Lorea Jordana

PhD Student at UNAV

Lorea is from Navarra. She holds an International Master in Innovative Medicine (IMIM), studied in Germany and Sweden.
Although during her studies she had great experiences in laboratories in those countries, she decided to come back home to develop her PhD.

'Thanks to the IMIM I was introduced to wonderful people and laboratories, and it showed me what was to become my main research pasion: immunotherapy'.

Working at CIMA under the supervision of Doctor Felipe Prósper, Hematology and Oncology specialist, Head of Cellular Therapy Unit and Co-director of Haematology and Haemotherapy Unit of CIMA Clínica Universidad de Navarra.

Research

Molecular mechanisms governing CAR T cell response in Multiple Myeloma (MM) patients at single cell level

Research objective: to provide new insights into regulatory mechanisms that instruct key cellular players during CAR T therapies. We aim to deepen the understanding on how these mechanisms are subverted in those patients who are refractory or present therapeutic failure, and how they might be targeted to improve treatment efficacy and quality of life.

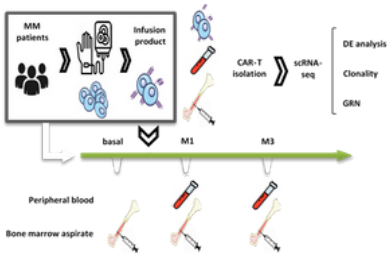
Abstract:

In the last decade, adoptive cell therapy strategies based on modified T lymphocytes with chimeric genes (CAR T cells) have evolved to become a real therapeutic option for patients with certain hematologic diseases and a promising therapy for many other types of tumors. Results with CAR T cells targeting CD19 antigen have been very impressive in patients with relapsed/refractory (R/R) Acute Lymphoblastic Leukemia, however, CAR T-based therapies still present some major limitations for other hematological malignances, including lack of long-term efficacy and treatment associated toxicities. This is the case in R/R Multiple Myeloma (MM) patients, that despite responses over 90% after CAR T administration, more that 50% relapse within a year. These relapses have been associated with poor CAR T cell persistence and development of tumor resistances.

Recent technological advances, such as single-cell sequencing, have allowed a notable progress in understanding the genomic landscape of CAR T cells ex vivo, providing some mechanistic insights and identifying factors involved in proper CAR T cell function. Functional commitment of CAR T cells depends on an orchestrated evolution of different T cell subpopulations that is affected by the microenvironment and it is governed by complex Gene Regulatory Networks (GRN). GRNs govern both the basal characteristics of CAR T cells as well as cell dynamics, instructing specific genomic configurations such as DNA methylation, histone modification and/or chromatin accessibility. These configurations are key to control transcription and, ultimately, CAR T functionality during the course of the therapy. However, there is a lack of studies with comprehensive integration of the molecular signatures and GRNs governing the function of CAR T cells and the surrounding immune cell population.

Thus, the central hypothesis is that single-cell technologies, coupled with machine learning algorithms, can help identifying key regulatory elements that could be modulated to foster the development of improved CAR T therapies. This project will shed light on the molecular behavior of key GRNs, providing new insights into regulatory mechanisms that instruct key cellular players during CAR T therapies.

To reach our goals we have divided the project in **three blocks:**



1. Decipher key GRNs and cell trajectories governing CAR T function. To perform single-cell profiling of CAR T cells, collected from paired samples of bone marrow (BM) and peripheral blood (PB) at different time points after infusion to infer the GRNs governing CAR T cell function as well as cell clonality of CAR T cells during the antitumoral response.

2. Characterize the cellular and molecular dynamics of immune cell populations. To follow the evolution of different immune cell populations, collected at different time points after CAR T cell infusion. By applying machine learning algorithms, we aim to elucidate their molecular dynamics as well as to infer cell-to-cell interactome between the immune populations and the CAR T cells.

3. Identify and validate determinants of response in CAR T cell therapies. To integrate the molecular mechanism uncovered in Aims 1 and 2 to define determinants of effective CAR T cell response, that will be further modulated for the development of improved CAR T therapies.

'I want to make a relevant contribution to the scientific community that hopefully can be translated to the society'.