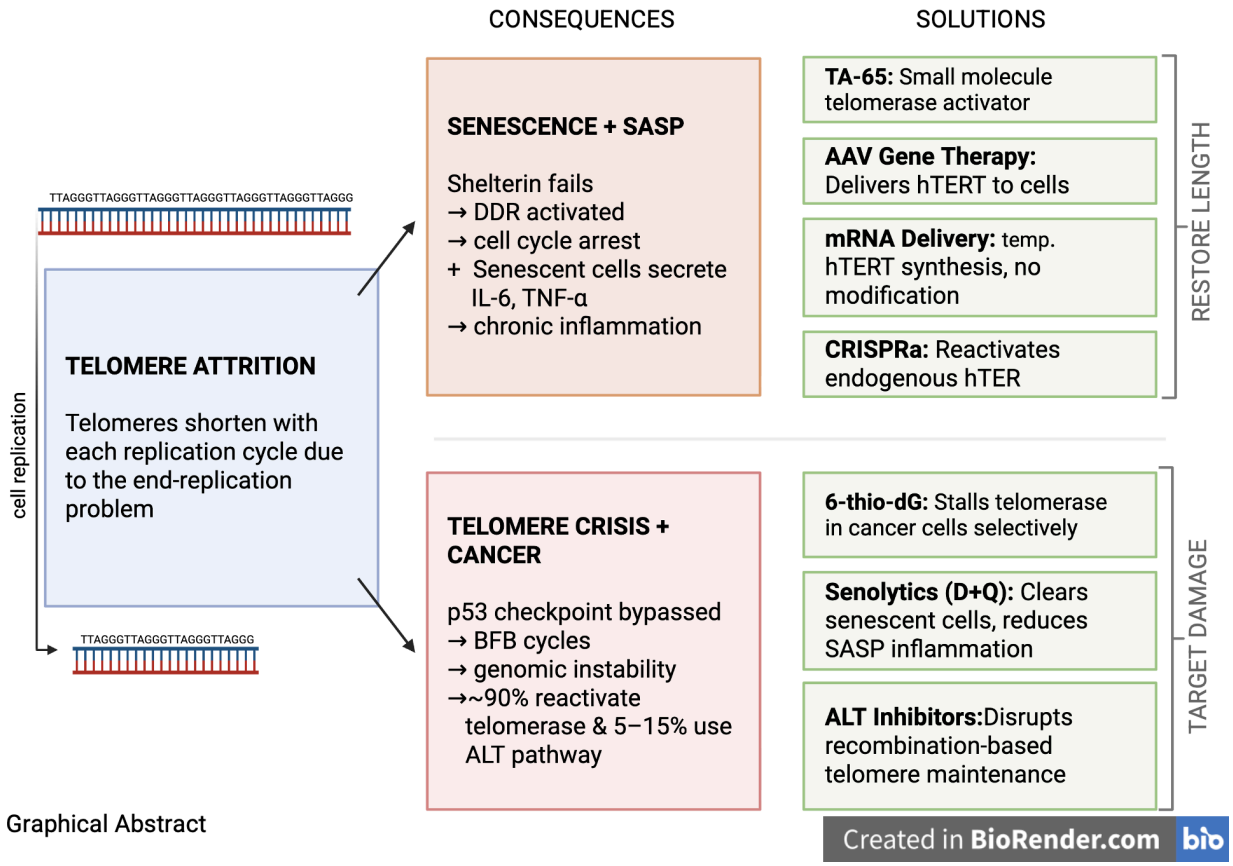
OXFORD JOURNAL
OF STUDENT
SCHOLARSHIP

# A Review of Telomere Biology and Therapeutic Strategies

Hassan Ahmed Metwally
hassanametwally@gmail.com

**ABSTRACT**

Telomeres protect chromosome ends and shorten with cellular replication, contributing to cellular senescence, pro-inflammatory senescence-associated secretory phenotype (SASP), genomic instability at critical lengths, and age-related pathology. This review examines telomere biology, its role in aging and disease, and related therapies. While telomere attrition suppresses tumors, critically short telomeres can lead to telomere crisis and genomic instability. To overcome this, 85-95% of human cancers reactivate the enzyme telomerase or utilize ALT pathways. Telomere Biology Disorders (TBDs), genetic diseases caused by mutations in telomere-maintenance genes, act as accelerated aging models and demonstrate the consequences of telomere attrition. Leading therapeutic strategies include telomerase activation via small molecules (e.g., TA-65) or adeno-associated virus (AAV)-based gene therapy, both shown to extend lifespan in animal models without increasing cancer risk. Advanced methods, such as CRISPR-mediated epigenetic editing (CRISPRa) and modified mRNA delivery, are precise and have transient effects. Additional methods include inhibiting alternative lengthening (ALT) pathways in cancer and senolytics (e.g., Dasatinib and Quercetin), which clear senescent cells. The most promising direction emerging from this review is a combined approach: transient telomerase activation to restore telomere length while avoiding permanent genomic modification and its associated cancer risk, paired with senolytics to eliminate the senescent cells responsible for chronic inflammation. Together, these strategies address telomere attrition at both its cause and its consequences.




*Graphical Abstract*

Overview of telomere attrition and therapeutic strategies. Telomeres shorten with each replication cycle due to the end-replication problem. Critically short telomeres produce two consequences: senescence and SASP, characterized by chronic inflammation, or telomere crisis and cancer in cells with bypassed checkpoints. Seven therapeutic strategies are grouped by goal, restoring telomere length (TA-65, AAV gene therapy, mRNA delivery, CRISPRa) or targeting downstream damage (6-thio-dG, senolytics, ALT inhibitors).

## INTRODUCTION

Chromosomes are capped by telomeres, repetitive 5'-TTAGGG-3' DNA sequences. They are 10-15 kilobases long at birth and prevent chromosomal damage by distinguishing natural chromosome ends from DNA double-strand breaks (Iskandar et al., 2025; Srinivas et al., 2020).

