Curebound Targeted Grant Fall 2022

Advancing Immune Checkpoint Inhibition of PSGL-1 for Treatment of Malignant Melanoma

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Scientific Abstract:

The goal of this project is *to develop a novel immune checkpoint blockade (ICB) therapy for metastatic melanoma by monoclonal antibody (mAb) antagonism of PSGL-1 (P-selectin glycoprotein 1),* which the Bradley lab discovered to be a T cell intrinsic inhibitory receptor that regulates T cell exhaustion and acts upstream of PD-1. This project combines the oncology expertise of Dr. Soo Park at MCC with the T cell exhaustion expertise of Dr. Linda Bradley at SBP. Although immune checkpoint blockade (ICB) targeting PD-1 and CTLA-4 on T cells benefits some patients, durable responses are atypical. **Thus, there is a critical unmet need to develop novel strategies to improve clinical outcomes**. We hypothesize that blocking PSGL-1 may offer a new avenue to overcome T cell exhaustion. We identified that a subset of functional PD-1^{+} tumor infiltrating T cells, which were identified in anti-PD-1 responsive melanoma patients, are enriched when PSGL-1 signaling is inhibited. Moreover, deletion or therapeutic blockade of PSGL-1 in an anti-PD-1 resistant melanoma model significantly inhibited tumor growth. Thus, PSGL-1 ICB may improve outcomes for melanoma patients whose tumors are refractory to existing ICB therapy. On the basis of our studies, we have generated anti-human PSGL-1 binding mAb and have selected 7 unique Abs for testing with tumor specific T cell responses of melanoma patients *in vitro* using HLA-A2 tetramers (Aim 1) and *in vivo* (Aim 2) with PBMC humanized mice bearing autologous tumors to identify a lead mAb for clinical advancement in the coming year.

Lay Abstract:

The goal of this project is to develop a novel immune system-based therapy for metastatic melanoma patients that employs monoclonal antibody treatment to block PSGL-1 (P-selectin glycoprotein 1), which the Bradley lab discovered to be a T cell inhibitory molecule that promotes the dysfunction of T cells that are required for tumor eradication. This project combines the oncology expertise of Dr. Soo Park at MCC with the T cell and tumor immunology expertise of Dr. Linda Bradley at SBP. Although current immune checkpoint blockade (ICB) therapies targeting PD-1 and CTLA-4 on T cells benefits some patients, durable responses are atypical. **Thus, there is a critical unmet need to develop novel strategies to improve clinical outcomes**. We hypothesize that blocking PSGL-1 may offer a new avenue to revive T cell tumor killing functions. We identified that a subset of functional tumor infiltrating T cells, which were identified in PD-1 blockade responsive melanoma patients, are enriched with inhibition of PSGL-1 signaling. Moreover, therapeutic blockade of PSGL-1 in a melanoma model that is resistant PD-1 blockade significantly inhibited tumor growth. Thus, PSGL-1 ICB may improve outcomes for melanoma patients whose tumors are refractory to existing ICB therapy. On the basis of our studies, we have generated human antibodies that bind to PSGL-1 and have selected 7 of these unique proteins for testing with T cell responses of melanoma patients in tissue culture and with humanized mice bearing matched patient tumors to identify a lead candidate for clinical advancement in the coming year.