

Rewiring Oncogenic Transcriptional Complexes with Domain-ALTERation Chimeras (DALTACs) in Prostate Cancer

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Background: Aberrant transcriptional programs are a hallmark of cancer, driving malignant transformation, particularly in enhancer-driven cancers such as mCRPC. AR is the central driver of mCRPC, recruiting coregulators to assemble cancer-specific neo-enhanceosome complexes, promoting oncogenic transcriptional programs. AR neo-enhanceosome activation requires specific histone modifications, mediated by key coactivators such as the paralogous lysine acetyltransferases p300 and CBP. Although inhibitors and degraders targeting p300/CBP have been developed for enhancer-driven malignancies, including CRPC9, global p300/CBP inhibition may cause toxicity in normal tissues, highlighting the need for more selective therapeutic strategies. Chemical-induced proximity (CIP) strategies have revolutionized therapeutic design by reprogramming protein–protein interactions to manipulate cellular function. Here, we introduce a mechanistically distinct modality, Domain-ALTERation Chimeras (DALTACs), that selectively reprogram endogenous protein complexes by enforcing neomorphic domain–domain interactions between physiological partners.

Methods: DALTAC-1 was generated by chemically conjugating an AR ligand-binding domain (LBD) binder to a p300/CBP bromodomain binder through a specifically designed linker. Its antiproliferative activity and lineage selectivity were evaluated across a panel of AR-positive and AR-negative prostate cancer cell lines. In vivo efficacy was assessed in multiple preclinical prostate cancer models. Formation of the DALTAC-1-induced AR–p300/CBP ternary complex was examined using biochemical and molecular and cellular assays in both purified-protein and intracellular systems. The mechanism of action of DALTAC-1 was further characterized using integrated multi-omic approaches, including ChIP–seq, RNA-seq, mass spectrometry–based global proteomics, and lysine acetylomics.

Results: DALTAC-1 induces synthetic proximity between the AR ligand-binding domain and p300/CBP-bromodomain, misconfiguring their native interface and locking the complex in a non-productive state. DALTAC-1 triggers a “super-inhibitory” effect, suppressing AR-driven transcription and proliferation more potently than combined AR and p300/CBP inhibition. Mechanistically, DALTAC-1 reprograms p300/CBP substrate engagement, abolishing the histone mark H2BNTac while inducing neomorphic acetylation of AR and coactivators, ultimately collapsing the AR neo-enhanceosome. Chromatin profiling revealed redistribution of AR and p300/CBP toward palindromic AREs, accompanied by disruption of cofactor and transcriptional machinery recruitment at oncogenic AR/ERG neo-enhancers. DALTAC-1 exhibits exquisite lineage selectivity, displaying potent activity in AR-p300/CBP dual-dependent cells while sparing AR-negative cells. In multiple in vivo models, DALTAC-1 induces deep and durable tumor regressions.

Conclusion: Our findings establish DALTACs as a broadly applicable strategy to rewire disease-defining complexes through domain-topology alteration, expanding induced-proximity therapeutics, while DALTAC-1’s precise lineage-selectivity supports its translational potential in AR-driven prostate cancer.

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Competing interests: S.W. and A.M.C. are co-founders and hold equity in Medsyn Biopharma. The University of Michigan has filed patents related to AR-p300 DALTACs which have been licensed to Medsyn. The University of Michigan has received a research contract from Medsyn for which S.W. serves as the principal investigator. S.W. is also a co-founder of Ascentage Pharma Group and Eradix Therapeutics and holds equity in Ascentage and Eradix. A.M.C. is a co-founder and serves on the scientific advisory board of Lynx Dx, NuLynx Therapeutics, Esanik Therapeutics, and Medsyn. A.M.C. serves as an advisor to Tempus, Aurigene Oncology, Ascentage Pharmaceuticals, and EdenRoc. The remaining authors declare no conflicts of interest.