



2022 Jawsome Shark Tank – Multidisciplinary Pilot Project Program

Developing dual specificity anti-ROR1 plus anti-Trop2 CARTs for targeting metastatic prostate and lung cancer

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Scientific Abstract:

Prostate and lung cancer are both heterogeneous tumors which can present as adenocarcinoma and/or small cell or neuroendocrine cancers. Therefore, novel treatments and treatment combinations need to target combinations of pathways. We propose to produce a new cell-based immunotherapy - a dual targeting CART cell - for the treatment of advanced cancers. The CART cells will target the fetal oncoprotein, ROR1, a non-canonical WNT5A receptor which is expressed on metastatic prostate and lung cancers, using the antibody therapeutic, Zilovertamab. The second target will be Trop2 which is expressed on sub-types in both these cancers. Trop2 has an FDA approved therapeutic antibody. This pre-clinical study will determine if dual-targeting ROR1+Trop2 CARTs are effective against prostate and lung cancers.

HYPOTHESIS: ROR1 and Trop2 expression on advanced metastatic prostate and lung cancer cells may impart cancer stem cell/tumor initiating properties and neuroendocrine features leading to cancer recurrence and resistance to standard-of care (SOC). In this proposal, we will test the hypothesis that a zilovertamab-based anti- ROR1+ anti-Trop2 dual targeting CAR T-cell will have the capacity to eradicate these lethal prostate and lung tumor cells *in vitro* and *in vivo* in pre-clinical tumor cell line and PDX model systems.

AIM 1. Develop next generation, dual targeting human Zilovertamab-based anti-ROR1+anti-Trop2 CAR-T cells to advance novel CAR-T cells against metastatic prostate and lung cancer. Test against human cell line and patient-derived models *in vitro*; Compare activity to Anti-ROR1 or Anti-Trop CART alone.

AIM 2. Test anti-ROR+anti-Trop2 CAR-T cells *in vivo* in ROR1+ PCa cell lines, PC3 and DU145, in our ROR1+ PDX PCSD13 and in the ROR1+ lung cancer cell line xenografts HCC827, PC9 and H1975.

Lay Abstract:

Prostate and lung cancer are both heterogeneous tumors which can present as adenocarcinoma and/or small cell or neuroendocrine cancers. Therefore, novel treatments and treatment combinations need to target combinations of pathways. We propose to produce a new cell-based immunotherapy - a dual targeting CART cell - for the treatment of advanced cancers.

Transdisciplinary Aspects of this Project: This proposal will address MCC goals: 1. To develop treatments that improve outcomes for two lethal cancers and 2. to define the biology of cancer progression to lethal prostate and lung cancer to reduce death using a new immunotherapy strategy. This proposal is transdisciplinary because it brings together several fields and expertise of investigators in immunology,

prostate cancer, lung cancer, urology, genitourinary oncology and thoracic oncology to address the urgent need for therapy in two types of cancers: prostate and lung. Understanding and targeting the expression of both these markers in sub-sets of lung and prostate cancer may be informative about pan-cancer targeting.