A New Safety Switch for CAR T Therapy May Promise Therapeutic Innovation

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Abstract

Cellectis, a French biopharmaceutical company, recently published a paper in the Scientific Reports, a publication of the Nature Publishing Group, and reported on the details of the CubiCAR developed by the company. CubiCAR is a novel chimeric antigen receptor (CAR) that carries a multifunctional tag for purification, detection, and depletion of CAR-T cells. These new features are expected to simplify the manufacturing process of CAR-T cells and improve the effectiveness of tracing and depleting CAR-T cells in the clinical environment.

Citation: Bella Smith A New Safety Switch for CAR T Therapy May Promise Therapeutic Innovation. **protocols.io** dx.doi.org/10.17504/protocols.io.rdwd27e
Published: 29 Jun 2018

Document

A New Safety Switch for CAR T Therapy May Promise Therapeutic Innovation

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CAR-T therapy is an emerging and rapidly developing cancer therapy in recent years. The CAR refers to an engineered chimeric antigen receptor, which is fused by an antigen-binding domain from an immunoglobulin molecule or a T cell receptor and an intracellular signaling domain in mediating cells to activate and enhance the function and persistence of T cells. CAR-T treatment firstly separates T cells from the patient and sends the engineered CAR to the T cells *in vitro* to produce antigen-specific T cells so that they can recognize and kill cancer cells. In theory, CAR-T can achieve a once and for all cure effect. Moreover, CAR-T therapy can target more than just cancer. Compared with physiologically existing antigen receptors, CARs can be designed to recognize proteins, carbohydrate glycolipids, HLA-peptide complexes, and so on, so in the future there is potential to treat other diseases based on T cells, such as autoimmunity, sexual diseases and AIDS, etc.
Despite a broad prospect, CAR T therapy is challenged by the complexity of its production and adverse events related to cellular activity, such as Cytokine Storm (CRS). Therefore, the development of drugs or therapies that can effectively regulate CAR-T is a research focus in this field. Many companies are developing CAR-T safety switches that are expressed on the cell surface. In contrast, Cellectis's products incorporate safety switches into the CAR itself.

The CubiCAR described in this published paper is a trifunctional CAR construct that allows detection, purification, and consumption of CAR-T cells using the FDA-approved antibody Rituximab. This novel

construct promises to simplify the production of CAR-T cells, improve the tracking of CAR-T cells, and increase their safety. Previously, antibody-mediated safety switches often took several days to take effect, and Cellectis's in vitro experiments showed that after using a clinical dose of rituximab, most of the CAR-T cells were depleted within 15 minutes. If successful in human experiments, this construction is expected to reduce the adverse events caused by CAR-T.

In this study, the researchers incorporated the CD20 mimotopes and CD34 epitopes into the CAR-T cell CAR construct, which targets the tumor necrosis factor (TNF) receptor superfamily17 (TNFRSF17, CD269), also known as B-cell maturation antigen (BCMA), is expressed on the surface of malignant plasma cells in most patients with multiple myeloma (MM) and also on normal plasma cells and on specific mature B cells. However, other organizations do not express this protein. CubiCAR takes this kind of construction and expects the CD20 mimotopes to allow cells to be depleted by anti-CD20 rituximab, while the CD34 epitope can play a role in the manufacture of CAR-T and can utilize anti-CD34 monoclonal antibodies to the product. Cell detection and purification are performed to create more chimeric cell products.

The results showed that in BCMA-positive multiple myeloma mouse models, both CubiCAR cells and CAR-T cells reduced MM cells in blood, bone marrow, and spleen. In mice treated with CubiCAR-T cells, injection of rituximab reduced CubiCAR-T cells and promoted MM cell proliferation, whereas unmodified CAR-T cells were not affected by rituximab This shows that CubiCAR cells can be effectively regulated by rituximab.

"The strength and novelty of this technology lies in the integration of multiple functions into a unique CAR molecule. To determine the optimal CAR structure, we chose 15 different CAR constructs and evaluated the ability to consume T cells and to cure the tumor construct," said Dr. Julien Valton, head of the Innovation Team at Cellectis."

“The availability of CubiCAR represents a significant step forward for CAR-T therapy in various cancer treatments,” added Dr. Philippe Duchateau, chief scientific officer of Cellectis. “The CubiCAR construct not only integrates a compact safety switch to fast efficiently consume CAR-T cells, but also compatible with CAR T scFv designed for car t cell target, thus having unique potential to make CAR-T cell immunotherapy safer."

Author Bio
As a global company, Creative Biolabs has more than 200 talented and well-trained scientists located in different continents working closely with partners from the entire world to develop and produce medicines of tomorrow. Specifically, we are the established leading expert in TCR and car t validation, as we offer the one-stop custom services that cover the entire new drug development pipeline. Additionally, we also offer an exclusive line of ready-to-use TCR and CAR T&NK cell construction products, such as virus packaging, purification, expansion and titer determination kits. Furthermore, we have built up a unique unparalleled CAR T design latform for all four CAR generations.