Anti-PEG IgG may be one of causes to induce anaphylaxis following administration of PEGylated therapeutics

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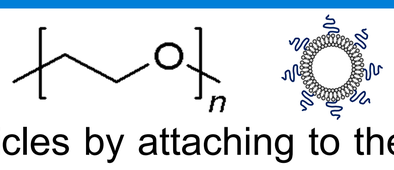
Purpose

1. To develop a mouse model bearing anti-PEG IgG

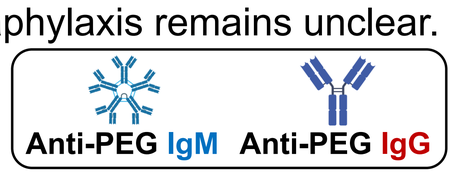
2. To investigate the effect of anti-PEG IgG on the anaphylaxis

Introduction

Polyethylene glycol (PEG) improves the stability and the circulation half-life of nanoparticles by attaching to their surface. PEG modification is widely used in pharmaceutical formulations such as Doxil® and mRNA vaccines. Despite the general recognition that PEG has low immunogenicity, recent reports demonstrated that **anti-PEG IgM** and **anti-PEG IgG** were detected in healthy adults. We have reported that PEG can become immunogenic and induce anti-PEG IgM when PEG is modified onto liposome[1)]. It is assumed that anti-PEG antibodies may contribute to anaphylaxis following administration of PEGylated therapeutics. However, due to the lack of animal models bearing anti-PEG IgG, the impact of anti-PEG antibody class on PEGylated therapeutics-related anaphylaxis remains unclear.

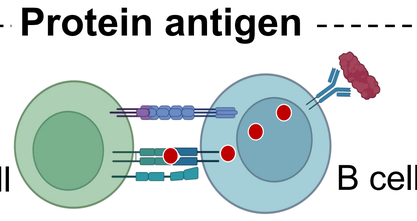


1) T. Ishida, *et al.*, *J. Control. Release* (2006), **112**, 15-25.



● Mechanisms of antibody induction

Protein antigen



B cells are activated by T cells via peptide fragments, inducing class switching.

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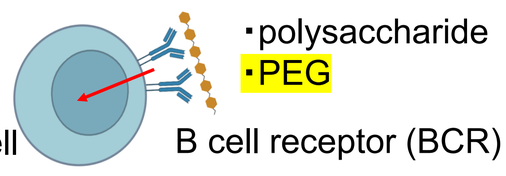
IgG antibodies are induced.

Non-protein antigen



Cross-linking of multiple BCRs by antigen epitopes activates B cells independently.

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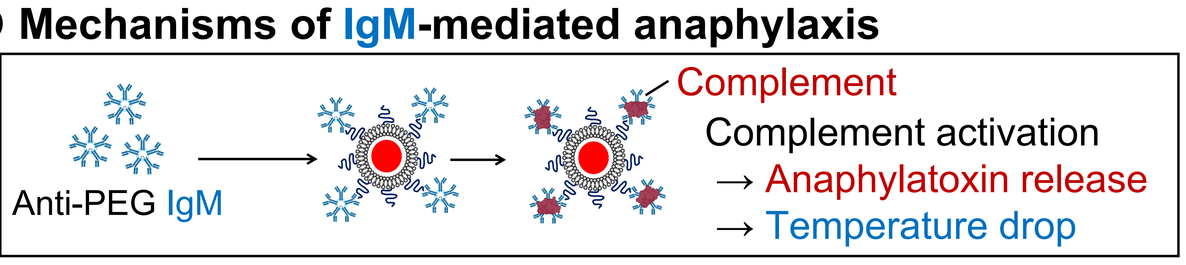
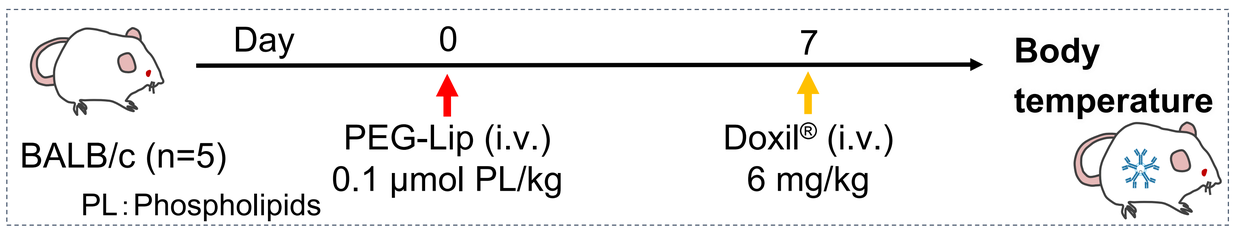
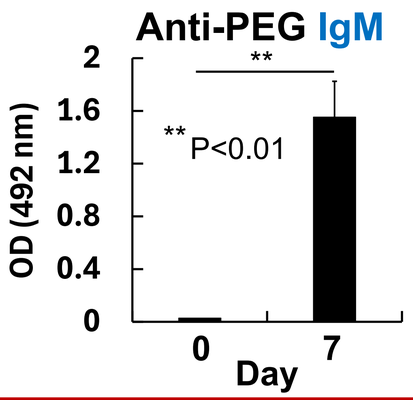
Only IgM antibodies are induced.

