PHYSICIAN SCIENTIST
LA MEDICINA INCONTRA LA RICERCA
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Principal Investigator	Bonecchi Raffaella
Hosting institution	Università Humanitas
Proposal title	Impact of IDH Mutation on immune dynamics in gliomas
Keywords	Glioma and/or glioblastoma; Hematopoiesis; Inflammation and/or inflammatory cytokines; Granulocytes; Chemokines
PhD project description	Mutations in isocitrate dehydrogenase (IDH) genes, particularly IDH1 and IDH2, have been identified in several tumor types, including gliomas. These mutations promote tumorigenesis by generating the oncometabolite 2-hydroxyglutarate, which disrupts cellular differentiation and reshapes the tumor microenvironment (TME). Routine screening for IDH mutations in glioma patients enables access to targeted therapies, expanding treatment options beyond first-line regimens. However, both primary and acquired resistance to these therapies remain common, and the mechanisms underlying off-target resistance are still poorly understood. Interestingly, despite arising from different tissues, IDH-mutant tumors share similar patterns of progression and survival, largely driven by IDH-associated mechanisms. For instance, lower-grade IDH-mutant gliomas typically exhibit a more favorable prognosis compared to their IDH-wild-type counterparts. Moreover, IDH mutations are associated with a modest but significant survival benefit and represent actionable targets for therapies that can moderately extend progression-free survival. This project aims to investigate the impact of IDH mutations in gliomas, with a focus on immune composition, cellular phenotypes, and their correlations with patient outcomes. The study will be structured around three main work packages: A comprehensive analysis of IDH-mutant and wild-type glioma samples using spatial transcriptomics and multiplex immune profiling; The development of novel, syngeneic, and clinically relevant mouse models of IDH-mutant and wild-type gliomas to enable in-depth characterization of the TME immune landscape; The evaluation of innovative therapeutic strategies using 3D spheroid systems for high-throughput drug screening. Through this integrated approach, the project seeks to identify immune-related therapeutic targets in IDH-mutant and wild-type gliomas and to deepen our understanding of TME dynamics and resistance mechanisms in this tumor type.
Main topics of the lab	Inflammation and cancer
Short description of the lab activity	The focus of the laboratory research is inflammation, with particular emphasis on innate immunity and a family of inflammatory chemical mediators known as chemokines. These molecules regulate the trafficking of leukocytes under both homeostatic and inflammatory conditions, thereby playing a central role in orchestrating effective immune responses. In the context of tumor biology, we employ three

	integrated approaches to investigate the role of innate immune cells and their mediators: Spatial transcriptomics and multiplex immune profiling to map the immune landscape within tumors; Development of novel, syngeneic, and clinically relevant mouse models enabling in-depth characterization of the tumor microenvironment (TME) and its immune components; Evaluation of innovative therapeutic interventions using 3D spheroid systems for high-throughput drug screening.
Main research area	Immunology
Group composition	1 post doc student 4 PhD students
Institutional page link	https://www.humanitas-research.com/researchers/raffaella-bonecchi/
Lab bibliography	Role of myeloid cells in the immunosuppressive microenvironment in gliomas. Locarno CV, Simonelli M, Carenza C, Capucetti A, Stanzani E, Lorenzi E, Persico P, Della Bella S, Passoni L, Mavilio D, Bonecchi R, Locati M, Savino B IMMUNOBIOLOGY 2020 Jan; 225: 151853