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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.