NKG2D Chimeric Antigen Receptor expressing T cells (CAR-T) for Acute Myeloid Leukemia Immunotherapy

A chimeric antigen receptor-expressing T cell that targets and kills NKG2D ligand expressing cancers such as acute myeloid leukemia (AML), multiple myeloma (MM), and myelodysplastic syndrome (MDS). The CAR construct works by using a novel NKG2D region to enable T cell targeting of NKG2D ligand expressing cancer cells and T-cell activation through the incorporation of co-stimulator and intracellular signaling regions. The NKG2D ligands, the MIC and RAET1/ULBP families, are expressed on the surface of stressed, malignant transformed, and infected cells.

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.
- NKG2D is a major recognition receptor for the detection and elimination of transformed and infected cells as its ligands are induced during cellular stress, either as a result of infection or genomic stress such as in cancer. All NKG2D ligands are homologous to MHC class I molecules and are divided into two families: MIC and RAET1/ULBP. NKG2D ligand is highly expressed on the surface of AML, MM and myelodysplastic syndrome cancer cells. A Phase I Trial of chimeric NKG2D CAR T cells in AML/MDS and MM was carried out by Celyad and found no DLTs in the first nine patients.
- 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 acquired Juno Therapeutics for $9B. Juno is also developing a CD-19 CAR-T therapy.

TECHNOLOGY

NKG2D sequences were identified and used to create chimeric CAR-T constructs. *In vitro* experiments showed that co-culturing NKG2D positive cancer cells with Jurkat T cells transduced with synthetic NKG2D chimeric 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 April 6, 2018 for Dr. Davila.

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