Background

Cancer immunotherapy has made significant advancements in revolutionizing cancer treatment, but the presence of T regulatory (Treg) cells within tumors presents a major hurdle. These cells can suppress the activation of effector immune cells induced by the immunotherapy, thus hindering the desired anti-tumor response. Specific depletion of tumor Tregs is proven to be an efficient strategy to improve efficacy of anti-PD-1/PD-L1 therapies.

Methods

mRNA-based combinatorial therapy options have evolved by recent advancements in the production, purification, and delivery of mRNA to cells. Today, mRNA therapies are a rapidly growing class of medications that can redefine how many diseases are treated. These therapies enable the production of biologics directly in the patient and mRNA LNPs are straightforward to manufacture at scale. Despite these key advantages, mRNA therapeutics are yet to show their true potential in oncology. Dose limiting toxicities of mRNA immunotherapies are driven, in part, by systemic payload (encoded protein) toxicity, which can be avoided by engineering the mRNA to improve its onco-selectivity and thereby reduce systemic target-mediated adverse events. To address that challenge, Kernal Biologics has developed onco-selective mRNA LNP therapies (KR-505) using a machine learning-enabled computational pipeline, targeting Treg cells within the immunosuppressive tumor microenvironment.

Results

In preclinical studies using a syngeneic tumor model (C57BL6/MC38), KR-505 demonstrated strong anti-tumor efficacy, leading to tumor regression, complete responses, and improved overall survival. These mRNA LNPs (lipid nanoparticles) were well-tolerated, promoting anti-tumor immune activation and modulating the tumor microenvironment. Furthermore, combination treatment with anti-PD-1 therapies showed even better efficacy. Notably, treatment with KR-505, but not the inactive drug analog, led to a significant reduction in Treg cell numbers within the tumors. Reimplantation of complete responders resulted in no tumor growth, indicating the development of anti-tumor immunity.

Conclusions

Our findings support the feasibility of onco-selective mRNA combination therapy as a potential solution for cancers characterized by an immunosuppressive tumor microenvironment and can help broaden the number of patients who can benefit from anti-PD-1 treatment.

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