Article

Telomerase: Biochemistry, biological functions, molecular mechanisms, therapeutic frontiers, and perspectives

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Abstract
Telomerase is a specialized ribonucleoprotein reverse transcriptase that maintains telomere length by adding repetitive DNA sequences to chromosome ends, thereby counteracting the progressive telomere shortening that occurs during DNA replication. The enzyme comprises two essential core components: the catalytic protein subunit telomerase reverse transcriptase (TERT) and the integral RNA component (TERC or hTR) that serves as the template for telomeric repeat synthesis. While telomerase is silenced in most normal human somatic tissues, it is reactivated in 85–90% of human cancers, making it an almost universal oncology target. Conversely, insufficient telomerase function underlies a spectrum of degenerative diseases collectively known as telomere biology disorders, including dyskeratosis congenita. This comprehensive review synthesizes current knowledge spanning the discovery, structure, biogenesis, and regulation of telomerase; its canonical and non-canonical functions in stem cell maintenance, tissue regeneration, immune function, and aging; its dual role as both a therapeutic target in cancer and a rejuvenation target in age-related diseases; and emerging frontiers including engineered telomerase RNA, CRISPR-based interventions, novel small-molecule activators such as TAC, artificial intelligence applications in drug discovery, and clinical progress with telomerase-based therapeutics. The review concludes with a critical assessment of remaining challenges and future research directions.

Keywords telomerase; TERT; TERC; telomere; cancer; aging; senescence; telomerase inhibitor; telomerase vaccine; immunotherapy; CRISPR; AI drug discovery; TAC; engineered telomerase RNA; clinical trials.

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1 Introduction

Telomeres are specialized nucleoprotein structures that cap the ends of linear eukaryotic chromosomes, protecting them from degradation, end-to-end fusion, and inappropriate activation of DNA damage responses (de Lange, 2005; Palm & de Lange, 2008). In humans and other vertebrates, telomeric DNA consists of tandem repeats of the hexameric sequence′ 5 -TTAGGG-3′, extending for approximately 5–15 kilobases at

birth and progressively shortening with each cell division due to the inherent limitations of semi-conservative DNA replication — a phenomenon known as the "end-replication problem" (Moyzis et al., 1988; Harley, 1991). When telomeres reach a critically short length, cells enter a state of irreversible growth arrest termed replicative senescence, which serves as an intrinsic tumor suppressor mechanism but also contributes to tissue aging and dysfunction (Campisi, 1997; Shay & Wright, 2019).

Telomerase is the specialized enzyme that counteracts telomere shortening by catalyzing the *de novo* addition of telomeric repeats to chromosome 3 ends (Greider & Blackburn, 1985; Morin, 1989). The enzyme is a ribonucleoprotein (RNP) complex composed of a catalytic protein subunit, telomerase reverse transcriptase (TERT), and an integral RNA component (TERC in humans, also designated hTR) that contains the template sequence for telomere synthesis (Feng et al., 1995; Nakamura et al., 1997; Meyerson et al., 1997). Telomerase activity is highly regulated in a cell type- and developmental stage-specific manner: it is robustly expressed in germline cells, embryonic stem cells, and many adult stem and progenitor cells; silenced or maintained at very low levels in most somatic tissues; and aberrantly reactivated in the vast majority of human cancers (Kim et al., 1994; Shay & Bacchetti, 1997; Hiyama & Hiyama, 2007). The clinical significance of telomerase is underscored by the recent FDA approval of imetelstat, the first telomerase-targeted therapeutic, for the treatment of lower-risk myelodysplastic syndromes (Siteni et al., 2024), and by the ongoing development of diverse telomerase-directed interventions ranging from small-molecule inhibitors and immunotherapeutic vaccines to gene therapy and novel small-molecule activators for age-related conditions.

This review provides a comprehensive synthesis of the current state of telomerase research, organized thematically to cover: (1) the historical discovery of telomerase and the progressive elucidation of its molecular composition; (2) the structural architecture, biogenesis, biochemical properties, and regulatory mechanisms governing telomerase function; (3) the pharmacological actions and physiological roles of telomerase, including its canonical functions in telomere maintenance, its non-canonical extra-telomeric activities, its essential roles in stem cell biology, tissue regeneration, and immune system function, and its complex involvement in aging; (4) the multifaceted role of telomerase in cancer, encompassing activation mechanisms, therapeutic targeting strategies, and the alternative lengthening of telomeres (ALT) pathway; (5) emerging frontiers including engineered telomerase RNA, CRISPR-based interventions, novel small-molecule activators such as TAC, newly discovered regulatory factors, and artificial intelligence applications; (6) clinical trials and therapeutic applications, including safety evaluations and quality control considerations; (7) remaining challenges and limitations; and (8) future research directions and concluding perspectives.

2 Discovery and Historical Milestones of Telomerase Research

2.1 The End-Replication Problem and Early Observations

The conceptual foundation for telomerase research was laid by the recognition that conventional DNA polymerases are unable to fully replicate the extreme termini of linear chromosomes. In the early 1970s, Alexey Olovnikov (1971, 1973) and James Watson (1972) independently articulated the "end-replication problem," proposing that progressive telomere shortening would occur with each cell division and that this shortening might serve as a molecular clock limiting cellular proliferative capacity. Olovnikov further hypothesized the existence of a specialized DNA polymerase that could compensate for this terminal sequence loss — a remarkably prescient prediction that anticipated the discovery of telomerase by more than a decade.

The experimental study of telomeres advanced significantly in 1978 when Elizabeth Blackburn and Joseph Gall cloned and sequenced the telomeric DNA from the ciliated protozoan *Tetrahymena thermophila*, revealing that it consisted of tandem repeats of the hexameric sequence TTGGGG (Blackburn & Gall, 1978). This discovery established the molecular identity of telomeres and provided the substrate for identifying the

enzyme responsible for their synthesis. Subsequently, Moyzis and colleagues (1988) identified the human telomere repeat sequence as TTAGGG, demonstrating its remarkable conservation across vertebrates and further underscoring the fundamental importance of telomere biology.

2.2 Discovery of Telomerase Enzymatic Activity

The landmark discovery of telomerase occurred in 1985 when Carol Greider and Elizabeth Blackburn identified a novel enzymatic activity in *Tetrahymena thermophila* cell extracts that could add telomeric repeats to synthetic oligonucleotide primers *in vitro* (Greider & Blackburn, 1985). They demonstrated that this activity — initially termed "telomere terminal transferase" — was distinct from conventional DNA polymerases in its ability to synthesize telomeric DNA without an exogenous template, instead using an intrinsic RNA component as the template for repeat addition. The enzyme exhibited sensitivity to both protease and RNase treatment, establishing its identity as a ribonucleoprotein complex (Greider & Blackburn, 1987, 1989).

This discovery was soon extended to human cells. In 1989, Gregg Morin demonstrated that HeLa cell extracts contained a similar ribonucleoprotein activity capable of adding TTAGGG repeats to telomeric primers, confirming that the telomerase mechanism was conserved in humans (Morin, 1989). The subsequent development of the telomeric repeat amplification protocol (TRAP) assay by Kim and colleagues (1994) enabled sensitive detection of telomerase activity in minute clinical samples and facilitated the landmark demonstration that telomerase activity is detectable in 85–90% of human cancers while being absent in most normal somatic tissues (Kim et al., 1994; Shay & Bacchetti, 1997).

2.3 Cloning of Telomerase Components

The molecular cloning of telomerase components represented a major advance in the field. In 1995, Feng and colleagues cloned the human telomerase RNA component (hTR, also designated hTERC), demonstrating that it contained an 11-nucleotide template region complementary to the telomeric repeat sequence (Feng et al., 1995). This discovery confirmed the mechanism by which telomerase uses its intrinsic RNA as a template for DNA synthesis.

The catalytic protein subunit proved more elusive but was independently cloned in 1997 by two groups. Nakamura and colleagues identified the human telomerase reverse transcriptase (hTERT) gene and demonstrated that its expression correlated tightly with telomerase activity in various cell types (Nakamura et al., 1997). Simultaneously, Meyerson and colleagues cloned the human TERT gene and showed that ectopic expression of hTERT in telomerase-negative cells was sufficient to reconstitute telomerase activity (Meyerson et al., 1997). These discoveries established that hTERT and hTR constitute the minimal catalytic core of human telomerase and that transcriptional regulation of hTERT is the primary determinant of telomerase activity in human cells.

