Optimized Lentiviral Vector for Stem Cell Gene Therapy of Hemoglobinopathies

Tech ID: 30498 / UC Case 2017-460-0

SUMMARY

UCLA researchers in the Department of Microbiology, Immunology and Molecular Genetics have developed a novel method to produce short lentiviral vectors with tissue-specific expression, with a primary focus on lentiviral vectors for treating sickle cell disease and other disorders of hemoglobin.

BACKGROUND

Sickle cell disease (SCD) is one of the most common monogenic disorders worldwide and is a major cause of morbidity and early mortality. SCD is cause by a single amino acid change in β-globin which leads to hemoglobin polymerization and red blood cell sickling. Although SCD is well characterized, there is still no ideal long-term treatment. Current therapies are based on induction of fetal hemoglobin to inhibit polymerization of sickle hemoglobin or transfusions to reduce the percentage of sickle hemoglobin. Stem cell transplantation is a promising technique but its reliance on a sibling donor significantly limits its widespread use. Transplantation of allogeneic cells is high risk due to graft-versus-host disease. Recently, gene therapy has emerged as a potential treatment, with lentiviral vectors as gene delivery modalities showing the most promise. Unfortunately, current β-globin expression vectors suffer from low vector titer and sub-optimal gene transfer, limiting the advancement of this gene therapy to the clinic.

INNOVATION

UCLA researchers have developed novel LVs for the treatment of SCD. These vectors are considerably smaller, up to half the number of base pairs of previous examples. Shorter vectors have higher titer, more complete packaged genomes, and better infectivity. Administration of early versions of these vectors resulted in 18.5% of total hemoglobin tetramers at week 20 (more than 10% provides therapeutic effect) in a mouse model of SCD. These optimized and shortened LVs with erythroid-specific enhancers, provided up to a 10-fold higher titer with superior gene transfer to hematopoietic stem cells while retaining robust expression levels. These enhanced vectors are particularly important in clinical situations where poor gene transfer to hematopoietic stem cells is an issue. Translation of this LV-based gene therapy to the clinic would be facilitated by lower costs due to higher titer and gene transfer. The methods developed in order to design these new shorter LVs can be translated to many other untreatable, chronic diseases.

APPLICATIONS

- Sickle cell disease treatment
- Treatment of hemoglobinopathies (e.g. Beta-thalassemia)
- Express other transgenes in erythrocytes, e.g. ADA, IDUA
- Apply to development of lentiviral vectors with expression specificity for other cell lineages (e.g. white blood cells, platelets, T cells, muscle, liver, neurons, etc.) to treat other diseases

ADVANTAGES

- Short vector length
- Lineage-specific enhancers
- Short sequence DNA enhancers
- Improved titer and gene transfer
- Efficient lentiviral vectors

STATE OF DEVELOPMENT

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OTHER INFORMATION

KEYWORDS

DNA enhancers, gene therapy, transduction, reporter assay, transgenes, cell-type specific, gene transfer, hemoglobinopathies, sickle cell disease, ß-thalassemia, lentiviral vector, erythroid cell, hematopoietic stem cell

CATEGORIZED AS

- **Biotechnology**
  - Genomics
- **Medical**
  - Delivery Systems
  - Disease: Genetic Diseases and Dysmorphic Syndromes
  - Gene Therapy
  - Research Tools

RELATED CASES

2017-460-0, 2018-862-0, 2019-616-0

The enhanced β-globin-expressing lentiviral vector demonstrated superior transduction of hematopoietic stem cells (human and mouse) and has been validated in in vivo models of Sickle Cell Disease. Administration of early versions of these vectors resulted in 18.5% of total hemoglobin tetramers (more than 10% provides therapeutic effect).

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	12,637,696	05/26/2026	2019-616
United States Of America	Issued Patent	11,976,293	05/07/2024	2017-460
United States Of America	Published Application	20220136007	05/05/2022	2018-862

RELATED MATERIALS

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- Romero Z, Urbinati F, Geiger S, Cooper AR, Wherley J, Kaufman ML, Hollis RP, de Assin RR, Senadheera S, Sahagian A, Jin X, Gellis A, Wang X, Gjertson D, Deoliveira S, Kempert P, Shupien S, Abdel-Azim H, Walters MC, Meiselman HJ, Wenby RB, Gruber T, Marder V, Coates TD, Kohn DB. ß-globin gene transfer to human bone marrow for sickle cell disease. J Clin Invest. 2013 Jul 1. PMID: 23863630

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- Gene Editing of Monogenic Disorders in Human Hematopoietic Stem Cells
- Augmentations to Lentiviral Vectors to Increase Expression
- Improvement To Retroviral Vectors Containing The Human Ubiquitin C Promoter
- Generation Of Minimal Enhancer Elements Using Massively Parallel Reporter Assays
- Transient Expression Of BCL-2 To Ameliorate Cytotoxicity Of Gene Modification Reagents In Stem Cells
- Fusion Protein For Anti-Cd19 Chimeric Antigen Receptor Detection

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