NEW THERAPEUTIC OPTION TO TREAT BONE MARROW FAILURE (BMF) IN PATIENTS WITH DYSKERATOSIS

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PATENT STATUS

Country	Type	Number	Dated	Case
Patent Cooperation Treaty	Published Application	WO/2023/183217	09/28/2023	2022-084

BRIEF DESCRIPTION

The inventors have developed a genome editing therapy for bone marrow failure (BMF) in people living with dyskeratosis (DC). This technology includes two novel endogenous, isogenic models to study TINF2-DC mutations.

Human embryonic stem cells (hESCs) engineered to carry the TIN2-DC T284R mutation recapitulated the short telomere phenotype observed in DC patients. Yet, telomeres in TINF2-DC hESCs did not trigger DNA damage responses at telomeres or show exacerbated telomere shortening when differentiated into telomerase-negative cells. Disruption of the mutant TINF2 allele by introducing a frameshift mutation in exon 2 restored telomere length in stem cells and the replicative potential of differentiated cells.

The inventors also established in vitro and in vivo human hematopoietic stem cell (hHSC) models to assess the changes in telomere length and proliferative capacity upon the introduction of TERT and TINF2 editing.

In addition, the inventors demonstrated that editing at exon 2 of TINF2 that restored telomere length in hESCs could be generated in TINF2-DC patient HSCs.

These experiments nominate TINF2 as a target for:

CRISPR/CAS9 to elongate telomeres in patient with TINF2 mutations,
CRISPR/CAS9 to elongate telomeres with other mutations causing TBD, andchemical interventions to elongate telomeres in general.
BACKGROUND

BMF is a major cause of morbidity and mortality in DC and other telomere biology disorders (TBDs). Mutations in the TINF2 gene, encoding the shelterin protein TIN2, cause telomere shortening and the inherited bone marrow failure syndrome dyskeratosis congenita (DC). A lack of suitable model systems limits the mechanistic understanding of telomere shortening in the stem cells and thus hinders the development of treatment options for bone marrow failure.

SUGGESTED USES

Treatment of patients with telomere shortening diseases.

Elogate telomeres in any condition.

ADVANTAGES

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INVENTORS

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OTHER INFORMATION

KEYWORDS

telomere, Dyskeratosis Congenita, telomere biology disorders, TINF2, TIN2, shelterin

CATEGORIZED AS

» **Biotechnology**

» Genomics

» **Medical**

» Disease: Genetic Diseases and Dysmorphic Syndromes

RELATED CASES

2022-084-0

The isogenic human embryonic stem cell model developed by the inventors, TINF2-DC, reveals the mechanism of the genetic mutation responsible for DC, and a potential therapeutic approach.

Currently, the only treatment options to address the BMF associated with DC/TBDs are androgen therapy, associated with treatment-limited toxicity in the majority of patients, allogeneic hematopoietic stem cell transplantation, which is restricted by donor availability and associated with risk of graft versus host disease (GVHD).

RELATED MATERIALS

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