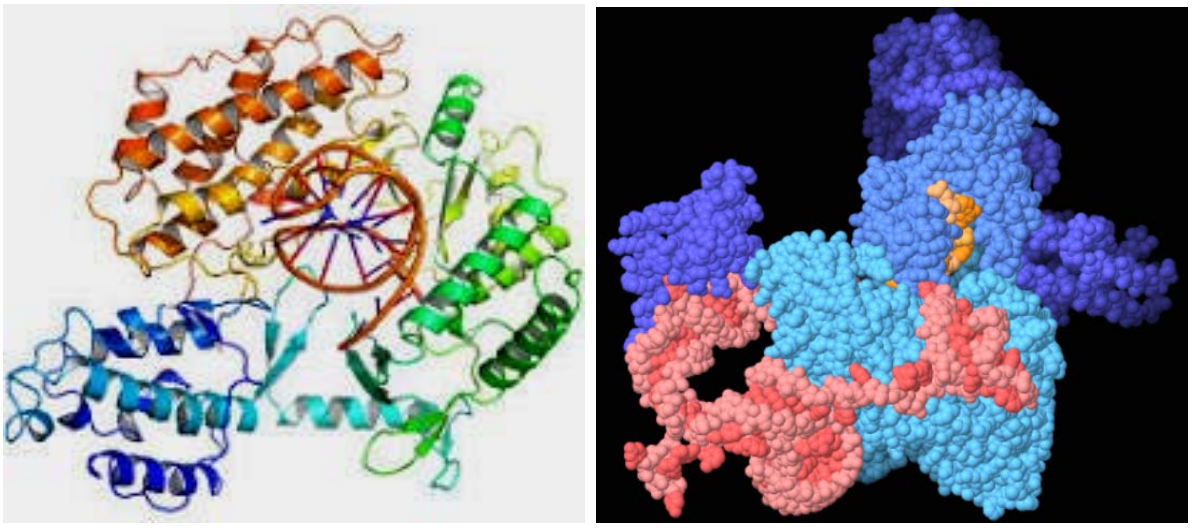
2.4 Nobel Prize Recognition and Subsequent Advances

The transformative impact of telomerase research was recognized in 2009 with the award of the Nobel Prize in Physiology or Medicine to Elizabeth Blackburn, Carol Greider, and Jack Szostak "for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase." The subsequent decades have witnessed remarkable advances in understanding telomerase structure, function, regulation, and therapeutic potential. High-resolution structural studies using cryo-electron microscopy have provided atomic-level insights into telomerase architecture (Jiang et al., 2013, 2018; Nguyen et al., 2018). The development of telomerase-targeted therapeutics has progressed from preclinical concepts to FDA-approved drugs (Siteni et al., 2024). Novel technologies including CRISPR-based genome editing, engineered RNAs, artificial intelligence, and advanced small-molecule screening have opened new frontiers for manipulating telomerase for therapeutic benefit (Nagpal & Agarwal, 2025; Shim et al., 2024; Kaur et al., 2025).

3 Structure, Biogenesis, Biochemistry, and Regulation of Telomerase

3.1 Molecular Composition and Structural Architecture

Telomerase is a multi-subunit ribonucleoprotein complex whose composition varies across species but universally includes a catalytic reverse transcriptase protein (TERT) and an integral RNA subunit (TER) that serves as the template for telomeric DNA synthesis (Collins, 2006; Blackburn & Collins, 2011). In humans, the telomerase holoenzyme comprises the catalytic subunit hTERT (1132 amino acids, approximately 127 kDa), the RNA component hTR (451 nucleotides), and a set of accessory proteins that are essential for hTR biogenesis, stability, and subcellular trafficking (Schmidt & Cech, 2015; Nguyen et al., 2018; Fig. 1).



(A) (B)

Fig. 1 A. Structure of telomerase molecule (Wikipedia, 2026); B. Telomerase in action (PDB101, 2026).

3.1.1 hTERT Domain Organization

The human TERT protein contains four conserved functional domains (Schmidt & Cech, 2015; Nguyen et al., 2018). The telomerase N-terminal (TEN) domain participates in catalysis and mediates telomerase recruitment to telomeres; this domain is essential for stabilizing the interaction between telomerase RNA and its DNA substrate (Akiyama & Stone, 2014). The TR-binding domain (TRBD) mediates high-affinity interaction with hTR. The reverse transcriptase (RT) domain contains the conserved catalytic motifs characteristic of all reverse transcriptases and houses the active site for nucleotide addition. Finally, the C-terminal extension (CTE) domain, analogous to the thumb domain of conventional polymerases, completes the TERT ring structure and contributes to processivity and template interactions (Gillis et al., 2008; Schmidt & Cech, 2015).

3.1.2 hTR Architecture

The human telomerase RNA (hTR) adopts a complex multi-domain secondary and tertiary structure that is essential for telomerase assembly and catalytic activity (Chen et al., 2000; Theimer et al., 2005). The RNA comprises 451 nucleotides and contains several functionally critical domains. The template/pseudoknot (t/PK) domain includes the 11-nucleotide template sequence (5′-CUAACCCUAAC-3′) that specifies the telomeric repeat sequence and forms a pseudoknot structure essential for catalytic activity. The CR4/CR5 domain (conserved regions 4 and 5) forms a three-way junction structure that is the primary binding site for hTERT and is absolutely required for telomerase reconstitution (Chen et al., 2000; Theimer et al., 2005). The H/ACA

domain, located at the 3′ end of hTR, adopts an H/ACA box small nucleolar RNA (snoRNA)-like structure and serves as the binding platform for the H/ACA protein complex comprising dyskerin, NHP2, NOP10, and GAR1, which are essential for hTR stability and nuclear retention (Mitchell et al., 1999; Egan & Collins, 2012). Additionally, a CAB box (Cajal body box) sequence within the H/ACA domain recruits the protein TCAB1, which directs telomerase localization to Cajal bodies for subsequent trafficking to telomeres (Venteicher et al., 2009).

3.2 Cryo-Electron Microscopy Structures

Recent advances in cryo-electron microscopy (cryo-EM) have revolutionized our structural understanding of telomerase holoenzymes. In 2013, Jiang and colleagues reported the architecture of the *Tetrahymena thermophila* telomerase holoenzyme, providing the first three-dimensional view of a complete telomerase complex (Jiang et al., 2013). Subsequently, in 2018, the same group reported the cryo-EM structure of substrate-bound human telomerase holoenzyme at subnanometer resolution, revealing a bilobed architecture with the catalytic core and the H/ACA RNP lobe flexibly tethered by RNA (Nguyen et al., 2018). This structure illuminated the organization of 10 protein subunits and hTR, providing critical insights into the structural basis of hTR motif functions and the molecular consequences of disease-causing mutations in telomerase components. Sekne and colleagues (2026) have emphasized that recent structural studies across multiple species — including *Tetrahymena thermophila*, *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, and humans — have significantly deepened our molecular understanding of both the mechanism of telomeric repeat synthesis and the biological roles of telomerase-associated proteins.

3.3 Biogenesis and Assembly

The biogenesis of functional human telomerase is a complex, multi-step process that requires coordinated assembly of protein and RNA components with the assistance of dedicated chaperone systems (Collins, 2006; Schmidt & Cech, 2015). The hTR RNA is transcribed by RNA polymerase II and undergoes extensive post-transcriptional processing, including 5′ cap hypermeth ylation to form a trimethylguanosine cap, 3′ end processing, and assembly with the H/ACA protein complex (Mitchell et al., 1999; Fu & Collins, 2003). The H/ACA proteins dyskerin, NHP2, NOP10, and GAR1 are essential for hTR stability, and mutations in these components cause dyskeratosis congenita and related telomere biology disorders (Mitchell et al., 1999; Vulliamy et al., 2001). The hTR-H/ACA complex is then bound by TCAB1, which directs the complex to Cajal bodies, nuclear subdomains that serve as sites of RNP assembly and maturation (Venteicher et al., 2009). hTERT is synthesized in the cytoplasm and must be imported into the nucleus, where it assembles with the mature hTR RNP. The fully assembled telomerase holoenzyme is then recruited to telomeres during S phase of the cell cycle, a process mediated by interactions with shelterin components, particularly TPP1 (Xin et al., 2007; Nandakumar et al., 2012).

Recent studies have revealed unexpected complexity in hTR biogenesis. Forino and colleagues (2024) used DMS-MaPseq to probe hTR structure in living human cells and discovered that approximately 15% of the steady-state hTR population adopts an alternative CR4/5 conformation lacking features required for hTERT binding. This misfolded population is not efficiently refolded by hTERT overexpression, suggesting the existence of dedicated RNA folding cofactors during telomerase biogenesis and indicating that kinetic traps for RNA folding may present barriers for RNP assembly *in vivo*.