In somatic cells, telomeres shorten during each replication cycle due to the "end-replication problem", a consequence of incomplete lagging-strand synthesis (Shay & Wright, 2019; Srinivas et al., 2020). Specifically, no free 3′-hydroxyl group is available once the RNA primer is removed. Therefore, the gap

cannot be filled, leading to the loss of DNA with each replication cycle. When cells reach the Hayflick limit, the maximum number of divisions possible, they undergo apoptosis or senescence (Shay & Wright, 2019; Srinivas et al., 2020).

Structurally, telomeres are stabilized by a six-protein complex known as shelterin, which facilitates the formation of a T-loop structure that protects the chromosome end (Iskandar et al., 2025; Lu et al., 2013). The enzyme telomerase, a ribonucleoprotein, uses its RNA component (hTERC) and its reverse transcriptase catalytic subunit (hTERT) to add new DNA repeats, to extend telomere length (TL) (Iskandar et al., 2025).

Telomere attrition contributes to age-related diseases. While telomere shortening functions as a tumor-suppressive mechanism by restricting uncontrolled replication, critically short telomeres cause genomic instability, which can instead promote cancer (Iskandar et al., 2025). Many cancers bypass this barrier by reactivating telomerase (Iskandar et al., 2025).

Telomeres are the focus of many biomedical fields. This has led to the development of a range of therapies (Iskandar et al., 2025), that attempt to either preserve or restore telomeres. This paper discusses telomere biology, its role in aging and disease, associated telomere syndromes, and the therapies designed to combat telomere attrition. Finally, this paper will evaluate the future of this field.

A glossary of key terms and abbreviations used throughout this review can be found at the end of this document.

## BIOLOGY OF TELOMERES AND TELOMERASE

Genomic stability depends on the structure and function of telomeres, which are supported by the shelterin complex and telomerase enzyme. The section discusses these factors.

### *2.1 Telomere Structure and Shelterin*

Telomeres, TTAGGG repetitions in DNA, create a 3' single-stranded guanine-rich overhang. This overhang forms the T-loop, which invades the double-stranded section of the telomere (Lu et al., 2013). This T-loop defines the chromosome's end and prevents DNA damage response (DDR) from misidentifying it as a double-strand break (DSBs) (Lu et al., 2013). The stability and function of telomeres are ensured by the six-protein shelterin complex, which binds specifically to telomeric DNA, comprising TRF2 and TRF1, TIN2, RAP1, TPP1, and POT1 (Lu et al., 2013). TRF2 (Telomeric Repeat-binding Factor 2) binds the double-stranded DNA and is required to form and stabilize the t-loop. TRF2 inhibits Ataxia Telangiectasia Mutated (ATM) kinase activity, preventing the DNA Damage Response (DDR) machinery from misidentifying telomeres as double-strand breaks (DSBs) (Karlseder et al., 1999). TRF1 also binds to double-stranded telomeric DNA and negatively regulates TL by limiting

telomerase access during replication (Lu et al., 2013). POT1 binds to the single-stranded overhang to protect it. This prevents the cell's repair proteins, like Replication Protein A (RPA), from recognizing it as a break. If RPA were to bind, it would trigger the Ataxia Telangiectasia and Rad3-related (ATR) pathway, which is a DDR that halts the cell cycle. TPP1 forms a heterodimer with POT1, enhancing its binding affinity. Additionally, it acts as the main recruiter of telomerase by providing a binding site (Lu et al., 2013). TIN2 acts as the central organizing factor by linking the TRF1 and TRF2 sub-complex with the TPP1 and POT1 sub-complex. RAP1 is recruited by TRF2, preventing incorrect non-homologous end joining (NHEJ) and contributing to transcriptional repression of nearby genes (telomere position effect) (Srinivas et al., 2020). The spatial organization of these components is illustrated in Figure 1.

