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Therapeutic Potential of Targeting Telomerase and Inducing Cellular Replicative Senescence in Cancer Treatment

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ABSTRACT

Telomerase is a ribonucleoprotein (RNP) complex which serves as a template for the addition of telomeric repeats to chromosome ends. Telomeres are protective caps on the ends of chromosomes. With every cell replication, a part of the telomere end is cleaved. Telomerase helps prevent over-shortening of the telomeres, allowing the cell to replicate indefinitely. Cellular replicative senescence can occur when the telomere caps have been cleaved to the point that the genome is at risk of degradation during replication. At this stage, the cell arrests its cell cycle and enters a dormant state. Cancer cells allow themselves to replicate indefinitely by increasing telomerase expression, preventing them from entering senescence. By decreasing telomerase expression in cancer cells, we can force them to enter senescence and limit their ability to proliferate, which can be a viable treatment option. In order to find viable treatment options, we need to compare the relationship between telomerase expression and cellular senescence between different treatments. In this paper, we discuss treatment options and their effectiveness of decreasing telomerase expression and triggering cellular senescence in cancer cells.

Keywords: Telomerase, Telomerase Inhibitors, Cellular Replicative Senescence, Cancer.

INTRODUCTION

Telomeres are protective caps, consisting of repeating nucleotides, at the ends of eukaryotic chromosomes. With every cell replication, a part of the telomere end is cleaved, because the DNA polymerase enzyme cannot fully replicate the end of a linear chromosome. Over time, this gradual shortening of telomeres acts as a molecular clock that marks the cellular aging process. Telomerase is a ribonucleoprotein (RNP) complex which serves as a template for the addition of telomeric repeats to chromosome ends, which helps prevent over-shortening of the telomeres, allowing the cell to replicate indefinitely. It consists of 2 subunits: a catalytic core composed of telomerase reverse transcriptase (TERT) and the non-coding

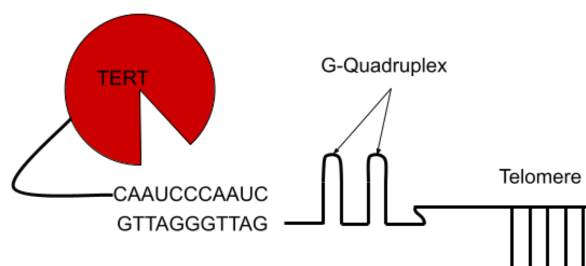

Figure 1 : The telomerase RNA component, which is connected to TERT (telomerase reverse transcriptase), binds to the Telomeric DNA to add DNA repeats and extend the telomere.

RNA, telomerase RNA component. TERT utilizes the template region (3'-CAAUCCCAAUC-5') of the RNA component to add "TTAGGG" DNA repeats to extend single stranded 3' telomeric strands (Gavory et al., 2002) (Figure 1). G-quadruplexes (G4s) are DNA structures that are formed by repetitive guanine sequences, which are extremely stable. G-quadruplexes are made up of stacked G-tetrads, which are cyclic arrangements of four guanines (Moye et al., 2015). There is some evidence that G-quadruplexes at telomeres may play a protective capping role on the telomere (Bryan, 2020).

Telomerase is significantly expressed during embryonic development because it allows these rapidly dividing cells to continue proliferating without suffering telomere shortening, which would otherwise limit the number of cell divisions and impair embryonic development (Hiyama & Hiyama, 2007). Telomerase is down regulated during differentiation of somatic cells and in normal human somatic cells, it is almost undetectable, which maintains genomic stability and prevents uncontrolled cell division, which could otherwise lead to cancerous growth. Since the telomerase RNA component is present in the cell at all times, telomerase activity is controlled primarily by the presence of TERT.

Cancer, a complex group of diseases characterized by uncontrolled cell growth and proliferation, is one of the leading causes of death and remains one of the most significant challenges in modern medicine. A cancer cell is a cell that divides indefinitely, evading cell growth control mechanisms. Cancer cells acquire the ability to divide uncontrollably, forming a mass of cells that can invade surrounding tissues and potentially spread to other parts of the body. Cancer cells have a wide spectrum of types, ranging from malignant to benign cancers. Malignant cancer can be spread throughout the body and poses a significant risk while benign cancer does not proliferate as significant. Cancer cells allow themselves to replicate indefinitely by increasing telomerase expression, preventing them from entering a dormant state, called replicative senescence, where the cell can't replicate.

