

Highlights from IMS 20th meeting 2023

Alessandra Romano

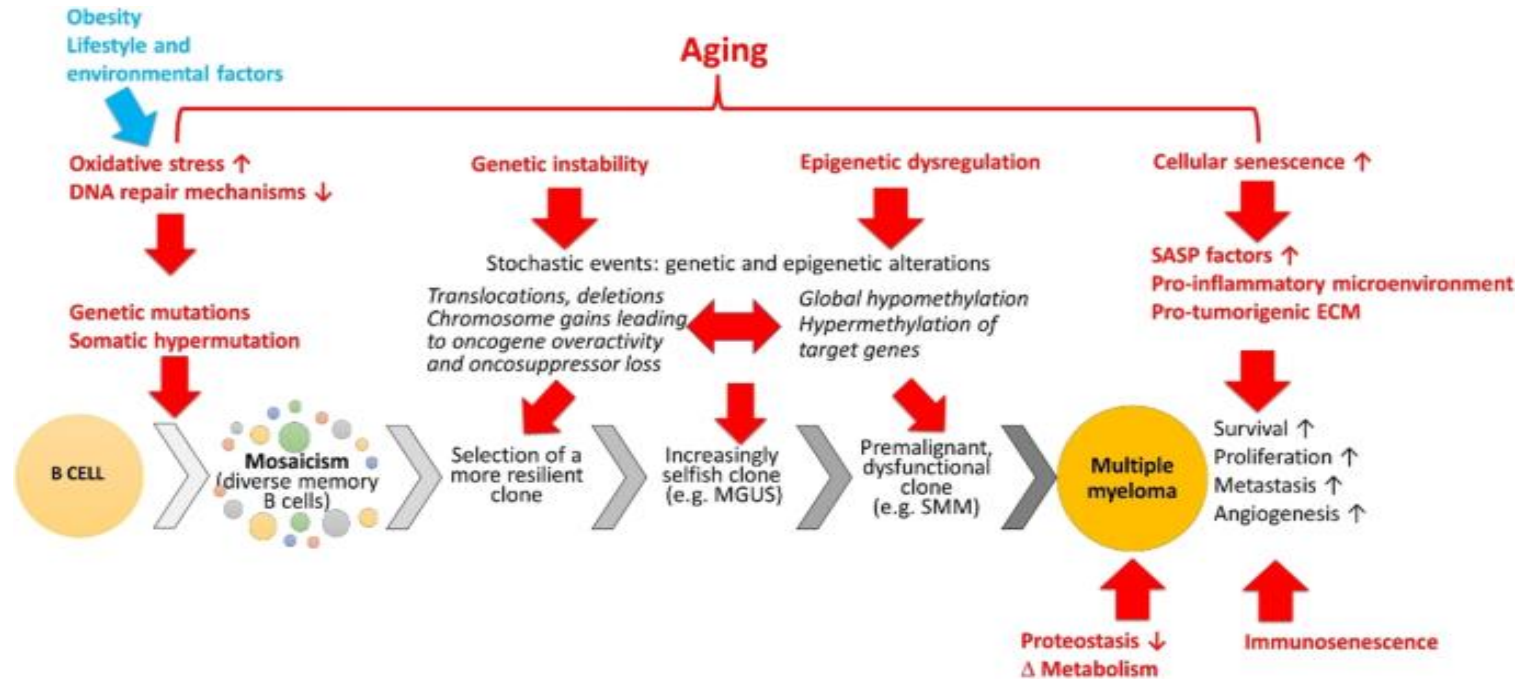
Drivers epigenetici ed
alterazioni metabolomiche

