Personalized Immunotherapy for the Treatment of Hematological Malignancies

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Abstract: Somatic mutations in the endoplasmic reticulum chaperone protein, calreticulin (CALR) and in core components of the spliceosome (e.g. SRSF2) have recently been identified as frequent cancer drivers across a spectrum of hematological malignancies. By their very nature, these mutations result in the generation of tumor-specific neo-antigens that may represent novel targets for anti-cancer immune therapy. The objective of our proposal is to determine the immunogenic potential of specific neo-epitopes generated by mutant CALR and mutant SRSF2 and to assess whether immune checkpoint inhibition can be harnessed to augment an anti-tumor response to these neo-epitopes. We hypothesize that the neo-antigens expressed by mutant CALR and/or mutant SRSF2 malignant hematopoietic cells can be targeted using immunotherapeutic approaches. In Aim 1 we will test this hypothesis in the context of mutant CALR and in Aim 2 in the context of mutant SRSF2. Using primary patient samples and in vitro cytotoxicity assays we will assess T-cell responses to specific neo-epitopes generated by mutant CALR and SRSF2. Using novel in vivo murine models that we have generated we will determine if mutant CALR and mutant SRSF2 expressing hematopoietic cells are preferentially targeted by immune checkpoint blockade. Our expectation is that mutant CALR and mutant SRSF2 generate neo-epitopes that are immunogenic and can be effectively targeted with immune therapy. Through this work, we will establish a biological rationale for the development of novel immunotherapeutic approaches for hematological malignancies that harbor CALR and SRSF2 mutations. We believe such approaches have curative potential in these diseases.