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SYSTEMIC THERAPY (J CORTES, SECTION EDITOR)

Importance of Breast Cancer Subtype in the Development of Androgen-Receptor-Directed Therapy

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Abstract The androgen receptor (AR) has re-emerged as a potential therapeutic target for breast cancer treatment. This stems from recent progress made in preclinical models, which have recognized important differences in the effect of AR expression on outcomes for patients with different breast cancer subtypes. In parallel, the clinical development of new generations of androgen-receptor-directed therapy for prostate cancer has begun to mature. The availability of these new agents has resulted in trials of their potential for treating breast cancer. It is critical that studies of the effect of AR expression and signaling in breast cancer should be context and subtype specific, to successfully translate AR modulation into a clinical strategy for breast cancer. We will review developments in preclinical studies, and recent clinical trials targeting AR in breast cancer.

Keywords Androgen receptor · Breast cancer · Breast cancer subtype · Androgen receptor directed therapy

Introduction

Sex steroid hormone receptors, including AR, estrogen receptor (ER), and progesterone receptor (PR), are critical to both the development and the progression of breast cancer. Of the three receptors, ER has been most extensively studied. It is expressed in 70 % of all breast cancer; the ER signaling pathway is a crucial determinant in the molecular subtyping of breast cancer [1]; and, most importantly, effective ER pathway antagonists have been used successfully in both the palliative and adjuvant setting [2]. On the other hand, an important function for androgens in breast cancer biology has long been hypothesized but remains to be fully elucidated. Despite the availability of AR and PR-targeted therapy, these are currently not widely used for patients with breast cancer.

AR is expressed in 50–80 % of invasive breast cancer and in approximately 85 % of ductal carcinoma in situ (DCIS) lesions in large cohort studies [3•, 4•, 5], although it is not routinely clinically measured. AR expression varies across the different molecular subtypes. In a large study of over 2,000 invasive breast cancer samples obtained from the Nurses' Health Study (NHS), AR was most highly co-expressed in luminal A and luminal B cancers (91 % and 68 %, respectively), and lowest in HER2+ and triple-negative tumors (TNBC; defined as ER-/PR-/HER2-; 59 % and 32 %, respectively) [3•]. Breast cancer subtypes were defined immunohistochemically in this study.

Although androgen is often thought of as a male-selective steroid, androgens and AR have important physiological functions in females as well. Studies of AR-knockout mice suggest a crucial function for androgens in breast development and normal female reproduction [6, 7]. In women, approximately 25 % of testosterone is ovarian in origin, 25 % is adrenal, and the remainder is derived from the peripheral conversion of androgen precursors [8]. The androgen dehydroepiandrosterone sulfate (DHEAS) is produced primarily by the adrenal gland [9], and can be converted either to androstenedione and then to estrone, or to 5-androstenediol and then to testosterone. Androgenic effects in tissue are mediated primarily via the binding of testosterone or 5α-dihydrotestosterone (DHT) to AR [8, 10]. Ligand binding of AR results in receptor dimerization and translocation to the nucleus which, after interactions with multiple, modulatory co-regulators, leads to expression of AR target genes.

A recent pooled analysis of seven prospective studies of premenopausal women, comprising 767 patients with breast cancer and 1,699 controls, found that breast cancer risk was

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associated with a doubling in concentrations of androstenedione (odds ratio (OR) 1.30, 95 % confidence interval (CI) 1.10–1.55), DHEAS (OR 1.17, 95 % CI 1.04–1.32), testosterone (OR 1.18, 1.03–1.35), and calculated free testosterone (OR 1.08, 95 % CI 0.97–1.21) [11•]. Circulating estradiol and estrone had similar positive associations with breast cancer risk, whereas luteal-phase progesterone and sex-hormone-binding globulin (SHBG) were not associated with risk. These results mirror those reported for postmenopausal women, but are lower in magnitude [12–14]. For postmenopausal women, the best summary of evidence on circulating androgens and breast cancer risk is from a pooled analysis of nine prospective studies [14]. In this analysis, testosterone was positively associated with breast cancer risk: the relative risks (95 % CI) for increasing quintile category (all relative to the lowest quintile of levels) were 1.3 (1.0–1.9), 1.6 (1.2–2.2), 1.6 (1.1–2.2) and 2.2 (1.6–3.1). Findings were generally similar for several other androgens measured. In a recent nested case-control study within the NHS, prospectively collected serum hormonal levels were compared for 707 postmenopausal breast cancer cases and 1,414 matched controls [12]. Women in the top quartile of testosterone, free testosterone, DHEAS, serum estradiol, and free estradiol levels had a 50–110 % higher risk of breast cancer compared with women in the lowest quartile. The relative risk of breast cancer extended to 20 years from when the serum levels were measured, and the association was strongest for ER+/PR+ cancers, whereas there was no association for ER−/PR− cancers.