30-31 gennaio 2024

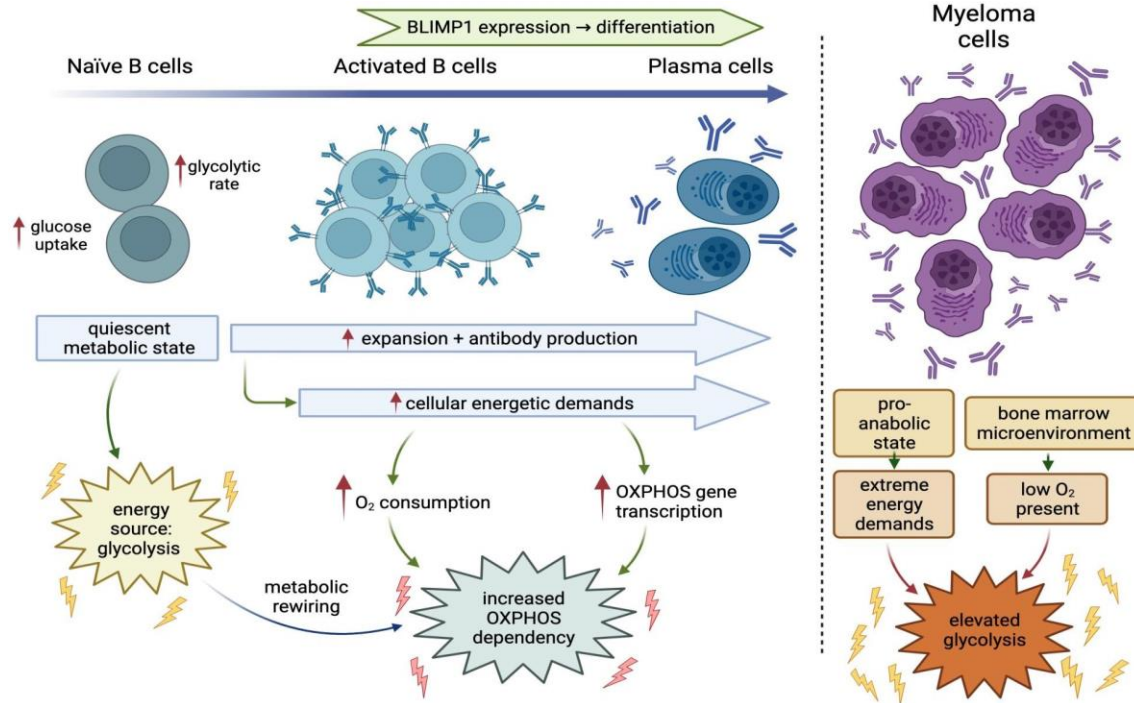
BOLOGNA, Royal Hotel Carlton

Disclosures of Alessandra Romano

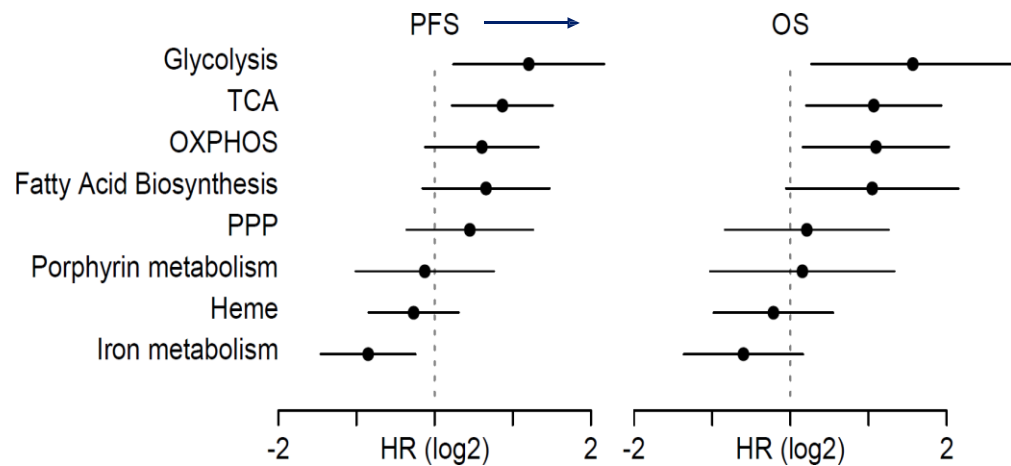
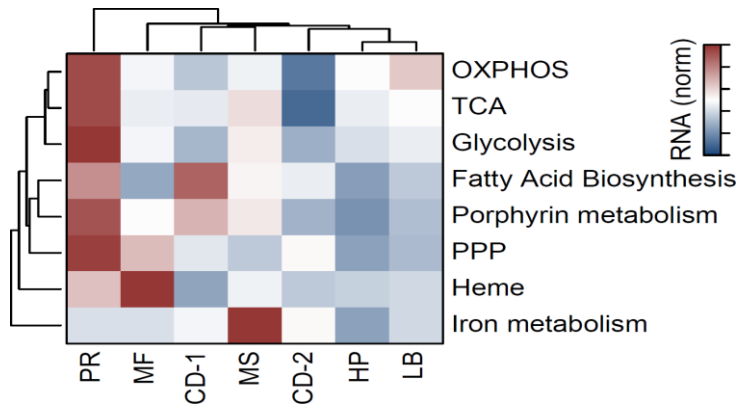
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Blueprint			x				
Takeda						x	
Janssen						x	



Plasma cells exhibit glycolysis and increased OXPHOS

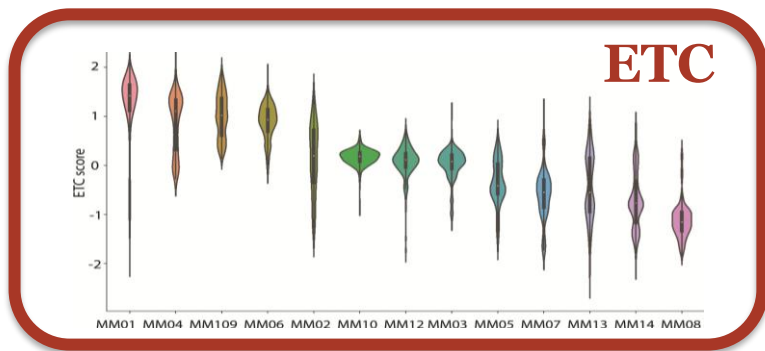
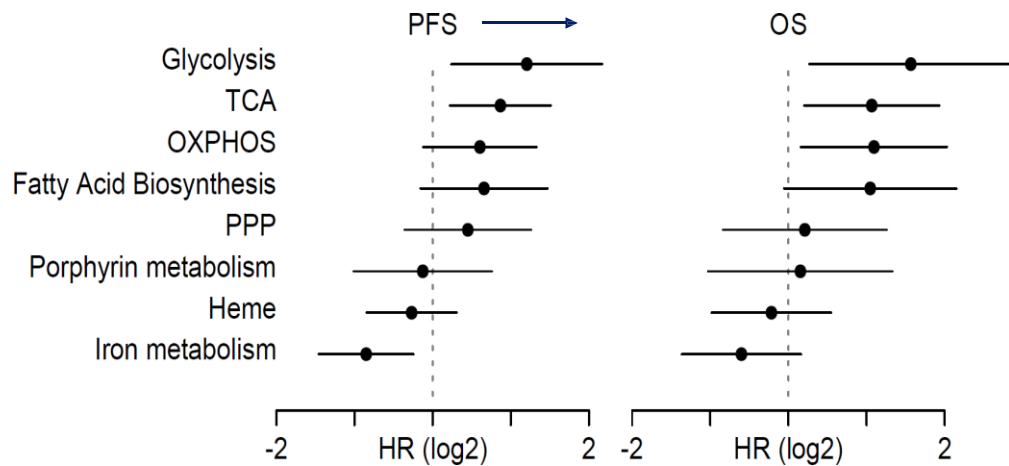
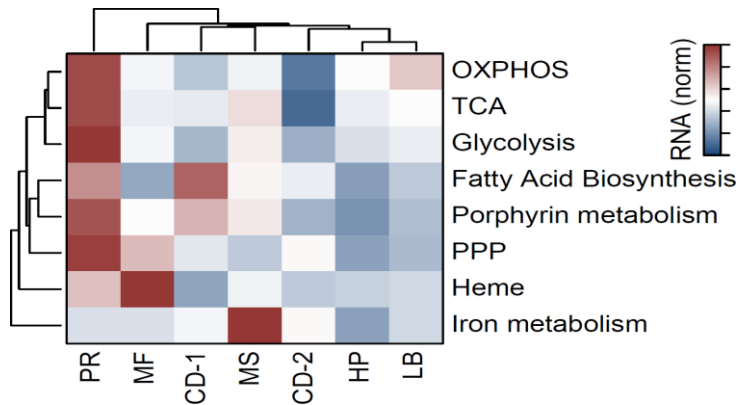


Elevated metabolic gene signatures correlate with poor PFS and OS



CoMMpass Analysis, Benjamin Barwick
Shanmugam, IMS 2023

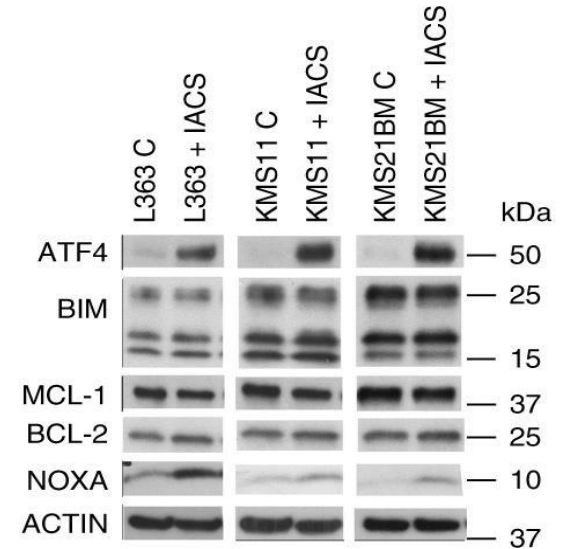
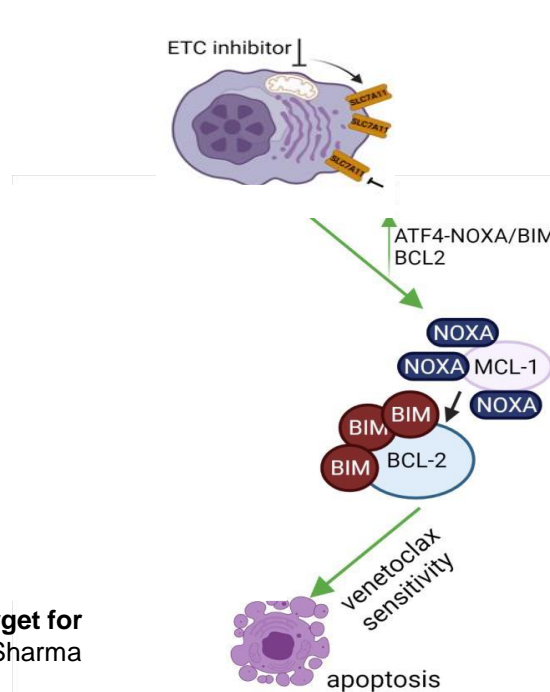
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Targeting metabolism impacts therapy sensitivity

