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Rapid Telomere Extension

Breakthrough R&D : nucleoside-modified mRNA safely reverses 15 years of telomere aging in 1 week

http://grantome.com/grant/NIH/R21-AG044815-02

Safe, Rapid Telomere Extension to Prevent and Treat Hypertension

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Abstract
We recently demonstrated a novel, uniquely-enabling drug for telomere extension: nucleoside-modified mRNA encoding telomerase. **Our mRNA drug extends telomeres in six days by approximately the amount by which telomeres shorten over 15 years of normal human aging on average, and our drug is transient, being turned over within a few days.**

Uniquely, this approach has the potential to enable safe telomere extension therapy, because it extends telomeres so rapidly that the treatment can be very brief (a few days), leaving the normal anti-cancer telomere-shortening mechanism intact immediately after the brief treatment ends. Our drug does not integrate with the genome, is non-immunogenic as it comprises the same modified nucleosides recently discovered to comprise mature mammalian mRNA, and can encode forms of telomerase which avoid post- translational regulation enabling telomere extension even in slowly-cycling cell populations such as some progenitors.

We and our collaborators are applying our drug to several age-related conditions mediated by short telomeres: hypertension and heart failure (Cooke and Blau labs), immunosenescence (Weyand lab), and vascular dementia (Yesavage lab) (see supporting letters). Each of these applications will be facilitated by this project: here we propose to initiate translation of our drug toward human studies by optimizing its intravenous delivery and demonstrating its safety and efficacy. To optimize i.v. delivery of our drug we will compare the best current and cutting-edge RNA vehicles. In 2007 it was discovered that in the human body, exosomes transport mRNA between cells via body fluids including blood, and in 2011 autologous exosomes were used to deliver nucleic acid via i.v. injection. We will test autologous exosomes as vehicles for i.v. delivery of our drug. We will use our best i.v. delivery method to extend telomeres of vascular endothelial cells to prevent or treat hypertension in the short-telomere mTERC-null mouse model of hypertension. Hypertension is the major risk factor in heart failure, and mice with short telomeres exhibit both hypertension and heart failure, and

short telomeres predict both conditions in humans. In both mice with short telomeres and in humans, a key causative mechanism of hypertension is excess endothelin-1 production by senescent endothelial cells, and we (the Cooke lab) have shown that telomere extension prevents endothelial cell senescence. Thus there is strong evidence supporting the hypothesis that extension of endothelial cell telomeres by our drug will help prevent or treat hypertension. We will also test the safety of our drug by quantifying immune response, tumor formation, and effect on lifespan in the short-telomere hypertensive mice.

If successful, this work will initiate translation of our rapid, safe telomere extension therapy toward the clinic for prevention and treatment of hypertension and other age-related conditions by us and our collaborators...

COMPOUNDS, COMPOSITIONS, METHODS, AND KITS RELATING TO TELOMERE EXTENSION
US2014242154 / WO2014130909
[PDF]

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Compounds and compositions for the transient expression of exogenous telomerase activity in a cell are provided. The compounds and compositions, which relate to a ribonucleic acid coding for a telomerase reverse transcriptase, are useful in the extension of telomeres in cells needing such treatment. Such cells include, for example, cells that contain shortened telomeres and cells from subjects that may benefit from telomere extension, for example subjects that suffer from, or are at risk of suffering from, age-related or other illnesses. Also provided are methods of extending telomeres through the administration of the provided compounds and compositions to animal cells, either in vitro or in vivo, and kits including the compounds and compositions and instructions for use.

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The mission of CELLSCRIPT is to provide the best products and technologies for making and using RNA for translation in cells for clinical research and therapeutics.

Current products include kits for in vitro transcription, 5' RNA capping using either a cap analog or capping enzymes, and 3' RNA polyadenylation, as well as all-in-one kits for making capped, poly(A)-tailed mRNA for translation in cells.

As documented in journal articles1–3 and patent applications, the technologies on which INCOGNITO RNA kits and other products are based were invented by Professors Katalin Karikó and Drew Weissman at the University of Pennsylvania and exclusively licensed to CELLSCRIPT for all fields of use. Drs. Weissman and Karikó showed that INCOGNITO mRNA, besides being less immunogenic, is translated into protein at much higher levels than the corresponding mRNA that does not contain modified nucleosides, both in cultured cells and in whole organisms. INCOGNITO-type - and m5C-modified mRNA encoding KLF4,

LIN28, cMYC, OCT4 and SOX2 that was repeatedly transfected into somatic cells, such as fibroblasts and keratinocytes, resulted in highly efficient generation of induced pluripotent stem cells.

The delivery of protein-encoding INCOGNITO mRNA to cells in culture or in vivo to an organism has the potential to produce a therapeutic effect by compensating for a missing or defective protein, overexpressing a desired protein, inducing a change in cellular phenotype, or triggering a disease-specific immune response. Thus, we believe INCOGNITO mRNAs will have many uses in regenerative medicine, such as for: cell reprogramming; cell therapies; cell, tissue or organ transplantation or repair; tissue or organ engineering; enzyme replacement therapies; and immunotherapies or immunomodulation therapies...

CELLSCRIPT recently introduced INCOGNITO™ RNA Transcription Kits for in vitro synthesis of RNA that contains modified nucleosides, such as pseudouridine (?) and/or 5-methylcytidine (m5C) in place of the corresponding U or C canonical nucleosides (Figure 1). These kits are so-named because the capped, polyadenylated and nucleoside-modified RNA products (called "INCOGNITO mRNAs") are disguised so they do not induce innate immune responses to the same extent as the corresponding unmodified mRNAs when transfected into mammalian cells that express a variety of RNA sensors...

US8278036
RNA containing modified nucleosides and methods of use thereof

Inventor(s): KARIKO KATALIN; WEISSMAN DREW

This invention provides RNA, oligoribonucleotide, and polyribonucleotide molecules comprising pseudouridine or a modified nucleoside, gene therapy vectors comprising same, methods of synthesizing same, and methods for gene replacement, gene therapy, gene transcription silencing, and the delivery of therapeutic proteins to tissue in vivo, comprising the molecules. The present invention also provides methods of reducing the immunogenicity of RNA, oligoribonucleotide, and polyribonucleotide molecules.

Related :

US2005009177
Telomerase interference

Inventor(s): ROWLEY PETER

The invention relates to nucleic acids encoding or comprising interfering RNAs which target telomerase RNA or mRNA encoding the telomerase reverse transcriptase (TERT). The invention includes methods for inhibiting telomerase activity expression vectors, and pharmaceutical compositions.
