# Pegylated Dendrimeric Scaffold Reduces Toxicity In Anticancer Bioactive Targeting

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**Summary**

Dendrimer conjugates for pharmaceutical development are capable of enhancing the local delivery of cytotoxic drugs. The ability to conjugate different targeting ligands to the dendrimer allows for the cytotoxic drug to be focused at the intended target cell while minimizing collateral damage in normal cells. Dendrimers offer several advantages over other polymer conjugates by creating a better defined, more monodisperse therapeutic scaffold. Toxicity from the dendrimer, targeted and nonspecific, is not only dependent upon the number of targeting and therapeutic ligands conjugated, but can be influenced by the repeating building blocks that grow the dendrimer, the dendrimer generation, as well as the surface termination. PEGylated dendrimers are a class of nanocarriers which are capable of effectively delivering high drug payloads relatively unharmed to attack cancer. PEGylated dendrimers not only drastically augment drug loading , but also eliminate the naked dendrimeric scaffold drawbacks of hemolytic toxicity, uncontrolled drug outflow, macrophageal uptake, short half-life, etc. PEGylation of dendrimers appreciably improves their kinetic stability and makes them useful for the extended delivery of bioactive species. PEGylation can also improve targeting to the active sites of action with reduced immunogenicity, antigenicity, and toxicity by shielding the dendrimers against destructive mechanisms of the body.

**Key words**; Dendrimer, Hemolytic toxicity, PEGylation

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## Introduction

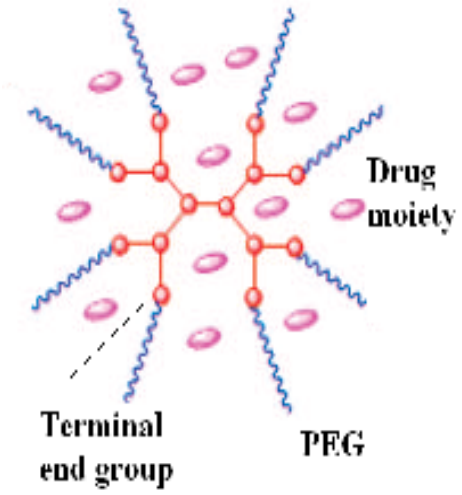
Dendrimers are novel synthetic, three dimensional, highlybranched, monodisperse, globular, macromolecules, synthesized by repetitive sequence of reaction steps, giving a précised branching structure, having precisely placed functional groups[1]. Dendrimers are produced from macromolecules such as polypropyleneimine (PPI), polyamidoamine (PAMAM) and polyarylether; and are highly branched an inner core. The particle size range between1to100nm although their sizes are mostly less than 10nm.[2] PEGylated dendrimers are a class of nanocarriers which are capable of effectively delivering high drug payloads relatively unharmed to attack cancer. PEGylated dendrimers not only drastically augment drug loading, but also eliminate the naked dendrimeric scaffold drawbacks of hemolytic toxicity, uncontrolled drug outflow, macrophageal uptake, short half-life, etc. PEGylation of dendrimers appreciably improves their kinetic stability and makes them useful for the extended delivery of bioactive species. PEGylation can also improve targeting to the active sites of action with reduced immunogenicity, antigenicity, and toxicity by shielding the dendrimers against destructive mechanisms of the body[1,2].

## Properties of PEG

Polyethylene glycol has the general formula HO-(CH2-CH2-O) n–CH2-OH with the typical molecular weight ranging into 500-20000. PEG is nontoxic, 3 non-immunogenic or poorly immunogenic. It can be used to precipitate proteins and nucleic acids. It forms two-phase system with an aqueous solution of other macromolecules, such as dextran or concentrated salt solutions[3]. PEG's covalent coupling with proteins, peptides exhibit following properties: Renders protein non-immunogenic and tolerogenic, prolongs the clearance time in vivo when conjugated with drugs, it alters the pharmacokinetics of various drugs, stabilize the physiological function of proteins and bioactive substances, separates biological macromolecules, membranes, cell particles.

## PEGylation

PEGylation is the technique that involves the modification of protein, peptide or non peptide molecules (Drugs) by covalent attachment of one or more polyethylene glycol (PEG) molecule for the purpose of enhancing therapeutic value. Advanced PEGylation involves attaching specific, modified polyethylene glycol polymers to biomolecules.The new PEGylation cofers rate of bioactivity, stability, purity, site specific PEGylation and single polyethylene glycol unit per drug molecule[4].