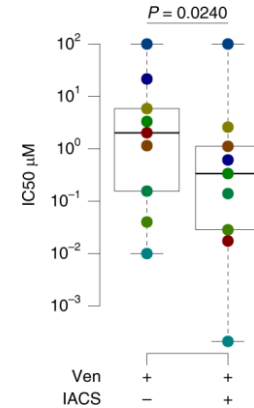
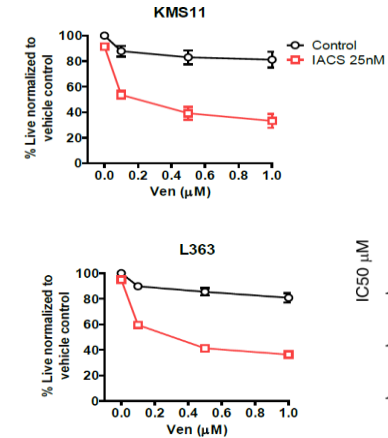
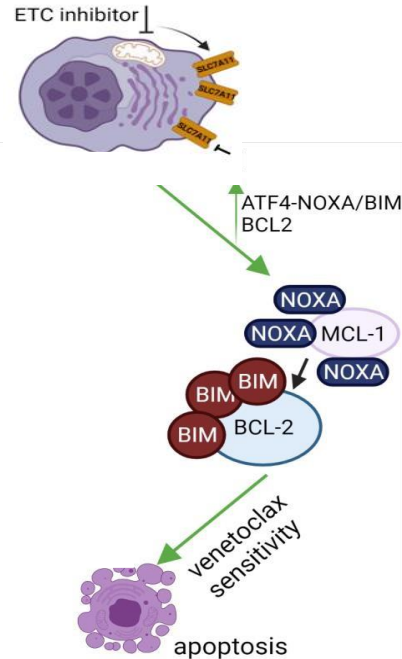
ETC inhibitors increase sensitivity to Venetoclax



Electron transport chain activity is a predictor and target for venetoclax sensitivity in multiple myeloma Bajpai R*, Sharma A*, Nature Communications (2020) Mar 6;11(1):1228

Targeting metabolism impacts therapy sensitivity

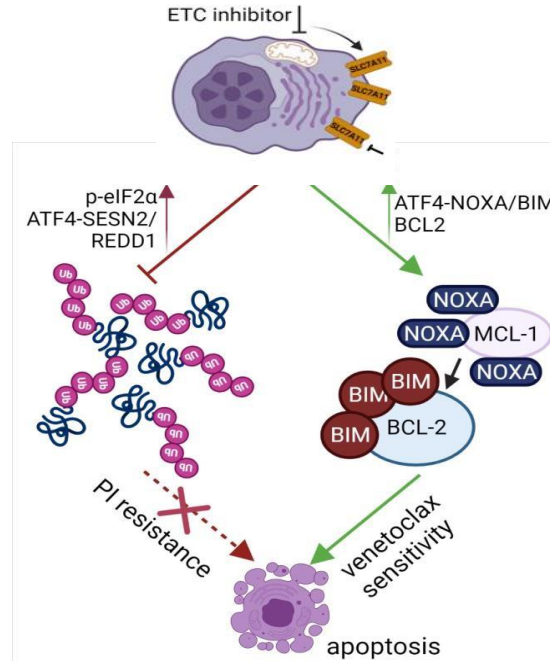
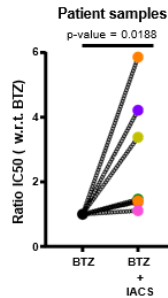
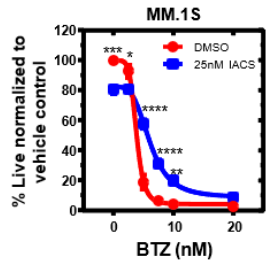
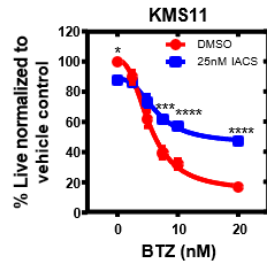
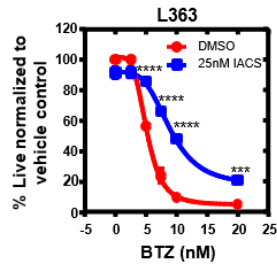
ETC inhibitors increase sensitivity to Ven



Electron transport chain activity is a predictor and target for venetoclax sensitivity in multiple myeloma Bajpai R*, Sharma A*, Nature Communications (2020) Mar 6;11(1):1228

Targeting metabolism impacts therapy sensitivity

ETC inhibitors increase sensitivity to Ven while promoting resistance to PIs

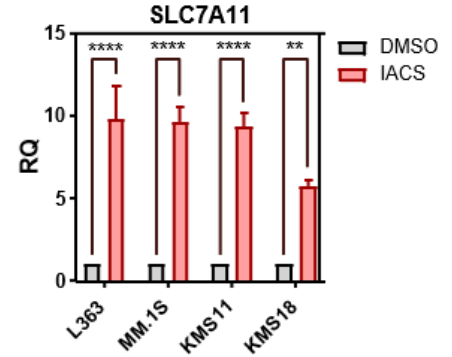
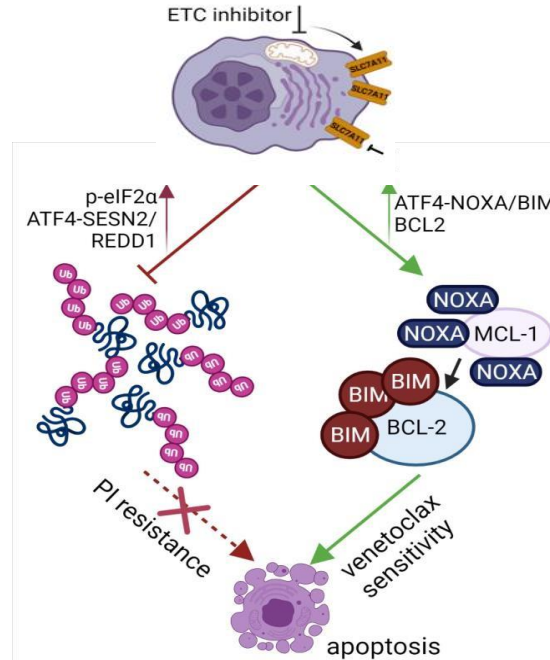
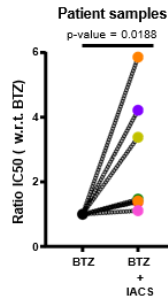
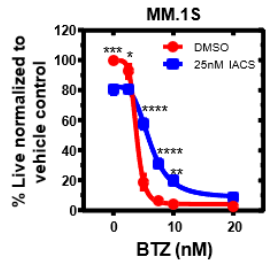
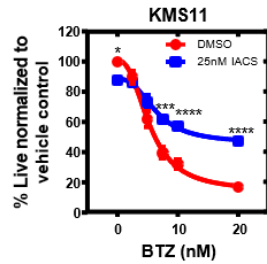
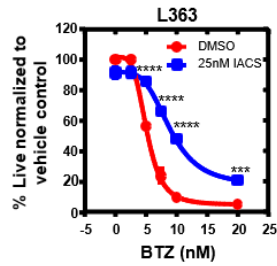


Shanmugam, IMS 2023 (oral communication)

Nair, IMS 2023 (poster 2023)