The prognostic effect of AR expression in breast cancer is dependent on breast cancer subtype. In a meta-analysis of nineteen studies of early-stage breast cancer, AR expression was associated with better overall survival and disease-free survival [15•]. In a subset of postmenopausal patients from the NHS with early-stage breast cancer, investigators performing multivariate analysis found that AR expression was associated with a 30 % reduction in breast cancer mortality for the ER+subgroup (n=1,164; 88 % AR+; hazard ratio (HR): 0.68; p=0.03), and a non-significant association of AR and poorer overall survival for the ER−subgroup (n=303; 43 % AR+; HR: 1.59; p=0.08) [4•]. A similar association was found between AR expression and patient outcomes for early-stage ER+ breast cancer after adjuvant endocrine or chemoendocrine therapy [16, 17]. Another study of 215 patients revealed a positive prognostic effect of the degree of AR expression for ER+ breast cancer, whereby multivariate Cox regression analysis indicated a 3.0-fold increased risk of relapse and a 4.6-fold increased risk of cancer-related death for patients with a lower-than-median percentage of AR positivity (i.e. <75 % for this patient cohort) in tumor cells [18].

In summary, current epidemiological evidence suggests that circulating androgen levels have a positive association with breast cancer risk, with a greater relative risk of developing ER+ than ER− cancer. AR expression has an effect on breast cancer progression, with different effects on patient outcomes depending on the ER status of the breast tumor. It is critical, therefore, that studies of the effect of AR expression and signaling in breast cancer be context and subtype specific, to successfully translate AR modulation into a successful clinical strategy for breast cancer [19].

The Function of AR in Breast Cancer Development

AR is expressed in approximately 20 % of normal mammary epithelium, primarily in the luminal cells [20]. The effect of AR expression on breast cancer risk is unclear. Several breast cancer risk factors, including physical activity and alcohol intake, have been hypothesized to operate, in part, by altering background levels of androgen. Insight into the oncogenic effects of AR in mammary epithelial cells may be gained by investigating the expression and functions of AR signaling in normal mammary epithelial cells. Substantial progress has been made in the delineation of the normal epithelial hierarchy, with the identification of cell surface markers that can be used to fractionate subpopulations of cells by flow-assisted cytometry. Antibodies against CD49f and EpCAM reproducibly fractionated lineage-negative mammary epithelial cells into four subpopulations [21]. These have been defined functionally by in-vivo cleared mammary-fat-pad transplantation studies and in-vitro culture experiments, and include mammary-stem-cell enriched ($CD49^{hi}EpCAM^{-}$), luminal progenitor ($CD49^{+}EpCAM^{+}$), mature luminal ($CD49^{-}EpCAM^{+}$), and stromal ($CD49^{-}EpCAM^{-}$) subpopulations. In this study, AR mRNA was most abundantly expressed in the mature luminal subpopulation, followed by the luminal progenitor cells. These findings were confirmed and expanded in a recent paper in which double immunofluorescent staining was used to reveal that, in sections of normal mammary lobules, all AR+ cells were luminal in origin, as defined by the expression of keratins 7 and 18, and claudin-4 [22•]. Interestingly, there was only a 44 % overlap of AR+ cells with ER+ cells (n=429), and no overlap with proliferating Ki-67+ cells. These studies have provided clarification of the lineage and distribution of AR+ cells in the normal mammary gland, and serve as a foundation for studying the effect of AR on breast cancer risk. The AR signaling program in these AR+ normal mammary epithelial cells has not yet been defined. By comparing the AR target genes, collaborating transcription factors, and androgen-stimulated gene expression profile in AR+ normal cells and breast cancer cells, it should be possible to distinguish those genes involved in AR signaling that are required for normal mammary epithelial function, and those that are aberrant in breast cancer.

