DMG-rPEG – A unique stealth lipid for next generation lipid nanoparticles

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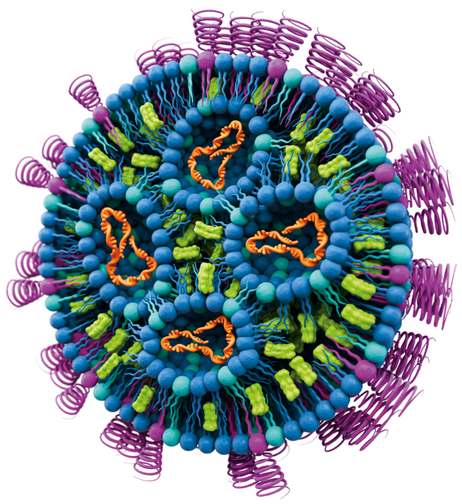
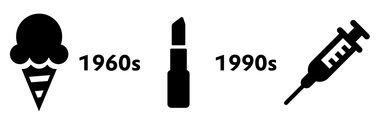
Lipid nanoparticle (LNP) composition

Nucleic Acid	▪ The active payload ▪ Defined weight ratio to the ionizable lipid
Ionizable Lipid	▪ ~50% ▪ Complexes the nucleic acid ▪ Destabilizes the endosome
Cholesterol	▪ ~38.5% ▪ Particle stability, encapsulation efficiency
Helper Lipid	▪ ~10% ▪ Stability and particle morphology
Stealth Lipid	▪ ~1.5% ▪ Colloidal stability and size regulation



The PEG dilemma

PEG is ubiquitous
e.g., in food, cosmetics, and pharmaceuticals.



Anti-PEG antibodies are abundant
e.g., APAs were found in ~½ of blood donors examined*

- Hypersensitivity reactions
- Complement activation
- Accelerated blood clearance
- ∑ **The PEG dilemma**

Lipid nanoparticles need stealth lipids
e.g., the Covid-19 vaccines use of PEG lipids

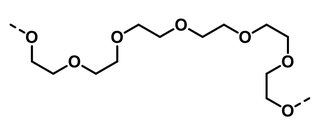
PEG-related immunogenicity
is a concern for RNA medicines.

*Average of four studies from 2011 – 2019, n=2431 blood donors.

rPEG: Hydrophilic units randomly distributed along a PEG backbone

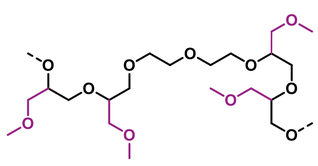
Structure | **Simulated polymer sequences**

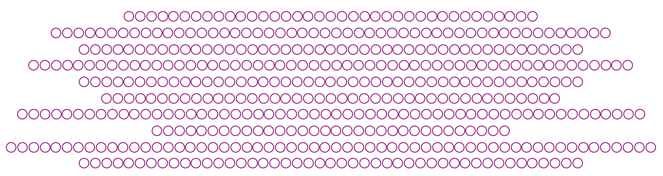
PEG



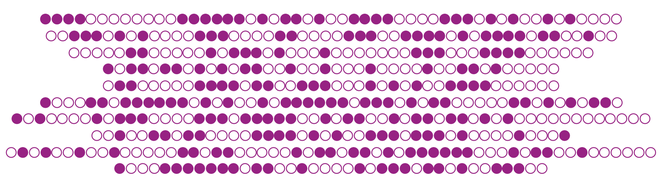
Constitutional isomers

rPEG



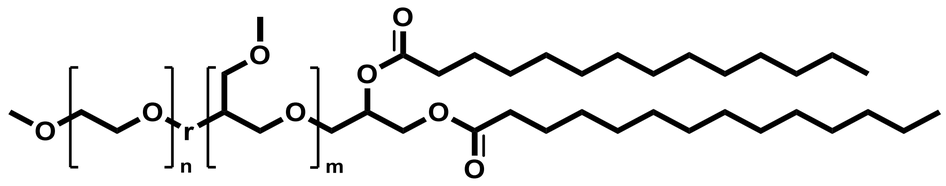


- Hydrophilic & flexible but low molecular diversity
- Every anti-PEG antibody (APA) binds every PEG

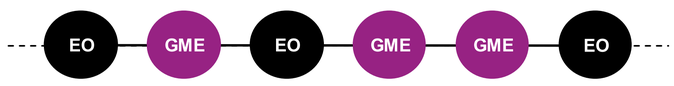


- PEG-like chemical properties
- No **APA** binding or „one shoe fits all" antibody

