07-11-01

A/PROV

PROVISIONAL APPLICATION COVER SHEET

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

	DOCKET NUMBER	ORT-1468

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TITLE OF THE INVENTION *(280 characters max)*

METHOD FOR TREATING AN HIV INFECTED HUMAN

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒	Specification	*Number of Pages* 19	☐	Application Data Sheet	
☐	Claims	*Number of Claims* ____	☐	CD(s), Number ____	
☐	Drawing(s)	*Number of Sheets* ____	☐	Other (specify)	

METHOD OF PAYMENT *(check one)*

☐ A check or money order is enclosed to cover the Provisional filing fees.	Provisional Filing Fee Amount ($)	$ 150.00
☒ The Commissioner is hereby authorized to charge filing fees and credit any overpayment to Deposit Account No. 10-0750/ORT-1468/MHM		

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:

Respectfully submitted,

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PROVISIONAL APPLICATION FILING ONLY

CSHL EXHIBIT 2010
BENITEC V. CSHL
IPR2016-00016

DOCKET NO. ORT-1468

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: SYMONDS et al.

For : METHOD FOR TREATING AN HIV INFECTED HUMAN

Express Mail Certificate

"Express Mail" mailing number: EL710607443US

Date of Deposit: July 10, 2001

I hereby certify that this complete application, including specification pages and Provisional Application Cover Sheet, is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

A Combined Declaration and Power of Attorney will be submitted to the United States Patent and Trademark Office upon receipt of the U.S. Serial Number for this patent application.

Karen Hall-Morgan

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CLINICAL PROTOCOL

1. GOAL AND OBJECTIVES

The overall goal of this Phase II trial is to determine the safety and efficacy of a cell delivered ribozyme gene transfer product in patients with chronic Human Immunodeficiency Virus Type 1 (HIV-1) infection. Specifically, autologous hematopoietic progenitor cells (CD34+ cells) will be transduced with the gene transfer product (RRz2) which consists of a Moloney Murine Leukemia Virus (MoMLV)-based retroviral vector (LNL6) containing a gene (Rz2) that encodes an anti-HIV-1 ribozyme directed against the *tat* HIV-1 regulatory gene.

The study will be a double blind, randomized, controlled trial. Patients whose plasma HIV-1 RNA (viral load) is completely suppressed (less than 50 copies/ml) for at least 6 months during the administration of their first or second regimen of potent, combination Anti-Retroviral therapy (ART) will be eligible for entry into the trial. They will be randomized into one of two treatment groups:

1. LNL6 group in which autologous CD34+ cells will be transduced with LNL6;

2. RRz2 group in which autologous CD34+ cells will be transduced with RRz2.

Beginning at 24 weeks after administration, ART will be interrupted (Analytical Treatment Interruption – ATI) for two separate periods of 8 weeks (25-33 weeks and 45-52 weeks). To achieve the overall goal, the primary and secondary objectives of the trial are as follows:

Primary Objective: To assess:

1. Efficacy of the RRz2 modified CD34+ cells at 51 and 52 weeks after their administration by analyzing the difference in viral load between the LNL6 and RRz2 groups.

Secondary Objectives: To assess:

1. Safety of the procedures used to mobilize, harvest, culture, transduce and re-infuse the CD34+ cells and of the re-infused CD34+ cells;

2. Secondary endpoint analyses of efficacy including differences between the two groups in: CD4+ T cell (CD4+ cell) count; proviral DNA; quantitative marking and expression of the gene transfer product by CD34+ cells and their progeny; time to re-initiation of ART in ATI#2; and sequence of the gene in the region targeted by Rz2.

2. SUBJECTS AND METHODS

2.1. TRIAL DESIGN

2.1.1. Overview

This will be an international, multi-center, Phase II clinical trial. The trial site in the USA will be the University of California Los Angeles (UCLA), CA.

The trial protocol is divided into six sequential steps:

Step I: Pre-infusion week. Preparation and infusion of autologous CD34+ cells transduced with either LNL6 or RRz2 in the absence of myeloablative therapy.

Step II: Weeks 1-24. Continuation of ART for 24 weeks.

Step III: Weeks 25 – 32. First Analytic Treatment Interruption (ATI#1) for 8 weeks.

Step IV: Weeks 33 – 44. Resumption of ART 12 weeks.

Step V: Weeks 45 – 52. Second ATI (ATI#2) for 8 weeks.

Step VI: Weeks 53 – 104. Continued ATI#2 until threshold values for viral load or CD4+ cell count have been attained or until the end of the study.

2.1.2. Rationale For Design

2.1.2.1. Phase I Trials

We have conducted two Phase I studies in which autologous cells from patients with HIV-1 infection were transduced with LNL6 or RRz2. One of those studies, conducted at UCLA, utilized CD34+ cells. After being harvested and purified, the cells were divided into two approximately equal aliquots, one of which was transduced with LNL6 and the other with RRz2. Both populations of cells were mixed and re-infused. There were no Serious Adverse Effects (SAEs) attributable to the gene transfer products. The transduced CD34+ cells contributed successfully to the expected hematopoietic cell lineages and in particular to CD4+ and CD8+ T-lymphocytes and monocyte/macrophages (See Section XXXX).

2.1.2.2. Analytic Treatment Interruptions

Two Analytic Treatment Interruptions (ATIs – withdrawal of ART) are an integral component of the trial design because they will allow for short periods of HIV-1 replication. Such replication should select for and enable proliferation of CD34+-derived progeny cells, which are relatively protected from HIV-1 infection and replication by the RRz2 gene construct. Therefore, viral load in the RRz2 group should be less than in the LNL6 group. Analytical Treatment Interruptions (ATIs), which are usually referred to as Structured Treatment Interruptions in the clinical setting, are increasingly becoming a component of standard clinical practice (REFS). They are used to give the patient a "holiday" from the often severe side effects of ART and to enhance the cytotoxic T lymphocyte response to HIV (REFS).

2.2. SUBJECTS

2.2.1. Trial Sample

Sixty six patients, males or females aged 18 – 45 years with chronic HIV-1 infection and whose plasma HIV-1 RNA (viral load) has been completely suppressed (less than 50 copies/ml) for at least 6 months during the administration of their first or second of ART, will be eligible for entry. At each clinical site, patients will be stratified by age and first or second ART regimen.

2.2.2. Inclusion Criteria

Subjects must meet all of the following entry criteria:

- HIV-1 infection for at least 6 months documented by positive ELISA antibody and confirmed by Western Blot.

2. Aged between 18 – 45 years.

3. Receiving either the first or second regimen of ART, defined as 3 or more potent Anti-Retroviral drugs in combination, for more than 6 months consecutively prior to study entry and maintaining complete suppression of viral load (less than 50 copies/ml) as measured by UltraSensitive Roche Amplicor HIV-1 Monitor™, during the same period. Substitution of drugs in the same drug class will not be considered to constitute a change from one ART regimen to another.

4. Viral load less than 50 copies/mL (UltraSensitive Roche Amplicor HIV-1 Monitor™) measured on two consecutive occasions at least seven days apart and within 45 days prior to study entry.

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