PROJECT 1

DoS: Georgia Fousteri

Title: **Primary immunodeficiencies: follicular helper and follicular regulatory T cells as disease biomarkers**

Curriculum: BAIO

Link to OSR/UniSR personal page:

https://research.hsr.it/en/institutes/diabetes-research-institute/regulation-of-adaptive-immunity.html

Project description (*Number of characters*, *including spaces*: 2.000 - 3.000):

Primary Immunodeficiencies (PID) are characterized by cellular and humoral defects, increased risk to infection, autoimmunity (AI), and hematological malignancies (1). Pathogen clearance and humoral immunity require B cell differentiation into memory cells and long-lived plasma cells (PCs) in the germinal centers (GCs) where T follicular helper cells (Tfh) are the master providers of B-cell help (2). Several genes and molecules are key to these interactions. Mutations in these genes can alter the quantity and quality of follicular T cell responses resulting in PID (3). Currently, little it is known about the exact underlying cellular and molecular mechanisms by which these mutations alter the GC response. Our goal is to identify the role of T follicular helper (Tfh) and follicular regulatory (Tfr) cells in the regulation of humoral immunity in patients with primary immunodeficiency driven by mutations in specific genes, e.g., Wiskott, ADA2, but also in patients where the genetic cause is unknown. Where therapy is ongoing (gene therapy, immunotherapy), Tfh and Tfr cells will be studied at defined intervals as putative biomarkers of response. This study aims to identify the role of follicular T cells in disease pathogenesis and test their utility as biomarkers of disease course and response to therapy. More specifically, with this proposal we aim to:

Analyze the pool of circulating memory Tfh and Tfr cells in patients with PID and their capacity to promote and control B cell responses, respectively.

The questions (Q) we are going to address in this aim are:

Q1: What is the frequency and number of the major circulating Tfh subsets, Tfh1, Tfh17, Tfh2, highly functional Tfh, activated Tfh and Tfr cells in patients with mutations in Wiskott, ADA2, NF-kB, CTLA4, and others, and do they change longitudinally as the disease progresses?

Q2: Do circulating Tfh cells and subsets and their ratio to Tfr cells associate with disease severity and how do they change after therapy?

Q3: Do plasma CXCL13 levels associate with GC activity and could they be used as biomarker to predict disease progression or remission after therapy?

Skills to be acquired by the student (*Number of characters*, *including spaces*: max 600):

The PhD student will develop concrete scientific knowledge and in the field of clinical and experimental immunology. More specifically, he/she will acquire proficient knowledge in genetics of primary immunodeficiency, in T cell immunology and particularly the mechanisms that drive and control antibody responses. The technical skills to be developed are: staining and analysis of single cells by flow cytometry (FC). FC-based sorting of cells that will be used in in vitro experiments and for gene expression profile analysis. ELISA and Bioplex assays for the detection of cytokines and chemokines in the patients' sera and in culture supernatants. Histology (multiple immunofluorescence) of secondary lymphoid organs for the detection of GCs. NGS data analysis and validation. He/she will acquire the ability to clearly and forcefully articulate his/her ideas-in person and in writing. He/she will learn to analyze data, interpret the results, present data at conferences and write scientific manuscripts and research proposals.

References (max. 15)

1) Meyts et al, Front Immunol. Primary Immunodeficiencies: A Decade of Progress and a Promising Future. 2021 625753
2) Vinuesa, Annu Rev Immunol. Follicular helper T cells. 2016 34:335-68.
3) Ma, Uzel, Tangye, Curr Opin Pediatr. 2014 26(6):720-6.