

# DCE-MRI and ICP-MS evaluation of biodistribution of contrast agents and chemotherapeutic agents to gliomas with a new pharmacological approach in F98 glioma cells implanted Fischer rats

Jerome Cote<sup>1</sup>, Luc Tremblay<sup>2</sup>, David Fortin<sup>3</sup>, Fernand Gobeil<sup>4</sup>, and Martin Lepage<sup>2</sup>

<sup>1</sup>CIMS, Université de Sherbrooke, Sherbrooke, Québec, Canada, <sup>2</sup>CIMS, Université de Sherbrooke, Sherbrooke, Québec, Canada, <sup>3</sup>Chirurgie, Université de Sherbrooke, Sherbrooke, Québec, Canada, <sup>4</sup>Pharmacologie, Université de Sherbrooke, Sherbrooke, Québec, Canada

## Introduction

Gliomas are the most common and deadly intrinsic tumors of the brain and are among the most aggressive of all tumor. No cure currently exists such that the prognosis is very poor. Moreover, very limited therapeutic progress has been made in the past three decades. Treatment of malignant gliomas is complicated, among other things, by its infiltrative phenotype and by the existence of the blood-brain barrier (BBB), the latter reducing bioavailability of chemotherapeutic agents to invading tumor cells in the periphery of the contrast enhancing lesion. Forward-looking approaches have been recently evaluated with the ultimate goal of improving delivery across the BBB (e.g. mannitol, ultrasound, bradykinin). We have developed a new and innovative pharmacological approach (temporarily named BM83) to transiently and non-invasively permeabilize the BBB at the tumor and its periphery, in order to increase drug accumulation at the sites where tumor cells are invading normal brain tissues. Dynamic-contrast enhanced magnetic resonance imaging (DCE-MRI) with intravenous Gd-DTPA (0.5 kDa) or Gadomer (17 kDa) was used to monitor and validate the selective increase of BBB permeability at the tumor of F98 glioma-bearing Fischer rats, induced by BM83 injected into the right external carotid, directly to the tumor-bearing hemisphere. We hypothesized that an effective permeabilization at the tumor and its periphery would increase the contrast agent distribution volume (CADV) and the total concentration of Carboplatin and Gd-DTPA.

## Methods

Rat glioma cells (F98) were inoculated stereotactically into the right caudate nucleus in a total of 24 Fischer rats. After ten days, MRI experiments were conducted on anesthetized animals placed in the supine position in a 7T animal MRI scanner. A pre-contrast T<sub>1</sub> map was acquired using T<sub>1</sub>-weighted images with different flip angles (TR/TE: 100/2.4 ms, FOV: 4 x 4 cm<sup>2</sup>, matrix: (128)<sup>2</sup>, α: [10-50°], NA: 4, 10 slices of 1.5 mm without gap). A bolus of either Gd-DTPA or Gadomer was injected into the tail vein with simultaneous and continuous monitoring by T<sub>1</sub>-weighted images (α: 30° for a time period of 30 min). This allowed the evaluation of the extent of the basal BBB permeability at the tumor and served as the reference values of CADV and total concentration. Twelve hours later, the same MRI experiments were repeated following infusion of BM83 (0.1 ml/min for 5 min) into the right external carotid artery (i.a.). The concentration of contrast agent was calculated for every image in the dynamic, using the pre-contrast T<sub>1</sub> map. In addition, the CADV was calculated based on a threshold analysis. Since the normal BBB prevents the delivery of both contrast agents, the CADV reflects the volume where the BBB is leaky or is permeabilised. In addition, tissue samples (tumor, periphery and contralateral) were collected after a single infusion, over 15 minutes (i.a.), with BM83 or vehicle, Gd-DTPA (143 mM) and Carboplatin (5 mg) in a final volume of 1 ml. These samples were weighted and then analyzed for the dosage of Gadolinium (Gd) and Platinum (Pt) using inductively coupled plasma mass spectrometry (ICP-MS).

## Results

Our results demonstrate that the intracarotid infusion of BM83, but not the vehicle, nearly doubled the uptake profiles of both contrast agents within rat glioma and surrounding brain tissue, as observed by an increase of both CADV and total contrast agent concentration in the implanted hemisphere (Fig. 1 A-D). Permeabilisation was not observed in the contralateral hemisphere (C), which suggests that the approach is selective. Preliminary ICP-MS measurements show that BM83 resulted in a 2-fold increase in the concentration of Carboplatin in comparison to vehicle, in the tumor (1277 vs 616 ng of Pt/g of tissue) and the surrounding tissues (903 vs 467 ng/g), but not in contralateral, healthy brain tissues (37 vs 27 ng/g).

