Project FR-1

Improving our understanding of the Meningococcal Disease with the Genomic sequencing for variants in complement genes

(Supervisors: **Prof. Veronique Fremeaux-Bacchi, Prof. Seppo Meri**)

Antibodies and complement undoubtedly play major roles in determining clinical outcomes following acquisition of a N. meningitidis strain, but in some instances it causes catastrophic invasive infection. The role of the opsonophagocytosis and the killing of bacteria via the membrane attack complex is well established in the defense again infection but it become more and more evident that host factors may contribute to disease severity. Meningococci use several mechanisms to evade killing by complement and is responsible for the liberation of complement activation product that can turn complement from a defense system to an aggressor that drives inflammatory diseases. The exacerbation of complement mediated damage on host cells in Nm and its link with the disease severity is poorly documented. The objective is to identified complement biomarkers and genetic predisposition for severe meningococcocal disease. Using blood patient suffering to Nm infection (cohort and biocollection under construction) our aims are to perform an extensive complement analysis with determination of the complement levels of the proteins and activated fragments. Current molecular tools can perform high throughput for complement analysis. Until now only complete deficiencies of complement proteins have been linked to meningococcal meningitis. We hypothesize that rare variants in heterozygous state or association several hypo functional variants and not only completely absent terminal complement proteins may result in fulminant infection. The PhD student will contribute to screen for rare variants in patients with recurrent or severe infections. He/She will also study what are the functional consequences of the identified rare variant in the complement cascade and how they predispose to meningococcocal disease. The PhD student will determine whether variations of the level and function of complement components and regulators (such as FH and FP) contribute to the disease susceptibility and severity. The goal is to show whether such variations and not only completely absent terminal complement proteins result in fulminant infections. In Helsinki the PhD student will study in vitro the effect of the genetic abnormalities found in FH/FHRs.

Objectives: 1. Screening for genetic abnormalities and variants in a set of complement genes of patients from a French cohort of patients with severe and recurrent meningococcal meningitis. 2. Prediction of the functional consequences of identified variants 3. Stratification of the disease outcome depending on the genetic abnormality

General description of your individual PhD-schedule:

- Your main university will be Sorbonne University (France) with Prof. Fremeaux-Bacchi as supervisor.
- You will have a 12-months research secondment at University of Helsinki (Finland) with Prof. Meri as supervisor, where you continue to scientifically work on your thesis project.
- You will have a 1-month clinical training at Tirol Kliniken Innsbruck (Austria).
- You will have a 1-month entrepreneur training at MSD Finland (Helsinki, Finland).
- You will finally receive a PhD issued by Sorbonne University and University of Helsinki if you fulfil the respective requirements.

Application

The position is advertised from 10.03.2020 – 10.05.2020 on **www.corvos.eu**. Please apply via this homepage during that time.