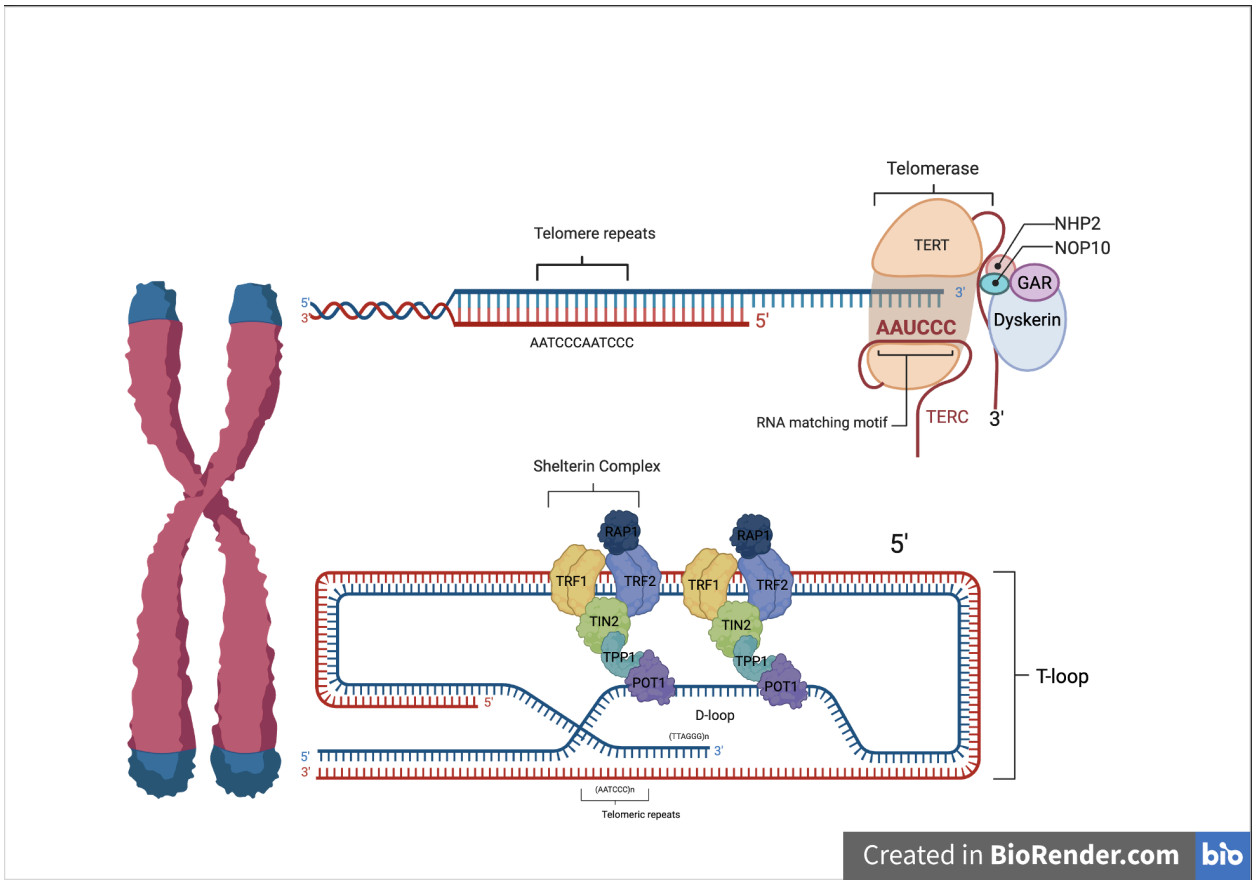



*Figure 1*

Structure of the telomere and the shelterin complex. The telomere consists of repetitive TTAGGG sequences capped at the chromosome end. The single-stranded 3' overhang folds back to form the T-loop and D-loop, shielding the chromosome end from the DNA damage response. The six shelterin proteins (TRF1, TRF2, RAP1, TIN2, TPP1, and POT1) bind the telomeric DNA to stabilize this structure. Telomerase, composed of hTERT and hTERC (supported by the Dyskerin complex including NOP10, GAR1, and NHP2), is recruited via TPP1 to extend telomere length.

### *2.2 The Telomerase Enzyme*

Telomerase, a ribonucleoprotein, conducts reverse transcriptase activity. It can synthesize telomeric DNA to counteract telomere shortening. Telomerase consists of two components: hTERT and hTERC (Iskandar et al., 2025).

hTERT (human telomerase reverse transcriptase) is the catalytic protein subunit that provides reverse transcriptase activity. The regulation of the hTERT gene limits telomerase activity in most cells. hTERC (human Telomerase RNA Component) is an integral RNA molecule that provides the template to synthesize the telomere repeats (Iskandar et al., 2025).

Telomerase is active in embryonic, germline, and adult stem cells, but most somatic tissue cells suppress it (Shay & Wright, 2019). The main way cells suppress the hTERT gene is through transcriptional silencing. This is often achieved with epigenetic modifications, such as hypermethylating the gene's promoter (Shin et al., 2003). This process acts as a tumor suppressor by limiting how many times a cell can divide. As a result, almost all tumors solve this obstacle by reactivating telomerase.

## TELOMERES AND AGING

Telomere attrition is considered one of the primary 'hallmarks of aging'. According to a review by Bär and Blasco (2016), telomere shortening can initiate other hallmarks such as genomic instability. Consequently, the average TL in a cell, especially in leukocytes (Vaiserman & Krasnienkov, 2021), has become a more accurate biomarker than chronological age. This section evaluates the evidence for telomere as a biomarker of aging and examines the factors that accelerate their attrition.

### *3.1 Telomere Length: A Biomarker of Aging*

The average telomere length has been validated as a significant predictor of morbidity and mortality by evidence from large-scale and multi-species studies (Wang et al., 2018). Animal models have demonstrated that early-life TL can predict overall lifespan, as observed in species such as the zebra finch (Bär & Blasco, 2016). Humans show similar findings. Bär and Blasco's review references the large-scale GERA cohort study, which surveyed over 100,000 individuals. This study provided definitive evidence that longer TL positively correlates with increased survival in subjects older than 75 years (Lapham et al., 2015). This supports earlier studies such as that by Cawthon et al. (2003). This consistent finding proves its clinical relevance as a biomarker of molecular damage and biological age (Wang et al., 2018; Sanders & Newman, 2013). Recent advances have improved how TL is measured, further supporting its value as a biomarker. Using a new long-read sequencing method called Telo-seq, Schmidt et al. (2024) revealed that individual chromosome arms within the same person can shorten at significantly different rates, and that these patterns vary between tissues. This chromosome-specific heterogeneity had not been detectable with earlier methods, and suggests that the biology of telomere attrition is more complex and individualized than previously understood (Schmidt et al., 2024).

### *3.2 Accelerated Telomere Attrition*

Telomere attrition is complex, influenced by intrinsic and environmental factors. Key drivers of this acceleration include oxidative stress and chronic inflammation (Tian et al., 2019). The accepted baseline rate of yearly shortening is about "31-72 base pairs per year" (Tian et al., 2019). Telomeres, which are guanine-rich, are vulnerable to reactive oxygen species (ROS) damage (Wang et al., 2025) and oxidative lesions, such as 8-oxoguanine. These disrupt DNA replication, increase the baseline rate of telomere attrition and contribute to tumorigenesis (Wang et al., 2025).

Chronic inflammation reinforces this rate. As summarized by Bär and Blasco (2016), lifestyle factors, like "smoking, an unhealthy diet (e.g. high cholesterol, alcohol intake), or obesity," can promote inflammation (Bär & Blasco, 2016). This inflammation can elevate ROS levels and demand for cell replacement, which causes more inflammation (Iskandar et al., 2025).

### *3.3 Cellular Senescence and SASP*

Telomeres are finite in length. Consequently, when a telomere shortens to a critical length, shelterin cannot bind properly, and the protective cap structure fails to maintain itself, which exposes DNA as a DNA strand break (Shay & Wright, 2019; Srinivas et al., 2020). This triggers cellular senescence, which prevents damaged cells from replicating and developing into tumors, enforced through p53/p21 and p16/pRb pathway activation (Iskandar et al., 2025; Lu et al., 2013).

