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The Broad Spectrum Oncolytic Activity of Newcastle Disease Virus, PV701, is a Result of a Functional Defect in the Antiviral Interferon Response of Tumor Cells

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PV701, a naturally attenuated, replication-competent, oncolytic strain of Newcastle disease virus, demonstrates selective lytic activity against tumor cells of multiple cellular origins compared to normal cells. In a co-culture experiment of normal fibroblasts and carcinoma cells, PV701 killed the tumor cells while the normal cells cleared the infection. Treatment of normal cells with neutralizing antibodies to IFN resulted in increased PV701 cytotoxicity demonstrating that normal cell resistance to PV701 cytotoxicity is IFN dependent. In a panel of 11 tumor cell lines and 3 normal cell strains, all normal cell strains were able to reduce viral antigen expression following pretreatment with as little as 5 IU/ml of IFN-alpha, while 10/11 tumor cell lines required 10 to 100 fold higher concentrations for the same effect. Tumor cells were found to exhibit varying degrees of dysfunction with respect to IFN utilization. For example, KB carcinoma cells were resistant to both IFN-alpha and IFN-beta while HT1080 fibrosarcoma cells were resistant to IFN-alpha but responded to 24 hour pretreatment with IFN-beta. However, when normal fibroblasts and HT1080 cells were treated with IFN-beta 8 hrs post-infection, only the normal cells effectively reduced PV701 cytotoxicity and replication. In conclusion, the oncolytic activity of PV701 is a result of an inability of many tumor cells to respond appropriately to the antiviral effects of IFN.

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Systemic Therapy of Fibrosarcoma Xenografts Using PV701, an Oncolytic Strain of Newcastle Disease Virus, in Combination with Carboplatin Demonstrates At Least Additive Antitumor Responses

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PV701, a replication-competent oncolytic strain of Newcastle disease virus, is in clinical testing by the IV route. As a single agent, PV701 demonstrated potent activity against human tumor xenografts following local or IV administration. We report here on the activity of IV administered PV701 in combination with IP carboplatin (CP) against HT1080 human fibrosarcoma xenografts. Because previous testing using this tumor model showed that an IV PV701 dose of 3E+08 PFU caused complete regression (CR) in ~90% of tumors, we selected a lower dose (6E+06 PFU) so that potential additive and/or synergistic effects with CP could be examined. For CP, doses near the MTD (60 to 80 mg/kg) were examined. Athymic mice were given subcutaneous injections of HT1080 cells (1E+07). When the tumors reached ~100 mm^3, mice were treated with CP, PV701, or both agents with PV701 given 2 days after CP (N=8 to 9). CP as sole therapy (80 mg/kg), PV701 (6E+06 PFU) as sole therapy, and a combination of both agents at these doses yielded 11%, 11%, and 67% complete regression (CR), respectively, by day 21. In further testing, CP alone (60 mg/kg), PV701 alone (6E+06 PFU), and the combination of both agents yielded CR rates of 13%, 11% and 67%. The only observed gross toxicity was transient weight loss, which was <5% in all groups. In summary, systemic PV701 in combination with carboplatin yielded at least additive antitumor responses. These studies provide a rationale for the clinical testing of PV701 with chemotherapeutic agents.