Telomerase as a Cancer Target. Development of New Molecules

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**Abstract:** Telomeres are the terminal part of the chromosome containing a long repetitive and non-coding sequence that has as function protecting the chromosomes. In normal cells, telomeres lost part of such repetitive sequence in each mitosis, until telomeres reach a critical point, triggering at that time senescence and cell death. However, in most of tumor cells in each cell division a part of the telomere is lost, however the appearance of an enzyme called telomerase synthetize the segment that just has been lost, therefore conferring to tumor cells the immortality hallmark. Telomerase is significantly overexpressed in 80–95% of all malignant tumors, being present at low levels in few normal cells, mostly stem cells. Due to these characteristics, telomerase has become an attractive target for new and more effective anticancer agents. The capability of inhibiting telomerase in tumor cells should lead to telomere shortening, senescence and apoptosis. In this work, we analyze the different strategies for telomerase inhibition, either in development, preclinical or clinical stages taking into account their strong points and their caveats. We covered strategies such as nucleosides analogs, oligonucleotides, small molecule inhibitors, G-quadruplex stabilizers, immunotherapy, gene therapy, molecules that affect the telomere/telomerase associated proteins, agents from microbial sources, among others, providing a balanced evaluation of the status of the inhibitors of this powerful target together with an analysis of the challenges ahead.

**Keywords:** Telomere, Telomerase, Inhibitor, Cancer, Preclinical, Clinical trials.

1. INTRODUCTION

Since the discovery of telomerase [1], an enzyme able to elongates telomeres, and the following discovery that such enzyme was mostly active in tumors [2], telomerase become a prominent target and different ways of inhibitions towards it were attempted. [3]. Telomerase has different components, a catalytic subunit, hTERT, a RNA component, hTR and associated proteins. But telomeres also comprise special structures, proteins that are associated with them and a variety of conformations, all of them allowing or not the activity of telomerase It is necessary then, to decode the structure of the complex telomere/telomerase in order to understand how each possible inhibitor functions and gain perspective about the chances of new developments.

1.1. Telomere and Telomerase Structure

The telomere is a nucleoprotein complex found in the extremes of the chromosomes, where their structure is different from the rest of the chromatin [4] consisting in short and repetitive sequences of [dT]\textsubscript{TTAGGG} [5, 6]. The G-rich strand of telomeric DNA is always oriented 5'-3' towards the terminal portion of the chromosome and had a protruding extreme of ∼200 nucleotides [7] as consequence of the problem of terminal replication. The 3’ protruding G-rich strand can form complex structures of telomeres [8,9]. We also can observe different telomeric proteins that bind to mammal telomeres. In humans, telomeres are bound by a six-protein complex called shelterin, [10,11] comprised of TRF1 and TRF2 [12, 13, 14] which in turn recruits RAP1, TIN2, TPP1 [15], and POT1 which interacts with DNA.

Another important structural parameter governing telomere function is that they also contain RNA, called TERRAs [telomere repeat containing RNAs] [16], implicated in the negative regulation of telomerase [17].

There are also TRF1 and TRF2 associated factors. The main factor associated to TRF1 is tankyrase, a positive regulator of telomere length [18]. PINX1 is a TRF1-associated telomerase inhibitor, which associates with TRF1 [19]. PINX1 a negative regulator of telomere length is able to simultaneously interact with the telomerase catalytic subunit providing the enzyme a physical link with TRF1 [20].

There is also a physical link between the human shelterin complex and telomerase providing new insight into the mechanism of processive telomere synthesis. [21].

In most mammals, the maintenance of telomeric length is carried out mainly by telomerase. The human holoenzyme telomerase is a ribonucleoprotein composed by a catalytic subunit, hTERT and an RNA component [hTR] which acts as a template for the addition of a short repetitive sequence [dT]\textsubscript{TTAGGG} in the 3’ end of the telomeric DNA and species-specific accessory proteins. These accessory proteins regulate telomerase biogenesis, subcellular localization and
function in vivo. For instance, analysis of affinity-purified telomerase from HeLa cells has identified integral protein components of human telomerase: dyskerin, NHP2; NOP10, pontin/reptin, Gar1 and TCAB1 [22] Fig. (1). As described the complex telomere/telomerase is integrated by numerous molecules with different functions elegantly reviewed by Rubtsova et al [23].

