Telomerase Biology Associations Offer Keys to Cancer and Aging Therapeutics

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Abstract: Background: Although telomerase has potential for age-related disease intervention, the overexpression of telomerase in about 90% of cancers, and in HIV virus reservoirs, cautions against use in anti-aging telomerase therapeutics. While multiple reviews document the canonical function of telomerase for maintenance of telomeres, as well as an increasing numbers of reviews that reveal new non-canonical functions of telomerase, there was no systematic review that focuses on the array of associates of the subunit of Telomerase Reverse transcriptase protein (TERT) as pieces of the puzzle to assemble a picture of the how specific TERT complexes uniquely impact aging and age-related diseases and more can be expected.

Methods: A structured search of bibliographic data on TERT complexes was undertaken using databases from the National Center for Biotechnology Information Pubmed with extensive access to biomedical and genomic information in order to obtain a unique documented and cited overview of TERT complexes that may uniquely impact aging and age-related diseases.

Results: The TERT associations include proper folding, intracellular TERT transport, metabolism, mitochondrial ROS (Reactive Oxygen Species) regulation, inflammation, cell division, cell death, and gene expression, in addition to the well-known telomere maintenance. While increase of cell cycle inhibitors promote aging, in cancer, the cell cycle check-point regulators are ambushed in favor of cell proliferation, while cytoplasmic TERT protects a cell cycle inhibitor in oxidative stress. The oncogene cMyc regulates gene expression for overexpression of TERT, and reduction of cell cycle inhibitors-the perfect storm for cancer promotion. TERT binds with the oncogene RMRP RNA, and TERT-RMRP function can regulate levels of that oncogene RNA, and TERT in a TBN complex can regulate heterochromatin. Telomerase benefit and novel function in neurology and cardiology studies open new anti-aging hope. GV1001, a 16 amino acid peptide of TERT that associates with Heat Shock Proteins (HSP’s), bypasses the cell membrane with remarkable anti-disease potential.

Conclusions: TERT “associates” are anti-cancer targets for downregulation, but upregulation in antiaging therapy. The overview revealed that unique TERT associations that impact all seven pillars of aging identified by the Trans-NIH Geroscience Initiative that influence aging and urge research for appropriate targeted telomerase supplements/stimulation, and inclusion in National Institute on Aging Intervention Testing Program. The preference for use of available “smart drugs”, targeted to only cancer, not off-target anti-aging telomerase is implied by the multiplicity of TERT associates functions.

Keywords: Aging, TERT, associates, cancer, oncogenes, cell cycle, diseases, viral infection.

1. INTRODUCTION

The promoter of the reverse transcription TERT gene, is a common non-coding mutation in cancer [1-3] and these mutations in the regulation of TERT expression represent a tumorigenic mechanism [2]. Regulation of telomerase by epigenetics results in TERT overexpression [4] and TERT function [5]. The discovery of the role of telomerase as a telomere ribonucleoprotein terminal transferase, i.e., the TERT reverse transcriptase protein with TERC (Telomerase RNA component), heralded a new area in telomere biology and is considered the canonical role of telomerase [6, 7]. Damage to telomeres can trigger DNA damage response, apoptosis and aging [8]. The association of telomere-dysfunction with diseases was recently reviewed [9]. Here, the non-canonical telomerase functions include the discovery that TERT expression regulates tolerance to oxidative stress in mitochondria linking telomerase, mitochondria, oxidative stress, aging diseases, and longevity [8-12]. Telomerase’s ability to reverse tissue degeneration in aged mice provides evidence for the potential for therapeutic TERT intervention.
Examples of telomerase benefits emerge in immunology [14], cardiology [15], chemotherapy-induced damage [16] and neurology [17, 18]. Epigenetics [19, 20] and splice variants of TERT RNA can regulate telomerase activity in cancer, and in different cells and tissues [21]. The recently discovered ability to target telomerase, and thereby also selectively target cancer cells, allows the elimination of cancer cells without downregulation of the positive roles of telomerase in other age-related diseases [22, 23]. The TERT peptide GV1001, promises to be an intervention drug in multiple diseases [24].

