H001 Treatment Results in AR:RIPTAC EP Teritary Complex Formation in VCaP Cells

H001 is Active in FLAR+ Prostate Cancer Cell Lines, Independent of Their Dependency on FL AR Signaling

H001 Demonstrates Superior Oral In Vivo Efficacy in Enzalutamide in an AR(A) - VT Castrate VCaP Model

H001 and not H002 is Active Against Castrate VCaP Tumors, Confirming RIPTAC MA in Viva

Background
Resistance to Androgen Receptor Signaling Inhibitors (AR-SIs) in prostate cancer occurs in almost all patients and is driven by many heterogeneous bypass resistance mechanisms including genomic and epigenomic changes in AR expression. In the metastatic castration-resistant (mCRPC) setting, more than 90% of patients harbor amplifications of the AR gene on the p-arm end of chromosome 8q, primarily due to translocations of 8q24, which harbor the AR gene. The death toll from prostate cancer in the USA is nearly 35,000/y, and median overall survival for metastatic castration-resistant prostate cancer is less than 2 years. There are currently urgent needs to tackle the disease, especially in its advanced, drug-resistant, and most lethal form.

Regulated Induced Proximity Targeting Chimeras or RIPTAC Therapeutics are a new class of Theranostic small molecules developed by Halda Therapeutics. RIPTAC Therapeutics recruit a tumor-specific targeting protein (TP) into a stable intravesicular complex, covalently linked to a protein essential for cell survival (Fig. 1). This results in tumor-specific abrogation of the essential protein (EP) function, and selective killing of cancer cells while sparing normal non-TP expressing cells. Applied to prostate cancer, our RIPTAC technology leverages selective AR expression to abrogate the function of an androgen-dependent gene.

Regulated Induced Proximity Targeting Chimeras (RIPTAC Therapeutic)

Cancer Selective Cell Death

Summary
We describe here H001, a novel orally bioavailable heterogeneous small molecular RIPTAC Therapeutic for prostate cancer. It recruits Androgen Receptor (AR) as the TP and an undisclosed Essential cellular Protein (EP) into a stable tertiary complex with AR (full length). Thereby abrogating the EP function and leading to cell death selectively in FLAR+ cells. H001 and denoted as an Androgen-Receptor-H001 (AR:RIPTAC) complex. In a randomized, Phase 2 clinical trial, in patients with castrate-resistant prostate cancer (HR=1.6, p=0.007).

H001 is Activated in Prostate Cancer Cells That Exhibits Complex Formation, and not FL-AR Inhibition

RIP THERAPIC Design is Adaped by Tertiary Complex

V-Cryo Tomography

H001 is Efficacious in an Enzalutamide-Adapted Castrate VCaP Model

Conclusions and Future Directions
• RIPTAC Therapeutics are novel heterogeneous small molecule therapeutic modality with applications in prostate cancer
• RIPTACs act by abrogating the function of a pan-essential protein selectively in tumor cells by sequestering it in a stable tertiary complex with a tumor-specific targeting protein, in this case AR
• H001 is an AR binding RIPTAC that blocks the function of an undisclosed essential protein selectively in prostate cancer cells
• H001 is potentially anti-proliferative in AR+/VT prostate cancer cell lines that are insensitive to AR signaling inhibitors like Enzalutamide
• H001 is orally bioavailable and efficacious in AR(A) - VT prostate cancer mouse models
• Halda's Prostate Cancer RIPTAC program has demonstrated oral exposure in rats and will begin PK/MD studies in 2023.

Methods
LECPSs were licensed from Johns Hopkins University. TR225 cells were purchased from Thermo Fisher. All other reagents were purchased from ATCC. Protein purification and structural studies were performed in collaboration with Saktis (Poland). PSA ELISA kits were purchased from Abcam. CellTiterGlo and Caspase 3/7 kits were purchased from Promega.

References

Novel heterofunctional Oral Therapeutic Strategy for Killing Cancer Cells

An Oral RIPTAC™ Therapeutic for Prostate Cancer

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