3.4 Enzymatic Mechanism and Catalytic Cycle

Telomerase catalyzes telomere elongation through a unique mechanism that combines reverse transcription with iterative template translocation (Collins, 1999, 2006; Blackburn & Collins, 2011). The catalytic cycle begins with telomerase binding to the single-stranded 3′ overhang of telomeric DNA. The 3′ end of the DNA primer base-pairs with the template region of hTR, positioning the primer terminus at the active site within the

RT domain of hTERT (Collins, 1999). Telomerase then catalyzes the sequential addition of deoxynucleotides complementary to the RNA template, extending the DNA primer by one nucleotide at a time.

Upon reaching the 5′ boundary of the template, telomerase executes a remarkable translocation step: the enzyme must reposition the template relative to the active site to enable additional rounds of repeat synthesis (Collins, 1999; Blackburn & Collins, 2011). This process, termed repeat addition processivity (RAP), is a defining feature of telomerase that distinguishes it from other reverse transcriptases. The translocation step involves dissociation of the DNA product from the template, realignment of the template with the newly synthesized DNA, and repositioning of the DNA 3′ end at the active site for the next round of synthesis . The efficiency of this process is influenced by the TEN domain, which stabilizes duplex formation between telomerase RNA and its DNA substrate (Akiyama & Stone, 2014). The enzyme can undergo multiple rounds of repeat synthesis before dissociating from the telomere, with processivity being a critical determinant of telomere length homeostasis (D'Souza et al., 2013).

3.5 Regulation of Telomerase Expression and Activity

Telomerase is subject to multiple layers of regulation that operate at transcriptional, post-transcriptional, post-translational, and subcellular localization levels (Cifuentes-Rojas & Shippen, 2011; Yuan et al., 2019; Liu et al., 2024).

3.5.1 Transcriptional Regulation of hTERT

Transcriptional control of the hTERT gene is the primary determinant of telomerase activity in human cells (Cong et al., 2002; Cifuentes-Rojas & Shippen, 2011). The hTERT promoter contains binding sites for numerous transcription factors, including c-Myc, Sp1, estrogen receptor, HIF-1, NF-κB, and AP-1, which can activate or repress transcription depending on cellular context (Yuan et al., 2019; Liu et al., 2024). In most somatic cells, the hTERT promoter is maintained in a repressed chromatin state characterized by histone deacetylation and DNA methylation (Cong et al., 2002). During tumorigenesis, multiple mechanisms converge to reactivate hTERT transcription, including promoter mutations, amplification of the hTERT locus, and activation of upstream oncogenic signaling pathways (Yuan et al., 2019). Recent work has demonstrated that TERT transcription can be activated through the MEK/ERK/AP-1 cascade, with c-Fos binding to AP-1 sites in the TERT promoter driving transcriptional activation (Shim et al., 2024).

3.5.2 Post-Transcriptional and Epigenetic Regulation

Beyond transcriptional control, telomerase is regulated by alternative splicing of hTERT pre-mRNA, which generates multiple splice variants, some of which lack catalytic activity and may function as dominant-negative regulators (Listerman et al., 2013). Epigenetic modifications, including histone acetylation, methylation, and DNA methylation at the hTERT promoter, play crucial roles in establishing and maintaining the silenced state in somatic cells (Cong et al., 2002; Cifuentes-Rojas & Shippen, 2011). The discovery of circHERC1 as a regulator of TERT transcription represents a novel layer of regulatory complexity: circHERC1 binds to the TERT promoter and facilitates recruitment of RNA polymerase II and c-Fos, thereby activating TERT expression (Cui et al., 2025).

3.5.3 Cell Cycle-Dependent Regulation and Telomere Recruitment

Telomerase activity is tightly coordinated with the cell cycle, with maximal activity occurring during S phase when telomeres are replicated (Collins, 2006; Blackburn & Collins, 2011). The recruitment of telomerase to telomeres is mediated by interactions with the shelterin complex, particularly the TPP1 protein, which directly binds hTERT through its OB-fold domain (Xin et al., 2007; Nandakumar et al., 2012). The TPP1-mediated recruitment mechanism is essential for telomerase function *in vivo* and represents a potential therapeutic target for modulating telomerase activity at telomeres.

3.6 Physicochemical Properties, Stability, and Pharmacokinetics

The physicochemical characterization of telomerase has been essential for understanding its biochemical behavior and for developing therapeutic agents targeting the enzyme. Human telomerase is a large ribonucleoprotein complex with an estimated molecular weight of approximately 550–670 kDa for the fully assembled holoenzyme (Schmidt & Cech, 2015; Fig. 1). The catalytic subunit hTERT has a molecular mass of approximately 127 kDa and comprises 1132 amino acids (Nakamura et al., 1997). The hTR RNA component has a monomeric molecular weight of approximately 6.4 kDa (as DNA counterpart) and forms a dimer in the functional complex.

Purified recombinant telomerase demonstrates stability when stored at −20°C to −80°C in appropriate buffer conditions (typically 50 mM Tris-Acetate, pH 7.5, 1 mM EDTA, and 20% glycerol), remaining stable for up to 12 months under these conditions, though freeze-thaw cycles should be avoided to preserve enzymatic activity. Studies evaluating telomerase stability have shown that the enzyme maintains adequate stability regarding storage period and freeze-thaw cycles, with efficacy, linearity, and reproducibility of the TRAP assay being acceptable for bio-analytical methods.

Pharmacokinetic characterization has been extensively performed for imetelstat, the first FDA-approved telomerase inhibitor. Imetelstat is a 13-mer N3′→P5′ thio-phosphoramidate oligonucleotide that binds with high affinity to the template region of hTR and acts as a competitive inhibitor of telomerase enzymatic activity (Siteni et al., 2024). Population pharmacokinetic modeling using a nonlinear mixed-effects approach has characterized the pharmacokinetic variability of imetelstat and identified covariates that influence drug exposure (González-Sales et al., 2024). The drug exhibits dose-dependent pharmacokinetics with lower clearance at higher dose levels, and telomerase inhibition has been observed in peripheral blood mononuclear cells at clinically relevant doses (Thompson et al., 2013). Importantly, nonclinical and clinical studies have demonstrated no significant proarrhythmic risk for imetelstat, supporting its favorable cardiac safety profile.

3.7 Extraction and Purification Methodologies

The purification of telomerase has been challenging due to its low abundance in cells, its complex multi-subunit architecture, and its dependence on proper RNP assembly for enzymatic activity. Various approaches have been developed for isolating native and recombinant telomerase from diverse sources.

Early studies relied on partial purification from cell extracts. Partially purified human telomerase, either from native cell extracts or recombinantly produced, has been shown to possess associated nuclease activity capable of removing 3′ nontelomeric nucleotides from substrates, followed by extension of the newly exposed telomeric sequence (Oulton and Harrington, 2004). Ciliate telomerases, particularly from *Tetrahymena thermophila*, have been extensively studied using partially purified cell extracts and have served as the most intensively investigated model systems for understanding telomerase biochemistry.

Affinity purification strategies have been developed to obtain highly purified telomerase complexes. An antisense affinity oligonucleotide displacement strategy enables purification of native and recombinant telomerase using biotinylated 2′-O-methyl RNA oligonucleotides complementary to the RNA subunit, followed by binding to NeutrAvidin beads (Kurth et al., 2005). This approach has facilitated the isolation of catalytically active telomerase complexes suitable for biochemical and structural studies.

Recombinant expression systems have been established in multiple host organisms. Human TERT has been successfully expressed and purified from insect cells using baculovirus expression systems, with partially purified FLAG-tagged hTERT retaining catalytic activity and enabling reconstitution of telomerase activity when combined with hTR (Masutomi et al., 2000). In *Saccharomyces cerevisiae*, co-overexpression of GST-Est2p (the yeast TERT ortholog) and Tlc1 (the yeast telomerase RNA) has enabled reconstitution and purification of the telomerase core complex through ammonium sulfate fractionation and glutathione affinity

chromatography (Liao et al., 2005). The purified recombinant yeast telomerase core enzyme exhibits the ability to perform one round of processive telomeric DNA synthesis, providing a valuable system for mechanistic studies.

A notable technical advance has been the demonstration of telomerase activity upon recombinant expression in a bacterial system, as detected by the TRAP assay (Hansen et al., 2016). This achievement is significant because recombinant telomerase expression had previously been accomplished only within eukaryotic backgrounds, and the bacterial system offers advantages for high-throughput screening and mechanistic studies.

