**Background**

- MYC is a master transcription factor (TF) critical for multiple cell physiologies.
- As a pleiotropic TF, MYC regulates the tumor microenvironment (TME) and impacts cancer cell initiation, growth, and survival.
- Although MYC expression is normally tightly controlled in normal cells, dysregulated MYC expression is a driver of oncogenic transformation in multiple tumor types. (e.g., HCC, NSCLC, Burkitt’s lymphoma).
- A direct MYC-targeting anti-cancer agent has remained elusive, largely due to the absence of a well-defined drug binding pocket and tight autoregulation.
- The MYC gene resides alone with its regulatory elements within an insulated genomic domain (IGD) and represents a potential therapeutic target for pre-transcriptional gene modulation via an epigenetic approach for the treatment of multiple cancers including HCC.
- We are developing programmable epigenomic mRNA designs to controllably tune gene expression, pre-transcriptionally, with defined durability with high specificity by targeting IGDs and regulatory elements within it.
- We have rationally designed Omega Epigenetic Controllers (MYC-OEC): clinical candidate OTX-002: development candidate MYC Lung OEC; and mouse sequence surrogate muMYC OEC) to downregulate MYC expression, thereby selectively killing cancer cells while sparing normal cells.
- We investigated the role of MYC-OECs in the modulation of the TME and enhanced antitumor activity of checkpoint blockade inhibitors (CBI) in vivo.

**Figure 1. Structure and Mechanism of Action of OECs**

**Omega Epigenetic Controller (OEC)**

**Mouse (mu)MYC OEC Decreases MYC mRNA and Protein and the Viability of Mouse Liver Cancer Cells**

**Figure 2. In vitro results in Hepa1-6 mouse liver cancer cells. Hepa1-6 mouse liver cancer cells were treated with muMYC OEC or control. The Hepa1-6 mouse liver cancer cell line was isolated from Hepa1-6 tumors treated with muMYC OEC in vivo.**

**Figure 3. OECs reduce interferon γ-induced surface expression of PD-L1 in HCC and NSCLC cell lines.**

**muMYC OEC Reduce Interferon γ-induced Surface Expression of PD-L1 in HCC and NSCLC Cell Lines**

**muMYC OEC Alone or in Combination With CBI Confers Immune Memory**

**Immune Cell Depletion Shows muMYC OEC Single Agent is Partially Driven Through Adaptive But Not Innate Immunity**

**Figure 4. muMYC OEC combination with checkpoint blockade inhibitors in Hepa1-6 syngeneic mouse model.**

**Figure 5. Combination of muMYC OEC and anti-PD1 in Hepa1-6 syngeneic mouse model of HCC to assess limiting immune cell subsets to the tumor microenvironment using flow cytometry.**

**Conclusions**

- MYC OECs downregulate MYC expression in HCC cells resulting in the loss of viability of MYC-addicted cancer cells.
- MYC OECs downregulate expression of PD-L1 protein on the surface of tumor cells.
- MYC OECs in combination with CBI (anti-PD-1 or anti-PD-L1) significantly reduce HCC xenograft tumor growth compared to either single agent alone at well-tolerated doses.
- Antitumor activity of MYC OECs is partially driven through an adaptive immune response (T-cells).
- MYC OECs as a single agent or in combination with CBI represses inhibitory Tregs to more effectively entrain the adaptive immune system to inhibit HCC tumors.

**Contact Information**

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**Effect of MYC-Targeting Programmable Epigenomic mRNA Therapeutics on TME and Immunotherapy Responses**


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