

HiPEG™ PEGylation Technology

The need to extend half-life. Why is PEGylation important?

Protein and peptide-based drugs are generally cleared from the body very quickly. Their rapid clearance results in decreased efficacy and the only clinical solution is to increase their frequency of dosing. This increases the risk of immunogenicity and the frequency of side effects. During preclinical studies it is difficult to conduct dose optimisation studies with a rapidly cleared molecule. Of all the technologies being developed to extend half-life, PEGylation is clinically proven to be safe and is the most widely used technology for increasing the duration of action of many different proteins.

What are the limitations of PEGylation ?

As a technology, there is a continued need (i) to improve the site-specificity of PEGylation to achieve better product homogeneity and (ii) to improve the efficiency of PEGylation so that more economic medicines can be produced. Our site-specific technologies (HiPEG™, TheraPEG™ and CyPEG™) provide for highly efficient, stable and precise addition of PEG to any protein or peptide.

What is HiPEG™?

HiPEG™ has been developed by PolyTherics to specifically attach PEG to histidine sequences expressed on the N or C terminal of proteins. Proteins are frequently expressed with histidine tags to enable their purification by affinity chromatography. HiPEG™ has been used to covalently conjugate branched, single and multiple linear PEG molecules to a diverse range of therapeutic proteins, including cytokines, antibody fragments and peptides.



Di-PEG anti-tumour necrosis factor (TNF)-α domain antibody (dAb). The histidine tag can be PEGylated with more than one PEG molecule.



The histidine tag remains available for affinity purification of the protein or peptide after PEGylation. The process has been shown to be scalable, robust and reproducible.

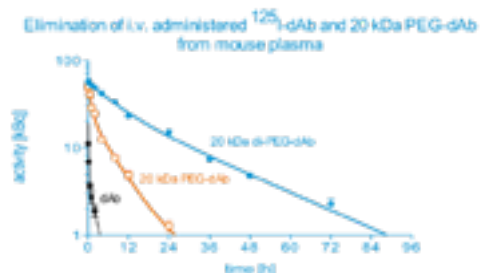
What are the key advantages of HiPEG™ ?

HiPEG™ PEGylation is site-specific with the PEG being conjugated to histidine sequences at either the N or C terminal to minimise effects on the protein-binding site. The technology is versatile, enabling the number and size of the PEG molecules to be adjusted to achieve the desired extension to half-life and thus duration of action to improve efficacy. There is precedent for the administration of proteins with a histidine tag to patients and several are currently in the clinic (e.g., Endostar, MFE-CP). HiPEG™ PEGylated proteins and peptides contain fewer isomers than those PEGylated by traditional methods and consequently their bioactivity and safety are more predictable and they can be manufactured more economically.

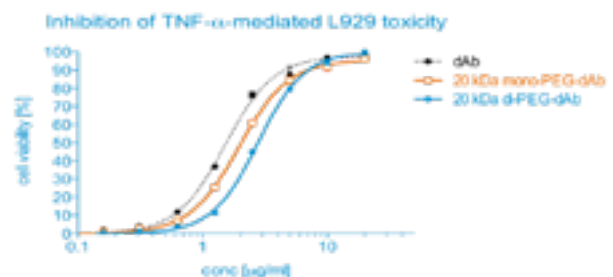
What data supports the use of HiPEG™?

HiPEG™ has been used to successfully PEGylate a wide range of proteins and peptides. Data for an anti-TNFα dAb expressed with a six-histidine tag to which a single 20 kDa and two 20 kDa PEGs were conjugated using HiPEG™ is shown below. The conversion of the dAb to PEGylated dAb was high (60%) and the PEGylated dAb was purified in a single step. (Also see the Fact Sheet for HiPEG™ Interferon α-2a).

Half-life >200-fold longer for di-PEGylated dAb



Activity retained by mono-PEGylated dAb



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