Fig. (1). Schematic representation of telomerase and its associated proteins.

### 1.2. Telomerase Inhibiting Strategies

As we just observed the complexity of the telomere/telomerase complex, we can understand that there is a wide variety of strategies to inhibit telomerase. This complexity allowed the development of several inhibitors and paves the way to the development of new ones. Although the numerous strategies and molecules can be classified in different ways, we choose to do so, based in the general approach to inhibition and then analyzing each molecule belonging to that group, but also understanding that one molecule can belong to more than one category

#### 1.2.1. Nucleosides

3-Azido-2,3'-dideoxythymidine [azidothymidine [AZT] or zidovudine] was the first reported telomerase inhibitor Fig. (2A) The similarity between HIV retrotranscriptase and telomerase led to the discovery that AZT was preferentially integrated into the telomeric region of CHO DNA [24]. Similar results, but by quantitative methods were found by us also [25]. Later, different groups demonstrated that AZT inhibited telomerase and/or reduce telomerase length [26, 27]. Moreover, we demonstrated that telomere shortening by AZT was an irreversible process, [28]. Similar results were founded by other researchers. [29, 30]. Similarly, synergistic interactions between paclitaxel and AZT [31] and between AZT and 5-fluorouracil [32] were described. In 2001, we found that chronic in vitro AZT exposure on F3II mouse mammary carcinoma cells with 800 µM AZT for at least 30 passages completely inhibited telomerase activity on F3II mammary carcinoma cells, leading to senescence and apoptosis [33], also corroborated by other authors [34]. Azidothymidine is used to treat several virus-associated human cancers [35]. In non-viral tumors, AZT has been used in phase I and II clinical trials alone or in combination for different solid tumors showing some rate of regression [36]. More clinical trials using AZT are needed to understand the full potential of this agent in a clinical setting.

Other nucleosides have been studied as potential inhibitors of telomerase. It has been demonstrated that carbovir, induced senescence-like processes in cultures of immortal mouse fibroblasts [37]. Also, it was reported that both AzddGTP and C.OXT-GTP, the triphosphate derivatives of 3-azido-2,3'-dideoxyguanosine [AZddG] and carbocyclic oxetanocin G [C.OXT-g] showed potent telomerase-inhibitory activity and induce telomere shortening in human HL60 cells [38]. Later on, the same group found that AZddAA caused telomere shortening in the same model [39]. Tendian et al studied the interaction of five dioxynucleosine nucleotide analogs, 6-thio-2-deoxyguanosine, 5-triphosphate [T-dGTP], 5-triphosphate of carbovir [CBV-TP], ddGTP, D-carbocyclic 2-deoxyguanosine 5-triphosphate [D-CdG-TP] and L-carbocyclic 2-deoxyguanosine 5-triphosphate [L-CdG-TP]. T-dGTP is the active metabolite of both 6-mercaptopurine and 6-thioguanine, which are two drugs used in the treatment of acute leukemia. CBV-TP is the active metabolite of Abacavir, an agent approved for the treatment of AIDS and D-CdG-TP is the active metabolite of D-CdG, an agent with activity against herpes simplex virus, cytomegalovirus, and hepatitis-B virus, founding that all of them inhibited telomerase activity by 50% [40]. Numerous acyclic nucleoside phosphonates [ANPs] possess excellent antiviral activities against a broad spectrum of DNA viruses and retroviruses as well as significant antiproliferative potency. In cells, ANPs are phosphorylated to their diphosphates active antimetabolites, which inhibit viral and/or cellular replicates and terminate nascent DNA chain. The group of Hajec analyzed the antitelomerase activity of 15 of these diphosphates of ANPs and found that the most effective compound studied was the guanine derivative PMEGpp [41]. It has been patented that acyclic nucleoside analogs such us acyclovir, ganciclovir, penciclovir and the corresponding pro-drugs, i.e., valacyclovir, valganciclovir and famciclovir, respectively have been identified as inhibitors or antagonists of telomerase [42]. The telomerase inhibitory effects of purine nucleosides bearing a 3’-down azido group were also investigated. It was found that AZddGTP is a selective inhibitor of telomerase, producing a reproducible telomere shortening [43]. In 2001, a potent telomerase inhibiting nucleoside was developed: 6-thio-7-deaza-2’-deoxyguanosine 5’-triphosphate [TDG-TP] with a low and high specificity [44]. Previously, the same group found human telomerase inhibition by 7-deaza-2’-deoxypurine nucleoside triphosphates using a cell-free biochemical telomerase assay [45].

