Background. Risk of prostate cancer (PCa) associates with reduced vitamin D receptor (VDR) signaling in African American (AA) compared to European American (EA) patients, but the mechanism remains enigmatic.

Methods. VDR-dependent ChIP-Seq and RNA-Seq was undertaken in EA (non-malignant HPr1AR and malignant LNCaP) and AA (non-malignant RC43N and malignant RC43T) cells, combined with transcriptomic studies in three PCa patient cohorts.

Results. AA cells have higher VDR protein expression, which genomically binds more frequently, and is more enriched in active and poised enhancers than EA models. SMAD4 and VDR motifs were common in all models, whereas AA peaks were enriched for a larger motif repertoire including RUNX2 and ZBTB33/KAISO, and ERG motifs were enriched in EA peaks. Overlapping with ~10,000 publicly available cistromes revealed that in AA models VDR significantly overlapped with core circadian rhythm transcription factors (e.g. NONO). Integrating VDR-dependent ChIP-Seq and RNA-Seq revealed significantly stronger VDR transcriptional responses in AA models, again enriched for circadian rhythm (NES 2.7) and inflammation.

Using clinical cohorts, we identified serum miRNA expression associated with progression from HGPIN to PCa. In AA men ~30% predicative miRNAs were VDR bound and $1\alpha,25(OH)_2D_3$ regulated in AA cell lines, whereas only ~5% of miRNAs in EA men were VDR-responsive in EA cell lines. For example, miR-199b down-regulation associates with AA progression from HGPIN to PCa, VDR binds and $1\alpha,25(OH)_2D_3$ up-regulates miR-199b in RC43N, but is repressed in RC43T. MiR-199b regulates NPAS2, a core circadian transcription factor. Similarly, we previously reported AA tumors are more $1\alpha,25(OH)_2D_3$-responsive *in vivo*, and we now revealed these genes are enriched for circadian transcriptional regulators (e.g. NOCT) and inflammatory signals. A genome-wide analyses of coregulators in TCGA identified significantly reduced BAZ1A/SMARCA5 expression in TMPRSS2:ERG fusion negative AA PCa. We are currently analyzing RNA-Seq from AA and EA cells with restored BAZ1A expression.

Together, these data suggest VDR transcriptional control in the prostate is most potent and dynamic in AA men, and is primed to govern inflammatory and circadian

pathways. This is suppressed, by altered BAZ1A/SMARCA5 expression and/or reduced environmental-regulated serum vitamin D_3 levels. Therefore, the VDR axis lies at the cross-roads of biopsychosocial processes that contributes to PCa health disparities.