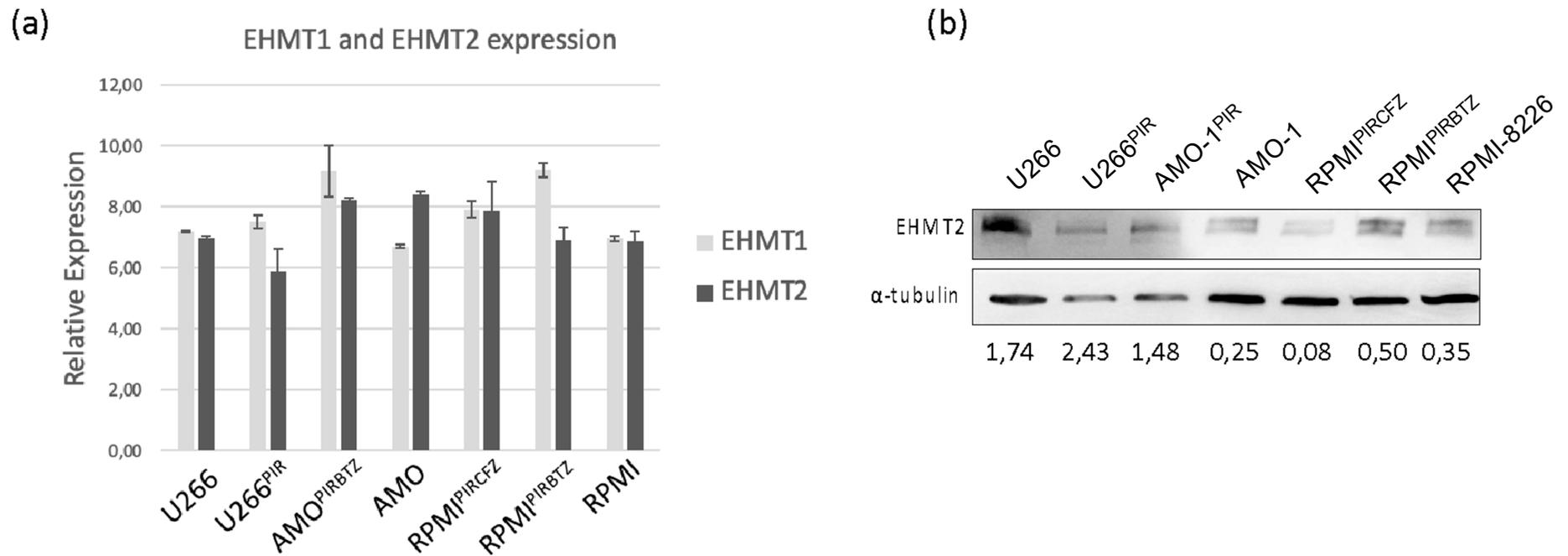
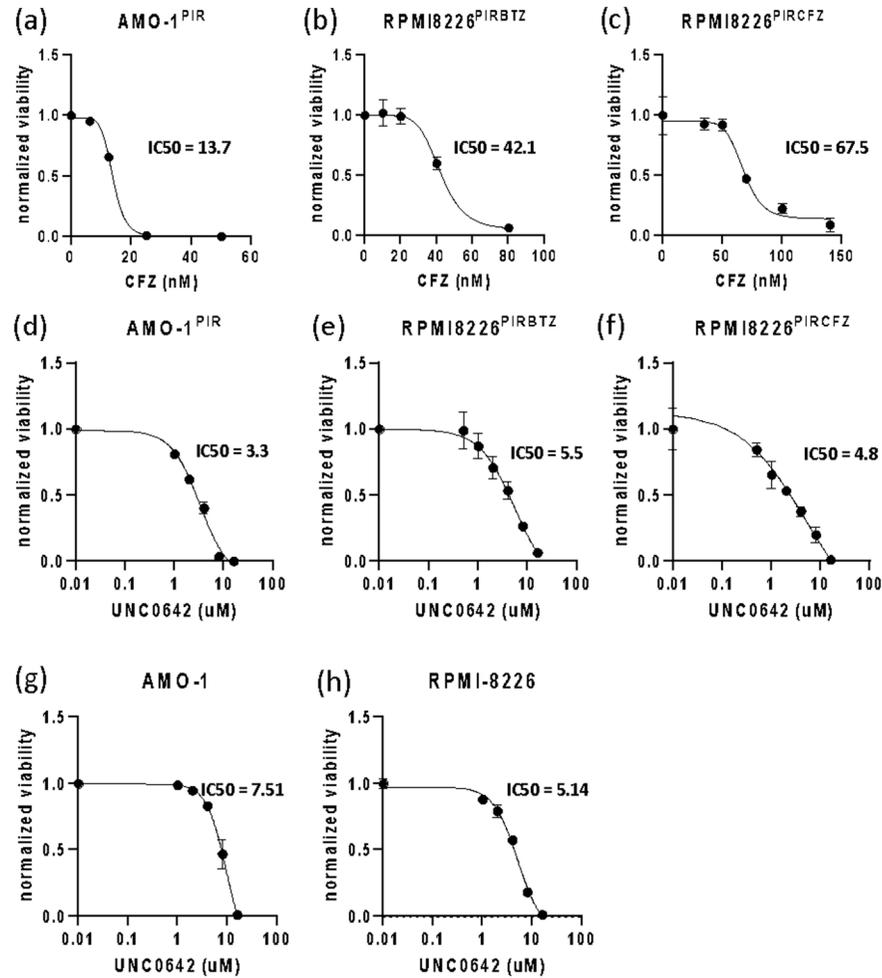