AR Biology in ER+ Breast Cancer

AR, often co-expressed with ER and PR, is present in most primary and metastatic invasive breast tumors [3•, 4•, 23]. AR expression has been revealed to be a positive prognostic factor

for ER+ breast cancer in several studies [4•, 16–18]. This clinical observation has been corroborated by laboratory studies that suggest that androgens may affect tumor growth differently in ER+ compared with ER− tumors, with AR decreasing proliferation in ER+ tumors by antagonizing ER [18], and AR stimulating tumor growth in ER− tumors [24] (Fig. 1). Although androgen metabolites of DHEAS can bind either to AR or to ER [25, 26], and have been hypothesized to be partial ER antagonists [25, 27], the function of androgens in ER signaling remains to be fully elucidated.

The physiological interaction of AR and ER signaling is complex. In ER+ breast cancer cell lines, AR signaling inhibits ERα transactivation activity, and thereby inhibiting 17β-estradiol-mediated growth [18]. Several potential mechanisms have been proposed to explain these effects. It has been suggested that estrogen induces a physical association between the AR amino-terminal domain and the ERα ligand-binding domain [28], and it has been hypothesized that AR competes with ER for chromatin binding to a subset of estrogen-response elements (EREs) and represses the activation of specific ER target genes that mediate the proliferative effect of estradiol on ER+ luminal breast cancer cells [18]. An alternative hypothesis is that ligand-bound AR and ER compete for common coregulators, but bind to independent sites in the genome, after which AR exerts its inhibitory effects on ER signaling (Fig. 1c) (19).

There is an added level of complexity in the interaction between AR and ER signaling in the context of anti-estrogen therapy. Retrospective studies have suggested that high AR expression is a significant predictor of responsiveness to endocrine therapy of ER+ breast cancers [4•, 17, 18]. In contrast, AR is highly expressed in tamoxifen-resistant MCF-7 breast cancer cells. Recently, investigators have revealed that exogenous overexpression of AR rendered ERα+ MCF-7 breast cancer cells resistant to the growth-inhibitory effects of tamoxifen by enhancing tamoxifen-agonist activity on ERα at ERE sites [29]. Treatment with the AR antagonist bicalutamide a non-steroidal AR antagonist, restored tamoxifen sensitivity in these cells. Potential mechanisms by which AR may interact with ER signaling include the displacement of corepressor proteins, the recruitment of coactivators, or potentially acting as a coactivator (Fig. 1d) [19, 29].

AR has been implicated as having a function in the growth-inhibitory effect of aromatase inhibitors (AIs) in ER+ tumors. During aromatase inhibition, androgen precursors can act directly on AR or be converted to DHT, subsequently exerting an antiproliferative effect by activating AR [30]. Blockade of AR by bicalutamide or RNA interference abolished the antiproliferative effects of both DHT and letrozole. These findings suggest that the antiproliferative action of AIs on ER+ breast tumors is partly mediated through increased androgen signaling, in addition to a reduction in peripheral estrogen production, and may explain the lower relapse-free survival for postmenopausal women treated with adjuvant AI therapy compared with those treated with tamoxifen.

In summary, the effect of AR and ER signaling is complex and needs to be assessed in a context-dependent fashion, taking into account whether the tumor is sensitive or resistant to ER-directed therapy, whether concurrent ER- and AR- directed therapy is given and, if so, what type of therapy, and the menopausal status of the patient. It is likely that the interactions between these two pathways may have opposing effects in different clinical scenarios.

AR Biology in HER2+Breast Cancer

In contrast with ER, most studies have not examined the prognostic value of AR by HER2 status. In our analysis of published

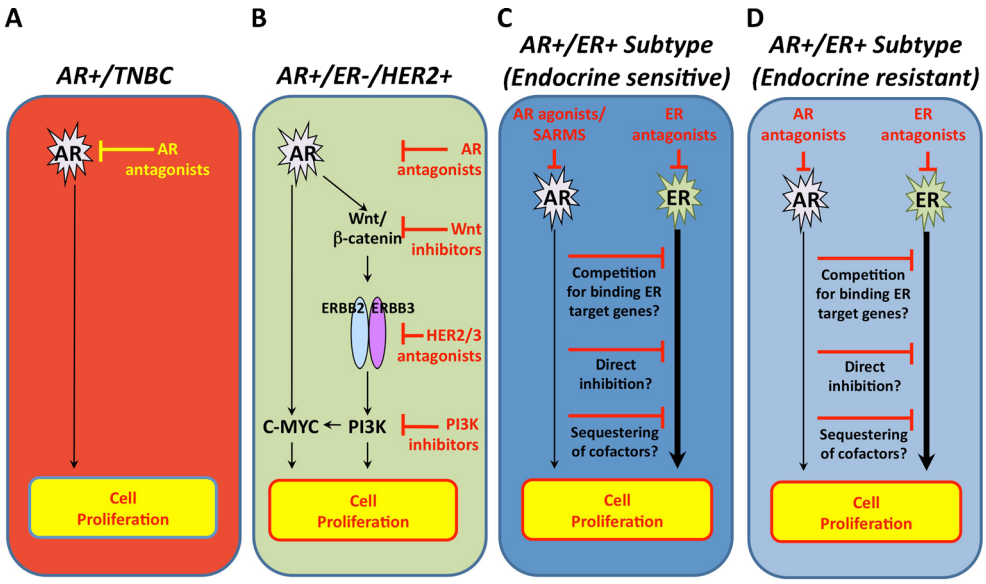

Fig. 1 Preclinical insights of AR signaling according to breast cancer subtype. AR antagonists have been shown to inhibit cell proliferation in **A**) TBNC AR+ and **B**) ER-HER2+AR+ breast cancer subtypes, the latter though its interaction with thte HER2/3, Wnt/β-Catenin and c-MYC pathways. On the other hand, AR antagonists results in increased cell proliferation in **C**) ER+AR+ breast cancer cells through its interaction with the ER signaling pathway, and AR agonists may therefore be of benefit in this setting. **D**) AR overexpression may be a mechanism of Tamoxifen resistance, ad inhibition of AR may be of benefit in this setting

microarray datasets of breast tumors, performed to gain an overall view of AR gene expression across different molecular subtypes in breast cancer [31–33], we found that high AR expression was correlated with HER2 amplification and overexpression [34••, 35], and, notably, that AR was not frequently expressed in the basal-like subtype. We also demonstrated that DHT, an androgen that cannot be converted by aromatase to estradiol, promoted growth in MDA-MB-453 (ER−/AR+/HER2+) breast cancer cells in an androgen-dependent manner; and the addition of bicalutamide abolished the DHT-stimulated growth of these cells [12]. In contrast, DHT significantly inhibited the estradiol-induced growth of ER+ T47D and ZR75-1 breast cancer cells. To understand the oncogenic function of androgen and AR in ER− breast cancer, we sought to determine the AR target genes through genomic profiling of the chromatin occupancy of AR and identify the androgen-responsive genes. The integrated analysis revealed that AR signals to the HER2 pathway by inducing the expression of HER3, which is primarily mediated by the Wnt signaling pathway. AR induction of WNT7B activated the nuclear translocation of β-catenin, which cooperated with AR to stimulate HER3 gene transcription; therefore describing a positive feedback loop between the AR and HER2/HER3 signaling pathways [34••].

More recently, we identified an additional positive-feedback mechanism whereby AR signaling is amplified by c-MYC [36]. AR directly activates *c-MYC* gene transcription, and AR-mediated activation of the HER2/HER3 signaling pathway increases the transcriptional activity of c-MYC by antagonizing MAD, the competitor of c-MYC binding to MAX. Consequently, c-MYC enhances the AR-activated gene transcription by acting on the promoters of AR target genes. These findings reveal a complex regulatory network of AR pathways in ER−/HER2+ breast cancer, in which AR cooperates with c-MYC and HER2 signaling pathways to drive oncogenic growth (Fig. 1b). A positive-feedback interaction between the AR and ERK signaling pathways has also been revealed to promote androgen and HER2-mediated cell proliferation in molecular apocrine breast cancer [37]. The combination of AR and MEK inhibitors not only resulted in synergistic therapeutic effects on MDA-MB-453 cells, but also overcame trastuzumab resistance in the derived MDA-MB-453-R resistant cells.

Taken together, these studies have further clarified the complex regulatory mechanisms of AR function, and the crosstalk between AR, HER2, and other signaling pathways in ER−/HER2+/AR+ breast cancer. These insights provide a preclinical rationale for investigating combinatorial therapy for this subset of breast cancer.

AR Biology in Triple-Negative Breast Cancer (TNBC)

Compared with ER+ breast cancer, the relation between AR expression and prognosis in ER− breast cancer is less clearly defined. Furthermore, because this is a less common subtype of breast cancer, most of the studies of AR in this subgroup are limited by small sample sizes. In the NHS, among women with ER− tumors (n=303, 42.9 % AR+), there was a non-significant positive association between AR status and increased risk of breast cancer-related death (HR=1.59) [4•]. In contrast, another smaller study found that AR positivity was associated with improved survival of ER− breast cancer (49 % AR positive, n=69, HR=0.33) [38]. It is important to note that the HER2 status was not factored into these analyses, and therefore these results are not representative of TNBC.

More recent studies have included HER2 in the analysis of AR expression in breast cancer. Most of the immunohistochemical studies have found that the AR+ tumors constitute a small subset within TNBC, ranging from 12–23 % [39, 40, 41•, 42, 43]. In a recent study, in which 23 % of tumors were AR+ (defined as ≥10 % nuclear staining, n=94), locoregional recurrence and both overall and disease-specific survival were similar for patients with AR+ and with AR− cancers, although AR-positivity was associated with more advanced disease [39].

A recent study further subdivided TNBC into multiple molecular subtypes in a large collection of publicly available gene expression profiles [44••]. One of the six TNBC subtypes (termed Luminal AR, representing 10–15 % of TNBC analyzed) was characterized by ER-negativity, but had the highest expression of gene ontologies that were enriched in hormonally regulated pathways, including steroid synthesis and androgen and estrogen metabolism. AR mRNA was nine-fold greater than was observed for all other subtypes of TNBC, and this correlated with the highest AR expression, as determined by immunohistochemistry for a small sample set. The authors went on to identify basal breast cancer cell lines that had a similar gene expression profile to the luminal AR subtype. These included MDA-MB-453, SUM185PE, CAL-148, and MFM-223 cells. These cell lines were sensitive to AR antagonists and HSP90 inhibitors in vitro, which supports the hypothesis that luminal AR tumors are driven by AR signaling (Fig. 1a). These results confirmed our studies of MDA-MB-453 cells, but these were classified as HER2-amplified in our studies and are probably more representative of HER2+/AR+ breast cancers than of TNBC [34••, 36]. Regardless, there is clearly a small subset of clinically defined TNBC tumors that are enriched for an AR-signaling gene signature, and AR is a logical therapeutic target in this subset.

A follow-up study looked at outcomes for patients diagnosed with TNBC who had residual tumor after neoadjuvant chemotherapy [45]. The TNBC subgroup that had a relatively favorable prognosis was characterized by high expression of "luminal-like" genes, such as AR and GATA3, in the residual tumor. This study suggests that there is heterogeneity in the tumors of patients who do not achieve a complete response to chemotherapy, and that luminal AR is a favorable subtype in this context.

Clinical Trials Targeting AR in Breast Cancer

Early trials targeting AR in breast cancer were largely failures, suffered from poor accrual, and did not adequately consider breast cancer subtype. In addition, these trials tested less effective AR antagonists, for example bicalutamide. Recent interest in targeting AR in breast cancer follows the successful development of next-generation AR-directed therapy for prostate cancer [46–48]. Of the breast cancer subtypes, therapy directed against AR is the first to be clinically evaluated for TNBC.

