Androgen ablation is the primary therapy for metastatic prostate cancer. However, within 3 years progression towards castration resistant PC (CRPC) cell occur. Despite low serum levels of testosterone (T) in patients under hormonal therapy, the androgen receptor (AR) remains active, indicating its remaining role in CRPC growth regulation. Previously, we demonstrated that conversion of adrenal androgens into T, rather than intratumoral pregnenolone (Preg), Prog, DHT and/or Abi, of Preg, Prog, DHT and/or Abi. CRPC clones were done in DCC with the addition of VCaP and DuCaP cell lines in steroid-stripped experiments using a subset of AR-overexpressing CRPC clones were generated by long term culture Cell proliferation was assessed by MTT-assay.

**Background & Aim**

**Materials & Methods**

**Conclusions**

**Results**

**Materials & Methods**

CRPC clones were generated by long term culture Cell proliferation was assessed by MTT-assay. Experiments using a subset of AR-overexpressing CRPC clones were done in DCC with the addition of Preg, Prog, DHT and/or Abi. Cell proliferation was assessed by MTT assay. mRNA levels of AR target gene (PSA) was assessed by RT-PCR. To study AR translocation HEP3B cells with GFP-tagged AR were used.

**Conclusions**

Progestrone at 100 nM can activate AR driven cell growth in AR overexpressing CRPC in vitro. The direct anti-androgen activity of Abi at exposures achieved in patients may counter the precursor hormone levels induced by its CYP17 inhibitor activity.

**Abiraterone may interfere with CRPC growth at two levels: CYP17 inhibition as well as direct AR inhibition.**

**Results**

**Figure 1**. In DuCaP CRPC cell line BIC-B, but not VCaP or VCaP CRPC cell lines, androgen precursors can induce cell growth despite adequate CYP17A1 blockade. In VCaP parental and CRPC cells, 10 nM R1881 induced AR regulated gene expression in VCaP parental and CRPC cells. 10 nM DHT induced substantial growth. In DuCaP BIC-B, these precursors do induce substantial growth. In DuCaP BIC-B, these precursors do induce substantial growth.

**Figure 2**. Higher levels of Abiraterone inhibit DHT-induced growth in both DuCaP and VCaP CRPC cell lines.

**Figure 3**: high concentrations (100 nM) of pregnenolone (Preg) and progesterone (Prog) induce AR regulated gene expression in parental VCaP cells. abiraterone completely blocks progesterone and pregnenolone induced AR regulated gene expression. Blocking CYP17A1 abiraterone completely blocks progesterone induced AR regulated gene expression.

**Figure 4**: Precursor hormones induce AR translocation. In HEP3B cells with a GFP-tagged AR showed AR translocation after treatment with 1 nM R1881. In HEP3B cells with a GFP-tagged AR showed AR translocation after treatment with 100 nM pregnenolone (Preg) and 100 nM progesterone (Prog) showed AR translocation.

**Figure 5**: Abiraterone slows down AR translocation. In HEP3B cells with an GFP-tagged AR showed AR translocation after treatment with 1 nM R1881. In HEP3B cells with an GFP-tagged AR showed AR translocation after treatment with 100 nM pregnenolone (Preg) and 100 nM progesterone (Prog) showed AR translocation after treatment with 1 nM R1881 and Abi.