3.8 Quality Control and Detection Assays

The telomeric repeat amplification protocol (TRAP) has been the most widely used method for assessing telomerase activity from cells and tissues since its development by Kim and colleagues (1994). The TRAP assay involves telomerase-mediated extension of a synthetic oligonucleotide primer followed by PCR amplification of the extended products, enabling sensitive detection of telomerase activity from minute clinical samples (Kim et al., 1994; Wright et al., 1995). However, the original TRAP assay is subject to artifacts including primer-dimer formation and PCR inhibition, and does not provide truly quantitative measurements (Krupp et al., 1997).

Modified versions of the TRAP assay have been developed to address these limitations. The real-time quantitative TRAP (RQ-TRAP) assay incorporates fluorescent detection and internal controls to enable reliable quantitative measurement of telomerase activity. This method has been validated for detecting telomerase activity in human mesenchymal stem cells and for assessing cell senescence and tumorigenic risks. The RQ-TRAP method has proven to be reliable and sensitive for quantitative detection of telomerase activity.

Advanced detection platforms continue to emerge, including CRISPR-driven colorimetric assays, electrochemical and optical biosensors, and nanomaterial-based detection systems. Biosensors designed for telomerase detection have shown promise for sensitive and specific measurement of telomerase activity, enabling early cancer detection and monitoring of therapeutic responses. The integration of nanotechnology and molecular recognition elements has enhanced the sensitivity and specificity of these platforms, though challenges remain in translating these technologies from laboratory to clinical settings.

4 Pharmacological Actions and Physiological Functions of Telomerase

Fig. 4 illustrates the pharmacological actions and physiological functions of telomerase.

4.1 Canonical Function: Telomere Maintenance and Cellular Immortalization

The canonical function of telomerase is the synthesis of telomeric DNA repeats onto chromosome ends, thereby compensating for the progressive telomere shortening that occurs during DNA replication (Greider & Blackburn, 1985; Blackburn & Collins, 2011). This activity is essential for maintaining telomere length homeostasis and enabling unlimited proliferative capacity in cells that express sufficient levels of telomerase, including germline cells, embryonic stem cells, and cancer cells (Kim et al., 1994; Shay & Bacchetti, 1997).

A landmark study by Bodnar and colleagues (1998) demonstrated that ectopic expression of hTERT in normal human fibroblasts was sufficient to reconstitute telomerase activity, elongate telomeres, and extend cellular replicative lifespan, providing direct evidence that telomerase is the limiting factor for telomere maintenance and cellular immortality in human somatic cells. This finding established the foundation for understanding how telomerase reactivation enables tumorigenesis and for developing telomerase-targeted cancer therapeutics.

4.2 Non-Canonical Functions of Telomerase Components

Beyond their well-established roles in telomere maintenance, both TERT and TERC have been shown to

possess diverse extra-telomeric, non-canonical functions that contribute to cellular physiology independently of telomere elongation (Armanios, 2012; Chiodi & Mondello, 2012).

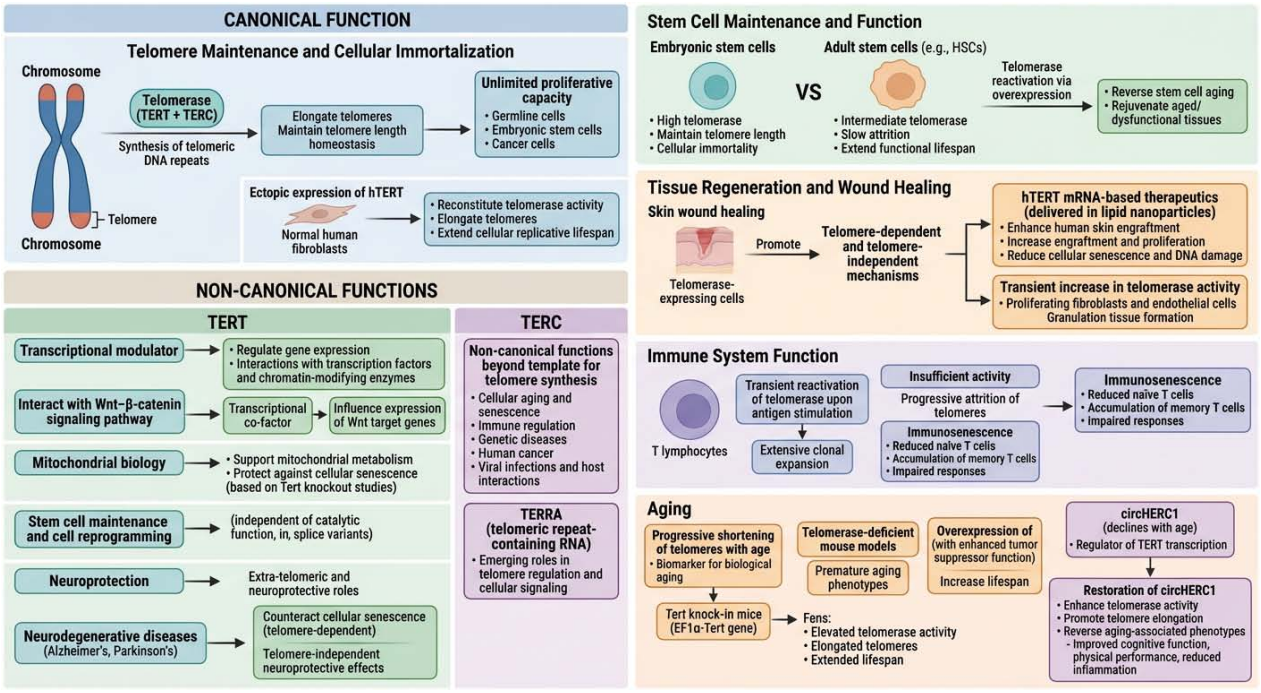


Fig. 2 Pharmacological actions and physiological functions of telomerase.

4.2.1 Non-Canonical Functions of TERT

TERT has been implicated in multiple telomere-independent cellular processes. As a transcriptional modulator, TERT can regulate gene expression through interactions with transcription factors and chromatin-modifying enzymes (Chiodi & Mondello, 2012; Armanios, 2012). Notably, TERT has been shown to interact with the Wnt–β-catenin signaling pathway, acting as a transcriptional co-factor that influences the expression of Wnt target genes (Park et al., 2009). In the context of mitochondrial biology, studies of mouse models with *Tert* knockout in specific cell types have revealed the importance of the telomere-independent noncanonical function of TERT in supporting mitochondrial metabolism and protecting against cellular senescence (Gao et al., 2026). TERT also contributes to stem cell maintenance and cell reprogramming processes in a manner independent of its canonical catalytic function, with some TERT splice variants that lack catalytic domains retaining these non-canonical activities (Armanios, 2012).

In the context of neuroprotection, TERT has been confirmed to exert extra-telomeric and neuroprotective roles in neurodegenerative diseases (Ding et al., 2020). TERT can counteract cellular senescence in a telomere-dependent manner but also exhibits telomere-independent neuroprotective effects, contributing to protection against Alzheimer‘s disease, Parkinson’s disease, and other neurodegenerative conditions (González-Giraldo et al., 2016; Ding et al., 2020).

4.2.2 Non-Canonical Functions of TERC

The telomerase RNA component TERC has also been shown to possess non-canonical functions beyond serving as the template for telomere synthesis (Cao et al., 2025). TERC has been implicated in cellular aging and senescence, immune regulation, genetic diseases, human cancer, and viral infections and host interactions

(Cao et al., 2025). The transcription product of telomere repeats, TERRA (telomeric repeat-containing RNA), represents another layer of complexity, with emerging roles in telomere regulation and cellular signaling (Cao et al., 2025). These non-canonical functions expand the therapeutic relevance of telomerase components and suggest that targeting TERC may have broader implications than previously appreciated.

4.3 Telomerase in Stem Cell Maintenance and Function

Telomerase plays essential roles in stem cell biology, with expression patterns and functional requirements varying across different stem cell populations (Flores et al., 2005; Hiyama & Hiyama, 2007).

In embryonic stem cells, telomerase is highly activated and maintains telomere length and cellular immortality, enabling the extensive proliferative capacity required for embryonic development (Hiyama & Hiyama, 2007; Shay & Wright, 2019). During differentiation, telomerase expression is progressively silenced, and telomere shortening resumes, establishing the finite replicative lifespan characteristic of somatic cells.