Stress, especially oxidative stress, impacts multiple age-related diseases (over 15,000 references on aging and oxidative stress are cited in the National Library of Medicine National Institutes in 2019). Oxidative stress age-related diseases include cancer, cardiac aging, cardiovascular diseases, skeletal muscle aging, Alzheimer’s Disease, Parkinson’s Disease, Hearing Loss, insulin resistance, diabetes [25], immunosenescence [26], frailty [27] and age-related vascular dysfunction [28] linked to TERT, since oxidative mitochondrial stress is regulated by mitochondrial TERT [8-12]. The associations of TERT with chaperones, mitochondrial DNA, mTOR pathway and brain mitochondria, glucose kinase, antioxidant pathways, inflammatory regulators, glucose and fat metabolism, oncogenes, generation of micro and interfering RNA gene regulators, cell cycle regulators of cancer, and evidence of critical roles in cardiovascular and neurological diseases are documented below with the promise of GV1001 in disease intervention. The extensive non-canonical participation of Telomerase subunit TERT with associations (Table 1) that impact aging and age-related signals need for appropriate telomerase age-related intervention therapy.

2. TERT CHAPERONES

Tert Chaperones: Required For Proper Protein Shapes For Telomerase Activity: Proteostasis, Macromolecular Functions And Tert-Terc-Telomere Functions [29-31].

2.1. TERT-Hsp90-23-TERT

The unique associations between heat-shock protein 90 chaperones, and stress-inducible HSP23, dictate TERT proper assembly with the RNA ligand template TERC. Components of the Hsp90 TERT chaperone of telomerase assembly, remain with active and are required for telomerase activity [29].

2.2. TCAB1-TERT

TCAB1-TERT (Telomerase Cajal Body protein 1 RNA splicers). Depletion of TRiC (TCP-1 Ring Complex Chaperone) is required for TCAB1 folding, or TCAB mutations, impair the control of telomerase activity for telomere elongation [30]. Telomerase depends upon the holoenzyme protein TCAB1, a target for cancer therapeutics [31].

3. INTRACELLULAR NUCLEAR

Intracellular Nuclear- mitochondrial travel. required for tert location to mitochondrial for functions in aging [32-35].

| Table 1. Telomerase, subunits, and associates regulate age-related functions. |
|-------------------------------------------------|-----------------|----------------|
| Functional Category                              | Associates      | Section |
| Nuclear telomere biology                         | Chaperones HSP90, TCA | 1, 2    |
| Mitochondrial Anti-oxidant Functions             |                  |         |
| Intracellular transport                          | Motor 90 Dynemin, FKB'S | 3       |
| Oxidative stress protection                      | Mitochondrial DNA, mTOR, NrF2 | 4.2     |
| Inflammation                                     | NrFkB, NrF2     | 5.1-5.3 |
| Metabolism                                       | NrF2 Glucose    | 5.4-5.5 |
| Fatty acids EZH2                                 |                  |         |
| Gene Regulation                                  | RMRP-RdRP, TBN, siRNA, microRNA | 6.1-6.2 |
| Immortality vs. Aging                            | P16 INKA        | 8       |
| Cytoplasmic Antioxidation Cancer                 | P15 RNA, TERT-TIA1 | 8       |
| TERT                                             | cMyc oncogene   | 9       |
| TERC                                             | cMyc oncogene   | 9.1     |
| Neuronal Health                                  | TELOMERASE      | 10      |
| Heart Health                                     | TELOMERASE      | 11      |
| Intervention                                     | GV1001          | 12      |
| Supplements                                      | -               | 13      |
TERT requires p90 dynactin motor (cytoplasmic motor for intracellular nuclear-mitochondrial travel to mitochondria) and FKBP52 (FKB506-binding protein immunophilins) and FKBP52-hTERT-Hsp90-Dynein-dynactin complex provides the motor for cytoplasmic transport of hTERT [32]. FK51and FKB52 proteins stimulate TERT in oxidative stress and thus a target for downregulation of cancer cells [32]. Hsp90-binding immunophilin FKBP51 forms complexes with hTERT enhancing telomerase activity and overexpression of the immunophilin is associated with resistance to induce cell death [33]. FK506-Binding Proteins (FKBPs) are co-receptors for immunosuppressants, and FKBPs inhibitors intervene in antimalarial, antilegionellal, and antihamyldial properties [34]. Conversely, approaches are necessary to intervene in protein misfolding in neurological diseases [35].

4. MITOCHONDRIAL TERT AND OXIDATIVE STRESS

Required for tert antioxidant function and macromolecular protection, and stress resistance [10, 36-48].

