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. Because γδ T cells are not MHC restricted this could be an “off the shelf” allogeneic CAR-T cell therapy.

COMMERCIAL OPPORTUNITY

- There were estimated to be 31,620 prostate cancer deaths in the US in 2019. Bone metastasis is a frequent complication in advanced prostate cancer, with the 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 accumulation of isopentenyl pyrophosphate (IPP) phosphoantigen in cancer cells.

- 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

NSG mice (n=10) were intratibially injected with PSCA/luciferase-expressing C4-2B (2x10⁵) castrate resistant prostate cancer cells. Tumors were allowed to establish for 10 days and then randomized into control or γδ CAR T (1.5x10⁷ 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 (2x10⁵), and randomized into control and zoledronate (30µg/kg) groups. After 10 days, mice received γδ T cells (3x10⁶). CD3-Vδ2 flow cytometry indicated increased γδ T cells in the tibia bone marrow from zoledronate groups. 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