Development of KSQ-001, an engineered TIL (eTIL™) therapy for solid tumors through CRISPR/Cas9-mediated inactivation of SOCS1

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Abstract

Background: Adoptive cell therapy with ex vivo expanded tumor infiltrating lymphocytes (TIL) offers a potentially curative treatment for cancer. However, the immunosuppressive tumor microenvironment limits the effectiveness of TIL therapy. To address this medical need, we used our Immune-CRISPRomics Platform to perform a series of genome-wide CRISPR/Cas9 screens to identify targets enhancing the ability of T cells to infiltrate and kill solid tumors in an in vivo setting. These screens identified SOCS1 as a top target that restrains T cell anti-tumor immunity. Based on these findings, we developed KSQ-001, an engineered TIL (eTIL™) therapy created via CRISPR/Cas9-mediated editing of SOCS1 for the treatment of solid tumors.

Methods: Genome-wide CRISPR/Cas9 screens were conducted in vitro in primary human T cell lines and cultures and in vivo in primary mouse OVA and PMEL TCR-OT T cells in syngeneic tumor models. The efficacy of surrogate murine KSQ-001 (mKSQ-001), in which the SOCS1 gene is inactivated by CRISPR/Cas9 in OVA or PMEL-TCR-OT T cells, was evaluated in both the B16-OVA and CRC-gp100 syngeneic tumor models. Both memory formation and efficacy evaluated both in the KSQ-001 was manufactured from human TIL using SOCS1-targeting sgRNAs selected for expression based on potency and saturation, with KSQ-001 characterized for in vitro function and in vivo anti-tumor efficacy.

Results: Upon adoptive transfer of a single dose into solid tumor-bearing hosts, KSQ-001 was found to robustly enhance anti-tumor efficacy and available tumors in B16 mouse in the PDL1-sensitve OT-1/OVA model and to drive responses in the PDL1 refractory PMEL-CRC-gp100 tumor model. KSQ-001 also showed a ten-fold increase in anti-tumor potency in vivo compared to unedited T cells, and established durable anti-tumor memory by persisting in the T cell memory pool contiguous to high frequency in the peripheral blood of complete responder mice. In the setting of lymphodepletion, mKSQ-001 also displayed heightened anti-tumor potency, accumulation, and memory formation in comparison to inactivation of PDL-1. Importantly, human KSQ-001 displayed a transcriptional signature indicative of increased anti-tumor function, produced increased amounts of pro-inflammatory cytokines, exhibited a hypersensitivity to IL-2 signaling, and demonstrated increased anti-tumor function both in vitro and in vivo solid tumor models.

Conclusions: Based on insights from our Immune- CRISPRomics platform and demonstrated efficacy across multiple preclinical tumor models, we have developed KSQ-001, a novel eTIL therapy. These preclinical data support clinical testing of KSQ-001 in a variety of solid tumor indications.

Figure 1: CRISPR/Cas9 inactivation of SOCS1 Enhances Murine KSQ-001 anti-Tumor Function and Persistence

• Robust mKSQ-001 efficacy & functional memory formation
• Enhanced accumulation of mKSQ-001 in tumor & depletion of Tregs
• Long-term persistence of mKSQ-001 as Tcm cells following tumor re-challenge

Figure 2: Human KSQ-001 Manufactured at Clinical Scale Demonstrates Enhanced Anti-Tumor Activity and Hypersensitivity to Cytokine Signals

• KSQ-001: An autologous, single-edit eTIL product manufactured using the baseline eTIL process, which includes an engineering step wherein Cas9/sgRNAs targeting the SOCS1 gene are electroporated (EP) into TIL

Methods

In Vivo Studies: Generation of mouse KSQ-001 cells (mKSQ-001)

KSQ-001 is Composed of CD45+ CD8+ TILs

Characterization of Human KSQ-001: Robust Editing of the SOCS1 gene

KSQ-001 displays enhanced anti-tumor function in comparison to TIL, including hypersensitivity to cytokines

Conclusions

• SOCS1 identified from KSQ’s Immune CRISPRomics Platform as a top target enhancing anti-tumor activity and memory formation of T cells in vivo
• KSQ-001 is a single-edit eTIL product with inactivation of the SOCS1 gene, and can be manufactured at clinical scale
• KSQ-001 displays enhanced anti-tumor function in comparison to TIL, including hypersensitivity to cytokines