4.1. TERT- mDNA (Mitochondrial DNA)

TERT binds to mDNA and protects mDNA from oxidative damage [10]. Telomerase protects mitochondria under oxidative stress [36]. Telomerase affects mitochondria DNA replication [37]. Oxidative DNA damage stalls the human mitochondrial replisome [38]. Telomerase overexpression protects cancer cells from apoptosis [39]. Telomerase affects the cellular response to oxidative stress by autophagy [40].

4.2. mTOR-TERT (Target of Rapamycin, Member of Phosphatidylinositol 3 Kinase)

Diet Restriction (DR) and rapamycin treatment (inhibitor of mTOR) stimulate TERT localization in rodent brain mitochondria, reduce Reactive Oxygen Species (ROS) as an antioxidant, and improve mitochondrial function [41, 42]. Signals from mTOR expression in aging and neuro-regeneration affect both metabolism and autophagy [43]. Inhibition of mTOR expression with rapamycin in a mouse model of Down’s syndrome intervenes in a cognitive loss by the improvement of autophagy and insulin signaling [44]. The mTOR inhibition modulates Aβ plaques deposition and tau tangle aggregation in Alzheimer’s disease [45] and promote inhibition in neurological disease and longevity [46] likely due to improvement in mitochondrial health [41, 42]. However, the PI3K/AKT/mTOR AKT kinase is central to glucose metabolism signaling pathway, as well as the promotion of TERT over expression of stem-like cancer cells suggests targeting both in cancer therapy [47]. The presence of TERT in the signaling complex implies that mTOR- mediates the control of telomerase activity [48]. Telomerase activity is inhibited by various phytochemicals such as isoprenoids, genistein, curcumin, epigallocatechin-3-gallate, and resveratrol [48].

5. METABOLISM, INFLAMMATION, IMMUNITY

Required for energy, anti inflammatory disease, infection resistance, and tumor progression [49-54].

5.1. NrF2-TERT

NrF2 (nuclear Factor erythroid 2 related factor that controls ARE antioxidant response element). Inhibition of human TERT reduces NrF2 and induces glioma cell apoptosis, while NrF2 overexpression increases TERT [49]. TERT inhibition results in a reduction in pentose phosphate intermediates and stimulation of glycogen [49]. In glucose deficit, both NrF2 and autophagy support breast cancer progression [50]. In cancer, NrF2 protects against ROS stress, inflammatory assembly, and regulates cancer promotion microRNAs [51]. While TERT and NrF2 are targets for downregulation in cancer, upregulation is desirable for intervention in ROS mediated diseases [52]. NrF2 activating compounds show down regulation of inflammasomes and inflammation, in non-cancer disease treatments [52]. NrF2 regulates activation of inflammasomes via regulation of the Trx1/TXNIP (thioredoxin interacting compound) complex [53] and up regulation of TXNIP may be anti-aging and anti-HIV, by down regulation of inflammation found in HIV immune cells [54].

5.2. TERT- NF-κB (Nuclear Factor Kappa Light Chain Enhancer of Activated B Cells)

The ability of NF-κB to alter cell functions reflects multiple gene activations or repressions [55]. In mice, telomerase binds to the NF-κB p65 [56].

5.3. TERT- NF-κB -STAT3 (Signal Transducer and Activator of Transcription)

In humans, STAT3- STAT1-NF-κB physically interact and stimulate cytokines IL6 (interleukin 6) and TNF α (tumor necrosis factor) inflammatory agents that increase telomerase activity and stem-like cancers [57]. In atherosclerosis, inflammation activates TERT [58]. STAT regulates inflammation and immunity [59]. The oriental anti-inflammatory agent, Withania somnifera is a likely drug candidate for human clinical trials in cancer [60]. Over- the counter anti-inflammatory agents are supplements suggested for cancer-induced inflammation treatment [61]. Telomerase supplements for arthritis have conflicting responses, likely due to the activation of different telomerase-associate pathways [15].

