Scientific abstract

OncoVEX^{GM-CSF} is a selectively replication competent herpes simplex type-1 virus (HSV1) for the treatment of solid tumours by intra-tumoural injection. The virus selectively replicates in tumours while sparing normal tissue – i.e. it is "oncolytic". The virus also expresses the gene for human granulocyte macrophage colony stimulating factor (hGM-CSF), a cytokine involved in the stimulation of T-cells and intended to boost the immune response to tumour associated antigens released following oncolytic virus replication. The aim is therefore to treat locally injected tumours by viral oncolysis, and that the induction of an anti-tumour immune response may enhance the therapeutic effect.

There has been considerable previous clinical work with oncolytic viruses including versions of adenovirus and HSV. In all cases a good safety profile has been seen, and in some cases there has been evidence of a therapeutic effect. HSV has advantages over other viruses which might be used for oncolytic therapy in that it is able to infect a wide variety of cell types, has a rapid replication cycle resulting in cell lysis, has the capacity to deliver single or multiple transgenes which may improve the oncolytic anti-tumour effect and is relatively easy to produce to high titre in quantities sufficient for clinical use.

OncoVEX^{GM-CSF} aims to build on the promising previous clinical work with oncolytic viruses, including with HSV, by the development of a virus backbone with enhanced oncolytic potency as compared to previous viruses, and to combine this with the delivery of a therapeutic gene, in this case GM-CSF. GM-CSF has given particular promise in cancer therapy, hence the inclusion of GM-CSF in OncoVEX^{GM-CSF}.

OncoVEX^{GM-CSF} was constructed using a new strain of HSV1 (strain JS1; ECACC Accession Number 01010209) and has been fully sequenced. To produce OncoVEX^{GM-CSF} two previously well characterised gene deletions were introduced into the virus. The first deletion is that of the gene encoding ICP34.5, the so-called neurovirulence factor. Deletion of ICP34.5 provides the greatest attenuation of any HSV gene which still allows the virus to replicate in culture and renders the virus non-pathogenic. The function of ICP34.5, and the properties of ICP34.5 deletion mutants, have been the subject of many studies and therefore considerable literature is available supporting this point. As well as generating a non-pathogenic virus, deletion of ICP34.5 provides the property of tumour selective replication, i.e. as required for an oncolytic virus. The second deletion is that of the gene encoding ICP47. Deletion of ICP47 alone has again been shown to render HSV non-pathogenic, and so OncoVEX^{GM-CSF} contains two separate mutations which individually attenuate the virus. The role of ICP47 is to block antigen presentation to MHC class I and II molecules by blocking the transporters associated with antigen processing (TAP 1 and TAP2). As an anti-tumour immune response following injection of OncoVEX^{GM-CSF} into a tumour would be expected to be beneficial, this deletion would be anticipated to aid the induction of such an effect. The deletion of ICP47 also allows the increased expression of the HSV US11 gene. It has been shown previously that such increased expression boosts the replication of ICP34.5 deleted HSV in tumour cells without affecting the level of attenuation of

the virus and tumour selectivity. The gene for human GM-CSF expression is inserted so as to completely replace the coding sequences for ICP34.5 and is under the control of the human cytomegalovirus immediate early promoter (hCMV IE). The construction of OncoVEX^{GM-CSF} is described in Liu et al 2003[1].

BioVex has conducted an extensive pre-clinical program with OncoVEX^{GM-CSF} showing it to have properties typical of an ICP34.5 deleted version of HSV. This includes multiple dose toxicology and bio-distribution in rodents and efficacy studies showing the improved anti-tumour properties of the product, including the protection of previously treated animals from tumour cell re-challenge.[1]

Previous oncolytic versions of HSV have been tested in clinical studies in both the UK and the US. As indicated above, these have demonstrated a good safety profile when used for direct intra-tumoral injection in glioma patients (UK and US) or melanoma patients (UK), or by hepatic artery infusion in liver cancer patients in the US. In addition, BioVex has conducted a Phase I clinical trial with OncoVEX^{GM-CSF} in the UK in approximately 30 patients where cutaneous or sub-cutaneous deposits of a number of tumour types (mainly breast cancer, melanoma and head and neck cancer) were injected with single or multiple doses of OncoVEX^{GM-CSF}. A good safety profile was seen, combined with evidence of an anti-tumour effect.

A phase II and a phase I/II study with OncoVEX are currently underway. In the United States a phase II clinical trial in melanoma (OncoVEX^{GM-CSF}/002/03) is underway after approval from RAC and the FDA and in the U.K. a phase I/II clinical trial in head and neck cancer (OncoVEX^{GM-CSF}/004/04) in combination with both radiotherapy and chemotherapy is underway after approval from GTAC and the MHRA. A total of 9 patients have so far been dosed in these studies (as of 13th June 2006). A Phase I/II study in up to 18 evaluable patients with locally advanced or metastatic adenocarcinoma of the pancreas (OncoVEX^{GM-CSF}/005/04) has been approved by RAC and the FDA but has not yet commenced dosing patients.

Following on from the studies described above, the current proposal describes a Phase II study to investigate the safety and efficacy of OncoVEX^{GM-CSF} in the treatment of hepatic metastases of colorectal cancer. There is considerable precedent for this approach using oncolytic viruses, mainly with the oncolytic adenovirus Onyx-015 where Phase II studies were performed providing indications of efficacy, and with the oncolytic HSV NV 1020 where a phase I study has been performed demonstrating tolerability[22,36]. The proposed study will be in colorectal cancer patients with liver metastases who have failed first line therapy and will be in two parts: 1) an open label, upward titration evaluating the safety and efficacy of up to four dose schedules of OncoVEX^{GM-CSF} in groups of up to three patients at each dose schedule. OncoVEX^{GM-CSF} will be given by injection into the hepatic artery via a femoral artery catheter advanced into the hepatic artery. If patients continue to progress after two doses of OncoVEX^{GM-CSF} alone, they will then be offered second line chemotherapy in combination with OncoVEX^{GM-CSF} 2) Following this, tumour response rates will be determined in a group of up to 25 patients receiving either the maximum dose or, if the maximum dose is not tolerated, the maximum tolerated dose. Again, if patients continue to progress after two doses of OncoVEX^{GM-CSF}, they will then be offered second line chemotherapy in combination with OncoVEX^{GM-CSF}.

[1]Liu BL, Robinson M, Han ZQ, Branston RH, English C, Reay P, McGrath Y, Thomas SK, Thornton M, Bullock P, Love CA, Coffin RS Gene Ther. 2003 Feb;10(4):292-303 ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumour properties