Senescent cells remain active and develop a harmful function called the senescence-associated secretory phenotype (SASP). This causes senescent cells to release damaging molecules, including pro-inflammatory proteins (e.g. interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α)), immune attractants, and enzymes that break down tissue (Razgonova et al., 2020). These molecules disrupt local tissue, which causes chronic inflammation and spreads senescence to nearby cells. This increase in damage drives functional decline and age-related pathologies.

## TELOMERES IN HUMAN DISEASE

Telomere attrition is a major contributor to human pathology, functioning paradoxically to protect against and, under certain conditions, promote cancer (Nassour et al., 2021). This section will inspect the cancer paradox, and then discuss telomere syndromes, which provide clear evidence for the importance of telomere maintenance (Nassour et al., 2021).

### *4.1 The Cancer Paradox*

In healthy cells, telomere shortening acts as a tumor suppressor. Putting a limit on the number of times a cell can divide creates an obstacle that prevents the unlimited replication required for a tumor to form. However, this protective measure can fail and, instead, initiate cancer (Nassour et al., 2021). Cells harboring mutations in cell cycle checkpoints, such as the p53 tumor suppressor gene, can circumvent these natural safeguards (Nassour et al., 2021). These damaged cells do not enter senescence and continue

replicating despite their short telomeres. This leads to a state of genomic instability called the telomere crisis.

During the telomere crisis, the telomeres are incorrectly recognized as DNA double-strand breaks and often fuse to other similar ends (Iskandar et al., 2025). When the cell attempts to divide, these fused chromosomes pull apart unevenly, causing breakage-fusion-bridge (BFB) cycles. This damaging cycle can repeat and destroy the genome by promoting mutations (Nassour et al., 2021). To survive this chaotic phase, human cancers stabilize their telomeres using one of two methods. Around 85-95% reactivate the enzyme telomerase (Shay & Wright, 2019). The remaining cancers use a different strategy called the alternative lengthening of telomeres (ALT) pathway, using homologous recombination (Iskandar et al., 2025; Nassour et al., 2021). The sequence of events from telomere attrition to cancer stabilization is illustrated in Figure 2.

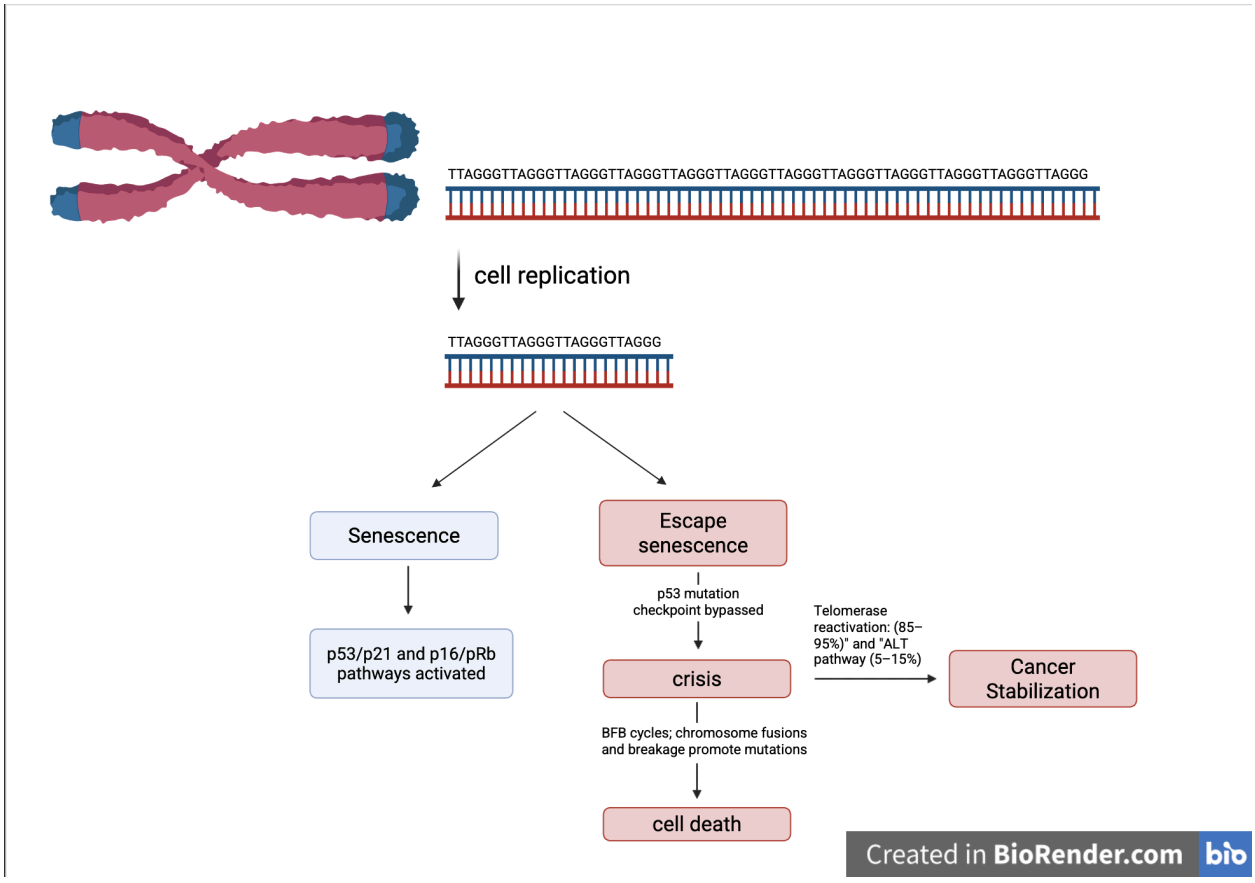



*Figure 2*

The telomere cancer paradox. Telomere shortening occurs with each cell replication cycle. In cells with intact checkpoints, critically short telomeres activate the p53/p21 and p16/pRb pathways, triggering senescence. In cells where the p53 checkpoint is bypassed, cells escape senescence and enter telomere crisis, characterized by chromosome fusions and breakage-fusion-bridge (BFB) cycles that promote mutations and drive most cells toward death. Surviving cells stabilize their

telomeres through telomerase reactivation (85–95%) or activation of the ALT pathway (5–15%), leading to cancer stabilization.

