Background: Outcomes of radiation therapy are highly positive for localized prostate cancer; however, local recurrence remains a potential negative outcome. One mechanism of recurrence is radioresistance. Current practice groups patients between active surveillance, prostatectomy, or radiation therapy based upon patient life expectancy and risk group. Physician-patient shared decision ultimately determines a treatment regimen which includes understanding the side effects, impact on life, and pitfalls of each treatment. Therefore, there is benefit in discovering a radiation therapy outcome specific biomarker to decipher between the two treatment regimens. Recently, SOX2, an established stem maintenance transcription factor, is emerging as a protein of interest in prostate cancer as a key driver of lineage plasticity and therapy resistance. Further, immunohistochemical analyses of prostate tumors demonstrate tumors are either ubiquitously SOX2 positive or negative, thus making it a potential ideal biomarker candidate.

Methods: We eliminated SOX2 expression in SOX2 endogenous prostate cancer cells, CWR-R1s, through CRISPR/Cas9 gene editing. ChIP-Seq and RNA-Seq was conducted to determine SOX2 binding sites and SOX2-associated gene regulation, and bioinformatic pathway prioritization determined potential SOX2-mediated pathways. Functional assays and protein analyses we conducted to mechanistically define roles for SOX2 in prostate therapy resistance.

Results: We found the loss of SOX2 led to decreased cell growth. Further, analyses prioritized SOX2-assoicted changes in DNA damage signaling and responses. DNA damage signaling genes via Qiagen pathway array showed differential expression between SOX2 expressing and non-expressing cells. This led us to examine the DNA damage sensing protein γH2AX, which demonstrated constitutive activation of γH2AX and accumulations of foci upon loss of SOX2.