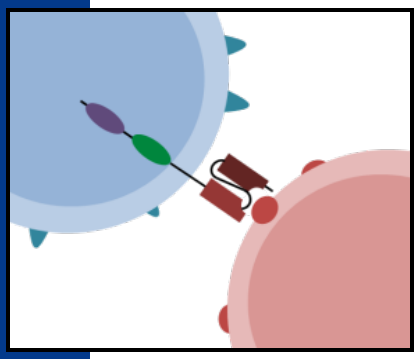
Bispecific CD33/CD123 CAR-T Cells for Acute Myeloid Leukemia Immunotherapy



CD33 or CD123 targeted Chimeric Antigen Receptor (CAR) T cell therapies have shown promise but struggle with on target off tumor toxicities, complicated allogeneic HSC transplants, and AML relapse. In response, novel bispecific human CD33/123 CAR T cells with split signaling costimulation domains were highly efficacious in vitro at killing target cells, proliferating and generating substantial amount of cytokines, and were able to control AML and relapse in a xenograft AML mouse model, eliciting a potent response that did not impact HSC differentiation.

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 2019 there were 21,450 patients who developed AML and 10,920 AML patients who died.
- 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.
- CD33 and CD123 are abundantly expressed on AML blasts but are also present on normal cells and can result in toxicity. CD33 is present on HSC, subsets of T cells, and Liver Kupfer cells. Consequently, CD33 targeted therapies such as Mylotarg have been accompanied by myelosuppression and cytopenia. While CD123 expression is low on HSCs and common myeloid progenitors, its expression on blood vessels has led to on target off tumor toxicity in a CD123 directed CAR T therapy clinical trial. Similar results using fresh AML blasts have been obtained from patients from Moffitt. A bispecific CAR-T cell might avoid these problems.
- The marketplace is attractive for CAR-T cell therapies, as Novartis received approval in August 2017 for Kymriah, its anti-CD19 CAR-T therapy for pediatric B-cell ALL with an ORR of 82.5%. 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. Kymriah had annualized sales of $243M in 2019, and Yescarta had sales of $456M in 2019. Also CMS in 2018 set Medicare Part B reimbursements for CAR T-cell therapies at $500,000 for Kymriah and $400,000 for Yescarta in the outpatient setting.

TECHNOLOGY

CD33/123 bispecific CARs can eliminate AML in a xenograft model. NSGS mice were injected via tail vein with $1x10^6$ MOLM13-GFP/Luciferase cells. BLI was performed to quantify engraftment and randomization of treatment groups. CD33/123 bispecific CAR T cells $5x10^6$ were injected followed with imaging every week for 3 more weeks. Mice were euthanized on week 4 and AML and CAR T cells from bone marrow were quantified via Flow cytometer.

PUBLICATION/PATENT

- Provisional Patent filed in May 2020 for Dr. Davila.

CONTACT

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

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