Once the telomeres have been cleaved to the point that the genome is at risk of degradation, the cell will arrest the cell cycle and enter replicative senescence. Normal somatic cells will arrest cell division after approximately 50-70 cell divisions (Hayflick limit) and will enter senescence (Groten et al., 2018). In normal cancer cells, senescence is triggered by the activation of tumor suppression genes; however, this is not efficient enough to treat cancer on its own (Rayess et al., 2012). Therefore, it is necessary to trigger senescence using external factors.

Telomerase becomes upregulated in approximately 90% of malignant cancers, leading to a restoration of telomere length and the potential for indefinite cell division (Trybek et al., 2020). This upregulation is driven by the activation of the TERT promoter, which involves various factors: a combination of genetic mutations, epigenetic changes like DNA methylation, and alterations in alternative splicing patterns. In normal somatic cells, this promoter is typically silenced, preventing excessive telomere lengthening and preventing the risk of uncontrolled cellular proliferation. In contrast, in cancer cells, this promoter is activated, granting the cells the ability to avoid cellular senescence and achieve indefinite replication (Betori et al., 2020).

Although several cancer therapies exist, there is no widely accepted treatment option Therefore, it is necessary to find new treatments and more effective treatments to treat malignant cancers. One possible

method could be by decreasing telomerase expression. By decreasing telomerase expression in cancer cells, we can force them to cleave their telomeres, causing them to enter senescence (Gomez et al., 2016). This would limit their ability to proliferate, slowing down the progression of the disease, and converting it from malignant to benign. Unlike conventional cancer treatment methods such as radiotherapy and chemotherapy, telomerase inhibitors specifically target a mechanism frequently dysregulated in cancer cells, would minimize harm to healthy tissues, and may induce reduced side effects. Unlike telomerase inhibition, radiotherapy can cause hair loss, memory damage and in some cases can lead to a second cancer (Liu et al., 2020). Telomerase inhibitors could also counter resistance development seen in these therapies.

Extensive research is being performed on telomerase inhibitors and their efficacy on converting cancer cells into senescent cells, and many drugs with telomerase inhibiting properties have been discovered. However, it is necessary to calculate and compare the efficacy of the drugs in order to determine which would be the best to use to treat cancer patients. In this paper, we compare the efficacy of different telomerase inhibitors on inhibiting telomerase and converting cancer cells into senescent cells to decrease their proliferative ability.

DISCUSSION

Current Treatments

There are several cancer treatments today based on inhibiting telomerase. Some of the most potent ones today are INVAC-1 developed by Invectys, Imetelstat developed by Geron, BIBR1532 developed by Calbiochem, and TmPyP4 developed by Calbiochem. Although they all target telomerase, they function through different ways: increasing immune response to TERT, binding to the RNA component of telomerase, binding to TERT, and stabilizing telomeric G-quadruplex structures, respectively (Figure 2). Each treatment is still in different stages of clinical trials, and results have shown varying efficacies.

