Accepted Manuscript

Advances in Oncolytic Adenovirus Therapy for Pancreatic Cancer

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PII: S0304-3835(18)30454-3

DOI: 10.1016/j.canlet.2018.07.006

Reference: CAN 13979

To appear in: *Cancer Letters*

Received Date: 26 April 2018

Revised Date: 28 June 2018

Accepted Date: 3 July 2018

Please cite this article as: C. Nattress, G. Halldén, Advances in Oncolytic Adenovirus Therapy for Pancreatic Cancer, *Cancer Letters* (2018), doi: 10.1016/j.canlet.2018.07.006.

Abstract

Survival rates for pancreatic cancer patients have remained unchanged for the last four decades. The most aggressive, and most common, type of pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC), which has the lowest 5-year survival rate of all cancers globally. The poor prognosis is typically due to late presentation of often non-specific symptoms and rapid development of resistance to all current therapeutics, including the standard-of-care cytotoxic drug gemcitabine. While early surgical intervention can significantly prolong patient survival, there are few treatment options for late-stage non-resectable metastatic disease, resulting in mostly palliative care. In addition, a defining feature of pancreatic cancer is the immunosuppressive and impenetrable desmoplastic stroma that blocks access to tumour cells by therapeutic drugs. The limited effectiveness of conventional chemotherapeutics reveals an urgent need to develop novel therapies with different mechanisms of action for this malignancy.

An emerging alternative to current therapeutics is oncolytic adenoviruses; these engineered biological agents have proven efficacy and tumour-selectivity in preclinical pancreatic cancer models, including models of drug-resistant cancer. Safety of oncolytic adenoviral mutants has been extensively assessed in clinical trials with only limited toxicity to normal healthy tissue being reported. Promising efficacy in combination with gemcitabine was demonstrated in preclinical and clinical studies. A recent surge in novel adenoviral mutants entering clinical trials for pancreatic cancer indicates improved efficacy through activation of the host anti-tumour responses. The potential for adenoviruses to synergise with chemotherapeutics, activate anti-tumour immune responses, and contribute to stromal dissemination render these mutants highly attractive candidates for improved patient outcomes.

Currently, momentum is gathering towards the development of systemically-deliverable mutants that are able to overcome anti-viral host immune responses, erythrocyte binding and hepatic uptake, to promote elimination of primary and metastatic lesions. This review will cover the key components of pancreatic cancer oncogenesis; novel oncolytic adenoviruses; clinical trials; and the current progress in overcoming the challenges of systemic delivery.