

Title: Development of a Domain-ALTERation Chimera (DALTAC) to Disrupt Polycomb Repressive Complex 2 in Prostate Cancer

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Background:

EZH2 is a histone methyltransferase which is part of Polycomb repressive complex 2 (PRC2), along with core members EED and SUZ12. PRC2 is crucial in development and disease owing to its role in transcriptional repression via deposition of histone H3 lysine 27 tri-methylation (H3K27me3). EZH2 is over-expressed in advanced prostate cancer, promoting the progression of both AR-positive and negative disease. PRC2 contributes to prostate cancer progression through multiple mechanisms, including through modulating androgen receptor (AR) signaling, via non-canonical co-activator function in conjunction with AR, through lineage-dependent roles in gene regulation, and through non-histone methyltransferase activity. Consistent with pre-clinical studies emphasizing the importance of PRC2, the EZH2 inhibitor mevinmetostat in combination with enzalutamide has shown promise in a recent phase 1/2 trial in castration-resistant prostate cancer, and phase 3 trials are now underway.

Chemical inducers of proximity (CIPs) are an upcoming therapeutic strategy that uses a heterobifunctional molecule to induce proximity between two proteins of interest. Proteolysis targeting chimera (PROTACs) are prototypical CIPs which cause targeted protein degradation. Newer CIPs, including RIPTACs and TCIPs, are designed to act via protein re-localization. Supported by the 2025 PCF Challenge Award, our laboratory pioneered the domain-alteration chimera (DALTAC), a CIP which reprograms native interactions within an oncogenic transcription complex to lock it in a defective conformation. Our first-in-class DALTAC targets AR and p300, potentially suppressing prostate cancer growth and transcription beyond that of inhibitors of the individual proteins.

Methods:

Building on the potential for DALTACs to create super-inhibitory effects on transcription and cell proliferation and the role of PRC2 as a transcriptional-repressive complex driver of prostate cancer, we sought to create a new DALTAC targeting PRC2. Using standard medicinal chemistry approaches, fourteen novel PRC2-targeting heterobifunctional molecules were designed, synthesized, and characterized. These molecules were evaluated *in vitro* for effects on prostate cancer cell proliferation with CellTiter-Glo as well as on-target PRC2 activity and downstream signaling with protein immunoblotting. The lead candidate underwent *in vivo* pharmacokinetics profiling with mass spectrometry and a pharmacodynamics assessment with protein immunoblotting.

Results:

Among the 14 novel compounds, we identified four that more strongly inhibit the *in vitro* proliferation of multiple prostate cancer models in comparison to PRC2 inhibitors. The lead candidate, SZ-3060, has the most potent effects on cell proliferation and robustly decreases H3K27me3. SZ-3060 has favorable intraperitoneal and intravenous bioavailability, and it decreases H3K27me3 in an *in vivo* pharmacodynamics study.

Conclusions:

We have generated SZ-3060, a PRC2-targeting DALTAC with superior efficacy *in vitro* compared to existing PRC2 inhibitors. These findings provide the foundation for this 2026 PCF Young Investigator Award project, which will define the mechanisms underlying SZ-3060's enhanced efficacy compared to PRC2 inhibitors and generate preclinical data to position SZ-3060 for clinical translation.

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Conflicts of Interest:

A.M.C. is a co-founder and holds equity in Medsyn Biopharma. A.M.C. is a co-founder and serves on the scientific advisory board of Lynx Dx, NuLynx Therapeutics, Esanik Therapeutics, and Eradix. A.M.C. serves as an advisor to Tempus AI, Aurigene Oncology, and Ascentage. The remaining authors declare no conflicts of interest.