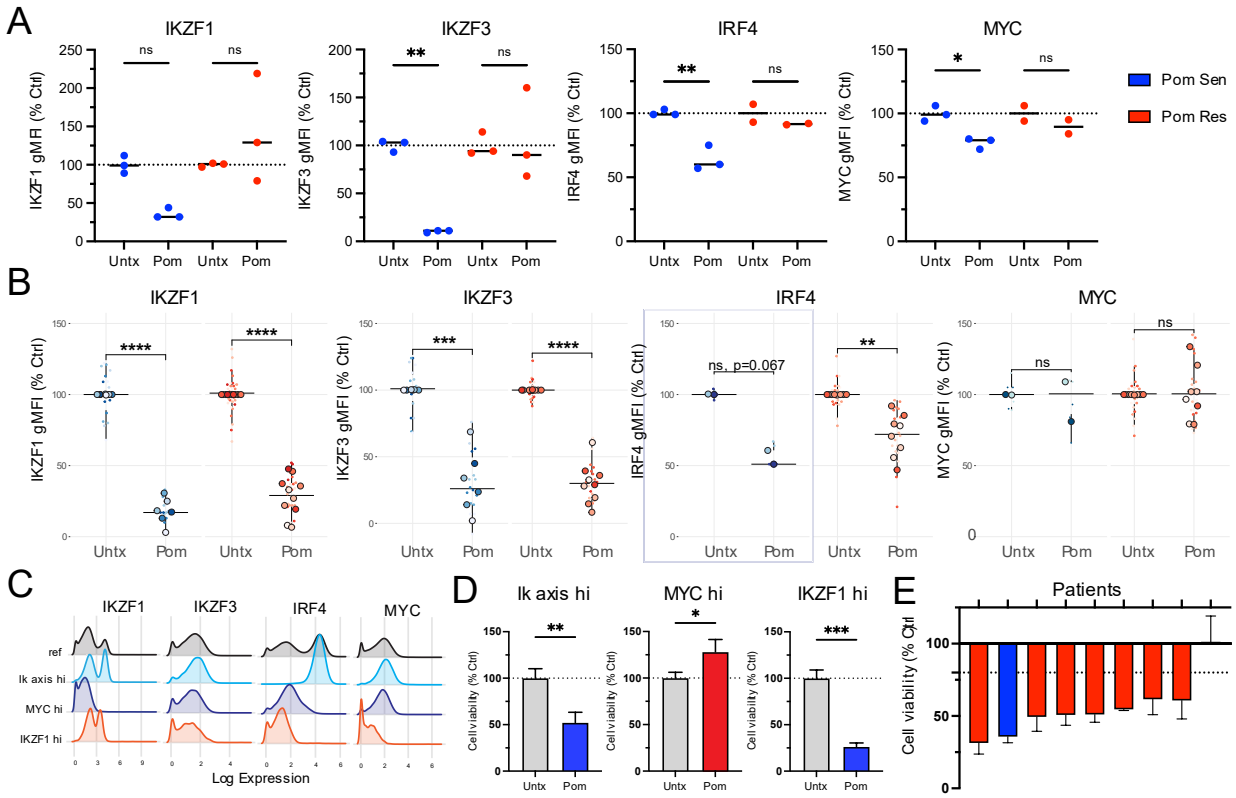
MYC Inhibition Overcomes IMiD Resistance in Heterogeneous Multiple Myeloma Populations. LN Davis (PhD, GS), ZJ Walker, D Ohlstrom, BM Stevens, PA Forsberg, TM Mark, and DW Sherbenou, Department of Medicine, University of Colorado, Aurora, CO

Multiple myeloma (MM) is an incurable plasma cell malignancy. Immunomodulatory drugs (IMiDs) are critical for disease control, yet resistance develops. IMiDs act by inducing Cereblon-dependent degradation of the transcription factors IKZF1 and IKZF3, which leads to IRF4 and MYC downregulation (collectively termed the “Ikaros axis”). We therefore hypothesized that in IMiD resistant MM, IMiDs fails to downregulate the Ikaros axis. To measure IMiD-induced Ikaros axis downregulation, we designed a flow cytometry assay to measure relative IKZF1, IKZF3, IRF4 and MYC protein levels in MM cells following IMiD treatment. We performed this in MM cell lines and patient samples grouped by ex vivo IMiD sensitivity. Our hypothesis was supported in MM cell lines, as resistant lines lost IMiD-induced decrease of all Ikaros axis proteins. However, when assessed in patient MM cells, we observed IMiD-induced downregulation regardless of IMiD sensitivity. We next used mass cytometry in patient samples to reveal that individual Ikaros axis proteins were differentially expressed between MM subpopulations. When correlating this with ex vivo IMiD sensitivity of subpopulations, we observed that low IKZF1/3 corresponded to resistance. Interestingly, most resistant populations still expressed MYC. We therefore assessed whether MYC is critical in resistant cells and found that 88% (7/8) of resistant patient samples were sensitive to MYC inhibition. While our findings in patients did not support our initial hypothesis, our data suggest a mechanism where the Ikaros axis no longer drives MYC expression in IMiD resistant MM, and resistant MM cells remain dependent on MYC. This suggests targeting MYC may be an effective strategy to eradicate IMiD resistant MM.



(A) Intracellular flow assay of MM1S parental (sensitive, blue) or IMiD (Pom) dose-escalated cells (resistant, red) showing decrease of IKZF1, IKZF3, IRF4 and MYC geometric mean fluorescent intensity (gMFI) relative to untreated (Untx) control. Each dot is a technical replicate. (B) Assay in isolated mononuclear cells from pom-sensitive (blue) or -resistant (red) patient samples gated on CD38+CD138+ MM cells. Shown are superplots representing each individual patient sample mean as a larger dot and their corresponding technical triplicates are smaller dots of the same shade. (C) Histograms of Ikaros axis log signal intensity in individual MM subpopulations from mass cytometry of representative patient 1389 (ref = all cells). (D) Ex vivo drug sensitivity of the three MM subpopulations from (C) to 10uM Pom treatment relative to untreated control. (E) Waterfall plot of ex vivo drug sensitivity of Pom-sensitive and -resistant MM patient cells to 1uM MYCi975.