



■ Abstract

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Mathieu, V.

De Nève, N.

Le Mercier, M.

Lefranc, F.

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## Combining Bevacizumab with Temozolomide Increases the Antitumor Efficacy of Temozolomide in a Human Glioblastoma Orthotopic Xenograft Model<sup>1</sup>

Véronique Mathieu,<sup>\*2</sup> Nancy De Nève,<sup>†</sup> Marie Le Mercier,<sup>\*2</sup> Janique Dewelle,<sup>†</sup> Jean-François Gaussin,<sup>†</sup> Mischaël Dehoux,<sup>†</sup> Robert Kiss,<sup>\*2</sup> and Florence Lefranc<sup>\*‡2</sup>

<sup>\*</sup>Laboratory of Toxicology, Institute of Pharmacy, Free University of Brussels [ULB], Brussels, Belgium

<sup>†</sup>Unibioscreen SA, Brussels, Belgium

<sup>‡</sup>Department of Neurosurgery, Erasme University Hospital, Brussels, Belgium

Address all correspondence to: Robert Kiss, PhD, Laboratory of Toxicology, Institute of Pharmacy, Free University of Brussels (ULB), Campus de la Plaine, Boulevard du Triomphe, 1050 Brussels, Belgium. E-mail: [rkiss@ulb.ac.be](mailto:rkiss@ulb.ac.be)

<sup>2</sup>F.L. is a Clinical Research Fellow and R.K. is a Director of Research with the *Fonds National de la Recherche Scientifique* (FNRS, Belgium); M.L.M. is a holder of a Grant FNRS-Télévie (FNRS, Belgium) and V.M. is a Postdoctoral Researcher supported by the Fonds Yvonne Boël (Brussels, Belgium).

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### Abstract

#### Purpose

The aims of the present work were to investigate the *in vitro* and *in vivo* antiangiogenic effects of chronic temozolomide treatment on various glioma models and to demonstrate whether bevacizumab (Avastin) increased the therapeutic benefits contributed by temozolomide in glioma.

#### Experimental Design

The expression levels of various antiangiogenic factors in four glioma cell lines were evaluated after chronic *in vitro* treatment with temozolomide by Western blot. Proliferation and migration assays were performed on human endothelial cells incubated with supernatants of glioma cells treated with and without temozolomide. Orthotopic glioma models were used to evaluate the antiangiogenic effects of temozolomide *in vivo* and the therapeutic benefits of different temozolomide treatment schedules used alone or in combination with bevacizumab.

#### Results

Temozolomide, a proautophagic and proapoptotic drug, decreased the expression levels of HIF-1 $\alpha$ , ID-1, ID-2, and cMyc in the glioma models investigated, all of which playing major roles in angiogenesis and the switch to hypoxic metabolism. These changes could be, at least partly, responsible for the impairment of angiogenesis observed *in vitro* and *in vivo*. Moreover, combining bevacizumab with temozolomide increased the survival of glioma-bearing mice in comparison to each compound administered alone.

#### Conclusions

In addition to the numerous mechanisms of action already identified for temozolomide, we report here that it also exerts antitumor effects by impairing angiogenic processes. We further emphasize that bevacizumab, which is an antiangiogenic drug with a different mechanism of action, could be useful in combination with temozolomide to increase the latter's therapeutic benefit in glioma patients.

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