PROGETTO

Supervisore:	STEFANIA CRIPPA
Titolo/*Title*:	Pre-clinical development of HSPC-GT for Morquio syndrome
Curriculum:	Molecular Medicine 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/pathogenesis-and-therapy-of-primary-immunodeficiencies.html

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

<u>Background/gap of knowledge</u>

Mucopolysaccharidoses (MPSs) are a group of inherited metabolic disorders caused by lysosomal enzyme deficiency, leading to the accumulation of undigested glycosaminoglycans responsible for multi-organ damage[1]. MPS IV is distinguished between type A (GALNS gene) and B (GLB1 gene), leading to keratan sulfate (KS) accumulation and, in the case of MPSIVA, also of chondroitin-6-sulfate (C6S). MPS IV patients manifest severe skeletal impairment. MPSIVB patients develop neurological symptoms in the presence of specific mutations[2]. Enzyme replacement therapy (ERT) and allogeneic Hematopoietic Stem Cell Transplantation (HSCT) are the currently approved therapies for some MPSs[3–5]. However, both procedures fail to completely correct the skeletal and neurological defects, leading to a high unmet medical need in this patient population who experiences poor quality of life. Recent studies conducted by our institute demonstrated the superior safety and efficacy of Hematopoietic Stem/Progenitor Cells (HSPC)-gene therapy (GT) in lysosomal storage disorders compared to standard therapies[6–10]. However, the cellular and molecular mechanisms leading to MPS skeletal diseases are still largely unknown, preventing fully exploiting the cross-correction mechanism in GT approaches.

<u>Rationale and hypothesis</u>

Building on the similar pathophysiological features of MPS, we hypothesize that the GT cross-correction mechanism could also work to treat other forms of MPS, including MPS IV. For this reason, we aim to develop at a preclinical level HSPC-GT for MPS IV in the disease-specific animal models (Galns-/- and Glb1 -/- mice) available in our laboratory and representatives of the human disease. Moreover, the mechanisms driving the onset and progression of skeletal defects in MPS patients are still largely unknown. Therefore, we aim to dissect the diseases'

molecular and cellular mechanisms in the diseased mouse bones with the final goal of optimizing the HSPC-GT.

Objectives and specific aims

1. HSPC-GT development at a preclinical level in MPS IV mouse models

The Ph.D. student will test the safety and efficacy of HSPC-GT compared to standard HSCT, performing in vivo transplantation experiments and evaluating the level of HSC engraftment, the metabolic correction in different tissues (restoration of enzymatic activity and substrate detoxification), and the correction of skeletal and neurological defects using several approaches in the disease mice untreated or transplanted with autologous gene-corrected or donor-derived HSPCs.

2. Study of the molecular and cellular mechanisms contributing to the MPS skeletal alterations.

The PhD student will contribute to elucidating the fundamental pathways involved in the onset and progression of skeletal defects in MPS animal models post-GT treatment using different genome-wide approaches and employ human MSC-based 3D models generating bone and hypertrophic cartilaginous to analyze cartilage cells, matrix maturation, and mineralization in a pre and post-GT setting.

Expected outcomes

This project will generate robust and comprehensive preclinical data to prove the safety and efficacy of ex-vivo HSPC-GT for MPSIV, with the ultimate goal of implementing a Phase I/II clinical trial. In addition, this project will generate genome-wide profiling data, revealing disease-associated pathways in association with the human skeletal 3D model characterization that could imrpove the efficacy of HSPC-GT.

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

The PhD student will acquire cellular skills, including cell culture, gene manipulation, lentiviral vector production, and molecular and biochemical techniques. He/she will also develop in vivo skills to perform transplantation study. The student will acquire the required scientific background and expertise to independently conduct his/her experiments, critically discuss the results and their biological significance, and propose project advancements. The student will discuss the project during internal, institutional, and international meetings.

Bibliografia (max. 15)

1. Hendriksz, C. J., et al. (2013). "Review of clinical presentation and diagnosis of Enzyme mucopolysaccharidosis IVA." Mol Genet and Metab 110:54-64.

2. Abumansour, I. S., et al. (2020). "Morquio-B disease: Clinical and genetic characteristics of a distinct GLB1-related dysostosis multiplex." JIMD Rep 51(1): 30-44.

3. Chen, H. H., et al. (2019). "Enzyme replacement therapy for mucopolysaccharidoses; past, present, and future." J Hum Genet 64(11): 1153-1171.

4. Biffi, A. (2017). "Hematopoietic Gene Therapies for Metabolic and Neurologic Diseases." Hematol Oncol Clin North Am 31(5): 869-881.

5. Krivit, W. (2004). "Allogeneic stem cell transplantation for the treatment of lysosomal and peroxisomal metabolic diseases." Springer Semin Immunopathol 26(1-2): 119-132.

6. Biffi, A. et al. Lentiviral hematopoietic stem cell gene therapy benefits metachromatic leukodystrophy. Science 341, 1233158 (1–11) (2013).

7. Sessa, M. et al. Lentiviral haemopoietic stem-cell gene therapy in early-onset metachromatic leukodystrophy: an ad-hoc analysis of a non-randomised, open-label, phase 1/2 trial. Lancet 388, 476–487 (2016).

8. Fumagalli, F., et al. (2022). "Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access." Lancet 399(10322): 372-383.

9. Visigalli, I., et al. (2010). "Gene therapy augments the efficacy of hematopoietic cell transplantation and fully corrects mucopolysaccharidosis type I phenotype in the mouse model." Blood 116(24): 5130-5139.

10. Gentner, B., et al. (2021). "Hematopoietic Stem- and Progenitor-Cell Gene Therapy for Hurler Syndrome." N Engl J Med 385(21): 1929-1940.