CD33 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 CD33 expressing cancers such as acute myeloid leukemia (AML). The CAR construct works by using a novel anti-CD33 scFv region to enable T cell targeting of CD33 expressing cancer cells and T-cell activation through the incorporation of co-stimulator and intracellular signaling regions. The anti-CD33 CAR-T cell mediated killing of CD33-expressing cells was demonstrated. CD33 is a transmembrane receptor of the SIGLEC family that is expressed on myeloid cells. It is an effective target for treating AML as shown by in vivo AML mouse model studies where anti-CD33 CAR-T cells reduced leukemic burden and improved survival. Also, the FDA recently approved Mylotarg, an antibody drug conjugate for the treatment of CD33(+) AML.

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 treatment 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.
- CD33 is highly expressed on AML blasts in 85–90% of patients and its absence on normal hematopoietic stem cells makes it an attractive target for AML therapy. The FDA recently approved Mylotarg, an antibody drug conjugate (gemtuzumab ozogamicin) for the treatment of adults with newly diagnosed CD33-positive AML and patients aged 2 years and older with CD33-positive relapsed/refractory AML. The drug had a new dosing regimen that resulted in a statistically significant improvement in event-free survival of 7.8 months. Also, Ziopharm plans to begin a phase 1 study in AML using anti-CD33 CAR-T cells.
- 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-CD33 sequences were identified by screening hybridomas derived from immunized mice. scFv VH domains and scFV VL domains were selected as polypeptides candidates. In vitro experiments showed that co-culturing CD33 positive cancer cells with Jurkat T cells transduced with synthetic anti-CD33 scFv regions elicited T-cell activation where the percentages of activated T-cells were measured by IFN-γ levels using flow cytometry. Anti-CD33 CAR-T cell mediated killing of CD33-expressing cells vs. CD20-expresing cells was measured using an xCELLigence® Real-Time Cell Analysis instrument. Two clones 6A11_1 and 27A3_1 showed strong killing while 27A3-2 and 27A3_3 showed medium killing between control and the strong killers.

PUBLICATION/PATENT

- Provisional Patent filed on February 20, 2017 for Dr. Davila.

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