#### 1.2.2. Oligonucleotides

Feng et al reported that antisense oligonucleotides complementary to sequences within or near the human telomeric template RNA resulted in suppression of telomerase activity while antisense oligonucleotides against targets that were more distant from the telomeric template failed to inhibit the action of the ribonucleoprotein [46]. The advances in antisense technology have led to improvements in the introduc-
tion of the molecules into cells, stability, lengthening of half-life, and specificity of target binding. Modifications of traditional antisense oligonucleotides used in telomerase inhibition include 2′-S′-oligoadenylate, 2′-O-methyl-RNA, phosphorothioate-modified oligodeoxynucleotides [PS-ODN], peptide nucleic acids [PNA] (Fig. 2B), and locked nucleic acids [LNA] [47]. PU27 is a sequence specific DNA oligonucleotide currently in preclinical stage for a wide variety of tumor type including leukemia, prostate cancer, renal cancer and breast cancer. PU27 has shown growth inhibitory effect because of its ability to bind and inhibit the enzymatic activity of α-enolase. It also demonstrated altered oncogene expression and inhibition of telomerase activity thus selectively inhibit cancer cell metabolism and cell growth. [48]

### 1.2.3. Small Molecule Inhibitors

Among many small molecules tried with different success aiming to inhibit telomerase activity BIBR1532 [2-[E]-3-naphthalene-2-yl-but-2-enoylamino]-benzoic acid is the best known Fig. (2C). It is a non-competitive inhibitor of TERT and hTR that in vitro reduces telomere length, inhibits cell proliferation, producing finally cell senescence [49]. Although good results have been observed in preclinical studies on breast, prostate and fibrosarcoma cancer cell lines no further progress or entrance in clinical trials has been shown. In the last years, BIBR1532 have been used as a tool to inhibit telomerase and demonstrating in that way that decreases alpha-fetoprotein expression [50] and was also demonstrated that glucose restriction increase the activity of this inhibitor [51].

### 1.2.4. Stabilization of G Quadruplexes

As explained in the telomere structure section, one indirect path to inhibit telomerase activity could be the stabilization of the G quadruplexes preventing hTR of recognizing the unfolded single-stranded telomere overhang. Most of these molecules contain a polycyclic heteroaromatic structure. In this group stands telomestatin (Fig. 2D) [52], RHP54 and BRACO19 [53]. Although effective they were poorly soluble or inefficient to cross biological barriers [54], therefore reducing their clinical significance. An extensive research has been carried out in the modification of telomestatin to increase its potency. More recently a series of macrocyclic molecules [telomestatin analogues] have been developed, with improved features over telomestatin parental structure [55]. Macrocyclic hexaaxazolL2H2-6M(2)OTD is one of the derivatives of telomestatin that interact with G-quadruplex by p-stacking and electrostatic interactions [56]. Telomestatin is currently under clinical trials [57].

Daunomycin is basically an anthracycin isolated from Streptomyces peucetius and it is well known for its DNA intercalation and G-quadruplex stabilization.

Distamycin A was isolated from Streptomyces distallicus. Distamycin-A stacks on the terminal G-quadrats and interacts with the flanking bases [58]. Distamycin inhibits protein interactions with G-quadruplex DNA. The first report of telomerase inhibitory activity of distamycin derivatives was by Zaffaroni et al. They tested the antagonistic activity of MEN 10,716, a derivative of distamycin in JR8 melanoma cell extracts [59]. Chemical modification of this compound has been carried out extensively to increase the potency of inhibition. A study shows that introduction of more number of pyrrole groups allows binding with mixed groove/G-quartet in a stacking mode [60]. Some other compounds more water-soluble have been developed such as quarflavin, quarfloxin:CX3543 [61] and RHP54 [62]. Quarfloxin has reached phase II clinical trials, although results are not available.

Ascididemin and Meridine are two marine compounds with pyridoacridine skeletons known to stabilize G-quadruplexes and inhibit telomerase in vitro. [63]

The interaction of berberine and 9 different berberine derivatives with human telomeric DNA indicated that these compounds could induce and stabilize the formation of anti-parallel G-quadruplex of telomeric DNA. Compared with berberine, the derivatives exhibit stronger binding affinity with G-quadruplex and higher inhibitory activity for telomerase [64].

