



Cover story

Attenuating the immunogenicity of PEGylated liposomes by gangliosides



PEGylation, the conjugation of polyethylene glycol (PEG), has been extensively applied in the pharmaceutical industry, particularly in the field of drug delivery, to improve the bioavailability of active pharmaceutical ingredients, in particular protein drugs. The crucial role of PEGylation derives mainly from the ability of PEG, a hydrophilic polymer, to attract water molecules, which results in a significant increase in the hydrodynamic size, and thereby, attenuates a rapid renal clearance of PEGylated products [1]. In addition, the steric stabilization that is imparted by the formation of a hydration zone around a PEGylated substance protects the PEGylated product against enzymatic degradation and against the surface binding of certain serum proteins (opsonins) that interact with the immune system [2]. Consequently, PEGylation efficiently evades the recognition of PEGylated products by the cells of mononuclear phagocyte system (MPS), which has hindered the therapeutic efficacy of many non-PEGylated products.

The useful property of PEGylated drugs has been compromised by the unfortunate inclination of PEG causing immune responses. Immunogenicity of PEG, manifested by the robust production of anti-PEG IgM, reduces not only the therapeutic efficacy but also the tolerance of PEGylated therapeutics, causing side effects. In a Phase I clinical trial treating patients with phenylketonuria, the anti-PEG antibody response against PEGylated phenylalanine ammonia lyase was claimed for the induction of severe allergic reactions in patients who were further treated with intramuscular injections of medroxyprogesterone acetate, a drug containing free PEG and polysorbate as excipients [3]. Hershfield et al. [4] reported that the occurrence of an infusion reaction was higher in anti-PEG antibody-positive patients than the antibody-negative patients. Povsic et al. [5] also recently reported the relevance of anti-PEG antibody with allergic reactions against the PEGylated drug. A strategy that can avoid and/or suppress the anti-PEG immune response is needed for further development of PEGylated drugs.

The paper by Professor Tatsuhiro Ishida and his team in this issue introduced a methodology for the attenuation of anti-PEG immunity via the insertion of porcine gangliosides, oligoglycosylceramides containing sialic acids, into the membrane of PEGylated liposomes [6]. They reported that liposomal membrane modification by gangliosides could efficiently attenuated the anti-PEG IgM response via inducing immunological tolerance against PEG through the ligation of sialic acid-containing gangliosides to B cell inhibitory co-receptors. They verified that such an immunosuppressive effect was only induced by the co-presentation of PEG and gangliosides on the same liposome, and that the sequestration of gangliosides and PEG from liposomes failed to attenuate the anti-PEG IgM response. Their results suggest that gangliosides alone do not activate or induce non-specific suppressor cells or their factors. Instead, upon co-presentation of gangliosides with PEG, ganglioside-modified PEGylated liposomes (G-PL) exert its immunosuppressive activity against PEG-reactive B cells presumably via the tolerance of PEG-

reactive B cells. Accordingly, decorating PEGylated nanocarriers with ganglioside (a siglec ligand) may be a promising method to abrogate or attenuate anti PEG immunity, and consequently, alleviate the incidence of the rapid clearance of subsequent doses of PEGylated therapeutics.

To date several PEGylated products have been approved for clinical use and more PEGylated products, such as PEGylated proteins and PEGylated nanocarriers, are expected to enter the market in the coming years. The existence of naturally occurring anti-PEG antibodies in patients [7] could potentially abrogate continued treatment with PEGylated products based on the increasing incidence of high titers of anti-PEG antibodies. This could compromise therapeutic efficacy and lead to the development of life-threatening hypersensitivity reactions [8]. Accordingly, new strategies need to be developed to outmaneuver the induction of anti-PEG immunity upon second sequential use of PEGylated drugs. The work by the Ishida team provides a great starting point in the search of new methods for attenuating the immunogenicity of PEGylated drug delivery systems.

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Kinam Park
 Purdue University
 Departments of Biomedical Engineering and Pharmaceutics
 West Lafayette, IN 47907, USA
 E-mail address: kpark@purdue.edu