Award ID:
DP150061

Project Title:
Preclinical Development of a Therapeutic Enzyme for Immune Checkpoint Inhibition in Cancer

Award Mechanism:
Bridging the Gap: Early Translational Research Awards

Principal Investigator:
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Entity:
The University of Texas at Austin

Lay Summary:

Cancer cells only survive if they can keep the immune system from recognizing and eliminating them. One way that some forms of cancers do this is through the product of the immunosuppressive molecule Kyn. Kyn is produced when the amino acid Tryptophan is oxidized by one of three possible enzymes (i.e. IDO1, IDO2, TDO). Kyn is then transported outside the cell where it initiates 'tumor tolerance' by impeding the function of crucial cancer-fighting T cells.

Therapeutics developed to specifically reverse this kind of tumor-induced immune suppression (i.e. "immune checkpoint inhibitors") are increasingly popular, as evident by the number of recently adopted clinical trials. In the case of Kyn, the primary strategy so far has been the development of small molecules to stop production of Kyn by inhibiting IDO1, IDO2, and TDO. While many small molecule drugs can be effective in treating various cancers, their application in the case of Kyn faces significant challenges. To be successful, small molecules would have to inhibit IDO1, IDO2, and TDO simultaneously, which will complicate and likely hinder pharmaceutical development. Additionally, cancers are known to develop resistance to small molecules drugs as a whole.

In an effort to overcome these problems, we developed a novel biologic drug for reversing the suppressive effects of Kyn on immune cells. Our approach uses an enzyme (Kynureninase) that degrades Kyn into safe byproducts and restores normal immune cell functions, resulting in dramatic growth retardation of mouse melanoma tumors. Note that this therapeutic works to inhibit Kyn production regardless of which IDO/TDO enzyme may be expressed by a cancer cell, and it avoids the pitfalls of using small molecule Kyn inhibitors. The goals of this project are to expand upon this discovery and execute the product development and preclinical studies needed to deliver a powerful immune checkpoint inhibitor into the clinic for cancer therapy.