Introduction
Gliomas are the most common and lethal primary brain tumors in the adult, with a median survival time of 12 to 15 months for grade IV gliomas, glioblastoma multiforme [1]. PBN and OKN007 are nitrones which have demonstrated beneficial effects in many aging diseases [2,3]. In this study, we evaluated the anti-tumor effects of PBN or OKN007 in several rodent glioma models (C6, RG2, and GL261) by assessing metabolite alterations with magnetic resonance spectroscopy (MRS).

Methods
PBN or OKN007 was administered in drinking water prior to or post tumor formation. MRI and short echo time, single-voxel point-resolved spectroscopy (PRESS) were obtained to assess tumor morphology and metabolites, respectively, following therapy. MRS data were processed using the “Bruker TopSpin” tool in the Paravision software and major metabolite ratios (Choline, N-acetyl aspartate (NAA), Lipid (methylene), and Lipid (methyl), all compared to Creatine) were calculated using a Mathematica program. Angiogenesis factors and apoptosis markers were detected in the tissues by immunohistochemistry.

Results
Nitrones, such as OKN007, decreased tumor volumes (Fig. 1) and induced tumor metabolism changes that resulted in restoring major metabolite ratios close to their normal levels, in the glioma regression phase. Nitrones (e.g. OKN007) treatment decreased the Lipid (methylene) to Creatine ratio significantly (Fig. 2), which can be a useful marker for evaluation of the efficacy of the treatments, and was found to be related with the reduction of necrosis. OKN007 was more effective than PBN when administered post-tumor formation in the C6 glioma model. OKN007 was able to inhibit angiogenic factors (VEGF, bFGF and HGF) and induce apoptosis (indicated by increase of the apoptosis marker m30 (Fig. 3)) in C6 gliomas, which might be potential mechanisms that are involved in the anti-glioma effects.

Conclusion
In conclusion, OKN007 and PBN are effective in inhibiting the growth of C6 gliomas and may be considered as potential therapeutics for a clinical trial in human gliomas.

References