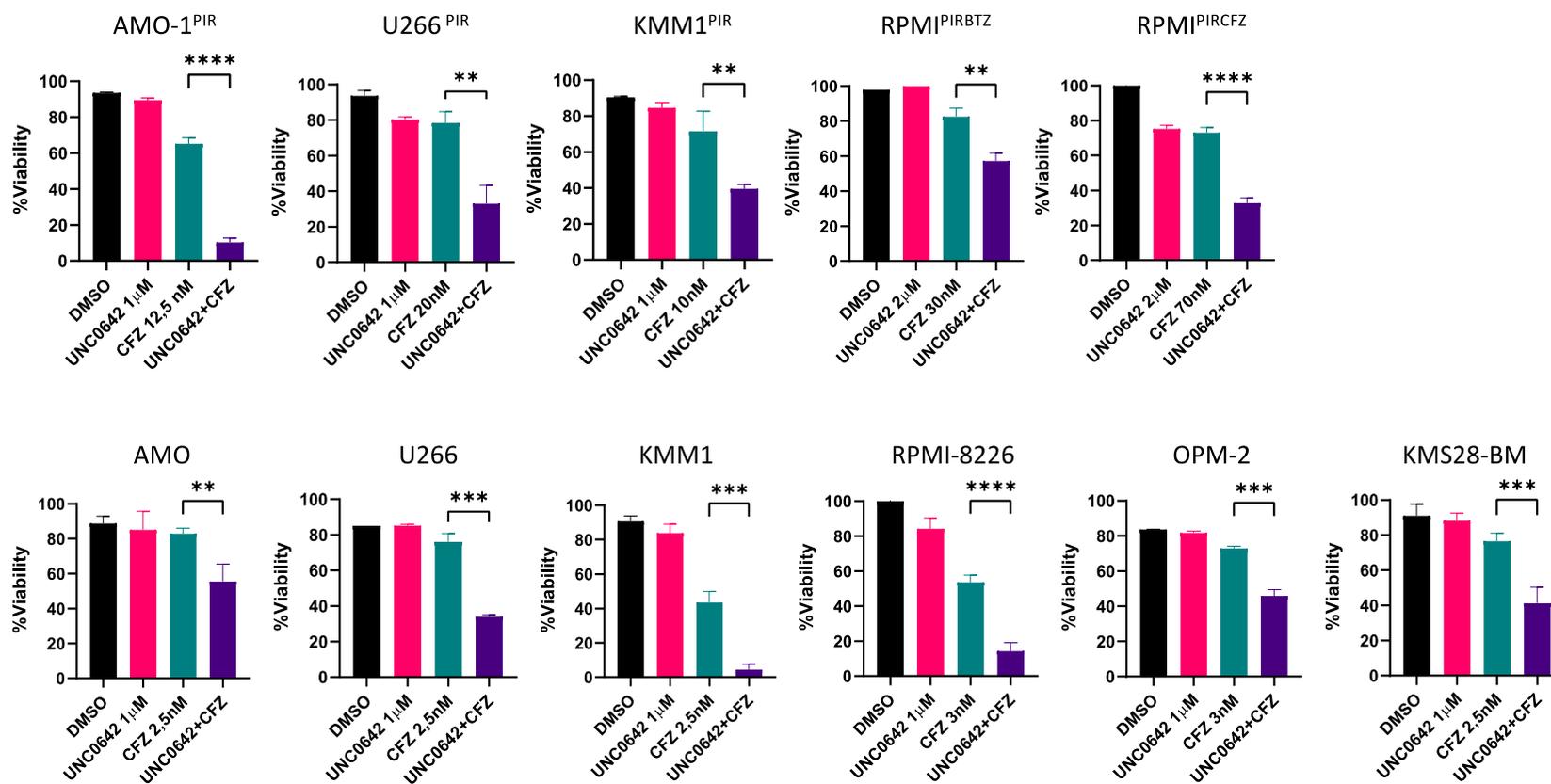
**Figure S1.** Roles of EHMT2 in cancer. EHMT2 interaction with co-repressors, such as HDAC, promotes histone methylation, recruitment of DNMTs and overall gene repression. Interaction with co-activators such as p300 and CARM1 stimulates recruitment of the mediators and overall gene activation. EHMT2 is capable of non-histone proteins methylation, an important post-translational modification that can regulate activity and degradation of proteins such as p53 and ATG-12.