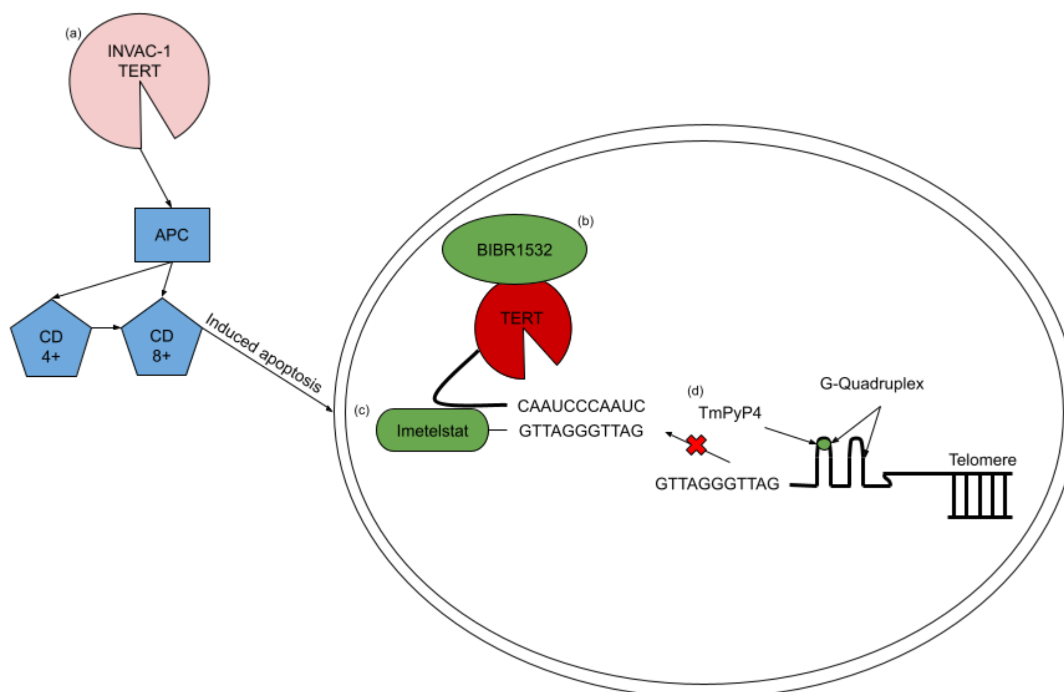

Figure 2 - (a) INVAC-1 activates CD8+ cytotoxic T cells and CD4+ T helper cells by introducing a modified hTERT protein, stimulating an immune response against cancer.(b) Imetelstat inhibits telomerase function by binding to its RNA component, competitively blocking the telomeres from interacting with telomerase, preventing telomere replication.(c) BIBR1532 alters the shape of TERT's active site by binding to a distinct site, preventing telomeric DNA from binding to telomerase and thus inhibiting telomere replication.(d) TmPyP4 stabilizes telomeric G-quadruplex structures by binding to them, making the telomere overhang inaccessible to the telomerase RNA template

INVAC 1/IVS-2001

INVAC-1 is a human telomerase DNA-based anti-cancer vaccine, consisting of a DNA plasmid encoding a modified human telomerase reverse transcriptase (hTERT) protein (Calvet et al., 2014). INVAC-1 has two cancer suppressing effects: activation of the CD8+ Cytotoxic T cells and CD4+ T helper cells. The DNA plasmid enters the antigen presenting cells (APC), which present the antigen to CD8+ Cytotoxic T cells and CD4+ T helper cells. The CD4+ T helper cells release helping molecules which help the CD8+ Cytotoxic T cells kill the cancer cells (Teixeira et al., 2020).

Imetelstat

Imetelstat is an oligonucleotide drug that targets the RNA component of telomerase and inhibits its function (Geron., 2013). It binds to the RNA template, preventing the telomeres from binding to telomerase as a competitive inhibitor. In order for the telomeres to be replicated and extended, they have to bind to the RNA template on telomerase. Therefore, blocking this access prevents the telomeres from being replicated, ultimately removing their ability to replicate forever (Frink et al., 2016).

BIBR1532

BIBR1532 is a non-competitive small-molecule inhibitor and binds to a site on TERT distinct from the sites for DNA primers (Doğan et al., 2019). This binding changes the shape of the active site and prevents the telomeric DNA from binding to the telomerase. This prevents the telomerase from replicating the telomeres (Pascolo et al., 2002).

TmPyP4

TmPyP4 is a cationic porphyrin (cyclic organic compounds made up of four pyrrole rings, connected by a series of single and double bonds to form a large ring) G-quadruplex stabilizer that specifically stabilizes telomeric G-quadruplex structures with minimal effect on non-telomeric regions (Kosiol et al., 2021). In human telomeres, a TTAGGG repeat overhang has the ability to form G-quadruplexes. TmPyP4, being a cyclic ligand, is able to bind to the G-quadruplex making the overhang inaccessible to the telomerase RNA template

Efficacy

INVAC-1 has completed its Phase 1 studies in patients with advanced solid tumors. Three INVAC-1 dose levels (100, 400, and 800 μg) were prepared for 3 sequential cycles. The majority of patients with advanced solid tumors (58%, 15 patients) experienced disease stabilization, meaning no new tumors developed and spread to other parts of the body, for 1.8 to 9.9 months. After INVAC-1 administration, a specific CD4 T-cell response against TERT was observed in 15 of 24 patients, of which 10 had spontaneous CD4 T-cell responses at baseline. Of these, 8 showed an increased response and 2 showed a sustained response after vaccination. CD4 T-cell responders showed significantly higher secretion of IL2 ($P = 0.016$), TNFa ($P = 0.008$), GM-CSF ($P = 0.008$), and IL13 ($P = 0.008$) (Teixeira et al., 2020).

