1. Introduction

Telomeres are non-coding DNA sequences at the ends of chromosomes. Traditional DNA polymerases are unable to replicate the ends of telomeres. This incomplete replication leads to the loss of telomeric DNA with each round of cell division. Therefore, telomeres act as a "mitotic clock": progressive telomere shortening limits cellular lifespan (fig. 1).

Telomerase is a ribonucleoprotein (hTR + hTERT) that counteracts progressive telomere shortening during cellular replication. Telomerase is not active in most human somatic cells, with the exception of proliferative stem cells.

Conversely, telomerase is reactivated in more than 85% of human cancers. The upregulation of telomerase maintains telomere length and provides cancer cells with cellular immortality (a hallmark of cancer) (fig. 1).

2. Telomerase: target for cancer therapy

Key advantages of telomerase as a target for cancer therapy:
1. Critical for cancer cell survival (fig. 2).
2. Widely expressed in >85% of human cancers.
3. Not expressed in most human somatic cells (specificity).
4. Low expression in stem cells of highly proliferative tissues (e.g., tretonycty).  
5. Cancer cells possess shorter telomeres than normal cells (wide therapeutic window).
6. Ability to target cancer stem cells (fig. 3).

3. Oligonucleotides as telomerase inhibitors: GRN163L (Imetelstat®)

Oligonucleotides used for cancer therapy are NA or PT phosphoramidates (DNA analogues).

Advantages of GRN163L for cancer therapy:
- NA or PT phosphoramidates (PTP) (fig. 4).
- High thermodynamic stability, enhanced cellular uptake, and lower half-life.
- High target sequence specificity.
- Consistent efficacy across tumor types.
- Lack of off-target reduction: reduces potential side effects of binding to unique RNAs.

- Lipid group attached to T (lipid soluble, cell permeable, enhanced cellular uptake (fig. 4)).
- Good bioavailability and efficient biodistribution to all major organs in vivo.
- Polyanionic compound not likely to be a substrate for common mechanisms of ribonucleoside resistance (important for targeting cancer stem cells).

4. GRN163L preclinical and clinical studies

4.1 Preclinical studies in vitro and in vivo.

A) Preclinical in vitro studies with human cancer cells

B) Preclinical in vivo studies using mouse models

4.2 Clinical studies

Table 1. GRN163L phase I and II clinical trials for various cancers.

Outcomes:
- Good safety profile and excellent pharmacokinetics and biodistribution properties.
- Maximum tolerated dose (MTD) = 2.5 mg/kg.
- Toxicities: Increased coagulation time (APTT), thrombocytopenia, and neutropenia at doses higher than MTD.

5. Conclusion and future prospects

Conclusion: Preclinical studies and clinical trials demonstrate that GRN163L is an effective and promising drug for human cancer therapy. Anyway, the following issues need to be further investigated:

What are the main safety concerns regarding telomerase inhibition therapies?

As normal stem cells transiently express telomerase, one major concern associated with the use of telomerase inhibitors is the potential decline of regenerative capacity in stem cells (not seen to date).

Will tumor cells evolve escape mechanisms to telomerase based therapies?

Pre-existing or newly refractory cancer cells are likely to be found regardless of the therapeutic approach. Therefore, a significant consideration is the potential for selecting for the alternative lengthening of telomeres (ALT) pathway.

Which are the drawbacks when using telomerase inhibitors such as GRN163L?

The phenotypic lag: treatment with telomerase inhibitors may require many rounds of cell division until telomeres become critically short and apoptosis is induced.

Which are the most suitable applications for telomerase inhibitor drugs like GRN163L?

Using GRN163L in combination with conventional chemotherapy and radiotherapy treatment should lead to a more durable response and decreased disease recurrence (fig. 12).