UC San Diego
MOORES CANCER CENTER

2022 Gleiberman Head and Neck Cancer Center Pilot Grant

Targeting Syk to improve immunotherapy efficacy in HNSCC

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Scientific Abstract:

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer, with a 5-year survival rate of only 60%. Immunotherapies- mainly immune checkpoint inhibitors (ICI) hold great promise for the treatment of HNSCC as anti-PD1 mAb, nivolumab has recently demonstrated potent anti-tumor activity in a subset of HNSCC patients. However, more than 80% of patients don't show clinical benefits with nivolumab. One immunological strategy to improve the response rates of ICI is to target the immunosuppressive tumor-associated macrophages (TAMs) that limit cytotoxic T-cell responses and hinder the efficacy of immunotherapy in HNSCC. Recently my group has discovered a novel signaling pathway within the tumor microenvironment (TME), in which spleen tyrosine kinase (Syk) is activated downstream of the α4β1 integrin to control the polarization of immunosuppressive macrophages during tumor progression. We have shown that Syk signaling in macrophages promotes stabilization of hypoxia-inducible factor (HIF1/2α) to limit cytotoxic CD8+ T-cell responses in solid tumors. Hence, the central hypothesis for this proposal is that Syk promotes immunosuppressive transcriptional programming in macrophages to promote HNSCC growth, and Syk inhibition combined with anti-PD1/PDL1 therapy will reverse macrophage-mediated immunosuppression and activate anti-tumor immune responses in HNSCC. In Aim 1, we will dissect the role of macrophage Syk in HNSCC tumor progression and identify downstream factors of Syk that mediates immunosuppression. In Aim 2, we will determine whether inhibition of Syk enhances responses to immunotherapy in HNSCC. Hence, this proposal aims to develop new therapeutic options targeting Syk to improve outcomes for patients with HNSCC**.**

Lay Abstract:

Head and neck squamous carcinoma (HNSCC) accounts for more than 600,000 cases annually worldwide. Immune checkpoint inhibitors have recently gained a great deal of attention as they have saved the lives of some patients with metastatic HNSCC, but these drugs have not worked in most patients. Hence, we are proposing a targeted strategy to make immunotherapy more effective in this cancer. In studies performed in different cancer models, we found that Syk, an enzyme, controls the response of innate immune cells called macrophages. When cancer cells start growing in the body, macrophages are initially recruited in the tumors to kill the cancer cells. However, quickly cancer cells transform these macrophages to support tumor growth and suppress the effect of other immune cells like T cells. This switching of tumor-killing macrophages into tumor-promoting macrophages alters the entry of T cells into the tumors and impedes the efficacy of immune checkpoint inhibitors. Our studies in different cancer models have shown that inhibiting the action of Syk caused macrophages and T cells to mount a continued response against solid tumors grafted onto mice. Moreover, we found that the FDA-approved Syk inhibitor, R788, when combined with checkpoint inhibitors, improved the survival of mice grafted with solid tumors. Since

macrophage response is suppressed in HNSCC cancer patients, these results might be translated into therapy against HNSCC and can be combined with checkpoint inhibitors to improve the survival of patients suffering from this disease.