Adult stem cells in highly proliferative tissues, including hematopoietic stem cells (HSCs), exhibit intermediate levels of telomerase activity. While this activity is insufficient to completely prevent telomere shortening, it slows the rate of attrition and extends the functional lifespan of the stem cell pool (Flores et al., 2005; Hiyama & Hiyama, 2007). The gradual exhaustion of stem cell pools due to telomere shortening contributes to tissue dysfunction and aging phenotypes, and telomerase reactivation via overexpression represents a potential strategy to reverse stem cell aging and rejuvenate aged or dysfunctional tissues (Flores et al., 2005). The role of telomerase in stem cells extends beyond telomere maintenance, with evidence suggesting that telomerase activity *per se* has a crucial role in regulating stem cell turnover and mobilization (Flores et al., 2005).

4.4 Telomerase in Tissue Regeneration and Wound Healing

Telomerase activity is dynamically regulated during tissue regeneration and wound healing. In the context of skin wound healing, telomerase-expressing cells are resistant to telomere dysfunction and can promote wound healing through both telomere-dependent and telomere-independent mechanisms (Osawa et al., 2002). Human telomerase reverse transcriptase (hTERT) plays a role in genomic DNA damage repair and protection against oxidative stress, contributing to enhanced regenerative capacity.

A significant recent advance has been the development of hTERT mRNA-based therapeutics for wound healing. Cooke and colleagues have demonstrated that hTERT mRNA delivered in lipid nanoparticles can enhance human skin engraftment for wound healing, increasing engraftment and proliferation while reducing cellular senescence and DNA damage (Cooke & Godin, 2024). This approach represents a promising strategy for improving outcomes in traumatic wounds, burns, and chronic non-healing wounds. The transient nature of mRNA expression addresses safety concerns associated with permanent genetic modification, as telomerase activity is temporally limited, reducing potential oncogenic risks.

Studies of telomerase activity in granulation tissue formation have shown that telomerase activity increases transiently in proliferating fibroblasts and endothelial cells during wound healing, suggesting that regulation of telomerase activity may play an important role in granulation tissue formation (Osawa et al., 2002). These findings support the concept that controlled, transient activation of telomerase could be harnessed for therapeutic tissue regeneration.

4.5 Telomerase in Immune System Function

The immune system, particularly lymphocytes, is critically dependent on telomerase for maintaining proliferative capacity and functional competence (Weng, 2008; Huang et al., 2024).

T lymphocytes are unique among somatic cells in their ability to transiently reactivate telomerase expression upon antigen stimulation (Weng, 2008). This activation enables the extensive clonal expansion required for effective immune responses. However, the telomerase activity in T cells is not sufficient to

completely prevent telomere shortening over the lifetime of an individual, and the progressive attrition of telomeres in T cells contributes to immunosenescence — the age-related decline in immune function characterized by reduced naïve T cell populations, accumulation of memory T cells, and impaired responses to new antigens and vaccines (Huang et al., 2024).

Telomerase reverse transcriptase (TERT) and telomerase have multifaceted roles in regulating cellular behavior, possessing the ability to counteract both replicative and premature senescence in lymphocytes (Huang et al., 2024). The overexpression of hTERT in CD8+ T lymphocytes extends their replicative potential, and human T lymphocytes regulate telomerase function through events independent of hTERT protein levels, including hTERT phosphorylation and nuclear translocation (Liu et al., 2001). Strategies aimed at inhibiting immunosenescence by augmenting TERT/telomerase activity represent a promising therapeutic direction for enhancing immune function in aging populations and in the context of cancer immunotherapy (Huang et al., 2024).

4.6 Telomerase and Aging

The relationship between telomerase, telomere length, and organismal aging has been a central theme in telomerase research since the enzyme‘s discovery (Harley et al., 1990; Bodnar et al., 1998; Shay & Wright, 2019). The progressive shortening of telomeres with age has been documented in human tissues, and telomere length in peripheral blood leukocytes has been proposed as a biomarker for biological aging, though its predictive value remains debated (Sanders & Newman, 2013).

Multiple lines of evidence support the concept that telomerase activity is an important determinant of organismal aging, though the relationship is complex (Blasco, 2005). Telomerase-deficient mouse models exhibit progressive telomere shortening and premature aging phenotypes across multiple generations (Blasco et al., 1997). Conversely, overexpression of telomerase has been shown to significantly increase the lifespan of mice when combined with enhanced tumor suppressor function (Tomás-Loba et al., 2008). A recent study demonstrated that *Tert* knock-in mice harboring the EF1α-*Tert* gene display elevated telomerase activity, elongated telomeres, and extended lifespan, with no spontaneous genotoxicity or carcinogenicity (Shim et al., 2024).

However, the relationship between telomerase and aging is not straightforward. Epigenetic aging has been shown to be distinct from senescence-mediated aging and is not prevented by telomerase expression, indicating that multiple aging mechanisms operate independently of telomere maintenance (Kabacik et al., 2018). Additionally, many cells in the body do not proliferate regularly and therefore do not experience significant telomere shortening, suggesting that telomere-driven senescence affects only certain tissues and cell types (Goyns and Lavery, 2000). In zebrafish, gut-specific telomerase expression has been shown to extend the lifespan of *tert-/-* animals by 40% while ameliorating natural aging, demonstrating that tissue-specific telomerase activation can have systemic anti-aging effects (El Maï et al., 2023).

The identification of circHERC1 as a regulator of TERT transcription that declines with age and whose restoration enhances telomerase activity, promotes telomere elongation, and reverses aging-associated phenotypes represents an exciting new avenue for anti-aging interventions (Cui et al., 2025). Delivery of circHERC1 using adeno-associated virus vectors or extracellular vesicles effectively restores telomerase activity, preserves telomere integrity, mitigates senescence, and leads to improvements in cognitive function, physical performance, and reduced inflammation (Cui et al., 2025).

5 Telomerase in Cancer: Mechanisms and Therapeutic Targeting

5.1 Telomerase Activation in Cancer

Telomerase is reactivated in approximately 85–90% of all human cancers, making it one of the most prevalent

molecular alterations in malignancy (Kim et al., 1994; Shay & Bacchetti, 1997; Siteni et al., 2024). This near-universal activation enables cancer cells to bypass replicative senescence and achieve unlimited proliferative capacity — a hallmark of cancer (Hanahan & Weinberg, 2011). The activation of telomerase in cancer occurs through multiple mechanisms, including promoter mutations, gene amplification, and transcriptional activation by oncogenic signaling pathways (Yuan et al., 2019; Liu et al., 2024).

5.1.1 TERT Promoter Mutations

TERT promoter mutations represent one of the most common non-coding mutations in human cancer (Horn et al., 2013; Huang et al., 2013). These mutations, typically C>T transitions at specific positions in the TERT promoter (-124 and -146 bp upstream of the transcription start site), create *de novo* binding sites for ETS transcription factors, leading to increased TERT transcription and telomerase activation (Horn et al., 2013; Huang et al., 2013). TERT promoter mutations are particularly prevalent in melanoma, glioblastoma, bladder cancer, and thyroid cancer, and have been associated with aggressive clinical behavior and poor prognosis (Vinagre et al., 2013). The development of deep learning approaches to decipher the impact of telomerase promoter mutations on metastatic progression and treatment resistance represents an emerging frontier in this area.

5.1.2 Alternative Splicing and Post-Translational Regulation

The TERT gene is subject to alternative splicing, generating multiple splice variants, some of which lack catalytic activity and may function as dominant-negative regulators (Listerman et al., 2013). The balance between full-length active TERT and inactive splice variants is dysregulated in cancer, contributing to altered telomerase activity. Post-translational modifications, including phosphorylation, ubiquitination, and acetylation, further regulate TERT protein stability, subcellular localization, and enzymatic activity (Yuan et al., 2019; Liu et al., 2024).

5.1.3 The Alternative Lengthening of Telomeres (ALT) Pathway

While the majority of cancers rely on telomerase for telomere maintenance, approximately 10–15% of tumors utilize a telomerase-independent mechanism known as the alternative lengthening of telomeres (ALT) (Bryan et al., 1997; Henson et al., 2002). The ALT pathway is a homologous recombination-based mechanism that extends telomeres through DNA repair processes rather than *de novo* synthesis (Cesare & Reddel, 2010; Muoio & Fouquerel, 2025). ALT-positive cancers are characterized by heterogeneous telomere lengths, the presence of ALT-associated PML bodies (APBs), extrachromosomal telomeric repeats (ECTRs), elevated replication stress, and telomere fragility (Henson et al., 2002; Muoio & Fouquerel, 2025).

