This is an author produced version of *Future clinical potential of oncolytic virotherapy for pediatric CNS tumors*.

White Rose Research Online URL for this paper:
http://eprints.whiterose.ac.uk/87766/

**Article:**

https://doi.org/10.2217/cns.13.25

© Future Medicines Ltd. This is an author produced version of a paper published in CNS Oncology. Uploaded in accordance with the publisher's self-archiving policy.
CNS tumors are the most common solid tumors of childhood [1]. Although treatment advances have improved survival for some pediatric CNS diseases, there unfortunately remains a group of tumors associated with significantly poorer prognosis. Among these are high-grade gliomas (HGG), which, despite aggressive management, usually recur and are associated with 5-year survival outcomes between 15–35% [2]. Diffuse intrinsic pontine glioma (DIPG), a highly malignant brainstem tumor with median survival of less than 1 year [3], remains a constant therapeutic challenge. High-risk metastatic medulloblastoma with cerebrospinal fluid dissemination at presentation is associated with 5-year survival rates between 40–70% despite intensive treatment regimens [4]. In addition, rare malignancies, such as atypical teratoid rhabdoid tumors, although often demonstrating response to chemotherapy, are associated with early relapse and a median survival of only 17 months [5]. Oncolytic virotherapy, which uses viruses to selectively infect and destroy cancer cells [6], offers a novel treatment approach for poor prognosis pediatric CNS tumors. While there is extensive literature on oncolytic virotherapy for adult brain malignancies, such as HGG, work on pediatric CNS tumors is currently only just gathering steam. With no open clinical trials focused on oncolytic virotherapy in pediatric CNS tumors we can currently only draw upon available preclinical models, alongside adult and limited pediatric clinical data, to progress the exciting future potential of this treatment modality.

The majority of preclinical studies of oncolytic virotherapy for pediatric CNS tumors evaluate efficacy in medulloblastoma. Over 15 years ago Lasner et al. published that herpes simplex virus (HSV) variant 1716 could infect and destroy D283 medulloblastoma cells and demonstrated that intratumoral injection of the virus into D283 tumor-bearing mice conferred a statistically significant increase in survival compared with control murine models [7]. Pyles et al. 1 year later also demonstrated therapeutic potential in a double mutated modified HSV strain 3616UB that was able to...
replicate in, spread through and arrest growth of DAOY cell xenografts in CD17 severe combined immunodeficiency mice [8]. In 2003, Yang et al. established the potential of human reovirus type 3 for oncolytic virotherapy in medulloblastoma. The authors demonstrated susceptibility of medulloblastoma cells to reovirus in five out of seven medulloblastoma cell lines, as well as in primary cultures derived from surgical specimens and in two cell lines obtained from spontaneously arising tumors in Patched-1

Preclinical studies have demonstrated the potential for oncolytic virotherapy as a treatment paradigm for childhood tumors...
Promising results have been demonstrated in adults in terms of safety, tolerability and multiple-dose delivery data in Phase I and II clinical trials using a range of different viruses for treatment of malignant gliomas [6,17]. Recently, a handful of oncolytic virus trials for pediatric patients with non-CNS solid tumors has been developed [22], which will begin to answer questions regarding dosing, safety and efficacy of virotherapy in children. The next step for the pediatric field is to amalgamate the knowledge gained from preclinical studies together with adult and pediatric clinical observations, in order to decide which viruses to take forward to clinical trials for pediatric CNS tumors.

There are many questions that must be answered before oncolytic virus therapy reaches its full potential for pediatric patients with CNS disease. First and foremost, safety issues must be addressed. One issue that relates solely to pediatric oncology and where minimal information is known, is the effect of oncolytic viruses on the developing brain and subsequent neurodevelopmental outcomes. Although a murine study showed that intracerebral injection of modified herpes virus G207 did not adversely affect cognitive or behavioral development in young mice when compared with saline-treated controls, some mice in the treatment group developed ventriculomegaly [23]. Although the study had limitations and the authors admitted concerns that the delivery method of the virus itself may have resulted in such findings, it does raise the possibility that hydrocephalus may be a potential problem for young children receiving intracranial virotherapy and that any subsequent trials should involve monitoring for this adverse effect [23]. Furthermore, tumor location must be considered when assessing safety. In particular, brainstem tumors, such as DIPG, may be of particular concern, as local pressure generated from immune and inflammatory responses alongside viral replication may cause critical, if not fatal consequences [24]. One obvious concern for pediatricians would be the risk of uncontrollable viral replication, resulting in encephalitis and subsequent neurodevelopmental sequelae. This risk could be overcome by ensuring availability of effective antiviral treatments if significant toxicity does occur. Effective administration and delivery of the virus must also be considered. Intratumoral injection limits the number of opportunities for treatment in children, whereas systemic delivery may be fraught with problems in effectively penetrating the blood–brain barrier and overcoming the potential for neutralization of the virus by the patient’s immune system before it can access its tumor target. Further research and clinical experience is required in order to optimize virus delivery to pediatric, as well as adult, intracranial tumors.

Additional questions relate to the immunotherapeutic properties of oncolytic viruses. There is clearly a fine balance between minimizing destruction of administered virus by the host immune system, while enhancing the immune system’s response to kill and ablate virus-infected cancer cells [6,25]. One avenue of research is currently focused on developing cellular carriers that deliver viruses to tumors while hiding them from the neutralizing effects of the immune system [6]. Furthermore, viruses can be modified to express tumor antigens, so that when they are appropriately delivered to the immune system the anti-tumor immune response is enhanced [6]. Specific to pediatrics is the fact that young children may not yet have been exposed to naturally occurring viruses that may subsequently be used for virotherapy, and, therefore, will not have built up specific antiviral immunity [24]. Whether or not this will enhance the efficacy and/or toxicity of systemic oncolytic virotherapy in the younger age group remains to be determined. Finally, the financial and logistical difficulties in orchestrating clinical trials with adequate power in relatively rare childhood conditions must be considered, as well as the time lag to interpretation of trial results while newer and more promising viruses are developed in this rapidly evolving field.

Despite recent advances in the field of pediatric neurooncology, morbidity and mortality for this patient group remains high and novel treatment avenues for unfavorable outcome pediatric CNS tumors are desperately required [6]. Preclinical studies have demonstrated the potential for oncolytic virotherapy as a treatment paradigm for these childhood tumors, although very limited, clinical observations in children have shown promise. The next step for the field is the development and delivery of Phase I trials for pediatric CNS tumors evaluating a range of potential oncolytic viruses. This will allow the opportunity to begin to answer a range of important clinical questions. Future research will concentrate on optimizing virus delivery, modulating the role of the child’s immune system to prevent viral elimination,...
enhancing anti-tumor immune responses and to evaluate the potential for synergistic interactions between oncolytic viruses and existing treatment modalities in children. Overall, the advent of oncolytic virotherapy for pediatric CNS tumors opens the door to an exciting new era for pediatric oncology with its potential to improve outcomes for the devastating disease that is cancer.

Financial & competing interests disclosure
JV Cockle is supported by a Yorkshire Cancer Research Clinical Research Training Fellowship. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References