

Targeting the WNT5A Receptor, ROR1, in Prostate Cancer

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Background: Prostate cancer preferentially metastasizes to bone and, although some treatments can slow its progression, there is no cure. We and others showed WNT5A expression is linked to poor prognosis in patients with bone metastatic prostate cancer. WNT5A is expressed in a sub-population of prostate cancer patient tissues and circulating tumor cells (CTCs). The interaction of WNT5A and its receptor, ROR1, is usually restricted to embryonic development but is re-activated in CLL and some solid tumors. In metastatic breast cancer, ROR1 expression increased in patients who developed resistance to paclitaxel. Cirmtuzumab, a therapeutic monoclonal antibody that binds to and inhibits ROR1, has successfully passed a Phase 1 trial in CLL. It is currently in clinical trials for CLL patients plus ibrutinib and metastatic breast cancer patients plus paclitaxel. We are characterizing WNT5A/ROR1 expression and function in our PDX and PDO models of bone metastatic prostate cancer and testing Cirmtuzumab to help identify the patient population for a Phase 1B clinical trial in metastatic prostate cancer patients.

Hypothesis: Therapy resistance in metastatic prostate cancer may arise due to increased expression and signaling of WNT5A and its receptor, ROR1. Cirmtuzumab may inhibit the growth of the ROR1-expressing, therapy resistant PCa cells that arise during treatment.

Methods: We analyzed WNT5A and ROR1 expression in our PDX and PDO models of bone metastatic prostate cancer using genome-wide expression profiling, qRT-PCR, RNAScope in situ hybridization, flow cytometry, and Western blotting. We are performing RNAScope and IHC analysis of WNT5A and ROR1 in in patient prostatectomy specimens. Using our patient and PDX derived PCSD1 and PCSD13 3D organoids we are testing Cirmtuzumab alone and in combination with Enzalutamide, Docetaxel and Radiation, in enzalutamide-sensitive and enzalutamide-resistant PDX models of bone metastatic prostate cancer

Results: WNT5A and ROR1 are expressed in the PDX, PCSD1, and the bone metastatic prostate cancer patient samples from which it was derived. ROR1 was expressed in PCSD13 which was confirmed by FACS. Cirmtuzumab treatment decreased the size of PCSD1 3D organoids that were resistant to enzalutamide plus docetaxel treatment. Immunofluorescence analysis of cytokeratins 5 and 8 showed the heterogeneity of cells in 3D organoids and Cirmtuzumab targeted cells. RNASeq and IFC analysis of enzalutamide-resistant PDXs revealed new bone-microenvironment signaling networks.

Conclusions: WNT5A and ROR1 are re-activated in a sub-set of bone-metastatic prostate cancer cells. This may present a unique therapeutic opportunity to use the ROR1-targeting monoclonal antibody, CIRMTUZUMAB, already in Phase 1B clinical trials for CLL and metastatic breast cancer to block WNT5A:ROR1 signaling and prevent growth and survival of metastatic prostate cancer. These pre-clinical studies will support the movement of this drug to the clinic for these patients who have no curative options.

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