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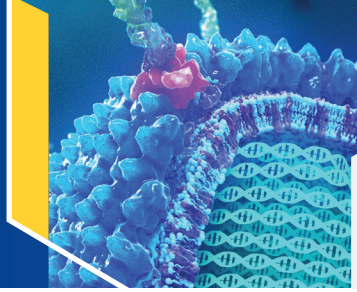
R&D TRENDS: ADDRESSING IMMUNOGENICITY IN PEGylated LIPID NANOPARTICLES



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Overview

PEGylation has been a breakthrough in pharmaceuticals for its capacity to enhance the pharmacokinetics of drug delivery systems. However, the issue of PEG immunogenicity must be overcome to enhance drug efficacy and safety.

Background: Modifying pharmaceuticals with polyethylene glycol (PEG) is a widely implemented approach to improve pharmacokinetics and enhance drug safety.

Market data: The global PEGylated proteins market size is expected to reach $2.1 billion by 2028, rising at a market growth of 11.3% compound annual growth rate.

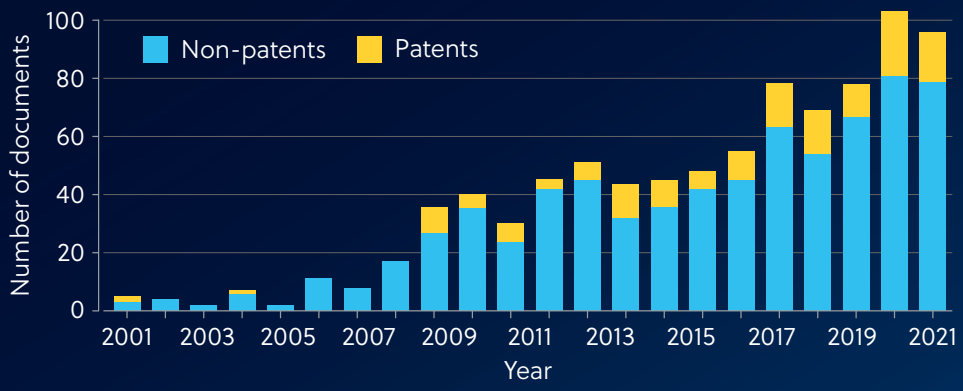
Opportunities: The use of PEG lipids in the COVID-19 mRNA vaccines has sparked considerable interest amongst research scientists, with efforts to improve the immune toxicology of nanomedicines.

Key benefits: Understanding the factors that impact anti-PEG antibody production is crucial to develop novel drug vehicles or optimizing administration and posology to ensure the highest treatment efficacy.

Key challenges: Continued translational success will require communication and collaboration between experts involved in all stages of pharmaceutical development of lipid nanoparticle (LNP) technologies.

Global documents related to immunologically induced adverse effects

The use of PEG-lipids in the COVID-19 mRNA vaccines has boosted the number of patent and non-patent documents related to immunologically induced adverse events such as anti-PEG antibodies generation, accelerated blood clearance (ABC), and complement activation-related pseudoallergies (CARPA).



Marketed products comprising PEG-lipid LNPs

PEG-lipids have been widely used in pharmaceutical LNP formulations. However, these agents have been associated with various immune-induced adverse effects.

Trade Name	Approval	Active ingredient	Lipid composition	Indications	Immuno-induced adverse effects
Doxil / Caelyx	1995, 1996	Doxorubicin	HSPC:Chol:PEG2000-DSPE (56:39:5)	Ovarian and breast cancer, Kaposi's sarcoma	ABC, CARPA
ThermoDox	2014	Doxorubicin	DPPC, MSPC, PEG 2000-DSPE	Hepatocellular carcinoma	CARPA
Onivyde	2015	Irinotecan	DSPC:mPEG-2000: DSPE (3:2: 0.015)	Metastatic pancreatic adenocarcinoma	Hypersensitivity, anaphylaxis
Onpattro (Patisiran)	2018	RNAi, transthyretin-directed siRNA	DLin-MC3-DMA, PEG2000-C-DMG, DSPC, Chol	hATTR amyloidosis	CARPA
Lipoplatin	2018	cisplatin	HSPC/DPPG/DSPE-mPEG2000	NSCLC, breast tumor, gastric tumor	N/A
BNT162b2 (Comirnaty; tozinameran)	2021	mRNA	ALC-0315:ALC-0159: Chol:DSPC (46.3:1.6:42.7:9.4)	COVID-19 vaccine	Anaphylaxis
mRNA-1273 (Spikevax)	2021	mRNA	SM-102:PEG2000-DMG: Chol:DSPC (50:1.5:38.5:10)	COVID-19 vaccine	Hypersensitivity, anaphylaxis

PEG-lipid structure: How does it relate to immunogenicity and efficiency?