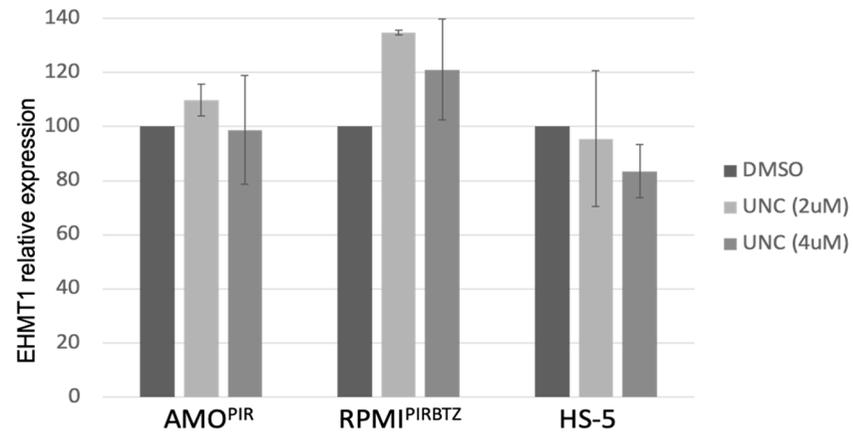
**Figure S2.** EHMT1/2 expression in MM cell lines. (a) RT-qPCR analysis of EHMT1 and EHMT2 expression in the indicated MM cell lines. Results are normalized to GAPDH expression. Shown are means of three technical replicates; error bars represent standard deviation (SD). (b) WB analysis of EHMT2 expression in the indicated MM cell lines and relative band quantification (EHMT2/ $\alpha$ -Tubulin)



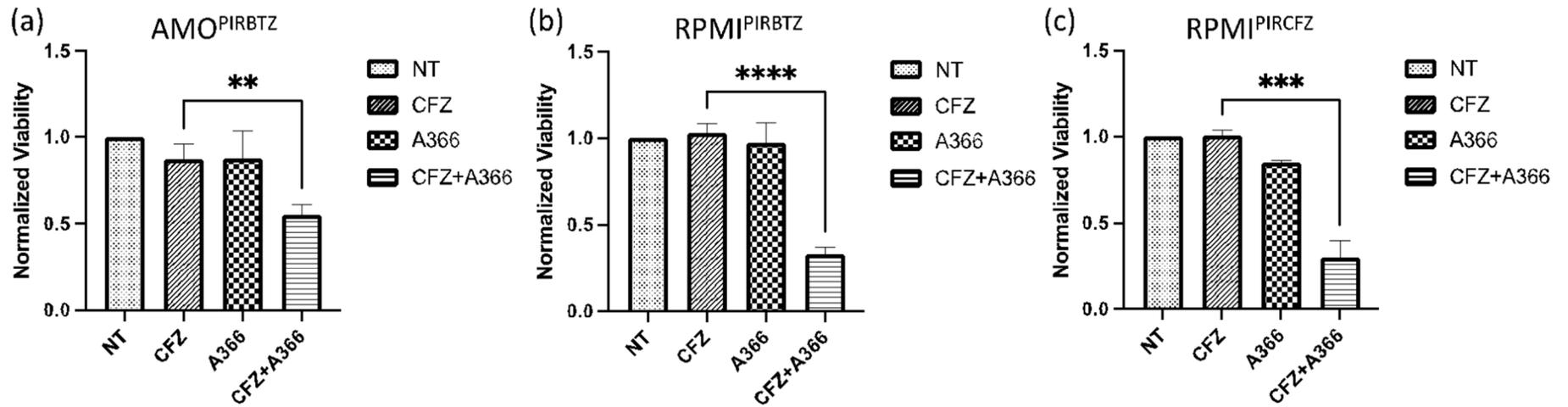
**Figure S3.** MM cells treated with different doses of CFZ (a-c) or UNC0642 (d-h). Viability was detected using cell growth luminescence assay 72h post treatment, error bars represent standard deviation (n=3).



