High interstitial fluid pressure (IFP) represents a barrier for drug uptake in human GBM, the most common malignant primary brain tumor in adults. Increased IFP is due to leakage of blood vessels and reduced drainage of fluid. This accumulation of fluid and high cell density compresses tumor tissue and promotes swelling of tumor cells. Although studies have clarified the role of tumor vasculature, it is still unclear if elevated IFP and swelling of cancer cells regulates tumor growth and drug uptake. Inhibition of NKCC1 (Na-K-Cl cotransporter) activity with bumetanide renders glioma cells unable to restore cell volume following osmotic challenges, blocks invasion in GBM xenografts, and augments temozolomide-mediated apoptosis in vitro. However, concerns about side-effects following bumetanide treatment warrants development of new approaches. Our preliminary data show that induction of antisecretory factor (AF), a regulator of fluid secretion, inhibited phosphorylation of NKCC1 in intracranial xenografts of human primary GBMs. Since AF therapy is safe in patients and lowers IFP in experimental models of solid tumors, we hypothesize that AF induction lowers IFP levels and increases drug uptake in xenografted GBMs. We have established novel methodology to study IFP in GBMs intracranially grafted into mice and the effects of compression in 3D-cultures. Our preliminary data show that elevated IFP and compression promotes tumor growth of GBMs. Our data suggest that AF induction lowers IFP levels by blocking restoration of cell volume and increases uptake of chemotherapy. Surprisingly, we found that AF induction alone reduced tumor growth and extended the survival of transplanted mice. Our work establish a role for IFP and cell swelling as potential therapeutic targets in GBMs and other solid cancers. As a novel pressure-reducing therapy, AF induction represents an attractive strategy to reduce tumor growth, increase drug uptake, and improve survival in brain tumor patients.