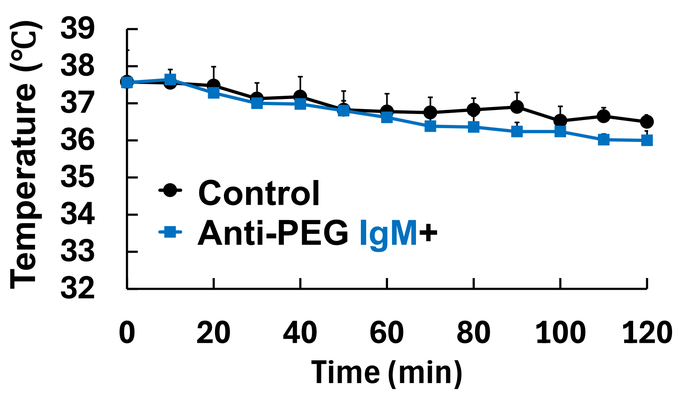
Anti-PEG IgG induction by PEG alone is challenging.

● Mechanisms of IgM-mediated anaphylaxis









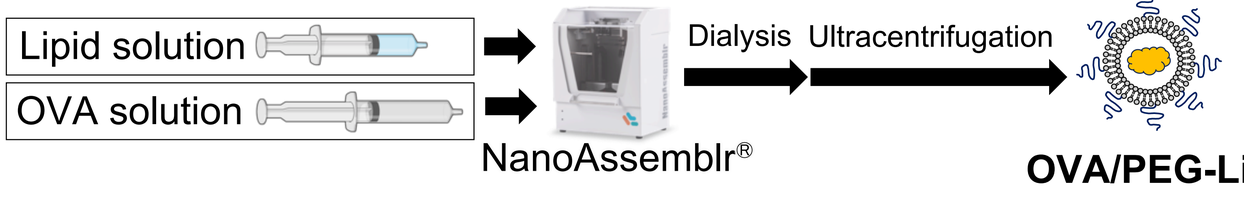
I.v. bolus injection of Doxil® did not cause any body temperature drop in **anti-PEG IgM**-bearing mice.

Hypothesize

We hypothesized that mixing a **protein** and **PEG** would enable the induction of **anti-PEG IgG**.

Fig. 1, Preparation of ovalbumin-containing PEGylated liposome

Lipid composition; HSPC:Chol:mPEG$_{2000}$-DSPE=1.85:1:0.15 (molar ratio)



Size	PDI	Zeta potential	Loading Efficiency
145.4±0.9 nm	0.22±0.01	-14.2±0.7 mV	19.7%

Conclusion

Our anti-PEG IgG bearing mouse model would be useful for safety evaluation of PEGylated therapeutics.

