co-localize with Aβ plaques, drive neuroinflammation and cause synaptic loss. In this project, we will investigate the hypothesis that HSV-1 infection changes the function of microglia from "protective" to "AD-promoting".

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

Research topics:
1. To investigate how herpesvirus infections influence the function of microglia *in vitro*
2. To investigate the relationship between HSV-infected neurons, microglia and Aβ plaques in brains of AD patients.

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 herpesvirus infections in humans. In this project, we will investigate how HSV-1 infections influence AD-relevant functions of microglia using various microglia models (immortalized human microglia-like cells, monocyte-derived microglia and iPSC-derived microglia). These studies will be complemented by detailed histological analyses on brain tissue from AD patients and controls, to investigate the spatial orientation and phenotype of microglia in relation to AD pathology and HSV-1

infected cells. The latter involves longstanding collaborations with the Netherlands Brain Bank (Amsterdam).

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 multiparametric flow cytometry), molecular biology (e.g. (RT)-qPCR, Sanger and Illumina sequencing, cloning and expression of proteins and single cell sequencing (10X) including bioinformatics) and multi-color flow cytometry, cell sorting) and *in situ* (e.g. multiparametric immunohistochemistry and *in situ* hybridization) techniques. In this project a variability of techniques will be considered, including: lymphocyte isolation, B- and T-cell culture, DNA/RNA isolation, (RT-)qPCR, functional T-cell assays, multi-color flow cytometry, multiparametric immunohistochemistry and potentially *in situ* hybridization, and antigen discovery using T-cells expressing the recombinant T-cell receptor of interest.

Selected publications of the HerpeslabNL related to the research project:

- Tran DN, Bakx ATCM, van Dis V, Aronica E, Verdijk RM, Ouwendijk WJD. No evidence of aberrant amyloid β and phosphorylated tau expression in herpes simplex virus-infected neurons of the trigeminal ganglia and brain. Brain Pathol. 2022;32:e13044. doi: 10.1111/bpa.13044. PMID: 34913212.
- Itzhaki RF. Overwhelming Evidence for a Major Role for Herpes Simplex Virus Type 1 (HSV1) in Alzheimer's Disease (AD); Underwhelming Evidence against. Vaccines. 2021;9:679. doi: 10.3390/vaccines9060679. PMID: 34205498.
- Olah M, Menon V, Habib N, Taga MF, Ma Y, Yung CJ, Cimpean M, Khairallah A, Coronas-Samano G, Sankowski R, Grün D, Kroshilina AA, Dionne D, Sarkis RA, Cosgrove GR, Helgager J, Golden JA, Pennell PB, Prinz M, Vonsattel JPG, Teich AF, Schneider JA, Bennett DA, Regev A, Elyaman W, Bradshaw EM, De Jager PL. Single cell RNA sequencing of human microglia uncovers a subset associated with Alzheimer's disease. Nat Commun. 2020;116129. doi: 10.1038/s41467-020-19737-2. PMID: 33257666
- Roy ER, Chiu G, Li S, Propson NE, Kanchi R, Wang B, Coarfa C, Zheng H, Cao W. Concerted type I interferon signaling in microglia and neural cells promotes memory impairment associated with amyloid β plaques. Immunity. 2022;55:879-894.e6. doi: 10.1016/j.immuni.2022.03.018. PMID: 35443157.

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.