

Targeting the androgen-indifferent state of prostate cancer through ferroptosis induction

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Background: Sensitivity to ferroptosis, a non-apoptotic form of iron-dependent cell death, has emerged as a conserved feature of therapy-resistant cancer cells across many types of cancer. Within the context of prostate cancer, this observation has led to the hypothesis that induction of ferroptosis may be a strategy to achieve tumor regression in patients suffering from androgen-indifferent CRPC, a lethal form of prostate cancer for which there are currently no targeted therapies.

Methods: To systematically test this hypothesis, we have procured and established eighteen different prostate cancer cell cultures representing a range of androgen indifference. These cultures have then been subjected to high-throughput small-molecule screening to profile their sensitivity to a panel of drugs representing androgen deprivation therapy (ADT), ferroptosis inducing agents and a variety of other cell-killing molecules.

Results: The results of these experiments reveal that androgen-indifferent prostate cancer cells emerging from resistance to ADT exhibit heightened ferroptosis sensitivity. However, prostate cancer cells engineered using genetic perturbations to model an androgen-indifferent state do not exhibit this heightened sensitivity to ferroptosis.

Conclusions and Future Directions: These findings are significant and impactful for two reasons: (1) they identify a subset of CRPC most likely to benefit from ferroptosis-inducing agents and (2) they uncover a key axis on which ADT-derived and genetically engineered models of androgen-indifference differ. Specifically, these findings suggest that genetic perturbations, such as NMYC overexpression and p53/Rb loss may not recapitulate some of the stress-response metabolic features and associated vulnerabilities that emerge in response to ADT-induced androgen indifference. This warrants further investigation and our research over the next two years will focus on illuminating the *in vivo* relevance and molecular basis of these differences.

References:

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Conflict of Interest: The authors declare no competing interests.

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Dedication: We dedicate this research to the late Dr. Andrew Hruszkewycz, who took a special interest in our work and buoyed us with his enthusiasm.