Docket #: S22-392

Targeting the DSIF Complex as a Therapeutic Method for Interfering with Telomere Lengthening in Cancer Cells

Inherently, the telomeres located at the ends of chromosomes shorten during each cycle of DNA replication and cell division, eventually topping DNA replication and leading to cell senescence and death. Cancer cells have unlimited replication potential and evade cell senescence by preventing telomere shortening. They depend on aberrant expression of the enzyme telomerase for their ability to continue to propagate in their victims. Consequently, development of anti-cancer therapies that target telomerase has been attempted. However, success of such therapies has been limited, and this has been attributed to the slowness of attrition of nucleotide repeat sequences of telomeric DNA, and importantly, to the ability of cancer cells to develop alternative (ALT) methods of telomere elongation. The technology being marketed teaches a novel approach to telomere shortening that is accomplished by preventing RNA transcript elongation on telomeric DNA templates.

Stanford researchers have identified SUPT4H1, a component of DSIF complex as a target for preventing growth of ALT-dependent cancer cells. Inhibiting SUPT4H1's action affects transcription of TERRA, a non-coding RNA synthesized using telomeric DNA as template. Inhibiting SUPT4H1's actions reduces the ability of the RNA polymerase to produce TERRA transcripts required by ALT, leading to telomere shortening (Figure 1) and consequently to cessation of cell division. The SUPT4H1 gene and its partner in formation of the DSIF complex can be inhibited using established gene silencing methods or chemical compounds. Some such compounds have been identified and have been shown to affect the actions of SUPT4H1 and SUPT5H in vitro and in vivo.

Figure

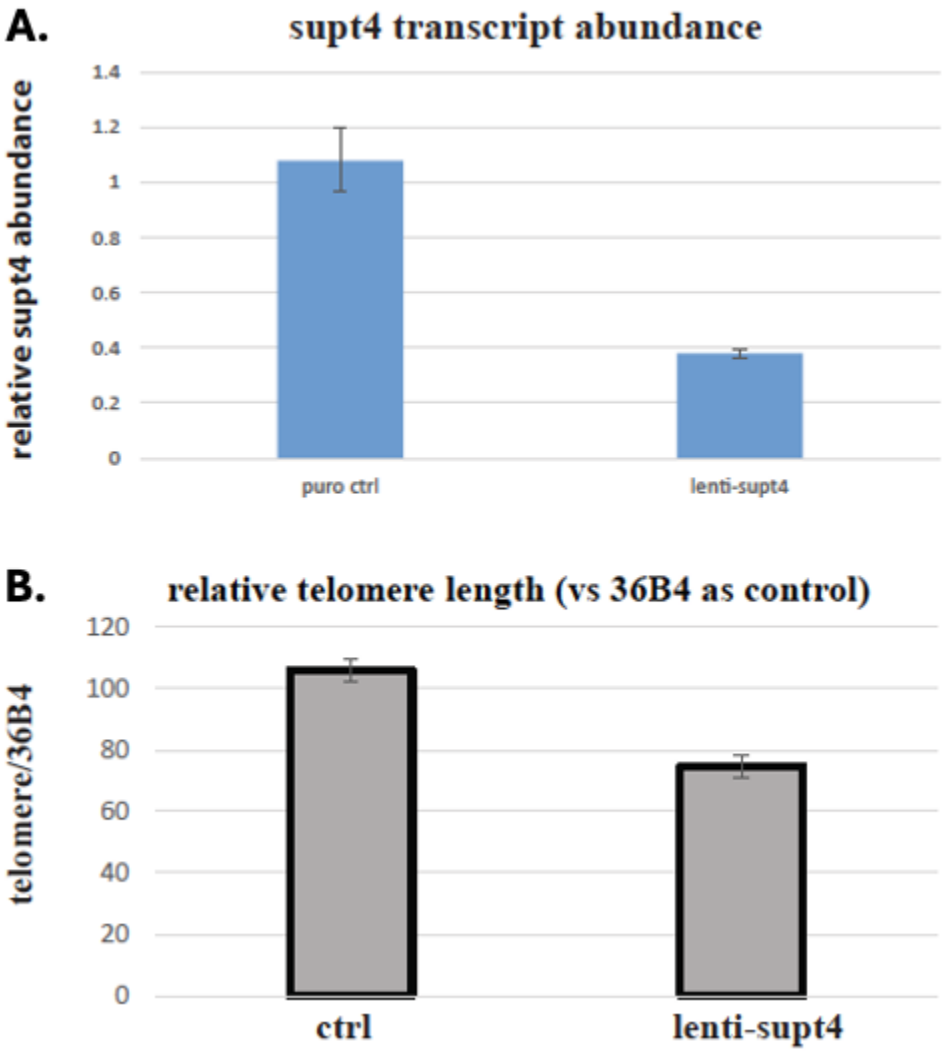

Figure Description: **A)** SUPT4H1 knock down in osteosarcoma cells using SUPT4 shRNA lenti-virus.
B) Resulting change in telomere length.

Stage of Development
In vitro data
"Hit" compounds identified

Applications

- Treatment of cancers by interference with telomere elongation.

Advantages

- Affects ALT-dependent telomere elongation
- Can be implemented using any of the established gene silencing techniques.
- No existing competitive product

Publications

- Deng, N., Wu, Y. Y., *et al*. (2022). Chemical interference with DSIF complex formation lowers synthesis of mutant huntingtin gene products and curtails mutant phenotypes. *Proceedings of the National Academy of Sciences of the United States of America, 119*(32), e2204779119.
- Gao, Y., Zhang, J., *et al*. (2017). Regulation of TERRA on telomeric and mitochondrial functions in IPF pathogenesis. *BMC Pulmonary Medicine, 17*(1), 163.

Patents

- Published Application: WO2024064192

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