A cryptolepine derivative containing indole and quinoline structures, SYUIQ-5 has been reported to induce and stabilize G-quadruplex, inhibiting c-myc promoter and telomerase activity [65].

In addition, cationic porphyrins are being studied as possible telomerase inhibitors due to their ability to bind and stabilize G-quadruplexes. The best studied molecule of this group is the cationic porphyrin TMPyP4. [66]

### 1.2.5. Immunotherapy

Many immunotherapeutic approaches are under development, either at preclinical or clinical levels [67]. Basically, antitelomerase immunotherapy sensitizes immune cells to tumor cells expressing hTERT peptides as surface antigens via the human leukocyte antigen [HLA] class I pathway. Some 26 different hTERT peptides have been utilized to generate an antitelomerase immune response, many of them showing good preclinical and clinical results [68]. In clinical assays, different peptides produce a good immunological response with low toxicity and some promising results were published. For instance, Vx001 and IS40 produced in responsive patients, a longer survival time than in those that were non-responsive [69]. However, biomarkers or indicators to point out which patients are going to be responsive remain to be developed.

Many clinical trials are currently ongoing with immunological peptides either alone or in combination. In phase I and phase II clinical trials: GRNVAC1, TERT and Survivin peptide loaded dendritic cells and dendritic cells transfected with TERT, surviving and p53 mRNA [70]. A promising vaccine is GV1001 [Tertomotide] Fig. (2E). This peptide vaccine consists of 15 amino acid epitope of hTERT. It generates telomerase-specific T-helper cells, activates antigen-presenting cells and cytotoxic T cells, generating a good immune response and has successfully already completed several phase I and II clinical trials either alone or in combination with the alkyllating agent Temozolomide. Currently it has reached phase III clinical trials [Telovac] for non-small cell lung cancer and one NDA were filed for pancreatic cancer. Unfortunately, there was no significant difference in overall survival between the groups that received the vaccine and the control group receiving chemotherapy [71]. Another vaccine currently going through phase I clinical trial for hormone refractory prostate cancer is TeloB-VAX. It is
composed of the patients' own circulating B-lymphocytes harboring a unique patented engineered plasmid DNA belonging to Adamis Pharmaceutical Corporation [72]. Another vaccine being studied by VAXON Biotech is Vx-001, composed of two separate peptides: the native cryptic peptide ARG-Vx001 [TERT572] and its optimized variant TYR-Vx001 [TERT572Y]. The study included in vivo experiments in mice, in vitro experiments on human lymphocytes, and a phase I/II clinical trial. Vx-001 vaccination of humanized mice protects them against tumor growth in vivo [73]. Furthermore, Vx-001 induces anti-tumor immune responses by human lymphocytes in vitro. Vx-001 has completed a phase I/II trial with 33 patients with NSCLC [74] demonstrating its safeness and tolerance and a strongly immunogenic response in 70% of patients.

Vx-001 entered a randomized phase IIb clinical trial in HLA-A*0201 positive patients with TERT expressing NSCLC [stage IV and distant recurrent stage I-III] who controlled disease after first line chemotherapy. Results are expected at the end of 2016. [75]

Peptide540-548, peptide611-626, peptide672-686 and peptide766-780, which are derived from human telomerase, constitute the immunogenic component of the GX301 cancer vaccine which is being tested in phase II clinical trial for prostate cancer [76]

1.2.6. Gene Therapy

Labs and companies have been working for a very long time to bring gene therapy to the clinic, yet very few patients have received any effective gene-therapy treatment. However, gene therapy is also a strategy used in the quest for targeting telomerase. Probably the best-known molecule is the antisense oligonucleotide Imetelstat or GRN163L [Geron Corporation] (Fig. 2F), a lipid-conjugated 13-mer oligonucleotide sequence that is complementary to hTERT that showed good in vivo and vitro results [77]. The molecule demonstrates high resistance to cellular nucleases, which confers stability in plasma and tissues. Such results led to a number of phases I and II clinical trials either with Imetelstat alone or in combination for multiple oncology and hematologic myeloid malignancies indications. [78]. Interestingly, it has been demonstrated that Imetelstat could cross the blood-brain barrier. Trials showed good results with the exception of a phase II clinical trial using Imetelstat plus paclitaxel in advanced breast cancer. This trial was stopped in September 2012 due to the results of an interim analysis showing a worse survival time in patients receiving Imetelstat. On November 13, 2014, Geron entered into an exclusive collaboration and license agreement with Janssen Biotech. Since then development of Imetelstat will proceed under a mutually agreed clinical development plan, which includes two phase II studies to be pursued initially, one in myelodysplasia, and one in myelodysplastic syndrome expected to be initiated during 2015.