PEGylated Dendrimeric scaffold

**Chemistry of PEGylation**

The Chemistry of PEGylation deals with study of how polyethylene glycol (PEG)is converted in to activated form. It is done to avoid cross-linking and for site specific PEGylation and it require that the specific active, reactive groups like amino, thiol and carboxyl can be used.

**Types of PEG Conjugates**

**Poly (ethylene )glycol bioconjugate types**

PEG can be attached with different molecules to form conjugates like; PEG conjugates with peptides and proteins, PEG conjugates with low molecular weight drugs, PEG conjugates with lipids, PEG conjugates with biological macromolecules.

**PEG conjugates with peptides and proteins**

Covalent coupling reaction between amino groups of proteins and MPEG (Mono methyl ether of PEG) equipped with an electrophilic functional group have been used in most of the PEG- protein conjugates.

**PEG conjugates with low molecular weight drugs**

Maximum approaches are based on the conjugation of PEG- OH with free carboxylic acid group (formation of PEG ester) present in low molecular weight drugs.

**PEG conjugates with lipids**

Derivatization of Phosphotidyl Ethanol amine (PE) and the amino functional group of the polymer lead to the formation of PEG-lipids to avoid quick recognition and clearance in vivo.

**PEG conjugates with biological macromolecules**

Several biological macromolecules, such as interleukins, interferons, oligonucleotides, polysaccharides and their analogs are conjugated with PEG. This type of PEGylation serves several advantages, including to nucleases, cell membrane permeability and improved solubility.

**Activated PEG derivatives**

Poly (ethylene) glycols which typically have one end capped as methyl ether and other end activated for conjugation with a biomolecules. Covalent attachment of PEG derivatives in the majority of cases has been achieved utilizing amino groups of protein molecules as a site of modification.

**Terminal end groups toxicity of Dendrimer and surface modification with Polyethylene glycol (PEG)**

Several groups have shown that cell toxicity strongly correlates with dendrimer end group functionality. Positively charged groups such as amines generally demonstrate dosedependent toxicity; for this reason, positively-charged groups are often capped with neutral molecules such as acetyl and glycidol groups or poly (ethylene oxide) chains . Recent studies have broadened the investigation of end groups on toxicity. The Schluter group examined the impact of peripheral functionality on the cytotoxicity of MCF-7 breast cancer cells in vitro using low generation (G0, G1, and G2) polyamidoamine-like polymers. The dendrimers were prepared featuring peripheral groups including tert-butoxycarbonyl or benzyloxycarbonyl-protected quaternized amines, tert-butoxycarbonyl-protected or unprotected L-phenylalanine, L-methionine, or L-aspartic acid amino acids, diaminopropionic acid (platinum-binding), or 5-dimethylaminonapthalene-1-sulphonyl (fluorescent label). The latter two end groups possess the capacity for the delivery of the anti-proliferative cisplatin or contrast imaging modalities, respectively. In general, most of the positively-charged materials led to cell toxicity, but interestingly not all, including diaminopropionic acid dendrimers, showed this effect. The dendrimer core structure did not seem to have an influence on toxicity for these low generation macromolecules. In another study by the Simanek group, the effect of surface groups on cytotoxicity, hemolytic, and acute in vivo toxicity was investigated using melamine polymers as drug delivery vehicles . Unmodified melamine dendrimers have previously shown to be hemolytic. To improve biocompatibility of these polymers, amine, boc-protected amine, guanidine, carboxylate, sulfonate, phosphonate, and PEGylated G3 melamine dendrimers were synthesized and added separately to red blood cells and acute toxicity and hemolytic was monitored. Positively-charged amine and

guanidine groups demonstrated dose and time-dependent hemolytic activity, negatively-charged sulfonate, phosphonate, and carboxylate dendrimers led to limited hemolytic only at high concentrations (~1 mg/mL compared to b0.01 mg/mL for amine-terminated at 24 h), and PEGylated melamine showed minimal activity[5].

## Conclusion

PEGylation, the process of attaching PEG to molecules is an example of a highly successful strategy for reduction of hemolytic and immunogenicity of dendrimers with amine end groups, as well as the PEGylation as a process will confer the alteration of pharmacokinetic, pharmacodynamic properties of drugs which are targeted to the site.

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