Normal Brain Cells Contribute to the Bystander Effect in Suicide Gene Therapy of Malignant Glioma

Hrvoje Miletic$^{1,2}$, Yvonne Heidemarie Fischer$^3$, Tsanan Giroglou$^3$, Maria Adele Rueger$^4$, Alexandra Winkeler$^4$, Huongfeng Li$^4$, Uwe Himmelreich$^5$, Werner Stenzel$^6$, Andreas H. Jacobs$^4$ and Dorothee von Laer$^3$

Authors' Affiliations: $^1$ Department of Biomedicine, University of Bergen; $^2$ Department of Pathology, Haukeland University Hospital, Bergen, Norway; $^3$ Georg-Speyer-Haus, Frankfurt am Main, Germany; and $^4$ Labor für Gentherapie und Molekulares Imaging, Max-Planck-Institut für Neurologische Forschung, Universität zu Köln; $^5$ In-vivo NMR Laboratory, Max-Planck-Institute for Neurological Research with Klaus-Joachim-Zülch-Laboratories of the Max Planck Society and the Faculty of Medicine of the University of Cologne; and $^6$ Abteilung für Neuropathologie, Universität zu Köln, Köln, Germany

Requests for reprints: Hrvoje Miletic, Department of Biomedicine, University of Bergen, Jonas Liesvei 91, 5009 Bergen, Norway. Phone: 47-55-58-6337; Fax: 47-55-58-6360; E-mail: Hrvoje.Miletic@biomed.uib.no

Purpose: Lentiviral vectors pseudotyped with glycoproteins of the lymphocytic choriomeningitis virus (LCMV-GP) are promising candidates for gene therapy of malignant glioma, as they specifically and efficiently transduce glioma cells in vitro and in vivo. Here, we evaluated the therapeutic efficacy of LCMV-GP and vesicular stomatitis virus glycoprotein (VSV-G) pseudotyped vectors.

Experimental Design: Therapeutic efficacy was tested for unmodified (9L) and DsRed-modified (9LDsRed) gliomas using the suicide gene thymidine kinase of the herpes simplex virus type 1 (HSV-1-tk). Positron emission tomography (PET) and magnetic resonance imaging (MRI) were done to analyze transduction of tumors and monitor therapeutic outcome.

Results: LCMV-GP pseudotypes mediated a successful eradication of 9LDsRed tumors with 100% of long-term survivors. Before initiation of ganciclovir treatment, a strong HSV-1-tk expression within the tumor was detected by noninvasive PET using the tracer 9-[18F]fluoro-3-(hydroxymethyl)butyl]guanine. Therapeutic outcome was successfully monitored by magnetic resonance imaging and PET imaging and correlated with the histopathologic data. In the 9L model, LCMV-GP and VSV-G pseudotyped lentiviral vectors displayed similar therapeutic efficacy. Further studies revealed that normal brain cells transduced with VSV-G pseudotypes were not eliminated by ganciclovir treatment and contributed significantly to the bystander killing of tumor cells.

Conclusions: Suicide gene transfer using pseudotyped lentiviral vectors was very effective in the treatment of rat glioma and therefore is an attractive therapeutic strategy also in human glioblastoma especially in conjunction with an imaging-guided approach. In addition, high selectivity of gene transfer to tumor cells may not always be desirable for therapeutic genes that exert a clear bystander effect.

http://clincancerres.aacrjournals.org/cgi/content/abstract/13/22/6761
http://www.brainlife.org/