

PhD in Basic and Applied Immunology and Oncology

Understanding the role of cytokines of the IL-17 family in multiple myeloma progression

Link: <https://research.hsr.it/en/divisions/immunology-transplantation-and-infectious-diseases/cellular-immunology/matteo-bellone.html>

We have recently unveiled a relevant crosstalk between intestinal microbiota and T helper (Th)17 lymphocytes that favors aggressiveness of multiple myeloma (MM), a neoplasia of plasma cells. Lack of functional IL-17A in transgenic Vk*MYC mice developing *de novo* MM, or disturbance of their microbiome delayed MM appearance. Similarly, in patients affected by smoldering MM (SMM), an asymptomatic phase that often precedes MM, higher levels of BM IL-17A predicted faster disease progression. Thus, IL-17A is driver of MM and a potential therapeutic target.

Production of IL-17A is under the control of several other cytokines of the IL-17 family like IL-17B, IL-17C and IL-17E. These cytokines are also relevant for maintaining integrity of the intestinal barrier, and they are in turn modulated by the gut microbiota. Aim of the proposed project is to investigate the role of other cytokines of the IL-17 family in regulating gut homeostasis and immunity during MM development and progression. Thus, multicolor flow cytometry, ELISA, genomic approaches, including single-cell RNA-Seq on sorted T cell populations, and microbiota modulation will be implemented in selectively immunodeficient mouse models to define mechanisms regulating IL-17A production in MM. We will also investigate in these mice the effectiveness of immune checkpoint blockade and other immunotherapies in the context of IL-17-microbiota axis perturbation.

We expect to extend our knowledge on the pathogenesis of MM. We will also provide the framework for new biological markers of disease progression and novel immunotherapies.

Skills to be acquired:

Project design

Independent design and execution of complex experiments

Science communication

Animal handling

Multiparametric flow cytometry acquisition and analysis

In vitro culture

In vitro cytokine release and titration assays

In vitro and in vivo cytotoxicity assays

PCR analysis

References:

- Brevi A, Cogrossi LL, Grazia G, Masciovecchio D, Impellizzieri D, Lacanfora L, Grioni M, Bellone M. Much More Than IL-17A: Cytokines of the IL-17 Family Between Microbiota and Cancer. *Front Immunol.* 2020 Nov 10;11:565470. doi: 10.3389/fimmu.2020.565470. eCollection 2020.
- Calcinotto A, et al. Microbiota-driven interleukin-17-producing cells and eosinophils synergize to accelerate multiple myeloma progression. *Nat Commun.* 2018 Dec 3;9(1):4832. doi: 10.1038/s41467-018-07305-8.
- Calcinotto A, Ponzoni M, Ria R, Grioni M, Cattaneo E, Villa I, Sabrina Bertilaccio MT, Chesi M, Rubinacci A, Tonon G, Bergsagel PL, Vacca A, Bellone M. Modifications of the mouse bone marrow microenvironment favor angiogenesis and correlate with disease

progression from asymptomatic to symptomatic multiple myeloma. *Oncoimmunology*.
2015 May 7;4(6):e1008850. eCollection 2015 Jun.