

Activation of AR signaling by Mifepristone enhances prostate cancer growth and impairs enzalutamide response

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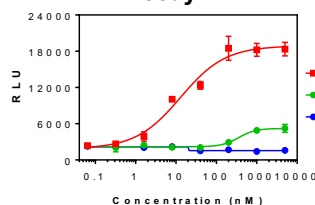


ABSTRACT

Androgen receptor (AR) signaling is crucial for normal development and homeostasis of the prostate, and is a key driver of prostate cancer initiation and progression. Hormone therapies that deprive the cancer of androgen have long been a mainstay of prostate cancer treatment. More recently, anti-androgens, such as abiraterone and enzalutamide, have been approved for use in metastatic castration resistant prostate cancer (mCRPC). Evidence also suggests that AR may play an oncogenic role in certain breast cancers. Several recent publications have demonstrated that activation of the Glucocorticoid Receptor (GR) can confer resistance to enzalutamide, and GR has also been shown to provide protection from conventional chemotherapies in other solid tumor indications. Mifepristone, is a synthetic steroidal antagonist of progesterone receptor, and to a lesser extent of GR and AR. It is currently being tested in clinical trials in combination with enzalutamide in mCRPC, and in combination with chemotherapy in triple negative breast cancer (TNBC). We sought to characterize the effect of mifepristone in pre-clinical models of prostate and breast cancer. Here we show that in the absence of androgen, mifepristone acts as a partial AR agonist, and this agonism can only be partially overcome by enzalutamide. We find that in low androgen conditions, mifepristone promotes the growth of prostate cancer cells in vitro and accelerates the growth of prostate tumors in xenograft models. Moreover, when given in combination, mifepristone significantly reduces the efficacy of enzalutamide in the LN-AR xenograft model. We are currently assessing the effects of mifepristone treatment in TNBC. Our findings suggest that partial AR agonist activity of mifepristone may have a negative impact in prostate and other AR positive cancers. We have developed a GR antagonist, OP-GR2, that is devoid of AR agonism to circumvent undesired effects on proliferation and drug response.

Results

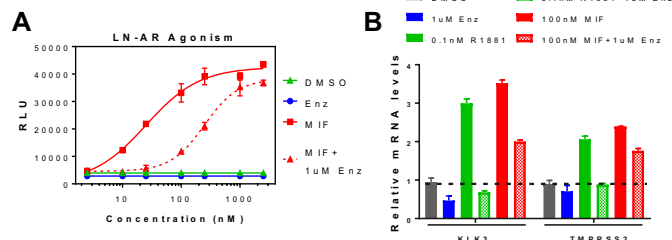
Agonist activity of Mifepristone in an AR-Reporter Assay



LNCAP-AR cells carrying an 4xARE-Luciferase reporter construct (LN-AR) were treated with Mifepristone (MIF), Bicalutamide (Bic) or Enzalutamide (Enz). Increased luciferase activity was observed in cells treated with Mifepristone, demonstrating its ability to agonize AR transcriptional activity.

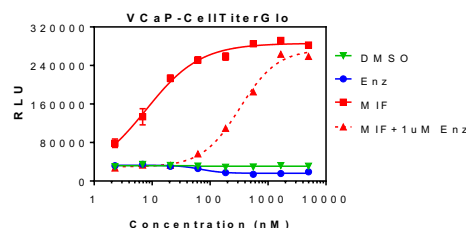
Results

Enzalutamide treatment does not fully block activation of AR by Mifepristone

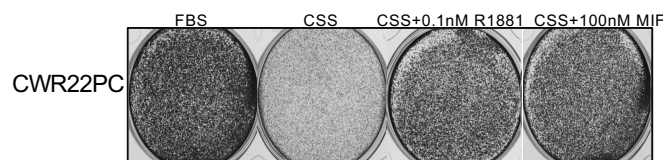


A) LN-AR cells were treated with Mifepristone, Enzalutamide or the combination. Induction of luciferase by Mifepristone still occurs in the presence of 1 μ M Enz. B) Endogenous AR target genes, KLK3 and TMPRSS2 are induced by synthetic androgen (R1881) and MIF. Enz inhibits R1881-induced expression, but does not fully inhibit MIF-induced expression.

Mifepristone stimulates proliferation of prostate cancer cells in the absence of androgen



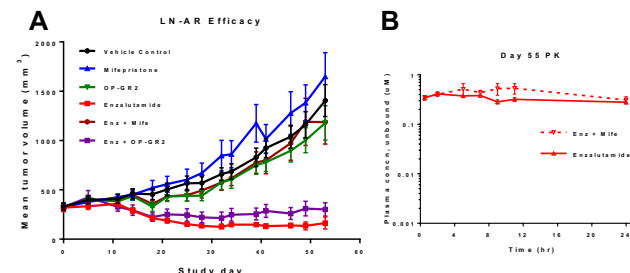
VCaP cells were treated with Mifepristone, Enzalutamide or the combination. MIF stimulates proliferation of VCaP cells even in the presence of 1 μ M Enz.



CWR22PC cells were plated at low density and grown under the indicated conditions. CWR22PC cells show limited growth in charcoal stripped serum (CSS). The addition of R1881 or Mifepristone rescues growth in CSS.

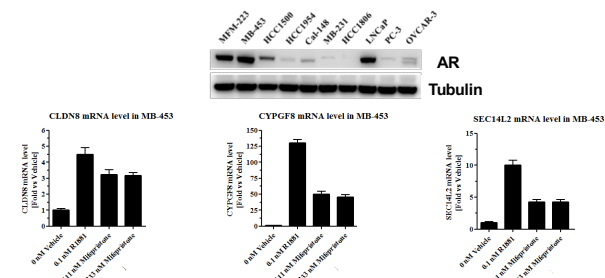
RESULTS

Mifepristone blocks Enzalutamide activity in vivo



A) Mice bearing LN-AR tumors were treated with Mifepristone, OP-GR2, Enzalutamide, or combinations thereof at clinically relevant doses as indicated. When combined, Mifepristone abrogated the activity of Enzalutamide, while OP-GR2 did not have a significant impact on the efficacy of Enzalutamide. B) Enzalutamide exposure is similar when dosed as a single agent or in combination with Mifepristone.

Mifepristone stimulates AR activity in AR+ TNBC Cells



Mifepristone stimulates AR target gene expression in the AR+ triple negative breast cancer line, MB-453.

CONCLUSIONS

- Mifepristone activates AR transcriptional activity in AR+ prostate and TNBC cells
- Mifepristone stimulates the proliferation/survival of AR+ prostate cancer cells grown in the absence of androgen
- Mifepristone abrogates Enzalutamide efficacy in vivo