Title	CNS delivery of VX-970: a selective ATR inhibitor for radiosensitization in GBM
Keywords	Glioblastoma, radiosensitizer, ATR, efflux transporters
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Abstract	Glioblastoma (GBM) is an aggressive and infiltrative primary brain tumor with a median survival of 14.6 months following the current treatment strategy of radiation and chemotherapy with temozolamide[1]. This grim prognosis suggests the limited efficacy and limited long term control of the tumor progression by using chemo and radiotherapy. Therefore, there is a need to develop strategies to enhance the efficacy of chemo-radiation treatments for GBM. DNA damage response signaling pathways play a critical growth in DNA repair and cell survival following radiation therapy and the inhibition of these pathways could augment the cytotoxicity associated with radiation providing a radiosensitizing effect. Ataxia Telangiectasia And Rad3-Related Protein (ATR) is a key regulator of the DNA damage response network and VX-970 is the first potent and selective inhibitor of ATR to enter clinical studies[2]. Preliminary in vitro studies from our lab to determine a dose dependent effect of VX-970 in combination with a radiation dose of 5 Gy on the cell survival indicated that administration of radiation led to an enhancement in the cell death with an increasing dose of VX-970 in the U251 human GBM cell line. We also aim to evaluate the BBB penetration of VX-970 and study the role of efflux transporters on the brain exposure of VX-970 in preparation for efficacy studies in PDX models of GBM. Brain distribution studies were performed in wild-type and Mdr1a/b-/- Bcrp1-/- (triple knockout) FVB mice (n=4) following oral administration of 20 mg/kg VX-970. Plasma and brain samples were collected 2 hrs post dosing and were analyzed using LC-MS. The brain-to-plasma (B/P) ratio in transporter (Pgp and Bcrp) knockout mice was 2.953 as opposed to 0.087 in transporter intact wild-type mice. This 33 fold increase in the B/P ratio in the triple knockout mice indicates that Pgp and/or Bcrp play a significant role in the efflux of VX-970 from the brain thereby limiting its brain penetration. We are in the process of conducting additional studies with intraperitoneal and intravenous administration at multiple time points to determine a more precise status of the role of efflux transporters in the brain delivery of VX-970. Additionally, we will determine the free fraction of VX-970 in the brain and plasma and relate the amount of free drug to a dose range associated with effective radiosensitization through efficacy studies in the PDX models of GBM.
References	1 Stupp , R. *et al.* Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. *New England Journal of Medicine* **352**, 987-996, doi:10.1056/NEJMoa043330 (2005). 2 Hall, A. B. *et al.* Potentiation of tumor responses to DNA damaging therapy by the selective ATR inhibitor VX-970. *Oncotarget* **5**, 5674-5685, doi:10.18632/oncotarget.2158 (2014).