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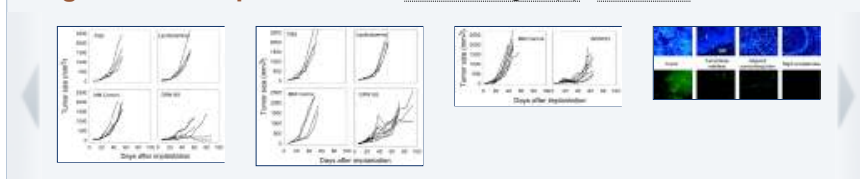
Antitumor effects of specific telomerase inhibitor GRN163 in human glioblastoma xenografts.

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Abstract

Telomerase is a ribonucleoprotein complex that elongates telomeric DNA and appears to play an important role in cellular immortalization of cancers. Because telomerase is expressed in the vast majority of malignant gliomas but not in normal brain tissues, it is a logical target for gliomaspecific therapy. The telomerase inhibitor GRN163, a 13-mer oligonucleotide N3'-->P5' thio-phosphoramidate (Geron Corporation, Menlo Park, Calif.), is complementary to the template region of the human telomerase RNA subunit hTR. When athymic mice bearing U-251 MG human brain tumor xenografts in their flanks were treated intratumorally with GRN163, a significant growth delay in tumor size was observed ($P < 0.01$ in all groups) as compared to the tumor size in mice receiving a mismatched oligonucleotide or the carrier alone. We also investigated biodistribution of the drug in vivo in an intracerebral rat brain-tumor model. Fluorescein-labeled GRN163 was loaded into an osmotic minipump and infused directly into U-251 MG brain tumors over 7 days. Examination of the brains revealed that GRN163 was present in tumor cells at all time points studied. When GRN163 was infused into intracerebral U-251 MG tumors shortly after their implantation, it prevented their establishment and growth. Lastly, when rats with larger intracerebral tumors were treated with the inhibitor, GRN163 increased animal survival times. Our results demonstrate that the antitelomerase agent GRN163 inhibits growth of glioblastoma in vivo, exhibits favorable intracerebral tumor uptake properties, and prevents the growth of intracerebral tumors. These findings support further development of this compound as a potential anticancer agent.

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