Project Title: Plasma Levels of exosomal PD-L1 and Gene Expression as Predictors of Response to Immune Checkpoint Inhibitors in Gastrointestinal Cancers
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Normal cells in our body are equipped with a "checkpoint" to prevent immune cells from attacking it. Cancer cells hijack this protective mechanism and escape death from immune cell attack. Discovery of the immune checkpoint pathways and subsequent invention of drugs that inhibit this pathway ie immune checkpoint inhibitors (ICI) have revolutionized cancer treatment. ICI target the interaction between a cancer cell and killer T cells. When Programmed death 1 (PD-1) on T cells binds to Programmed death ligand 1(PD-L1) on cancer cells the T cells will not destroy the cancer. ICI therapy reverses that, allowing the T cell to recognize the cell as a cancer that needs to be destroyed. Response to ICI treatment varies widely among different patients and existing predictive biomarkers do not accurately identify patients who benefit from ICI. This is particularly important since ICI treatment comes with severe side effects and high costs. One of the greatest challenges is the determination of which patients will benefit from ICI therapy and which should receive more conventional treatments, avoiding unnecessary financial costs, loss of time, and severe side effects.

A developing technique to improve the ability to accurately diagnose cancer and to predict a patient's response to therapy is the liquid biopsy. Biofluids, such as blood or urine, contain many components that can be analyzed to understand what is happening inside the body. Exosomes are small vesicles that are released by all cells, but in excess by tumors. When released by cancer cells they carry cancer-related genes and proteins that not only can spread cancer growth but can also influence the function of cells with which they communicate. The protein PD-L1 has been identified on exosomes found in the blood of cancer patients and in patients with melanoma the amount of PD-L1 correlates with patient outcomes.

Gastrointestinal (GI) cancers have been shown to respond well to ICI, but many patients do not experience favorable results. There is a critical need to be able to predict which patients will respond to the treatment.

We hypothesize that exosomal PD-L1 (EXO-PDL1) can be used as a biomarker to predict if a patient will respond to ICI therapy. We propose to test this hypothesis by evaluating GI cancer patient's plasma exosome levels of PD-L1 before, during, and after treatment. PD-L1 levels will then be compared with clinical outcomes and correlation will be assessed. We will focus both on the predictive power of pre-treatment levels and the significance of EXO-PDL1 changes during treatment. With biomarkers, it is rare for a single gene or protein to provide sufficient information on which to base clinical decisions. Therefore, we will also identify the expression levels of additional exosome-bound immune-related genes and proteins that correlate with outcomes and create a predictive panel of biomarkers. Following completion of this study, these results will be directly translated into clinical trials to evaluate the effectiveness of these biomarkers in predicting therapy response prior to therapy initiation.