Disrupting the CD47-SIRPα anti-phagocytic axis by a humanized anti-CD47 antibody is an efficacious treatment for malignant pediatric brain tumors.

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Morbidity and mortality associated with pediatric malignant primary brain tumors remain high in the absence of effective therapies. Macrophage-mediated phagocytosis of tumor cells via blockade of the anti-phagocytic CD47-SIRPα interaction using anti-CD47 antibodies has shown promise in preclinical xenografts of various human malignancies. We demonstrate the effect of a humanized anti-CD47 antibody, Hu5F9-G4, on five aggressive and etiologically distinct pediatric brain tumors: group 3 medulloblastoma (primary and metastatic), atypical teratoid rhabdoid tumor, primitive neuroectodermal tumor, pediatric glioblastoma, and diffuse intrinsic pontine glioma. Hu5F9-G4 demonstrated therapeutic efficacy in vitro and in vivo in patient-derived orthotopic xenograft models. Intraventricular administration of Hu5F9-G4 further enhanced its activity against disseminated medulloblastoma leptomeningeal disease. Notably, Hu5F9-G4 showed minimal activity against normal human neural cells in vitro and in vivo, a phenomenon reiterated in an immunocompetent allograft glioma model. Thus, Hu5F9-G4 is a potentially safe and effective therapeutic agent for managing multiple pediatric central nervous system malignancies.

The concern has been that the response with xenografts is higher than it is with a syngeneic model. Next the levels of the antibody in the csf is ten percent of the levels in the plasma in this report. We do not know if it is that high because the blood brain barrier was damaged or because the presence of cd47 in the brain is somehow aiding the transmission of the antibody across the blood brain barrier or there is some sort of active transport that is currently unknown. We do know that TTI621 should have even better transport across the blood brain barrier because of its lower molecular weight.

We decided that it might be wise to have a backup if the peripheral venous injection is insufficient to prime the antigen presenting cells. A number of approaches were considered. Obviously, Trillium Therapeutics did not wish to consider an acceptable intrathecal form of the medication so that ruled out intrathecal administration via lumbar or the cisternal approach. Intrarterial administration was deemed to be too dangerous. etoposide has been given in rabbits by intrarterial injection and opened the blood brain barrier for three days but humans are not rabbits. Stereotactic intratumoral injection was also considered and rejected for obvious reasons. Having the fc fusion product attached to a carrier such as the ones from armagen or bioasis was considered but that would make it a new product and would require an nda. Opening the blood brain barrier for a few hours with mri guided low intensity focused ultrasound seemed a poor approach. There is no shunt in place so that approach would not be feasible either. An epidural approach lumbar could be done but again the medication has preservatives in it and a cervical epidural with the requirement for fluoroscopy and dye was not acceptable. That left us with only one backup approach which is the injection into the cervical venous plexus. The anatomy is clearcut and if the medication is placed in the veins of the plexus it will eventually reach the intended target. If it is simply injected into the interspinous area it will not do so. Studies in animals, studies in cadavers and human studies show the connections.

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Perhaps we are being overly cautious. There is a chance the the metronomic therapy will do the job. There is a chance that the TTI621 by peripheral vein will be sufficient as a priming agent or better.