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March 11, 2022

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APPLICATION NUMBER: ***61/502,649***
FILING DATE: ***June 29, 2011***

Certified by

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for Intellectual Property
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PTO/SB/16
OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Electronically Filed

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
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☐ *Additional inventors are being named on the _____ separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

COMPOSITIONS AND METHODS FOR TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA

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ENCLOSED APPLICATION PARTS (*check all that apply*)

■ Specification *Number of Pages* 71 ☐ CD(s), Number

■ Drawing(s) *Number of Sheets* 15 ☐ Other (specify):

☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ Applicant claims small entity status. See 37 CFR 1.27.

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$110.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☐ No.

☒ Yes, the name of the U.S. Government agency and the Government contract number are: This invention was made with government support under K24 CA11787901 and R01CA120409 awarded by the National Institutes of Health (NIH).

Signature _____

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Docket No. 46483-6001-P2-US.600881

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

TITLE OF THE INVENTION

COMPOSITIONS AND METHODS FOR TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with government support under K24 CA11787901 and R01CA120409 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.

In most cancers, tumor-specific antigens are not yet well defined, but in B cell malignancies, CD19 is an attractive tumor target. Expression of CD19 is restricted to normal and malignant B cells (Uckun, et al. *Blood*, 1988, 71:13-29), so that CD19 is a widely accepted target to safely test CARs. While CARs can trigger T-cell activation in a manner similar to an endogenous T-cell receptor, a major impediment to the clinical application of this technology to date has been limited *in vivo* expansion of CAR+ T cells, rapid disappearance of the cells after infusion, and disappointing clinical activity (Jena, et al., *Blood*, 2010, 116:1035-1044; Uckun, et al. *Blood*, 1988, 71:13-29).

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

BRIEF DESCRIPTION OF THE DRAWINGS

The following detailed description of preferred embodiments of the invention will be better understood when read in conjunction with the appended drawings. For the purpose of illustrating the invention, there are shown in the drawings embodiments which are presently preferred. It should be understood, however, that the invention is not limited to the precise arrangements and instrumentalities of the embodiments shown in the drawings.

Figure 1, comprising Figures 1A through 1C, depicts a schematic representation of the gene-transfer vector and transgene, gene modified T cell manufacturing and clinical protocol design. Figure 1A depicts the lentiviral vectors and transgene that show the major functional elements. A vesicular stomatitis virus protein G pseudotyped clinical grade lentiviral vector (designated pELPs 19BBz) directing expression of anti-CD19 scFv derived from FMC63 murine monoclonal antibody, human CD8α hinge and transmembrane domain, and human 4-1BB and CD3zeta signaling domains was produced. Constitutive expression of the transgene was directed by inclusion of an EF-1a (elongation factor-1α promoter); LTR, long terminal repeat; RRE, rev response element. (cPPT) and the central termination sequence (CTS). Figure is not to scale. Figure 1B depicts T cell manufacturing. Autologous cells were obtained via an apheresis, and T cells were enriched by mononuclear cell elutriation, washed and residual leukemia cells depleted by addition of anti-CD3/CD28 coated paramagnetic beads for positive selection and activation of T cells. Lentiviral vector was added at the time of cell activation and was washed out on day 3 post culture initiation. Cells were expanded on a rocking platform device (WAVE Bioreactor System) for 8-12 days. On the final day of culture the beads were removed by passage over a magnetic field and the CART19 T cells harvested and cryopreserved in infusible medium. Figure 1C depicts the clinical protocol design. Patients were given lymphodepleting chemotherapy as described, followed by CART19 infusion #1 by i.v. gravity flow drip over a period of 15-20 minutes. The infusion was given using a split dose approach over 3 days (10%, 30%,

60%) beginning 1 to 5 days after completion of chemotherapy. Endpoint assays were conducted on study week 4. At the conclusion of active monitoring, subjects were transferred to a destination protocol for long term follow up as per FDA guidance.

Figure 2, comprising Figures 2A through 2F, is a series of images demonstrating sustained *in vivo* expansion and persistence in blood and marrow of CART19 cells. DNA isolated from whole blood as depicted in Figure 2A through 2C or marrow as depicted in Figure 2D through 2F, samples obtained from UPN 01 as depicted in Figure 2A and 2D, UPN 02 as depicted in Figure 2B and 2E and UPN 03 as depicted in Figure 2C and 2F was subjected in bulk to Q-PCR analysis using a qualified assay to detect and quantify CART19 sequences. Each data point represents the average of triplicate measurements on 100-200 ng genomic DNA, with maximal % CV less than 1.56%. Pass/fail parameters for the assay included pre-established ranges for slope and efficiency of amplification, and amplification of a reference sample. The lower limit of quantification for the assay established by the standard curve range was 2 copies transgene/microgram genomic DNA; sample values below that number are considered estimates and presented if at least 2/3 replicates generated a Ct value with % CV for the values 15%. CART19 cells were infused at day 0, 1, and 2 for UPN 01 and UPN 03, and days 0, 1, 2 and 11 for UPN 02.

Figure 3, comprising Figures 3A through 3D, is a series of images demonstrating serum and bone marrow cytokines before and after CAR T cell infusion; longitudinal measurements of changes in serum cytokines, chemokines and cytokine receptors in UPN 01 as depicted in Figure 3A, UPN 02 as depicted in Figure 3B and UPN 03 as depicted in Figure 3C, on the indicated day after CART19 cell infusion and serial assessments of the same analytes in the bone marrow from UPN 03 as depicted in Figure 3D. Samples were subjected to bulk to multiplex analysis using Luminex bead array technology and pre-assembled and validated multiplex kits. Analytes with a >=3 fold change are indicated, and plotted as relative change from baseline as depicted in Figure 3A through 3C or as absolute values as depicted in Figure 3D. Absolute values for each analyte at each time-point were derived from a recombinant protein-based standard curve over a 3-fold 8-point dilution series, with upper and lower limits of quantification (ULOQ, LLOQ) determined by the 80-120% observed/expected cutoff values for the

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