Proposal for the International PhD program

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Title: Human genetic predisposition to fungal diseases

Summary:
Most fungal diseases (FD) occur in patients with known acquired or primary immunodeficiencies (ID) and, less frequently, in otherwise healthy patients without any overt ID. We hypothesize that these “idiopathic” FD may be caused by single-gene inborn errors of immunity. We intend to investigate patients with proven idiopathic FD. We will identify and characterize the underlying genetic defects by a strategy combining powerful genome-wide explorations and in-depth functional experiments.

Project:
Fungal diseases (FDs) can be life-threatening infections that usually occur in patients with immunodeficiencies (IDs), either iatrogenic, acquired, or primary (PIDs), often associated with other severe conditions. They represent a major public health problem with a rapidly growing at-risk population of patients, and the emergence of resistant strains of fungi. Thus, FDs generate considerable morbidity and mortality worldwide. As they frequently develop in patients with multiple conditions, the pathogenesis of these FDs remains poorly understood. In rare cases, however, FDs occur in otherwise healthy patients without any known risk factors. These “idiopathic” FDs represent a unique opportunity to gain insight into FD pathogenesis. We hypothesized that these FDs may be due to as yet undiscovered “pathogen-specific” inborn errors of immunity, which we aim to discover and decipher. Our hypothesis is based on the observations that (i) idiopathic FDs affect a very small minority of individuals while these fungi are ubiquitous in the environment, (ii) some well-characterized PIDs are associated with FDs and (iii) an increasing number of infectious diseases are being shown to result from single-gene inborn errors of immunity, including some FDs, as we have recently reported. We will focus our project on the three most prevalent invasive FDs (IFDs) in Western Europe, namely cryptococcosis, aspergillosis and candidiasis. This project capitalizes on a unique collection of patients with proven idiopathic IFDs enrolled thanks to a worldwide network. We have enrolled 95 patients and we intend to recruit, within the next three years, a total of 200 patients. We will search for and characterize the underlying genetic defects using 1) cutting-edge genome-wide strategies, including next-generation sequencing (NGS) technologies, and 2) in-depth functional studies to validate the genetic variants identified. The immunogenetic dissection of IFDs will shed new light on the molecular and cellular mechanisms conferring protective immunity against specific fungi, Cryptococcus neoformans and gattii, Aspergillus fumigatus and Candida albicans in particular, and provide insight into the underlying pathogenesis. The expected clinical implications of this project will benefit the patients and their families in terms of diagnosis, treatment and outcome. Moreover, these advances will pave the way for novel prophylactic or curative therapeutic interventions, in the settings of these inherited IDs but also in patients with iatrogenic or acquired IDs, based on a rational understanding of the pathogenesis.

Main recent publications on the topic:


