OR05-06: The Androgen Receptor Is a Tumour Suppressor in Estrogen Receptor Positive Breast Cancer

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There is strong interest in targeting the androgen receptor (AR) in estrogen receptor (ER) positive breast cancer, but widespread confusion exits as to what therapeutic strategy - agonism or antagonism - is appropriate. Current understanding of AR predominantly stems from the field of prostate cancer, where AR is the key oncogenic driver and therapeutic target. An ensuing assumption is that AR promotes malignancy in breast cancer and should be therapeutically antagonised. However, compelling pre-clinical data to support this assumption is lacking. Since estrogen stimulates and androgen inhibits the development of normal breast tissue, we hypothesized that AR acts as a tumour suppressor in the breast and that AR agonism is the appropriate therapeutic strategy for ER-driven breast cancer. We tested this hypothesis using a large suite of cell line and patient-derived explant (PDE) and xenograft (PDX) models of breast cancer, including those that were resistant to current therapies and those harbouring genomic anomalies of ESR1 associated with treatment-resistant disease. Across the diverse models we found compelling evidence that AR agonism, but not antagonism, potently and durably inhibited tumour growth. A signature of AR activity derived from the xenograft models positively predicted disease survival in multiple large clinical cohorts of ER+ breast cancer, out-performing other breast cancer-specific prognostic signatures. We also show that an AR agonist can be combined with current ER target therapies such as Tamoxifen or a CDK4/6 inhibitor to maximize growth inhibition. Mechanistically, agonist-bound AR opposed ER signalling by repositioning ER and the co-activator p300 in the chromatin landscape, resulting in down-regulation of cell cycle genes. Introduction of an AR DNA binding mutant had no effect on ER signalling or estrogen-stimulated growth in breast cancer cells. As part of this study, we have generated consensus AR cistromes representing ER+ breast cancer cell lines and ER+ tumours that provide a new understanding of AR activity and clearly show differences to those associated with prostate cancer cell lines and tumours. In conclusion, our data provides a compelling biological rationale for AR agonism as a therapeutic strategy in multiple, clinically relevant contexts of ER-positive breast cancer. These findings should dispel widespread confusion over the role of AR in ER-driven breast cancer, an issue that currently hinders progress in leveraging modern AR-targeted therapies (e.g. selective androgen receptor modulators) that lack the undesirable side-effects of androgens for clinical benefit.