UNIVERSITY OF MIAMI
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Therapeutic potential of nitric oxide signaling pathway agonists against castration resistant prostate cancer

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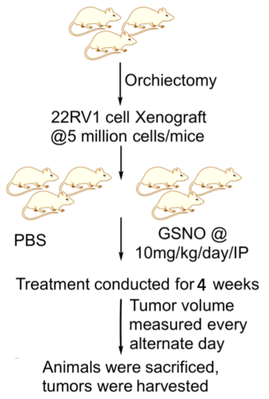
AIM To evaluate if exogenous Tadalafil (PDE5 inhibitor), a known inducer of cGMP, could affect the tumor microenvironment and suppress Prostate Cancer growth in a similar way that GSNO does.

INTRODUCTION

- The role of increased nitric oxide (NO) levels have been explored as a putative therapeutic option against castration resistant prostate cancer (CRPC).
- A variety of mechanisms for progression to CRPC are being studied, but the tumor microenvironment has been implicated to play a vital role in tumorigenesis.
- S-nitrosoglutathione (GSNO) is an active NO donor which has been shown to reduce CRPC tumor burden by targeting the tumor microenvironment and activating M1 macrophages.
- Tadalafil (Cialis), is a well-known PDE-5 inhibitor that also acts through the nitric oxide pathway, but its effect on CRPC is unknown.

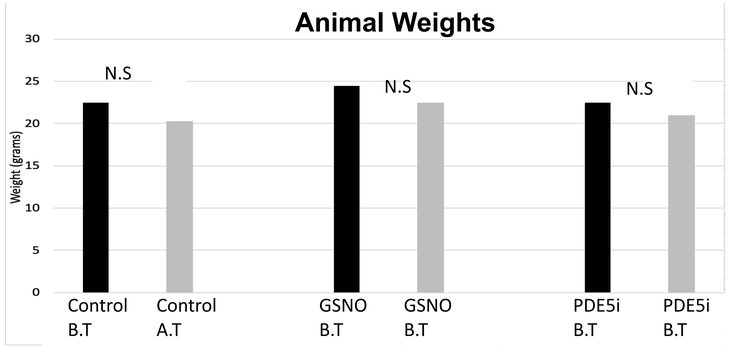


METHODS

Experiment plan. We grafted SCID mice with 22RV1 cells (AR-v7 subtype of CRPC) to generate CRPC murine models. Once the tumors became palpable, treatment with GSNO (10 mg/kg) and Tadalafil (1 mg/kg) was initiated and continued for 30 days.

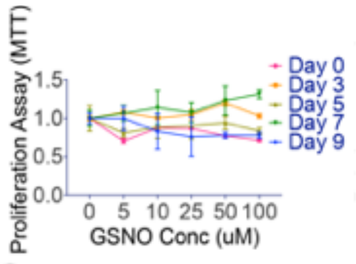
HYPOTHESIS: Although GSNO and Tadalafil both act via the nitric oxide pathway, GSNO can decrease CRPC tumor burden via tumor microenvironment.

Increased NO levels showed no significance in animal wt



Animal weights showed no significant differences between the treatment groups or from before and after treatment was given

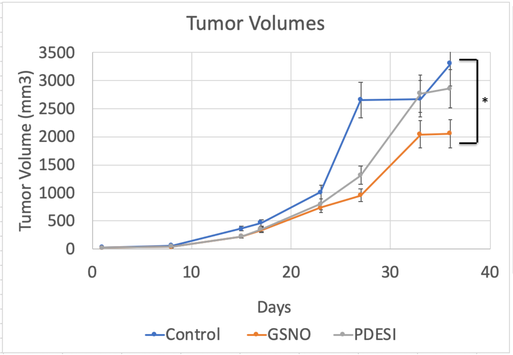
GSNO showed no differences in cellular proliferation



In vitro studies showed GSNO (shown here) treatment had no effects on cellular proliferation. There was a significant decrease ($p < 0.5$) in the cell proliferation when treated with Tadalafil at varying concentrations.

In vivo analysis showed no significant tumor reduction in mice treated with PDE5i compared to controls

A



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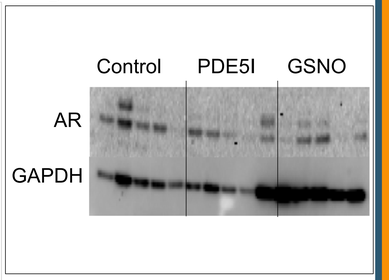

A) No significant difference in tumor volumes was seen between controls and PDE5i treated mice. However, there was a significant difference seen in GSNO treated mice. B) GSNO treated mice showed a decrease in AR in 3/5 mice while having a generally increased GAPDH. PDE5i showed a decrease in AR in only 2/5 mice.

CONCLUSION

- Although both GSNO and Tadalafil are acting through the nitric oxide signaling pathway, their effects on reducing castration resistant prostate cancer are independent.
- inhibition of PDE-5 leading to a build-up of cyclic GMP does not regulate CRPC and therefore confirming the mechanism of NO donor action on the tumor microenvironment.

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