Pharmaceutical composition for chemical inhibition of TGS1 as therapeutic treatment for telomeropathies

KEYWORDS

- ❑ TELOMERES
- ❑ TELOMEROPA-THIES
- ❑ DYSKERATOSIS CONGENITA
- ❑ TGS1
- ❑ SINEFUNGIN

AREA

- ❑ PHARMACEUTICAL

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Patent for invention.

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Sapienza Università di Roma 75%, Università degli Studi di Trieste 25%.

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Industrial & Commercial Reference
Pharmaceutical companies.

Time to Market
TRL 3 – experimental proof of concept-3 years.

Availability
Cession, Licensing, Research, Development, Experimentation and Collaboration.

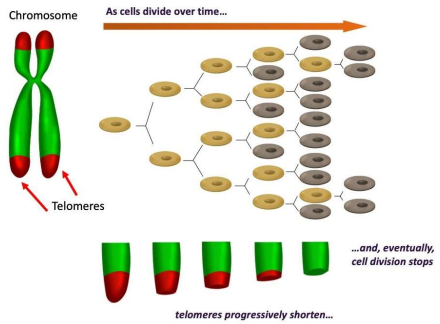


Fig. 1 Relation between telomere length and proliferative capacity of human cells.

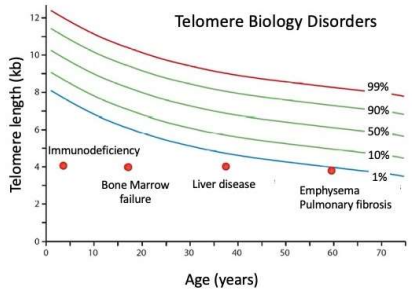
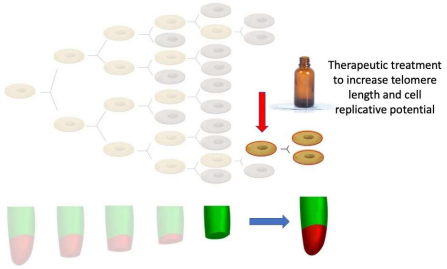


Fig. 2 Diagram of the distribution of telomere lengths in percentiles. Red circles show average length of telomeres at the onset of disease.



Abstract
Telomeropathies are multiple organ diseases characterized by abnormal telomere shortening caused by mutations in genes regulating telomerase activity. A promising therapeutic strategy aims to increase the expression of TERC, one of the telomerase components. TGS1, a gene that negatively regulates TERC levels, is a possible target. The present invention uses the compound sinefungin to inhibit TGS1 activity. TGS1 inhibition results in an increase of telomerase activity and in telomere lengthening. The invention represents a new therapeutic strategy for telomeropathies.

Pubblicazioni

❖ Chen L, Roake CM, Galati A, Bavasso F, Micheli E, Saggio I, Schoeftner S, Cacchione S, Gatti M, Artandi SE, Raffa GD. Loss of human TGS1 hypermethylase promotes increased telomerase RNA and telomere elongation. (2020) Cell Reports 30, 1358-1372. doi: 10.1016/j.celrep.2020.01.004

Fig. 3 Scheme of the therapeutic strategy.

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Technical Description

The composition contains Sinefungin, an inhibitor of the enzyme TGS1 (Trimethylguanosine synthase 1). TGS1 negatively regulates the level of TERC, the RNA component of telomerase. The compound used in our treatment competes with the substrate of TGS1 inhibiting its catalytic activity. Consequently, in human cells TERC levels and telomerase activity increase, and telomeres substantially lengthen. The invention provides a new pharmacological therapy for diseases caused by defects of telomerase activity or generally for pathologies characterized by short telomeres, including discheratosis congenita and idiopathic pulmonary fibrosis.

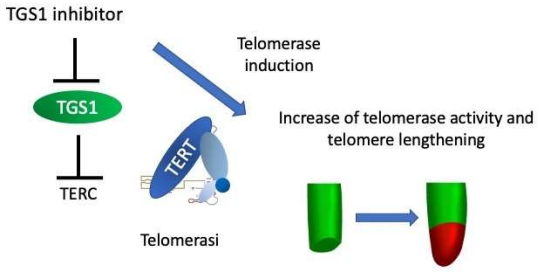

Fig. 4 Schematic representation showing the mechanism of the invention. TGS1 negatively regulates the abundance of the RNA telomerase component, TERC. Pharmacological inhibition of TGS1 causes the increase of TERC levels, and consequent increase of telomerase activity and telomere length.

Technologies & Advantages

There are no current effective treatments that directly target the causative factors of telomeropathies. Transplantation represents the only hope to alleviate the tissue damages consequent to the reduction of the replicative potential of several types of staminal cells, and in particular of the hematopoietic cell line. The strength of the patent is that the invention targets specifically the primary causative effect, that is short telomeres. The discovery that the enzyme TGS1 is a negative regulator of TERC, the RNA component of telomerase, suggests that TGS1 might be an excellent therapeutic target. The present invention consists in the pharmacological inhibition of the TGS1 enzyme and in the consequent lengthening of telomeres, which could potentially counteract the progression of short telomere diseases.

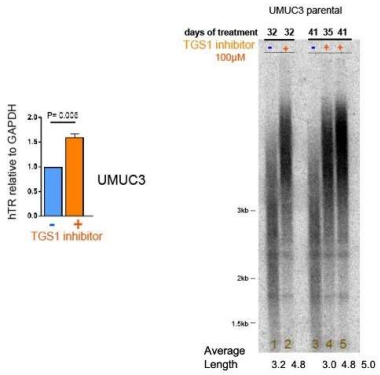

Fig. 5 Pharmacological inhibition of TGS1 in cultured human cells causes the increase of the RNA component of telomerase (left) and the increase of telomere length (right).

Applications

The present invention is targeted to the therapeutic use in diseases such as discheratosis congenita (DC), aplastic anemia, idiopathic pulmonary fibrosis, Hoyeraal–Hreidarsson syndrome. All these genetic diseases have in common the same primary defect: abnormally short telomeres and strong decrease of the replicative potential of several types of stem cells. The used compound causes a remarkable increase of telomere length in several cell types. The development of the invention has two main goals. The first is the preparation of pharmacological compositions that can be directly administered to patients. The second goal is treating in vitro stem cells of the patients until a significant increase of telomere length is reached. Then, treated stem cells may be reintroduced in the patient.

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