The androgen receptor (AR) is a critical steroid receptor required for prostatic luminal cell survival. In its unbound state, AR is initially localized to the cytoplasm and has been demonstrated to interact with a host of scaffold proteins and kinases such as c-Src (1) in a non-genomic fashion (2). Once bound by its natural ligand, dihydrotestosterone (DHT), AR forms a homo-dimer with itself, translocates into the nucleus, recruits transcriptional coactivators, and binds to DNA androgen-response elements (AREs) positively regulating prostate-specific antigen (PSA) and a variety of other AR target genes that control cellular division and survival (3). In prostate cancer, AR continues to remain a central target in both localized and castration-resistant disease states. Suppression of testosterone synthesis or inhibition of AR signaling using pharmacological modalities represents an effective approach for the treatment of hormone-sensitive and castration-resistant disease because tumor cells are still dependent on AR for their growth and survival. However, most men receiving these therapies will eventually become resistant to such hormonal manipulations, which is heralded by an increase in PSA level or a clinical worsening of metastases while on these therapies. This can be ascribed to a range of resistance mechanisms including activating mutations in the AR ligand-binding domain, hormonal independence via generation of mRNA splice variants of the AR (notably AR-V7), as well as induction of alternative steroid receptors such as the glucocorticoid and progesterone receptors which hijack promoters/enhancers of AR-responsive genes (3,4).

In the paper that accompanies this editorial, Rosati et al. 2018 (5) developed and tested a flavonoid agent that successfully disrupted AR signaling through an epigenetic mechanism involving ERK1. Using LNCaP, VCaP and 22RV1 castration-resistant prostate cancer cell lines, and by performing chromatin immunoprecipitation (ChIP) and competitive ligand-binding assays, the authors were able to demonstrate that a lead small-molecule compound, KCI807, had the ability to bind directly to AR and block the recruitment of an ETS-family transcriptional coactivator, ELK1. AR/ELK1 complexes bound to specific sites of DNA enhancer/promoter regions, and KCI807 was able to reduce mRNA expression levels of downstream target genes regulated by the AR/ELK1 transcriptional complex. Importantly, KCI807 did not appear to impede the recruitment of AR to canonical ARE sites, for example those associated with expression of PSA or TMPRSS2. Knockdown experiments using siRNAs against ELK1 and AR further potentiated the action of KCI807; this resulted in increased levels of Fam112b relative to the ELK1 and AR knockdown experiments. Notably, in 22RV1 cells that harbor the AR-V7 splice variant, KCI807 was also effective at inhibiting promoter activation and transcription of AR-V7 target genes in these cells. Intriguingly, however,
KCI807 did not suppress the level of protein expression of the wild-type AR or the AR-V7 splice variant. Finally, the authors also tested their agent at a concentration of 250 mg/kg and compared it against enzalutamide in an in vivo 22RV1 xenograft mouse model, and demonstrated the ability of KCI807 to delay tumorigenesis more so than enzalutamide in vivo. Altogether, the authors performed well-controlled experiments to evaluate KCI807 binding to AR, its effects on AR/ELK1–regulated genes, inhibition of cell proliferation, and suppression of tumorigenesis in vivo.

What are the potential clinical implications of this work? First, the development of therapeutic strategies capable of targeting AR-V7–expressing human castration-resistant prostate cancer (CRPC) represents one of the holy grails of advanced prostate cancer treatment. With the exception of taxane chemotherapies (6) and perhaps immune checkpoint blockade therapy (7), attempts to target AR-V7–positive prostate cancers have been discouraging (8,9) and this continues to represent an unmet medical need. To this end, if KCI807 (or its derivative) is capable of extinguishing AR-regulated gene expression at both the AR/ELK1 and the AR-V7/ELK1 transcriptional levels, then this strategy should theoretically be effective in many human CRPC tumors that usually co-express both wild-type and aberrant AR isoforms. Such an approach could either be used as a monotherapy in patients who have previously failed abiraterone and/or enzalutamide, or could be developed as a combination strategy together with abiraterone and/or enzalutamide in CRPC patients who have not yet received either agent. The combinatorial approach may serve to prolong the duration of responses to abiraterone/enzalutamide, or to subvert secondary (i.e., acquired) resistance that invariably develops in most patients.

A second potential clinical utility of KCI807 (or its derivatives) would be for the treatment of neuroendocrine prostate cancer which is a rapidly lethal phenotype of CRPC that is usually refractory to most forms of androgen/AR ablation, and for which novel therapeutic strategies are sorely needed (10). Interestingly, ELK1 gene amplification and/or mRNA overexpression occurs in about 25–30% of human neuroendocrine CRPC cases (11) compared to <5% of conventional acinar CRPC cases (11) compared to conventional acinar CRPC cases, while the related ETS-family genes ELK3 and ELK4 are also amplified in many neuroendocrine prostate cancers. These findings might theoretically imply that disruption of the AR/ELK1 transcriptional axis in neuroendocrine prostate cancers might lead to effective therapies for at least a subset of these cases. This hypothesis could be further tested pre-clinically by administering KCI807 to mice harboring patient-derived xenografts (12) consisting of neuroendocrine CRPC, especially those demonstrating amplification or high expression of ELK1. Finally, although only hypothesis-generating, it would be attractive to also explore potential synergy between ELK1 modulators and platinum agents in neuroendocrine prostate cancers, since the latter is currently being used commonly for the clinical management of neuroendocrine CRPC.

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Footnote

Conflicts of Interest: ES Antonarakis is a paid consultant/advisor to Janssen, Astellas, Sanofi, Dendreon, Medivation, ESSA, AstraZeneca, Clovis, and Merck; he has received research funding to his institution from Janssen, Johnson & Johnson, Sanofi, Dendreon, Genentech, Novartis, Tokai, Bristol Myers- Squibb, AstraZeneca, Clovis, and Merck; and he is the co-inventor of a biomarker technology that has been licensed to Qiagen. JC Zarif declares no potential conflicts of interest.

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