5.4. Telomerase-Glucose Hexokinase Telomerase

Telomerase-Glucose and Hexokinase. Telomerase downregulates glycolytic pathway genes, decreases glucose consumption and lactate production. Inhibition of telomerase RNA expression reduces metastasis, glucosemetabolism, lactate [62]. Hexokinases, also known as glucokinases, catalyze the first step in glucose metabolism [63]. Deletion of hexokinase intervenes in cancer [64]. Hexokinase has a role in growth or death, via starvation induced autophagy by TORC [65]. The TOS binding site for TORC substrates is conserved in vertebrates [66]. Telomerase links cell death, hexokinase, and autophagy [67]. The role of telomerase in glucose metabolism links telomerase to glucose metabolism in innate immunity [68] and immune CD4- and CD8- cells [69]. Recently, a protein was found to code from the RNA ligand of telomerase Tert, called TERP, [70] whose role in biology of cancer is unknown.
5.5. TERT-EZH2

TERT-EZH2 (also known as Zeste homolog 2, histone H3K27 methyltransferase) is required for epigenetic methylation control in lipid metabolism.

Downregulation of TERT decreases EZH2, and correlates with an excess of lipids, and stimulation of ATM damage response in glioma model [70]. TERT in association with EZH2 is a stress responder to DNA damage [71].

6. TERT-RMRP

(RNA component of mitochondrial RNA Polymerase, ligand mitochondrial exonuclease, also known as RNase MRP RNA, RNA component of Mitochondrial RNA Processing RNA required for regulation of gene expression and RNA dependent RNA polymerase function.

6.1. TERT-RMRP

TERT-RMRP generates RdRP (RNA dependent RNA Polymerase). TERT interacts with the same RNA ligand component as RNase MRP (RNA component of the mitochondrial RNA endonuclease, RMRP, that self-regulates RMRP level by siRNA [72] and generates short RNAs in cancer cell lines [73]). Endogenous siRNAs other than RMRP are also found with the ability of sequence-specific inhibition of micro RNAs [74]. TERT protein levels correlate with RdRP activity in cancer and identify RdRP as a target for anticancer therapeutics [73-75]. In a study, knockdown of RMRP by shRNA inhibited mammary cancer cell replication [75]. The ability of RdRP to generate siRNA was independently confirmed [76] though attempts to generate siRNA to control RNase MRP RNA with siRNA of RMRP were unsuccessful or complicated by pleiotropic unintended target effects [77]. Using the selective gene scissors, Crisper-Cas9 (Clusters of regularly interspaced palindromic repeats for gene editing) the RMRP locus, results in the deadly accumulation of preribosomal RNA in human HEla cells [78].

6.2. RMRP Oncogene

RMRP regulation is altered in multiple cancers [79-82]. RMRP is known as an oncogene upregulated in lung cancers and promotes inhibition of mi RNA-206 [79-80]. MicroRNA 206 modulates cyclin D2, cell division, and invasion in cancers [81-83]. Recent reviews show that RMRP acts as an oncogene that regulates glycolysis, ROS, and apoptosis in humans, and document that RMRP is a target for anticancer therapeutics [84, 85].

7. TBN COMPLEX

TERT-BRG1-Nucleostemin (BRG1- ATPase of the SWI/SNF chromatin remodeling complex that remodels chromatin to control gene expression and chromosome centromere) required for regulation of heterochromatin in gene regulation and centromeres epigenetics.

7.1. TERT in TBN

TERT is prominent in cancer and cancer initiating cells; BRG1 interacts with histone deacetylase 2 and alters telomerase activity in cancer cells [86]. Levels of BRG1 correlate with cancer cell replication levels [87]. Nucleostemin is associated with malignancy in cancer cell line [88]. TBN (TERT-BRG1-Nucleostemin) is prominent in tumor-initiating cells [89]. TERT is involved in heterochromatin maintenance [90], RNA dependent RNA polymerase siRNA production [91], and chromosome segregation [92]. The complex of TERT-BRG1-Nucleostemin (TBN) is reminiscent of heterochromatin complex control in lower organisms and may be potentially useful in targeting cancer [93]. TERT also regulates microRNA [94]. Telomerase intervenes in telomere aneuploid induced replication stress [95]. In summary, TBN directs RNA synthesis, heterochromatin, centromeres, mitosis, siRNA, miRNA, and cell replication targets in cancer therapeutics.