### *4.2 Telomere Biology Disorders*

Telomere Biology Disorders (TBDs), a group of genetic disorders, act as direct evidence for telomere attrition as a cause of human disease (Savage, 2022). TBDs come from mutations in genes controlling telomere maintenance, such as those encoding telomerase (TERT, TERC) or its support proteins. TBDs cause abnormally short telomeres at birth, which leads to abnormally early aging diseases (Savage, 2022).

A fitting example of a TBD is Dyskeratosis Congenita (DC). The Dyskerin complex, including Dyskerin and other components (NOP10, NHP2, GAR1), stabilizes the telomerase RNA component (hTERC), which supports hTERT function (Qin et al., 2024). Patients with DC exhibit accelerated telomere attrition, leading to the premature failure of high-turnover tissues that rely on rapid cell division (Savage, 2022). This translates to conditions like bone marrow failure and pulmonary fibrosis, and related degenerative conditions (Savage, 2022).

## THERAPEUTIC INTERVENTIONS

These disorders require therapies that can combat them. This section examines these developing therapies, which include pharmacological activations of telomerase, advanced genetic techniques, biological pathway targeting, and lifestyle changes.The specific mechanisms, key research studies, and primary limitations of these diverse strategies are summarized in Table 1 below.

### *5.1 Telomerase Activation Therapies*

The most direct strategy to counteract telomere attrition is to enhance telomerase activity. Currently, this is achieved through either small-molecule compounds that activate telomerase or gene therapy that directly provides the cell with hTERT, allowing the cell to produce its own telomerase.

Several natural and synthetic compounds can directly activate the hTERT components of the telomerase enzyme. For example, the natural compound resveratrol can activate hTERT. It is also a well-known SIRT1 activator, which enhances cellular stress resistance, as SIRT1 regulates chromatin (Pyo et al., 2020). TA-65, a small molecule, is the most thoroughly studied (Harley et al., 2011). An observational study (Harley et al., 2011) reported a significant reduction in the percentage of critically short telomeres, though no significant change in median TL was observed. Later, “a randomized, double-blind, placebo-controlled study” (Salvador et al., 2016) in humans showed that a low dose of TA-65, taken over 12 months, led to a statistically significant increase in median TL (Salvador et al., 2016). Importantly, this study did not find any major side effects. This provided the first proof of concept for humans (Salvador et al., 2016).

Another well-known approach to telomere maintenance is gene therapy, specifically the delivery of the hTERT gene using an AAV vector. This is a non-integrative method (Bernardes de Jesus et al., 2012). This method provides the cell with the genetic code to produce its own telomerase enzyme. The proof of concept for this came from a 2012 study by Bernardes de Jesus et al. In that research, a single injection of AAV carrying the hTERT gene was sufficient to delay age-related disease in adult and old mice (Bernardes de Jesus et al., 2012). The therapy improved health markers like bone density, neuromuscular coordination, and significantly extended their average lifespan by up to 24% (Bernardes de Jesus et al., 2012). This study was especially important because it did not increase the percentage of cancer (Bernardes de Jesus et al., 2012). This shows potential in treating telomere syndromes and other age-related diseases transiently (Bernardes de Jesus et al., 2012). Telomerase can also be targeted in the opposite direction to fight cancer. Because 85–95% of cancer cells rely on telomerase to maintain their telomeres, selectively blocking it can drive telomere shortening and cell death. Sanford et al. (2025) demonstrated that the compound 6-thio-deoxyguanosine (6-thio-dG) achieves this by being incorporated by telomerase, trapping the enzyme in a non-productive, stalled state that prevents further telomere elongation without significantly impairing normal DNA polymerases. Cancer cells with already-shortened telomeres were the most sensitive to treatment, as they are most dependent on active telomerase, while normal somatic cells, which already suppress telomerase, remain relatively unaffected (Sanford et al., 2025).

### *5.2 Advanced & Experimental Therapies*

To address the oncogenic concern of telomerase activation, new methods are being researched to provide more transient and more precise solutions.

Reactivating the body's own inactive hTERT genes instead of adding foreign copies, is another method (Wen et al., 2020). This utilizes a modified CRISPR-Cas9 system where the DNA-cutting function is disabled (dCas9). Instead of making a cut, the CRISPRa system uses its guide RNA (gRNA) to guide the activator complex to the promoter region of the hTERT gene. This approach successfully activates telomerase, which leads to longer telomeres and reduces symptoms of telomere syndromes (Wen et al., 2020).

Another approach can provide short-term telomerase activity without long-term risks associated with gene modification. Instead of delivering a gene directly, modified mRNA molecules that code for the hTERT protein is delivered (Ramunas et al., 2015). The cell's ribosomes then read the mRNA and synthesize the telomerase enzyme. This allows for telomere lengthening without permanent genetic modification. This method is supported by a 2015 study by Ramunas et al., which showed statistically significant TL increases.

### *5.3 Other Therapeutic Strategies*

Alongside direct telomerase activations, it is important to review ALT pathways in cancers and senolytics, which reduce the consequences of past telomere attrition.

For the 5-15% of cancers that maintain their telomeres without the reactivation of telomerase, therapies are being researched to fight ALT pathways (Nassour et al., 2021). The first method is to inhibit the ALT pathway directly, forcing telomere shortening and cell death by targeting proteins like ATRX (Alpha Thalassemia/Mental Retardation Syndrome X-Linked) (Zhang & Zou, 2020). ATRX is a chromatin remodeling protein whose suppression allows for ALT pathways to become active (Zhang & Zou, 2020). Another method is to induce a state of "hyperactive ALT" that creates genomic instability to the point of cancer cell death (Zhang & Zou, 2020).

