1113 PAYLOAD SCREENING IDENTIFIES ENHANCED T CELL RESPONSIVENESS AIMED FOR CIRCADE, A CIRCULAR RNA DELIVERY SYSTEM, TOWARDS TREATMENT OF SOLID TUMORS

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Background We have previously demonstrated successful delivery of a granulocyte-macrophage colony-stimulating factor (GM-CSF) payload to solid tumors through the adenoviral vector ONCOS-102, resulting in robust clinical benefit hallmarked by increased T-cell infiltration and activation of immune-related genetic pathways (e.g., cytotoxicity and co-stimulatory gene ontologies). Persistence of ONCOS-102 and durability of GM-CSF expression in tumor biopsies correlated with positive clinical outcomes, suggesting that repeat dosing and extended payload expression may further improve the therapeutic benefit. Therefore, we have performed a screen aiming to identify an optimized payload combination for use in our proprietary vector system circAde, a circular RNA (circRNA)-based platform for enhanced and durable protein expression in solid tumors.

Methods In this screening, we co-cultured peripheral blood mononuclear cells from healthy donors with tumor cells transiently expressing an mRNA-encoded payload in the presence of a tumor cell-specific T-cell engager to study payload effects on T cell responsiveness.

Results We identified a potent combination of the T-cell-engager with a co-stimulatory payload, which was able to expand and enhance activation and functionality of T-cells. Both CD4+ and CD8+ T-cell subsets responded with increased proportion of proliferating cells, as well as expression of surface markers associated with activation and expression of functionally important molecules. Proliferation of CD8 + T-cells exceeded that of CD4+ T-cells by 5 to 10 -fold, both in terms of proportion of proliferating cells and the maximal number of cell divisions observed.

Conclusions Continued screening and characterization of additional immunostimulatory payloads are ongoing, with the aim to further strengthen the results generated using mRNA-encoded constructs by introducing circRNA-encoded payloads to demonstrate the potency of the circAde platform. By deploying a circRNA-based expression system for these payloads, we aim to achieve a more durable payload expression, which is expected to further potentiate and extend the anti-tumor immune response.

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