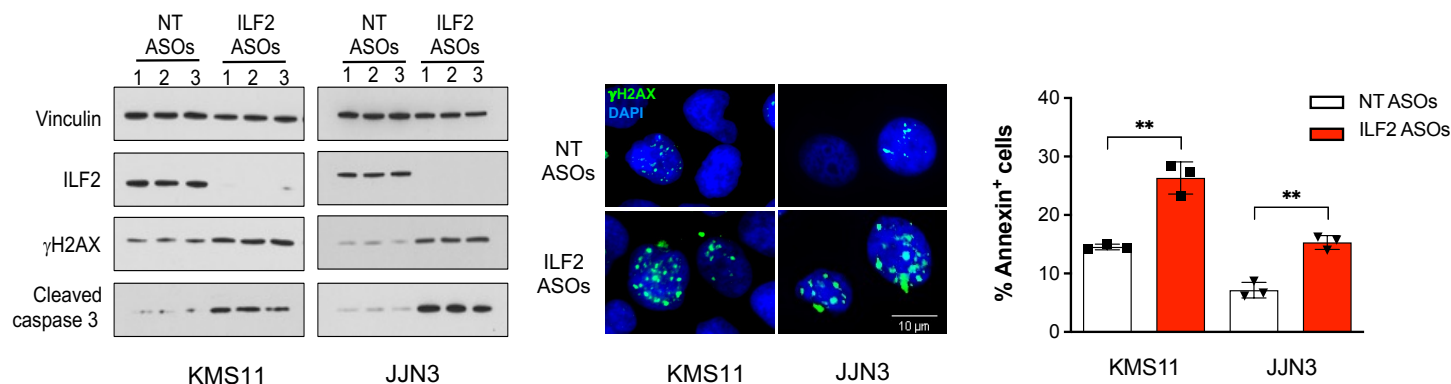


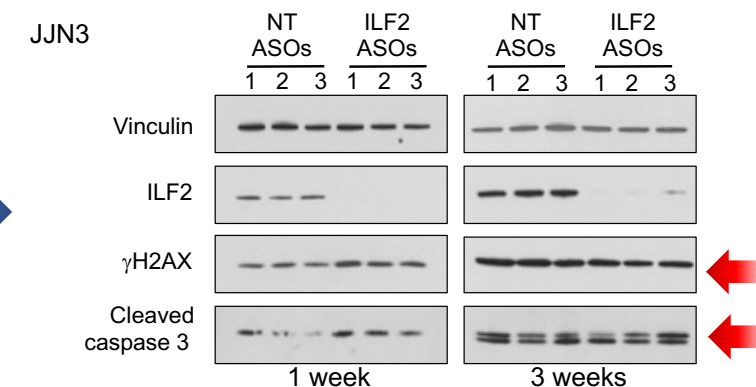
Targeting DNA2 Overcomes Metabolic Reprogramming in 1q21 Multiple Myeloma

Antisense therapy targeting ILF2 (ILF2 ASOs) induces DNA damage in 1q21 MM cells.



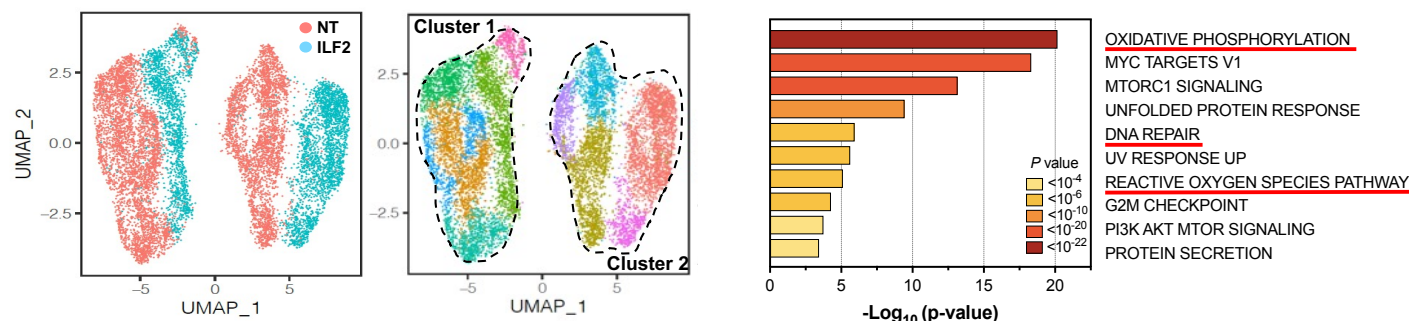
Western blot (left), immunofluorescence (middle), and apoptosis (right) analyses in KMS11 and JJN3 cells treated with non-targeting (NT) or ILF2 ASOs for 1 week.

