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Abstract for "Advances in Translational Research & Medicine"
The Ramanbhai Foundation 5th International Symposium

Treatment of Metabolic Diseases with Proteins Optimized for Pharmacological Use

Therapeutic proteins confer great target specificity, while minimizing off-target toxicity. Despite these salutary attributes, many potentially useful proteins display suboptimal pharmacokinetics, requiring high parenteral dosing, frequent administration, or both. These limitations are particularly acute in metabolic diseases such as obesity and diabetes, where the modulating endocrine signals are often tonic and the therapy chronic. Many approaches have been advanced toward improving time of action for proteins. Depot and liposomal formulations, fusions with long-acting protein fragments, or conjugation with polymers to reduce clearance, have significant limitations. In particular, the use of conventional pegylation while successful is unable to exactly specify the location or stoichiometry of chemical modification. We have developed means of pegylating therapeutic proteins with exact stoichiometry and unrestricted in site selection, thereby optimizing pharmaceutical and pharmacological properties. The application of these methods in the treatment of obesity and diabetes will be presented.

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