Lynch syndrome Colorectal Cancer Immunoprevention using Recurrent Neoantigen Peptide Vaccination

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Abstract: Germline mutations in DNA mismatch repair genes cause Lynch syndrome (LS). LS predisposes to colorectal cancer (CRC) and other cancers, affecting >1 million Americans. LS CRCs have hyper-elevated frameshift mutation rates. These include “shared” hotspot mutations recurrently arising in CRCs across patients, such as the same *TGFβR2* one basepair deletion frameshift mutation occurring in >60% of LS CRCs.

Frameshift mutations create novel open-reading frames, which lead to the most immunogenic tumor neoantigens. Recently members of our team showed that neoantigen peptide vaccination can elicit robust T-cell responses in advanced cancer patients in the adjuvant setting.

As preliminary data, we show that in LS mouse models vaccination with as few as four recurrent colorectal adenoma frameshift neoantigen peptides enhances T-cell immunity, reduces CRC incidence and prolongs survival. Here, we will perform exome sequencing on LS colorectal adenomas and integrate with publicly available advanced mismatch repair deficient CRC mutation data. First, we will delineate the most immunogenic recurrent neoantigens in LS colorectal adenomas. We will then elucidate whether these neoantigens are presented on MHC in LS colorectal adenoma cells and test the hypothesis that T cells from LS patients with colorectal adenomas recognize, and are cytotoxic against, recurrent colorectal adenoma neoantigens.

Overall, this study will use state-of-the-art tools to establish an innovative approach for an LS CRC immunoprevention vaccine, provide insights into LS premalignant neoantigen immunoediting and create a novel paradigm of recurrent tumor “hotspot” mutation peptide vaccination for pre- symptomatic patients with increased cancer predisposition.