MM cells can overcome ILF2 ASO-induced DNA damage.



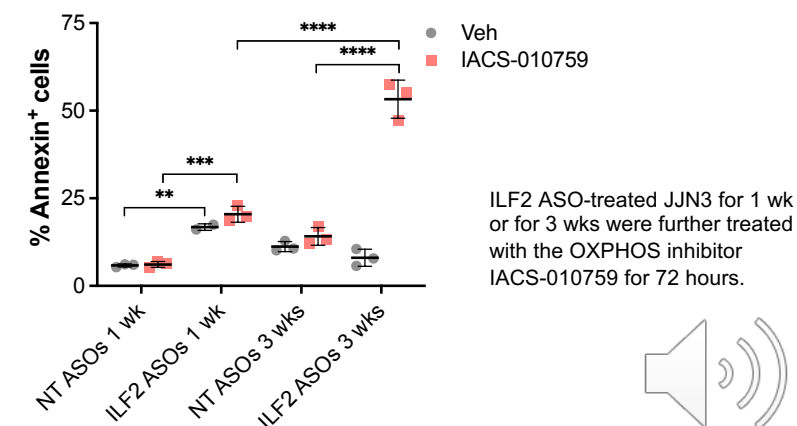
Aim #1: To dissect the molecular mechanisms by which MM cells overcome ILF2 ASO-induced DNA damage

- Resistance to ILF2 ASOs is not induced by clonal selection (scRNA-seq)
- ILF2 ASO-resistant MM cells undergo metabolic switch and are dependent on oxidative phosphorylation to maintain survival (scRNA-seq and metabolomic analysis)



Single cell RNA-seq and metabolomic analysis were performed in JJN3 treated with NT or ILF2 ASOs for 3 weeks.

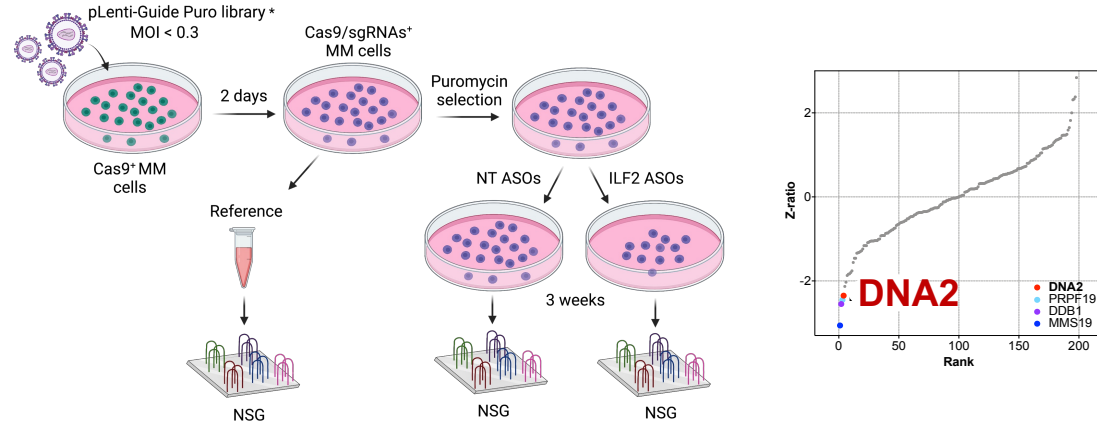
OXPHOS mediates MM resistance to ILF2 ASOs.