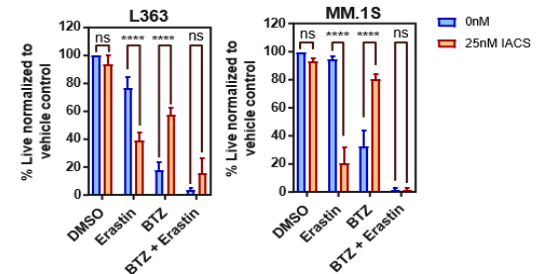
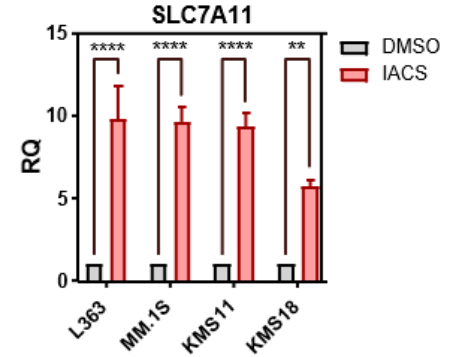
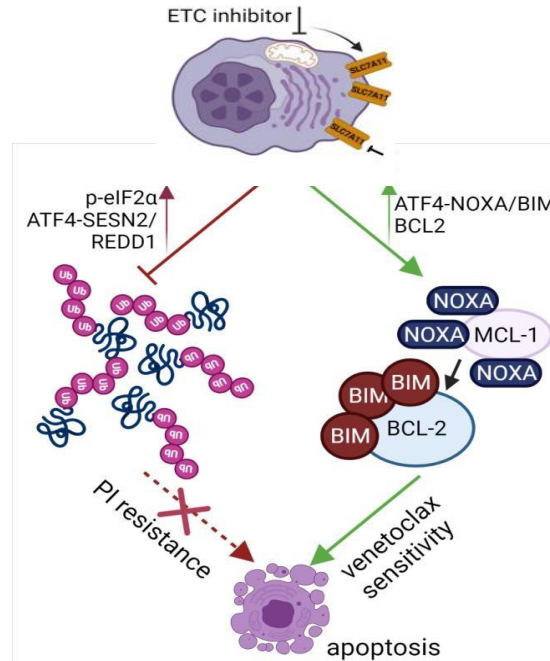
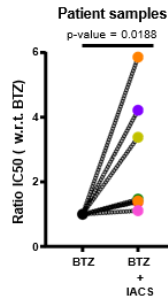
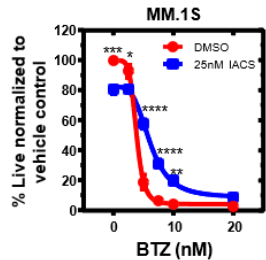
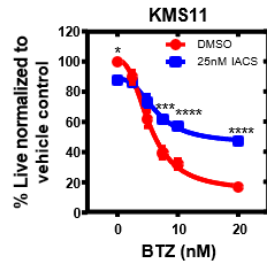
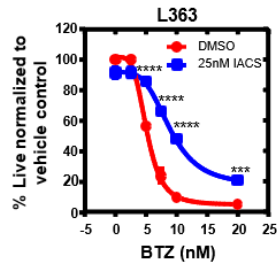
Targeting metabolism impacts therapy sensitivity

ETC inhibitors increase sensitivity to Ven while promoting resistance to PIs



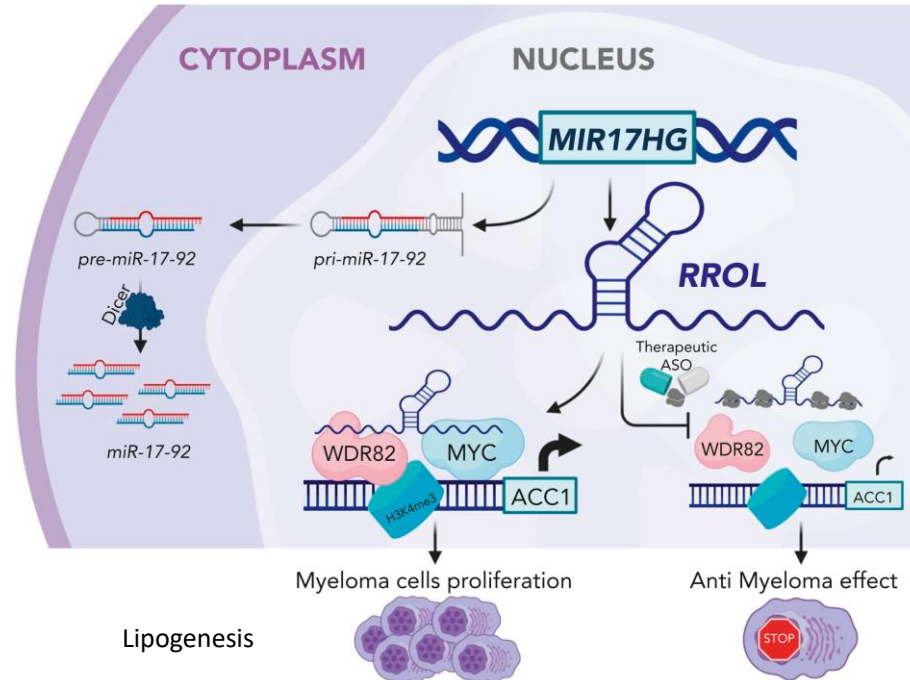
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Shanmugam, IMS 2023 (oral communication)
Nair, IMS 2023 (poster 2023)

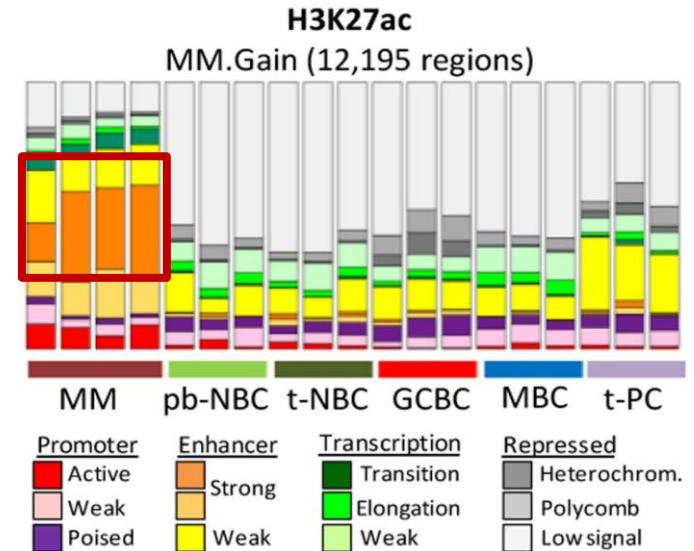
A long noncoding RNA provides an essential chromatin scaffold for protein interaction and myeloma growth