8. TERT-P16 INKA

TERT-P16 INKA aliases CDKN2A, ARF, CDK4, CDKN cyclin-dependent kinase inhibitor 2A, P16-INK4A: Regulator of cell cycle: required for cell cycle control, brain protection [96-101]. The mammalian INK4a/ARF locus (alternate reading frame) encodes p16INK4a protein and ARF regulators of Retinoblastoma (RB) and p53 pathways that impact and regulate cancer and aging [96, 97]. The interaction of stimulation or inhibition of cell cycle describes the difference in cancer types versus the activation of p16 can intervene in cancer [98]. Cells, with activated p16 INK4a promoter, accumulate p16 and exhibit inflammation, and display senescence [99]. Both TERT and p16 are players in glioblastomas; p16 suppresses hTERT in a human mammary epithelial cell by p16 activation of methylation that irreversibly blocks the hTERT promoter in normal and human breast cancer [100]. Thus, the dual role of p16 includes not only inhibition of cell cycle progression, but also the transcriptional suppression of the TERT promoter in mammalian cells. Bmi-1 (B-cell specific Moloney murine virus integration site 1) is a member of the Polycycomb Repressor Complex 1 that regulates chromatin structure for renewal of both normal and cancer stem cells, and lengthens the potential doubling of human cells by inhibition of p16/INK4a [101]. Bmi has the potential for antiaging for self-renewal of normal cells, but, the danger of protection of cancer cells [101].

Modifications of p15, p16 and TERT are inducible; epigallocatechin-3-gallate, found in green tea, inhibits growth and induces apoptosis in cancer cells by activation of the cell cycle inhibitor p16 and downregulation of telomerase [102, 103]. TGF β (transforming growth factor) induces a 30X increase of p15 in stress [104] and the TGFβ pathway stimulation induces aging in glioblastoma cells [105]. The antiapoptotic role of telomerase involves BC12 (B-cell lymphoma 2 family of anti-cell death proteins) the over expression of which protects cancer cells from apoptosis [106]. The drug used to target BCL2, Venetoclax in HIV reservoirs, may be effective in cancer to counteract TERT induced antiapoptosis [107]. The low dose of the drug RGI08 methylation inhibitor activates TERT and blocks ROS and inflammation, and at high dose, it activates tumor suppressor p16 INKA [108, 109].

In fully differentiated neurons, the largest pool of cytoplasmic TERT is in the complex (TERT -TIA1- p15INK4b
mRNA) and under oxidative stress, p15INKA4b translation occurs and neuronal survival increases [110]. While TERT knockdown promotes apoptosis, TERT induced overexpression reduces apoptosis and TERT exhibits translational control of p15 messenger RNA cell cycle inhibitor expression in oxidative stress and neuronal survival [110]. Studies show mammalian brain with TERT specifically in neurons [111-113].

9. TERT-cMyc

C-Myc is a transcription factor protein and oncogene) Required for cancer progression [114-118]. Gliomas show increased TERT mRNA, and telomerase activity [114]. TERT protects cMyc by after-translational regulation of cMyc ubiquitination and thereby protects cMyc from degradation in carcinogenesis [114]. A cMyc-MAX dimer binds to promoters of TERT and cyclin DD that enhance their transcription for TERT overexpression [115], while cMyc represses cyclin-dependent kinase inhibitors p15 and p21 to result in inhibition of cell cycle [116-118]. The upregulation of telomerase and downregulation of cell cycle regulation provide the perfect environment for cancer promotion in post-mitotic cells.

TSC-22 (transcription factor) reacts with c-MYc and prevents the suppression of p15 promoters but enhances overexpression of TERT [119], separating two promoters of cancer for anticancer activity.

9.1. TER C-cMYC

Telomerase RNA component epigenetic control of cancer [120]. cMyc occupies the TERC locus, and mediates excess TERC RNA, while TERC inhibition reduces prostate cancer [120], therefore, both TERT and TERC independently interact with cMyc to modulate cancer pathology. Although TERC has been considered a non-coding RNA, the protein TER P has been found protecting cell viability [70].

