

Master Project Proposal

Title: Impact of malaria infection during infancy on thymic function and immune competence

Synopsis:

The immune system has the exceptional ability to successfully combat most of the countless types of pathogens we are exposed to throughout life. T lymphocytes play a central role in adaptive immunity against these external threats, while maintaining tolerance to self, a feature that is warranted by their criterious selection in the thymus, the primary organ for T cell production. Reductions in thymic T cell output and diversity, as found in infections, ageing or upon thymectomy, have been linked to a reduced ability of the immune system to generate antigen-specific responses to pathogens and vaccination, as well as to increased susceptibility to autoimmune diseases and cancer.

Malaria remains the world's most prevalent infectious disease, with ~260 million cases reported worldwide, and ~70% of the estimated 445 000 malaria fatalities being from children under the age of 5 (World Malaria Report 2017). We hypothesize that malaria infection during infancy, at a stage when immunity has not yet been fully developed, may hinder future responses to pathogens due to deficient repertoire formation. In support of this, infection of mice with the malaria-causing parasite *Plasmodium* results in pathogen invasion of the thymus and disruption of its microenvironment through apoptosis, changes in cell migration-related molecules and premature egress of immature thymocytes, and the effects of such damage remain after anti-malarial treatment.

In this project we propose to investigate the effect of malaria infection during infancy on immune competence later in life. We will determine the impact of a single vs. multiple episodes of malaria infection on the ability of young individuals to generate a diverse T cell repertoire, as well as the capacity to develop antigen-specific responses or respond to vaccination later in life. Our approach will rely on the use of mouse models, as well as on multiple cellular and molecular biology techniques including multiparametric flow cytometry, confocal microscopy and real time RT-PCR.

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