Universidad de Navarra
Facultad de Ciencias

MÁSTER EN INVESTIGACIÓN BIOMÉDICA
Research Project Proposal
Academic year 2026-2027

Project Nº 41

Title: *Targeting the epigenetic regulator KAT2A in Multiple Myeloma: from functional characterization to therapeutic strategies.*

Department/ Laboratory: *Laboratory of Epigenetics. Hemato-Oncology program. CIMA Universidad de Navarra.*

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Multiple Myeloma (MM) is an incurable hematological malignancy characterized by the clonal proliferation of plasma cells in the bone marrow. Despite recent therapeutic advances, most patients eventually relapse, highlighting the need to identify novel molecular vulnerabilities. Epigenetic dysregulation is a hallmark of MM and represents a promising source of therapeutic targets. In this context, our group has developed innovative epigenetic therapies, including small-molecule inhibitors such as CM-272, a dual G9a/DNMT inhibitor with potent antitumor activity (*San José-Enériz E. Nature Communications 2017; Rabal O. Journal of medicinal chemistry 2018a; Rabal O. Journal of medicinal chemistry 2018b; Bárcena-Varela M. Hepatology 2019; Segovia C. Nature Medicine 2019; García-Gómez A. Nature Communications 2021; De Beck L, Frontiers in Immunology 2022; Exposito F. Cell death & disease 2024*), as well as novel deacetylase inhibitors (*Rabal O. Journal of medicinal chemistry 2021; San José-Enériz E. Nature Communications 2024)* and PROTAC-based strategies targeting epigenetic regulators in MM. Building on these studies, we have undertaken a systematic effort to identify novel epigenetic dependencies in MM using functional approaches. Among the candidates identified, the epigenetic regulator KAT2A has emerged as a potential key dependency in MM cells. The main objective of this project is to characterize the role of KAT2A in MM pathogenesis and to explore its potential as a therapeutic target. First, we will define the molecular mechanisms regulated by KAT2A by integrating its localization identified by CUT&RUN or ChIP-seq, chromatin accessibility profiling (ATAC-seq) and transcriptomic analyses (RNA-seq), and the study of post-translational modifications, including acetylation, lactylation, crotonylation and succinylation, in both histone and non-histone proteins. Second, we will develop innovative therapeutic strategies targeting KAT2A using RNA-based approaches, including siRNAs delivered through lipid nanoparticles, and evaluate their anti-myeloma activity *in vitro* and *in vivo*. Finally, we will identify synergistic therapeutic combinations that enhance anti-myeloma activity through functional drug screening approaches. Altogether, this project integrates mechanistic and translational approaches to validate KAT2A as a novel therapeutic target in MM, contributing to the development of new epigenetic therapies and improved outcomes for patients.

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