PROJECT 1

DoS: Luca Vago

Title: Identifying new actionable epigenetic drivers of leukemia immune escape

Curriculum: Basic and Applied Immunology and Oncology

Link to OSR/UniSR personal page: https://research.hsr.it/en/divisions/immunology-transplantation-and-infectious-diseases/immunogenetics-leukemia-genomics-and-immunobiology.html

Project description:

Acute myeloid leukemia (AML) is an aggressive blood cancer originating from the uncontrolled proliferation and abnormal differentiation of highly-pluripotent hematopoietic progenitors. Allogeneic hematopoietic cell transplantation (allo-HCT) represents one of the most effective strategies to cure AML, thanks to the anti-leukemic effect mediated by donor immune cells transferred to the patient as part of the graft. However, it is becoming increasingly recognized that the malignant cells can evade immune responses by multiple mechanism (1), and recent studies from our group and from others demonstrated the immune resistant variants frequently do no carry additional genetic abnormalities, indicating a primarily epigenetic driver of the immune privilege (2,3).

In the present project, the successful candidate will employ an innovative platform for high-throughput transcriptomics (DRUG-seq) to test on primary patient AML cells the immunological effects of a library of more than 300 chemical compounds targeted against known epigenetic regulators. Results of the drug screening will be validated in a larger set of samples by orthogonal technologies, confirming the most interesting associations between epigenetic alterations (determined by RRBS, ATAC-seq, or histone modification proteomics, as appropriate) and leukemia immunological features (assessed through multiparametric flow citometry and functional immunological assays). The most promising candidate epigenetic targets will be validated through targeted genome editing of epigenetic regulators and/or their target regulatory regions in a PDX model of graft-versus-leukemia finetuned in the hosting lab. By taking its lead from the screening of compounds in active clinical development, we expect a direct translational potential of results originated from the project, to tackle the issue of post-transplantation disease recurrence but also potentially applicable to other therapeutic settings in the rapidly growing field of cancer immunotherapy.

Skills to be acquired by the student:

During his/her training the candidate will acquire skills in primary AML samples processing and collection, flow cytometry and cell sorting, molecular biology tools, next generation sequencing library preparations, bisulfite sequencing, chromatin accessibility assays, handling of PDX models, establishment of ex-vivo AML cultures on stromal cells, ex-vivo and in vivo treatments with epigenetic drugs. Furthermore, the candidate will analyze and interpret the data collected, present his/her findings in weekly lab meetings and yearly departmental seminars, develop scientific communication skills.

References:

1. Vago L, Gojo I. "Immune escape and immunotherapy of acute myeloid leukemia." J Clin Invest. 2020 Apr 1;130(4):1552-1564.
2. Toffalori C, Zito L, Gambacorta V et al. "Immune signature drives leukemia escape and relapse after hematopoietic cell transplantation." Nat Med. 2019 Apr;25(4):603-611.
3. Christopher MJ, Petti AA, Rettig MP, et al. "Immune Escape of Relapsed AML Cells after Allogeneic Transplantation." N Engl J Med. 2018 Dec 13;379(24):2330-2341.