TIM3 Targeting Chimeric Antigen Receptor Expressing T cell (CAR-T) for Acute Myeloid Leukemia Immunotherapy

A chimeric antigen receptor-expressing T cell that targets and kills TIM3 expressing cancers such as acute myeloid leukemia (AML). The CAR construct works by using a novel anti-TIM3 scFv region to enable T cell targeting of TIM3 expressing cancer cells and T-cell activation through the incorporation of co-stimulator and intracellular signaling regions. TIM3 is overexpressed on AML cells. Because TIM3 is also a leukemic stem cell surface marker in 85-90% of AML subtypes and is not expressed in normal hematopoietic stem cells, the anti-TIM3 CAR-T cells might also kill leukemic stem cells leading to a lower probability that minimum residual disease might lead to AML recurrence. Anti-TIM3 CAR-T cell mediated killing of TIM3-expressing cells was demonstrated.

COMMERCIAL OPPORTUNITY

- AML is a type of blood cancer where the bone marrow makes abnormal myeloblasts. AML accounts for nearly one-third of all new leukemia cases each year. The American Cancer Society estimates that in 2017 there will be 21,380 patients who develop AML and 10,590 AML patients will die.
- The standard of care for AML treatment has changed little over the past four decades. Intensive chemotherapy followed by hematopoietic stem cell transplantation remains the most effective treatment. However, most newly diagnosed elderly patients are ineligible for intensive chemotherapy, and there are no effective second line treatments for patients with relapse/refractory disease. As a result, the 5-year overall survival rates is 27%, and is less than 10% for patients over age 60. It is anticipated that the existing treatment for around 17,000 newly diagnosed AML patients will not be effective.
- AML cells and AML leukemic stem cells have been shown to have an almost ten-fold greater expression of TIM3 than normal cells. AML resistance and relapse to chemotherapies may originate from leukemic stem cells (LSCs), so targeting and eradicating LSCs might improve AML patient survival.
- The marketplace is attractive for CAR-T development, as Novartis received approval in August 2017 for its anti-CD19 CAR-T therapy for children and young adults with B-cell ALL that is refractory or relapsed at least twice. The list price is $475,000 for a one-time treatment; however, Novartis said that only those patients who respond by the end of the first month will need to pay. The Novartis trial had an overall response rate of 82.5% (52/63). Also in August 2017, Gilead acquired Kite Pharma that was also developing an anti-CD19 CAR-T therapy for $11.9B.

TECHNOLOGY

Anti-TIM3 sequences were identified by a next generation sequencing screening. This screening procedure for identifying anti-TIM3 sequences involved: 1) immunizing mice, 2) isolating splenic B cells, 3) isolating RNA, 4) FuzeSeq™ (GENEWIZ) antibody sequencing, 5) analyzing bioinformatics data of IgH and IgL rearrangements to select putative anti-TIM3 sequences based on frequency, and 6) in vitro screening to validate the clones. Two scFv VH domains, IGHV812 and IGHV1S81, and four scFV VL domains, IGKV1385, IGKV539, IGKV486, and IGKV461 were selected as top polypeptide candidates. In vitro experiments showed that co-culturing TIM3 positive cancer cells with Jurkat T cells transduced with synthetic anti-TIM3 scFv regions elicited T-cell activation where the percentages of activated T-cells were measured by IFN-γ levels using flow cytometry. Anti-TIM3 CAR-T cell mediated killing of TIM3-expressing cells vs. CD20-expressing cells was measured using an xCELLigence® Real-Time Cell Analysis instrument.

PUBLICATION/PATENT

- Provisional Patent filed on February 22, 2017 for Dr. Davila.

CONTACT

Haskell Adler PhD MBA
Senior Licensing Manager
Haskell.Adler@Moffitt.org
(813) 745-6596

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