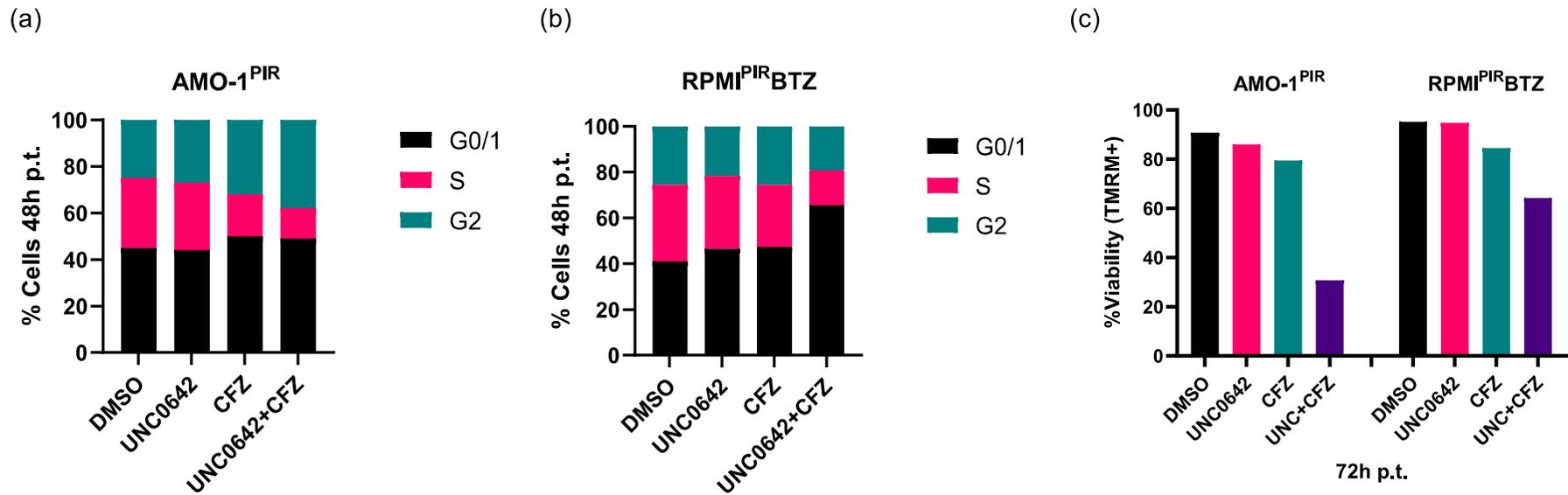
**Figure S4.** MM cells were treated with different dose of CFZ and UNC0642. Data are the mean of three independent experiments, error bars represent standard deviation. Analysis performed 72h post-treatment with FACS or CellTiterGlo assay (n=3).



**Figure S5.** EHMT1 expression in AMO-1<sup>PIR</sup>, RPMI<sup>PIRBTZ</sup>, and HS-5, 24h post UNC0642 treatment. Data were normalized on DMSO control, error bars represent standard deviation (n=3).



**Figure S6.** MM cells were treated with CFZ (RPMI<sup>PIRBTZ</sup> and RPMI<sup>PIRCFZ</sup> CFZ dose: 40nM, AMO<sup>PIRBTZ</sup> CFZ dose: 20nM), A366 (30uM) and the combination of both. Cell Viability was assessed with cell growth luminescence assay 72h (RPMI<sup>PIRCFZ</sup>) or 96h (RPMI<sup>PIRBTZ</sup> and AMO<sup>PIRBTZ</sup>) post treatment. Shown are means of three replicates; error bars represent standard deviation



**Figure S7.** UNC0642/CFZ synergistic interaction is not dependent on cell cycle perturbation. Cell cycle analysis of (a) AMO-1PIR and (b) RPMIPIRBTZ cells 48h post-treatment with the indicated drugs. (c) Cell viability analysis with TMRM staining 72h post-treatment confirmed that AMO-1PIR cells are more sensitive to UNC0642/CFZ combination as compared to RPMIPIRBTZ cells. Drugs doses: 12,5nM CFZ, 1uM UNC0642 (AMO-1<sup>PIR</sup>), 30nM CFZ, 2uM UNC0642 (RPMI8226<sup>PIRBTZ</sup>)