Targeting SSTR1 to overcome resistance to androgen receptor signaling inhibition in prostate cancer

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Background: Resistance to androgen receptor signaling inhibitors (ARSIs), such as abiraterone or enzalutamide, is a major obstacle to improving outcomes for patients with prostate cancer. We previously identified *SSTR1* to be transcriptionally downregulated in ARSI-resistant prostate cancer. *SSTR1* encodes somatostatin receptor type 1, which mediates anti-proliferative effects when binding to somatostatin or its analogues. Here, we studied the biology of SSTR1 in prostate cancer, focusing on its relationship with ARSI resistance and potential as a therapeutic target.

Methods: To examine the impact of ARSI on SSTR1 expression, we treated C42B and 22Rv1 cells and LTL484 and LTL331 patient-derived organoids (PDOs) with enzalutamide and determined SSTR1 expression after the treatment. To investigate the function of SSTR1, we generated stable knockdown (using CRISPR interference), CRISPR knockout, and stable lentiviral over-expression lines of C42B and 22Rv1. Using these cell lines, we assessed live cell number with and without enzalutamide treatment. To evaluate the therapeutic potential of targeting SSTR1, we tested CH275, an SSTR1-specific agonist, and pasireotide, the only FDA-approved SSTR1 agonist with a pan-SSTR activity. The effects of these SSTR1 agonists, alone or in combination with enzalutamide, were evaluated in C42B and 22Rv1 cells by live cell number, and in LTL484 and LTL331 PDOs by cell viability and apoptosis.

Results: SSTR1 protein levels decreased after enzalutamide treatment in both cell lines and PDOs, consistent with decreased mRNA levels in tumor biopsies. CH275 and pasireotide decreased the live cell number of C42B and 22Rv1 cells. *SSTR1* knockdown and knockout increased live cell number and attenuated the anti-proliferative effect of CH275, whereas *SSTR1* overexpression decreased live cell number and enhanced the effect of CH275. Moreover, both SSTR1 agonists (CH275 and pasireotide) synergized with ARSIs (enzalutamide and apalutamide) in suppressing live cancer cells. *SSTR1* knockdown and knockout attenuated the synergistic effects of combination treatment in both cell lines. Similar trends were observed in LTL484 and LTL331 PDOs treated with pasireotide, enzalutamide, and their combination.

Conclusions:
ARSI treatment in CRPC models decreased SSTR1 expression. Activation of SSTR1 via agonists, in combination with ARSIs, exhibited enhanced efficacy in suppressing prostate cancer cells. These findings motivate the testing of SSTR1 agonists *in vivo* as a potential therapeutic approach and understanding the mechanisms of the synergistic effect of combination therapy to improve treatment response and outcomes for patients with prostate cancer.

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Conflicts of Interest:

A.Ashworth is a co-founder of Azkarra Therapeutics, Kytarro, Ovibio Corporation, Tango Therapeutics and Tiller Tx; a member of the board of Cambridge Science Corporation, Cytomx, Ovibio; a member of the scientific advisory board of Ambagon, Bluestar/Clearnote Health, Circle, GLAdiator, HAP10, Interdict Bio Inc., Earli, ORIC, Phoenix Molecular Designs, Trial Library, Yingli/280Bio; a consultant for Next RNA, Novartis, ProLynx; and holds patents on the use of PARP inhibitors held jointly with AstraZeneca from which he has benefited financially (and may do so in the future). R. Aggarwal reports grants from Janssen, Amgen, Zenith Epigenetics, and Xynomic Pharmaceuticals; grants and personal fees from AstraZeneca, Merck, and Novartis; personal fees from Dendreon, Elsevier, Exelixis, Jubilant Therapeutics, Bayer, Pfizer, and Alessa Therapeutics outside the submitted work. E.J. Small reports other support from Fortis, Harpoon, Teon, Janssen, Johnson & Johnson, and Ultragenyx during the conduct of the study; other support from Fortis, Harpoon, Teon, Janssen, Johnson & Johnson, and Ultragenyx outside the submitted work. F.Y. Feng reports personal fees from Janssen Oncology, Bayer, PFS Genomics, Myovant Sciences, Roivant Sciences, Astellas Pharma, Foundation Medicine, Varian, Bristol Myers Squibb (BMS), Exact Sciences, Clearnote Health, Novartis, and Tempus; other support from Serimmune and Artera outside the submitted work.