The ALT pathway is particularly prevalent in sarcomas, glioblastomas, and neuroepithelial tumors, and is associated with loss-of-function mutations in the chromatin remodeling proteins ATRX (α-thalassemia/mental retardation syndrome X-linked) and DAXX (death domain-associated protein) (Heaphy et al., 2011; Lovejoy et al., 2012). ALT-positive tumors often exhibit poor prognosis and resistance to standard therapies, underscoring the need for targeted therapeutic approaches. Recent research has identified potential therapeutic strategies targeting ALT, including disruption of APBs, stabilization of G-quadruplex structures, and inhibition of replication stress proteins such as FANCM and SMARCAL1 (Muoio & Fouquerel, 2025). The shelterin proteins TRF1 and TRF2, chromatin remodeling factors ATRX and DAXX, and the dysregulated cGAS-STING pathway have been identified as key facilitators of ALT activity, providing novel therapeutic avenues (Muoio & Fouquerel, 2025).

5.2 Therapeutic Targeting of Telomerase in Cancer

The differential expression of telomerase between cancer cells and normal somatic tissues makes telomerase an attractive therapeutic target. Multiple approaches have been developed to exploit this difference, including direct telomerase inhibitors, telomerase-based vaccines, G-quadruplex DNA-interacting ligands, and

telomerase promoter-driven attenuated viruses (Harley, 2008; Siteni et al., 2024).

5.2.1 Direct Telomerase Inhibitors

Imetelstat (GRN163L) is a first-in-class, 13-mer N3′→P5′ thio -phosphoramidate oligonucleotide that binds with high affinity to the template region of hTR and acts as a competitive inhibitor of telomerase enzymatic activity (Asai et al., 2003; Harley, 2008). In June 2024, imetelstat received FDA approval for the treatment of adult patients with lower-risk myelodysplastic syndromes (LR-MDS) with red blood cell transfusion-dependent anemia, representing the first approved telomerase-targeted therapeutic (Siteni et al., 2024). Imetelstat has also shown activity in myelofibrosis and essential thrombocythemia, though myelosuppression is a notable dose-limiting toxicity (Baerlocher et al., 2015; Tefferi et al., 2015).

BIBR1532 is a non-nucleoside small-molecule telomerase inhibitor that has served as an important tool compound for studying telomerase inhibition (Damm et al., 2001). However, BIBR1532 exhibits suboptimal pharmacokinetic properties, and efforts have been made to design novel BIBR1532-based analogues with improved drug-like characteristics (Al-Karmalawy et al., 2022). These ligand-based design approaches, combined with molecular docking and ADME studies, have identified promising candidates with enhanced telomerase inhibitory activity and antitumor efficacy.

Other telomerase inhibitors under investigation include MST-312, which has shown synergistic effects with imatinib in chronic myeloid leukemia cells, suggesting potential combination therapy approaches.

5.2.2 Telomerase-Based Vaccines and Immunotherapy

Given that hTERT is expressed in the vast majority of cancers and can be recognized by the immune system as a tumor-associated antigen, telomerase-based vaccines represent a promising immunotherapeutic strategy (Vonderheide, 2002; Mizukoshi & Kaneko, 2019). Several vaccine platforms have been developed, including peptide vaccines, DNA vaccines, dendritic cell-based vaccines, and adoptive cell transfer therapies (Wang et al., 2024).

Multiple clinical trials have evaluated telomerase-targeted immunotherapies across various cancer types. The UV1 telomerase vaccine has been tested in combination with ipilimumab and nivolumab for pleural mesothelioma in the NIPU phase II randomized trial, investigating the potential synergy between telomerase vaccination and immune checkpoint blockade (Haakensen et al.,2024). Another phase I trial evaluated a telomerase-based vaccine combined with pembrolizumab in advanced melanoma, demonstrating encouraging safety and preliminary efficacy (Ellingsen et al., 2023). The combination of the CD4 Th1-inducer cancer vaccine UCPVax (derived from telomerase) with atezolizumab and bevacizumab is being evaluated in unresectable hepatocellular carcinoma in the TERTIO-PRODIGE 82 phase II study (Vienot et al., 2023).

A phase I clinical trial evaluated plasmid DNA-encoded hTERT immunotherapy (INO-1400 and INO-1401) with or without IL-12 DNA plasmid in adult patients with solid tumors at high risk of relapse (Vonderheide et al., 2021). The immunotherapy was well-tolerated, with immune responses noted across all tumor types, and a specific CD8+ phenotype increased by the immunotherapy was significantly correlated with survival in pancreatic cancer patients (Vonderheide et al., 2021).

Comprehensive reviews of telomerase-targeted cancer immunotherapy have highlighted the promising prospects of this approach for improving patient survival expectancy, with the main clinical application direction being combination with other drugs and treatment modalities, including traditional chemotherapy and immune checkpoint inhibitors (Wang et al., 2024). The therapeutic effectiveness of telomerase vaccines is influenced by the tumor microenvironment and can be substantially increased by combining them with immune checkpoint inhibitors.

5.2.3 G-Quadruplex DNA-Interacting Ligands

The single-stranded G-rich telomeric DNA can form stable four-stranded structures known as G-quadruplexes

(G4), which inhibit telomerase access to telomeres (Neidle & Parkinson, 2002). Small molecules that stabilize G-quadruplex structures have been developed as indirect telomerase inhibitors, with the rationale that G4 stabilization prevents telomerase from binding to and extending telomeres. Several G4 ligands have entered clinical development, though none have yet received regulatory approval (Neidle, 2017).

5.3 Targeting Non-Canonical Telomerase Functions

The recognition that telomerase components possess extra-telomeric activities that contribute to cancer cell survival, proliferation, and malignancy has expanded the therapeutic rationale for targeting telomerase (Armanios, 2012; Chiodi & Mondello, 2012). Novel small-molecule inhibitors that simultaneously disrupt telomere maintenance and the non-canonical activities of telomerase components may offer enhanced therapeutic efficacy. State-of-the-art drug discovery techniques are being harnessed to find novel cancer therapeutics that exploit the multifaceted biological functions of core telomerase components.

6 Emerging Frontiers in Telomerase Research

6.1 Engineered Telomerase RNA (eTERC)

A major recent advance in telomerase therapeutics is the development of engineered telomerase RNA component (eTERC) as a potential lncRNA medicine for extending replicative lifespan and telomere length (Nagpal & Agarwal, 2024, 2025). The telomerase RNA component TERC is a long non-coding RNA that has been shown to extend telomere length in human stem cells, but its complex structure and susceptibility to degradation have posed challenges for therapeutic development.

Nagpal and Agarwal (2025) have demonstrated the synthesis and enzymatic stabilization of TERC, incorporating a distinct trimethylguanosine 5′ cap and self-limited 2′-O-methyladenosine tailing catalyzed by the non-canonical polymerase TENT4B. This enzymatic stabilization method can be applied to RNAs of any size and is critical for optimal eTERC function in cells (Nagpal & Agarwal, 2025). A single transient exposure to eTERC forestalls telomere-induced senescence in telomerase-deficient human cell lines and lengthens telomeres in induced pluripotent stem cells from patients carrying mutations in telomere-maintenance genes, as well as primary CD34+ blood stem/progenitor cells (Nagpal & Agarwal, 2025). These results provide proof of functional reconstitution for a stabilized, synthetic human lncRNA and suggest that eTERC may have therapeutic potential to safely extend replicative capacity in human stem cells without the oncogenic risks associated with permanent TERT overexpression (Nagpal & Agarwal, 2024, 2025).

6.2 Novel Small-Molecule TERT Activator: TAC

The identification of TAC (TERT activator compound) represents a landmark advance in telomerase activation for anti-aging applications (Shim et al., 2024). Through screening of approximately 653,000 compounds in human fibroblasts carrying an hTERT-Rluc reporter, Shim and colleagues (2024) identified TAC as a potent small-molecule activator that upregulates TERT transcription via the MEK/ERK/AP-1 cascade. TAC is a 400 Da lipophilic agent that crosses the blood–brain barrier, elevates TERT transcription within brain, heart, and skeletal muscle, and lengthens telomeres while suppressing DNA damage foci (Shim et al., 2024).

In aged mice (26–27 months) treated with TAC daily for six months, the compound improved hippocampal neurogenesis, reversed neuromuscular decline, and enhanced cognition (Shim et al., 2024). Mechanistically, these gains trace to a MEK/ERK/FOS/AP-1 signaling cascade that drives TERT expression and, in turn, epigenetically silences p16INK4a via DNMT3b-mediated promoter hypermethylation (Shim et al., 2024). Concomitantly, the senescence-associated secretory phenotype (IL-1β, IL-6, MMP-3, VEGF; Huang and Zhang, 2012; Li and Zhang, 2013; Zhang, 2016a-b, 2017, 2018) is down-regulated, systemic low-grade inflammation subsides, and no neoplastic lesions appear (Shim et al., 2024). Importantly, crossing TAC-treated mice into a late-generation *Terc*-knockout background confirmed that the compound fails to

rescue phenotypes when telomerase is absent, proving on-target specificity (Shim et al., 2024). While translational considerations remain — including the shorter telomeres and lack of constitutive telomerase in humans compared to mice — TAC represents a promising chemical route to compress morbidity and potentially extend healthspan.

