NOVEL INHIBITORS OF THE LUMINAL LINEAGE TRANSCRIPTION FACTOR PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA (PPARG) DURABLY ERADICATE TUMORS IN UROTHELIAL CANCER (UC) ANIMAL MODELS

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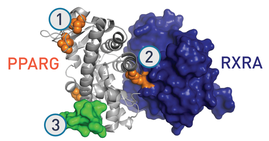
Poster 084

FLARE THERAPEUTICS

BACKGROUND

- PPARG is a lineage determining transcription factor in the luminal urothelium.
- Two-thirds of advanced UC is classified as luminal and overexpression of PPARG is characteristic of this molecular subtype.
- Currently, there is a poor understanding of how recurrent missense mutations in PPARG and its obligate heterodimer retinoid X receptor alpha (RXRA) impact PPARG function; previous tool compounds (i.e., SR10221 and T907)[1,2] designed to inhibit PPARG have minimal phenotypic activity in UC cell lines.

FIGURE 1. PPARG-RXRA Mutations Are Distributed Across the Complex



1. Ligand Binding Pocket
2. Dimer Interface
3. Co-Activator Site

No Consensus in Field on Role of Mutations

FTX-6746 Biochemical and Cellular PD Data	
Wild Type Biochemical Assay IC_{50} (nM) (% max response)	707 (170)
5637 Wild Type Cell PD Assay IC_{50} (nM)	1.9
Mutant Biochemical Assay IC_{50} (nM) (% max response)	200 (170)
HT1197 RXRA Mutant Cell PD Assay IC_{50} (nM)	1.4

FIGURE 2. Recurrent UC Missense Mutations Cause Altered Conformations of PPARG

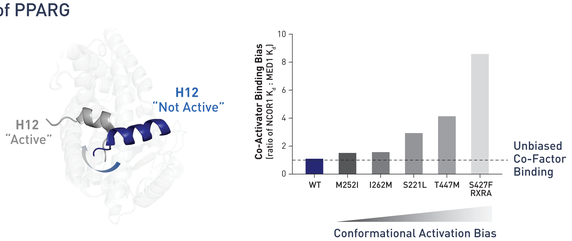


FIGURE 3. Driving an Enhanced Repressive Conformation to Overcome UC Mutations

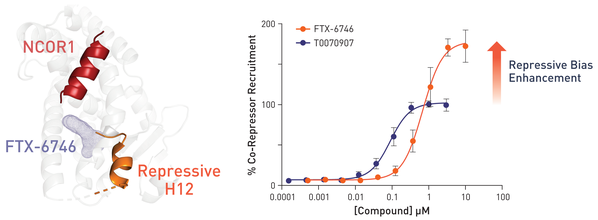


FIGURE 4. Highly Selective Engagement of PPARG by FTX-6746

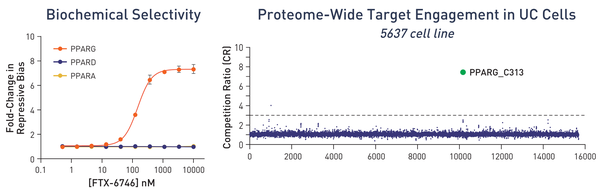
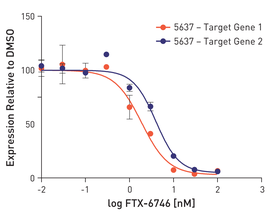


FIGURE 5. Potent PPARG Target Gene Suppression in UC Cell Lines



Cell Line	Target Gene 1 (IC_{50}, nM)	Target Gene 2 (IC_{50}, nM)
5637	1.9	4.3
HT1197	5.2	8.3
UMUC9	6.2	6.3

FIGURE 6. The Extent of Conformational Bias Predicts Phenotypic Response

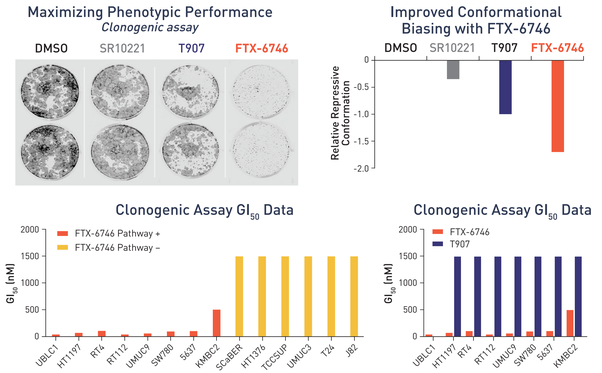


FIGURE 7. FTX-6746 Suppresses PPARG Target Genes in UC Xenograft Models

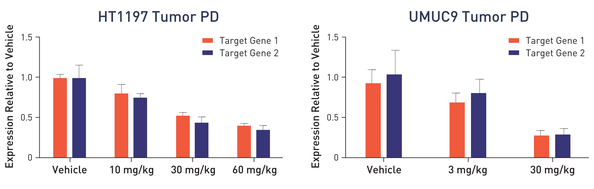


FIGURE 8. FTX-6746 Robustly Suppresses Tumor Growth in PPARG Amplified UMUC9 UC Xenograft Model

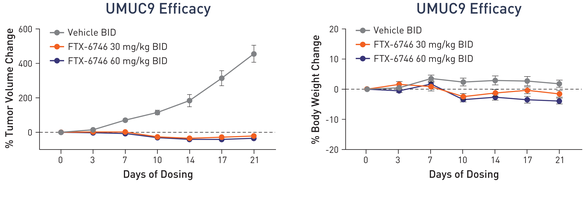
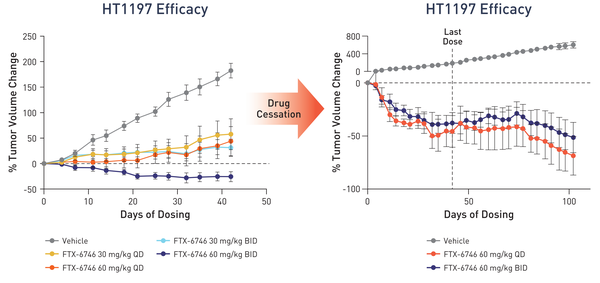


FIGURE 9. FTX-6746 Robustly and Durably Suppresses Tumor Growth in RXRA Mutant HT1197 UC Xenograft Model



SUMMARY/CONCLUSION

- Biochemical studies indicate that patient-derived missense mutations in PPARG and RXRA bias an active conformation of PPARG, mimicking an agonist-bound state.
- Addressing the limitations of previous tool compounds, we discovered novel inverse agonists that drive a powerful repressive conformation of PPARG with high specificity (>100X selective over PPARA/PPARD).
- FTX-6746 treatment results in robust PPARG target gene silencing in cells (average IC_{50} = ~5 nM), and in vitro growth inhibition is preferentially observed in cell lines with activated PPARG signaling.
- Tumor growth inhibition or regression was observed in two PPARG activated UC xenograft models at well-tolerated oral doses with no tumor regrowth upon cessation of treatment.
- These data suggest inhibition of PPARG in luminal urothelial cancer patients will be an effective therapy and supports stratification of advanced UC patients based upon PPARG status as a defining feature of the luminal phenotype (see Abstract 333, Poster 113).

References

1. Marciano et al, *Nat Commun* 2015.
2. Lee et al, J *Biol Chem* 2002.

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Abstract 94, Poster 084

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Abstract 333, Poster 113