



Master level project proposal

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Place: Helleday Laboratory, SciLifeLab, OnkPath, KI

Timing: 2019/2020; duration at least 6 months

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Investigation of host immune pathways during Zika virus infection and treatment with a novel antiviral compound

The re-emergence of Zika virus in the Americas in 2015 caused a major public health crisis all over the world. Although infection by Zika virus usually causes only mild and short disease with symptoms like cutaneous rash and fever, it has also been linked to serious neurological disorders such as severe microcephaly in fetuses, if women are infected during pregnancy.

Latest research has shown, that infection by Zika virus itself is only partly responsible for the damage inferred. The immune system, usually a safe-guard for the human body, has been found to play an important role in facilitating neuronal damage. Zika virus has been shown to activate inflammatory reactions in the infected neuronal cells. The resulting cytokine release triggers further inflammatory responses in surrounding, non-infected cells, leading to further neuronal damage.

At Helleday laboratory, we have developed and characterized a small molecular inhibitor with antiviral properties against Zika virus infected cells. Now we aim to investigate the immune activation caused by Zika virus infection and determine how it is modulated by the newly identified antiviral compound. We would like to determine how our compounds influence immune pathways which are altered by Zika virus infection.

To answer this question, we infect peripheral blood nuclear cells (PBMCs) from healthy donors with Zika virus, treat with our compounds and look at different parameters like cytokine release upon infection with Zika virus and compound treatment, and gene expression levels of immune genes.

The overall aim of this project is to investigate in detail the compound effect on key immune pathways altered by Zika virus infection.

Specific objectives:

- ✓ **Objective 1:** Gene expression analysis of regulatory and downstream genes in key immune pathways upon Zika virus infection and treatment with compounds from our library.

Expression of a few key immune genes upon infection with Zika virus and treatment with our compounds has been investigated in PBMCs. Findings will be validated and investigated in subsets like Macrophages and Monocytes by qPCR.

- ✓ **Objective 2:** Investigation of antiviral effects of our compounds in PBMCs after Zika virus infection

Zika virus load in PBMCs with and without treatment with our compounds will be determined using high-throughput imaging techniques (immunofluorescence).

Skills and competences to be acquired (learning outcomes):

1. Extensive cell culture knowledge, including extracting and cultivating various subtypes of blood cells from blood donations from healthy donors
2. RNA extraction and quality control
3. qPCR and gene expression analysis
4. Flow cytometry to identify subtypes of blood cells
5. High-throughput imaging techniques and analysis
6. Theoretical knowledge about innate antiviral immune mechanisms
7. Experiment planning, big data analysis and data interpretation

Requirements:

- Bachelor degree in biomedicine, biology, biochemistry or similar subjects
- Experience in basic molecular and cellular techniques (cell culture, working with RNA, qPCR)
- The candidate should be highly motivated and pro-active, have good communication skills and ability to interact effectively and work productively in a team.
- Fluency in English.

The selected student will be a part of the Helleday laboratory that takes a multidisciplinary approach involving close collaboration between biochemists, medicinal chemists, molecular biologists, virologists and pharmacologists. The high diversity of methods and competences is a unique chance to acquire a very broad skillset depending on motivation of the chosen candidate.

The research group focuses on understanding basic cellular processes and developing novel drugs for treating a variety of diseases related to these cellular pathways.