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Advanced Three-dimensional Bioprinting of Patient-Derived Models for Head and Neck Cancer

The incidence of head and neck cancers (HNC) are increasing worldwide despite well recognized risk factors including tobacco, alcohol, and certain viruses (e.g. human papilloma virus [HPV] and Epstein-Barr virus [EBV]). HNC is typically managed in a multimodality fashion, especially in the oral cavity setting, where patients will often receive initial surgical resection followed by adjuvant radiation with or without chemotherapy depending on pathological criteria. Despite complete surgical resection and aggressive radiation and chemoradiation approaches, about 50% of patients will have their tumor recur. Recent advances, including the emergence of immune checkpoint blockade, especially in patients with high combined positive scores (CPS) for PD-L1, have provided additional therapeutic options. Nevertheless, HNC local failures and distant relapses are frequent and difficult to manage using current therapy. As such, there is a critical need for novel approaches for aggressive HNC.

One of the barriers to successful development of new HNC therapies has been the inherent limitations of most preclinical model systems. For decades, highly reproducible immortalized cancer cell lines have been the predominant preclinical tool for understanding disease biology, drug discovery, and drug development. Unfortunately, there is growing consensus that established cell line model systems are seriously limited because the tumor cells have been selected to thrive in artificial environments containing surplus nutrients (high oxygen tension, high serum-derived growth factors, high glucose concentrations). These selection pressures rapidly promote growth of a subset of highly proliferative cells that demonstrate marked differences from the original tumor. While immortalized cancer cell line panels (e.g., NCI 60) have shown some utility in the past, their poor representation of the human disease has contributed to high failure rates of cancer therapies in clinical trials. As such there is significant interest in developing patient-derived models of cancer (PDMC) which may overcome several of the above challenges. There are many different types of PDMC's with variable complexity and throughput, but mounting evidence indicates that these are more clinically relevant models. Indeed, the past few years has seen an increase in PDMC strategies in HNC supporting their use in preclinical and translational avenues.

Our OMS Foundation proposal seeks to utilize a three-dimensional (3D) bioprinting strategy to establish reproducible and scalable HNC PDMC's to explore their heterogeneity, therapeutic sensitivity and relationship with the tumor microenvironment. We hypothesize that the clinical behavior of HNC is a function of the inherent molecular biology of the tumor cells and the extrinsic pressure of the tumor microenvironment. We will test that hypothesis through the following specific aims.

Aim 1: Establish 3D Bioprinting Protocol for Primary Head and Neck Cancer and Cancer Associated Fibroblasts.

Aim 2: Determine relationship between immune-oncology signature and standard of care response of 3D head and neck constructs.