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Title: Novel combinatorial therapy to combat abiraterone resistance in castration resistant prostate cancer

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Background. Abiraterone acetate (Abi), a drug for the treatment of castration-resistant prostate cancer (CRPC), exhibits a survival advantage in patients. However, ~30% of patients develop resistance after treatment. Abi-resistant tumors poorly respond to chemotherapy and other treatment modalities. Therefore, identification of an effective therapeutic alternative is needed.

We have demonstrated that a combination of simvastatin (SIM) and metformin (MET) is effective in CRPC with minimal effect on prostate epithelial cells. We investigate whether SIM and MET could be effective in the treatment of Abi-resistant cells.

Methods. C4-2B-Abi resistant cells were developed by continuous Abi exposure (1-20 μ M) over 60 days and maintained in 5 μ M Abi in the culture medium. Cells were treated with SIM (4 μ M) and MET (2mM) individually and in combination, followed by assessment of various cell growth and functional assays.

Results. C4-2B-Abi cells treated with SIM and MET at pharmacological doses (500nM-4 μ M SIM and 250 μ M-2mM MET). Combination treatment with 4 μ M SIM and 2mM MET led to significant inhibition of cell viability, migration, invasion, and cell cycle blockade in cancer cells. Individual treatments with SIM or MET exhibited a minimal effect on these cells. Furthermore, the SIM+MET combination decreased the expression of AR, PSA, and Wnt signaling members including cyclinD1 and c-Myc, an effect more pronounced than the treatment with Wnt inhibitors ICG001.

Conclusion. Our results suggest that the combination of SIM+MET may be an effective regimen for treatment of Abi-resistant prostate cancer.