PROJECT 2 (optional)

DoS: Georgia Fousteri

Title: **Immune therapy with genetically engineered regulatory T cells to establish tolerance in type 1 diabetes**

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):

Induction of immune tolerance is a fundamental requirement for any therapy aimed at halting the autoimmunity of type 1 diabetes (T1D). Polyclonal Treg therapy was demonstrated to be effective in mouse models and safe in patients with T1D; however, novel approaches are needed to direct Treg specificity and to enhance Treg suppression at an early stage of seroconversion (1). Our objective is to apply our expertise in follicular regulatory T cell biology and T-cell genetic modification and expansion to generate a sufficient quantity of murine and human islet-specific Treg "avatars" to support preclinical development of an optimized cellular therapy product capable of restoring humoral immune tolerance to β-cell antigens in subjects that have high risk for developing T1D (2).
Pancreatic islet transplantation is a curative option for patients with T1D. Similar to the approach described above that aims to restore tolerance in patients at a preclinical stage of the disease, here we aim to control allo-reactive responses by engineering antigen-specific Treg avatars (specific for a miss-matched HLA) to eventually treat patients that undergo pancreatic islet transplantation (3).
We will conduct a series of Aims to: 1) generate genetically-engineered murine and human Treg avatars specific for β-cell and HLA antigens and validate their function and migration properties in vitro and in vivo, and 2) evaluate the efficacy and safety of Treg avatars in mouse models of T1D and during non-T1D-associated scenarios such as viral infection. These proposed studies are expected to provide essential proof-of-concept data facilitating early phase Treg cell-based therapies for immune prevention of T1D. They also aim to provide a more effective and safer alternative to immunosuppression that might guarantee a permanent cure for T1D.

Skills to be acquired by the student:

The PhD student will develop concrete scientific knowledge in the field of experimental immunology. More specifically he/she will acquire proficient knowledge in genetic engineering of human and mouse Treg cells, and delineating the mechanisms that lead to antigen-specific immune tolerance. 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 for transduction with constructs expressing antigen-specific TCR (T cell receptor) or CAR (chimeric antigen receptor), chemokine receptor and markers of isolation for selecting and expanding Treg avatars. In vitro T cell migration assays. ELISA and Bioplex assays for the detection of cytokines and chemokines in the mouse sera and in culture supernatants. Mouse models. Use of mouse models of T1D and pancreatic islet transplant transplantation. Histology (multiple immunofluorescence) of secondary lymphoid organs and tissues (pancreas and graft site). 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. 3)

1) J.A. Bluestone, Q. Tang, Treg cells-the next frontier of cell therapy, Science, 362 (2018) 154- 155.
2) N.A.J. Dawson, J. Vent-Schmidt, M.K. Levings, Engineered Tolerance: Tailoring Development, Function, and Antigen-Specificity of Regulatory T Cells, Front Immunol, 8 (2017) 1460.
3) A. Sicard, D.A. Boardman, M.K. Levings, Taking regulatory T-cell therapy one step further, Curr Opin Organ Transplant, 23 (2018) 509-515