CD83 Targeting Chimeric Antigen Receptor Expressing T cell (CAR-T) to prevent GVHD

A chimeric antigen receptor (CAR) that works by using an anti-CD83 scFv region to enable an immune effector cell to target dendritic cells (DCs) expressing CD83. CD83 CAR-T cells target alloreactive host and donor DCs in a subject receiving a transplant. CD83 is expressed on the surface of mature antigen presenting DCs but not on immature DCs. CD83 CAR-T therapy therefore marks mature DCs for elimination and spares immature DCs to maintain DC-mediated beneficial immune tolerance, subsequent maturation and antigen presentation for adaptive resistance to infection.

COMMERCIAL OPPORTUNITY

- 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.
- CD83 antibodies have been shown to target activated DC, preventing GVHD but not interfering with engraftment of human T cells. CD83 antibodies have been shown to suppress the human immune response in vitro and in vivo.

TECHNOLOGY

Human T cells were incubated with dendritic cells at DC:T ratio of 1:30. CD83 CAR T cells were added to DC at different ratios 3:1 to 1:10. T cell proliferation was measured by Ki-67 after 5 days. The positive alloresponse of the T cells was 36.5% proliferating T cells against DCs. The CD83 CAR T potently reduced alloreactive proliferation from 3:1 to 1:3, and still reduced alloreactivity by 50% at 1:10 Control CAR T that did not express a chimeric antigen receptor did not have a suppressive effect, and caused increased alloreactivity. In addition, CD83 targeted CAR T cells prevent GVHD in animal models as assessed by survival, tissue infiltration, and clinical scoring. While this technology is initially being developed for GVHD it is also being adapted to treat autoimmunity and prevent rejection of off-the-shelf CAR T cells.

PUBLICATION/PATENT

- Provisional patent application filed February 23, 2018 for Dr. Davila and Dr. Betts.

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