

[0028] Disclosed herein are chimeric antigen receptors (CAR) which specifically recognize antigens associated with autoimmune diseases. In particular, the CARs can be specific for post-translationally modified antigens. In particular, the CARs can be specific for binding to citrullinated polypeptides, including vimentin, citrullinated filaggrin and citrullinated fibrinogen. In one aspect, the present disclosure refers to a chimeric antigen receptor (CAR) comprising an antigen-binding domain, a hinge domain, a transmembrane domain, one or more co-stimulatory domains, and an intracellular signaling domain, wherein the antigen binding domain specifically binds to three or more different citrullinated proteins or citrullinated fragments thereof, and comprises complementarity-determining regions (CDRs) from VH and VL domains of SEQ ID NO:1 and SEQ ID NO:4.

[0029] Chimeric antigen receptors (CAR) were engineered to specifically target post-translationally modified proteins, namely citrullinated vimentin, citrullinated filaggrin and citrullinated fibrinogen, that are expressed in the extracellular matrix of inflamed joints in patients with Rheumatoid Arthritis (RA). In some examples, the single chain fragment variable (scFv) part of the CAR is obtained from an antibody highly specific for citrullinated proteins isolated from the peripheral blood of an RA patient. In one example, specific scFv chains were inserted into a second-generation CAR construct. In some examples, the scFv chains were inserted into a CAR construct cloned in a lentiviral vector. In the detailed description, references to antibodies are applicable to antigen-binding domains of the CARs of the present disclosure unless the context indicates otherwise.

[0029a] In one aspect, the present disclosure refers to a nucleic acid encoding the CAR as disclosed herein.

[0029b] In one aspect, the present disclosure refers to an expression vector comprising an expression control sequence operatively linked to the nucleic acid sequence as disclosed herein.

[0029c] In one aspect, the present disclosure refers to a modified T cell that has been modified to express the chimeric antigen receptor (CAR) as disclosed herein.

[0029d] In one aspect, the present disclosure refers to a pharmaceutical composition comprising a plurality of the modified T cells as disclosed herein, and a pharmaceutically acceptable carrier.

[0029e] In one aspect, the present disclosure refers to use of the pharmaceutical composition as disclosed herein for the manufacture of a medicament for treating rheumatoid arthritis.

[0029f] In one aspect, the present disclosure refers to a method comprising: (a) enriching T cells from a biological sample for T regulatory (Treg) cells; (b) transfecting the enriched Treg cells with an expression vector encoding the CAR as disclosed herein; and (c) expanding the transfected Treg cells.

DETAILED DESCRIPTION

I. Definitions

[0030] Unless otherwise specified, terms and symbols of biochemistry, nucleic acid chemistry, molecular biology, developmental biology and molecular genetics follow those of standard treatises and texts in the field, for example, Sambrook et al, *Molecular Cloning: A Laboratory Manual*, 2nd Edition (Cold Spring Harbor Press, 1989); Alberts and Singer, *Developmental Biology*, Eighth Edition (Sinauer Associates Inc., Sunderland, MA, 2006); Kornberg and Baker, *DNA Replication*, Second Edition (W.H. Freeman, New York, 1992); Gaits, ed., *Oligonucleotide Synthesis: A Practical Approach* (IRL Press, Oxford, 1984); Lehninger, *Biochemistry*, Second Edition (Worth Publishers, New York, 1975); Eckstein, ed., *Oligonucleotides and Analogs: A Practical Approach* (Oxford University Press, New York, 1991); and the like.

[0031] As used herein, the terms “antigen,” “immunogen,” and “antibody target,” refer to a molecule, compound, or complex that is recognized by an antibody, i.e., can be bound by the antibody. The term can refer to any molecule that can be recognized by an antibody, e.g., a polypeptide, polynucleotide, carbohydrate, lipid, chemical moiety, or combinations thereof (e.g., phosphorylated or glycosylated polypeptides, etc.). One of skill will understand that the term does not indicate that the molecule is immunogenic in every context, but simply indicates that it can be targeted by an antibody.