

<b>Principal Investigator</b>	<b>BODEGA BEATRICE</b>
<b>Institute of Affiliation</b>	Fondazione "Istituto Nazionale Genetica Molecolare - INGM"
<b>Title of the proposed project:</b>	Translational development of LINE1-targeting RNA therapeutics to restore anti-tumor T-cell function
<b>Short description of the project</b>	<p>T-cell dysfunction is a major barrier to effective anti-cancer immunity and limits the clinical benefit of immunotherapy in many patients. Our laboratory recently identified a new RNA-based regulatory mechanism controlling human T-cell states: LINE1-derived transcripts accumulate at chromatin in dysfunctional T cells and contribute to the repression of activation and effector programs. In Marasca et al., Nature Genetics, we showed that targeting LINE1-containing transcripts with antisense oligonucleotides (ASOs) can restore effector functions in exhausted tumor-infiltrating lymphocytes, supporting LINE1-derived RNAs as a new class of actionable immune-regulatory molecules. Building on this published work and on our ongoing AIRC Investigator Grant, this PhD project will develop LINE1-targeting RNA therapeutics for translational immuno-oncology. We have already generated solid single-cell RNA-sequencing datasets from CD3+ T cells infiltrating non-small-cell lung cancer and colorectal cancer, allowing us to characterize dysfunctional T-cell states and identify recurrent, TIL-associated LINE1 transcripts suitable for therapeutic targeting. The project will pursue three integrated objectives. First, the candidate will prioritize recurrent LINE1-containing transcripts associated with exhausted T-cell states across NSCLC and CRC samples and use this information to design transcript-informed ASOs. Second, selected ASOs will be tested in clinically relevant models of T-cell dysfunction, including in vitro exhausted T cells, ex vivo patient-derived TILs and tumor-T-cell co-culture systems, measuring target engagement, exhaustion markers, cytokine production, cytotoxicity and tumor-cell killing. Third, the project will explore T-cell-directed delivery strategies, including targeted lipid nanoparticles and antibody-guided approaches, to improve therapeutic selectivity and translational feasibility. This project is designed for a physician scientist interested in cancer immunology, RNA therapeutics and translational oncology. It will provide training in patient-derived immune profiling, RNA-targeting drug development, functional immunological assays and clinically oriented therapeutic validation, with the long-term goal of developing new strategies to overcome T-cell dysfunction and resistance to immunotherapy.</p>
<b>Main research area for the project</b>	Molecular Biology
<b>5 key words for the project</b>	Immunotherapy, Bioinformatics, Immunosuppression and/or suppressor cells, Tumor-Infiltrating Lymphocytes (TIL), Transcriptome/Transcriptomics

LAB INFO	
<b>Main topic/s of the lab</b>	RNA and epigenetic mechanisms controlling immune cell states and cancer progression.
<b>Short description of the lab activity</b>	My research program focuses on the role of epigenetic and RNA-based regulatory mechanisms in human cell identity, immune function and cancer. In particular, my laboratory investigates how coding and non-coding RNAs and retrotransposon-derived transcripts shape cell states, with a major focus on T cell dysfunction, tumor-immune interactions and therapy resistance. The group combines experimental and computational approaches, including molecular and cellular biology, functional perturbation, genomics, epigenomics, long-read and single-cell transcriptomics, advanced imaging of the nucleus, and bioinformatic method development. A central translational direction of the laboratory is the identification of RNA programs that can be exploited as biomarkers or therapeutically targeted, with particular emphasis on antisense oligonucleotide strategies (ASOs) and RNA-based intervention in cancer and immune dysfunction.
<b>Recent bibliography</b>	<ul style="list-style-type: none"> <li>- LINE1 are spliced in non-canonical transcript variants to regulate T cell quiescence and exhaustion. NAT GENET 2022 Feb; 54: 180</li> <li>- LINE1 modulate human T cell function by regulating protein synthesis during the life span. SCI ADV 2024 Oct; 10: eado2134</li> <li>- IRescue: uncertainty-aware quantification of transposable elements expression at single cell level. NUCLEIC ACIDS RES 2024 Oct; 52: e93</li> <li>- Early-onset cancers: Biological bases and clinical implications. Cell Rep Med 2024 Sep; 5: 101737</li> </ul>
<b>Group composition</b>	My research group currently includes approximately 16-18 members, spanning senior scientists, postdoctoral fellows, PhD students, predoctoral fellows and master's students. The group has a balanced wet-lab and dry-lab structure, integrating experimental molecular biology, genomics, epigenomics, transcriptomics and computational analyses.
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