



## RESEARCH TOPIC MECM11

### T cell intrinsic regulation of genome integrity in cancer immunology and immunotherapy MECM standard

#### Research Area

Immunology

#### Laboratory name

Lab of Translational Immunology

#### Research Supervisor

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#### Abstract

T lymphocytes in human tumors are characterized by loss of effector functions and proliferation that are otherwise reinvigorated by checkpoint blockade immunotherapy. It is unknown how these lymphocytes can maintain genome integrity following intense proliferation and thus guarantee successful immune responses. We have identified novel molecular signals regulating the genome integrity of stem-like T cells and regulatory CD4+ T cells (Tregs) in the tumor microenvironment that we want to manipulate, so to obtain long-lived T cell responses that are resistant to immunosuppression. Several human samples from cancer patients undergoing clinical trials with immunotherapy are routinely available for this purpose thanks to collaborations with the Humanitas Hospital. We will apply novel genome-wide sequencing technologies and high-dimensional single cell profiling to primary samples to uncover genome organization and regulation of anti-tumor immunity.

#### Main technical approaches

Cellular and molecular immunology, genomics including at the single cell level, cellular and DNA metabolomics, high-dimensional flow cytometry, bioinformatics (with the support of in-lab expertise) genetic perturbations and functional assays applied to human patients' samples

#### Scientific references

1. Whiteside SK, et al. Acquisition of suppressive function by conventional T cells limits antitumor immunity upon T(reg) depletion. *Science immunology*. 2023;8(90):eabo5558.
2. Wischnewski V, et al. Phenotypic diversity of T cells in human primary and metastatic brain tumors revealed by multiomic interrogation. *Nat Cancer*. 2023;10.1038/s43018-023-00566-3.
3. Alvisi G, et al. Multimodal single-cell profiling of intrahepatic cholangiocarcinoma defines hyperactivated Tregs as a potential therapeutic target. *J Hepatol*. 2022;77(5):1359-1372.



4. Galletti G, et al. Two subsets of stem-like CD8(+) memory T cell progenitors with distinct fate commitments in humans. Nat Immunol. 2020. Accompanying commentary by Chu et al "Two parallel worlds of memory T cells".
5. Alvisi G, et al. IRF4 instructs effector Treg differentiation and immune suppression in human cancer. J Clin Invest. 2020;130(6):3137-50.

### **Type of contract**

Two scholarships of € 24.500 gross per year each awarded by Istituto Clinico Humanitas. This sum is subject to IRPEF income tax and exempt from social security contributions.

Due Borse di studio pari a € 24.500 annui l'una lordi erogata da Istituto Clinico Humanitas. Importo soggetto a tassazione IRPEF ed esente da contribuzione previdenziale.