

BET inhibitors downregulate the expression of the essential lncRNA *SMILO* in multiple myeloma through regulation of the transcription factor FLI1

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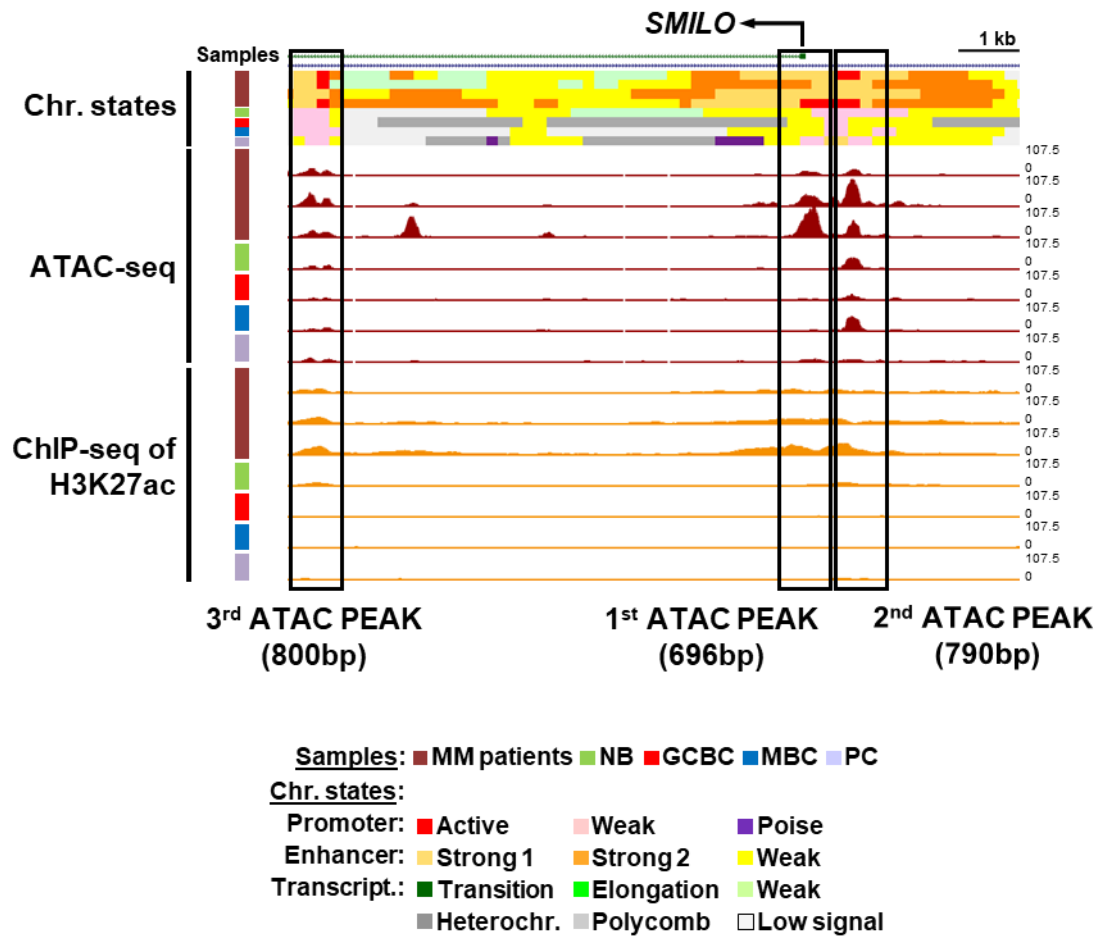
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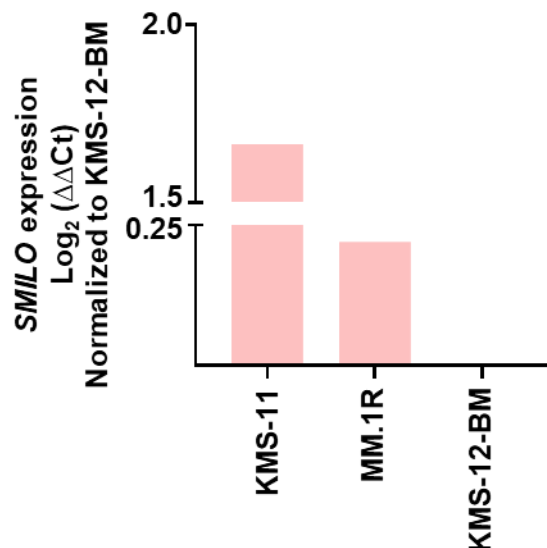
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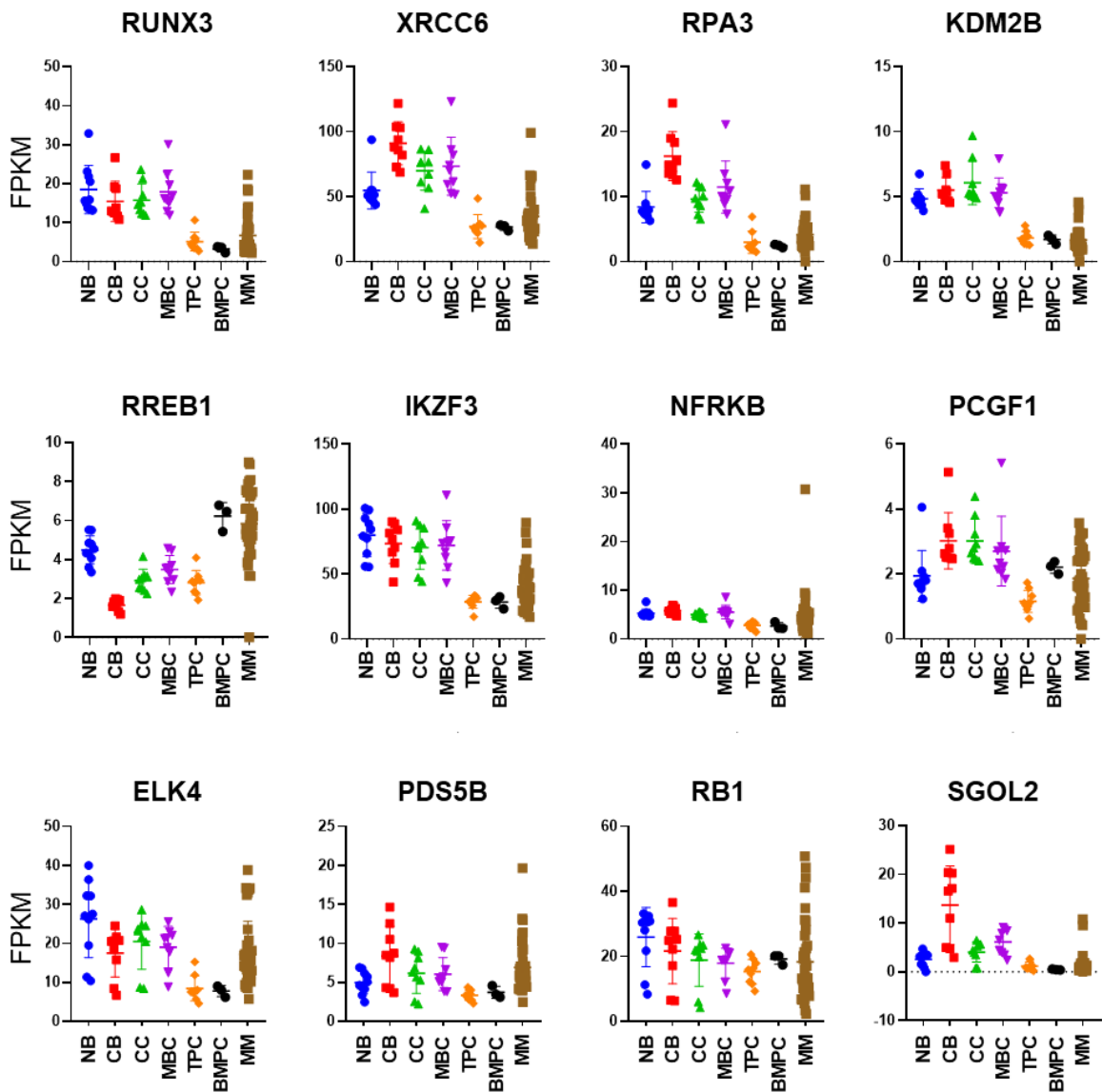
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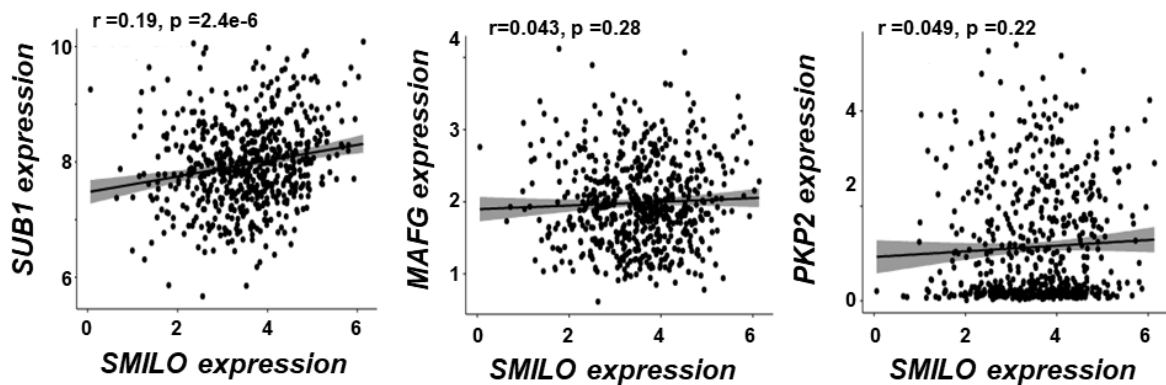
Supplementary figure S1. SMILO study in MM. A) Selected chromatin regions from *SMILO* to be analyzed by Reverse-ChIP technique: the figure shows the chromatin states, the chromatin accessibility (ATAC-seq) and the histone acetylation (H3K27ac ChIP-seq) in MM samples compared to healthy B cells. The three highlighted regions through black

