PROJECT 1

DoS: ALESSANDRA MORTELLARO

Title: Understanding the role of adenosine deaminase 2 in mediating the immune dysregulation associated with ADA2 deficiency: from molecular mechanism to therapeutic application

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/pathogenesis-and-therapy-of-primary-immunodeficiencies/index.html

Project description:

Deficiency of adenosine deaminase type 2 (ADA2) is caused by autosomal recessive mutations in the cat eye syndrome critical region candidate 1 (CECR1) gene, which results in a rare Primary Immunodeficiency characterized by inflammatory vasculitis, stroke, intracranial hemorrhages, systemic inflammation, B cell immunodeficiency and cytopenias. A substantial proportion of ADA2-deficient patients remains undiagnosed and without treatment die. So far, anti-TNF drugs are the only therapeutic option that has shown some efficacy in ADA2-deficient patients. However, their efficacy is partial. Hematopoietic stem cell transplantation (HCT) was shown to be effective in severe cases of ADA2-deficiency syndrome leading to rapid and sustained immune reconstitution in concomitance with the resolution of the systemic inflammation. The morbidity and potential mortality of the HCT procedure, however, are hardly acceptable in less severe cases and HLA-compatible donors are not available for all the patients. Therefore, there is a high unmet medical need for the development of novel therapies to treat these patients. However, the pathophysiological mechanisms causing ADA2-deficiency syndrome are unclear and targeted therapies are currently unavailable. Therefore, a better understanding of the underlining mechanisms regulated by ADA2 during immune response will significantly contribute to the identification of targeted therapeutic strategies for ADA2-deficiency syndrome. In this context, the goals of this Ph.D. project are:

1) To define the immune signaling pathways regulated by ADA2 in normal and ADA2-deficient cells.
2) To evaluate the feasibility and efficacy of a gene therapy approach mediated by hematopoietic stem and progenitor cells transduced by ADA2-encoding lentiviral vectors.

To address these aims, the student will be supported by a team of renowned experts comprising research and clinical scientists with experience in basic research in the field of Primary Immunodeficiencies, auto-inflammation, and gene therapy.

Skills to be acquired by the student:

- Molecular biology techniques: cDNA cloning in a plasmid, gene delivery, DNA and RNA sequencing, RNA isolation and real-time qPCR, gel electrophoresis.
- Cellular biology techniques: ELISA, Western blot, immunoprecipitation of proteins, immunofluorescence microscopy, flow cytometry and cell sorting.
- Cell culture techniques: isolation of immune cells from blood, mouse bone marrow and spleen, maintenance of immune and non-immune cell lines.
- Basic and advanced in vivo experimentation techniques: mouse handling, generation and maintenance of colonies, genotyping, administering injections, bone marrow transplant, isolation of immune organs.
- The student will be prepared to integrate scientific method and critical thinking, to present in English information clearly and effectively to small/medium audience. The student will be empowered with effective writing skills.