



Research Article

# Histone deacetylase inhibitor FR901228 enhances the antitumor effect of telomerase-specific replication-selective adenoviral agent OBP-301 in human lung cancer cells

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## Abstract

Replication-competent oncolytic viruses are being developed for human cancer therapy. We previously reported that an attenuated adenovirus OBP-301 (Telomelysin), in which the human telomerase reverse transcriptase promoter element drives expression of E1A and E1B genes linked with an internal ribosome entry site, could replicate in and causes selective lysis of human cancer cells. Infection efficiency in target cancer cells is the most important factor that predicts the antitumor effects of OBP-301. The objectives of this study are to examine the effects of the histone deacetylase inhibitor FR901228 on the level of coxsackie and adenovirus receptor (CAR) expression and OBP-301-mediated oncolysis in human non-small cell lung cancer cell lines. Flow cytometric analysis revealed up-regulated CAR expression in A549 and H460 cells following treatment with 1 ng/ml of FR901228, which was associated with increased infection efficiency as confirmed by replication-deficient  $\beta$ -galactosidase-expressing adenovirus vector. In contrast, neither CAR expression nor infection efficiency was affected by FR901228 in H1299 cells. To visualize and quantify viral replication in the presence of FR901228, we used OBP-401 (Telomelysin-GFP) that expresses the green fluorescent protein (GFP) reporter gene under the control of the cytomegalovirus promoter in the E3 region. Fluorescence microscopy and flow cytometry showed that FR901228 increased GFP expression in A549 and H460 cells following OBP-401 infection in a dose-dependent manner, but this effect did not occur in H1299 cells. In addition, OBP-301 and FR901228 demonstrated a synergistic antitumor effect in A549 cells *in vitro*, as confirmed by isobologram analysis. Our data indicate that FR901228 preferentially increases adenovirus infectivity via up-regulation of CAR expression, leading to a profound oncolytic effect, which may have a significant impact on the outcome of adenovirus-based oncolytic virotherapy.

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## Introduction

Replication-selective, oncolytic viruses provide a new platform to treat a variety of human cancers [1,2]. Promising

clinical trial data have shown the antitumor potency and safety of mutant or genetically modified adenoviruses [3–6]. We previously constructed an adenovirus vector (OBP-301, Telomelysin), in which the human telomerase reverse transcriptase (hTERT) promoter element drives expression of E1A and E1B genes linked with an internal ribosome entry site (IRES). We showed that OBP-301 caused efficient selective killing in human cancer cells, but not in normal cells [7]. Although OBP-301 demonstrated a broad-spec-

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