PHYSICIAN SCIENTIST
LA MEDICINA INCONTRA LA RICERCA
promosso da: AIRC Fondazione CARIPLO | con il supporto di: IEMM Istituto Europeo di Oncologia Molecular Medicine | UNIVERSITÀ DEGLI STUDI DI MILANO

2026 Physician Scientist Call

AVAILABLE POSITIONS

| **Principal Investigator** | **CHIARLE ROBERTO** |
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| **Institute of Affiliation** | Università degli Studi di Torino |
| **Title of the proposed project:** | In vivo transduction of engineered TCRs for next-generation lung cancer therapy |
| **Short description of the project** | ALK-positive non-small cell lung cancer (ALK+ NSCLC) is a molecular subtype of lung cancer driven by oncogenic ALK fusion proteins that promote tumor growth and survival. Although ALK tyrosine kinase inhibitors (TKIs) have dramatically improved outcomes, most patients with advanced disease eventually develop resistance and experience relapse. As a result, ALK+ NSCLC remains largely incurable, highlighting the need for therapeutic strategies capable of eradicating residual disease and achieving durable remission. This project aims to develop ALK-directed T-cell receptor (TCR) immunotherapy delivered directly in vivo. Building on the identification of human and murine TCRs that specifically recognize ALK-derived antigens, we will evaluate approaches to engineer endogenous T cells through targeted delivery of ALK-specific TCR constructs using viral vectors or lipid nanoparticle (LNP)-based platforms. This strategy has the potential to overcome the complexity, cost, and manufacturing challenges associated with conventional ex vivo T-cell therapies while enabling scalable generation of ALK-reactive T cells within the patient. The anti-tumor activity of these in vivo-engineered ALK.TCR T cells will be assessed in preclinical models of ALK+ NSCLC, including models that mimic minimal residual disease and acquired resistance following ALK inhibitor therapy. We will also investigate how engineered T cells interact with the tumor microenvironment and host immune system to identify mechanisms that enhance therapeutic efficacy. Importantly, these studies will be conducted in parallel with a first-in-human clinical trial of ALK.TCR T-cell therapy for patients with ALK+ NSCLC, planned to open at the Dana-Farber Cancer Institute (DFCI) in summer 2027. This integrated translational effort will enable rapid bidirectional exchange between laboratory and clinical investigations, accelerating the development of a novel, scalable, and potentially curative immunotherapeutic strategy for patients with ALK+ NSCLC and other ALK-driven malignancies. |
| **Main research area for the project** | Molecular therapy |
| **5 key words for the project** | Tyrosine kinase receptors (TKR) and/or inhibitors, Gene therapy, Neuroblastoma, CAR engineered cells |

| **LAB INFO** | |
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| **Main topic/s of the lab** | Development of novel immunotherapies for solid and hematologic cancers |
| **Short description of the lab activity** | Dr. Chiarle's laboratory research work is focused on the biology and therapy of tumors driven by genetic alterations of the Anaplastic Lymphoma Kinase (ALK) gene, which is involved in |

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| | the pathogenesis of neuroblastoma, Anaplastic Large Cell Lymphoma (ALCL), Non-Small Cell Lung Cancer (NSCLC), and other tumors (Chiarle et al. Nat Medicine, 2005, Chiarle et al. Nat Rev Cancer, 2008, Menotti et al., Nat Medicine 2019, Mastini et al Science TM 2023, Voena et al, Nat Rev Cancer, 2025). Some of these discoveries lead to the implementation of trials, such as the opening of a Phase I trial (NCT07001384) to test the combination of ALK TKI with Duvelisib in patients with ALK+ ALCL based on the discovery described in Mastini et al Science TM 2023). In this context, one main area of research aims at discovering novel immunotherapies for ALK-driven tumors, including the development of an ALK vaccine and ALK CAR T cells. To study these immunotherapies, we have developed mouse models for ALK-rearranged lymphoma, ALK-rearranged lung carcinoma and ALK- mutated neuroblastoma. Leveraging on these models, we recently developed an ALK vaccine that primes the immune system to recognize and eradicate ALK-rearranged lymphoma and lung cancer cells (Chiarle et al. Nat Medicine, 2008, Voena et al. Cancer Immunology Research 2015, Cheong et al, Nat Commun 2024). We also demonstrated that patients with ALK-rearranged NSCLC or ALCL spontaneously develop an immune response against ALK (Awad et al. Oncotarget 2017, Stadler et al, Cancer Immunol Res 2025). Preliminary data generated in Dr. Chiarle lab demonstrated the potent therapeutic efficacy of the peptide-based ALK vaccine in mouse models (Mota et al, Nature Cancer 2023) and were key to secure financial support for a Phase I clinical trial to be implemented in 2026. Additionally, Dr. Chiarle's lab has recently developed CAR T cells that specifically recognize the ALK receptor expressed on the surface of neuroblastoma cells (Bergaggio et al, Cancer Cell 2023), and Dr. Chiarle was approved by the FDA to be the sponsor and IND holder of a Phase I clinical trial to test ALK.CAR T cells in the treatment of children with relapsed/refractory neuroblastoma. The trial is now open for enrollment (NCT06803875) and already successfully recruited two patients. Related to this application, Dr. Chiarle's laboratory discovered and patented ALK-specific T Cell Receptors (TCRs) that were used to generate engineered TCR-T cells with potent and specific activity against ALK+ NSCLC in vitro and in vivo. Dr. Chiarle founded ALKEMIST Bio, a company with the goal to implement a Phase I trial to evaluate ALK.TCR T cells in patients with ALK+ NSCLC. |
| **Recent bibliography** | - ALK peptide vaccination restores the immunogenicity of ALK-rearranged non-small cell lung cancer. Nature Cancer 2023 Jul; 4: 1016<br>- ALK inhibitors increase ALK expression and sensitize neuroblastoma cells to ALK.CAR-T cells. CANCER CELL 2023 Dec; 41: 2100<br>- ALK in cancer: from function to therapeutic targeting. NAT REV CANCER 2025 May; 25: 359<br>- Mechanistic patterns and clinical implications of oncogenic tyrosine kinase fusions in human cancers. |

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| | NAT COMMUN 2024 Jun; 15: 5110<br>- Epigenetic changes by EZH2 inhibition increase translocations in B cells with high AID activity or DNA repair deficiency.<br>BLOOD 2025 Oct; 146: 2203 |
| **Group composition** | 1 Associate Professor 2 University technicians 2 postdoctoral fellows 5 PhD students 3 Master Students 1 MD in specialty |
| **Institutional page link** | https://www.mbc.unito.it/it/roberto-chiarle |
| **Lab website link** | https://chiarlelab.com |