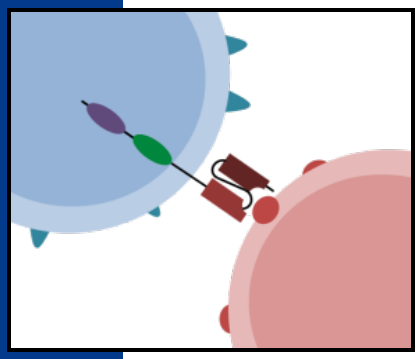
CLEC12A Targeting Chimeric Antigen Receptor Expressing T cell (CAR-T) for Acute Myeloid Leukemia Immunotherapy



A chimeric antigen receptor-expressing T cell that targets and kills CLEC12A expressing cancers such as acute myeloid leukemia (AML). The CAR construct works by using a novel anti-CLEC12A scFv region to enable T cell targeting of CLEC12A expressing cancer cells and T-cell activation by incorporating co-stimulator and intracellular signaling regions. CLEC12A (C-type lectin 12A/hMICL) is a tumor associated antigen over-expressed on AML blasts and leukemic stem cells. CLEC12A's low or absent expression on normal hematopoietic stem cells makes it an attractive target for therapy as fewer adverse side effects are expected.

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 rate is 27%, and is less than 10% for patients over age 60.
- CLEC12A is a promising target for AML as it is aberrantly expressed in about 90% of AML patients and is a stable and reliable marker of leukemic stem cells. In contrast, CLEC12A expression is low or absent on normal hematopoietic stem cells. Several therapies targeting CLEC12A are in or are about to begin clinical development. Novartis, in collaboration with UPenn, published a pre-clinical study demonstrating the successful targeting of CLEC12A-positive leukemic cells with CLEC12A CAR-T cells. Merus is developing a bispecific T-cell engagement antibody binding CD3 and CLEC12A that is in a Phase I trial for AML in Europe and is pending IND approval in the US.
- The marketplace is attractive for CAR-T development, as Novartis received approval in August 2017 for Kymriah, its anti-CD19 CAR-T therapy for pediatric B-cell ALL. The trial had an overall response rate of 82.5% (52/63). Although the list price for Kymriah is $475,000 for a one-time treatment, Novartis has said only those patients who respond by the end of the first month will need to pay. In October 2017, Gilead's Yescarta, an anti-CD19 CAR-T, was approved for large B-cell lymphoma and is listed at $375,000. In 2017, Gilead acquired Kite Pharma for $11.7B, and in 2018, Celgene has agreed to acquire Juno Therapeutics for $9B. Juno is also developing a CD-19 CAR-T therapy.

TECHNOLOGY

Anti-CLEC12A sequences were identified by a next generation sequencing screening coupled with a monoclonal antibody producing procedure. scFv VH domains and scFV VL domains were selected as polypeptide candidates. *In vitro* experiments showed that co-culturing CLEC12A positive cancer cells with Jurkat T cells transduced with synthetic anti-CLEC12A scFv regions elicited T-cell activation where the percentages of activated T-cells were measured by IFN-γ levels using flow cytometry.

PUBLICATION/PATENT

- Provisional Patent filed on January 9, 2018 for Dr. Davila.

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