6.3 CRISPR-Based Interventions

CRISPR-Cas9 technology has emerged as a powerful tool for manipulating telomerase expression and studying telomerase biology (Xi et al., 2015; Huang et al., 2024). Several distinct CRISPR-based strategies have been developed for telomerase-related applications.

A two-step CRISPR-Cas9 genome editing strategy has been developed to introduce precise modifications at the endogenous TERT locus in human cell lines, providing a useful tool for studying telomerase biology and suggesting a general approach to edit loci with low targeting efficiency and to purify and visualize low-abundance proteins (Xi et al., 2015).

CRISPR/dCas9-based epigenetic modifiers and transcriptional activators have been utilized to reactivate the endogenous TERT gene in resting T cells within peripheral blood mononuclear cells (Huang et al., 2024). Using CRISPR/dCas9 fused to p300 histone acetyltransferase, TET1 DNA demethylase, or transcriptional activators VPH and VPR, researchers have successfully expanded resting T cells and delayed their cellular senescence for at least three months through TERT reactivation, without affecting T-cell marker expression or inducing accelerated cell division (Huang et al., 2024). TERT reactivation and replicative senescence delay were achieved without inducing malignant transformation, as demonstrated by cellular senescence assays, cell cycle analysis, proliferation rate, cell viability, and karyotype analyses (Huang et al., 2024). This strategy of cell immortalization can potentially be adopted and generalized to delay cell death or immortalize other cell types for research and therapeutic applications.

6.4 Novel Regulatory Factors

The discovery of new regulatory factors continues to expand our understanding of telomerase control mechanisms. The identification of circHERC1 as a regulator of TERT transcription represents a novel layer of regulatory complexity (Cui et al., 2025). circHERC1 binds to the TERT promoter, facilitating the recruitment of RNA polymerase II and c-Fos, thereby activating TERT expression (Cui et al., 2025). circHERC1 expression declines with age, correlating with reduced telomerase activity, and its restoration enhances telomerase activity, promotes telomere elongation, and reverses aging-associated phenotypes (Cui et al., 2025). Delivery of circHERC1 using adeno-associated virus vectors or extracellular vesicles effectively restores telomerase activity, preserves telomere integrity, and mitigates senescence, leading to improvements in cognitive function, physical performance, and reduced inflammation (Cui et al., 2025).

6.5 Artificial Intelligence and Machine Learning Applications

Artificial intelligence and machine learning are increasingly being applied to telomerase research, particularly for drug discovery applications. TeloPred is a pioneering structure-activity machine learning classification model for predicting small molecules as telomerase inhibitors, advancing anti-cancer drug discovery (Kaur et al., 2025). TeloPred was developed using a curated dataset of telomerase inhibitors with IC50 values from ChEMBL and trained on molecular fingerprints generated with PaDEL software (Kaur et al., 2025). The best-performing model, a Support Vector Classifier, achieved 87.2% accuracy on the test set and 89% on training, with low false positive/negative rates (Kaur et al., 2025). External validation yielded an enrichment factor of 21, indicating strong predictive strength, and SHAP analysis revealed aromatic groups, amide linkages, and carbonyl groups as critical for telomerase inhibition (Kaur et al., 2025). Screening of a natural compound library narrowed the search space by 83%, identifying 10 leads with promising activity (Kaur et al., 2025). TeloPred will be available on a public webserver for global use, enabling efficient virtual screening of

large compound libraries for telomerase inhibitor discovery.

Computational methods have also been applied to predict natural products as telomerase activators for anti-aging applications. A computational study used molecular docking and pathway analysis to examine how patchouli plant (*Pogostemon cablin* Benth.) components could work as telomerase enzyme activators in the PI3K-Akt pathway, demonstrating the potential of *in silico* approaches for discovering telomerase-modulating compounds (Harnelly et al., 2025).

Deep learning approaches are being used to decipher the impact of telomerase promoter mutations on metastatic progression and treatment resistance, providing insights that may inform personalized therapeutic strategies. Advanced AI algorithms are also being employed to predict alternative functional states of telomerase-associated proteins and to identify promising small-molecule ligands through AI docking algorithms.

7 Clinical Trials and Therapeutic Applications

7.1 Telomerase Inhibitors in Clinical Development

The clinical development of telomerase inhibitors has progressed significantly over the past two decades, culminating in the FDA approval of imetelstat in 2024 (Siteni et al., 2024). Imetelstat is approved for the treatment of adult patients with lower-risk myelodysplastic syndromes (LR-MDS) with red blood cell transfusion-dependent anemia, based on phase II/III clinical trial data demonstrating transfusion independence and hematologic improvement (Platzbecker et al., 2024). The drug is administered as a 2-hour intravenous infusion every 4 weeks and exhibits dose-dependent pharmacokinetics with a lower clearance at higher dose levels (González-Sales et al., 2024). Telomerase inhibition has been observed in peripheral blood mononuclear cells at clinically relevant doses, confirming target engagement (Thompson et al., 2013).

Additional clinical trials with imetelstat are ongoing or completed in various hematologic malignancies and solid tumors. In essential thrombocythemia, a phase II study demonstrated rapid and durable hematologic and molecular responses in patients who had not responded to or were intolerant of prior therapies (Baerlocher et al., 2015). In myelofibrosis, imetelstat showed activity but also had the potential to cause clinically significant myelosuppression (Tefferi et al., 2015). A phase I trial of imetelstat in children with refractory or recurrent solid tumors demonstrated that pharmacokinetics is dose-dependent and that telomerase inhibition could be achieved, with two confirmed partial responses observed (Thompson et al., 2013).

Safety evaluations have demonstrated that imetelstat has a low proarrhythmic risk based on nonclinical and clinical studies, with *in vitro* studies showing no proarrhythmic risk at >140× the clinical Cmax and *in vivo* studies showing no risk at >2.6× the clinical Cmax (González-Sales et al., 2024). Myelosuppression remains the primary dose-limiting toxicity, consistent with the role of telomerase in maintaining hematopoietic stem cell function.

7.2 Telomerase Vaccines and Immunotherapies

Telomerase-targeted immunotherapies have been evaluated across more than 30 clinical trials spanning nearly two decades, with vaccines representing the primary treatment modality (Wang et al., 2024). Several vaccines have advanced to phase III clinical trials, and the main clinical application direction is combination with other drugs and treatment modalities.

The UV1 telomerase vaccine, a peptide-based vaccine targeting hTERT, has been evaluated in combination with immune checkpoint inhibitors. The NIPU phase II randomized trial investigated the addition of UV1 to ipilimumab and nivolumab as second-line treatment for pleural mesothelioma (Haakensen et al., 2024). Another phase I trial combined a telomerase-based vaccine with pembrolizumab in advanced melanoma, demonstrating encouraging safety and preliminary efficacy, with randomized phase II trials currently ongoing

(Ellingsen et al., 2023).

The UCPVax vaccine, a CD4 Th1-inducer cancer vaccine derived from telomerase, is being evaluated in combination with atezolizumab and bevacizumab in unresectable hepatocellular carcinoma in the TERTIO-PRODIGE 82 randomized phase II study (Vienot et al., 2023). A phase I trial of hTERT vaccination combined with therapeutic strategies to control immune-suppressor mechanisms demonstrated that the vaccine regimen was safe and associated with antigen-specific immunological responses (Zareian et al., 2024).

Plasmid DNA-encoded hTERT immunotherapy (INO-1400 and INO-1401) with or without IL-12 DNA plasmid (INO-9012) has been evaluated in a phase I clinical trial in adult patients with solid tumors at high risk of relapse following definitive surgery and standard therapy (Vonderheide et al., 2021). Among 93 enrolled patients who received at least one dose, 88 had at least one adverse event, the majority of which were grade 1 or 2 and related to injection site (Vonderheide et al., 2021). At 18 months, 54.8% of patients were disease-free, and median disease-free survival had not been reached by the end of the study (Vonderheide et al., 2021). For patients with pancreatic cancer, the median disease-free survival was 9 months, and a specific CD8+ phenotype increased by the immunotherapy was significantly correlated with survival (Vonderheide et al., 2021).

