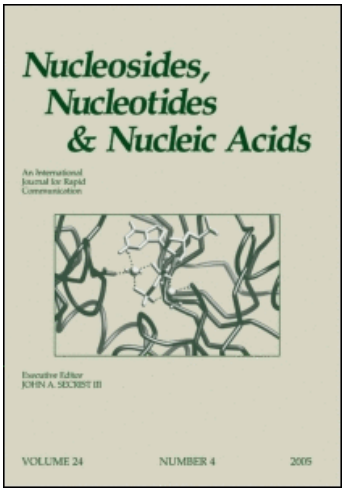

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OLIGONUCLEOTIDE CONJUGATE GRN163L TARGETING HUMAN TELOMERASE AS POTENTIAL ANTICANCER AND ANTIMETASTATIC AGENT

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□ *Telomerase is one of the key enzymes responsible for the proliferative immortality of the majority of cancer cells. We recently introduced a new telomerase inhibitor, a 13-mer oligonucleotide N3′→P5′-thio-phosphoramidate lipid conjugate, designated as GRN163L. This compound inhibits telomerase activity in various tumor cell lines with IC_{50} values of 3-300 nM without any cellular uptake enhancers. GRN163L demonstrated potent and sequence specific anti-cancer activity in vivo in multiple animal models. This compound was able to significantly affect not only the growth of primary tumors, but also the spread and proliferation of metastases. GRN163L is currently in Phase I and Phase I/II clinical studies in patients with solid tumors and CLL, respectively.*

Keywords Telomerase; phosphoramidates; GRN163L; anticancer; morphology; adhesion

RESULTS AND DISCUSSION

We previously determined that an oligonucleotide N3′→P5′ *thio*-phosphoramidate telomerase template antagonist, GRN163L, inhibited telomerase and the tumorigenic potential of A549-luciferase expressing human lung cancer cells (A549-luc) in vitro and in vivo[1]. Further studies revealed that A549-luc cells, as well as breast cancer derived MDA-MB-231 cells, were also significantly morphologically altered by exposure to GRN163L.

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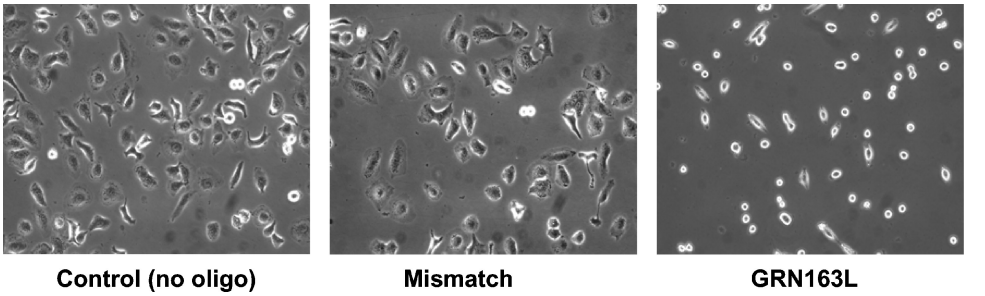

FIGURE 1 A549-Luc cells after 24-hour exposure to the oligonucleotides: 5′-Palm-TAGGGTTAGACAA (GRN163L) or 5′-Palm-TAGGTGTAAGCAA (Mismatch). The compounds (1 μM) were added to the media immediately after the cell plating.

Thus, A549-luc cells treated at the time of cell plating and attachment with a single dose of GRN163L (1 μM) rapidly changed their morphology from a stretched epitheloid or spindle like shape to much smaller rounded spheres. These profound morphological changes were accompanied by an inhibition of the cells' adhesion properties, as measured by est. 50% reduction in cellular attachment and a 3-fold decrease in the cell spread area. Telomerase activity of A549 cells was also inhibited (>90%) by 1 μM of GRN163L, as measured by an in vitro TRAP assay after 72 hours. At the same time, mismatch (MM) control oligonucleotide (1 μM) treated cells maintained a typical epitheloid appearance, surface adhesion/attachment and spreading properties, and their telomerase activity was not affected (Figure 1).

Further experiments demonstrated that the observed morphological changes were independent of telomerase or hTERT expression levels, and were unrelated to the telomere length of the cancer cells. Moreover, these changes were completely reversible upon removal of GRN163L from the cells. Importantly, morphology and adhesion properties of normal noncancerous BJ fibroblasts or bladder epithelial cells were not affected by GRN163L.

Similarly, GRN163L affected the clonogenic, migration in soft agar and surface anchorage properties of MDA-MB-231 breast cancer cell line. Colony formation and matrigel infiltration assays performed with various breast cancer cells briefly exposed to GRN163L revealed a significant reduction in their ability to form colonies in soft agar, whereas the MM-control oligonucleotide had no effect.[2,3]

These anti-adhesion effects of GRN163L on cancer cells were also observed in vivo in different mouse models. Thus, in vivo administration of GRN163L resulted in a marked reduction in the ability of both A549-luc lung cancer and MDA-MB-231 breast cancer cells to either form primary tumors or to metastasize in mice lungs post primary tumor resection.[3]

Further studies of the origin and detailed mechanism of anti-cancer cell adhesion activity of GRN163L is currently in progress.

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