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CAR T Cells for Treating Severe Atopic Allergic Diseases

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Abstract

The prevalence of allergic diseases is rising rapdly in the US and the world. While antibody drugs and corticosteroids can provide symptom relief, they cannot cure allergic diseases. Described herein is a novel approach to treating severe atopic allergic diseases - chimeric antigen receptor-engineered T cells - that target and eliminate the cells that produce the causative agent of all atopic allergic diseases, immunoglubulin E (IgE).

> "Essentially it boils down to two questions: Can we identify a population of cells that are bad? And can we target them specifically? Whether that's asthma or chronic diseases or lupus, if you can find a bad population of cells and get rid of them, then CAR T cells could be therapeutic in that context." – Dr. Carl June, renowned University of Pennsylvania CAR T cell pioneer.[1]

Chimeric Antigen Receptor-Engineered T Cells

Chimeric antigen receptor-engineered T cells (CAR T cells) are a relatively new class of biologic product originally developed to treat hematologic malignancies. Four products have been approved for treating B-cell leukemia and lymphoma, and two for treating multiple myeloma.[2] Growth in the field is explosive and many more products are in development for treating blood and solid organ cancers.

A chimeric antigen receptor (CAR) is a synthetic receptor that is engineered into immune effector cells, typically T cells. A CAR is composed of several domains including a targeting domain, a transmembrane domain, an activation domain derived from the T cell receptor, and a co-stimulatory domain. While CAR T cells are the most common type of product, CAR NK cell, and CAR macrophage products are also being developed. All marketed products to date are composed of autologous CAR T cells, where the patient provides the cells for CAR engineering. The patient's white blood cells are collected by an apheresis instrument (leukapheresis), and shipped to a central manufacturing center, where the T cells are selected, activated, expanded and engineered with the CAR. The product is shipped to the cancer center where it is infused into the patient.[3]

Four CAR T cell products have received FDA approval for treating B-cell lymphoma and B-cell leukemia – Kymriah® (Tisagenlecleucel), Yescarta® (Axicabtagene ciloleucel), Tectarus® (Brexucabtagene autoleucel) and Breyanzi® (Lisacabtagene maraleucel). All target CD19, a pan B cell marker present on both healthy and cancerous B cells. Two CAR T cell products have been approved for treating multiple myeloma, a plasma cell cancer – Abecma® (Idecabtagene vicleucel) and Carvykti® (Ciltacabtagene autoleucel).

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Both target B Cell Maturation Antigen (BCMA), present on both healthy and cancerous plasma cells.

Expression of a CAR T cell target should ideally be restricted to tumor cells, or, if not, off-tumor, on-target toxicity should be manageable. In the case of the CD19 and BCMA-targeted CAR T cells, healthy B cells and plasma cells are eliminated, resulting in hypogammaglobulinemia, necessitating the periodic infusion of donor-derived intravenous immunoglobulins (IVIG).

Moving CAR T Cells Beyond the Treatment of Cancer to the Treatment of Immune-Mediated Diseases

CAR T cells targeting CD19 and BCMA are now being applied to the treatment of autoimmune diseases. By targeting and eliminating all B cells and plasma cells, the cells that produce autoantibodies are also eliminated.[4] Autoimmune disease indications that are being investigated for treatment by CD19-targeted CAR T cells include systemic lupus erythematosus, lupus nephritis, and systemic sclerosis.

We have been developing CAR T cell therapies to target another class of immune-mediated diseases, atopic allergic diseases. Here, instead of targeting and eliminating all B cells and plasma cells, we target and eliminate only the B cells and plasma cells that produce immunoglobulin E (IgE), the cause of all atopic allergic diseases.[5] As a living drug, CAR T cells have been shown to persist for more than a decade in humans.[6] Our approach therefore holds the promise of achieving long-term symptom relief, or even a cure, of allergic diseases, with a single treatment. Since IgE constitutes very small fraction (~0.1%) of total immunoglobulin compared with IgG, elimination of IgE should not significantly impact overall humoral immune response and does not require IVIG infusions.

The molecular marker targeted by our CAR T cells is the transmembrane form of IgE (mIgE), the B-cell antigen receptor exclusively present on all IgE-producing B cell types.[7] We have developed two unique CAR designs for targeting membrane IgE– the EMPD CAR and the ACED CAR (Figure 1). The EMPD CAR recognizes the extracellular membrane-proximal domain (EMPD), a 52-aa region present only on mIgE, not on secreted IgE. The EMPD CAR empolys a traditional deisng, using a single chain variable fragment (scFv) derived from an EMPD-specific monoclonal antibdy for target binding. The ACED CAR, in contrast, uses the alpha chain extracellular domain of the high affinity IgE receptor FcεRI.[8] The affinity of the targeting domain has been optimized to prevent binding to serum IgE. In preclinical *in vitro* and *in vivo* studies, both EMPD CAR T cells and ACED CAR T cells specifically target cells expressing membrane IgE, and not cells that have passively bound secreted IgE to their Fc receptors.