squares correspond to three regions studied by Reverse-ChIP named: first, second, and third ATAC peaks. The three DNA regions were selected as follows: the first ATAC peak was localized at the beginning of *SMILO*, presented *de novo* ATAC peak and *de novo* acetylation marks in MM patient samples; the second ATAC peak, was localized before the *SMILO* start site, contained an ATAC peak common to healthy B cells but presented *de novo* chromatin activation marks in MM patient samples; and the third ATAC peak, localized in the middle of *SMILO*, presented two small ATAC peaks common to healthy B cells with *de novo* acetylation marks in MM patient samples. The oligonucleotides used for the Reverse-ChIP were: CTTAAGCCCCAGGACATAAGAA and AGACTGGCTCACACGTAACA as forward (Fw) and reverse (Rv) primers, respectively, for the first peak; ATTGCACCTGGGATCCTGAA and GCCATCAACCAACCTATGCA as Fw and Rv, respectively, for the second peak; and ACGACCTTTTCCCCTGTTGT and CCATCTTTAAGCATCTCTGGGT as Fw and Rv, respectively, for the third peak. Chr: Chromatin; NBC: Naïve B cells; GCBC: Germinal center B cells; MBC: Memory B cells; PC: Plasma cells; MM: Multiple myeloma; **B**) qPCR of *SMILO* in different MM cell lines: the expression was analyzed in three MM cell lines (KMS-11, MM.1R, RPMI 8226) relative to the expression of *SMILO* in KMS-12-BM cell line.

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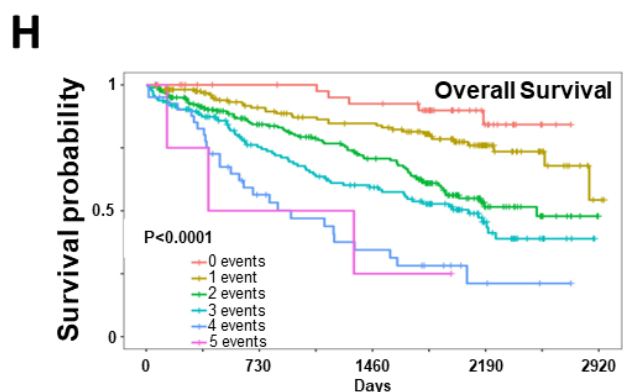
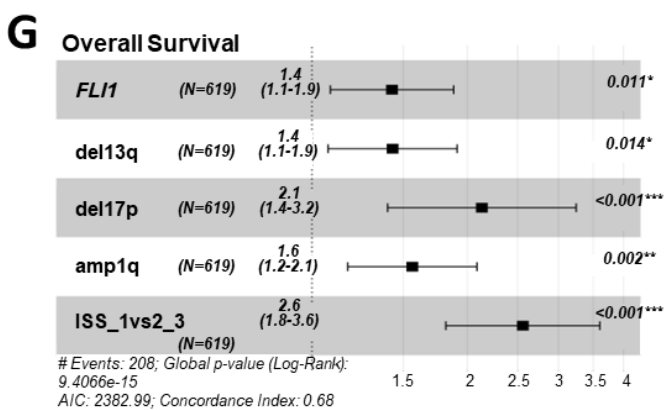
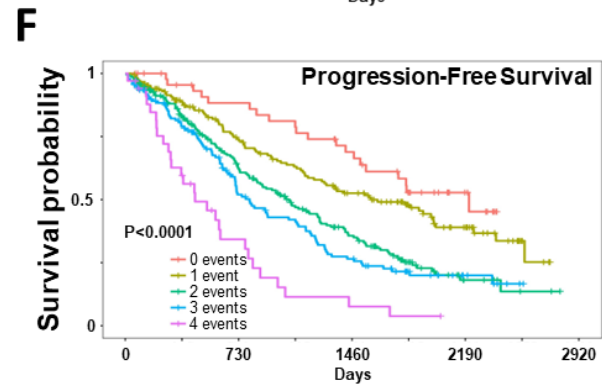
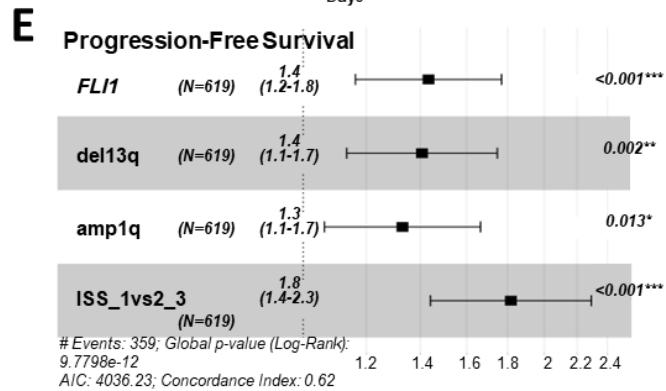
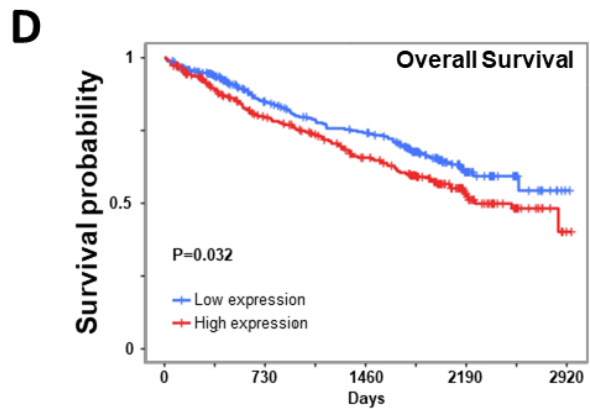
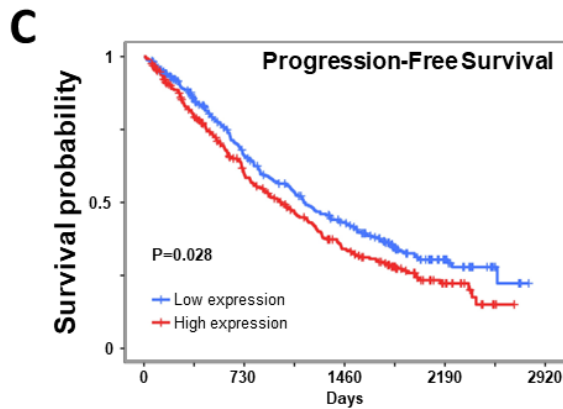
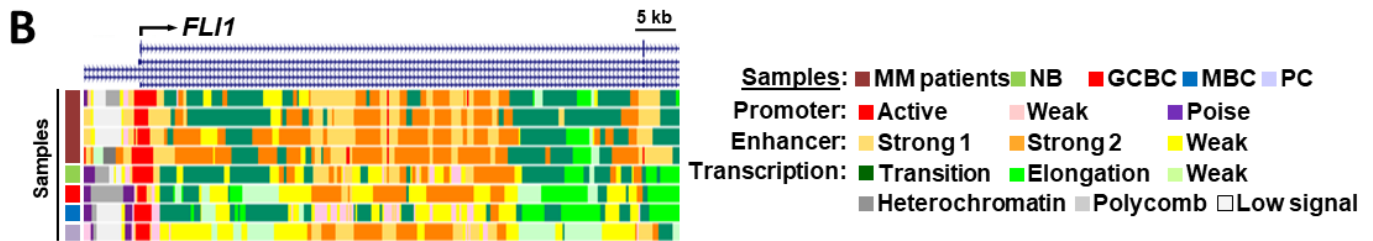
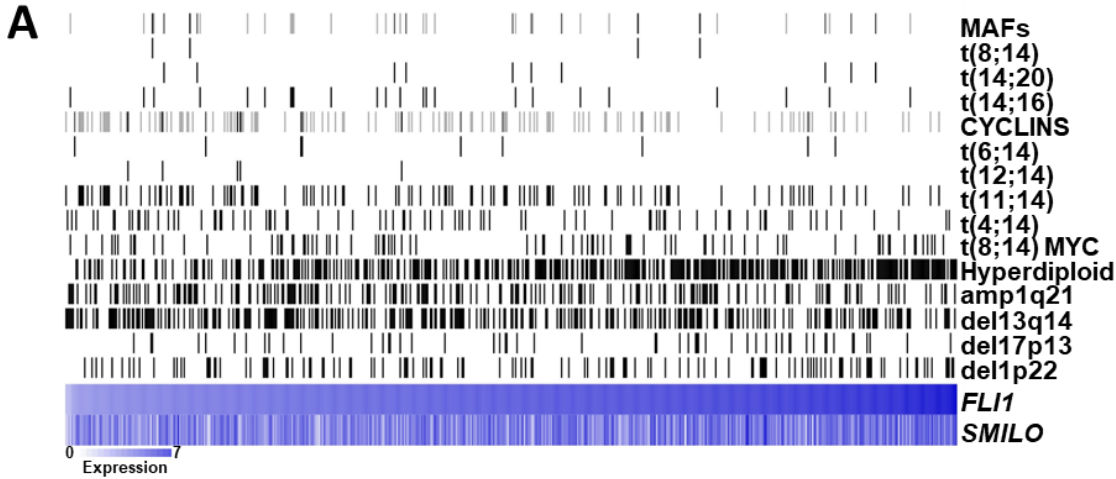


B



Supplementary figure S2. Reverse-chip protein candidate selection criteria. **A)** Gene expression of the 12 protein candidates that were not overexpressed in MM in comparison to healthy subpopulations of normal B cells. **B)** Expression correlation of the three candidate proteins with *SMIL0*. This analysis was performed using CoMMpass cohort

