The CAR construct works by using an anti-PSCA scFv region to enable T cell targeting of PSCA expressing cancer cells and T-cell activation by incorporating co-stimulator and intracellular signaling regions. PSCA is a tumor associated antigen over-expressed on prostate cancers. PSCA’s low or absent expression on normal adult tissues makes it an attractive target for therapy. γδ CAR-T cells show enhanced recruitment and activation in bone when patients are treated with bisphosphonates. In a mouse model, γδ PSCA-targeted CAR T cells induce prostate tumor regression in bone and extend survival, protect against tumor-associated bone disease, and significantly mitigate tumor-induced osteolysis. The dual antigen recognition (via CAR and via TCR) achieved by γδ CAR-T cells allows for enhanced cytolytic effect.

COMMERCIAL OPPORTUNITY

- Prostate cancer is responsible for >29,000 deaths/year in the US alone. Bone metastasis is a frequent complication in advanced prostate cancer, with the resultant lesions significantly contributing to patient morbidity and mortality. While next generation hormone ablation therapies and bone protecting bisphosphonates offer survival improvement of a few months, the disease remains incurable, and new therapeutic approaches are needed.
- The use of gamma delta CAR-T cells is important because whereas conventional CAR T cell therapies utilize αβ T cells, γδ CAR T cells home to bone metastases when administered with bisphosphonates. Patients treated with bisphosphonates such as zoledronate exhibit enhanced recruitment and activation of the γδ subset of T cells in bone due to intracellular accumulation of isopentenyl pyrophosphate (IPP) phosphoantigen.
- 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 was also developing a CD-19 CAR-T therapy.

TECHNOLOGY

NSG mice (n=10) were intratibially injected with PSCA/luciferase-expressing C4-2B (2x10^5) castrate resistant prostate cancer cells. Tumors were allowed to establish for 10 days and then randomized into control or γδ CAR T (1.5x10^7 via tail vein) groups. Subsequent bioluminescent imaging indicated a rapid and significant (p=0.0006) regression of tumors in the γδ CAR T cell group, leading to increased overall survival (5/5 γδ CAR T vs. 0/5 control after 68 days, p=0.0002). Ex vivo bone morphometry analysis also demonstrated the significant protective effect of γδ CAR T associated bone disease. To determine whether bisphosphonates could further enhance the homing of γδ CAR T to bone, NSG mice (n=30) were intratibially injected with C4-2B (2x10^5), and randomized into control and zoledronate (30µg/kg) groups. After 10 days, mice received γδ T cells (3x10^6). CD3-Vδ2 flow cytometry indicated increased γδ T cells in the tibia bone marrow from zoledronate groups (Day 1=61%, Day 3=32%, and Day 5=57%). In vitro results show that, when tumor cells are exposed to bisphosphonates, γδ CAR-T cells can recognize (and kill) tumor cells via 2 mechanisms: CAR (specific for PSCA) and the endogenous TCR (responsive to the accumulation of phosphoantigens induced by the bisphosphonates).

PUBLICATION/PATENT

- PCT Patent Application filed on August 7, 2019 for Dr. Daniel Abate-Daga