









trol. Rel. 2000; 65:271) to postulate the enhanced permeation and retention (EPR) effect. Due to the higher permeability of blood vessels, PEGylated drugs can better penetrate into these tissues, and due to reduced or absent lymphatic drainage, are not easily eliminated. Overall, PEGylation results in a significant increase in retention time of the API in the blood circulation, passive targeting by the EPR effect, reduction of immunological side effects, reduction in application frequency and thus general enhancement of patient compliance and adherence to therapy.

### PEG Linker Strategies

However, PEGylation also faces several challenges. Early *N*-hydroxysuccinimide chemistries involving attachment of PEG to amino functions did result in random PEGylation. This resulted in considerable challenges to production uniformity and quality assurance. In addition, PEG sites may be closely located to the reactive or binding site of the protein, which may impair its activity or binding affinity to the API's receptor. This, however, may not be true in every case, as shown in Tab. 2 for a number of proteins.

While PEG-aldehyde chemistry allowed to target the *N*-terminus more specifically by variation of the reaction pH, more advanced thiol and maleimide chemistries allowed the specific PEGylation of free sulfhydryl moieties. Examples for the strong effect of binding after random or site-specific PEGylation of antibodies and antibody fragments are given in Tab. 3. PEGylation can lead to a reduction of *in vitro* activity of the modified molecule, which does not necessarily correspond to a loss in biological activity *in vivo* (Tab. 4). It is thought that biopharmaceuticals may have a higher binding affinity to their targets than needed for cellular activity, and that this affinity is only partially reduced by PEGylation (Pearce et al., Biochemistry 1999; 38:81). In general, a poor *in vitro/in vivo* correlation is observed for PEGylated compounds, making candidate selection processes tedious and time-consuming.

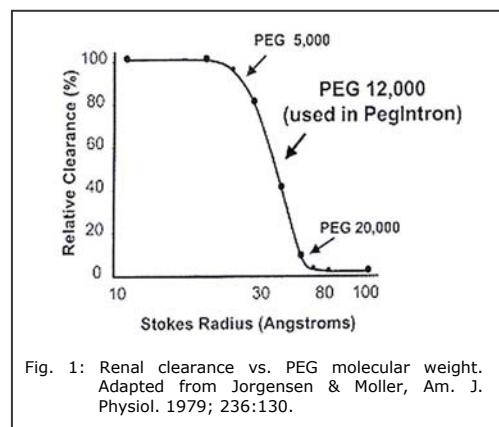


Fig. 1: Renal clearance vs. PEG molecular weight. Adapted from Jorgensen & Moller, Am. J. Physiol. 1979; 236:130.

Tab. 2: PEGylation at or near binding domains may not result in loss in biological activity

PEG-Protein	Binding Domain	PEG-Site	Biol. Activity
IFN	Cys <sup>29</sup> -Asp <sup>35</sup> Phe <sup>-123</sup> -Trp <sup>140</sup>	Lys <sup>31</sup> Lys <sup>121,131,134</sup>	+
G-CSF	Glu <sup>19</sup>	Lys <sup>16,23,34,40</sup>	+
Epoietin	Sugars	Sugars	+
*Insulin	Gly <sup>1</sup>	Gly <sup>1</sup>	+

\* Caliceti & Veronese, Proc. Intl. Symp. Control Rel. Bioact. Mat. 27 (2000); Bailon & Ehrlich "Innovative Drug Delivery Systems" Symposium (2002)

New avenues for permanent PEGylation are being pursued by companies such as Neose and Polytherics. The former has developed technology to glycosylate proteins expressed in *E. coli*, or optimize glycosylation patterns by specific enzymatic GalNAc glycosylation of serine and threonine. Successively, sialic acid conjugated PEG is enzymatically transferred to these GalNAc residues. The technology has been successfully applied to *E. coli* expressed G-CSF, interferon-alpha, and GM-CSF (DeFrees et al., Glycobiology, Advance Access May 22, 2006). Comparison of pharmacokinetic data of the thus PEGylated compounds to 'traditionally' PEGylated G-CSF revealed a two-fold increased AUC for the glycoPEGylated compound. The company has recently concluded a PEG-erythropoietin Phase I trial in Europe, and expects to commence Phase II trials in the 4<sup>th</sup> quarter of 2006. Together with BioGenerix, Neose will also perform a Phase I trial of their glycoPEG-GCSF in Q3/06 in Europe.

Tab. 3: Random vs specific PEGylation, effect on Ag binding.

Antibody	Random PEGylation	Site-Specific PEGylation	Ag Binding Effect	Reference
Hu Anti-Hepatitis B IgG	4xPEG 1.7kDa	-	30% Loss	Suzuki, 1984
Hu Anti-Hepatitis B IgG	15xPEG 1.7kDa	-	> 80% Loss	Suzuki, 1984
Mu A5B7 F(ab') <sub>2</sub>	2xPEG 5kDa	-	12% Loss	Pedley, 1994
Mu A5B7 DFM (diFab')	1-2xPEG 25kDa	-	40% Loss	Casey, 2000
Hu diFab'	1xPEG 40kDa	-	78% Loss	Chapman, 2002
Mu A5B7 Fab'	2xPEG 5kDa	-	20% Loss	Pedley, 1994
Anti-Tag-72 scFv	1xPEG 20kDa	-	40% Loss	Lee, 1999
Hu Fab'	1xPEG-40kDa	-	47% Loss	Chapman, 2002
Hu Fab'	-	1xPEG 25kDa	107% Retention	Chapman, 2002
Hu Fab'	-	2xPEG 25kDa	100% Retention	Chapman, 2002
Hu Fab'	-	1xPEG 40kDa	102% Retention	Chapman, 2002



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**OUR MISSION STATEMENT:**

Modern drug delivery research and development is a truly multidisciplinary approach and must combine all relevant scientific, technical, medical and regulatory aspects required for the design, preparation, testing, manufacturing and registration of drug delivery systems and their components. It is the mission of the APV Drug Delivery Working Group to foster and promote all aspects of research and development required to transform drug molecules into safe, applicable and acceptable drug delivery systems, which provide therapeutic benefit, convenience to the patient and improve patient compliance.

**Our mission includes in particular the following tasks:**

- Thoroughly understanding the physical-chemical and biopharmaceutical properties of the drug substance to be delivered and the components of the drug delivery system
- Understanding the biological barriers and the interactions of the drug molecule and its delivery system with the biological environment and the biological target including PK/PD and PK/safety relationships
- Research on excipients, materials and technologies required for the design, preparation and manufacturing of drug delivery systems for a selected route of administration
- Development and understanding of methods for in vitro and in vivo evaluation of drug delivery systems and their components
- Knowledge of regulatory requirements for clinical testing, manufacturing and registration of drug delivery systems

All disciplines relevant to the above mentioned areas of drug delivery R&D are invited to contribute to the APV Drug Delivery Group:

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