UC San Diego
MOORES CANCER CENTER

2020 Gleiberman Head and Neck Cancer Center Pilot Grant

Combining anti-CD40 antibody with checkpoint blockade and radiation to improve B-cell immune responses in head and neck cancer

Andrew Sharabi, MD, PhD
Whitney Sumner, MD

Scientific Abstract:

Studying the immune system is now at the forefront of oncology. In 2016 PD-1 blockade was FDA approved for relapsed refractory head and neck squamous cell carcinoma (HNSCC). However, objective response rates to PD-1 blockade in HNSCC are on the order of 16-20% and additional combinatorial strategies are needed. While many groups have focused on the role of T-cells in anti-tumor immune responses, we have recently identified that B-cells play a critical role in overall survival of HNSCC patients. In order to enhance B-cell development and function we have focused on activating B-cell surface co-stimulatory receptors. In particular CD40 is a critical costimulatory receptor found on antigen presenting cells including B-cells. Activation by CD40L induces robust B-cell activation and differentiation. Interestingly there are currently no ongoing trials evaluating anti-CD40 antibody in HNC. Our preliminary data has identified that agonist CD40 antibodies have robust anti-tumor activity and can combine with radiation therapy (RT) to improve tumor control. In this pilot study we propose investigating the role of B-cell agonist CD40 antibodies combined with RT and PD-1 blockade to enhance anti- tumor immune responses and HNSCC tumor control. Our hypothesis is that CD40 agonists combined with PD-1 blockade and RT will enhance B-cell activation and differentiation resulting in improved objective response rates and anti-tumor responses in HNSCC.
Ultimately these findings will significantly enhance our understanding of the role that B-cells play in HNSCC and could be directly translated into clinical trials to improve outcomes for HNSCC patients.

Lay Abstract:

Perhaps the most exciting avenue in cancer therapeutics is harnessing the immune system to promote tumor recognition and treatment response. In head and neck cancer (HNC), there have been limited advancements in the use of immunotherapy with modest response to checkpoint blockade inhibitors (CBI). Despite our eagerness to utilize immunotherapy in this heterogeneous population, there is limited knowledge of the immune response garnered by our combined therapies. There are, however, promising new agents on the horizon that warrant attention, one of which includes anti-CD40 antibody. In preclinical data, anti-CD40 antibodies have demonstrated a promising capacity to activate B-cells and other antigen- presenting cells with early clinical studies showing enhanced tumor response in pancreatic cancer and hematologic malignancies. Additionally, there are several ongoing trials seeking to exploit the non-redundant pathways of anti-CD40 antibody and CBI in other primary sites. To date, however, there have been limited pre-clinical studies and no ongoing trials evaluating anti-CD40 antibody

in HNC.

We hypothesize that anti-CD40 antibody combined with radiotherapy will enhance B-cell activation and differentiation resulting in enhanced tumor response in HNC. We then aim to show that adding CBI to this regimen represents a non- redundant pathway of immune augmentation to further strengthen tumor response and reduce metastatic potential. Ultimately, these findings serve to augment our understanding of B-cell populations following exposure to radiotherapy and non-redundant immunotherapeutic regimens. Of critical interest is the impact of these regimens on tumor response across multiple cell lines of HNSCC in order to predict response and guide future clinical trials.