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TITLE OF THE INVENTION

Compositions and Methods for Treatment of Chronic Lymphocytic Leukemia

STATEMENT REGARDING FEDERALLYSPONSORED RESEARCH OR DEVELOPMENT

This invention was made with U.S. government support under Grant Nos. 1RO1CA105216, RO1AI057838 and RO11113482 awarded by the National Institutes of Health (NIH). The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

The large majority of patients having B-cell malignancies, including chronic lymphocytic leukemia (CLL) will die from their disease. One approach to treating these patients is to genetically modify T cells to target antigens expressed on tumor cells through the expression of chimeric antigen receptors (CARs). CARs are antigen receptors that are designed to recognize cell surface antigens in a human leukocyte antigen-independent manner. Attempts in using genetically modified cells expressing CARs to treat these types of patients have met with very limited success. See for example, Brentjens et al., 2010, Molecular Therapy, 18:4, 666-668; Morgan et al., 2010, Molecular Therapy, published online February 23, 2010, pages 1-9; and, Till et al., 2008, Blood, 112:2261-2271.

Thus, there is an urgent need in the art for compositions and methods for treatment of CLL. The present invention addresses this need.

DETAILED DESCRIPTION

The present invention provides compositions and methods for treatment of CLL.

Compositions

As exemplified elsewhere herein, the present invention includes a vector comprising an αCD19 CAR transgene. Preferably, the vector is a retroviral vector. More preferably, the vector is a self-inactivating lentiviral vector as described elsewhere herein.

The invention also includes autologous cells that are transfected with the vector of the invention. Preferably, the cells are T cells and more preferably, they are autologous T cells.

Methods of Treating

As described in detail elsewhere herein, the invention includes a method of treating an patient with CLL, wherein the method comprises administering to the patient autologous T cells that have been transfected so as to express a CD19 CAR antigen. Preferably, the cells are administered to the patient by infusion.

The precise protocols used to treat patients are described elsewhere herein and can also be found at clinicaltrials.dot.gov under trial no NCT01029366. Interim results from this study, where three patients were treated, establish that successful expansion and transduction of T cells was accomplished in all three patients. The actual manufacturing of final product was more difficult in CLL patients than in previous trials. CARs with 4-1BB:z signaling domains have massive expansion in vivo in two of three patients with advanced CLL. The cells persisted in blood and migrated to bone marrow for at least sixty days in substantial numbers post-infusion. CAR T cells expanded in vivo compared to the infused amount. Anti-tumor effects were observed: patient 1 CR, patient 2 PR, patient 3 CRn. And, the treatment was promising in chemotherapy refractory patients.

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those

described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described.

As used herein, each of the following terms has the meaning associated with it in this section.

The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

"About" as used herein when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of ±20% or ±10%, more preferably ±5%, even more preferably ±1%, and still more preferably ±0.1% from the specified value, as such variations are appropriate to perform the disclosed methods.

The term "antibody" as used herein, refers to an immunoglobulin molecule, which is able to specifically bind to a specific epitope on an antigen. Antibodies can be intact immunoglobulins derived from natural sources or from recombinant sources and can be immunoactive portions of intact immunoglobulins. Antibodies are typically tetramers of immunoglobulin molecules. The antibodies in the present invention may exist in a variety of forms including, for example, polyclonal antibodies, monoclonal antibodies, Fv, Fab and $F(ab)_2$, as well as single chain antibodies and humanized antibodies.

The term "antigen" or "Ag" as used herein is defined as a molecule that provokes an immune response. This immune response may involve either antibody production, or the activation of specific immunologically-competent cells, or both. The skilled artisan will understand that any macromolecule, including virtually all proteins or peptides, can serve as an antigen. Furthermore, antigens can be derived from recombinant or genomic DNA. A skilled artisan will understand that any DNA, which comprises a nucleotide sequences or a partial nucleotide sequence encoding a protein that elicits an immune response can encode an "antigen" as that term is used herein. Furthermore, one skilled in the art will understand that an antigen need not be encoded solely by a full length nucleotide sequence of a gene. It is readily apparent that the present invention includes, but is not limited to, the use of partial nucleotide sequences of more than one gene and that these nucleotide sequences can be arranged in various combinations to elicit the desired immune response. Moreover, a skilled artisan will understand that an antigen

need not be encoded by a "gene" at all. It is readily apparent that an antigen can be generated synthesized or can be derived from a biological sample. Such a biological sample can include, but is not limited to a tissue sample, a tumor sample, a cell or a biological fluid.

A "coding region" of a gene consists of the nucleotide residues of the coding strand of the gene and the nucleotides of the non-coding strand of the gene which are homologous with or complementary to, respectively, the coding region of an mRNA molecule which is produced by transcription of the gene.

A "coding region" of an mRNA molecule also consists of the nucleotide residues of the mRNA molecule which are matched with an anti-codon region of a transfer RNA molecule during translation of the mRNA molecule or which encode a stop codon. The coding region may thus include nucleotide residues corresponding to amino acid residues which are not present in the mature protein encoded by the mRNA molecule (*e.g.*, amino acid residues in a protein export signal sequence).

"Encoding" refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (*i.e.*, rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting therefrom. Thus, a gene encodes a protein if transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

Unless otherwise specified, a "nucleotide sequence encoding an amino acid sequence" includes all nucleotide sequences that are degenerate versions of each other and that encode the same amino acid sequence. Nucleotide sequences that encode proteins and RNA may include introns.

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