CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170399

Project Title:
Elimination of hypoxia sensitizes resistant solid tumors to immunotherapy

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

Unfortunately, as they form, cancers evolve means to hide from and locally dampen the immune system allowing them to thrive when they would otherwise be eliminated. In melanoma, we have shown that by blocking key molecules which cancers engage to shut off the immune system, even bulky metastatic tumors can be immunologically rejected. Unlike most therapies for solid tumors, immunotherapy has the potential to effectively cure a patient of all cancer and ward against its return. Despite these dramatic responses in some cancers, metastatic solid tumors such as prostate cancer respond poorly to immunotherapy. Discovering the mechanisms driving the immunotherapy resistance of these tumors and how to overcome them has become a major goal of the field.

Oxygen-starved hypoxic zones decorate tumors like holes in Swiss cheese. Long known to promote chemo- and radiotherapy resistance, we find them also to be critical drivers of immune suppression and immunotherapy resistance. We are studying a novel approach to break down immune resistance from within tumors by disrupting these oxygen-starved cores which act both to deny the immune system access to the tumor and to kill any immune cells which do make it through. In our preliminary studies, we have shown for the first time that spontaneously arising tumors in the most aggressive mouse models of prostate cancer can be controlled or eliminated by this combination of hypoxia ablation and immunotherapy. Remarkably, this remains true even in settings where, as in patients, the immunotherapy alone has no benefit. By breaking down immune resistance from within, and using immunotherapy to drive tumor killing from without, we hope to induce rejection of metastatic prostate cancer. The agents we are studying or equivalent ones are already in clinical trials; therefore, little time would be required before any effective combinations we find could enter the clinic and begin benefitting metastatic prostate cancer patients.