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THERAPEUTIC APPLICATIONS OF SAMMSON LNCRNA INHIBITION IN UVEAL MELANOMA

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Uveal melanoma is the most common intraocular malignancy in adults. The lack of an effective treatment results in a median survival time less than one year for patients with metastatic disease. Recently, our lab identified the melanoma-specific long non-coding RNA (lncRNA) SAMMSON as a novel therapeutic target in skin melanoma.

Analysis of a PAN cancer RNA-sequencing dataset revealed consistent expression of SAMMSON in uveal melanoma tumors. Although SAMMSON expression was lower in uveal compared to skin melanoma, over 90% of uveal melanoma tumors showed detectable SAMMSON expression. Further analysis also revealed SAMMSON expression in conjunctival melanoma, another form of ocular melanoma. To evaluate the therapeutic potential of SAMMSON inhibition in uveal and conjunctival melanoma, we treated 8 representative cell lines with SAMMSON-specific ASOs and observed a strong reduction in cell viability, accompanied by induction of apoptosis. In line with the role of SAMMSON in modulating mitochondrial metabolism, SAMMSON knock down resulted in decreased mitochondrial oxygen consumption.

Uveal melanomas are characterized by activated MEK-signaling through mutations in GNA11/GNAQ. Combining SAMMSON-specific ASOs with the MEK-inhibitor Trametinib, induced strong synergistic effects, resulting in a nearly complete abrogation of tumor cells at nanomolar concentrations of Trametinib. The in vivo effects of SAMMSON inhibition, whether or not in combination with Trametinib, are currently being investigated in a uveal melanoma PDX model.

Together, our results demonstrate the efficacy of SAMMSON inhibition as a novel treatment option for uveal melanoma and demonstrate its synergism with MEK inhibition making SAMMSON a promising anti-cancer target for uveal melanoma patients.