Ganciclovir Pharmacokinetics in Rats with Brain Glioma
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Purpose
Ganciclovir has a pivotal role in the Herpes simplex virus thymidine kinase suicide gene therapy and the effectiveness of the therapy depends upon exposing tumor cells to adequate concentrations ganciclovir. The purpose of this study was to investigate the pharmacokinetics and tumor uptake of ganciclovir in rats with brain glioma.

Methods
In vivo pharmacokinetics as well as brain and glioma uptake of ganciclovir was investigated by in vivo microdialysis in glioma rats after 25 mg/kg ip injection. In addition, the ability of ganciclovir to cross blood-brain and blood-tumor barriers was determined in tumor bearing rats with in situ brain perfusion using 100 µM ganciclovir. Finally, the ability of ganciclovir to permeate across glioma cell membrane was determined in BT4C cells in vitro.

Results
The area under the concentration curve (0-300 min) in plasma, brain and tumor extracellular fluid was 6157 µM×min, 1658 µM×min and 4834 µM×min, respectively. Maximum concentration was achieved in 60 min and was 46.9 µM, 11.8 µM and 25.8 µM in plasma, brain and tumor, respectively. The ganciclovir uptake across blood-brain and blood-tumor barriers was 0.55 nmol/g and 1.79 nmol/g, respectively. Ganciclovir uptake into BT4C cells at 100 µM was 0.12 %.

Conclusion
Ganciclovir is able reach extracellular space in tumor at higher concentrations than that in healthy brain tissue. Highly polar ganciclovir is likely to cross the blood-tumor barrier by paracellular diffusion as the angiogenetic vasculature has fenestrations unlike the fully functional blood-brain barrier. However, ganciclovir uptake in glioma cells in vitro was low suggesting that only small fraction of ganciclovir found in tumor extracellular space is able to reach the intracellular space. Thus, the efficacy of suicide gene therapy could be improved by enhancing ganciclovir uptake into glioma cells.