CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180690

Project Title:
Engineering Cancer Immunotherapeutics for Enhanced Activity in the Low pH Tumor Microenvironment

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
The University of Texas at Austin

Lay Summary:

In spite of the exquisite specificity and high affinity of antibody-based cancer therapies, they often cause damage to healthy cells since the cancer antigens are present on healthy and tumor cells. A perfect example of this phenomenon is the widely prescribed breast cancer antibody Trastuzumab, which has significant, well-documented cardiotoxic side effects in many patients because it binds a molecule found on the surface of certain breast cancer cells and also on heart cells. If present, the heart damage is often reversible, but cardiac function is monitored throughout Trastuzumab therapy and therapy may be delayed in some severe cases. This is especially problematic for those patients who are elderly, diabetic, or have existing high blood pressure or coronary artery disease.

We aim to protect cardiac tissue from the off-target effects of Trastuzumab therapy by taking advantage of the unique low pH environment near tumor cells. Because cancer cell grow quickly, they produce and accumulate acidic waste products in the tumor tissue. Normal blood and tissue have a neutral pH, so creating therapeutics that are more effective in the acidic pH of the tumor could reduce the side effects of anti-cancer drugs in normal tissues. We will engineer the Trastuzumab antibody to selectively bind its target, HER2, at low pH and to selectively interact with cancer killing immune cells at low pH, introducing complimentary mechanisms to improve specificity of an already effective breast cancer therapeutic. These improvements should increase tolerability and accessibility of Trastuzumab therapy. The methods we develop for Trastuzumab will be transferrable to other tumor-targeting antibodies, allowing more precise control over the tissues impacted by cancer therapy.