The telomerase inhibitor Imetelstat was tested in preclinical trials in nine non-small cell lung cancer (NSCLC) cell lines (Calu-3, H157-luc, H358, H460, H1648, H1819, H2087, H2887, and HCC827) which vary in telomere lengths, patient characteristics and oncogenotypes. One NSCLC cell line found telomere shortening from ~5.2 kb to ~4.3 kb. At 40 weeks of Imetelstat treatment, telomere length was 12 kb shorter to 2.6 kb. For reference, the average adult human somatic cell has a telomere length of about 3 kb. After 2 weeks without treatment, telomeres lengthen to 3.4 kb. At 4 weeks after removal of treatment, some H157-luc telomeres returned to parental length and all returned to parental length and remained there after 6 weeks in the absence of Imetelstat. Cellular senescence was also tracked. Calu-3 with an initial telomere length of 1.5 kb and reached senescence in approximately 4 population doublings (11 days). H1648 with an initial telomere length of 2 kb and reached senescence in approximately 15 population doublings at ~2 months. H2887, HCC827 and H460 had initial telomere lengths of 2 kb to 5 kb and reached senescence at ~12 population doublings (~25 days), 40 population doublings (~100 days) and 50 population doublings (~70 days), respectively (Frink et al., 2016). In another study, 20 patients received Imetelstat of a starting dose of 225 mg/m2 with dose escalations in ~30% increments to 285 mg/m2 and 360 mg/m2. The effect of Imetelstat on telomerase activity was analyzed using telomeric repeat amplification protocol (TRAP). The TRAP assay is a popular method to determine telomerase activity. The TRAP assay includes three steps: extension, amplification, and detection. In the extension step, telomeric repeats are added to the telomerase substrate by telomerase (Mender and Shay, 2015). In

the amplification step, the extension products are amplified by the polymerase chain reaction (PCR) using specific primers, and in the detection step, the presence of telomerase is analyzed by electrophoresis. Telomerase inhibition in peripheral blood mononuclear cells (PBMCs) was observed in 5 of 6 patients. Of the 3 patients at the phase 2 dose, telomerase inhibition was sustained through Day 8 in one patient and returned by the second dose of drug on Day 8 in the other two patients. Of the 3 patients at the 360 mg/m2 level, two showed inhibition of telomerase activity in PBMCs which returned by the second dose of drug on Day 8 (Thompson et al., 2013).

A study analyzed the effect of BIBR1532 on cell lines from feline oral squamous cell carcinoma (FOSCC). FOSCC cell lines SCCF1, SCCF2, and SCCF3 were plated in 6-well plates, and after 24 h, BIBR1532 diluted at 25, 50, and 100 μM in culture medium was added to wells. In control plates, the drug was replaced with the same amount of DMSO for each dose. BIBR1532 blocked telomerase activity by limiting the amount of nucleotide repeats available for substrate elongation. The cells were cultured for 48 hours and subjected to TRAP assay. The results showed detectable telomerase activity at control conditions in SCCF1, SCCF2, and SCCF3, and gel scans showed reduction of telomerase activity with a dose-dependent trend. SCCF1 and SCCF2 showed significant telomerase inhibition from 50μM onward (Figure 3). The treatment induced growth inhibition in SCCF1, SCCF2, and SCCF3 even at the lowest dose (Altamura et al., 2021) (Figure 4).