Addressing the problem of telomere attrition, drugs known as senolytics are designed to clear senescent cells. The cells contribute to aging through inflammation (Islam et al., 2023). In a 2023 study by Islam et al., a Dasatinib and Quercetin (D+Q) combination was used and proven to effectively eliminate senescent cells (Islam et al., 2023). This reduced inflammation and improved health span (Islam et al., 2023). Related compounds, known as senomorphics, regulate SASP without killing senescent cells (Islam et al., 2023). This work has begun to move into human clinical trials. Nambiar et al. (2023) conducted the first randomized, placebo-controlled pilot trial of D+Q in patients with idiopathic pulmonary fibrosis (IPF), an age-related lung disease closely associated with premature senescence. The regimen was found to be feasible and well-tolerated, representing an important early step toward validating senolytic therapy in humans (Nambiar et al., 2023).

**Table 1:**

***Summary of Telomere-Targeted Therapeutic Strategies and Research Insights***

| Strategy Name | Mechanism of Action | Key Study | Primary Limitation |
|---|---|---|---|
| **Small-Molecule Activators (TA-65)** | Enhances hTERT components to directly activate telomerase. | Salvador et al. (2016) | May reduce the percentage of short telomeres without increasing median length. |
| **Telomerase Inhibition (6-thio-dG)** | Induces a stalled non-productive enzyme complex that halts further telomere elongation in cells. | Sanford et al. (2025) | Only effective against telomerase-expressing cancers; long-term safety in humans not yet established. |
| **AAV Gene Therapy** | Delivers the hTERT gene via viral vectors to induce telomerase production. | Bernardes de Jesus et al. (2012) | Currently validated primarily in animal models (mice). |

| | | | |
|---|---|---|---|
| **Modified mRNA Delivery** | Provides temporary genetic code for hTERT protein synthesis. | Ramunas et al. (2015) | Effects are transient and do not result in permanent genetic modification. |
| **CRISPRa (Epigenetic Editing)** | Uses dCas9 to guide activators to the endogenous hTERT promoter. | Wen et al. (2020) | Experimental stage; requires precision to avoid off-target effects. |
| **Senolytics (Dasatinib + Quercetin)** | Selectively clears senescent cells to stop pro-inflammatory SASP. | Islam et al. (2023) | Addresses the consequences of attrition rather than restoring length. |
| **ALT Pathway Inhibitors** | Disrupts recombination-based telomere maintenance in specific cancers. | Zhang & Zou (2020) | Only applicable to the 5–15% of cancers that do not use telomerase. |

### *5.4 Lifestyle Interventions*

The primary factors affecting telomere health are lifestyle-dependent. Diets rich in antioxidants and omega-3 fatty acids (Farzaneh-Far et al., 2010) are associated with longer telomeres. Regular physical activity, including both endurance and high-intensity training, has been also shown to increase TL (Bär & Blasco, 2016). Finally, psychological and oxidative stress correlate with shorter telomeres (Epel et al., 2004; Bär & Blasco, 2016).

## CHALLENGES AND FUTURE DIRECTION

It is challenging for researchers to translate research into clinical therapies. The key issues are managing the risk of cancer and creating sustainable, long-term treatment plans. The future will likely depend on overcoming these issues.

### *6.1 Oncogenic Risk*

The primary challenge for any telomerase-activating therapy is the oncogenic risk (Bär & Blasco, 2016). Since 85-95% of cancers depend on telomerase for their unlimited replication, there is a risk that telomeric activation could promote cancer. On the other hand, preventing telomeres from becoming critically short also inhibits cancer because it maintains TL. The optimal solution is likely to focus on therapies that are transient and targeted, which will help avoid permanent gene modification of cells.

### *6.2 Future Direction and Conclusion*

The most promising future for telomere-based medicine will consist of an integrative approach, combining multiple methods. An example is the use of senolytics to clear senescent cells and to reduce

damage, followed by transient telomerase activators (mRNA administration, AAV gene therapy) to restore TL. Lifestyle changes would support this entire process to minimize telomere attrition.

## CONCLUSION

Telomere attrition is a fundamental factor in cellular aging, which contributes to age-related diseases. This document details several methods to intervene in this process, from direct telomerase activators to senolytics, which clear senescent cells. While oncogenic risks remain a concern, telomere-targeted interventions offer significant potential to mitigate the burden of age-related pathologies. An integrated approach combining transient telomerase activation, senolytics, and personalized medicine shows great potential for real-world effective applications.

## REFERENCES

Bär, C., & Blasco, M. A. (2016). Telomeres and telomerase as therapeutic targets to prevent and treat age-related diseases. F1000Research, 5, 89. https://doi.org/10.12688/f1000research.7020.1

Bernardes de Jesus, B., Vera, E., Schneeberger, K., Tejera, A. M., Ayuso, E., Bosch, F., & Blasco, M. A. (2012). Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer. EMBO Molecular Medicine, 4(8), 691–704. https://doi.org/10.1002/emmm.201200245

BioRender. (2025). Figure created using BioRender. Retrieved from https://www.BioRender.com

Cawthon, R. M., Smith, K. R., O'Brien, E., Sivatchenko, A., & Kerber, R. A. (2003). Association between telomere length in blood and mortality in people aged 60 or older. The Lancet, 361(9355), 393–395. https://doi.org/10.1016/S0140-6736(03)12384-7

Epel, E. S., Blackburn, E. H., Lin, J., Dhabhar, F. S., Adler, N. E., Morrow, J. D., & Cawthon, R. M. (2004). Accelerated telomere shortening in response to life stress. Proceedings of the National Academy of Sciences of the United States of America, 101(49), 17312–17315. https://doi.org/10.1073/pnas.0407162101

Farzaneh-Far, R., Lin, J., Epel, E. S., Harris, W. S., Blackburn, E. H., & Whooley, M. A. (2010). Association of marine omega-3 fatty acid levels with telomeric aging in patients with coronary heart disease. JAMA, 303(3), 250–257. https://doi.org/10.1001/jama.2009.2008