PEG part

Although PEG is considered of low immunogenicity, there is growing evidence that it initiates immunogenic responses, especially when conjugated with other materials such as proteins and nanocarriers. PEG length, architecture, terminal group, and density can all impact the activity and safety of PEGylated liposomes and LNPs.

Lipid part

The lipid hydrophobic chain structure in PEG-lipids affects LNP biological activity. Differing properties that impact the safety and efficiency of PEGylated LNPs include hydrocarbon length, lipid headgroup charge, and the lipid anchoring group.

LNP composition and properties

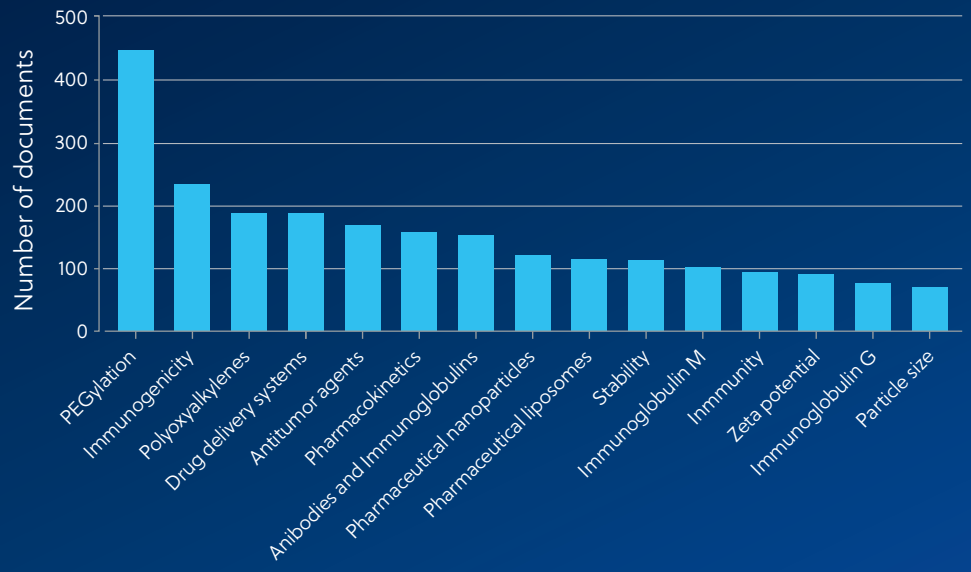
The composition of LNP lipids can impact the propensity of complement activation, and the choice of phosphatidylcholines can influence particle uptake and intracellular delivery. The size and surface charge of LNPs can also impact safety and immunogenicity.

Pharmaceutical parameters

In addition to the factors highlighted above, pharmaceutical parameters such as drug dosage, frequency, route, and mode of administration have also been shown to have an impact. For instance, intravenous bolus infusions are less causative of ABC compared with a slow infusion.

Major concepts in PEG-lipid immunogenicity

The key concepts in PEG-lipid immunologically induced adverse effects reveal the breadth of the field and the areas that are receiving the greatest research effort. Cancer is currently the largest disease class targeted by PEG-lipid pharmaceuticals; research into immunoglobulin M and G reveals the two most common PEG-specific antibodies currently researched for PEG-lipid immunogenicity.



Looking ahead

Though the immune toxicology of nanomedicines is a largely unexplored research area, the topic has attracted interest in recent years due to the use of PEG-lipids in the COVID-19 mRNA vaccines. To maximize the potential of these nanomedicines, a thorough understanding of the correlations between PEG-lipids' structural parameters, the immune-related adverse effects of the PEGylated LNPs, and their biophysical and physiological background is essential.

Learn more at cas.org/insights

More comprehensive information and references can be found at: cas.org/PEG-LNP

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