CD123 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 CD123 expressing cancers such as acute myeloid leukemia (AML). The CAR construct works by using a novel anti-CD123 scFv region to enable T cell targeting of CD123 expressing cancer cells and T-cell activation through the incorporation of co-stimulator and intracellular signaling regions. The anti-CD123 CAR-T cell mediated killing of CD123-expressing cells was demonstrated. CD123 (IL-3 receptor α subunit) is a tumor associated antigen over-expressed on AML blasts and leukemic stem cells. CD123's low or absent expression on normal hematopoietic stem cells makes it an attractive target for therapy as developers expect fewer adverse side effects.

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.
- CD123 is a promising target for AML as it is overexpressed in about 45% of AML patients but is overexpressed on leukemic stem cells in a majority of AML patients, and in contrast is low or absent on normal hematopoietic stem cells. Several therapies targeting CD123 are in or are about to begin AML phase 1 trials including an anti-CD123 antibody-drug conjugate by Seattle Genetics, T cell recruiting antibody constructs by MacroGenics, Xencor and Genmab, and anti-CD123 CAR-T therapies by Mustang, TheraVectys and Cellectis.
- 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-CD123 sequences were identified by screening hybridomas from immunized mice. scFv VH domains and scFV VL domains were selected as polypeptide candidates. In vitro experiments showed that co-culturing CD123 positive cancer cells with Jurkat T cells transduced with synthetic anti-CD123 scFv regions elicited T-cell activation where the percentages of activated T-cells were measured by IFN-γ levels using flow cytometry. Anti-CD123 CAR-T cell mediated killing of CD123-expressing cells vs. CD20-expresing cells was measured using an xCELLigence® Real-Time Cell Analysis instrument. Two clones 15A12_22 and 15A12_21 showed strong killing while seven other clones showed varying degrees of killing between the control and the strong killers.

PUBLICATION/PATENT

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

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