from MMRF (Multiple Myeloma Research Foundation). NB: Naïve B cells; CB: Centroblast B cells; CC: Centrocyte B cells; MBC: Memory B cells; TPC: Tonsillar plasma cells; BMPC: Bone marrow plasma cells; MM: Multiple myeloma; FPKM: Fragments Per Kilobase Million.



Supplementary figure S3. FLII regulate the expression of *SMILO*. **A)** Correlation of *FLII* and *SMILO* expression with classic genetic alterations of MM patients. This analysis was performed using CoMMpass cohort (IA18) from MMRF (Multiple Myeloma Research Foundation). **B)** Chromatin states of *FLII* gene in B cell differentiation and MM patient samples. **C)** Univariate analyses of the Progression Free Survival (PFS) of the MM patients from CoMMpass cohort IA18 (619 MM patients) considering the expression of *FLII*. **D)** Univariate analyses of the Overall Survival (OS) of the MM patients from CoMMpass cohort considering the expression of *FLII*. **E)** Forest plot of the multivariate analysis representing the Progression Free Survival (PFS) in MM patients considering high expression of *FLII* and classic high-risk genetic alterations in MM ((del(1p), amp(1q), del(17p), del(13q), hypodiploidy, mutations of TP53, t(4;14), t(11;14), t(12;14), t(6;14), t(8;14), t(14;16), and t(14;20)) and ISS stage). **F)** Kaplan-Meier curves showing the PFS of patients with MM considering expression of *FLII* and different high-risk alterations in a multivariate analysis. **G)** Forest plot of the multivariate analysis representing the Overall Survival (OS) in MM patients considering *FLII* high expression and classic high-risk genetic alterations in MM. **H)** Kaplan-Meier curves showing the OS of patients with MM considering expression of *FLII* and different high-risk alterations in a multivariate analysis. NB: Naïve B cells; GCBC: Germinal center B cells; MBC: Memory B cells; PC: Plasma cells; MM: Multiple myeloma.