Brushing off antigenicity

Conjugation of a diabetes drug with a brush polymer reduces the reactivity of the drug conjugate towards pre-existing polymer antibodies in human plasma and improves the drug’s performance in diabetic mice.

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Therapeutic peptides and proteins can make safe and effective drugs for humans. Over 100 such drugs have so far been approved for clinical use, and interest in developing more is high given the increased rate of discovery of new biological targets and of new peptides and proteins with untapped therapeutic potential. However, naturally occurring antigens are often unstable or have poor physicochemical properties or are not found in patients taking PEG–drug conjugates with molecular weights in the range of a PEG molecule (20,000–50,000 Da). Although significant progress has been made in the synthesis of PEG molecules carrying site-specific functional groups or having specific shapes, developing an optimum form of PEGylated biologics, suitable to be scaled-up for clinical testing, is not trivial, and is further limited by low production yield, complicated purification and lack of site-specificity.

Humans develop antibodies towards PEG because of the chronic exposure to the polymer, which is present in many consumer products, foods and pharmaceuticals. In patients, anti-PEG antibodies can reduce the efficacy of PEGylated drugs and increase the risk of hypersensitivity reactions. In fact, anti-PEG antibodies have abrogated the clinical efficacy of pegaspargase (1-asparaginase) and pegloticase (porcine-like uricase) — two PEGylated non-human proteins. This suggests that the formation of anti-PEG antibodies may depend on the immunogenicity, triggered by T-cell recognition of foreign (that is, non-human) epitopes, of the conjugated peptides or proteins. Because of this, the FDA currently requests anti-PEG antigenicity analyses in patients treated with PEGylated compounds that are under clinical development.

Chilkoti and co-authors covalently attached poly(oligo(ethylene glycol) methyl ether methacrylate) (POEGMA) to exendin (currently marketed as Byetta) — a peptide agonist of the glucagon-like peptide-1 receptor that facilitates the peptide sequence lysine–proline–glutamic–acid–threonine–glycine (LPETG) fused to the C-terminus of the peptide that is recognized by sortase A.
brush by using OEGMA monomers with varying side-chains.

Unlike conventional polymer-conjugation strategies involving multiple purification steps and low yields, Chilkoti and co-authors’ approach leads to high-purity peptide–polymer conjugates at a high production yield (>80%) by using easy purification steps. In a type 2 diabetes mouse model, the exendin–POEGMA conjugate showed extended half-life and improved pharmacodynamics, comparable to what had been obtained by using a site-specific PEGylated peptide7. Remarkably, the authors also demonstrate that the PEG antigenicity of exendin–POEGMA can be eliminated without compromising exendin efficacy by optimizing the side-chain length of the polymer brushes.

Although the safety of PEGylated drugs is not in dispute and patients with pre-existing anti-PEG antibodies treated with PEGylated interferons did not experience any reduction in the half-life or efficacy of their treatment1, the potential negative impact of PEG antigenicity should not be underestimated, and ought to be monitored during the early stages of PEGylated drug development. Chilkoti and co-authors’ POEGMA-conjugation approach provides a possible solution for the elimination of PEG antigenicity triggered by PEGylated drugs. However, to establish POEGMA conjugates as clinically suitable biologics, it will be necessary to demonstrate that the approach works for other types of therapeutic peptides and proteins such as (l-asparaginase and uricase). Also, as the authors recognized, any immunogenic reactions to POEGMA will need to be carefully investigated in multiple species, including humans5. All things considered, Chilkoti and colleagues have provided a strategy for overcoming the many limitations of traditional PEGylation techniques.

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