

## Original Article

Cancer Gene Therapy advance online publication 18 April 2008; doi: 10.1038/cgt.2008.23

### Primary neural stem/progenitor cells expressing endostatin or cytochrome P450 for gene therapy of glioblastoma

A Lorico<sup>1</sup>, J Mercapide<sup>1</sup>, V Solodushko<sup>1</sup>, M Alexeyev<sup>1</sup>, O Fodstad<sup>1</sup> and G Rappa<sup>1</sup>

<sup>1</sup>Mitchell Cancer Institute, University of South Alabama, Mobile, AL, USA

Correspondence: Dr A Lorico, Mitchell Cancer Institute, University of South Alabama, 307 N University Blvd, Mobile, AL 36688, USA. E-mail: [alorico@usouthal.edu](mailto:alorico@usouthal.edu)

Received 16 July 2007; Revised 22 January 2008; Accepted 10 February 2008; Published online 18 April 2008.

## Abstract

Despite recent technical improvements in surgical excision techniques and adjuvant radio- and chemotherapy, the clinical outcome of patients with grade IV astrocytoma (glioblastoma) remains very poor, with a median survival of less than 12 months. A promising approach to therapy employs gene-engineered neural stem/progenitor cells (NSCs) as a cellular therapeutic delivery system, to track glioblastoma cells and deliver anticancer molecules. However, most results on their tumor tropism have been derived by immortalized NSCs. We now report that primary murine gene-engineered NSCs displayed *in vivo* tropism for glioblastoma cells. Ten days after injection into the brain, many NSCs continued to express the transgene and the NSC marker, nestin. NSCs transduced with a retroviral vector co-expressing a secretable form of human endostatin and eGFP (NSC/endo-eGFP) released potentially antiangiogenic concentrations of endostatin into the culture medium. Conditioned medium of NSC/endo-eGFP cells inhibited the growth of mouse pulmonary microvascular endothelial cells (PMVECs). A good correlation between endostatin levels and PMVEC growth inhibition was observed. In NSCs co-expressing cytochrome P450 2B6 (CYP2B6) and eGFP (NSC/CYP2B6-eGFP), the forced expression of CYP2B6 resulted in intracellular activation of CPA and subsequent cell death. In the presence of NSC/CYP2B6-eGFP, we observed CPA cytotoxicity to DsRed-expressing U87Mg glioma cells. *In vivo* treatment of intracranial GL-261 glioblastoma with NSC/endo-eGFP caused a 65% reduction in tumor size, compared to untreated control mice or mice treated with NSC/eGFP cells. Our data suggest that primary NSCs transduced with retroviral vectors expressing endostatin and/or CYP2B6 have a potential role in glioblastoma therapy.

**Keywords:** glioblastoma, neural stem cells, endostatin, cytochrome P450