

## Correspondence

## Reply

To the Editor:

We thank Dr Kelso for his correspondence<sup>1</sup> regarding our recent article<sup>2</sup> in which we demonstrated that polyethylene glycol (PEG)-containing substances are not reliable surrogates for skin testing for allergy to the BNT162b2 COVID-19 vaccine. Although PEGylated liposomal drugs induced basophil activation *ex vivo* in 3 patients with PEG allergy, PEG alone did not. Dr Kelso highlights 3 important questions raised by this research that are worth discussing.

The first question relates to why 2 patients who had previously demonstrated a positive skin test result in response to PEG-containing substances appeared to have lost their reactivity. We were also intrigued by this; however, loss of skin test positivity is not uncommon in drug allergy,<sup>3</sup> and has recently been documented in patients with PEG allergy.<sup>4</sup> As these 2 participants reacted to PEGylated liposomal vaccine, we suggest that the inconsistent skin testing results are a consequence of PEG being poorly allergenic in its native state. In support of this, we present a fourth patient, a 38-year-old female with a history of anaphylaxis following PEG3350-containing bowel prep and PEG excipient-containing drugs. Her skin prick testing was initially performed at another institution, and the results were negative in relation to PEG200, 400, 600, 3350, 2000, and 6000. However, upon oral challenge with 35 mg of PEG3350 (Movicol; Norgine, Sydney, Australia), definite urticaria was observed at multiple sites within 30 minutes. Six weeks later, the patient underwent skin testing panel as we described elsewhere<sup>2</sup> with a positive result in response to the BNT162b2 vaccine. In agreement with our original case series, basophil activation testing demonstrated positivity in response to the vaccine and to PEGylated liposomal doxorubicin

(Fig 1) but not to PEG alone. This case suggests that skin testing with “free” PEG does not necessarily equate to hypersensitivity, and as such, skin testing with PEGylated liposomal drugs is useful not only for the assessment of vaccine risk but also in the diagnosis of PEG allergy.

The second question relates to the mechanism by which PEGylated liposomes induce basophil activation. Dr Kelso suggests measuring vaccine-specific IgE level in these patients as an indicator that basophil activation in response to the vaccine is IgE dependent as opposed to involving IgE-independent mechanisms such as complement activation–related pseudoallergy. Although this is valid, there are technical issues with measuring antibodies against PEG or against conformationally intact liposomes.<sup>5</sup> The involvement of IgE can, however, be directly tested by selective depletion of IgE in an indirect basophil activation test. This is something that we intend to address.

The third question is whether these patients are representative of those experiencing anaphylaxis following administration of the vaccine. We certainly believe that these patients are at risk given their history of anaphylaxis in response to PEG and their *in vitro* and *in vivo* reactivity to the vaccine, and we therefore agree with the existing recommendations against using PEGylated liposomal vaccines for vaccination of patients with PEG allergy. Nonetheless, we agree that it is important to now apply basophil activation testing in those who react to administration of the vaccine, and we invite contribution of patients from outside our small local population in South Australia.

Griffith Perkins, BSc (Adv)<sup>a,b</sup>

Alexander Troelnikov, MBBS, BMedSci (Hons)<sup>a</sup>

Pravin Hissaria, MD, MBBS, FRACP, FRCPA<sup>c</sup>

From <sup>a</sup>SA Pathology, Adelaide, Australia; <sup>b</sup>the School of Biological Sciences, University of Adelaide, Adelaide, Australia; and <sup>c</sup>the Immunology Department, Royal Adelaide Hospital, Adelaide, Australia. E-mail: [pravin.hissaria@sa.gov.au](mailto:pravin.hissaria@sa.gov.au).

Supported by the Hospital Services Charitable Gifts Board, Royal Adelaide Hospital.

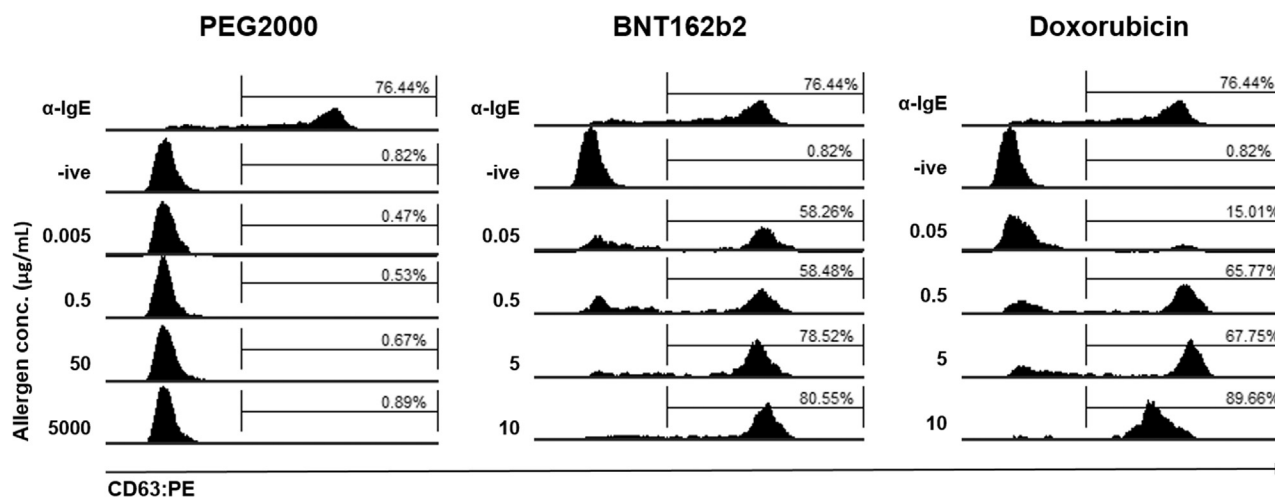


**FIG 1.** *Ex vivo* basophil activation in response to PEG2000, the PEGylated liposomal COVID-19 vaccine BNT162b2, and PEGylated liposomal doxorubicin in a patient with a positive result of PEG3350 oral challenge with a concurrent negative result of skin prick testing in response to PEG200, PEG400, PEG600, PEG2000, PEG3350, and PEG6000.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

## REFERENCES

1. Kelso J. *In vivo* and *in vitro* testing with PEGylated nanoparticles. *J Allergy Clin Immunol* 2021;148 xxx.
2. Troelnikov A, Perkins G, Yuson C, Ahamdie A, Balouch S, Hurtado PR, et al. Basophil reactivity to BNT162b2 is mediated by PEGylated lipid nanoparticles in PEG allergic patients. *J Allergy Clin Immunol* 2021;148:91-5.
3. Blanca M, Torres MJ, García JJ, Romano A, Mayorga C, de Ramon E, et al. Natural evolution of skin test sensitivity in patients allergic to  $\beta$ -lactam antibiotics. *J Allergy Clin Immunol* 1999;103:918-24.
4. Bruusgaard-Mouritsen MA, Jensen BM, Poulsen LK, Johansen JD, Garvey LH. Optimizing investigation of suspected allergy to polyethylene glycols. *J Allergy Clin Immunol* 2021;184:107229.
5. Schellekens H, Hennink WE, Brinks V. The immunogenicity of polyethylene glycol: facts and fiction. *Pharm Res* 2013;30:1729-34.

<https://doi.org/10.1016/j.jaci.2021.06.003>