lundi, août 1, 2022

INTERNATIONAL PhD PROPOSAL

PhD Supervisor full name **Annarita Miccio**

PhD PROPOSAL IDENTIFICATION

PhD Project title	EDIting strategies for Treating Hemoglobinopathies
Project Acronym	EDITH
Project Keyword	genome editing, gene therapy, gene regulation, beta-hemoglobinopathies

LABORATORY PRESENTATION

Laboratory Team Name	Laboratory of Chromatin and gene regulation during development
Department IP	Institute of genetic diseases Imagine, INSERM UMR1163
Doctoral school	BIOSPC
University	Paris Cite' University
Laboratory website	https://www.institutimagine.org/en/annarita-miccio-189

PhD PROPOSAL

PhD Supervisor full name	Annarita Miccio
PhD Supervisor position	Lab Director
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PhD Proposal abstract (1000 characters maximum)

β-hemoglobinopathies, the most common monogenic disorders worldwide, are caused by mutations that reduce adult β-globin production or generate a mutant β-globin. β-globin disorders are associated to a severe clinical phenotype characterized by anemia, and multi-organ damage. Genetic correction of autologous hematopoietic stem cells (HSC) is an attractive therapeutic option for patients affected by β-hemoglobinopathies.
The aim of this project is to develop novel and safe therapeutic approaches for β-hemoglobinopathies. The student will explore novel editing strategies to target disease modifiers in patient cells, such as the fetal β-like gamma-globin and the α-globin genes. In fact, mutations leading to elevated fetal hemoglobin or reduced α-globin expression are associated with a better clinical phenotype. These approaches will be tested first in erythroid cell lines and then in hematopoietic cells obtained from patients with β-hemoglobinopathies in vitro and in vivo.

PhD Proposal (4000 characters maximum)

Sickle cell disease (SCD) and β-thalassemias are genetic diseases caused by mutations affecting the production of the adult hemoglobin β-chain. They represent the most common monogenic disorders worldwide. In β-thalassemia, the reduced (β^{+}) or absent (β^{0}) production of β-chains causes α-globin precipitation and death of red blood cell (RBC) precursors. In sickle cell disease (SCD), a single amino acid change ($\beta 6^{Glu \rightarrow Val}$) in the adult hemoglobin (Hb) β^{S}-chain causes Hb polymerization with consequent RBC sickling, vaso-occlusive crises, organ damage and reduced life expectancy. So far, the only curative treatment is represented by hematopoietic stem cell (HSC) transplantation from a compatible donor, but it is available only to less than 30% of the patients.
Therapies that are in the experimental stages include pharmacological intervention and gene therapy. In the first approach, efforts are underway to identify compounds that raise the expression of the fetal g-globin genes. The rationale for this treatment is based on the long-standing observation that patients with linked mutations that trigger elevated g-globin expression, which are normally expressed only during fetal life, experience a more benign clinical course of the disease. Unfortunately, pharmacological therapies are life-long treatments and can be associated with some toxicity. Gene therapy based on the transplantation of autologous, genetically modified hematopoietic stem cells (HSCs) is an attractive, deficitive therapeutic option. However, current gene therapy strategies based on the use of lentiviral vectors or CRISPR/Cas9 nuclease are not equally effective in all the patients and/or raise safety concerns.
The aim of the proposed project is to provide the knowledge for developing safe therapies to SCD and β-thalassemias based on novel editing approaches aimed to targeting disease modifiers such as g-globin and α-globin genes. The mechanisms and the regulatory elements that control globin gene expression will be exploited to develop genetic therapies for β-hemoglobinopathies. The PhD student will evaluate of the efficacy and safety of these therapeutic approaches. He/she will apply novel molecular technologies and techniques (e.g. novel editing technologies and genome-wide analyses) by using cutting-edge cellular models. First, the student will use genome editing tools to modify the target genomic regions and modulate the expression of disease modifiers in erythroid cell lines. The best performing approaches will be tested in patient HSCs *in vitro* and *in vivo*. The long-term goal of this project is to provide sufficient proof of efficacy and safety to enable the clinical development of safely edited HSCs for the therapy of β-hemoglobinopathies.

All the expertise/facilities required for carrying out this project are established in our lab/institute and in those of our collaborators. This research program is ideally placed on the Necker campus given the strong expertise in hematology/gene therapy, the presence of a clinical gene therapy center (Biotherapy Department) and a reference center for SCD.

5 main publications in the last 5 years

1. Magrin E, …., **Miccio A**, Bartolucci P, Leboulch P, Cavazzana M.Nat Med. 2022 Jan;28(1):81-88. PMID: 35075288
2. Ramadier S, …., **Miccio A.**Mol Ther. 2022 Jan 5;30(1):145-163. PMID: 34418541
3. Weber L, **Miccio A.**Sci Adv. 2020 Feb 12;6(7):eaay9392. PMID: 32917636
4. Lattanzi A, …., **Miccio A.**Mol Ther. 2019 Jan 2;27(1):137-150. PMID: 30424953
5. Antoniani C, …., **Miccio A.** Blood. 2018 Apr 26;131(17):1960-1973. PMID: 29519807

Expected profile of the candidate

- Master degree in a relevant subject (Molecular and cellular biology, Biotechnologies)
- Expertise in molecular and cellular biology (required)

- Expertise in genome editing (appreciated)