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.