

Title: Plasma Epigenomic Profiling Predicts Therapeutic Target Expression and Response to Cell-Surface-Targeted Therapy in Advanced Prostate Cancer

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Background: PSMA PET imaging is required to select patients for PSMA-targeted radioligand therapy (LuPSMA), yet metastatic tissue is rarely available to characterize the tumor biology underlying treatment response and resistance. Genomic liquid biopsy cannot address this gap, as PSMA and other cell-surface targets are regulated epigenetically rather than genomically. As additional cell-surface-targeted therapies enter late-phase clinical development, a scalable, blood-based platform capable of non-invasively resolving multiple targets is needed to guide patient selection.

Methods: We profiled plasma cell-free DNA histone modifications (H3K4me3, H3K27ac) and DNA methylation in a prospective cohort of mCRPC patients treated with LuPSMA, with baseline PSMA PET imaging in a subset and paired baseline-progression plasma in a further subset. An independent cohort of patients with biopsy-confirmed neuroendocrine prostate cancer (NEPC) was also profiled. Plasma epigenomic signal was used to infer genome-wide gene regulatory activity, model PSMA PET SUVmean, and quantify a multiplexed panel of clinically actionable cell-surface targets (PSMA, KLK2, STEAP1, STEAP2, PSCA, TROP2, DLL3, SEZ6, CEACAM5). All pathway-level and clinical association analyses adjusted for ctDNA fraction.

Results: Plasma epigenomic profiling non-invasively predicted PSMA PET SUVmean and was prognostic for time to next treatment (TTNT), with discrimination comparable to observed PSMA PET and generalizing to an independent subcohort lacking PET imaging. Luminal, AR-driven transcriptional programs were associated with PSMA expression and favorable TTNT, while basal, stem cell, WNT, and EMT programs were associated with the inverse pattern, consistent with independent patient-derived organoid data. This association persisted after adjusting for observed PSMA PET SUVmean, indicating that luminal and non-luminal biology carries prognostic value independent of PSMA status itself. At progression, loss of predicted PSMA expression occurred concordantly with loss of this same luminal, AR-driven axis, with emergence of AR-independent, proliferative programs (mTOR, Notch, MAPK signaling, cell cycle). Beyond PSMA, the platform resolved a multiplexed panel of cell-surface targets, with co-expression architecture validated against tumor tissue and target-specific IHC. A recurrent PSMA-low, KLK2/STEAP1-high tumor state was identified, nominating patients for KLK2- or STEAP1-directed agents (pasritamig, xaluritamig; both now in phase 3 trials) as an alternative to LuPSMA. Target expression evolved dynamically under treatment, with PSCA and TROP2 rising as PSMA declined at progression.

Conclusions: Plasma epigenomic profiling non-invasively predicts PSMA PET phenotype, is prognostic for clinical benefit from LuPSMA, and resolves transcriptional heterogeneity underlying treatment response and resistance. To our knowledge, this represents the largest gene regulatory dataset characterizing LuPSMA response and resistance. This platform extends beyond PSMA to a dynamic, multiplexed panel of clinically actionable cell-surface targets, offering a scalable approach to real-time, biology-guided treatment selection as additional targeted therapies enter the clinic.

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