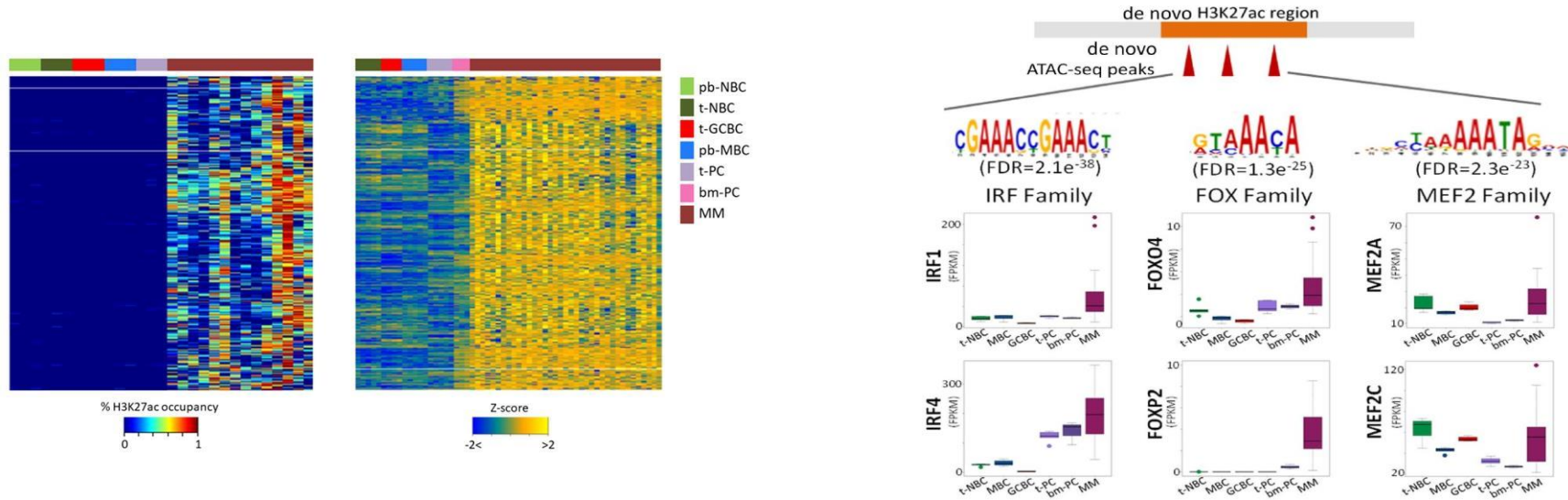
Chromatin states in Multiple Myeloma

MM displays an **epigenetic configuration distinct from normal B cell subpopulations**, including significant gains of marks associated with **active enhancers and promoters** (H3K27ac, H3K4me1, and H3K4me3)

De novo chromatin activation is preferentially located in **regulatory elements**, which arise from **heterochromatic regions** in normal B cells



De novo chromatin activation affects genes related to MM pathogenesis

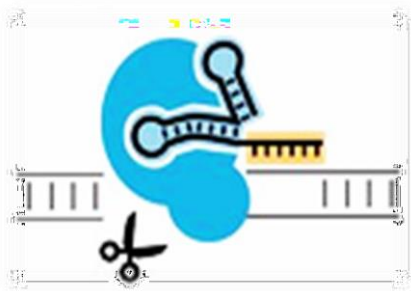


de novo active regions, with increased chromatin accessibility in MM are enriched in **binding motifs of TF families** involved in the **pathogenesis of MM**

Functional categories associated with the target genes include a variety of **functions previously described to be altered in MM** (osteoblast differentiation, NF- κ B signaling, MTOR, the TP53 pathway, NOTCH pathway, or oxidative stress responses)

Functional studies to understand the role of epigenetics in MM

CRISPR-CAS9



GENE EDITING

314 selected genes
197 *de novo* active
56 TFs
61 epigenetic genes

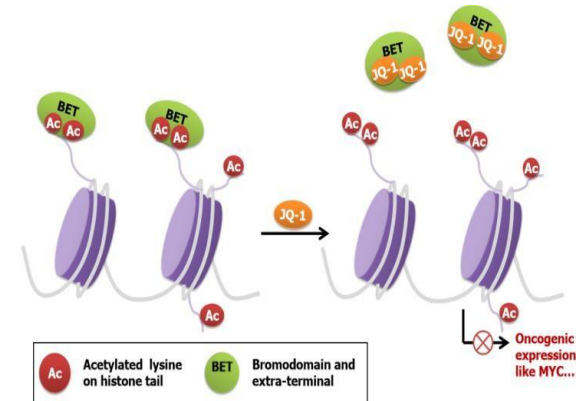
CRISPRi-dCAS9



GENE REPRESSION

372 selected lncRNAs
Specifically expressed in MM
89 *de novo* active

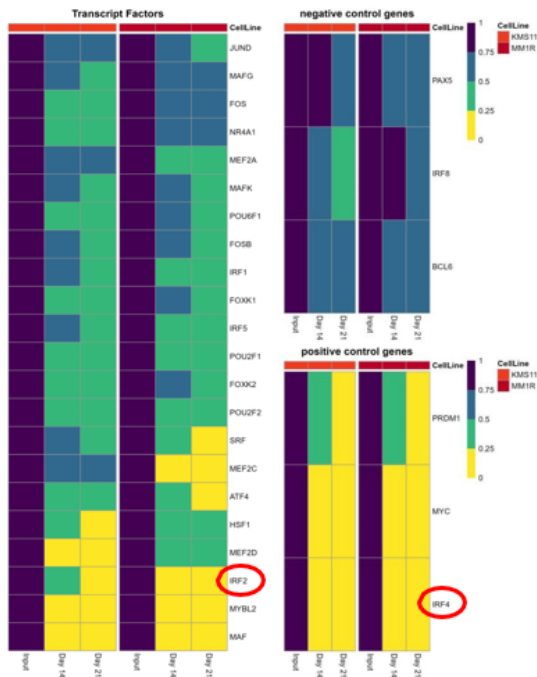
BET Inhibitors (JQ-1)



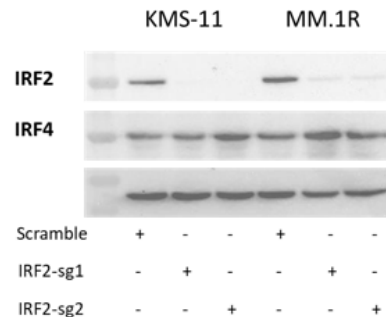
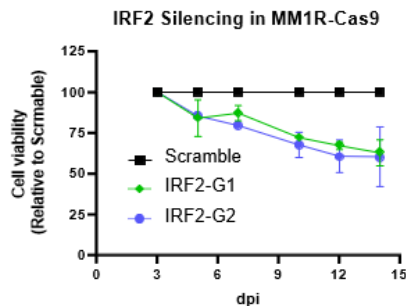
GENE REPRESSION

**Regulates acetylated active
enhancer and promoter
regions**

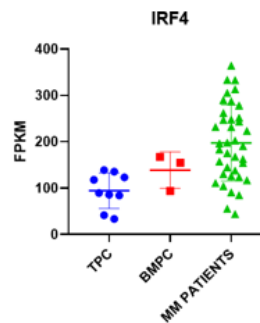
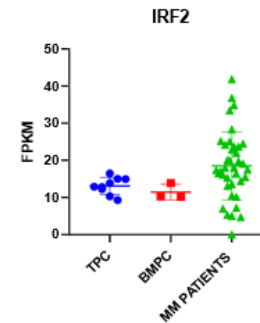
The transcription factor IRF2 is essential for MM survival



