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Antitumor effect of oncolytic virus and paclitaxel encapsulated in extracellular vesicles for lung cancer treatment M. Garofalo^{1,2,&}, H. Saari^{1,1}, P. Somersalo^{1,2,1}, D.Crescenti², L.Kuryk^{1,3,4}, L. Aksela¹, C. Capasso⁵, M.Madetoja⁶, K. Koskinen⁷, T. Oksanen¹, A. Mäkitie⁸, M. Jalasvuori^{1,7}, V. Cerullo³, P. Ciana², M. Yliperttula^{1,*} marjo.yliperttula@helsinki.fi ¹Division of Pharmaceutical Biosciences and Centre for Drug Research, University of Helsinki, Helsinki, Viikinkaari 5, 00790, Finland. ²Department of Oncology and Hemato-Oncology, Center of Excellence on Neurodegenerative Diseases, University of Milan, Milan, Via Balzaretti 9, 20133, Italy ³National Institute of Public Health – National Institute of Hygiene, Department of Virology, 24 Chocimska str. 00-791 Warsaw, Poland ⁴Targovax Ov, R&D, Clinical Science, R&D, Saukonpaadenranta 2, 00180 Helsinki, Finland ⁵Laboratory of ImmunoViroTherapy, Drug Research Program, Faculty of Pharmacy, University of Helsinki, Helsinki, Viikinkaari 5,00790, Finland. ⁶Made Consulting, Tykistökatu 4 B, FI-20520 Turku, Finland ⁷Biological and Environmental Science, Nanoscience Center, University of Jyväskylä, Survontie 9C, 40500, Finland ⁸Department of Otorhinolaryngology – Head and Neck Surgery, Helsinki University Hospital and University of Helsinki, P.O.Box 263, FI_00029 HUS, Helsinki, Finland

*Corresponding author.

ABSTRACT

Standard of care for cancer is commonly a combination of surgery with radiotherapy or chemoradiotherapy. However, in some advanced cancer patients this approach might still remain inefficient and may cause many side effects, including severe complications and even death. Oncolytic viruses exhibit different anti-cancer mechanisms compared with conventional therapies, allowing the possibility for improved effect in cancer therapy. Chemotherapeutics combined with oncolytic viruses exhibit stronger cytotoxic responses and oncolysis. Here, we have investigated the systemic delivery of the oncolytic adenovirus and paclitaxel encapsulated in extracellular vesicles (EV) formulation that, *in vitro*, significantly increased the transduction ratio and the infectious titer when compared with the virus and paclitaxel alone. We demonstrated that the obtained EV formulation reduced the *in vivo* tumor growth in animal xenograft model of human lung cancer. Indeed, we found that combined treatment of oncolytic adenovirus and paclitaxel encapsulated in EV has enhanced anticancer effects both *in vitro* and *in vivo* in lung cancer models. Transcriptomic

¹ shared co-authorship, [&]co-correspondance

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