



Can the interplay between androgen signaling and PSMA expression be leveraged for theranostic applications?

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Despite numerous approved therapies for metastatic prostate cancer (PCa) that offer advantages in progression free survival, actual cure rates remain dismal (1). Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein that is nearly universally expressed in PCa (2) and has emerged as one of the most promising targets for novel therapies that are being developed to address PCa (3). Of note, PSMA expression levels have a relationship with androgen signaling that may have important clinical implications for treatment with PSMA-targeted theranostic agents.

Evans and colleagues have shown through *in vitro* experiments that PCa cell lines that were androgen receptor- (AR-) positive and hormone responsive also expressed PSMA, while the AR negative cell lines were PSMA negative (4). Additionally, there was an inverse relationship between PSMA expression/mRNA levels and exogenous androgen stimulation, and they observed similar suppression in *in vivo* xenograft models. They also observed that enzalutamide, a second-generation antiandrogen drug, had an interesting effect on cells overexpressing AR, wherein treatment with the drug caused increased expression of PSMA. They were able to quantify downregulation of PSMA (by testosterone or dihydrotestosterone) and upregulation with antiandrogen therapy (enzalutamide) using ⁶⁴Cu-J591 PET imaging. The authors highlighted the importance and possible treatment implications of novel non-invasive molecular imaging modalities monitoring response to targeted AR signaling in clinical practice (4).

Similarly, Hope *et al.* in 2016 reported tumor size reduction and increased PSMA expression by ⁶⁸Ga-PSMA-11 PET imaging in xenograft models after androgen deprivation (medically or surgically) (5). They also reported first-in-human experience where a patient with castration-sensitive PCa treated with apalutamide demonstrated a 7-fold increase in PSMA uptake as well as thirteen new lesions after starting the therapy, concluding that AR inhibition increases PSMA expression in PCa metastases and increases the number of lesions identifiable on PSMA-based PET imaging (5). A more complex scenario was observed by Zukotynski *et al.* in their description of a patient imaged with PSMA-targeted ¹⁸F-DCFPyL PET/CT 10-weeks after initiation of enzalutamide therapy (6). A flare phenomenon was seen within osseous metastatic sites but not within affected lymph nodes, suggesting mechanisms other than AR-PSMA inverse regulation may also be present. Some of the possible mechanisms posited included neovascularization, cell infiltration from bone repair, or osteoblastic turnover, which may variably contribute to changes in observed PSMA expression as well inter-lesion variability in patients receiving second line anti-androgen therapies (6).

However, it has been a recent study by Lückérath *et al.* in which the concepts hinted at in earlier studies have been most directly applied to the burgeoning field of PSMA-targeted theranostics (7). The authors performed experiments using AR-positive C4-2 PCa cell line that also expresses PSMA. In non-castrated xenograft models, a temporal trend of expression of PSMA was visualized

using ^{68}Ga -PSMA PET (initially peaking and then slightly decreasing, although always remaining above baseline) and flow cytometry (peaking and then decreasing) at fixed time points after treatment with AR blockade consisting of bicalutamide or enzalutamide. There was also delay in tumor progression. With the hypothesis that increased PSMA expression would result in better treatment outcomes by combining enzalutamide and PSMA targeted radioligand therapy with ^{177}Lu -PSMA-617, the efficacy of this combination protocol was also assessed. Treatment with enzalutamide induced upregulation of PSMA and enhanced the radioligand-therapy-induced DNA damage as documented by reversible increase in phosphor- $\gamma\text{H2A.X}$ (using flow cytometry). Although, additional tumor control and improved survival were observed with radioligand therapy plus enzalutamide compared to enzalutamide alone, this synergistic benefit was lacking when radioligand therapy plus enzalutamide was compared to radioligand therapy alone (7). Lack of androgen deprivation and results from a single cell line confer some of the limitations of this study.

Ultimately, the results from Lückérath *et al.* (7) suggest that further study is necessary in order to fully understand whether there is any role for androgen-targeted agents as an adjunct to treatment with PSMA-targeted radioligand therapies. Driving PSMA expression in order to improve response to PSMA-targeted radioligand therapy is an appealing strategy and may merit further investigation, although existing data is not definitive. As the primarily retrospective studies in the PSMA-targeted theranostic space begin to give way to prospective trials (8), there will be ample opportunity to investigate therapeutic combinations, including concomitant or temporally separated androgen-targeted therapies with PSMA-targeted radioligand agents.

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None.

Footnote

Conflicts of Interest: MG Pomper is a co-inventor on a U.S. patent covering ^{18}F -DCFPyL and as such is entitled to a portion of any licensing fees and royalties generated by this technology. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict-of-interest policies. SP Rowe is a consultant to Progenics Pharmaceuticals, the licensee of ^{18}F -DCFPyL.

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