IRF2 (and IRF4) decreased
MM cell proliferation

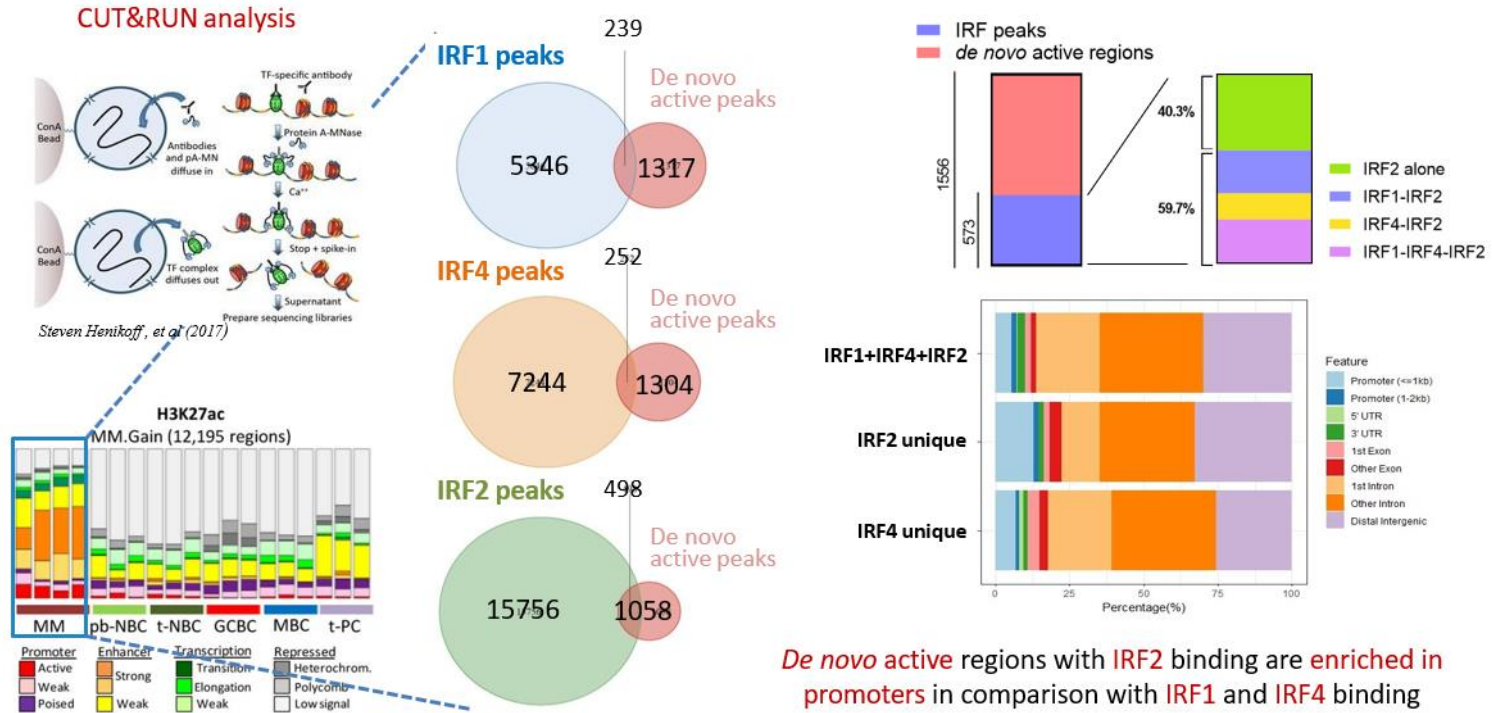


The guides of IRF2 did not present
off-target effects in IRF4



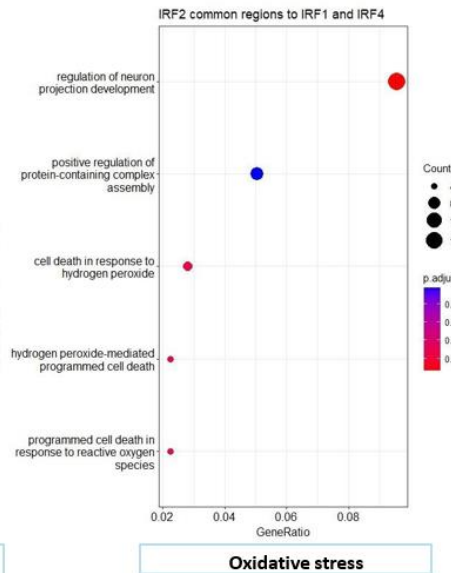
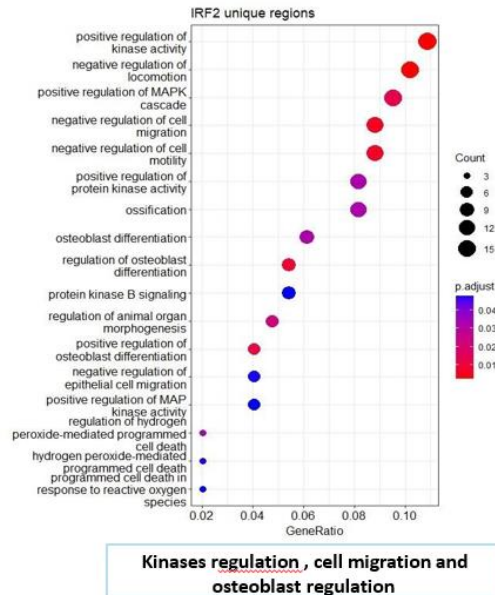
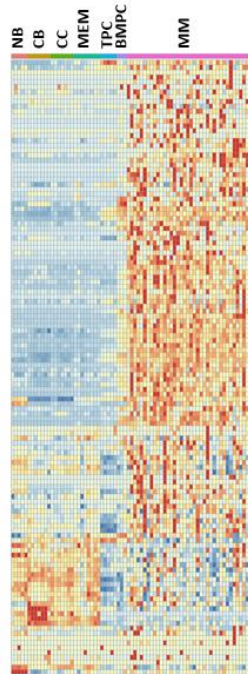
F. Prospero, IMS 2023

IRF2 regulation of promoters in *de novo* active regions in MM



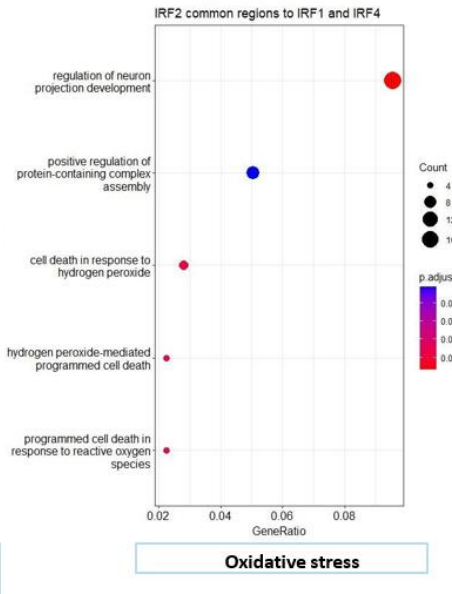
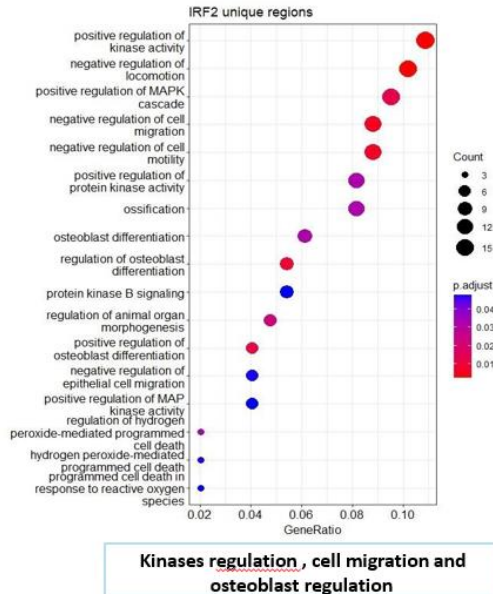
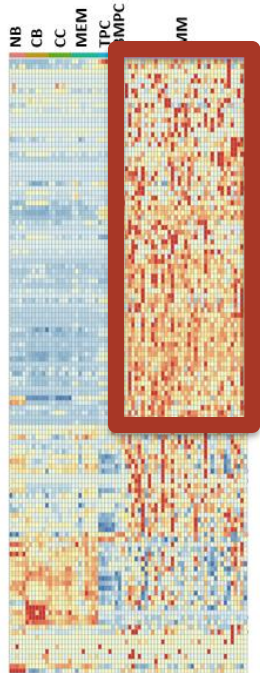
De novo active regions with IRF2 binding are enriched in promoters in comparison with IRF1 and IRF4 binding

