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Basic and Translational Investigations

New therapeutic approach for brain tumors: Intranasal delivery of telomerase inhibitor GRN163

Rintaro Hashizume ^{1*}, Tomoko Ozawa ¹,
Sergei M. Gryaznov ², Andrew W. Bollen ³,
Kathleen R. Lamborn ¹, William H. Frey II ⁴,
Dennis F. Deen ¹

¹ Brain Tumor Research Center of the Department of Neurological Surgery, University of California San Francisco, San Francisco, CA, USA

² Geron Corporation, Menlo Park, CA, USA

³ Department of Pathology, University of California San Francisco, San Francisco, CA, USA

⁴ Alzheimer's Research Center, HealthPartners Research Foundation at Regions Hospital, St. Paul, MN, USA

* To whom correspondence should be addressed. E-mail: rintaro.hashizume@ucsf.edu.

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▶ Abstract

The blood-brain barrier is a substantial obstacle for delivering anticancer agents to brain tumors, and new strategies for bypassing it are greatly needed for brain-tumor therapy. Intranasal delivery provides a practical, noninvasive method for delivering therapeutic agents to the brain and could provide an alternative to intravenous injection and convection-enhanced delivery. We treated rats bearing intracerebral human tumor xenografts intranasally with GRN163, an oligonucleotide N3'→P5'thio-phosphoramidate telomerase inhibitor. 3'-Fluorescein isothiocyanate (FITC)-labeled GRN163 was administered intranasally every 2 min as 6 µl drops into alternating sides of the nasal cavity over 22 min. FITC-labeled GRN163 was present in tumor cells at all time points studied, and accumulation of GRN163 peaked at 4 h after delivery. Moreover, GRN163 delivered

intranasally, daily for 12 days, significantly prolonged the median survival from 35 days in the control group to 75.5 days in the GRN163-treated group. Thus, intranasal delivery of GRN163 readily bypassed the blood-brain barrier, exhibited favorable tumor uptake, and inhibited tumor growth, leading to a prolonged lifespan for treated rats compared to controls. This delivery approach appears to kill tumor cells selectively, and no toxic effects were noted in normal brain tissue. These data support further development of intranasal delivery of tumor-specific therapeutic agents for brain tumor patients.

Key Words: brain tumors, GRN163, intranasal delivery, telomerase inhibitor, xenografts

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