

Comment on the Current CAR-T Technology

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CAR T-cell refers to T cells engineered with the chimeric antigen receptor (CAR) technology, [1-3] which is a hottest topic of immunooncology. The CARs contain an extracellular single chain variable fragment (scFv) that recognizes and binds the target protein on cancer cells, an intracellular signaling (and costimulatory) domain that sends the activation signal to the cell and a transmembrane domain connecting the extracellular and intracellular domains. Depending on the number of costimulatory domains in each CAR, three generations of CAR have been developed [2]. Recognition and binding to the target protein brings and retains the CAR T-cells in close proximity to the cancer cell, which subsequently triggers T cells activation for cancer cell killing.

In T cell mediated immune responses, T cells recognize tumor antigens that are processed into fragments of peptides and presented with major histocompatibility complex (MHC), and tumor cells can down regulate expression of MHC to avoid recognition by T cells [4,5]. CAR T-cells, on the other hand, recognize intact tumor antigens through the extracellular scFv region, which does not rely on MHC, and therefore can circumvent the above mechanism. Moreover, given the variety of targets recognized by scFv, it is possible for CARs to recognize tumor antigens such as those of carbohydrate origin, thereby expanding its scope of treatment [5].

One of the major side effects or risk of CAR-T therapy is cytokine storm, which is the release of high levels of proinflammatory cytokines lead by extensive activation of CAR-T cells infused into patients [6]. To reduce such syndrome, investigators are working on different strategies such as introducing inhibitory switches that can down regulate T cell activation.

There are many biotech and pharma companies racing to get CAR-T into clinical use. Since the first clinical report by Novartis in 2011 [7], there are companies such as Novartis, Juno Therapeutics and Kite Pharma leading this race. Recently, FDA halted a phase 2 study of CD19-targeted CAR-T cell therapy JCAR015 by Juno therapeutics in adults with relapsed or refractory B-cell acute lymphoblastic leukemia, due to three deaths in this trial from cerebral edema. Although this

hold was removed by FDA after less than a week, it did raised concerns on safety of CAR-T therapy. In Juno's new protocol design that was approved by FDA, pre-treatment of chemotherapy drugs were changed to cyclophosphamide alone, in contrast to the cocktail of fludarabine and cyclophosphamide in the previous protocol. As a purine analog, fludarabine is commonly used as a chemotherapy drug. There was report that pathological examination in patient receiving standard dose of fludarabine (25 mg/m²/day for 5 days) showed cerebral edema [8].

The clinical trial of CAR-T is only about 5 years. It is still too early to draw a conclusion whether it can completely cure the cancer. But it is unquestionable there is early success. With more and more study spent on it, as well as more improvement made to this technology, we should look forward to better news for CAR-T.

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