## Abstract: P869

# Title: TRANSCRIPTOMIC ANALYSIS OF METABOLISM-ASSOCIATED GENES AS BIOMARKERS AND POTENTIAL THERAPEUTIC TARGETS FOR MULTIPLE MYELOMA

**Abstract Type: Poster Presentation**

**Topic: Myeloma and other monoclonal gammopathies - Biology & translational research**

**Background:**

Aberrant metabolism is a key hallmark of cancer and its study has revealed new vulnerabilities in different human tumors. The recently available large-scale transcriptomic data sets in MM allow a different approach to study metabolism-related genes by analyzing their expression.

**Aims:**

The aim of our work is to analyze the alterations in the metabolic transcriptome in patients with MM with the goal of identifying new metabolic vulnerabilities as well as biomarkers.

**Methods:**

We analyzed the transcriptome of 619 MM patients (MMRF-CoMMpass cohort) and focus on the expression data of 2753 metabolic genes (metabolic transcriptome) (from Possemato et al., 2011). Non-negative matrix factorization was performed to define metabolic profiles.

**Results:**

Principal component analysis revealed that the metabolic transcriptome of plasma cells from MM clustered separate from normal B cell subpopulations (Naive, centroblasts, centrocytes, memory, tonsillar plasma cells and bone marrow plasma cells), also indicating a great inter-patient metabolic transcriptome heterogeneity. MM patients were classified in six distinct metabolic groups each one showing a well-defined metabolic pathway affected and a clear association with the main cytogenetic alterations in MM (**Fig. 1A**). These results were confirmed in two other independent cohorts of MM patients. Interestingly, hyperdiploid patients were characterized by 2 different metabolic transcriptional profiles define as MM5 and MM6 as well as a significant worse Progression Free (PFS) and Overall Survival (OS) for patients in MM5 (**Fig. 1B**). A transcriptional analysis of patients MM5 (not restricted to metabolic genes) showed a significant enrichment of 1) pathways related to myeloid categories and myeloid progenitor cell markers, such as megakaryocyte-erythroid progenitor and granulocyte-monocyte progenitor markers (**Fig. 1C**), 2) dormant cell gene expression signature (**Fig. 1D**) and 3) regulons showing myeloid TFs, like CEPBE and NFE2, regulating the expression of specific metabolic, myeloid and dormant cells related genes overexpressed in MM5 group. Among these specific genes of MM5 group, we focused in two genes that regulate lipid metabolism, ACSL1 and ALOX5AP. We observed that the inhibition of ACSL1 and ALOX5AP genes by CRISPR-CAS9 strategy decreased the MM cell proliferation (**Fig. 1E**), underscoring their essentiality and highlighting their potential as promising therapeutic targets for the treatment of MM patients of MM5 group.

**Summary/Conclusion:**

We have demonstrated that MM patients show a heterogeneous metabolic transcriptome, classifying them in 6 distinct groups, associated with specific MM genetic alterations. Among these 6 groups, we focus on MM5 hyperdiploid group that shows a poor prognosis related to its myeloid and dormant cells characteristics. Moreover, we have identified the metabolic genes ACSL1 and ALOX5AP as promising metabolic therapeutic targets for the treatment of patients in the MM5 group.

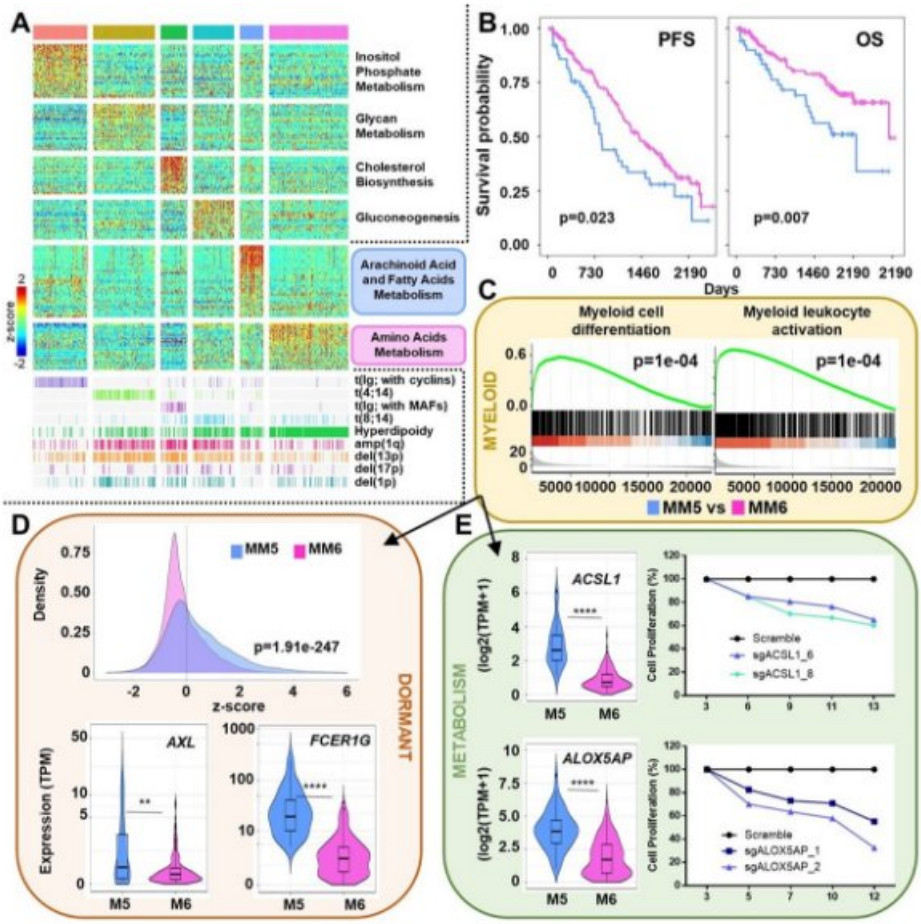


**Figure 1: MM shows a heterogeneous metabolism related transcriptome. A)** Heatmap of the expression of the metabolic transcriptome signatures of the six defined groups in MM and genetic alterations of each patient. Each column annotation represents a different metabolic cluster, whereas the rows represent the metabolic gene signatures. Gene expression is scaled along patients (z-scores). **B)** Kaplan-Meier curves of the Progression Free Survival (PFS) and Overall Survival (OS) of the patients of groups MM5 and MM6. **C)** Gene Set Enrichment Analysis (GSEA) showing the enrichment of myeloid categories in MM5 respect to MM6 groups. **D)** Density plot of the expression in z-scores of dormant cell markers in MM5 and MM6; and expression of AXL and FCER1G dormant genes in MM5 and MM6 groups. **E)** Expression of metabolism related genes ACSL1 and ALOX5AP in MM5 and MM6 groups; and cell proliferation of KMS28BM cell line after ACSL1 or ALOX5AP knockdown by CRISPR-Cas9.

**Keywords:** Multiple myeloma, Lipid metabolism, Gene transcription