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Schuelke, M, Evgin, L, Kottke, T et al. (8 more authors) (2016) Balancing Anti-Tumor Efficacy with Local Inflammatory Toxicity for the Treatment of Diffuse Intrinsic Pontine Glioma and Other Brain Tumors. In: Molecular Therapy. 19th Annual Meeting of the American-Society-of-Gene-and-Cell-Therapy (ASGCT), 04-07 May 2016, Washington DC, USA. Nature Publishing Group , S77-S77.

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Balancing Anti-Tumor Efficacy with Local Inflammatory Toxicity for the Treatment of Diffuse Intrinsic Pontine Glioma and Other Brain Tumors.

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We have shown previously that multiple rounds of a systemic treatment of GM-CSF, followed by intravenous reovirus, leads to effective treatment of subcutaneous melanomas (Ilett et al., Mol. Ther. 2015). We show here that a similar regimen is also effective at treating both melanoma (B16) and glioma (GL261) tumors growing intra-cranially. As a result of these pre-clinical studies, we initiated a Phase I clinical trial in paediatric patients with gliomas of GM-CSF and reovirus therapy. To date, three patients have been treated. In two of three of these patients there were possible indications of pseudoprogression and intra-cranial inflammation, both of which were clinically resolved upon treatment with dexamethasone.

Whilst this trial continues to recruit, we have investigated additional treatments for paediatric brain tumors, especially those in which direct virus injection may allow greater local access to tumor. In this respect, there is a constant tension between the pro-inflammatory, anti-tumor nature of oncolytic viroimmunotherapy and the need to reduce potentially toxic local inflammatory reactions within the brain. Our overall hypothesis is that it will be possible to balance the anti tumor effects of viral oncolysis, in part caused by inflammatory reactions to the virus, with the associated toxicity. Nowhere is this more relevant than for the treatment of Diffuse Pontine Gliomas (DIPG), which grow in the brain stem. Our experiments show that it is indeed possible to treat tumors growing in the pons/and or medulla, with inflammatory, immune based therapies (both T cell mediated and locally cytotoxic) without increasing toxicity over that caused by tumor growth alone. Therefore, we have screened multiple oncolytic virus types for their ability to kill DIPG cell lines both *in vitro* and *in vivo*. In particular, we have compared viruses with different speeds of oncolysis and different inflammatory properties to investigate how the efficacy can be balanced with local toxicity, using standard of care anti inflammatory treatments (with dexamethasone) as well as with novel agents and viruses designed to suppress local inflammatory reactions.