TLR-9 Targeting Chimeric Antigen Receptor-Expressing T cell (CAR-T) for MDS and AML Immunotherapy

Our technology is a chimeric antigen receptor-expressing T cell that targets TLR-9 present on the surface of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) cells. The CAR enables T cell targeting of the cancer via the antigen binding domain, as well as T cell activation through the incorporation of several co-stimulator and intracellular signaling regions. Because normal tissues that express TLR-9 do so only in the intracellular compartment, these normal tissues are rendered 'invisible' to the CAR-T. This enhances the specificity of our CAR-T for the treatment of MDS.

COMMERCIAL OPPORTUNITY

- MDS is the most common bone marrow failure syndrome, with 13,000 patients diagnosed a year according to the American Cancer Society. MDS is a diverse group of blood disorders characterized by low levels of properly functioning red blood cells. About 30% of MDS patients progress to acute myeloid leukemia (AML), with 19,000 new diagnoses a year.
- Current approved treatments for MDS include lenalidomide for the 15% of patients with the del(5q) mutation, or DNA methyltransferase (DMT) inhibitors. 76% of lenalidomide-treated patients will show a positive response; however, less than 20% of patients treated with a DMT inhibitor like decitabine will achieve a complete or partial response. Costly stem cell transplants are currently the only known cure for MDS, and pose potentially fatal side effects. Hence, there is a need for additional MDS therapeutics.
- The marketplace is attractive for CAR-T development, as 27 current CAR-T clinical trials are being carried out by companies like Kite Pharma (market cap $2.3B), Juno Therapeutics (market cap $2.0B), Cellectis (market cap $614.4M), and Bluebird Bio (market cap $2.9B).
- Of the current CAR-T therapeutics in clinical trials, several have received orphan drug status that could result in a seven-year market exclusivity period by the FDA, or they have received the breakthrough therapy designation that could result in priority review by the FDA. There are however currently only two studies investigating this technology for treating MDS.

TECHNOLOGY

Ten 2nd generation CAR constructs were designed and cloned into a MSGV-1 retroviral vector. Constructs included a primary intracellular domain CD3ζ, and a second costimulatory domain being CD28, 4-1BB, CD27, or BTNL3. A novel, mutagenized antibody constant region (CH1) is the antigen binding domain. These constructs specifically recognize TLR-9 on the surface of SKM1 cells, a line from an MDS patient who progressed to AML. Upon recognition, these CAR-T cells release 3-7 times more interferon gamma (IFNγ), a cytokine indicative of T cell tumor killing.

PUBLICATION/PATENT

- Provisional patent filed for Dr. Abate-Daga, Dr. Wei, and Dr. List in December 2016.

CONTACT

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

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