## Conclusion

With DCE-MRI and ICP-MS, we demonstrated that a new pharmacological approach can double the bioavailability of two contrast agents and a chemotherapeutic agent (Carboplatin) across the BBB of gliomas. Survival studies are underway to confirm that the larger biodistribution of Carboplatin is translated to a longer survival of F98-inoculated Fischer rats.

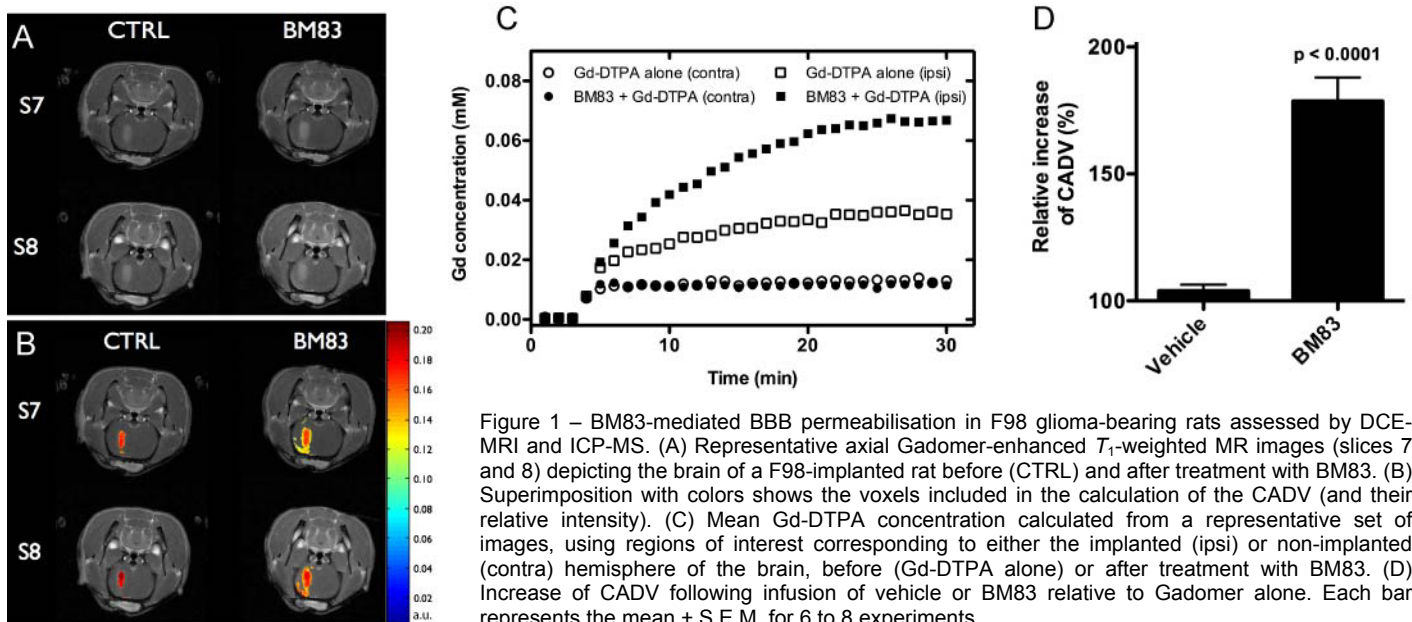


Figure 1 – BM83-mediated BBB permeabilisation in F98 glioma-bearing rats assessed by DCE-MRI and ICP-MS. (A) Representative axial Gadomer-enhanced T<sub>1</sub>-weighted MR images (slices 7 and 8) depicting the brain of a F98-implanted rat before (CTRL) and after treatment with BM83. (B) Superimposition with colors shows the voxels included in the calculation of the CADV (and their relative intensity). (C) Mean Gd-DTPA concentration calculated from a representative set of images, using regions of interest corresponding to either the implanted (ipsi) or non-implanted (contra) hemisphere of the brain, before (Gd-DTPA alone) or after treatment with BM83. (D) Increase of CADV following infusion of vehicle or BM83 relative to Gadomer alone. Each bar represents the mean ± S.E.M. for 6 to 8 experiments.