Other approach involves “suicide gene therapy”, viral vectors that are genetically modified to encode a prodrug activating enzyme [i.e. cytosine deaminase or carboxypeptidase G2] which in turn will replicate only in TERT-overexpressing cells, activating the effect of cytotoxic prodrugs like 5-flucytosine or ZD2767P [79].

Furthermore, other strategy has already reached the clinical phases. Telomelysin is an attenuated adenovirus-5 vector whereas TERT promoter element drives expression of E1A and B genes linked with and internal ribosome entry site. In this way, it induces virus-mediated lysis of cancer cells after viral propagation in the TERT-overexpressing cells. The drug is in phase I/II development stage for hepatocellular carcinoma and esophageal cancer [80]

1.2.7. Targeting Telomere and Telomerase-Associated Proteins

One interesting strategy is targeting the associated proteins rather than the main molecules. One interesting case is targeting tankyrases with PARP inhibitors. Also is interesting the approach on inhibition of the chaperone HSP90. Studies show that HSP90-p23 co-chaperone complex is required for maturation and activation of telomerase [78]. With that idea on mind, Geldanamycin [GA] (Fig. 2G) was used. However since HSP90-P23 has low solubility and high hepatotoxicity, the analogs 17-AAG [Tanespimycin] and 17-DAG were developed and are being tested in clinical trials at the moment [81]. Small interfering small RNAs having as a target TRF1, TRF2 and TIN2 have been studied. Some molecules against POT1 also have been analyzed [82].

1.2.8. Telomerase Inhibitors from Microbial Sources

Telomerase inhibitors were isolated from various fungal, bacterial and actinomycetes sources (for review see [83]. Some of them are chemically modified in order to increase their potency and some were synthesized as such in the laboratory [84].

Actinomycetes spp. is the most widely explored microorganism for telomerase inhibitors since possesses benzofuran and benzo dipyr ans rings, which have been found to be potential inhibitors of telomerase. Rubromycins (Fig. 2H) isolated from Streptomyces collinus are extensively studied for their ability to induce apoptosis in cancer cells; however, their telomerase inhibitory activity was explored recently. They are primarily aromatic naphthoquinone and isocoumarin ring systems that competitively interact with the hTERT and/or hTERT subunits of telomerase enzyme. Studies proved that the spirotetal moiety of rubromycin is the key pharmacophore for telomerase inhibitory activity [85]. Griseorhodins are another group of compounds that possess quinine moieties and inhibit telomerase in vitro. Fungi also have become sources of telomerase inhibitors among them Thelavin A and B, which are isolated from Thielavia terricola [86] and di azaphilonic acid, isolated from Talaromyces flavus [87].

1.3. Other Molecules

Oleic acid is a fatty acid that occurs naturally in various animal and vegetable fats and oils Fig. (21). In chemical terms, oleic acid is classified as a monounsaturated omega-9 fatty acid and was found to be inhibitor of human telomerase [88]. Helenalin, a natural sesquiterpene lactone, is a potent and selective inhibitor for human telomerase [89]. Five new alkaloids, dictyodendrins A-E were isolated from the marine sponge Dictyodendrilla verongiformis as telomerase inhibitors. Dictyodendrins are pyrrolecarbazole derivatives containing three or four p-hydroxybenzene
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**Fig. (2).** a) Structure of the most important inhibitory molecules belonging to each group. A) Nucleosides. B) Oligonucleotides. C) Small molecule inhibitors. D) Stabilizers of G quadruplex. E) Immunotherapeutic molecules. F) Gene therapy constructs. G) Molecules that target telomere and telomerase associated proteins. H) Inhibitors from microbial sources. I) Other inhibitors.

