

Safety profile of EGFR-targeted hybrid vector system composed of PAMAM dendrimer and oncolytic adenovirus

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We would like to thank Huang *et al.* for comments on our recent report, which assessed the “antitumor effect and safety profile of systemically delivered oncolytic adenovirus complexed with epidermal growth factor receptor (EGFR)-targeted poly(amidoamine) (PAMAM)-based dendrimer (1)”. We read the comments with great interest and acknowledging that this is an area urgently requiring more research to improve safety of nanomaterials in gene therapy for clinical application.

The main concerns the author deal with is the immunotoxicological response of nanomaterials. As Huang emphasized, the immune response and liver toxicity of carrier should be extensively examined for successful gene therapy. In our report, we have also addressed these concerns that highly cationic PAMAM dendrimer has narrow clinical applications due to PAMAM’s poor biocompatibility and biodegradability which causes nonspecific internalization into nontarget cells and severe toxicity (2,3). To overcome this limitation of PAMAM, we have generated oncolytic Ad complexed with PAMAM dendrimers modified with poly(ethylene glycol) and EGFR targeting moiety, Erbitux, (PPE) to reduce the toxicity of the PAMAM dendrimer while improving EGFR-targeting ability and pharmacokinetics profile of the carrier.

We have shown that both PEGylated polymers [PEGylated PAMAM (PP) and PPE] exhibits marginal toxicity up to 100 µg/mL, a markedly higher concentration of polymer than those required for the generation of PPE-

complexed oncolytic adenoviruses (oAd) co-expressing decorin (DCN) and short hairpin RNA targeting Met (shMet) (oAd/DCN-shMet/PPE) complex utilized *in vivo* system (Figure 1). These findings are consistent with previous reports where PEGylation of cationic polymer reduced toxicity through reduction of polymer’s surface charge and improved the solubility of the carrier, minimizing aggregation of particulates (2,4). Furthermore, PP- or PPE-coated oAd induced no observable damage to the liver (Figure 9B,C), further elucidating that quantity of PP or PPE used for the systemic delivery of oAd was well-tolerated.

Even though we have not evaluated immunogenicity of PP or PPE, there are other studies demonstrating that immunogenicity of PAMAM dendrimers can be greatly reduced by surface-modification using PEG chains (5,6). Furthermore, oAd/DCN-shMet/PP and oAd/DCN-shMet/PPE induced minimal innate immune response (Figure 6A), suggesting that PP or PPE is either weakly or non-immunogenic. Based on these reports and our findings, both PP and PPE seem to have no glaring immunogenicity issues.

Lastly, we would like to explain why two different types of mice were used *in vivo*. Nude mice were utilized to establish human lung tumor xenograft to accurately assess oAd/DCN-shMet/PPE’s therapeutic efficacy against EGFR-overexpressing human lung tumors (7). However, immunogenicity of our complex cannot be adequately addressed in nude mice as they lack adequate immune

system, thus immunocompetent Balb/C mice was used to accurately analyze immunogenicity of our treatments. Others have also utilized nude mice and immunocompetent mice in conjunction to demonstrate two different aspects of oncolytic virotherapy (antitumor efficacy and immune responses, respectively) as murine tumor cells are not permissive toward infection with human serotype 5-based oncolytic Ad and prevents efficient replication of the virus (8,9).

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Footnote

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

References

1. Yoon AR, Kasala D, Li Y, et al. Antitumor effect and safety profile of systemically delivered oncolytic adenovirus complexed with EGFR-targeted PAMAM-based dendrimer in orthotopic lung tumor model. *J Control Release* 2016;231:2-16.
2. Park TG, Jeong JH, Kim SW. Current status of polymeric gene delivery systems. *Adv Drug Deliv Rev* 2006;58:467-86.
3. Chollet P, Favrot MC, Hurbin A, et al. Side-effects of a systemic injection of linear polyethylenimine-DNA complexes. *J Gene Med* 2002;4:84-91.
4. Zhu S, Hong M, Zhang L, et al. PEGylated PAMAM dendrimer-doxorubicin conjugates: in vitro evaluation and in vivo tumor accumulation. *Pharm Res* 2010;27:161-74.
5. Luong D, Kesharwani P, Deshmukh R, et al. PEGylated PAMAM dendrimers: Enhancing efficacy and mitigating toxicity for effective anticancer drug and gene delivery. *Acta Biomater* 2016;43:14-29.
6. Thakur S, Kesharwani P, Tekade RK, et al. Impact of pegylation on biopharmaceutical properties of dendrimers. *Polymer* 2015;59:67-92.
7. Budhu S, Wolchok J, Merghoub T. The importance of animal models in tumor immunity and immunotherapy. *Curr Opin Genet Dev* 2014;24:46-51.
8. Jung SJ, Kasala D, Choi JW, et al. Safety profiles and antitumor efficacy of oncolytic adenovirus coated with bioreducible polymer in the treatment of a CAR negative tumor model. *Biomacromolecules* 2015;16:87-96.
9. Na Y, Choi JW, Kasala D, et al. Potent antitumor effect of neurotensin receptor-targeted oncolytic adenovirus co-expressing decorin and Wnt antagonist in an orthotopic pancreatic tumor model. *J Control Release* 2015;220:766-82.

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