DMG-rPEG – our front runner rPEG-lipid



Well-defined random copolymers with controlled topology

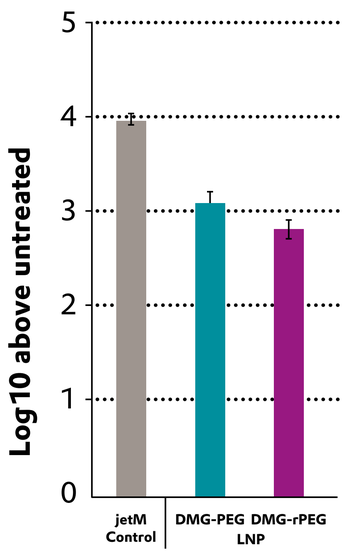


Established conjugation chemistry

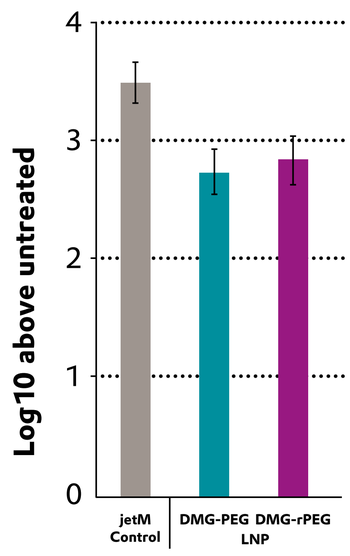
Scalable in existing Evonik Pharma-PEG assets

DMG-rPEG transfection in vitro and in vivo

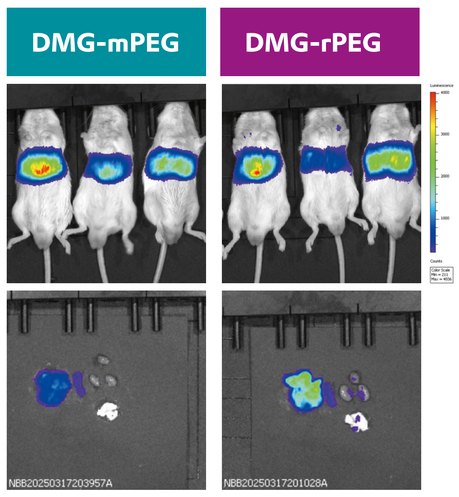
TRANSFECTION – 2D (HepG2)



TRANSFECTION – 3D (HepG2)



TRANSFECTION – IN VIVO (BALBc)



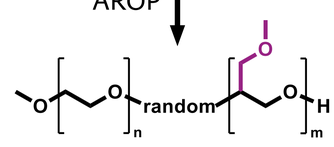
DMG-rPEG LNPs deliver mRNA primarily to the liver.

DMG-rPEG LNPs efficiently delivered LNPs – in vitro and in vivo

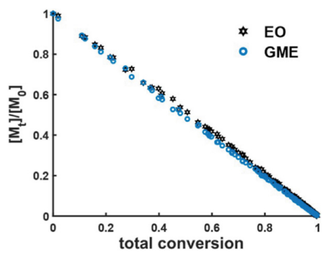
rPEGs are not recognized by monoclonal anti-PEG antibodies (APAs)

ANIONIC RING OPENING POLYMERIZATION

Ethylene oxide **(EO)** + Glycidyl methylether **(GME)**

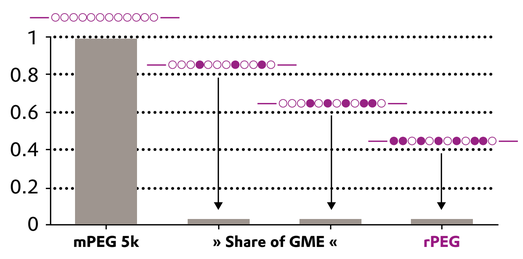


IN SITU ^{1}H NMR

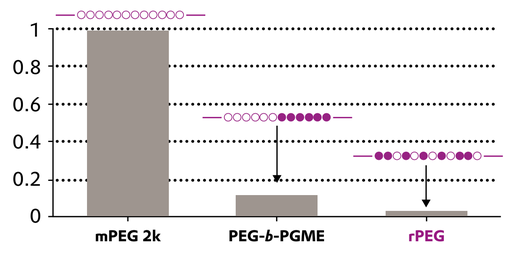


EVONIK PEG ASSETS

ELISA WITH MONOCLONAL ANTI-PEG ANTIBODIES (BACKBONE-SPECIFIC)



GME CONTENT VS. APA RECOGNITION



POLYMER TOPOLOGY VS. APA RECOGNITION

Summary

- Well defined rPEG polymer (M_N) with narrow dispersity (**PDI**)
- High purity by HPLC
- Controllable LNP size, **<100 nm**
- Narrow LNP formulation PDI, **0.02 – 0.2**
- Drop-in solution for established LNP formulations (commonly used amounts)
- Well tolerated by HepG2 and HeLa cells at more than 10-fold higher concentrations compared to DMG-mPEG
- High encapsulation efficiency **>90%**
- Do not bind to anti-PEG antibodies
- High transfection **on par** with benchmark formulations in vitro
- Transfection efficacy **in vivo** (single injection) **on par** with DMG-mPEG LNPs
- Transfection efficacy **improved** for **repeated dosing** compared to DMG-mPEG LNPs
- Transfection efficacy not impacted by PEG immunization

DMG-rPEG

- Nucleic Acid
- **Stealth Lipid**
- Structural Lipid
- Cholesterol
- Ionizable Cationic Lipid

Partners

Safer and more efficient RNA therapeutics

DMG-rPEG is a beyond-PEG stealth lipid to boost your formulation

EVONIK
Leading Beyond Chemistry