b). Mechanism of action of the most important inhibitory molecules belonging to each group. A) AZT: Integrates into the telomeric DNA. B) PNA: This modified antisense oligonucleotide is complementary to sequences within or near the human telomeric template. C) BIBR1532: Competing inhibitor of TERT and hTR. D) Telomestatin: stabilizes G quadruplexes preventing hTR of recognizing the unfolded single stranded telomere overhang. E) Tertomide Generates telomerase specific T helper cells, activates antigen presenting cells and cytotoxic T cells, generating a good immune response. F) Imetelstat: A lipid-conjugated 13-mer oligonucleotide sequence that is complementary to hTR. G) Gedanamycin: targets the HSP90.P23 co.chaperone complex, required for maturation and activation of telomerase. H) Rubromycin: competitive interact with the hTERT and/or hTR subunits of telomerase enzyme. I) Oleic acid. The three-dimensional structure of the active site of telomerase (i.e., the binding site of the primer and dNTP substrate) might have a "pocket" that could "join" these compounds.
Clearly, founding mors. Patients will limited solubility, difficulties to pass through biological barriers. Many times are not successful due to poor pharmacokinetics. Other aspects to consider is that clinical results have demonstrated the complex relationship between telomere/telomerase at the different levels of regulation of telomerase activity and with their relationship with associated proteins. Interestingly, those associated proteins could be an excellent target in our fight against cancer.

We should take also into account some possible shortcomings. For instance, in the case of AZT, as the shortening of telomeres is a slow process, the dynamics of the disease could put at risk the life of the patient before the action of the drug is effective. Therefore, concerns must be expressed when attempting to treat advanced tumors with AZT [91]. However, AZT treatment could constitute a good adjuvant therapy in cases where conventional treatments reduce the bulk of the tumor giving time for AZT to act in the remnant surviving tumor cells.

Firstly, the number of AZT-treated passages could be insufficient for a senescence program to be triggered, and secondly telomeres shortening to a critical length could induce a compensatory mechanism of preservation so preventing further losses, known as alternative lengthening of telomeres or ALT [92]. Thirdly, an AZT-resistant phenotype could have been developed because of selection following treatment.

However, one of the advantages of telomerase targeting therapies is that rapidly proliferating cancer cells have shorter telomeres [5kb] compared to normal somatic cells and stem cells [10-20 kb] that have not yet reached critical lengths [78]. Some authors consider that in some cases, functional p53 may be required to induce the response to telomerase inhibitors in cells with critically shortened telomeres, [93]. Other aspect to consider is that clinical results many times are not successful due to poor pharmacokinetics: limited solubility, difficulties to pass through biological barriers, etc [94] which leads to the search of other solubilizers or carriers.

In addition, we should consider that some of these inhibitors start their tumor deleterious effect after a variable amount of time. After telomerase inhibition, the telomere will start to become shorter, but tumor senescence and death will only start when reaching a critical length. Most often patients who join phase I clinical trials have advanced metastatic cancer leaving this kind of inhibitor without the chance of demonstrating its effectiveness in less advanced tumors. Some authors have mentioned the importance of founding a “window of opportunity” for these inhibitors. Clearly, that will be the case of smaller tumors that requires a bigger number of mitosis, allowing the inhibitors to exert its action. Some other authors are suggesting changes in clinical trials policies to allow this kind of molecules to have the chance to demonstrate its effectiveness without compromising the safety of the patient or the seriousness of the trial. Although clinical trials are, the basis where daily clinical practice should be based on, such evidence is scarce at the end-of life of cancer patients. Research in this patient’s population is hampered by the lack of clear definition of the study population, the study design, the definition of meaningful endpoints and ethical considerations [95]. In the meantime, some authors have advanced the path of therapy combination with established oncological treatments. This approach is promising since it is tested as maintenance/consolidation treatments to prolong remission in patients with advanced cancers. Some examples are combinations with radiotherapy [96], trastuzumab [97], paclitaxel [98], doxorubicin [99], docetaxel [100] and etoposide [101]. Since many telomerase targeting molecules have a long lag time to produce critically shorter telomeres a combination therapy of telomerase inhibitors and standard of care may be the best approach to target effectively cancer cells.

With their advantages and pitfalls, telomerase inhibition remains as one of the hottest targets in the quest for new antitumor drugs. More research in the subject will guarantee the answers to our questions, and eventually the finding of a blockbuster molecule.

CONFLICT OF INTEREST

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