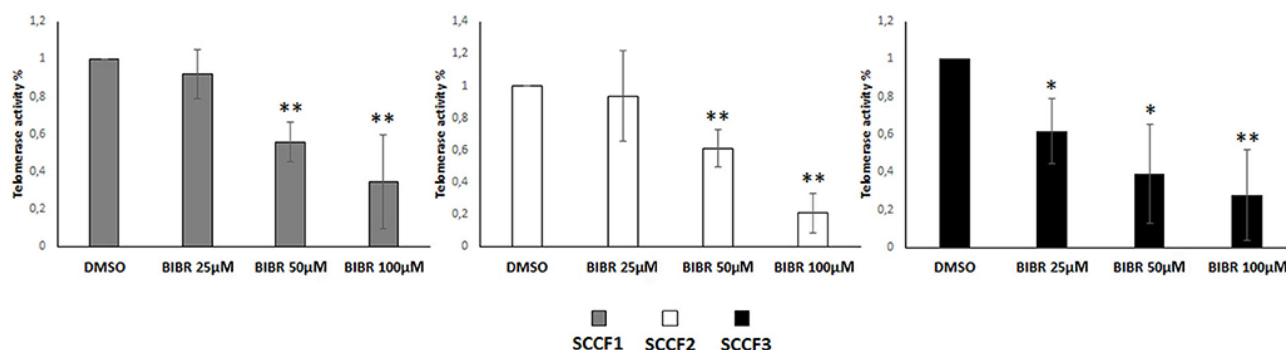

Figure 3 - Telomerase Activity (TA) dropped approximately 50% between DMSO and 50μM for and 70% between DMSO and 100μM for SCCF1. TA dropped approximately 40% between DMSO and 50μM for and 80% between DMSO and 100μM for SCCF2. TA dropped approximately 60% between DMSO and 50μM for and 70% between DMSO and 100μM for SCCF3. This signifies an overall trend of decreasing telomerase activity with increasing dosage of BIBR in all three cell lines(Altamura et al., 2021).

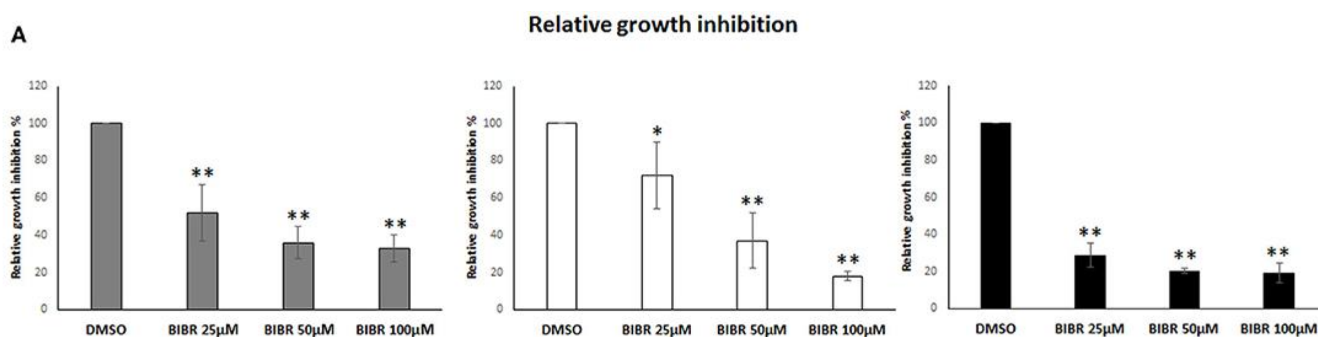

Figure 4 - The inhibitory effect of each dose of BIBR1532 was expressed as % of decrease compared with its respective DMSO control set as 100%. All three cell lines demonstrate an induced growth inhibition in a dose-dependent manner(Altamura et al., 2021).

