UC San Diego
MOORES CANCER CENTER

2023 Gleiberman Head and Neck Cancer Center Pilot Grant

Targeting SUMOylation to Treat HPV+ Head and Neck Cancers

Yuan Chen, PhD

Scientific Abstract:

Background: Standard care of head and neck cancer (HNC) includes surgery and adjuvant radiation or adjuvant chemoradiation. However, a significant percentage of patients develop permanent tissue damage that impacts quality of life and many patients with very advanced disease recur after standard of care treatment. To address these challenges, we propose to investigate post-translational modification by the small ubiquitin-like modifiers (SUMO) as a novel target for treating HNC, particularly for human papillomavirus associated (HPV+) HNC. SUMOylation is a unique target that is actionable by clinical-stage and clinical ready therapies that simultaneously activates anti-tumor immune cells and inhibits tumor cells. In addition, our group and others have also shown that inhibiting SUMOylation in tumor cells inhibits Myc-dependent oncogenesis and repair of DNA damage induced by radiation therapy. In preliminary studies, we also found that HPV+ HNC cells are more sensitive to SUMOylation inhibition than HPV- HNC cells, suggesting HPV status be a potential biomarker.
Hypothesis/Objectives: We hypothesize that SUMOylation inhibition will induce durable remissions in HPV+ HNC and will enhance efficacy of standard of care radiation through Myc-dependent mechanisms and immune- mediated effects. We will test the hypothesis using syngeneic mouse models and primary tissues from patients. **Impact**: Our studies will lead to significantly improved tumor control and minimize long-term morbidity. A SUMOylation inhibitor has already been demonstrated to be well tolerated in clinical trials, and thus our studies are timely and likely lead to major federal funding in the near future to impact on-going clinical trial design and correlative studies.

Lay Abstract:

Scientific Objective and Rationale. Current treatment of head and neck cancers (HNC) involves surgery and adjuvant radiation or chemoradiation, causing morbidity issues in basic functions such as eating and speaking that result in significant quality of life challenges for survivors. Immune therapy has induced durable remissions in several solid tumor types, but not in majority HNC. To address these challenges, we will investigate a novel mechanism to enhance durable remission of HNC to improve long-term survival and quality of life for patients. This mechanism is unique in that it simultaneously activates anti-tumor immune response while inhibiting cancer cell survival. The high potential of this approach is supported by our exciting preliminary in inducing complete tumor regression and protective anti-tumor immunity.
Impact and Applicability. HNC is a common cancer with 51,540 new cases diagnosed and 10,030 deaths in the United States. Human papillomavirus (HPV) -associated oropharyngeal cancers are increasing to more than 70% of HNC. Immune therapy with PD-1/L1 blocking antibodies and in combination with chemotherapy have induced durable remission and transformed the lives of less

than 18% of HNC patients only. Our proposed studies could significantly change the paradigm by both increasing the survival rate for advanced and locally advanced diseases and improving the quality of lives of survivors of all stages of the disease. We anticipate that such therapies would transform HNC therapy by not only increasing survival, but also allowing preservation of functions to improve quality of life of survivors.