PROGETTO

Supervisore::	OMER Attya
Titolo/*Title:*	Mobilization and Antibody-Mediated Conditioning: A Dual Approach to Maximize Chemotherapy-free Hematopoietic Stem Cell Therapy
Curriculum:	Medicina Molecolare/*Molecular Medicine* > Terapia Genica e Cellulare/*Gene and Cell Therapy*
Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento:	_____ https://research.hsr.it/en/institutes/san-raffaele-telethon-institute-for-gene-therapy/gene-transfer-technologies-and-new-gene-therapy-strategies/attya-omer.html

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

Background/Gap of Knowledge

Current hematopoietic stem and progenitor cell gene therapy (HSPC-GT) requires the mobilization, ex vivo genetic correction, and infusion of hematopoietic stem cells (HSPCs) following myeloablative conditioning. This process traditionally involves chemo/radiotherapy, which can lead to significant acute and long-term side effects. Although alternatives like antibody-drug conjugates (ADCs) promise reduced toxicity, their clinical application is complicated by off-target effects and prolonged antibody half-lives, which delay subsequent therapeutic interventions and potentially compromise patient outcomes [1-3].

Rationale and Hypothesis

To overcome these challenges, we propose a non-genotoxic conditioning strategy that synergistically combines HSPC mobilization with targeted, antibody-mediated conditioning [4]. This strategy leverages the natural mobilization process to enhance the accessibility of HSPCs to conditionally active antibodies, potentially reducing the required antibody dosage and associated toxicity. We hypothesize that this approach will enable more effective and safer engraftment of gene-edited HSPCs, achieving clinically relevant levels of chimerism without the adverse effects associated with traditional conditioning methods.

Objectives and Specific Aims

The primary aim of this study is to develop and validate a novel, synergistic conditioning protocol, termed Mobilization/Antibody/RNA-based Strategy (MARS), to enhance the engraftment of gene-edited HSPCs without relying on irradiation or chemotherapy. Specifically, our project aims to:

1. Validate the efficacy of engineered antibody variants targeting CD117 with reduced half-lives through comprehensive in vitro and in vivo assessments [5-6].

2. Implement mRNA-based transient overexpression of a drug-resistant CD117 and the homing factor CXCR4 in HSPCs to optimize engraftment efficiency [7-8].

3. Explore the synergy between mobilization and antibody-based conditioning to enhance the survival and persistence of transplanted HSPCs, minimizing the risk of adverse events.

Expected Outcomes

By integrating cutting-edge gene editing technologies, innovative antibody engineering, and advanced delivery systems, this project expects to:

- Establish a novel, non-genotoxic conditioning regimen that significantly reduces the toxicity associated with hematopoietic stem cell transplantation.
- Demonstrate improved engraftment efficiency and survival of gene-edited HSPCs in humanized mouse models, setting the stage for clinical trials.
- Expand the therapeutic applications of HSPC-GT by providing a safer, more effective alternative to current conditioning protocols, thereby improving outcomes for patients with hematologic disorders and genetic diseases amenable to gene editing.

Competenze che deve acquisire lo studente (Max 600 caratteri spazi inclusi):

The PhD candidate will strongly implement his/her competences thanks to the training-through-research activities: in the field of HSPCs biology (*in vitro* HSPCs culture, clonality, and transcriptional landscape); in the field of editing technology (Cas9 nuclease and base/prime editor applications); in the field of gene therapy (AAV/LV transduction, conditioning regimens and *in vivo* mouse modeling approaches). Importantly, the rich environment for scientific discussion in Naldini's lab will strengthen the candidate analytic and communication skills essential for research dissemination.

Bibliografia (max. 15)

[1] Russkamp NF, Myburgh R, Kiefer JD, Neri D, Manz MG. Anti-CD117 immunotherapy to eliminate hematopoietic and leukemia stem cells. Exp Hematol. 2021 Mar;95:31-45. doi: 10.1016/j.exphem.2021.01.003. Epub 2021 Jan 20. PMID: 33484750.

[2] Marone R, Landmann E, Devaux A, et al. Epitope-engineered human hematopoietic stem cells are shielded from CD123-targeted immunotherapy. J Exp Med. 2023;220(12):e20231235. doi:10.1084/jem.20231235

[3] Wellhausen N et al. Epitope base editing CD45 in hematopoietic cells enables universal blood cancer immune therapy. Sci Transl Med. 2023;15(714):eadi1145. doi:10.1126/scitranslmed.adi1145

[4] A. Omer Javed, G. Pedrazzani, L. Albano, S. Ghaus, C. Latroche, M. Manzi, S. Ferrari, M. Fiumara, A. Jacob, V. Vavassori, A. Nonis, D. Canarutto, and L. Naldini. *Mobilization-based chemotherapy-free engraftment of gene-edited human hematopoietic stem cells.* Cell (2022)

[5] Stapleton, N.M., Brinkhaus, M., Armour, K.L. et al. Reduced FcRn-mediated transcytosis of IgG2 due to a missing Glycine in its lower hinge. Sci Rep 9, 7363 (2019). https://doi.org/10.1038/s41598-019-40731-2

[6] Selby MJ, Engelhardt JJ, Quigley M, Henning KA, Chen T, Srinivasan M, Korman AJ. Anti-CTLA-4 antibodies of IgG2a isotype enhance antitumor activity through reduction of intratumoral regulatory T cells. Cancer Immunol Res. 2013 Jul;1(1):32-42. doi: 10.1158/2326-6066.CIR-13-0013. Epub 2013 Apr 7. PMID: 24777248.

[7] Casirati G. et al. Epitope editing enables targeted immunotherapy of acute myeloid leukaemia. Nature. 2023;621(7978):404-414. doi:10.1038/s41586-023-06496-5

[8] Vavassori V, Ferrari S, Beretta S, Asperti C, Albano L, Annoni A, Gaddoni C, Varesi A, Soldi M, Cuomo A, Bonaldi T, Radrizzani M, Merelli I, Naldini L. Lipid nanoparticles allow efficient and harmless ex vivo gene editing of human hematopoietic cells. Blood. 2023 Aug 31;142(9):812-826. doi: 10.1182/blood.2022019333. PMID: 37294917; PMCID: PMC10644071.