



The Progress of Oncolytic Reovirus in Hematologic Malignancies: Can We Combat Blood Cancer with the Cold?

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Oncolytic reovirus continues to pick up momentum as a novel agent in the treatment of cancer. Since the initial discovery of the virus' tendency to preferentially replicate in transformed cell lines from studies in the late 1970s, reovirus has rapidly progressed from preclinical to clinical trials evaluating its efficacy across a spectrum of malignancies, including hematologic.

Reovirus is a non-enveloped double-stranded RNA (dsRNA) virus with three distinct serotypes (Type 1 Lang, Type 2 Jones, Type 3 Abney, and Type 3 Dearing) and member of the *Reoviridae* family of viruses [1-6]. The *Reoviridae* family of viruses is comprised of six genera, three of which are known to infect animals and humans (rotavirus, orbivirus, and reovirus), while the remaining three primarily infect plants and insects [1,2]. In humans, reovirus pathogenicity can be highlighted by mild respiratory and enteric symptoms despite its name having been derived from the fact that it is commonly isolated from the respiratory and enteric tract, often without causing symptoms of disease, or an orphan virus [1-5]. Structurally, reovirus is a non-enveloped virus approximately 80 nm in diameter and comprised of an icosahedral capsid with both outer and inner protein shell components that house its genome of ten segments of dsRNA [1,2,4,6].

The anticancer potential of wild-type reovirus was first identified more than 30 years ago in studies that demonstrated its preferential replication in transformed cell lines but not in normal cells [7,8]. Extensive research has since been performed to elucidate the mechanism(s) of reovirus preferential replication in cancer cells, or oncolysis. In turn, activated Ras signaling, involving mediators both upstream and downstream of Ras, appears crucial in permitting sensitivity to reovirus oncolysis [9]. In particular, activated Ras signaling has been shown to promote reovirus oncolysis by enhancing viral uncoating and disassembly, releasing inhibition of viral translation as induced by dsRNA-activated protein kinase (PKR), enhancing generation of viral progeny with increased infectivity, enhancing viral progeny release, and enhancing virus spread in subsequent rounds of infection [9]. The exact mechanism(s) by which reovirus usurps an activated Ras signaling pathway to induce cancer cell death remain unknown. However, this has not precluded its preclinical and clinical development as an anticancer agent given the wide-reaching implications of activated *Ras* mutations in human cancers.

with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) in the treatment of L1210 murine leukemia cells and EL4 murine lymphoma cells that prolonged survival in ascites tumor mouse models when compared to controls [10,11]. The near absence of *N-Ras* mutations particularly in chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphomas (NHLs) such as follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) posed a perplexing dilemma regarding their susceptibility to reovirus infection [12,13]. However, it was postulated that certain hematologic malignancies may still be responsive to reovirus therapy given the knowledge of relationships between activated Ras signaling pathways and pathogenesis of several lymphomas and leukemias [3,13]. Indeed, reovirus treatment of human lymphoma cells produced antitumor effects in DLBCL cell lines and Burkitt lymphoma cell lines *in vitro*, in a Burkitt cell line *in vivo*, and all human primary CLL samples and a majority of NHL samples including Burkitt lymphoma, mantle cell lymphoma, and DLBCL *ex vivo*, highlighting the concept that activated Ras signaling rather than mutations in the Ras protein itself can be important to disease pathogenesis [13].

Reovirus has also demonstrated marked antitumor responses in acute myeloid leukemia (AML) cell lines *in vitro* and AML specimens *ex vivo*, mixed responses in mantle cell lymphoma cell lines correlating with levels of activated Ras and proteolytic disassembly of reovirus *in vitro*, and meaningful responses in a majority of multiple myeloma cell lines *in vitro* and multiple myeloma models *in vivo* [14-16]. Interestingly, reovirus has also demonstrated success as a novel purging strategy for autologous stem cell transplantations in DLBCL, CLL, Waldenström macroglobulinemia, small lymphocytic lymphoma, breast cancer, and multiple myeloma [17-19].

The only clinical trial so far involving reovirus in the treatment of hematologic cancer is the National Cancer Institute (NCI)-sponsored phase I study (OSU-11148) [20]. Preliminary results have included stable disease (SD) in 5 of 12 patients (42%) with relapsed or refractory multiple myeloma treated with 60-minute intravenous (IV) infusion of reovirus from 3×10^9 tissue culture infectious dose-50 (TCID₅₀) to 3×10^{10} TCID₅₀ on days 1-5 every 28 days [20]. Grade 2 or higher toxicities have so far included leukopenia, anemia, myalgias, neutropenia, thrombocytopenia, and hypophosphatemia though a maximum-tolerated dose (MTD) was not reached and no dose-limiting toxicities (DLTs) were observed [20].

