



MASTER'S DEGREE IN BIOMEDICAL RESEARCH

Research Project Proposal

Academic year 2023-2024

Project Nº 36

Title: Identification of essential epigenetic genes and development of Epi-DRUGs for the cure of Multiple Myeloma.

Department/ Laboratory *Multiple Myeloma-Myeloid malignancies (Lab 1.02), Hematology-Oncology Program, CIMA Universidad de Navarra*

Director 1 *Xabier Agirre Ena*

Contact: *xaguirre@unav.es*

Codirector: *Edurne San José Enériz*

Contact: *esanjose@unav.es*

Summary

In spite of the advances in Multiple Myeloma (MM) research and therapy, MM is still an incurable disease. As others and we have demonstrated, epigenetic alterations contribute to the pathogenesis of MM (Agirre X. Genome Research 2015; Ordoñez R. Genome Research 2020; Carrasco-León A. Leukemia 2021; Valcarcel LV. Leukemia 2021; Amundarain A. Am J Hematol 2022). In addition, due to the reversibility of epigenetic, targeting the epigenetic enzymes becomes an important area for the development of anti-cancer drugs (San José-Enériz E. Nature Communications 2017; Segovia C. Nature Medicine 2019; Fresquet V. Cancer Discovery 2021; García-Gómez A. Nature Communications 2021; Rabal O. J Med Chem 2021).

Based on our results obtained in the epigenome characterization of MM patients and the study performed in MM cell lines using a CRISPR/Cas9 library against 61 epigenetic enzymes, we will select 2 essential epigenetic target candidates for continue with the project. Next, we will validate the selected targets using CRISPR and ASO systems. Then, we will develop a therapy against the selected targets using RNA-base therapies, small molecules or PROTAC strategies. We will determine the in-vitro efficacy of our Epi-DRUGs analyzing the cell cycle, proliferation and apoptosis and their in-vivo potential in MM transgenic models. We will validate, both in-vitro an in-vivo, the correct inhibition of the epigenetic target by dot-blot, western blot or ChIP-PCR. Finally, we will carry out RNA-seq, Bis-seq, ATAC-seq, ChIP-seq, CUT&RUN or CUT&TAG analyses in order to elucidate the mechanism of action of our novel Epi-drugs.

We hope this work will be the basis for a new epigenetic therapy that will improve the treatment and quality of life of patients with MM.

yes	X
no	

Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?