**Miriam Gothe** • 6 years ago

https://www.nature.com/articles/nature10358

On behalf of Tibor Bakacs

Oncolytic NDV therapy effective for years

There is no need to speculate whether intravenous pharmacological dosing of JX-594 oncolytic poxvirus is able to transiently saturate native mechanisms of viral clearance such that repeated intravenous delivery will be feasible (1). More than a decade ago Csatary et al. (2) had demonstrated in 30 cancer patients receiving an attenuated Newcastle disease virus (NDV) vaccine for up to 8 years that repeated intravenous delivery of virus is not only feasible but necessary for clinical efficacy in the presence of neutralizing antibodies.

In contrast to your editorial claim, (3) infection of tumours with oncolytic viruses is not a new type of treatment (4). Out of a total of 53 viruses tested as anticancer agents, 38 exerted antineoplastic effects in either animals or humans (5). Notwithstanding, developers of the JX-594 oncolytic poxvirus appear to be unmindful of relevant experiences obtained in patients with NDV during the last 50 years. Therefore, it is perhaps useful to bring the recent past of oncolytic NDV virotherapy into sharper focus in order to avoid some risky strategies (e.g. immunosuppression by cyclophosphamide to potentiate viral replication and hence enhance tumour oncolysis (6)).

Among the non-engineered oncolytic viruses NDV has a long history as a broad-spectrum oncolytic agent that can destroy tumour cells and stimulate the immune system. NDV is a single-stranded RNA virus, whose natural host is poultry. As early as 1965 NDV was reported to have interesting anti-neoplastic properties (7). Several NDV strains (MTH-68/H, NDV-PV701, NDV-Ulster, NDV-HUJ) have been the subject of systematic clinical studies in patients who had exhausted all conventional cancer treatments (8) (9) (10) (11) (12). NDV-infected patient-de rived tumor cell vaccines were also used to achieve long-lasting T cell mediated systemic anti-tumor immune memory (12). A randomized-controlled prospective study demonstrated that NDV helped to induce post-oncolytic anti-tumor immunity which improved 10-year survival of colon cancer patients operated from liver metastases (13). In addition, various studies from different institutions in Europe reported responsiveness of high-grade glioblastoma multiforme (GBM) to NDV treatment including tumour remissions and improved survival (14) (15) (16) (17).

In contrast to native pox virus, native NDV shows tumor-selectivity a priori in its replication behavior in mammalian cells, including human (12) (18). NDV derived hemagglutinin-neuraminidase (HN) proteins were demonstrated to activate NKp46 receptors and tumor-killing activity in NK cells (19) and to stimulate a strong type I interferon response in monocytes, macrophages and plasmacytoid and myeloid dendritic cells (12) (18) (20). While such interferon response explains the very good tolerability of even high NDV doses, many tumor cells are incapable to prevent oncolytic NDV replication due to their deficient interferon response. Tumor targeting of NDV could be

improved by bispecific antibodies (21). Delivery of additional therapeutic genes via recombinant NDV strains has also been reported (22).

A tumor cell line which was entirely resistant to NDV (MTH 68/H) in vitro could nevertheless be affected in vivo after metastasis to the liver upon locoregional (but not upon intravenous) virus delivery (23). Lessons obtained from cancer treatment with oncolytic NDV in animals and cancer patients over decades in Germany demonstrated that oncolysis is not the only mechanism that matters in vivo. In situ activation of host anti-tumor immune mechanisms including long-term T cell mediated tumor-specific memory may be equally if not more important for improvement of long-term overall survival with cancer.

Why should neuroblastoma patients have to wait for matching tumour features with 131 different drugs that might help treat diseases for which they weren't designed (24), when NDV has already proved to be a powerful weapon against the most malignant neuroectodermal tumour, GBM (15) (16) (17) (18) (25)?

We have no competing financial interests.

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