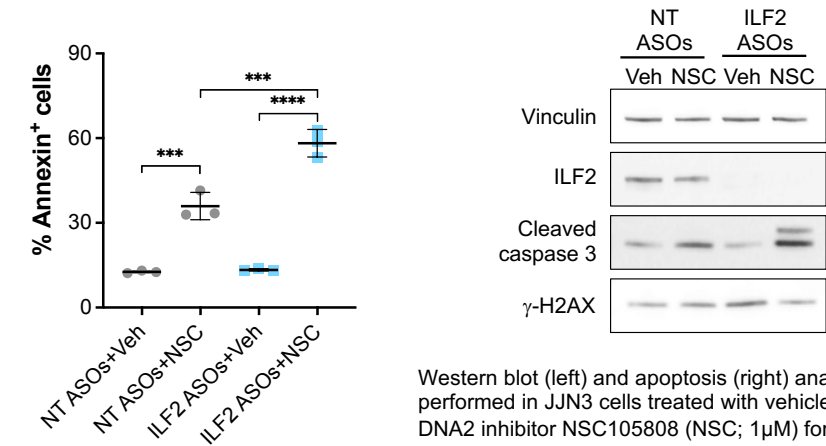
ILF2 ASO-treated JJN3 for 1 wk or for 3 wks were further treated with the OXPHOS inhibitor IACS-010759 for 72 hours.



CRISPR/Cas9-based screening to identify DNA repair effectors whose loss of function suppresses MM cells' resistance to ILF2 ASO-induced DNA damage

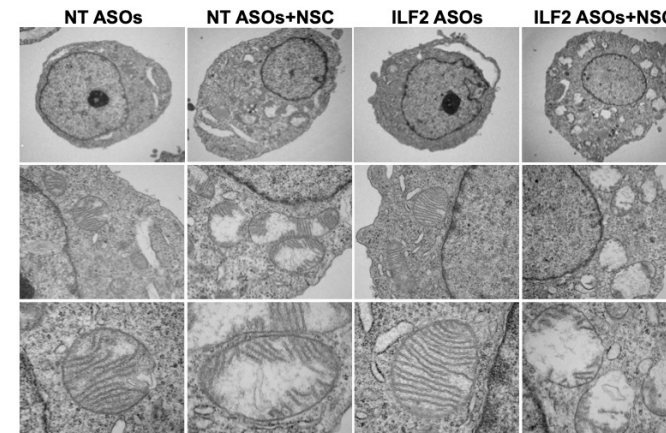
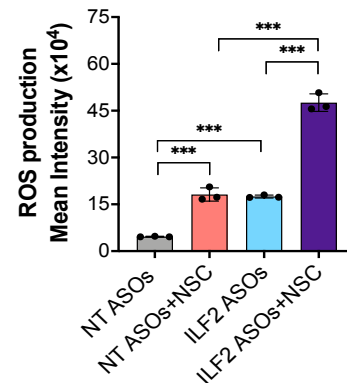
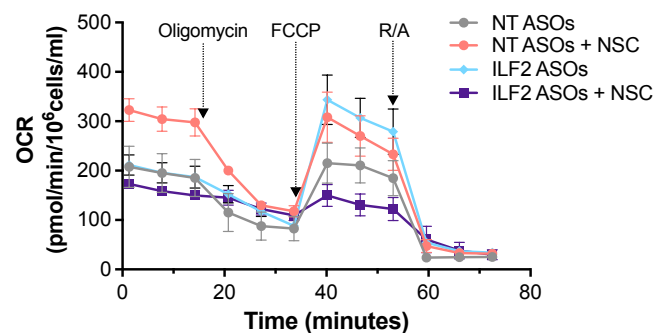


Targeting DNA2 enhances ILF2 ASO-induced apoptosis in JJN3 cells.