7.3 Clinical Applications in Aging and Regenerative Medicine

While telomerase-targeted therapeutics for aging and regenerative medicine are at an earlier stage of clinical development, several approaches have entered human testing. The oral telomerase activator TA-65, a natural product-derived compound, has been evaluated in a randomized, double-blinded controlled study to assess safety and efficacy in myocardial infarction patients aged over 65 years (Harley et al., 2011). TA-65 was shown to activate telomerase and has been marketed as a dietary supplement, though its clinical efficacy for age-related conditions requires further rigorous investigation.

A clinical trial (NCT04110964) is evaluating hTERT delivered via adeno-associated virus (AAV) transduction for treating critical limb ischemia (CLI) and other age-related diseases, with the goal of extending telomeres to prevent, delay, or reverse pathology development. The safety and efficacy of such gene therapy approaches require careful long-term monitoring given the oncogenic potential associated with constitutive telomerase activation.

7.4 Safety Considerations and Toxicity

Safety is a paramount concern for telomerase-targeted therapeutics, particularly for strategies that involve telomerase activation for anti-aging or regenerative applications. The primary theoretical risk is the promotion of tumorigenesis, given that telomerase is activated in the vast majority of human cancers (Shay & Bacchetti, 1997; Siteni et al., 2024).

For telomerase inhibitors, the primary toxicity observed clinically is myelosuppression, which is consistent with the role of telomerase in maintaining hematopoietic stem cell function (Baerlocher et al., 2015; Tefferi et al., 2015). Other reported adverse events include gastrointestinal symptoms, fatigue, and injection site reactions for vaccine-based approaches (Vonderheide et al., 2021). Long-term safety surveillance is essential for all telomerase-targeted therapeutics, particularly those intended for chronic use in non-cancer indications.

For telomerase activation strategies, safety data for TAC in aged mice have shown no excess tumors over a six-month treatment period, but long-term surveillance is obligatory given telomerase biology (Shim et al., 2024). The transient nature of eTERC activity and the use of inducible expression systems may mitigate oncogenic risks by avoiding permanent telomerase activation (Nagpal & Agarwal, 2025). CRISPR/dCas9-based approaches that reactivate endogenous TERT in resting T cells have been shown not to induce malignant transformation in various cellular senescence assays, cell cycle analyses, proliferation rate assessments, cell viability tests, and karyotype analyses (Huang et al., 2024).

8 Challenges, Limitations, and Future Research Directions

8.1 Current Challenges and Limitations

Despite remarkable progress in telomerase research and therapeutic development, significant challenges and limitations remain.

The lag time between telomerase inhibition and clinical response represents a fundamental challenge for telomerase-targeted cancer therapies (Siteni et al., 2024). Because telomerase inhibition does not immediately induce cell death but rather requires progressive telomere shortening to reach critically short lengths that trigger senescence or apoptosis, there is an inherent delay of weeks to months before therapeutic effects become apparent. This characteristic makes telomerase inhibitors less suitable for rapidly progressive cancers and necessitates combination with therapies that provide more immediate tumor control.

Myelosuppression is a significant dose-limiting toxicity for telomerase inhibitors, reflecting the dependence of hematopoietic stem cells on telomerase for sustained function (Baerlocher et al., 2015; Tefferi et al., 2015). This toxicity limits the doses and treatment durations that can be safely administered and necessitates careful monitoring of blood counts during therapy.

For telomerase activation strategies, the oncogenic risk associated with telomerase reactivation remains the primary safety concern (Shim et al., 2024; Nagpal & Agarwal, 2025). While transient activation approaches such as eTERC and controlled induction of endogenous TERT may mitigate this risk, long-term safety data in humans are lacking, and rigorous surveillance will be essential for any clinical application.

The alternative lengthening of telomeres (ALT) pathway represents a significant therapeutic challenge, as ALT-positive cancers are inherently resistant to telomerase inhibitors (Cesare & Reddel, 2010; Muoio & Fouquerel, 2025). The development of targeted therapies for ALT-positive tumors is an active area of research, but no approved therapies currently exist for this subset of cancers.

The development of resistance to telomerase-targeted therapies, whether through upregulation of ALT, alternative telomere maintenance mechanisms, or other adaptive responses, is a concern that requires ongoing investigation (Muoio & Fouquerel, 2025). Combination strategies that target multiple vulnerabilities may help prevent or overcome resistance.

8.2 Future Research Directions

Several promising directions for future research emerge from the current state of telomerase science.

The development of next-generation telomerase inhibitors with improved pharmacokinetic properties, reduced toxicity, and enhanced efficacy remains a priority. AI-driven drug discovery platforms such as TeloPred offer the potential to accelerate the identification of novel telomerase inhibitors from large compound libraries (Kaur et al., 2025). Structure-based drug design leveraging high-resolution cryo-EM structures of human telomerase may enable rational development of more selective and potent inhibitors (Nguyen et al., 2018; Sekne et al., 2026).

Combination therapy strategies that pair telomerase inhibitors or vaccines with conventional chemotherapy, targeted therapies, or immune checkpoint inhibitors warrant further investigation. The synergy between telomerase vaccination and immune checkpoint blockade has shown promise in early clinical trials, and optimizing these combinations may enhance therapeutic efficacy (Wang et al., 2024; Haakensen et al.,2024).

For telomerase activation strategies, the development of safe and effective approaches for transient, controlled telomerase activation in specific tissues is a key priority. eTERC represents a promising platform for transient telomere elongation without permanent genetic modification (Nagpal & Agarwal, 2025). Inducible expression systems that enable precise temporal control of telomerase activity could further enhance safety. The identification of TAC as a small-molecule TERT activator opens new avenues for pharmacological telomerase activation, though optimization of dosing, pharmacokinetics, and long-term safety in primates and

humans is required before clinical translation (Shim et al., 2024).

The development of targeted therapies for ALT-positive cancers is an urgent unmet need. Recent advances in understanding the molecular mechanisms of ALT, including the roles of ATRX, DAXX, shelterin proteins, and DNA repair factors, have identified potential therapeutic vulnerabilities that warrant further investigation (Muoio & Fouquerel, 2025). Strategies targeting APBs, G-quadruplex stabilization, and replication stress proteins represent promising directions.

Personalized approaches to telomerase-targeted therapy based on tumor telomere biology and TERT promoter mutation status may improve patient selection and outcomes. Deep learning approaches to decipher the impact of TERT promoter mutations on disease progression and treatment response could inform personalized therapeutic strategies.

The non-canonical functions of telomerase components represent an underexplored therapeutic opportunity. Developing small-molecule inhibitors that simultaneously disrupt telomere maintenance and non-canonical activities may offer enhanced efficacy (Cao et al., 2025). Conversely, understanding the non-canonical functions of TERT and TERC in normal physiology may reveal additional therapeutic applications for telomerase modulation beyond cancer and aging.

8.3 Concluding Perspectives

Telomerase research has evolved from the foundational discovery of a novel enzymatic activity in ciliate extracts to a mature field with direct clinical impact, exemplified by the FDA approval of imetelstat in 2024. The enzyme‘s unique position at the nexus of cancer, aging, and stem cell biology ensures its continued relevance for both fundamental biological inquiry and translational medicine.

The dual nature of telomerase — as a therapeutic target in cancer and a rejuvenation target in aging — presents both opportunities and challenges. In cancer, the near-universal activation of telomerase provides a rationale for therapeutic targeting, but the lag time to response and dose-limiting toxicities necessitate innovative approaches to maximize clinical benefit. In aging and regenerative medicine, the potential of telomerase activation to extend healthspan and enhance tissue repair is tantalizing, but the oncogenic risks demand rigorous safety evaluation and the development of precisely controllable activation strategies.

The convergence of advanced technologies — including cryo-EM, CRISPR-based genome and epigenome editing, engineered RNAs, AI-driven drug discovery, and high-throughput small-molecule screening — has accelerated progress across all domains of telomerase research. The identification of novel regulatory factors such as circHERC1, the development of eTERC as a lncRNA medicine, the discovery of TAC as a small-molecule activator, and the application of machine learning to inhibitor discovery exemplify the transformative potential of these technologies.

As the field moves forward, interdisciplinary collaboration spanning structural biology, biochemistry, genetics, pharmacology, immunology, and clinical investigation will be essential to translate fundamental discoveries into safe and effective therapies for the many human diseases in which telomerase plays a central role. The coming decade promises continued advances in understanding telomerase biology and realizing its therapeutic potential across the spectrum from cancer to aging and regenerative medicine.

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