Project IT-1

Role of pentraxin and interaction with complement in immune defence against opportunistic infections

(Supervisors: Prof. Cecilia Garlanda, Prof. Seppo Meri)

PTX3 is a soluble pattern recognition molecule which acts as a key component of humoral innate immunity in opportunistic infections of fungal and bacterial origin. PTX3 binds microbial structures and activates effector functions (complement, phagocytosis). Moreover, it has a complex regulatory role in inflammation and tissue remodeling. PTX3 allelic variants are associated with increased susceptibility to fungal as well as bacterial infections. PTX3 modulates all three complement pathways by interacting with key molecules involved in activation and/or regulation of the complement cascade. PTX3 interacts with ficolins and MBL, leading to enhanced complement deposition on the surface of fungi and phagocytosis of the pathogen. Finally, PTX3 interacts with complement negative regulators, such as FH and C4BP, modulating complement activation and preventing an excessive inflammatory response to tissue injury, while increasing the deposition of opsonic molecules. PTX3 also interacts with fibrinogen/fibrin and plasminogen at acidic pH, promoting fibrin degradation. Aspergillus fumigatus evades complement recognition and promote tissue damage by recruiting FH and plasminogen, respectively.

The major aim of this PhD thesis project is to investigate whether PTX3 interferes with the binding of FH and plasminogen to Aspergillus fumigatus, thereby affecting complement deposition, plasmin activation and fibrinogen degradation, thus counteracting Aspergillus complement evasion and tissue infiltration strategies. A second aim is to analyse the interaction between PTX3 and other fungal and bacterial microbes and to investigate the consequences on complement activation.
To achieve the goals, IT-1 will use recombinant molecules available in the consortium and in vitro approaches (IF, confocal microscopy, FACS, biochemical assays, phagocytosis assays, in vitro fibrinolysis assays). An in vivo Aspergillus infection model and treatment with PTX3 variants, domains and muteins will be used to validate the relevance of results obtained in vitro.
In Helsinki (FI), IT1 will analyze potential novel interactions of PTX3 with other microbes, like Candida, streptococci and staphylococci, plus the protozoan parasite Plasmodium falciparum and its individual surface components. Functional studies will include the effect of these interactions on the activation and regulation of the complement system. Moreover, respective individual binding sites on interacting molecules will be mapped, thus promoting the development of PTX3-based therapeutic strategies.

General description of your individual PhD-schedule:

- Your main university will be Humanitas University Milano (Italy) with Prof. Garlanda as supervisor.
- You will have a 6-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 Research Center Borstel Hospital (Germany).
- You will have a 1-month entrepreneur training at MSD Finland (Helsinki).
- You will finally receive a PhD issued by Humanitas University and Helsingin Yliopisto (FI) if you fulfil the respective requirements.

Application

The position is advertised from 10.09.2019 – 10.11.2019 on **www.corvos.eu**. Please apply via this homepage during that time.