XBP-1 Inhibitor B-I09 for the Treatment of Acute GVHD and Solid Organ Rejection

The technology, B-I09, is a small molecule inhibitor of XBP-1 that acts as an immunotherapeutic agent which regulates DC response to inflammatory stimuli, preventing acute GVHD in DC-allostimulated human T cells, while maintaining Treg function and anti-tumor activity by CTLs and NK cells. In NSG mice transplanted with human skin xenografts, B-I09 protects human skin grafts from alloreactive T cell rejection in vivo. B-I09 significantly decreased tissue destruction in skin grafts by allogeneic T cells (P < .01), decreasing lethal-grade GVHD (stage 3) to non-lethal-grade GVHD (stage 1). B-I09 also significantly decreased tissue destruction in liver and lung grafts by decreasing lethal-grade GVHD to non-lethal-grade GVHD.

COMMERCIAL OPPORTUNITY

- The Xbox binding protein 1 (XBP-1) transcription factor is a critical regulator of endoplasmic reticulum (ER) stress in dendritic cells (DC) and coordinates inflammasome activation via NLRP3 allowing DCs to promote Th17 differentiation that is relevant to graft-versus-host disease (GVHD).
- Graft-versus-host-disease (GVHD) is a major cause of non-relapse mortality in patients receiving an allogenic hematopoietic cell transplantation (alloHCT), of which approximately 8,000 are performed in the US annually. GVHD is caused by alloreactive donor T cells. GVHD prevention typically includes immunosupressive drugs that broadly suppress donor T cells. However this approach also impairs beneficial regulatory T cells (Treg) required for immune tolerance and cytotoxic T lymphocytes (CTL) that mediated the anti-tumor activity of the transplant.
- Ultimately, GVHD can add a cost of up to $67,000 to the treatment of a patient who has undergone a transplant. The number of patients likely to develop GVHD within 100 days of the transplant in the United States alone can be as great as 4,000/year, bringing the market size to $268 million.
- Today about 35,000 allogeneic Hematopoietic Stem Cell transplants are carried out annually worldwide and they are increasing each year. Around 40-60% of HSCT recipients will develop aGVHD. 30% of GVHD cases result in death.

TECHNOLOGY

In vitro experiments demonstrated that B-I09 significantly reduces human DC migration (34.4% v 12.8% CCL19 chemotaxis, P < .05) and stimulatory potency against allogeneic T cells (90.5% v 30.7% 5-day proliferation, P < .01) compared to a DMSO control. To test the efficacy of B-I09 in vivo, NSG mice were transplanted with a human skin graft (1 cm^2) and later injected with $5x10^6$ human peripheral blood mononuclear cells (PBMC) allogeneic to the skin. B-I09 was administered at 30 mg/kg by intraperitoneal injection five days a week for three weeks. Blinded pathologic scoring of recipient skin grafts at day +21 showed B-I09 significantly decreased tissue destruction by the allogeneic T cells (P < .01). A reduction in xenogeneic GVHD (murine liver, P < .05) was also observed. B-I09 also decreased tissue destruction in liver and lung grafts by decreasing lethal-grade GVHD (stage 2) to non-lethal-grade GVHD (stage 1 in lung and stage 0.5 in liver).

PUBLICATION/PATENT

- PCT patent application was filed September 10, 2017 for Dr. Betts.

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17MB051.2018.06