Figure 1. The EMPD and ACE CARs that recognize mIgE

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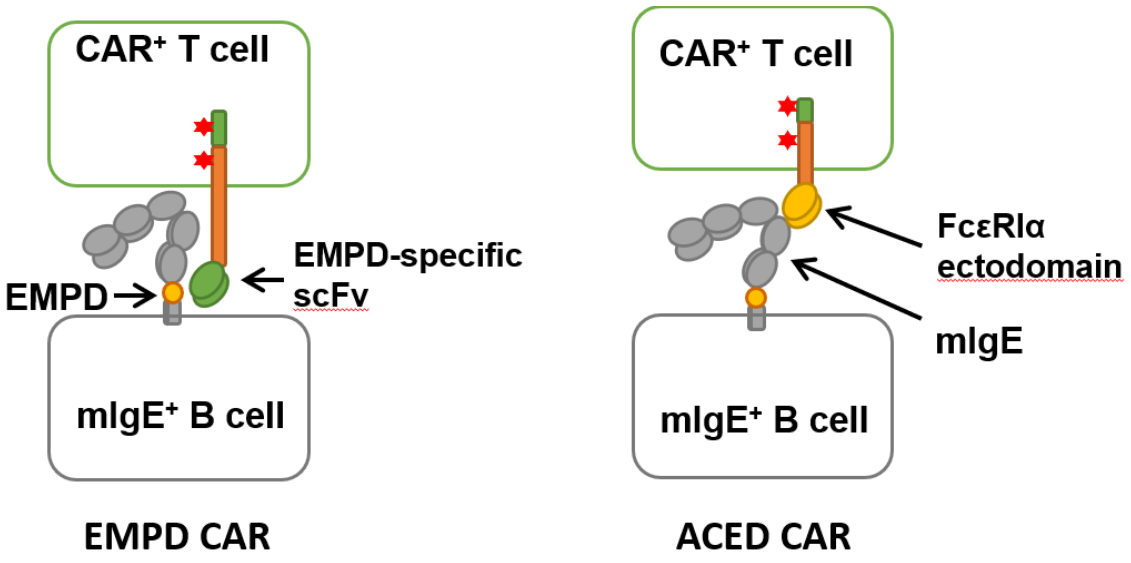

Clinical Applications of mIgE-targeted CAR T Cells

A CAR T cell product that can eliminate serum IgE can be efficacious in the treatment of all atopic allergic diseases including allergic asthma, food allergy, atopic dermatitis, chronic rhinitis, and chronic urticaria. The potential long-term efficacy of the CAR T cell approach is particularly attractive for treating severe allergic asthma and food allergy, two diseases that remain difficult to manage despite of the development of targeted approaches such as monoclonal antibody drugs.

Uncontrollable Severe Alleric Asthma

Asthma is a heterogeneous inflammatory disease of the airways characterized by a clinical history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. Approximately 25 million Americans have asthma.[9] From 2008 to 2013, asthma accounted for $81.9 billion each year in total economic cost in the USA: $50.3 billion per year in health care costs, $29.0 billion per year in mortality costs, and $3.0 billion per year in costs due to missed school days and workdays.[10] Allergic asthma is the leading type of childhood asthma. About 6.5% of children aged <18 years in the US have asthma, while about 8% of adults in the US have asthma.

Between 5-10% of asthma patients have severe asthma. About 20% of those with severe asthma are uncontrolled despite adherence to therapy and proper use of inhalers. Individuals with uncontrolled severe asthma cannot achieve symptom control despite maximal therapy with inhaled corticosteroids (ICS). Quite often, maintenance oral corticosteroids (OCS) are necessary to avoid life-threatening exacerbations. Uncontrolled asthma is associated with significant health and economic costs because of frequent and intense episodes of symptoms that may increase risk of emergency department visits, hospitalizations, and work and school absenteeism. Uncontrolled asthma will cost the US economy an estimated $300 billion (in 2018 dollar values) in the next 20 years in direct medical costs alone.[11,12]

Racial disparities exist in the prevalence and mortality of asthma.[13] Non-Hispanic African Americans were 40 percent more likely to have asthma than non-Hispanic Whites. Non-

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Hispanic Blacks are almost three times more likely to die from asthma related causes than the non-Hispanic White population and non-Hispanic Black children have a death rate eight times that of non-Hispanic White children.

