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Title: High Dose Acetaminophen Re-Invigorates Exhausted T-Cells for the Treatment of Non-Small Cell Lung Cancer

Acetaminophen (AAP) is the most common drug ingredient in America. AAP with n-acetylcysteine (NAC) rescue has shown promising anti-cancer activity with limited toxicity in early phase clinical trials. However, more advanced phase clinical trials have not been performed, in part due to lack of mechanistic understanding. In the present proposal, we outline preliminary data suggesting that high dose AAP has profound anti-tumor activity in a syngeneic orthotopic lung cancer model. However, the activity of AAP is lost in immune-compromised mice, suggesting an immune-modulatory mechanism of action. Additionally, AAP suppresses expression of TOX, the master regulator of T-cell exhaustion, as well as inhibitory receptors PD-1 and LAG-3. In Specific Aim #1, we will comprehensively evaluate the effects of AAP on T-cell exhaustion using assays such as flow cytometry, immunohistochemistry with Vectra Polaris imaging, and cytokine ELISAs. In Specific Aim #2, we will determine the role of STAT3 in mediating T-cell exhaustion using genetic knockdown and overexpression models. We will additionally study if effects of AAP on T-cell exhaustion are STAT3 mediated by studying phenotypic changes induced by AAP on STAT3 modified T-cells. This Pilot proposal would synergistically complement our current VA funded Career Development Award, which aims to determine if AAP depletes the cancer stem cell pool via inhibition of STAT3 phosphorylation. Ultimately, the data generated from this proposal will form the basis of VA Merit and RO1 grant proposals to be submitted in 2024.