DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

42nd CYCLE

Research line

Title: Rewiring immune evasion in high-risk neuroblastoma through TLS-driven immunotherapy

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Summary (max 250 words)
High-risk neuroblastoma (HR-NB) is a leading cause of pediatric cancer mortality, with survival rates below 40% despite intensive therapy. Its immunologically “cold” phenotype, marked by defective antigen presentation, low immune infiltration, and absence of tertiary lymphoid structures (TLS), limits the efficacy of immune checkpoint blockade (ICB), underscoring a critical unmet clinical need.
We propose that tumor-intrinsic programs actively enforce immune exclusion by disrupting antigen presentation and chemokine networks required for effector cell recruitment and TLS formation. We aim to therapeutically induce TLS in HR-NB through combinatorial immunomodulatory strategies, thereby restoring immune competence and sensitizing tumors to ICB.
We will employ rational combinations of immunomodulatory agents to trigger TLS neogenesis *in vivo*, assessing their impact on tumor architecture, chemokine production, and immune activation. Translational validation will be performed using patient-derived tumoroids co-cultured with autologous immune cells and a retrospective cohort of 104 human NB samples to identify predictive biomarker signatures.
This project will define actionable mechanisms of immune resistance and establish TLS induction as a novel therapeutic strategy to convert HR-NB into an ICB-responsive disease. By integrating preclinical and patient-derived models, we will deliver predictive biomarkers and clinically relevant combination approaches, accelerating the development of effective immunotherapies for HR-NB and other immune-cold tumors.

Pertinent Publications of the proponent (last 5 years)
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3. Discovery of a new selective ERAP1 inhibitor for Hedgehog-dependent cancer treatment. Bufalieri F, Cucinotta A, Cammarone S, Agnoli F, Basili I, Ferri G, Quaglio D, Caimano M, Capriotti AL, Montone CM, Lospinoso Severini L, Tempora P, D'Amico S, Juretich F,

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4. Combined IFN-γ and TNF-α treatment enhances the susceptibility of breast cancer cells and spheroids to Natural Killer cell-mediated killing. Barberini F, Pietroni R, Ielpo S, Lucarini V, Nardozi D, Melaiu O, Benvenuto M, Focaccetti C, Palumbo C, Rossin F, Fruci D, Olive D, Masuelli L, Bei R, Cifaldi L. Cell Death Dis. 2025 Oct 16;16(1):729. doi: 10.1038/s41419-025-08021-0.
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8. ERAP1 Activity Modulates the Immunopeptidome but Also Affects the Proteome, Metabolism, and Stress Responses in Cancer Cells. Nikopaschou M, Samiotaki M, Stylianaki EA, Król K, Gragera P, Raja A, Aidinis V, Chroni A, Fruci D, Panayotou G, Stratikos E. Mol Cell Proteomics. 2025 May;24(5):100964. doi: 10.1016/j.mcpro.2025.100964.
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11. Manipulating the tumor immune microenvironment to improve cancer immunotherapy: IGF1R, a promising target. Pellegrino M, Secli V, D'Amico S, Petrilli LL, Caforio M, Folgiero V, Tumino N, Vacca P, Vinci M, Fruci D, de Billy E. Front Immunol. 2024 Feb 14;15:1356321. doi: 10.3389/fimmu.2024.1356321. eCollection 2024.
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