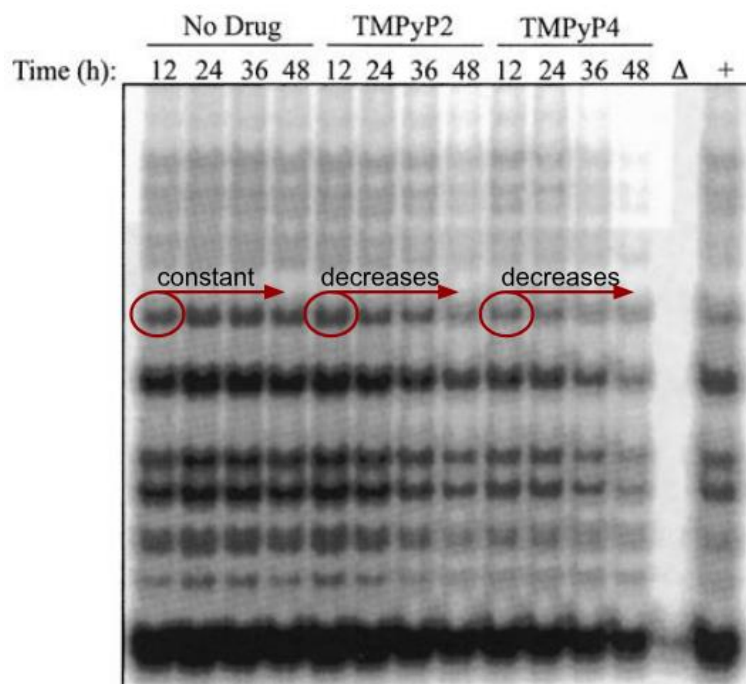

Figure 5 - MiaPaCa-2 cells show a decline in telomerase activity when treated with TMPyP2 and further decline in telomerase activity when treated with TMPyP4. Telomerase activity also decreases over time for the cells treated with TMPyP2 and TMPyP4(Grand et al., 2002).

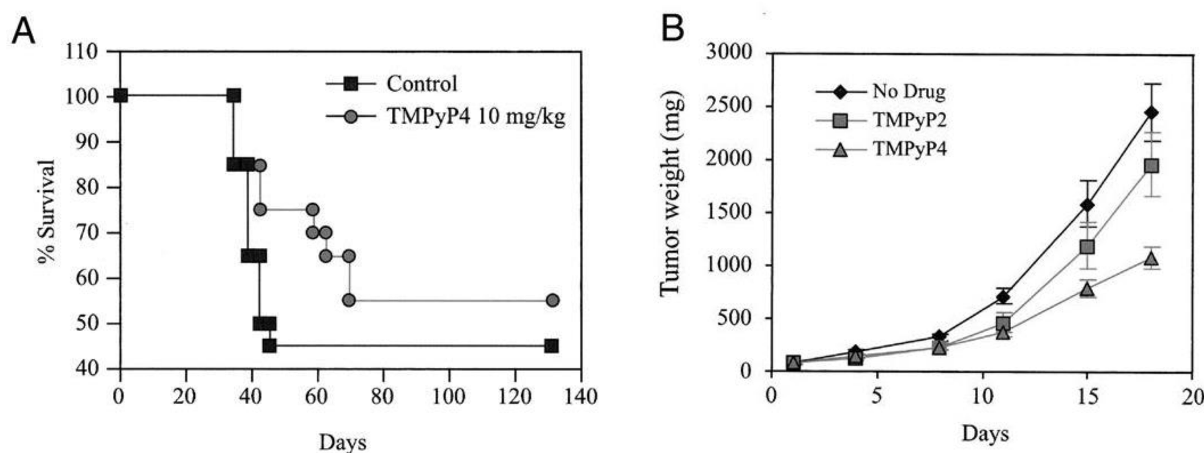

Figure 6 – (a) Percent survival of TMPyP4 versus control. At day 60, survival was improved from 45 to 75% with TMPyP4 treatment and at day 100, survival was improved from 45 to 55%. (b) Slowing of tumor growth by TMPyP4. Mean tumor growth rates were calculated to be 132 ± 15 mg/day for control mice, 104 ± 16 mg/day for TMPyP2-treated mice, and 50 ± 6 mg/day for mice treated with TMPyP4, demonstrating significant inhibition(Grand et al., 2002).

To analyze the effects of TmPy4 on cancer cells, HeLa S3 (human cervical carcinoma metastasis) and MiaPaCa-2 (human pancreatic tumor) were cultured in 100 μm TMPyP2 and TMPyP4. MiaPaCa-2 cells were treated with 100 μm TMPyP4 for 12, 24, 36, and 48 h, and subjected to a TRAP assay. The only difference between TMPyP2 and TMPyP4 is the position of the N-methyl group on the pyridyl ring (Han et al., 1999). Gel electrophoresis showed that TMPyP4 could inhibit telomerase activity in MiaPaCa-2 cells (Figure 5), showing a significant decrease in concentration after 48 hours of exposure (Grand et al., 2002).