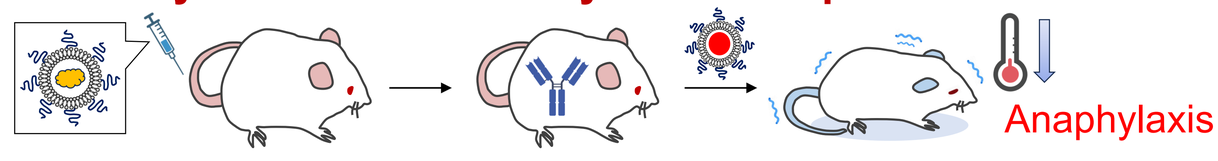
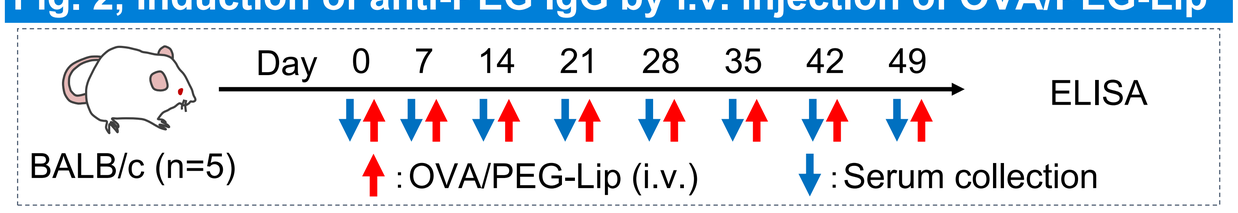
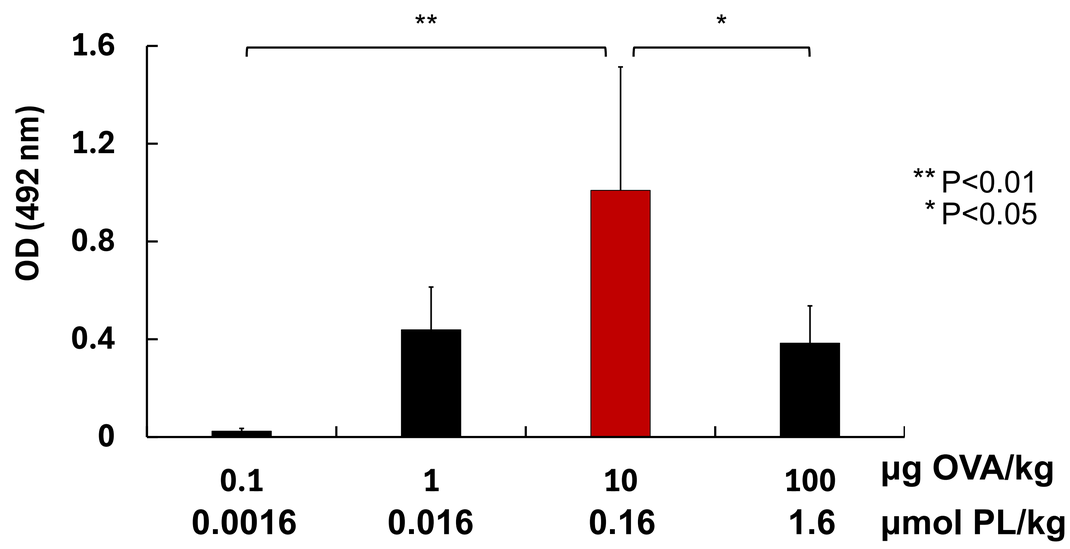


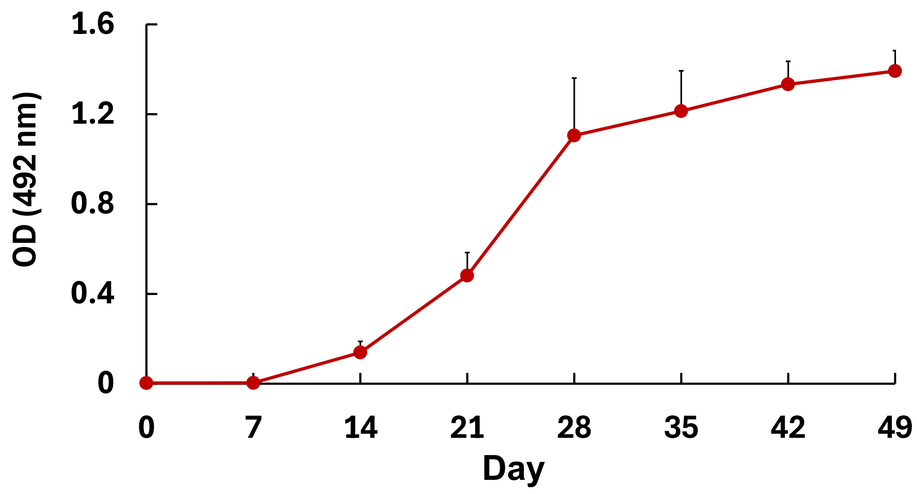
Fig. 2, Induction of anti-PEG IgG by i.v. injection of OVA/PEG-Lip