IRF2 target genes are upregulated in MM



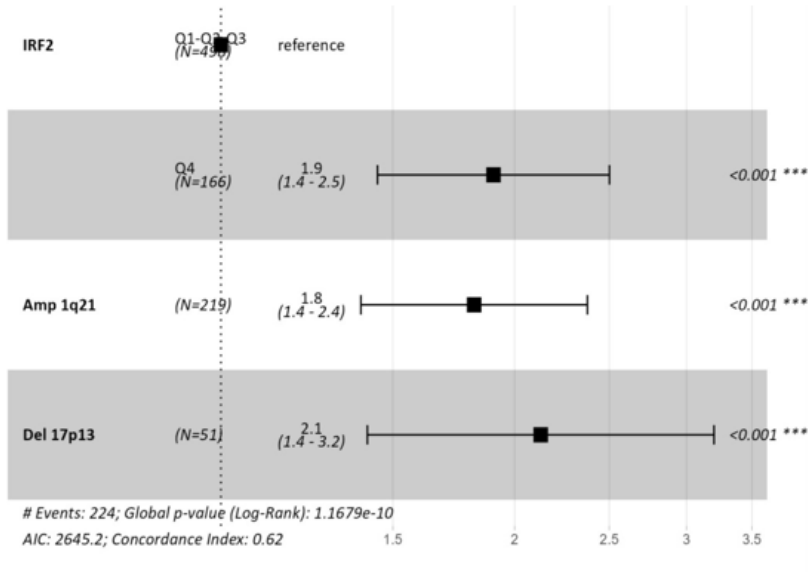
- Genes related to *de novo* active regions and regulated by IRF2 are upregulated in MM
- IRF2 regulated genes are implicated in kinases, cell migration and osteoblast regulation

IRF2 target genes are upregulated in MM and its precursor stages

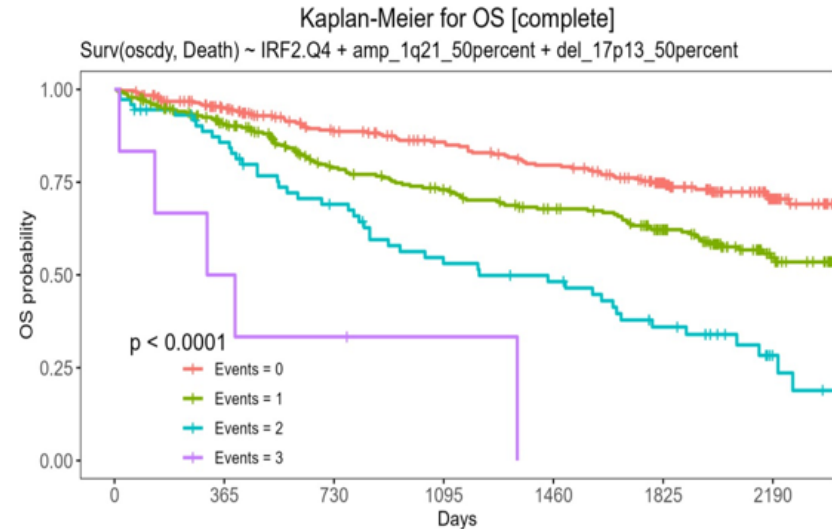


- Genes related to *de novo* active regions and regulated by IRF2 are upregulated in MM
- IRF2 regulated genes are implicated in kinases, cell migration and osteoblast regulation

IRF2 expression could be included as prognostic biomarker in MM

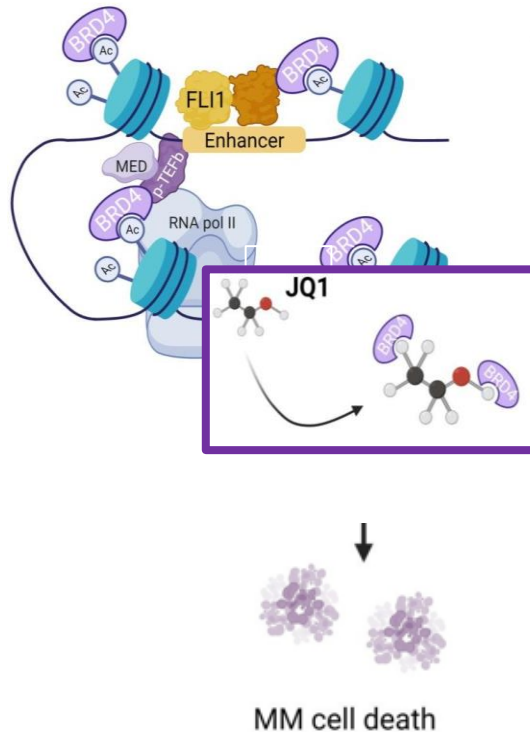


664 MM patients (CoMMPass)

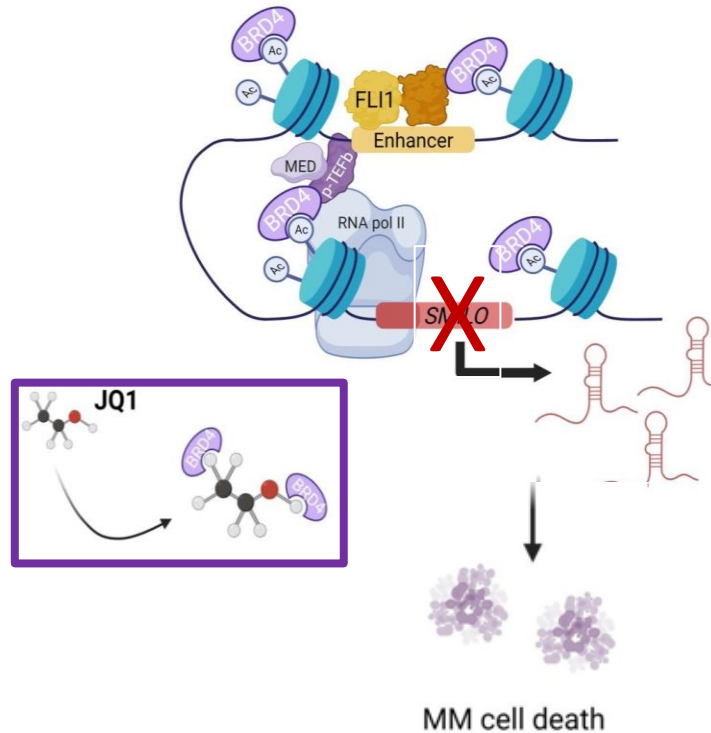


The combination of the **IRF2 expression** with established **genetic** biomarkers has a better impact on the prognosis of MM patients

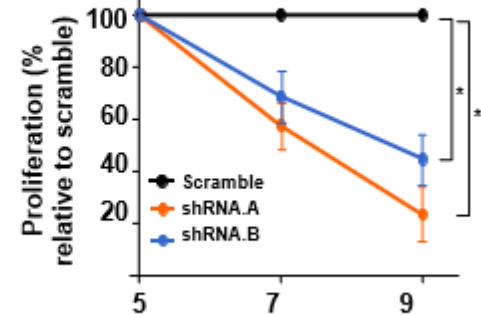
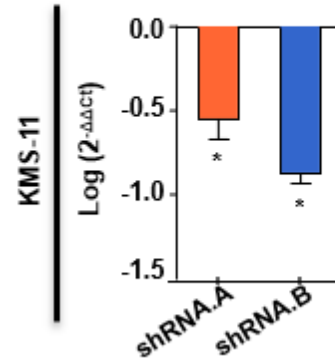
Pharmacological regulation of *de novo* active regions in MM