TMPyP4 was also tested on human breast (MX-1) and prostate tumor (PC-3) xenografts, a tissue derived from humans and inserted in mice. Treatment with TMPyP4 resulted in an increase in survival. At days 60 and 100, survival was 70% *versus* 45% and 55% *versus* 45% for animals administered TMPyP4 *versus* vehicle, respectively. (Figure 6A).

Control tumors grew at a rate of 132 ± 15 mg/day, whereas TMPyP4 treatment slowed tumor growth to 50 ± 6 mg/day (Grand et al., 2002) (Figure 6B).

FUTURE PERSPECTIVES

The research into telomerase inhibition as a potential treatment strategy for cancer has shown promising results in preclinical and early clinical trials. However, several important questions and areas of exploration remain on the horizon.

While the telomerase inhibitors INVAC-1, Imetelstat, BIBR1532, and TmPyP4 have demonstrated significant potential in inhibiting telomerase activity and inducing senescence in cancer cells, it is crucial to continue investigating their efficacy in larger and more diverse patient populations. Understanding which inhibitors work best for specific types of cancers or genetic profiles could help tailor treatment strategies for individual patients. Additionally, it is important to monitor potential side effects and long-term consequences of these inhibitors. Ensuring that the benefits of inducing senescence in cancer cells outweigh any negative impacts on healthy tissues and the overall health of the patient is essential.

To fully realize the potential of telomerase inhibition in cancer therapy, further research is needed to differentiate telomerase activity across various cancer types. While many cancers upregulate telomerase, the degree of upregulation and the specific mechanisms involved likely differ between different types of cancer. Telomerase upregulation has been linked to stress and may differentiate depending on the aggressiveness of the cancer. Detailed profiling of telomerase expression, change in telomere length, and telomere maintenance mechanisms in diverse cancer cell lines and tumor samples would not only solidify the connection between cancer type and telomerase upregulation but would also guide which telomerase inhibitors may be most effective for specific cancer subtypes. Controlled preclinical studies testing different inhibitors across panels of cancer cell lines of varying origins could provide crucial data to match inhibitors to cancer types.

Further research should also closely investigate the phenotypic changes induced in cancer cells by telomerase inhibition to validate that senescence is being induced as expected. Assays measuring biomarkers of senescence, such as p16, p21, and senescence-associated β-galactosidase activity, in cancer cells and tumor samples after telomerase inhibitor treatment can confirm induced senescence. Long-term tracking of telomerase-inhibited cancer cells can determine if the senescence is maintained stably or can be evaded. Monitoring the secretome of telomerase inhibitor-treated cancer cells could uncover how senescent cells influence the surrounding tumor microenvironment.

The future of cancer therapy likely lies in combination treatments that target multiple pathways and mechanisms involved in cancer progression. Combining telomerase inhibitors with other traditional treatments, such as traditional cancer treatments like radiotherapy and chemotherapy, or newer non-telomerase strategies, can potentially enhance the effectiveness of cancer therapy. By inducing senescence with telomerase inhibitors, the growth of cancer is slowed, creating a larger window for other drugs, that specifically focus on killing cancer cells, to come into play. For example, combining telomerase inhibitors with chemotherapy could take advantage of the senescent state induced by telomerase inhibition, making cancer cells more susceptible to the cytotoxic effects of chemotherapy

CONCLUSION

Telomerase inhibition represents a promising therapeutic strategy to induce senescence and suppress malignant growth in cancer cells. The telomerase inhibitors INVAC-1, Imetelstat, BIBR1532, and TmPyP4 have shown preliminary success in preclinical and early clinical studies. However, further research is still needed to optimize treatment approaches. Clarifying differences in telomerase activity between cancer types and validating senescence induction will help guide development of tailored telomerase inhibitor treatments. Combination

regimens with chemotherapy, radiotherapy, or other agents may also enhance efficacy. With continued research to address these key questions, telomerase inhibition can become an important component of the anticancer treatments, providing targeted suppression of cancer cell immortality. Inducing senescence by telomerase inhibition, rather than complete cytotoxicity, represents a novel approach that has immense promise to advance cancer treatment, and ongoing research in this exciting field will be essential to fully optimize their therapeutic potential.

Conflict of interest: The authors declare that they have no conflict of interest.

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