Dose-dependent induction of anti-PEG IgG on day28



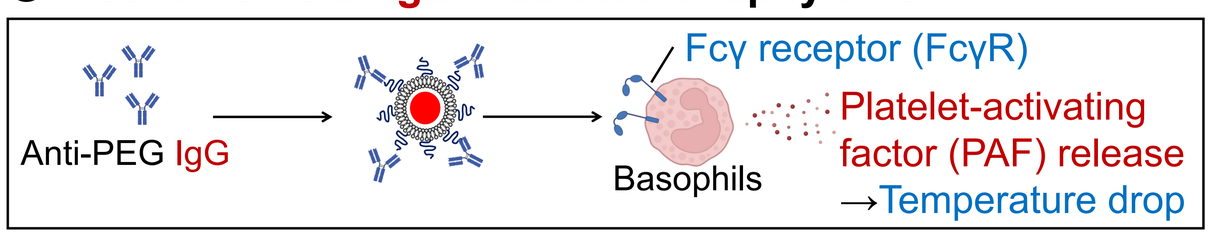
Anti-PEG IgG level as a function of time at 10 μg OVA/kg dose

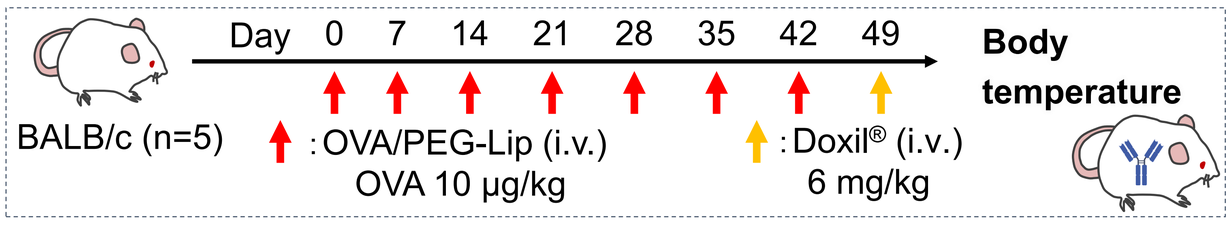


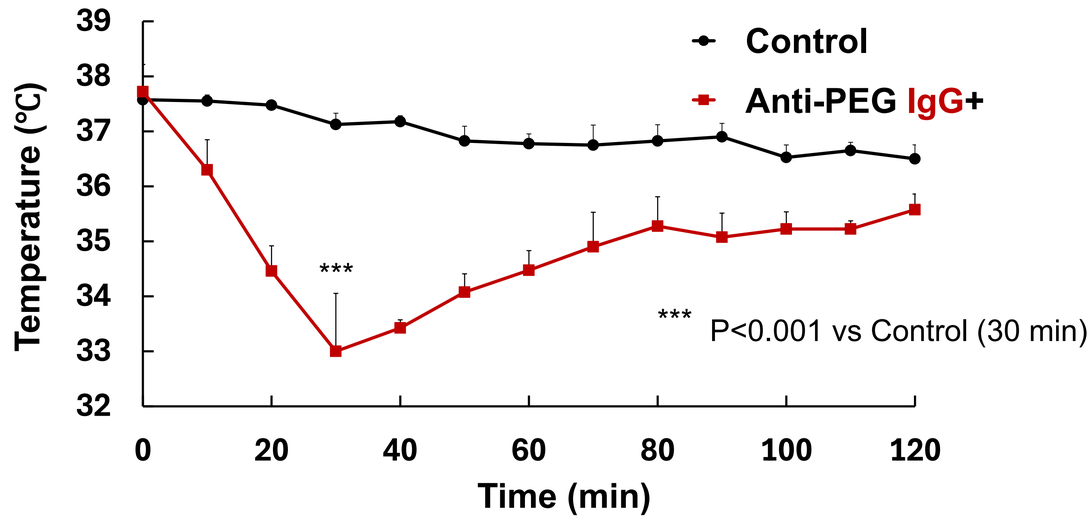
We finally could obtain the first reported anti-PEG IgG-bearing mice.

Fig. 3, Temperature change following Doxil® injection in anti-PEG IgG-bearing mice

● Mechanisms of IgG-mediated anaphylaxis







I.v. bolus injection of Doxil® caused severe body temperature drop in **anti-PEG IgG** bearing mice.