The earliest preclinical studies involved reovirus in combination

Although reovirus in the treatment of blood cancers is only

in early stages of clinical development, its promising potential as a therapeutic agent in this area is underscored by its heightened preference for replication in cancer cells and well-tolerated toxicity profile highlighted by nausea, vomiting, fatigue, fever, myalgias, and other constitutional symptoms characteristic of its relatively mild and benign pathogenicity in humans [1,2,4,6]. Furthermore, the potential of reovirus as an anticancer agent, in general, is rapidly being recognized as its clinical development has currently expanded to 32 clinical trials (both ongoing and completed) involving a spectrum of cancers. Should we therefore sneeze on blood cancer? Can we combat blood cancers with the cold? We will have to wait and see if reovirus fulfills its potential as a novel therapeutic agent against hematologic malignancies. For now, the clinical horizon remains bright for reovirus as the medical and scientific community eagerly awaits the results of its continuing clinical development.

References

- Vidal L, Yap TA, White CL, Twigger K, Hingorani M, et al. (2006) Reovirus and other oncolytic viruses for the targeted treatment of cancer. *Targ Oncol* 1: 130-150.
- Comins C, Heinemann L, Harrington K, Melcher A, De Bono J, et al. (2008) Reovirus: viral therapy for cancer 'as nature intended'. *Clin Oncol (R Coll Radiol)* 20: 548-554.
- Norman KL, Lee PW (2000). Reovirus as a novel oncolytic agent. *The J Clin Inv* 105: 1035-1038.
- Kelly K, Nawrocki S, Mita A, Coffey M, Giles FJ, et al. (2009) Reovirus-based therapy for cancer. *Expert Opin Biol Ther* 9: 817-830.
- Norman KL, Lee PW (2005) Not all viruses are bad guys: the case for reovirus in cancer therapy. *Drug Discov Today* 10: 847-855.
- Harrington KJ, Vile RG, Melcher A, Chester J, Pandha HS (2010) Clinical trials with oncolytic reovirus: moving beyond phase I into combinations with standard therapeutics. *Cytokine Growth Factor Rev* 21: 91-98.
- Hashiro G, Loh PC, Yah JT (1977) The preferential cytotoxicity of reovirus for certain transformed cell lines. *Arch Virol* 54: 307-315.
- Duncan MR, Stanish SM, Cox DC (1978) Differential sensitivity of normal and transformed human cells to reovirus infection. *J Virol* 28: 444-449.
- Gong J, Mita MM (2014) Activated Ras signaling pathways and reovirus oncolysis: an update on the mechanism of preferential reovirus replication in cancer cells. *Front Oncol* 4: 167.
- Kollmorger GM, Cox DC, Killion JJ, Cantrell JL, Sansing WA (1976) Immunotherapy of EL4 lymphoma with reovirus. *Cancer Immunol Immunother* 1: 239-244.
- Williams ME, Cox DC, Stevenson JR (1986) Rejection of reovirus-treated L1210 leukemia cells by mice. *Cancer Immunol Immunother* 23: 87-92.
- Bos JL (1989) Ras oncogenes in human cancer: a review (1989) *Cancer Res* 49: 4682-4689.
- Alain T, Hirasawa K, Pon KJ, Nishikawa SG, Urbanski SJ, et al. (2002) Reovirus therapy of lymphoid malignancies. *Blood* 100: 4146-4153.
- Hall K, Scott KJ, Rose A, Desborough M, Harrington K, et al (2012) Reovirus-mediated cytotoxicity and enhancement of innate immune responses against acute myeloid leukemia. *Biores Open Access* 1: 3-15.
- Alain T, Muzik H, Otsuka S, Chan S, Magliocco, et al. (2010) Susceptibility of mantle cell lymphomas to reovirus oncolysis. *Leuk Res* 34: 100-108.
- Thirukkumaran CM, Shi ZQ, Luider J, Kopciuk K, Gao H, et al. (2012) Reovirus as a viable therapeutic option for the treatment of multiple myeloma. *Clinical Cancer Research* 18: 4962-4972.
- Thirukkumaran CM, Luider JM, Stewart DA, Cheng T, Lupichuk SM, et al. (2003) Reovirus oncolysis as a novel purging strategy for autologous stem cell transplantation. *Blood* 102: 377-387.
- Thirukkumaran CM, Luider JM, Stewart DA, Alain T, Russell JA, et al. (2005) Biological purging of breast cancer cell lines using a replication-competent oncolytic virus in human stem cell autografts. *Bone Marrow Transplant* 35: 1055-1064.
- Thirukkumaran CM, Shi ZQ, Luider J, Kopciuk K, Bahlis N, et al. (2014) Reovirus as a successful ex vivo purging modality for multiple myeloma. *Bone Marrow Transplant* 49: 80-86.
- Sborov DW, Nuovo G, Stiff A, Mace T, Lesinski G, et al. (2013) A phase 1 trial of reolysin alone in patients with refractory or relapsed multiple myeloma. *Blood: (Suppl; abstr 3208)*.