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

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.


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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**

**Enzalutamide treatment does not fully block activation of AR by Mifepristone**

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

**Mifepristone stimulates target gene expression in the AR+ triple negative breast cancer cell 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.

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**Data from the laboratory of Dr. Kai-lung Kwok.**