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Ex-vivo tumor responses to immunotherapy and the association with clinical response: Developing personalized cancer immunotherapy using a tumor explant approach

The development of immune checkpoint inhibitors (ICI) has transformed the field of oncology in recent years. Anti-PD-1 monoclonal antibodies, such as nivolumab and pembrolizumab, have proven efficacious in a diverse range of malignancies including head and neck squamous cell carcinoma (HNSCC). However, only about 17% of patients with HNSCC will respond to anti-PD-1. Use of biomarkers such as PD-L1 expression and tumor mutational burden (TMB) can enrich for patients who are more likely to respond to therapy, but no biomarker so far can definitively predict response. Therefore, better biomarkers are needed to identify which patients will respond to ICI therapy, as well as which patients will not benefit and for whom therapy would lead to unnecessary risk of serious toxicities. This will become increasingly important as applications of immunotherapy in HNSCC advance beyond recurrent and metastatic (R/M) disease and into the curative (i.e. surgical) setting.

Our group has previously demonstrated that the tumor explant platform can rapidly screen responses to immunotherapy in human and mouse tumors treated with an innate immune agonist, STING ligand, and that the explant responses correlated with response to therapy in mouse models. By testing immunotherapies on fresh tumor with intact stromal and immune cells, functional response to therapy can be assessed in a milieu that more accurately replicates the in situ tumor microenvironment in patients compared with other tumor models. We hypothesize that 1) human HNSCC tumor explants can be used to identify the diversity of responses to anti-PD1 and anti-GITR, two immunotherapies that have demonstrated meaningful synergy in cancer models and are now being tested as combination therapy in human cancers, and 2) that these responses may be informative in the selection of appropriate treatment for patients and/or monitoring treatment response.

In Aim 1 of this proposal, we will use a highly specific protein detection platform, Olink proteomics, to measure differences in cytokine production and expression of intracellular and cell-surface proteins involved in the anti-tumor immune response in tumor explants treated with either anti-PD1, anti-GITR, combination anti-PD1 and anti-GITR, or no treatment. These tumor samples will be obtained from patients who will go on to receive neoadjuvant pembrolizumab in a clinical trial that is currently enrolling at our institution, which will allow us in Aim 2 to correlate these functional responses with immune-related pathologic response as described by Cottrell et al (Ann Oncol 2018). We hypothesize that immune responses to therapy in tumor explants will be more often seen in patients who demonstrate pathologic response to therapy, and therefore tumor explants could be utilized as a biomarker for selecting patients who are appropriate for treatment.

Numerous new immunotherapeutic agents are in development for the treatment of HNSCC, either alone or in combination with anti-PD1. However, the development of new therapies is arduous, requiring incredible allocation of time and resources, and the complexities of evaluating combination therapies are far greater still. Therefore, there is a pressing need for alternative approaches to screening the activity of anti-cancer therapeutics. We hypothesize that functional responses of human tumor explants may inform methods of assessing response to immunotherapy. Aim 3 will use Olink Proteomics to assess for changes in the concentration of proteins identified in Aims 1 and 2 – which are differentially expressed in tumor explants from responders – over time in the serum of patients with R/M HNSCC receiving anti-PD-1 and anti-GITR in another clinical trial at our institution. This data will provide mechanistic insights into the anti-tumor activity of anti-PD1 and anti-GITR therapy and could direct further efforts at real-time monitoring of treatment responses in immunotherapy clinical trials.