PHYSICIAN SCIENTIST
LA MEDICINA INCONTRA LA RICERCA
promosso da: AIRC Fondazione CARIPLO | con il supporto di: SEMM European School of Molecular Medicine, UNIVERSITÀ DEGLI STUDI DI MILANO

2026 Physician Scientist Call

AVAILABLE POSITIONS

Principal Investigator	GEGINAT JENS ALBRECHT
Institute of Affiliation	Fondazione "Istituto Nazionale Genetica Molecolare - INGM"
Title of the proposed project:	Dissecting the IL-10/IL10R axis in human Melanoma: Spatial immunophenotyping to predict immunotherapy response.
Short description of the project	Background: Cytotoxic T cells (CTL) mediate anti-tumor responses and are mainly CD8+, but CD4+ T-cells can also differentiate to CTL and exert complementary functions. CD4+ regulatory T cells (Treg) are in contrast immunosuppressive and impair effective CTL responses, thus playing a pro-tumorigenic role. There are at least two subsets of Tregs, i.e. FOXP3+Tregs and EOMES+ type 1 regulatory T cells (Tr1) that are enriched in tumors and possess IL-10 producing capacities. The identity of cells that actually produce IL-10 in human tumours and their targets are however unknown. We demonstrated previously that EOMES^{+}Tr1-like cells accumulate in melanomas, were associated with poor survival but also with response to ICB. Moreover, unpublished data suggests that IL-10 produced by Tr1-cells inhibits CD8+T-cell responses, promotes tumor growth and is required for the therapeutic effect of ICB in melanoma-bearing mice. Aims: The proposal will identify IL-10 producing immune cells and their targets in primary melanomas with different responses to ICB. Experimental Design: We will use imaging mass spectrometry and/or the multiparametric MACSIMA immaging platform on FFPE human melanoma sections to characterize tumor-infiltrating lymphocytes. We will assess the relevance of IL-10-associated immune phenotypes for immunotherapy responsiveness by analyzing tumor sections from melanoma patients who received ICB with documented positive or negative clinical outcomes. Moreover, FRET-based imaging with the Abberior Stedycon super-resolution system will be used to identify IL-10/IL-10R interactions. Impact on cancer: This project combines innovative technologies with clinically relevant human samples to achieve a mechanistic understanding with high translational potential. Indeed, unraveling the cellular and molecular mechanisms that cause resistance to Immune checkpoint blockade (ICB) in melanoma is crucial to improve treatment efficacy and stratify patients. By establishing the identity of IL-10-producing cells and their targets within the tumor microenvironment, we might also provide a rationale to block IL-10 to treat melanoma.
Main research area for the project	Immunology
5 key words for the project	Melanoma, Immunotherapy, Treg Cells, Cytokines/Interleukins, T cells/TCR

LAB INFO	
Main topic/s of the lab	Immune regulation, T lymphocytes, Interleukin-10, cancer, autoimmunity

Short description of the lab activity	Introduction CD4+ T-cells are central players of adaptive immune responses, because they co-ordinate the activity of several other immune cells such as dendritic cells (DC), B cells and cytotoxic CD8+T-cells. CD4+T-cells can be subdivided into two broad subsets of helper and regulatory cells, which promote and suppress immune responses, respectively. Both regulatory and helper T-cells can produce Interleukin-10 (IL-10), which is a potent anti-inflammatory cytokine but also promotes cytotoxic T-cell responses and B-cell antibody production. Consequently, IL-10 has a dual role in autoimmunity and cancer: On the one hand, it is required to maintain intestinal immune homeostasis and to prevent colitis, but on the other hand it could promote the generation of pathogenic autoantibodies in systemic lupus erythematosus (SLE) or cytotoxic anti-tumor T-cell responses. Role of IL-.10 producing regulatory T-cells in human immune-mediated diseases Regulatory T-cells can be sub-divided into the well-defined CD25+Tregs, which express the lineage-defining transcription factor FOXP3, and the enigmatic Tr1-cells, which produce high levels of IL-10. It is debated whether Tr1-cells represent an independent differentiation lineage or a transient and unstable activation stage. We identified a population of cytotoxic Tr1-like cells in human tissues that produce high levels of IL-10 and are generated upon chronic antigenic activation. They stably express the lineage-defining transcription factor EOMES and are probably derived from pro-inflammatory EOMES+Th1-cells. EOMES+Tr1-like-cells are involved in several immune-mediated diseases. Thus, EOMES+Tr1-like cells, but not FOXP3+Tregs, were functionally impaired in systemic lupus erythematosus and in inflammatory bowel diseases (IBDs). In multiple sclerosis they were enriched and clonally expended in the cerebrospinal fluid, and they produced IL-10 in brain lesions. However, they were activated by EBV, but failed to respond to myelin-derived self-antigens, possibly explaining why they fail to prevent CNS damage. Furthermore, they were enriched and clonally expanded in different types of human tumors. Tumour-infiltrating Tr1-like cells were associated with poor prognosis, but also with response to immunotherapy in melanoma. Unpublished evidence indicates a key role for Tr1-derived IL-10 in tumor growth and immunotherapy responsiveness in melanoma patients.
Recent bibliography	- Characterization of human CD4+EOMES+GzmK+ T-cell subsets unveils an uncoupling of suppressive functions from IL-10-producing capacities. Eur J Immunol 2024 Apr; 54: e2350675 - Ex vivo microRNA and gene expression profiling of human Tr1-like cells suggests a role for miR-92a and -125a in the regulation of EOMES and IL-10R. Eur J Immunol 2021 Dec; 51: 3243 - Eomesodermin-expressing type 1 regulatory (EOMES+ Tr1)-like T cells: Basic biology and role in immune-mediated diseases. Eur J Immunol 2023 May; 53: e2149775

	- The Human Bone Marrow May Offer an IL-15-Dependent Survival Niche for EOMES+ Tr1-Like Cells. Eur J Immunol 2025 May; 55: e202451644 - Clonally expanded EOMES+ Tr1-like cells in primary and metastatic tumors are associated with disease progression. Nat Immunol 2021 Jun; 22: 735
Group composition	PI (1) Staff Scientist (1) Post-doc (3) Ph.D students (3) Graduate Students (1) Undergraduate students (1)
Institutional page link	https://ingm.org/en/
Lab website link	https://ingm.org/en/geginat_lab_eng/
Social media links	https://www.researchgate.net/profile/Jens-Geginat