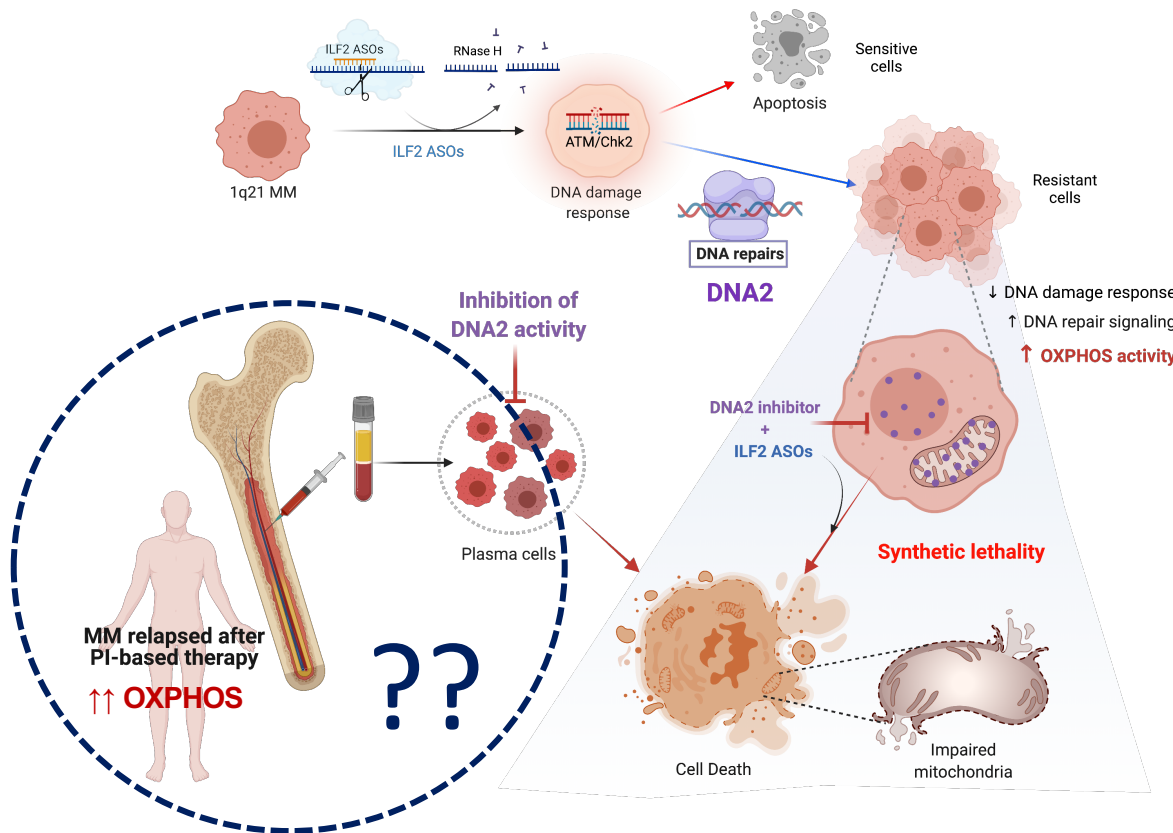
Aim #2: To dissect the mechanisms of DNA2 inhibition-induced synthetic lethality in MM cells undergoing metabolic reprogramming in the context of ILF2 depletion

DNA2 inhibition decreases the oxygen consumption rate and increases ROS production in ILF2-depleted cells.



Seahorse experiments (left) were performed in JJN3 cells treated with ASOs for 7 days prior to receiving NSC for 72 hours. Quantification of ROS production (middle) and transmission electron microscopy (right) were performed in JJN3 cells treated with ASOs for 7 days prior to receiving NSC for 48 hours.

Working model & Conclusion



- ✓ DNA2 is essential to maintain oxidative phosphorylation and metabolic reprogramming in MM cells.
- ✓ DNA2 inhibition is a synthetic lethal approach to targeting 1q21 MM cells in the setting of ILF2 depletion-induced DNA damage.

Future direction

- To evaluate whether inhibition of DNA2 activity is synthetically lethal in MM plasma cells from patients whose disease failed previous therapies, such as therapy with proteasome inhibitors.

