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KEYWORDS – Multiple Myeloma, Drug Resistance, Drug Repurposing

MAIN FIELDS OF RESEARCH; ABSTRACT

Multiple Myeloma (MM) is a malignancy of plasma cells accumulating in the bone marrow that represents one of the most common hematological malignancies. Proteasome inhibitors (PI) have evolved to be a backbone for the treatment of MM and significantly contributed to improve patients’ outcomes. However, the vast majority of myeloma patients initially respond to PI-based therapy, but develop resistance over the course of the disease, and ultimately die from PI-refractory MM. Therefore, finding effective treatments for patients with PI-refractory MM is an unmet clinical need. The biology of PI-refractory MM is poorly understood in-vivo, and we lack treatment approaches that target the underlying mechanisms of PI-resistant MM. We hypothesize that under the long-term selective pressure of proteasome inhibition in-vivo, the bone marrow microenvironment changes the properties of the MM plasma cell population to survive the cytotoxic effect of proteasome inhibition. We further hypothesize that these changes fundamentally differ from PI-sensitive cells and allow them to evolve features commonly seen in refractory MM patients. The aim of this project is to use an orthotopic MM mouse model to dissect the molecular landscape of transcriptional changes of human MM cells upon exposure to 2nd generation PI Carfilzomib (CFZ), using single cell RNA-Sequencing (scRNA-Seq). To achieve this, we will compare samples obtained from a) in-vitro, b) in-vivo during active growth (untreated) and c) in-vivo, once the MM cells become refractory towards CFZ treatment. Finally, we aim to identify specific genes and pathways that confer the bone marrow-mediated PI-resistance in MM which consequently might provide potential therapeutic targets. Based on the findings from the scRNA-Seq we will, in a second step, perform the CRISPR-Cas9 loss-of-function gene editing to validate if previously identified targets are involved in CFZ-resistance in-vivo with the aim to discover new treatment approaches with currently FDA approved drugs (drug repurposing). The results of this project will likely significantly advance the current knowledge in the biology of the PI-resistance in MM.

SPECIAL TECHNIQUES AND EQUIPMENT

Single Cell RNA Sequencing, CRISPR-Cas9 gene editing