A phase II trial of bicalutamide (150 mg daily PO) for metastatic breast cancer was recently completed [41•]. This trial involved a prospective screening step, in which TNBC tumors were assessed for AR expression before being assigned to therapy. The frequency of AR expression, defined as >10 % nuclear staining on immunohistochemistry, was low at 12 % (n=51 of 424 screened). The primary end point of a clinical benefit rate, defined as the proportion of patients who had a clinical response or stable disease for >6 months, was 19 %, and median progression-free survival was 12 weeks. Importantly, bicalutamide was well tolerated; the most common treatment-related adverse events included fatigue, hot flushes, limb edema, and transaminase elevations. Major limitations of bicalutamide are its partial agonist activity towards AR, the low affinity with which it binds to AR, and that it has been revealed to induce escape mechanisms in prostate cancer [49]. Clinical results have not equaled the promise shown in vitro for AR+ breast cancer cell lines.

Enzalutamide has been developed as an AR antagonist for use in prostate cancer, and its affinity for AR is six-fold higher than that of bicalutamide. It targets multiple steps in the AR signaling pathway, including inhibition of AR nuclear translocation, DNA binding, and co-activator recruitment of the ligand–receptor complex [47]. In contrast with bicalutamide, it has not been found to have agonist activity. This improvement in AR antagonist activity has translated into improved survival for men with metastatic, castration-resistant prostate cancer after chemotherapy in a phase III clinical trial, and has led to its FDA approval for this clinical setting [46]. Enzalutamide is currently being evaluated in a phase I safety study of women with advanced breast cancer (ClinicalTrials.gov Identifier: NCT01597193), and in a phase II safety and efficacy study of patients with advanced AR+ TNBC at a dose of 160 mg daily (ClinicalTrials.gov Identifier: NCT01889238) (Table 1). Another second-generation AR antagonist, ARN-509, which has activities very much like those of enzalutamide, is in development for the treatment of castration-resistant prostate cancer (48). Interestingly, preclinical models have suggested it has greater efficacy and a higher therapeutic index than enzalutamide. Trials of this agent for treating castration-resistant prostate cancer have just begun, and there are no current trials of this agent for breast cancer.

The clinical development of AR-directed therapy for the ER+ and HER2+ breast cancer requires more complex trial design: as other effective targeted therapies are used to treat these subtypes, suggesting the possibility of combination therapy. For ER+breast cancer, as summarized above, numerous studies have revealed that AR expression is associated with improved breast cancer outcomes. Furthermore, androgens have been used in the treatment of ER+ breast cancer, alone or in combination with tamoxifen [50–52]. These results have not been consistently positive, and androgen is not a frequently used therapy in this setting. Although there is evidence that AR signaling inhibits ER activation of growth stimulatory genes in vitro [18], other studies have revealed that the antagonism of AR may restore tamoxifen sensitivity by inhibiting the ER-agonist response of tamoxifen [29]. Thus the use of

Table 1 Clinical trials of AR-directed therapy for breast cancer

Therapy	Phase	Breast cancer subtype	Site and/or sponsor	Clinical trials.gov	Enrolment
Letrozole 2.5 mg PO daily+DHEA 500 mg or 1000 mg PO daily	1	ER− advanced disease in postmenopausal patients	OHSU Knight Cancer Institute	NCT00516542	Jul 2007–Dec 2010; terminated because of poor accrual
Bicalutamide 150 mg PO daily	2	AR+ TNBC, advanced disease	Memorial Sloan–Kettering Cancer Center	NCT00468715	May 2007–Oct 2013; completed
Enzalutamide 80 mg and 160 mg PO daily	1	Advanced disease	Medivation	NCT01597193	May 2012–present; ongoing
Enzalutamide 160 mg PO daily	2	AR+ TNBC, advanced disease	Medivation	NCT01889238	Jun 2013–present; ongoing
Abiraterone acetate	1 and 2	Advanced disease in postmenopausal patients	Cancer Research UK	NCT00755885	Oct 2008–present, ongoing
Enobosarm 9 mg PO daily	2	ER+ advanced disease, in patients who previously responded to hormone therapy	GTx	NCT01616758	April 2012–present; ongoing

DHEA, dehydroepiandrosterone; TNBC, triple-negative breast cancer

AR antagonists in ER+/AR+ breast cancer needs to be carefully considered, taking into account the clinical context.