Three FDA approved antibody products are used to treat uncontrollable severe atopic allergic asthma: Xolair® (omalizumab), Dupixent® (dupilumab), and Tezspire® (tezepelumab).[14] The half-life of these whole molecule antibodies is approximately three weeks, and so they must be administered once of twice monthly, perhaps for the lifetime of the patient. Cessation of therapy frequently results in relapse. Neither Xolair, Dupixent nor Tezspire can cure uncontrollable severe atopic allergic asthma. They can reduce but not eliminate severe disease exacerbations. Two, Xolair and Dupixent, can reduce, but not eliminate, the use of corticosteroid drugs.

Compared to these products, mIgE-targeted CAR T cells can offer substantial improvements in patient care. CAR T cells are living organisms that persist in patients, perhaps for ten years or longer. Administered as a single product infusion, CAR T cells have been shown to result in long-term efficacy in the treatment of hematological malignancies.[15] By eliminating the production of IgE, it is expected that mIgE-targeted CAR T cells can eliminate atopic allergic asthma disease exacerbations, can eliminate the use of corticosteroids, and can possibly even cure the disease.

Food Allergy

Food allergy is an IgE-mediated immune system reaction that occurs soon after eating a certain food. Even a tiny amount of the allergy-causing food can trigger signs and symptoms. The symptoms of an allergic reaction to food can range from mild (itchy mouth, a few hives) to severe (throat tightening, difficulty breathing). Anaphylaxis is a serious allergic reaction to food allergens that is sudden in onset and can cause death.

Approximately 32 million people in the United States have food allergies. Ten percent of adults in the US suffer from food allergies; as do 7.7% of children.[16] Eight major food allergens – milk, egg, peanut, tree nuts, wheat, soy, fish and crustacean shellfish – are responsible for most of the serious food allergy reactions in the United States. Between 1997 and 2008, the prevalence of peanut or tree nut allergy appears to have more than tripled in American children. African American children are at higher risk of developing food allergies than non-Hispanic White children, as are children from urban centers, and children from households earning less that $50,000 per year.

The quality of life of children with food allergy is very low. They have a higher likelihood of being bullied. Normal behaviors like dining out at restaurants, play dates at friends' houses, or camp sleepovers, are curtailed. Physical development can be compromised by the avoidance of milk and eggs. Parents of children with food allergies have greater psychological stress and exhibit higher blood pressure than parents of children without food allergies.[17] Childhood food allergy results in significant direct medical costs for the US health care system and even larger costs for families with a food-allergic child. According to a 2013 study by the Northwestern Feinberg School of Medicine, the overall economic cost of food allergy was estimated at $24.8 billion annually ($4184 per year per child). Costs borne by the family totaled $20.5 billion annually, including lost labor productivity, out-of-pocket, and opportunity costs.[18]

There are no approved drugs to treat food allergy. Once a serious allergic reaction (anaphylaxis) starts, epinephrine is the only effective treatment. Epinephrine should be injected within minutes of the onset of symptoms. More than one dose may be needed. Not treating anaphylaxis promptly with epinephrine increases the risk of a fatal reaction.

Palforzia®, an oral immunotherapy for the mitigation of allergic reactions to peanuts, has recently been approved for use in the USA. The product is a powder composed of defatted peanut flour, and is administered orally in a 6-10 month series of dose escalations in the physician's office.[19] The product is not a cure, and at best, lessens the frequency and severity of allergic reactions to peanuts. Adverse events related to therapy are not uncommon, and 20% of patients cannot complete therapy. Food avoidance must continue. The product must not be administered to patients with uncontrolled asthma.

Compared to Palforzia, mIgE-targeted CAR T cells are administered one-time only, and can completely eliminate disease exacerbations, The CAR T cells are a universal food allergy treatment solution and no do not require continual food avoidance. Long-term efficacy, perhaps even a cure of severe food allergies, may be possible.

Conclusions

Chimeric antigen receptor engineered T cells are now moving beyond the treatment of cancer to the treatment of immune-mediated diseases including autoimmune diseases and severe allergic diseases. The pan B cell target, CD19, and the plasma cell target, BCMA, have been convenient CAR T cell targets for eliminating all immunoglobulin-producing cells, and within this population, the B cells and plasma cells that produce autoimmune antibodies. Targeting membrane IgE enables a more specific CAR T cell approach, eliminating only IgE-producing cells without significant side effects. mIgE-targeted CAR T cells are disease-modifying, and not merely symptom-reducing, unlike all marketed products for treating severe allergic diseases. The approach holds the promise of achieving long-term symptom relief, perhaps even a cure, from a single product administration.

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