PROJECT 1

DoS: GREGORI SILVIA

Title: **Engineered human dendritic cell immunotherapy to restore tolerance in T-cell mediated diseases**

Curriculum: Basic and Applied Immunology and Oncology

Link to OSR/UniSR personal page:
http://research.hsr.it/en/institutes/san-raffaele-telethon-institute-for-gene-therapy/mechanisms-of-peripheral-tolerance/silvia-gregori.html

Project description (*Number of characters*, *including spaces*: 2.000 - 3.000):
The design of novel approaches to control antigen(Ag)-specific pathogenic T cell responses and restore tolerance represents an ambitious goal for the management of autoimmune diseases. The prominent role of dendritic cells (DC) in promoting T-cell tolerance and the development of methods to generate clinical grade products allowed the clinical application of tolerogenic DC-based therapies for the control of unwanted immune responses (1). The concluded clinical trials demonstrated the safety and feasibility of this approach. However, the stability of the infused DC products and the maintenance of their tolerogenic properties *in vivo* remain open issues to be tackled for improving the safety and the efficacy of DC-based cell therapies.
Our hypothesis is that infusion of tolerogenic DC genetically modified by newly developed tolerogenic lentiviral vectors (LV) encoding autoAg epitopes (tolLV-DC) will promote the *in vivo* generation of Ag-specific tolerance *via* down-regulation of autoAg-specific pathogenic T cell responses and induction of long-living autoAg-specific T regulatory cells. To this aim we developed LV-platforms that allow the expression of specific autoAg epitope and pro-tolerogenic molecules. The clinical translation of our LV-based gene transfer approach requires the selection of the optimal combination of autoAgs to modulate HLA-restricted Ag-specific T cell responses in humans, and the *in vitro* validation using primary cells from patients,. To generate an efficient and clinically translatable method to divert autoAg-specific T cells from a pathogenic fate and promote tolerogenic responses, we will develop different tolerogenic DC-based treatments and identify the optimal tolLV-DC cell product to prevent and cure disease development in pre-clinical humanized models (2).
This research may lead to the definition of the feasibility and efficacy of novel tolerogenic approach based on DC-based therapeutic interventions aimed at promoting/restoring immunological tolerance in T-cell mediated diseases, including autoimmunity, cell and organ transplantation, and after gene therapy.

Skills to be acquired by the student:

- Generation of lentiviral vectors
- Protocol for human DC differentiation and functions
- Generation of engineered human DC
- Multifluorimetric flow cytometric analysis
- *In vitro* proliferative and suppressive assays and cytokine production profiles
- *In vivo* studies in humanized mice

References (max. 3)

1. Moreau A, Varey E, Beriou G, Hill M, Bouchet-Delbos L, Segovia M, Cuturi MC (2012) Tolerogenic dendritic cells and negative vaccination in transplantation: from rodents to clinical trials. Front Immunol. 3: 218. doi: 10.3389/fimmu.2012.00218
2. Serr I, Fürst RW, Achenbach P, Scherm MG, Gökmen F, Haupt F, Sedlmeier EM, Knopff A, Shultz L, Willis RA, Ziegler AG, Daniel C. Type 1 diabetes vaccine candidates promote human Foxp3(+)Treg induction in humanized mice. Nat Commun. 2016 Mar 15;7:10991. doi: 10.1038/ncomms10991