Pre-Clinical Testing of Anti-CD19 CAR Therapy for Lupus

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Technology description

The Problem:

Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmune disease characterized by wide-spread inflammation, immune disturbance and multi-organ tissue damage. SLE consists of periods of remission followed by episodes of disease activity that correlate with a need for adjustment in pharmacotherapy. B cells are the main culprits in producing pathogenic autoantibodies that are diagnostic and potentially pathogenic due to their ability to form immune complexes, resulting in glomerular dysfunction and fibrosis. For this reason, B cells are a common target of several lupus therapies that are either approved or in development. However, progress in developing effective and targeted treatments has been slow and disappointing. SLE ranks among the most costly of several chronic diseases including rheumatoid arthritis. About 25-60% of SLE patients develop renal disease over time and thus may require costly treatments and procedures such as dialysis and kidney transplant. Currently, there are no curative therapies for SLE; therefore, there is an immediate demand for novel therapeutic interventions specifically targeting B cells.

The Technology Solution:

Researchers in the Department of Microbiology, Immunology and Biochemistry at the University of Tennessee Health Science Center have demonstrated that cytotoxic T lymphocytes (CTL), engineered in vitro to express a chimeric antigen receptor (CAR) directed against CD19, can be used to deplete B cells that are the main source of tissue-damaging autoantibodies. In addition, the researchers have demonstrated that CAR constructs directed against CD19 can be used to reverse manifestations of autoimmune disease in a murine model of lupus.

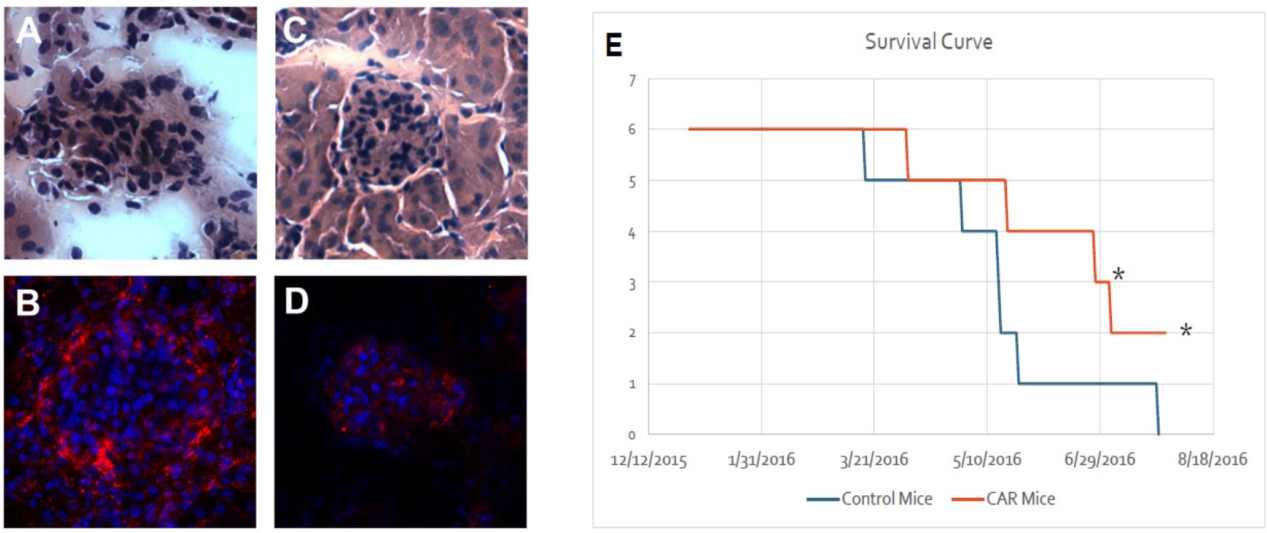

Figure 1.Effect of the anti-CD-19 CTL treatment following 6 months of CTL administration.Cryosections of CAR-treated or untreated control mice were analyzed by H&E staining and by immunofluorescence with anti-IgG antibody. Untreated control mouse shows cellular infiltrate in the glomeruli that, as a result, appear enlarged (A) and exhibit deposits reactive with anti-IgG antibody (B). A CAR-treated mouse, approaching 1-year of age, showed glomeruli of near normal appearance (C) lacking IgG deposits (D). In mice that were successfully reconstituted with CAR-expressing CTL (red line), B cell depletion was maintained over 6 months (E), or until mice were sacrificed for analysis (asterisks). Control mice died before reaching the age of 12 months.

The CTLs were infected in vitro with retrovirus vectors encoding CAR and subsequently infused into recipient mice. B cells are a key player in the immunopathogenesis of autoimmune diseases such as SLE. With the recent success of CAR mediated B cell modalities in animal models of hematologic cancers, it has become possible to target B cells therapeutically. The present invention differs from current lupus therapies because it applies the therapeutic efficacy and targeting specificity of CAR T cells to a clinical problem that currently lacks effective treatments.

Mice (NZBxNZW F1 female mice) that received CAR T cells showed a reduction in B cell numbers that was long lasting and could extend the life span to beyond 1 year of age in this murine model of lupus. In addition, CAR-treated mice showed decreased immune complex deposits in the glomeruli (Figure 1); and, long term surviving mice showed a decrease in circulating antibody levels and anti-DNA autoantibodies (Figure 2). These findings demonstrate that CAR T cells can specifically recognize B cells and display the therapeutic efficacy of CAR treatment in a murine model of lupus.

Figure 2.Measurement of anti-DNA IgG titers in control NZBxNZW F1 mice (A) and in CAR-CTL-treated littermates (B). Three months after administration of anti-CD19 CAR CTL, the IgG anti-DNA titers were near background levels.

Advantages

Depletion of B cells by engineered cytotoxic CAR T cells ameliorated lupus manifestations in a mouse model of lupus (NZBxNZW F1).

Mice that received anti-CD19 T cells showed a reduction of B cell numbers that was long lasting and extended the life span in this model beyond 1 year of age.
Mice showed a reduced immune complex deposition in kidneys.

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