University of Alabama at Birmingham
PI: Carissa Thomas, MD, PhD, FACS
Co-I: Anthony Morlandt, MD, DDS, FACS

Oral Squamous Cell Carcinoma has a Unique Oral Microbiome that Increases Invasiveness and Predicts Risk of Metastatic Disease

Problem: Rates of overall survival for patients with oral squamous cell carcinoma (OSCC) have remained poor and relatively stagnant for decades. Regional lymph node (LN) metastases is one of the most important prognostic factors in OSCC but our ability to identify and mitigate risk of LN metastases is limited to aggressive surgery plus radiation and chemotherapy. Novel prognostic and treatment response markers are urgently needed as well as greater understanding of mechanisms of tumor invasion and metastases.

Gap: Effective prevention of metastases in patients with OSCC is elusive because of limited understanding of the drivers and mechanisms of invasion and the inability to predict those most at risk.

Rigor of Prior Research: Dynamic interactions between the microbiome (community of bacteria) and human host play a role in carcinogenesis. Characterization of the oral microbiome in OSCC is limited. Preliminary studies demonstrate increased Fusobacterium and decreased Streptococcus, but an in-depth understanding of the OSCC microbiome to species level is necessary to understand how bacteria communicate with OSCC tumor and tumor microenvironment (TME). Tumor Associated Macrophages (TAM) in the TME are associated with a poor prognosis due to increased tumor cell motility. Bacteria may increase TAM abundance and tumor cell invasiveness and subsequent metastases to regional LNs. Finally, elevated levels of VEGF plus tumor features of worst pattern of invasion, perineural invasion, and low lymphocyte invasion are associated with LN metastases.

Proposed Research: We hypothesize that the oral microbiome of metastatic OSCC has unique bacteria that play a mechanistic role in metastases. Patients with OSCC will be recruited and oral swab samples will be taken of the mucosal surface of the tumor leading edge and contralateral normal side. We will perform microbial species-specific analyses to investigate the overall patterns of bacteria composition and their association with the host characteristic of metastatic disease. We will combine this novel finding (oral microbiome) with established factors (VEGF and Brandwein tumor scoring) associated with metastatic disease to develop a metastasis risk score based on a retrospective cohort of patients. Finally, mechanistic studies will be done studying bacteria of interest in an OSCC-macrophage co-culture system. Bacteria-induced macrophage differentiation will be determined by flow cytometry and a Matrigel invasion assay system will be used to determine the invasive potential of OSCC tumor cells.

Innovation & Impact: Completion of a prospective study with high enrollment numbers will allow for direct comparisons between metastasizing and non-metastasizing OSCC to identify an unique oral microbiome in metastatic OSCC that can serve as a prognostic biomarker. This biomarker will be more robust when combined with known features of metastatic disease, and will potentially guide treatment in OSCC.

Species level identification of oral bacteria will allow for mechanistic studies of bacterial interactions with tumor cells and TME. Unique bacteria in metastatic OSCC may polarize macrophages to TAMs and increase invasiveness of OSCC cells. Finally, identifying specific bacterial drivers of TAMs and OSCC invasion will allow for modification of the oral microbiome to create a more favorable phenotype, decrease metastases, and improve treatment outcomes and survival.

Future Directions: The composition of the OSCC microbiome will be manipulated to create a tumorsuppressive environment and change the metastatic potential of OSCC. This grant will provide data to justify future grants for meta-transcriptomics as well as prospective clinical studies to validate biomarkers for utility in treatment decision making. Preliminary data from this grant will lay the foundation for an R series grant targeting the 2023 notice of special interest: Advancing Head and Neck Cancer Early Detection Research (NOT-CA-20-031).