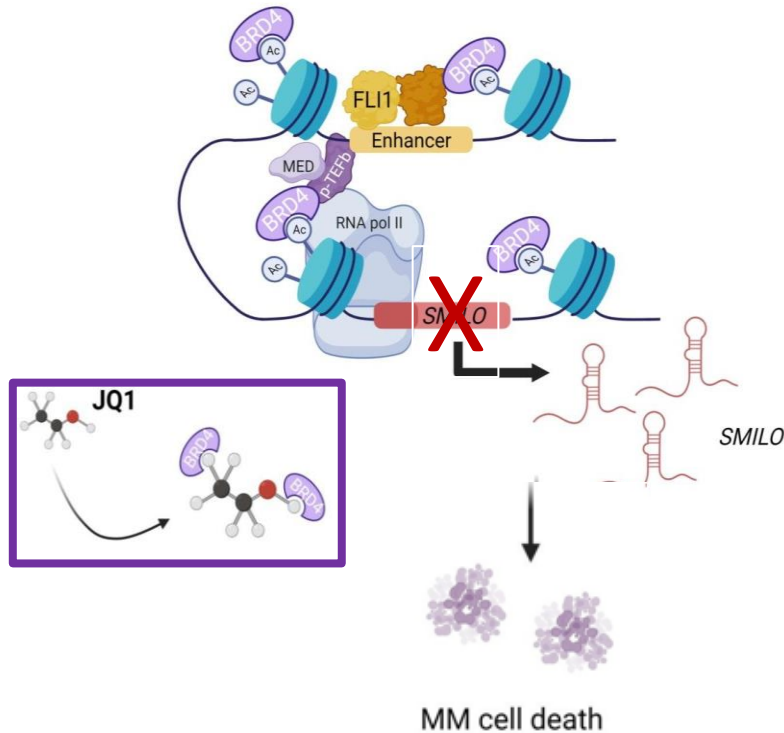
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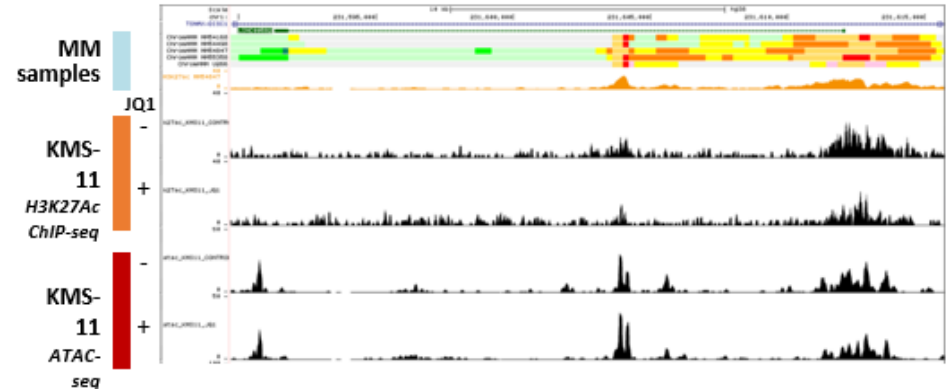
lncRNA *SMILO* is the most downregulated gene after JQ1



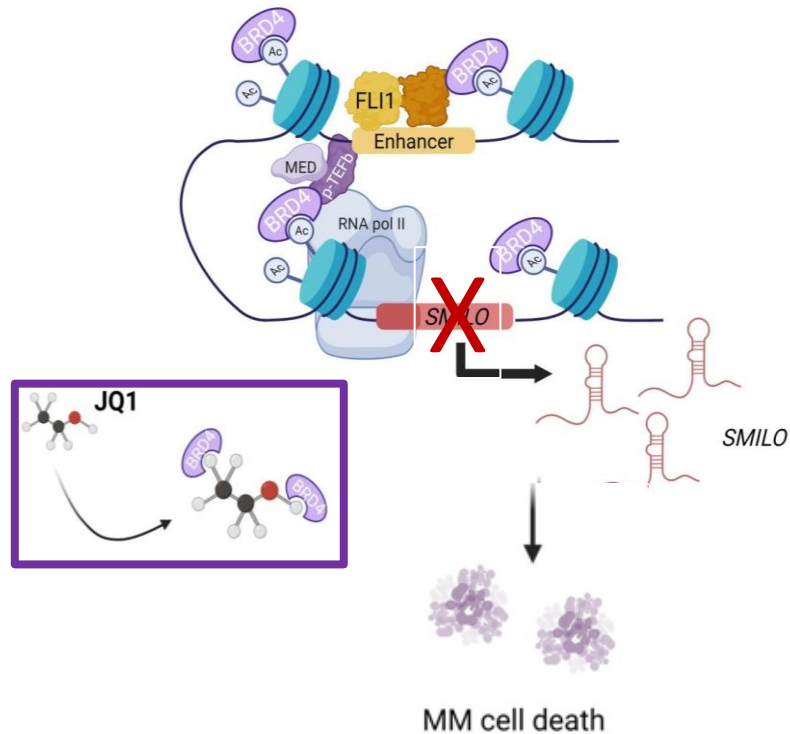
Pharmacological regulation of *de novo* active regions in MM



***SMIL0* downregulation after JQ1
is not due to chromatin modifications.**

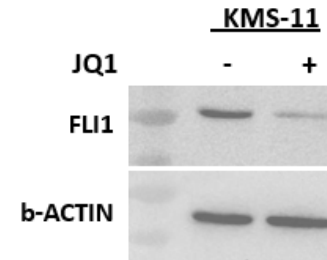
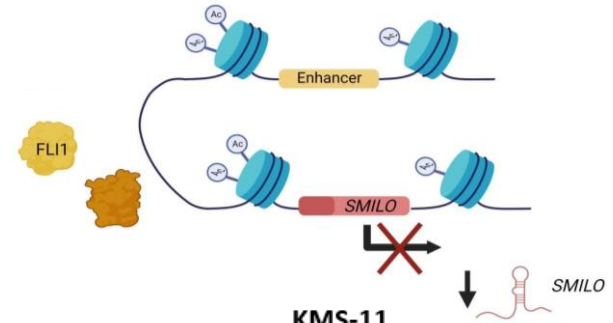


Pharmacological regulation of *de novo* active regions in MM



Reverse-ChIP demonstrated that FLI1 TF binds to the *de novo* chromatin regions related to *SMIL0*

JQ1 decreases
FLI1 expression



To wrap up

- ❑ Basal metabolic states predict therapy sensitivity: **Low ETC/OXPHOS** correlates with venetoclax sensitivity
- ❑ Targeting metabolism impacts therapy sensitivity: **ETC inhibitors increase sensitivity to Ven while promoting resistance to PIs**
- ❑ MM plasma cells are characterized by **de novo chromatin activation** of regulatory regions (**promoters and enhancers**) which are associated with activation of transcriptional programs involved in MM
- ❑ **IRF2** is a key transcription factor involved in the pathogenesis of MM, through transcriptional upregulation of kinases, cell migration and osteoblast regulation, **independently of IRF4 activity**
- ❑ Using **genetic** and **pharmacological** approaches **lncRNAs** involved in the pathogenesis of MM as **SMILO** have been identified as epigenetically regulated