

Deciphering the role of herpes virus simplex reactive T-cells in human corneas and sensory ganglia

Group leader: Dr Georges M.G.M. Verjans MSc PhD
Supervision project: Drs Gülce Sari MSc PhD and Michiel van Gent MSc PhD
Email: herpeslabnl@erasmusmc.nl
Website: <https://www.herpeslab.nl>



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

About 60-70% of the adults in the US and Netherlands are latently infected with the neurotropic herpes simplex virus type 1 (HSV-1). The hallmark of HSV-1 is its ability to establish a lifelong chronic infection (latency) in neurons of sensory ganglia, especially the trigeminal ganglia (TG), and reactivate intermittently to cause diseases ranging in severity from mild (e.g. herpes labialis) to sight-threatening (e.g. herpetic keratitis and uveitis) or even life-threatening diseases (e.g. herpetic encephalitis). Virus-specific adaptive immunity, especially T-cells, are pivotal in not only preventing reactivation of latent HSV-1 but are also considered detrimental in ocular diseases. These T-cell responses orchestrate their beneficial or detrimental role locally, most likely as tissue-resident memory T-cells (T_{RM}), in the TG and cornea of latently HSV-1-infected individuals, respectively.

Mouse studies, that only partly mimic human disease, provided conclusive evidence on their dual function. However, the role of HSV-1 reactive T-cells in humans, the only natural reservoir of this virus, remains largely unknown. Unravelling the differential characteristics of virus-specific T-cells, both their fine antigen specificity and functional features, in human TG and corneas of patients with herpetic keratitis will provide clues for vaccine development and modulating their immunopathogenic role in ocular diseases, respectively.

Research lab:

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

Research topics:

1. To study the phenotype, function, clonality and fine antigen specificity of T-cells residing in cornea and ganglion tissues of (latently) HSV-1-infected individuals.
2. To study the spatial orientation of HSV-1 reactive T-cells in surplus cornea and ganglion tissues of the individuals studied in topic #1.

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. The current research project is performed in longstanding collaborations within Erasmus MC (dept Hematology and Pathology), the Netherlands Brain Bank (Amsterdam), Rotterdam Eye Hospital (Rotterdam) and the Dept of Medicine, Division of Allergy and Infectious Diseases (University of Washington, Seattle, USA). The project is funded by the National Institute of Allergy and Infectious Diseases (75N93019C00063-0-9999-1).

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:

- [Unger PP](#), [Oja AE](#), [Khemai-Mehraban T](#), [Ouwendijk WJ](#), [Hombriink P](#), [Verjans GM](#). T-cells in human trigeminal ganglia express canonical tissue-resident memory T-cell markers. *J Neuroinflamm.* 2022. *In Press*.
- [St Leger AJ](#), [Koelle DM](#), [Kinchington PR](#), [Verjans GMGM](#). Local Immune Control of Latent Herpes Simplex Virus Type 1 in Ganglia of Mice and Man. *Front Immunol.* 2021;12:723809. doi: 10.3389/fimmu.2021.723809. PMID: 34603296
- [Ouwendijk WJD](#), [Geluk A](#), [Smits SL](#), [Getu S](#), [Osterhaus AD](#), [Verjans GM](#). Functional characterization of ocular-derived human alphaherpesvirus cross- reactive CD4 T cells. *J Immunol.* 2014;192(8):3730-9. doi: 10.4049/jimmunol.1302307. PMID: 24623134.
- [van Velzen M](#), [Jing L](#), [Osterhaus AD](#), [Sette A](#), [Koelle DM](#), [Verjans GM](#). Local CD4 and CD8 T-cell reactivity to HSV-1 antigens documents broad viral protein expression and immune competence in latently infected human trigeminal ganglia. *PLoS Pathog.* 2013;9(8):e1003547. doi: 10.1371/journal.ppat.1003547. PMID: 23966859.

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.