Biomere

COMMUNITY BLOG

A RARE BREED: GAMMA DELTA CAR-T THERAPIES

CAR-T or chimeric antigen therapy T-cells are a major breakthrough in personalized cancer therapies. The premise of CAR-T is that a patient's T-cells are isolated, genetically engineered to express a receptor that binds to tumor cells and reintroduced into the circulation to specifically attack and kill tumor cells. This approach has been successful and currently 2 CAR-T therapies are commercially available for hematological cancers. The first therapy, Kymriah® (tisagenlecleucel) was approved in 2018 for certain pediatric and young adult patients with refractory or relapsed acute lymphoblastic leukemia (ALL)[1]. Yescarta® (axicabtagene ciloleucel) was the second CAR-T therapy approved for certain diffuse large B-cell lymphomas (DLBCL), a specific type of non-Hodgkin's lymphoma[2]. While CAR-T therapies have been successful in hematological cancers, the treatment of solid tumors has been more challenging and several novel approaches are being used to develop next-generation CAR-T therapies for solid and hematological cancers. One such approach is the use of gamma delta T cells as the source for genetically engineered CAR-T cells.

Gamma delta T-cells are a rare population (1-5%) of T-cells in the peripheral blood. These cells express T-cell receptors that are composed of gamma and delta chains in contrast to the more abundant T-cells that express T-cell receptors composed of alpha and beta chains. Gamma delta T-cells are a part of the innate immune system and have the unusual and important characteristic of being activated in an MHC-independent manner. Conventional T-cells require a foreign antigen to be presented by the MHC (major histocompatibility complex) to activate a response restricting the response. Gamma delta T-cells have also been reported to have T-cell receptor independent activation in response to phosphorylated metabolites that are produced in tumor cells due to dysregulated metabolism. Another attractive characteristic of gamma delta T-cells is the preference to attack tumor cells compared to normal tissues. Gamma delta T-cells express NK (natural killer) cell receptors such as NKp44 and NKp30 that bind to ligands overexpressed on the cell surface of many tumor cells but have low expression on normal cells. Additionally, the gamma delta T-cells secrete high levels of cytokines and chemokines to induce an inflammatory response and activate other immune cells.

One of the important endpoints in immunotherapy trials is the presence of tumor infiltrating lymphocytes (TILs). Several studies have been published to identify gamma delta T-cells infiltrated in tumors. The most commonly used methods for this analysis are transcriptomic analysis of bulk tumors, immunohistochemistry analysis using an antibody against a pan-gamma delta T-cell marker and phenotypic studies. The presence and percentage of gamma delta T-cells varies between tumor types with one study reporting up to 20% of TILs being identified as gamma delta T-cells. Some studies have shown that gamma delta T-cells tend to localize around the tumor periphery suggesting that activating tumor infiltration will drive T-cell mediated tumor killing. More studies across various tumor indications will drive understanding of the presence of gamma delta T-cells in and around tumors.

The MHC independence is a major reason why gamma delta T-cells are being evaluated for T-cell based immunotherapies in an allogeneic setting. Currently, CAR-T cells are being used in an autologous setting where the patient is the T-cell donor, limiting scale up and increasing cost. In contrast, allogeneic CAR-T therapies will help increase scale of use and manage costs but the challenge is the develop of graft vs host disease in patients treated with CAR-T cells derived from other donors. Gamma delta T-cells have the potential to support allogeneic T-cell therapies and avoid graft vs host disease.

It is evident that there is continued clinical interest in using gamma delta T-cell therapies to treat various tumor indications. In the past couple of years, a few Phase I clinical trials have been initiated and one of the interesting trials that is in progress is sponsored by Incysus Therapeutics where gamma delta T-cells plus standard of care chemotherapy are being tested in glioblastoma multiforme[3]. Given the success of Kymriah and Yescarta in hematological cancers, there are likely to be more clinical trials using engineered gamma delta T-cells for various tumor indications in the future.

1 https://www.fda.gov/news-events/press-announcements/fda-approval-brings-first-gene-therapy-united-states
2 https://www.fda.gov/news-events/press-announcements/fda-approves-car-t-cell-therapy-treat-adults-certain-types-large-b-cell-lymphoma
3 https://www.globenewswire.com/news-release/2019/04/01/1790600/0/en/Incysus-Therapeutics-Announces-FDA-Approval-of-IND-Application-for-a-Novel-Gamma-Delta-%CE%B3%CE%B4-T-Cell-Therapy-for-Treatment-of-Patients-With-Newly-Diagnosed-Glioblastoma.html