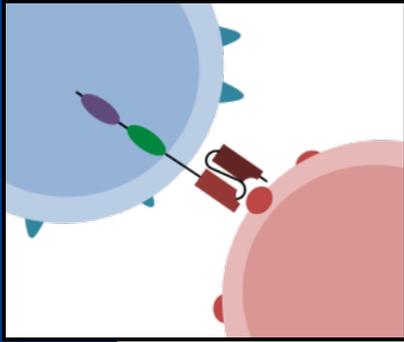


Chimeric Antigen Receptor Tumor Infiltrating Lymphocytes (CAR-TILs) for Solid Tumor Therapy



To date, chimeric antigen receptor T-cell (CAR-T) therapy has had notable success in the treatment of certain hematologic malignancies. In contrast, solid tumors have been treated more successfully with immune checkpoint inhibitors and tumor infiltrating lymphocyte (TIL) therapy. Given that about 90% of cancer related deaths have been due to solid tumors, there is a strong unmet need for immunotherapies that are more effective at killing solid tumors. CAR-T cells in the clinic and on the market have been made from activated peripheral blood T cells; however, peripheral blood T cells are not biologically equipped to penetrate solid tumor masses. CAR-TILs would use TILs as the vehicle to penetrate solid tumors and destroy the cancer. The technology allows any CAR construct against a solid tumor to be introduced into a TIL, and standard CAR-T cell manufacturing processes could be employed. Moreover, as a proof of principle, an anti-IL13R α 2 CAR TIL has been successfully generated.

COMMERCIAL OPPORTUNITY

- In mouse models, TILs exhibit tumor tropism, for example almost all adoptively transferred TIL from CD45.2+ donor mice go directly to the tumors in a recipient tumor-bearing mouse (CD45.1+). This could enhance the current response rate in humans of about 9% in a review of 22 solid tumor CAR-T studies up to June 1, 2018 compared to a response rate for pediatric B-cell ALL of 82.5%.
- The marketplace is attractive for CAR-T cell 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 was also developing a CD-19 CAR-T therapy.
- TIL therapy has been shown to be clinically effective as demonstrated by a 24% Complete Response rate in 101 metastatic melanoma patients by Dr. Steven Rosenberg at the NCI. With a median potential follow-up of 40.9 months, only one of 24 patients who achieved a CR recurred. TIL company valuations could be represented by Iovance Biotherapeutics that has a market cap of \$3B. Iovance's most advanced product is a TIL therapy in a registration trial for melanoma.

TECHNOLOGY

MC38 tumors were generated in donor mice (CD45.2+) by subcutaneous injection of a tumor cell suspension. Once the tumors are established, CD45.2+ TIL were isolated and expanded ex vivo in presence of IL-2. These were injected in recipient tumor-bearing mice (CD45.1+). The tissue distribution of the adoptively transferred TIL were tracked by flow cytometry. By day 7 post-infusion, virtually all transferred TIL (and all CD8+ transferred TIL) had trafficked to the tumors. Tumor infiltrating lymphocytes from a melanoma patient were expanded and were transduced with a retroviral vector encoding an anti-IL13R α 2 CAR (Hu07-28z). CAR expression was evaluated by flow cytometry following staining with biotinylated Protein-L and PE-conjugated streptavidin.

PUBLICATION/PATENT

- Provisional Patent filed on June 12, 2018 for Dr. Mule.

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LICENSING OPPORTUNITY

