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Jean-François Fonteneau

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## Recent Progresses of Oncolytic Immunotherapy

Jean-François Fonteneau\*

INSERM UMR892, CNRS UMR6299, Institut de Recherche en Santé de l'Université de Nantes, 8 quai Moncousu, BP70721, 44007 Nantes Cedex1, France.

\*Corresponding author: Jean-François Fonteneau, INSERM UMR892 Institute of Health Research of the University of Nantes, 8 Quai Moncousu, BP70721, 44007, Nantes Cedex1, France, Tel: 33-228080239; Fax: 33-228080204; E-mail: [jean-francois.fonteneau@inserm.fr](mailto:jean-francois.fonteneau@inserm.fr)

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### Abstract

Oncolytic immunotherapy, also known as anti-tumor virotherapy, is a therapeutic approach using oncolytic viruses that preferentially or exclusively infect and kill tumor cells. In this short review, we discuss recent advances of this therapeutic strategy.

### Introduction

Oncolytic immunotherapy is a therapeutic approach for treatment of cancer based on the use of oncolytic viruses (OV). OV are attenuated replicative viruses that have been selected and/or modified to preferentially or exclusively infect and kill tumor cells without arming healthy cells [1]. Furthermore, tumor cell death induced by OV is an immunogenic cell death that can induce or stimulate the antitumor immune response [2]. Immunogenic cell death is characterized by the release of danger signals or damage associated molecular patterns (DAMPs) that are able to activate innate and adaptive immunity, notably antigen presenting cells (APC) [3]. OV contained pathogen molecular patterns (PAMPs) that are also strong activators of the immune response via cytoplasmic or membrane-bound pathogen recognition receptors (PRR) [4]. Finally, OV-infected tumor cells also release tumor-associated antigens (TAA) that can be phagocytosed, processed and presented by APCs, such as dendritic cells (DC), via HLA molecules to stimulate TAA specific T cell responses [5-7].

Year 2015 is marked by the release of the results of the phase III oncolytic immunotherapy clinical trial that evaluated Talimogene Laherparepvec (T-vec), also known as OncoVEXGM-CSF, for the treatment of metastatic melanoma [8]. T-vec is a herpes simplex type I virus (HSV1) that is selected to infect cancer cells. T-vec is also modified to encode the granulocyte-macrophage colony-stimulating factor (GM-CSF) to stimulate immunity and the US11 protein to increase viral replication. T-vec is deleted of two virulence factors: ICP47 that normally inhibits class I antigen presentation in the infected cell and ICP34.5 a neurovirulence factor. This OV was compared with GM-CSF for the treatment of 436 metastatic melanoma patients randomly assigned. It was well tolerated and resulted in a higher duration response rate and longer median overall survival. These clinical benefits led an expert panel of the food and drugs administration (FDA) to approve the use of T-vec for the treatment of metastatic melanoma with a majority of 22 to 1, in May 2015. T-vec may be the first FDA approved OV. Interestingly enough, 60% of the patients that have received the T-vec were seropositive for HSV-1 and the therapy was as efficient in these patients as the seronegative ones.

Other OV have reached phase III clinical trials, such as Adenovirus and Reovirus. CG0070 is an oncolytic modified type 5 adenovirus that encode GM-CSF [9]. Its replication is dependent of an inserted E2F promoter that induces replication in transformed cells with an inactive

RB pathway. Furthermore, the virus is deleted of the E3 protein that normally inhibits antigen presentation by HLA class I molecules in the infected cells. In phase I clinical trial, impressive clinical results were obtained for the treatment of nonmuscle invasive bladder cancer in patient by intravesicular injection of the CG0070. 48.6% of complete response rate was observed with CG0070 in patients that had failed the first line therapy consisting in injection of BCG and chemotherapy [9]. This clinical trial has now reached the phase III (NCT01438112). Reolysin is an oncolytic reovirus that infects preferentially transformed cells with an activated Ras pathway [10]. It spares healthy cells that do not have activated RAS pathway. Several reports of phase I and II clinical trials have been published for the treatment of different solid tumors such as melanoma or lung carcinoma [11]. This OV was also evaluated in a completed phase III clinical trial for the treatment of platinum-refractory head and neck cancers, but results are not yet published (NCT01166542).

The last OV to reach phase III clinical trial is the JX594, also known as pexastimogene devacirepvec (Pexa-Vec). JX594 is a recombinant Wyeth strain of vaccinia poxvirus that has been modified by addition of the GM-CSF gene to stimulate the anti-tumor immune response and deletion of the thymidine kinase gene. Thymidine kinase activity is required for replication of this virus and can be found in tumor cells where this activity is high. After encouraging clinical results of the phase II clinical trial to treat advanced hepatocellular carcinoma patients by intratumor injection of JX594 [12], a phase III clinical trial is planned by SillaJen Biotherapeutics and Transgene SA [13]. Like in the case of T-vec, no difference of efficiency was observed between vaccinia seropositive and seronegative patients.

This year, interesting clinical results were obtained with measles virus (MV) for the treatment of chemotherapy resistant ovarian cancer [14]. MV-NIS is an oncolytic Edmonston strain of MV that encodes the sodium iodide symporter (NIS). It allows following of viral replication after injection of iodine-123 to the patient. MV targets tumor cells that often overexpress the MV entry receptor CD46 compared to healthy cells [15]. In addition, replication of MV is favored in cancer cells with deficient antiviral type I interferon response [16]. In a phase I clinical trial, median overall survival of ovarian cancer patients receiving high doses of MV was more than the double of median overall survival of ovarian cancer patients receiving low doses of MV. Furthermore, infection of tumor cells after intraperitoneal injection of MV induces an antitumor T cell response that probably helps efficacy of the treatment. A phase II clinical trial is starting comparing MV-NIS to chemotherapy.

Recently cancer immunotherapy has been deeply modified by the use of check point inhibitors (anti-CTLA4, anti-PD1...), that restore the antitumor activity of T lymphocytes that infiltrate tumor [17]. Lots of preclinical and clinical studies are now evaluating the combination of OV to induce the lymphocyte infiltrate and check point inhibitor to

arm the infiltrating lymphocytes. Thus, these combinations probably represent the future of oncolytic immunotherapy that hopefully will be soon a new weapon in the therapeutic arsenal to fight cancer.

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