Harley, C. B., Liu, W., Blasco, M., Vera, E., Andrews, W. H., Briggs, L. A., & Raffaele, J. M. (2011). A natural product telomerase activator as part of a health maintenance program. Rejuvenation Research, 14(1), 45–56. https://doi.org/10.1089/rej.2010.1085

Iskandar, M., Barbero, M. X., Jaber, M., Chen, R., Gomez-Guevara, R., Cruz, E., & Westerheide, S. (2025). A review of telomere attrition in cancer and aging: Current molecular insights and future therapeutic approaches. Cancers, 17(2), 257. https://doi.org/10.3390/cancers17020257

Islam, M. T., Tuday, E., Allen, S., Kim, J., Trott, D. W., Holland, W. L., Donato, A. J., & Lesniewski, L. A. (2023). Senolytic drugs, dasatinib and quercetin, attenuate adipose tissue inflammation, and ameliorate metabolic function in old age. Aging Cell, 22(2), e13767. https://doi.org/10.1111/acel.13767

Karlseder, J., Broccoli, D., Dai, Y., Hardy, S., & de Lange, T. (1999). p53- and ATM-dependent apoptosis induced by telomeres lacking TRF2. Science, 283(5406), 1321–1325. https://doi.org/10.1126/science.283.5406.1321

Lapham, K., Kvale, M. N., Lin, J., Connell, S., Croen, L. A., Dispensa, B. P., Fang, L., Hesselson, S., Hoffmann, T. J., Iribarren, C., Jorgenson, E., Kushi, L. H., Ludwig, D., Matsuguchi, T., McGuire, W. B., Miles, S., Quesenberry, C. P., Jr, Rowell, S., Sadler, M., Sakoda, L. C., ... Blackburn, E. H. (2015). Automated assay of telomere length measurement and informatics for 100,000 subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort. Genetics, 200(4), 1061–1072. https://doi.org/10.1534/genetics.115.178624

Lu, W., Zhang, Y., Liu, D., Songyang, Z., & Wan, M. (2013). Telomeres-structure, function, and regulation. Experimental Cell Research, 319(2), 133–141. https://doi.org/10.1016/j.yexcr.2012.09.005

Nambiar, A., Kellogg, D., Justice, J., Goros, M., Gelfond, J., Pascual, R., Hashmi, S., Masternak, M., Prata, L., LeBrasseur, N., Limper, A., Kritchevsky, S., Musi, N., Tchkonia, T., & Kirkland, J. (2023). Senolytics dasatinib and quercetin in idiopathic pulmonary fibrosis: Results of a phase I, single-blind, single-center, randomized, placebo-controlled pilot trial on feasibility and tolerability. eBioMedicine, 90, 104481. https://doi.org/10.1016/j.ebiom.2023.104481

Nassour, J., Schmidt, T. T., & Karlseder, J. (2021). Telomeres and cancer: Resolving the paradox. Annual Review of Cancer Biology, 5(1), 59–77. https://doi.org/10.1146/annurev-cancerbio-050420-023410

Pyo, I. S., Yun, S., Yoon, Y. E., Choi, J. W., & Lee, S. J. (2020). Mechanisms of aging and the preventive effects of resveratrol on age-related diseases. Molecules, 25(20), 4649. https://doi.org/10.3390/molecules25204649

Qin, J., Garus, A., & Autexier, C. (2024). The C-terminal extension of dyskerin is a dyskeratosis congenita mutational hotspot that modulates interaction with telomerase RNA and subcellular localization. Human Molecular Genetics, 33(4), 318–332. https://doi.org/10.1093/hmg/ddad180

Ramunas, J., Yakubov, E., Brady, J. J., Corbel, S. Y., Holbrook, C., Brandt, M., Stein, J., Santiago, J. G., Cooke, J. P., & Blau, H. M. (2015). Transient delivery of modified mRNA encoding TERT rapidly extends telomeres in human cells. FASEB Journal, 29(5), 1930–1939. https://doi.org/10.1096/fj.14-259531

Razgonova, M. P., Zakharenko, A. M., Golokhvast, K. S., Thanasoula, M., Sarandi, E., Nikolouzakis, K., Fragkiadaki, P., Tsoukalas, D., Spandidos, D. A., & Tsatsakis, A. (2020). Telomerase and telomeres in aging theory and chronographic aging theory. Molecular Medicine Reports, 22(3), 1679–1694. https://doi.org/10.3892/mmr.2020.11274

Salvador, L., Singaravelu, G., Harley, C. B., Flom, P., Suram, A., & Raffaele, J. M. (2016). A natural product telomerase activator lengthens telomeres in humans: A randomized, double blind, and placebo controlled study. Rejuvenation Research, 19(6), 478–484. https://doi.org/10.1089/rej.2015.1793

Sanders, J. L., & Newman, A. B. (2013). Telomere length in epidemiology: A biomarker of aging, age-related disease, both, or neither? Epidemiologic Reviews, 35(1), 112–131. https://doi.org/10.1093/epirev/mxs008

Sanford, S. L., Badstübner, M., Gerber, M., Mannherz, W., Lampl, N., Dannenberg, R., Hinchie, A., Schaich, M. A., Myong, S., Hedglin, M., Agarwal, S., Alder, J. K., Stone, M. D., & Opresko, P. L. (2025). Therapeutic 6-thio-deoxyguanosine inhibits telomere elongation in cancer cells by inducing a non-productive stalled telomerase complex. Nature Communications, 17(1). https://doi.org/10.1038/s41467-025-66534-w