Regarding HER2+/AR+ tumors, we and others have revealed in preclinical studies that the AR and HER signaling pathways interact, and that AR-directed therapy, alone or in combination with HER2-directed therapy, results in tumor responses [34••, 36]. The logical step forward is therefore to evaluate this combination in a clinical trial. This is not without challenges, however, because there are many new and effective HER2-directed therapy developed in recent years, meaning the addition of an AR antagonist would require a strong effect if it were to improve tumor response rates and patient outcomes above and beyond that derived from HER2-directed based therapies. Regardless, there is biological rationale to target both receptors, and the crucial challenge is to identify the ideal combination with which to move forward, and in what clinical setting to use it.

An alternative strategy for targeting AR is to inhibit the enzyme *CYP17A1*, which is required for androgen synthesis. Abiraterone works via this mechanism, and has been FDA-approved for the treatment of castration-resistant prostate cancer [53, 54]. This drug is currently being evaluated in a phase I and II trial in the UK, which includes postmenopausal women with advanced breast cancer of all three clinical subtypes (ClinicalTrials.gov Identifier: NCT00755885). Finally, enobosarm (GTx-024) is a selective AR modulator that induces conformational changes in AR upon binding, selectively altering the interaction of AR with coactivator and corepressor proteins, and therefore the resultant AR signaling. This novel therapy has been evaluated in the setting of cancer-associated cachexia [55], and there is currently a phase I trial for patients with advanced ER+ breast cancer who have previously received and responded to up to three hormonal therapies (ClinicalTrials.gov Identifier: NCT01616758).

Finally, one must consider whether AR expression alone is sufficient to determine the presence of AR signaling. One potential strategy for identifying a more robust indicator of AR signaling is to define a breast cancer subtype-specific AR-target gene signature that encapsulates other components of AR signaling, similar to the approach that was used to define the Luminal AR subtype of TNBC [44••].

Novel PET tracers have recently been developed for AR in the setting of prostate cancer. Preliminary clinical studies have revealed that ^{18}F-fluoro-5α-dihydrotestosterone (FDHT) localizes to prostate cancer, and the uptake of FDHT in tumors is reduced with administration of AR-directed therapy [56–58]. In a recent study, FDHT-PET was also used to reveal the binding of enzalutamide to AR [59]. All patients who underwent PET imaging (n=22) had reduced FDHT uptake after one month of enzalutamide treatment, and an association was found between a greater FDHT response and higher drug doses, despite varying serum drug levels. FDHT has not yet been evaluated for imaging breast cancer, and may be potentially useful for noninvasive tumor characterization, patient stratification, and evaluating response to anti-androgen therapy in breast cancer patients.

Concluding Remarks

Clinically targeting AR in breast cancer treatment has recently become the focus of greater interest. This is the result of an improved understanding of breast cancer subtype-specific AR signaling, and of progress in developing new AR-directed therapy for prostate cancer. We can now begin to translate observations from pre-clinical studies into rationally designed clinical trials. Fundamental insights have been achieved regarding the identification of a luminal AR subtype in TNBC, and the interaction between the AR and HER2 pathways. These have translated into the completion of the first wave of clinical trials for TNBC, and trials of the next generation of AR-directed therapy are in progress for this cancer subtype. There is also a preclinical rationale for targeting AR and HER2, and it is likely that these combinatorial strategies will be investigated in clinical trials in the near future. The interactions of AR and ER signaling are complex, and although progress has been made in understanding the different ways and contexts in which these pathways interact, targeting AR appropriately in ER+ breast cancer remains a challenge.

Compliance with Ethics Guidelines

Conflict of Interest Elgene Lim has received a DF/HCC SPORE grant (P50 CA168504) and a fellowship from the National Health and Medical Research Council of Australia. Myles Brown has received grants from the Breast Cancer Research Foundation, National Cancer Institute, Novartis Pharmaceuticals, Medivation Inc. (pending), and has served on a scientific advisory board for Susan G. Komen for the Cure and is a consultant for Novartis. Min Ni, Aditi Hazra, Shiliang Cao, and Rulla M. Tamimi declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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