

Epidermal growth factor receptor-targeted poly(amidoamine)-based dendrimer complexed oncolytic adenovirus: is it safe totally?

Min Huang^{1*}, Chun-Sheng Yang^{2*}, Yong Xin¹, Guan Jiang³

¹Department of Radiotherapy, the Affiliated Hospital of Xuzhou Medical University, Xuzhou 221002, China; ²Department of Dermatology, the Affiliated Huai'an Hospital of Xuzhou Medical University, Huai'an 23002, China; ³Department of Dermatology, the Affiliated Hospital of Xuzhou Medical University, Xuzhou 221002, China

*These authors contributed equally to this work.

Correspondence to: Guan Jiang, MD, PhD. Department of Dermatology, the Affiliated Hospital of Xuzhou Medical University, Xuzhou 221002, China. Email: dr.guanjiang@gmail.com.

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Oncolytic adenoviruses (OAds) express shRNA (1) and selectively replicate in and lyse cancer cells. Therefore, they are commonly used as vectors in clinical trials for cancer gene therapy (2). However, because the oncolytic antitumor activity is insufficient to effectively eliminate tumors, “armed” (e.g., polymers, liposomes, or nanoparticles) oAd have been devised to extend the circulation time, reduce immunogenicity, and result in an increased antitumor effect, as well as lower the accumulation and toxicity in the liver (3). To overcome the non-specificity of conventional chemotherapeutics, an epidermal growth factor receptor (EGFR) inhibitor, Erbitux (ErbB), was developed as a well-documented and efficacious antibody against EGFR (4), and is now widely used to treat lung cancer patients (5).

In the study by Yoon *et al.* (6) published in the *Journal of Controlled Release* [2016], the authors observed that an ErbB-conjugated and PPE could reduce the toxicity of the Ads while improving the specificity and therapeutic efficacy against EGFR-positive lung tumors. This innovative work combines gene therapy with nanoparticle carriers and monoclonal antibody inhibitors, providing a novel approach to cancer therapy. Therefore, oAd/DCN-shMet/PPE may be a promising therapeutic for EGFR-overexpressing lung cancer.

To evaluate the efficacy of the EGFR-targeted dendrimer-shielded oAds in EGFR-expressing lung tumors, the authors selected EGFR-positive human lung cancer

cells (A549), EGFR-negative breast cells (MCF7), and EGFR-negative normal cells (HDF) as the target cells. The therapeutic gene expression and cancer cell killing effect induced by oAd/DCN-shMet/PPE in these cells were compared with PP, PPE, oAd/DCN-shMet, and oAd/DCN-shMet/PP. The results indicated that oAd/DCN-shMet/PPE can enhance the efficacy of cancer cell killing in EGFR-expressing cancer cells, while protecting non-targeted cells from the cytolytic activity of the oAds. The innate and adaptive immune response against Ads and the toxicity of oAd/DCN-shMet/PPE *in vivo* were also analyzed. The results were then compared with PBS, oAd/DCN-shMet and oAd/DCN-shMet/PP controls. The authors found that oAd/DCN-shMet/PPE can efficiently attenuate both the Ad-associated innate and adaptive immune responses, and no hepatic injury was detected. This demonstrated that oAd/DCN-shMet/PPE can also reduce the Ad-associated liver toxicity *in vivo*.

According to the described experiments, the immune response induced by Ad may be attenuated by a dendrimer coating. However, several recent studies have indicated that nanoparticle carriers also possess immunogenicity. In particular, PAMAM dendrimers have been reported to affect the secondary structure and conformation of γ -golbulin, as well as inhibit complement activation, indicating that the immune response can be activated by PAMAM dendrimers (7).

Naha *et al.* (8) assessed the immunotoxicological response of three generations of cationic PAMAM dendrimers and concluded that they may be useful as a vaccine delivering agent due to the enhanced levels of cytokine production. Additionally, Bertero *et al.* (9) analyzed the role of dendrimer surface functionalisation with regards to toxicity and immune cell activation, raising concerns about possible inflammatory reactions. In Yoon's article, the toxicity of the PAMAM dendrimer was reduced by generating ErbB-conjugated PEGylated PAMAM. However, we wonder how to deal with the immunogenicity of PPE.

For biomedical purposes, especially *in vivo* applications, toxicity is a critical factor to consider when evaluating their potential. In particular, the uses of nanoparticles for the delivery of therapeutics are often coated with bioconjugates, such as DNA, proteins, and monoclonal antibodies depending on the target cells (10). The primary form of nanoparticle toxicity is cytotoxicity, which can be tested by a visual inspection of the cells with bright-field microscopy (11). Yoon *et al.* evaluated the reduced toxicity of PPE-coated oAd by examining the level of nonspecific liver uptake. However, the analysis of the nanoparticle toxicity appears to have been ignored and was not carried out.

Furthermore, for the initial characterization experiments in section 2.10, Balb/c mice were used, while in the later experiments described in section 2.12, nude mice were used. Since the authors stressed repeatedly that oAd/DCN-shMet/PPE can efficiently attenuate both the Ad-associated innate and adaptive immune responses, it is unclear why the T cell deficient mouse model was used in the later experiments.

Although novel advances in nanoparticles have facilitated new prospects in gene therapy, long-term safety concerns (e.g., immune response and toxicity) still limit the development of nanoparticles in gene therapy for clinical applications. Nano materials (e.g., polymers, liposomes, and peptides) have reportedly overcome these drawbacks; however, the side effects including immunogenicity and toxicity themselves cannot be ignored. With the development of nano materials, it will be a major breakthrough to use them as a carrier for gene therapy in the near future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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