

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

Shu Chen^{1,2}, Tianyi Liu^{1,3}, Jun Zhu^{1,3}, Imene Boukhalifa^{1,3}, Haolong Li^{1,3,4}, David A. Quigley^{1,5}, Alan Ashworth^{1,2}, Rahul R. Aggarwal^{1,2}, Eric J. Small^{1,2}, Felix Y. Feng^{1,3}, Xiaolin Zhu^{1,2}

¹ Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA

² Division of Hematology and Oncology, Department of Medicine, University of California San Francisco, San Francisco, CA

³ Department of Radiation Oncology, University of California San Francisco, San Francisco, CA

⁴ Human Biology Division, Fred Hutchinson Cancer Center, Seattle, WA

⁵ Department of Urology, University of California San Francisco, San Francisco, CA

**Presenting author*

Background: Resistance to androgen receptor signaling inhibitors (ARSIs), such as abiraterone or enzalutamide (ENZ), 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, anti-invasive, and anti-angiogenic effects when binding to somatostatin or somatostatin analogues. Here, we studied the biology of SSTR1 in prostate cancer, focusing on its relationship with ARSI resistance and its 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 cell lines of C42B and 22Rv1. Using such cells, we assessed xenograft growth and live cell number with and without enzalutamide treatment. To evaluate the therapeutic potential of targeting SSTR1, we tested CH275, a 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, in LTL484, LTL331, LuCaP 35CR and LuCaP 96CR PDOs by cell viability and apoptosis and in LuCaP 35CR and LuCaP 96CR PDXs by xenograft volume/body weight/organ weight measurement, histology, TUNEL, immunohistochemistry and ELISA assays.

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 effect of CH275 and ENZ, whereas SSTR1 overexpression decreased live cancer cell number, suppressed xenograft growth and enhanced the CH275 and ENZ effect. Moreover, both SSTR1 agonists (CH275 and pasireotide) synergized with ARSIs (enzalutamide and apalutamide) in eliminating live cells. Similar trends were observed in LTL484, LTL331, LuCaP 35CR, LuCaP 96CR PDOs and LuCaP 35CR, LuCaP 96CR PDXs treated with pasireotide, enzalutamide, or their combination. The combination therapy is well tolerated without altering mice body and organ weight. SSTR1 knockdown and knockout attenuated the synergistic effects of combination treatment in both cell lines.

Conclusions: ARSI treatment in CRPC models decreased SSTR1 expression. SSTR1 agonists enhanced the efficacy of ARSI in suppressing prostate cancer growth. These findings provide a strong rationale for advancing the combination of the SSTR1 agonist pasireotide and the ARSI enzalutamide into clinical evaluation as a potential therapeutic strategy to improve treatment response and outcomes in patients with prostate cancer.

Funding Acknowledgments: PCF (2022 Young Investigator Award supported by Dr. Elliot and Nan Abramowitz); CDMRP PCRP Physician Research Award (HT9425-24-1-0506)

Conflicts of Interest: The authors declare no conflicts of interest related to this work.