10. TERT, STEM CELLS, NEURONAL HEALTH, AND MTOR

Telomerase in neuronal health stem cell neurogenesis. Required for antioxidant and stem cells [121-129]. Adult human neurogenesis was discovered in the dentate gyrus of adult humans throughout life [121]. Retrospective birth dating is possible to measure human cell turnover from by use of the known C14 from nuclear bomb testing generated in the atmosphere as the DNA date mark when a cell duplicates its chromosomes [122]. New human hippocampal cells using 14C, reveal and new neurons are added each day, with minimal aging decline [123] and sparks hope of maintenance of brain functions in aged! Ectopic telomerase expression delays amyotrophic lateral sclerosis [124]. Hippocampal neurogenesis has a potential role in memory and spatial learning [125]. Telomerase is required for the benefits of neurotropic growth factor, Brain-Derived Neurotrophic Factor (BDNF) in early hippocampal brain development [126]. The TERT-mTor association’s role in neuronal mitochondrial health provides hope for intervention in neurological disorders [41-45]. TERT plays a role in the dynamics of neurogenesis, regulated by mitochondria throughout the lifespan [127].

Neural Stem Cells (NSCs) and Neural Progenitor Cells (NPCs), implicated telomerase for an important role in the developing and adult brains of humans and rodents. Recent studies have demonstrated that telomerase in NSCs/NPCs functions in cell proliferation, neuronal differentiation, neuronal survival and neurogenesis [129].

11. TELOMERASE HEART HEALTH

Reviews of the role of telomerase as a therapeutic tissue-specific target relative to cardiovascular health [11] and off-target damage by chemotherapy highlight the importance of telomerase in heart health and drug induced cardiac damage [16]. Telomerase is beneficial in treatment of Coronary Artery Disease (CAD) via protection from ROS [15, 16]. In Ischemia- Reperfusion injury, injury telomerase deficit predisposes heart failure [130]. Telomerase has a critical role in microcirculation since decreased telomerase activity promotes Nitric oxide conversion to peroxide in Coronary Artery Disease (CAD), while telomerase increase restores normal function [131]. Telomerase has potential for intervention in pulmonary hypertension [132]. Telomere attrition is characteristic of cardiac hypertrophy and cardiomyocyte-specific telomere shortening is a human marker of heart failure, and cardiomyocytes with the shortest telomeric lengths are typically correlated with reduced ejection [133] (Fig. 1).

12. GV1001

Telomerase peptide intervention potential in antiaging disease activators -inflammation, oxidative stress related diseases, and amyloid toxicity in neuronal diseases. The16 amino acid peptide of telomerase, used as the cancer vaccine, GV1001, unexpectedly also shows Cell Penetrating Properties, (CPPs), with, ease of cytosolic cargo passage across the plasma membrane for delivery of drug macromolecules via heat shock proteins HSP90 and HSP70 [20, 133]. GV1001 functions properties are anti-inflammatory [134, 135], antioxidant [136, 137], antiviral [138] and anti-amyloid toxicity [139].

13. TERT SUPPLEMENTS

Telomerase supplements were reviewed previously (15). The telomerase activator TA-65 supplement extends telomeres and increases disease free longevity in mice, without cancer promotion [140], and may have potential in telomere attrition found associated with frailty [141]. TA-65 telomerase activator does not increase cancer in mice [142]. Different TERT drugs activate different TERT associated functions (11); i.e., the PGC-1a/TERT (peroxisome proliferator-activated receptor gamma coactivator pathway-1a), activated by drug Catalpol, intervenes in atherosclerosis by downregulation of ROS and inflammation [143] and likely would benefit multiple age-related diseases aggravated by oxidative stress and inflammation. The TERT tissue specific positive effects on endothelial, and pathological effect in vascular smooth muscle and atherosclerosis, are modulated by different supplements yielding conflicting benefit results [15].

14. ANTI CANCER TERT

An unexpected role of telomerase in cancer is impacted by biology of TERT and subsequent chemotherapy [144]
that challenges the existing paradigm that indicts telomerase in carcinogenesis, when associates may be the villains.

CONCLUSION

TERT “associates” are anti-cancer targets for downregulation, but upregulation in antiaging therapy. The role of TERT with associates identifies roles for TERT in proteostasis, epigenetics, molecular damage, stress tolerance, metabolism, inflammation, and stem cells, i.e., the seven pillars of aging identified by the Trans-NIH Geroscience Initiative that influence aging and disease. The emerging appreciation of telomerase benefits to health and disease intervention, heart diseases, mental health, and anti-malignancy highlight the urgency for research for targeted telomerase stimulation for improvement of health at any age, delay of age-related pathologies, and encouragement for National Institute on Aging Intervention Testing Program, to research TERT stimulators for treatment without the risk of cancer.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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