Savage S. A. (2022). Dyskeratosis congenita and telomere biology disorders. Hematology. American Society of Hematology Education Program, 2022(1), 637–648. https://doi.org/10.1182/hematology.2022000394
Schmidt, T. T., Tyer, C., Rughani, P., Haggblom, C., Jones, J. R., Dai, X., Frazer, K. A., Gage, F. H., Juul, S., Hickey, S., & Karlseder, J. (2024). High resolution long-read telomere sequencing reveals dynamic mechanisms in aging and cancer. Nature Communications, 15(1). https://doi.org/10.1038/s41467-024-48917-7
Shay, J. W., & Wright, W. E. (2019). Telomeres and telomerase: three decades of progress. Nature Reviews Genetics, 20(5), 299–309. https://doi.org/10.1038/s41576-019-0099-1
Shin, K. H., Kang, M., Dicterow, E., et al. (2003). Hypermethylation of the hTERT promoter inhibits the expression of telomerase activity in normal oral fibroblasts and senescent normal oral keratinocytes. British Journal of Cancer, 89(8), 1473–1478. https://doi.org/10.1038/sj.bjc.6601291
Srinivas, N., Rachakonda, S., & Kumar, R. (2020). Telomeres and telomere length: A general overview. Cancers, 12(3), 558. https://doi.org/10.3390/cancers12030558
Tian, Y., Wang, S., Jiao, F., Kong, Q., Liu, C., & Wu, Y. (2019). Telomere length: A potential biomarker for the risk and prognosis of stroke. Frontiers in Neurology, 10, 624. https://doi.org/10.3389/fneur.2019.00624
Vaiserman, A., & Krasnienkov, D. (2021). Telomere length as a marker of biological age: State-of-the-art, open issues, and future perspectives. Frontiers in Genetics, 11, 630186. https://doi.org/10.3389/fgene.2020.630186
Wang, J., Li, C., Han, J., Xue, Y., Zheng, X., Wang, R., Radak, Z., Nakabeppu, Y., Boldogh, I., & Ba, X. (2025). Reassessing the roles of oxidative DNA base lesion 8-oxoGua and repair enzyme OGG1 in tumorigenesis. Journal of Biomedical Science, 32(1), 1. https://doi.org/10.1186/s12929-024-01093-8
Wang, Q., Zhan, Y., Pedersen, N. L., Fang, F., & Hägg, S. (2018). Telomere length and all-cause mortality: A meta-analysis. Ageing Research Reviews, 48, 11–20. https://doi.org/10.1016/j.arr.2018.09.002
Wen, L., Zhao, C., Song, J., Ma, L., Ruan, J., Xia, X., Chen, Y. E., Zhang, J., Ma, P. X., & Xu, J. (2020). CRISPR/Cas9-mediated TERT disruption in cancer cells. International Journal of Molecular Sciences, 21(2), 653. https://doi.org/10.3390/ijms21020653
Zhang, J. M., & Zou, L. (2020). Alternative lengthening of telomeres: From molecular mechanisms to therapeutic outlooks. Cell & Bioscience, 10(1), 30. https://doi.org/10.1186/s13578-020-00391-6

## GLOSSARY

**6-thio-dG (6-thio-deoxyguanosine):** A nucleoside analogue incorporated by telomerase in cancer cells, causing the enzyme to stall and preventing further telomere elongation.

**ALT (Alternative Lengthening of Telomeres):** A recombination-based mechanism used by 5–15% of cancers to maintain telomere length without telomerase.

**ATM (Ataxia Telangiectasia Mutated):** A kinase that detects DNA double-strand breaks and activates the DNA damage response.

**ATR (Ataxia Telangiectasia and Rad3-related):** A kinase activated by single-stranded DNA exposure that halts the cell cycle in response to DNA damage.

**AAV (Adeno-Associated Virus):** A small, non-integrating virus used as a delivery vehicle in gene therapy.

**BFB (Breakage-Fusion-Bridge) Cycle:** A damaging cycle of chromosome breakage and re-fusion that drives genomic instability during telomere crisis.

**CRISPRa:** A modified CRISPR-Cas9 system that activates gene expression without cutting DNA.

**DDR (DNA Damage Response):** A cellular signaling network that detects and repairs damaged DNA.

**Dyskeratosis Congenita (DC):** A Telomere Biology Disorder caused by mutations in telomere-maintenance genes, leading to premature tissue failure.

**gRNA (Guide RNA):** A short RNA molecule that directs the CRISPR system to a specific location in the genome.

**Hayflick Limit:** The maximum number of times a normal somatic cell can divide before entering senescence.

**hTERC (Human Telomerase RNA Component):** The RNA subunit of telomerase that provides the template for adding telomere repeats.

**hTERT (Human Telomerase Reverse Transcriptase):** The catalytic protein subunit of telomerase responsible for synthesizing new telomeric DNA.

**IL-6 (Interleukin-6):** A pro-inflammatory protein secreted by senescent cells as part of SASP.

**ROS (Reactive Oxygen Species):** Chemically reactive molecules that cause oxidative damage to DNA, accelerating telomere shortening.

**RPA (Replication Protein A):** A protein that binds exposed single-stranded DNA and triggers the ATR damage response.

**SASP (Senescence-Associated Secretory Phenotype):** The harmful secretion of inflammatory molecules by senescent cells that damages surrounding tissue.

**Senescence:** A state in which a cell permanently stops dividing, typically triggered by critically short telomeres.

**Senolytics:** Drugs that selectively eliminate senescent cells to reduce inflammation and improve tissue health.

**Shelterin:** A six-protein complex (TRF1, TRF2, POT1, TPP1, TIN2, RAP1) that binds and protects telomeres.

**TBDs (Telomere Biology Disorders):** A group of genetic diseases caused by mutations in telomere-maintenance genes, resulting in abnormally short telomeres and premature aging.

**Telomerase:** A ribonucleoprotein enzyme that extends telomere length by adding DNA repeats to chromosome ends.

**Telomerase inhibition:** A cancer therapy strategy that blocks telomerase activity in tumor cells, causing progressive telomere shortening and eventual cell death.

**Telomere Crisis:** A state of genomic instability caused by critically short, unprotected telomeres in cells that bypass normal checkpoints.

**TL (Telomere Length):** The measured length of telomeric DNA, used as a biomarker of biological age.

**TNF-α (Tumor Necrosis Factor-Alpha):** A pro-inflammatory signaling protein released by senescent cells as part of SASP.

**T-loop:** A protective loop structure formed when the telomere's single-stranded overhang folds back and invades the double-stranded region, shielding the chromosome end.