**BACKGROUND**

The SWI/SNF chromatin remodeling complex is a central regulator of nucleosome positioning. ARID1A encodes BAF250, a subunit of the human SWI/SNF complex.

ARID1A is the 4th most commonly mutated gene overall, and the most commonly mutated epigenetic gene in bladder cancer. Inactivating ARID1A mutations occur in up to 30% of metastatic bladder cancers.

ARID1A mutations are associated with poorer prognosis and decreased response to standard-of-care chemotherapy. Previous studies have shown that ARID1A mutated (ARID1Amut) ovarian cancer cells are sensitized to treatment with bromodomain and extraterminal (BET) protein inhibitors.

Using the EpiDQ Diamond compound library, we also previously determined that BET protein inhibitors also potently inhibited the viability of ARID1A wild-type (ARID1AWT) 5637 and J82 bladder cancer cell lines.

**OBJECTIVE**

To test the overall hypothesis that ARID1Amut bladder cancer cells are even more potently sensitized to the pan-BET inhibitor OTX-015 (birabresib) than ARID1AWT bladder cancer cells.

**METHODS**

- ARID1AWT 5637 cells and ARID1Amut HT1197 cells were treated with OTX-015 to assess cell viability.
- Cells were treated with eight ascending concentrations of OTX-015 (0.1 nM – 100 µM) and incubated for 72-120 h. Cell viability was assessed by Cell-TiterGlo (Promega, Madison WI).
- IC50 values were calculated using a four-parameter non-linear regression model using GraphPad Prism 9 (Prism, San Diego CA).
- All data were normalized to a GAPDH was used as a loading control.

**RESULTS**

OTX-015 8-times more potently inhibited viability in ARID1AWT HT1197 cells than ARID1Amut 5637 cells after 120 h incubation.

OTX-015 (1 µM) significantly reduced ARID1B mRNA expression in ARID1Amut cells vs. ARID1AWT cells (83% vs. 82%, P=0.02) at 48 h.

OTX-015 (1 µM) significantly reduced RAD51 mRNA expression in ARID1Amut cells vs. ARID1AWT cells (86% vs. 57%, P=0.001) at 48 h.

Unexpectedly, OTX-015 (1 µM) did not significantly reduce MYC gene expression after 25% reduction, P=0.31) in ARID1Amut cells, but was reduced in ARID1AWT cells (57% reduction, P=0.0001) at 48 h.

OTX-015 (1 µM) resulted in more dramatic protein expression reductions in c-MYC and BAF250B after 72 h in ARID1AWT HT1197 cells than 5637 ARID1Amut cells.

OTX-015 (1 µM) significantly reduced expression of all other SWI/SNF genes assessed in ARID1AWT HT1197 cells but did not significantly reduce any targets in ARID1Amut 5637 cells.

OTX-015 (5 µM) resulted in reduced BAF57 protein expression in both cell lines after 48 h incubation.

Transfection of ARID1Amut 5637 cells with an ARID1A-targeting siRNA significantly reduced ARID1A gene and BAF250A and BAF250B protein expression but unexpectedly, significantly increased ARID1B gene expression (118% increased, P=0.003).

Conclusions: These preliminary results support future lines of inquiry into the molecular mechanisms that underlie sensitization of ARID1Amut cells to BET protein inhibition. Ongoing efforts characterizing gene and protein expression after exposure to OTX-015 may reveal compensatory mechanisms of SWI/SNF function after ARID1A mutation and loss.

**DISCUSSION AND CONCLUSIONS**

None of the authors of this presentation have any disclosures concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

**REFERENCES**

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**FUTURE DIRECTIONS**

Figure made with BioRender.com

**AUTHOR DISCLOSURES**

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