PASTEUR PARIS UNIVERSITE (PPU) INTERNATIONAL DOCTORAL PROGRAM 2020

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PROJECT

- **FILE #03**
- **ACRONYM:** GEN-IPD
- **TITLE:** The human genetic and immunological basis of invasive pneumococcal disease

LABORATORY

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LABORATORY PRESENTATION AND RESEARCH TOPICS

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- **SPECIFY THE TEAM NAME:** Human genetics of infectious diseases – Bacterial team

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DESCRIPTION OF THE PROPOSED PROJECT

- **KEYWORDS:** severe bacterial infection, Streptococcus pneumoniae, inborn errors of immunity, NF-kB pathway

- **ABSTRACT**

Invasive pneumococcal diseases (IPD) is a major threat to children with inborn errors of immunity (IEI) associated with antibody or complement deficiency. However, most IPD occur in children without known IEI and despite anti-pneumococcal vaccination. We hypothesize that these "idiopathic" IPD may be caused by single-gene IEI. We intend to study patients with idiopathic IPD. We will identify and characterize the underlying genetic defects by a strategy combining genome-wide search for candidate variants and their in-depth experimental validation.

- **DESCRIPTION OF THE PROJECT**

Streptococcus pneumoniae is a Gram-positive encapsulated bacterium, which is almost ubiquitous, with the prevalence of asymptomatic carriage in the rhinopharynx approaching 90% in healthy children. Pneumococcus is also a common pathogen of childhood, causing substantial morbidity and mortality worldwide estimated to half million/year (WHO). It is a leading cause of benign conditions such as otitis media, and may cause more serious illnesses of the respiratory tract, such as pneumonia. In rare cases, pneumococcus may cause invasive diseases, such as arthritis, septicemia, and meningitis (designated as IPD). IPD is life-threatening, not only because of its rapid clinical course, but also because of the spread of antibiotic-resistant bacterial strains. Most children with IPD are between the ages of 3 months and 3 years. Current preventive measures are insufficient for the eradication of IPD, as non-conjugated pneumococcal vaccines (protecting against only a fraction of known serotypes) are poorly protective in children under 18 months of age, and the conjugated vaccines protect against even fewer serotypes. The annual incidence of children with IPD is similar in most Western countries; there are about 100 cases per year in France. The advent of anti-pneumococcal vaccination has significantly reduced the burden of IPD. However, vaccination campaigns have progressively led to the emergence of new pathogenic serotypes, not targeted by the existing vaccines. Thus, childhood IPD poses a major public health problem.

Environmental factors, such as socioeconomic conditions, probably account for the higher incidence of IPD in developing countries. However, the occurrence and rarity of IPD in Western countries suggest that host factors also play a prominent role in its pathogenesis. Some acquired and inherited host factors have been identified. The best-known acquired factors are co-infection with human immunodeficiency virus, splenectomy, certain cancers, and traumatic cerebrospinal fluid fistulas. Host genetic factors include drepanocytosis and certain IEIs (1). Children with isolated congenital asplenia (ICA), deficiency in the early components of complement and most B-cell deficiencies, including XR agammaglobulinemia, IgG2D, and SPAD, are particularly prone to IPD. Children with T-cell deficiency are also prone to IPD, largely due to their impaired Ab response. Nevertheless, children with ICA or impaired complement- or Ab-mediated opsonization are specifically susceptible to encapsulated bacteria, pneumococcus in particular. Remarkably, the greatest risk factor for IPD is IPD itself, with a 2-4% recurrence rate.

Within this context and accelerated by recent advances in Next Generation Sequencing (NGS) technologies, a search for IPD-predisposing single gene lesions was initiated about 15 years ago in our laboratory, with the aim of identifying new IEIs conferring a selective predisposition to IPD. Our first breakthrough came in 2001, with the discovery of hemizygous mutations in the X-linked *NEMO* gene, in male patients with anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) (2). In these patients, impaired NF-κB signaling results in susceptibility to multiple pathogens, including pneumococcus in particular. Children with EDA-ID fail to mount an Ab response to capsular glycans. Later on, we and others identified other inborn errors of NF-κB pathways (3-6), all leading to high susceptibility to IPD. In 2003 and 2008, we discovered 2 inborn errors in IRAK4 (7) and Myd88 (8), impairing the IL-1R and TLR pathways (except TLR3) and leading to susceptibility to only bacteria, including pneumococcus.

Altogether, we recently found that up to 10% of French children with IPD, recurrent or not, had a known IEI, based on a candidate gene approach (9). The genetic epidemiological features of childhood IPD had also not been subject to in-depth study until our own French survey. **We hypothesize IPD may result from inborn errors of immunity in a sizeable proportion of patients, which we aim to discover and decipher**. Our hypothesis is based on the observations that (i) idiopathic IPD affect a very minority of individuals while these bacteria are ubiquitous in the environment, (ii) some well-characterized IEIs are associated with IPDs 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. This project capitalizes on a unique collection of patients with proven idiopathic IPDs enrolled thanks to a worldwide network. We have enrolled and sequenced 300 patients and we intend to recruit, within the next three years, a total of 500 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 IPDs will shed new light on the molecular and cellular mechanisms conferring protective immunity against specific bacteria, *Streptococcus pneumoniae* 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.

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EXPECTED PROFILE OF THE CANDIDATE

- **EXPERIENCE REQUIRED**