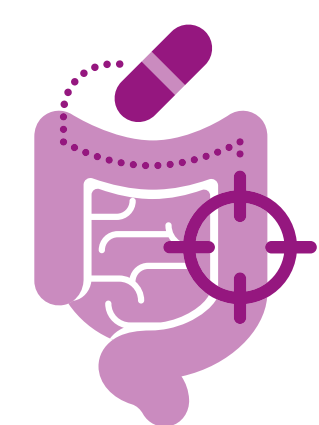# Beyond PEG – DMG-rPEG as a unique stealth lipid for RNA delivery
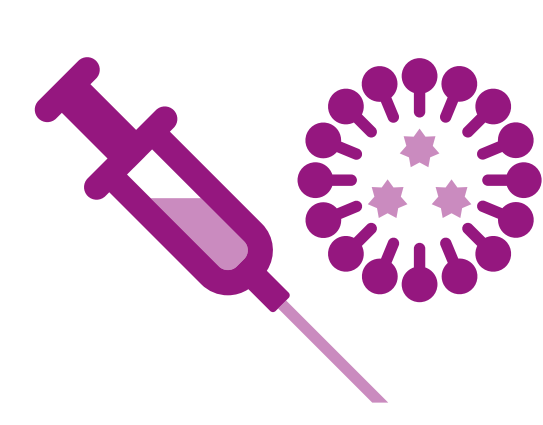
Dr. Johannes M. Scheiger
Dr. Thomas Endres
Dr. Lukas Hahn
Dr. Anne Benedikt
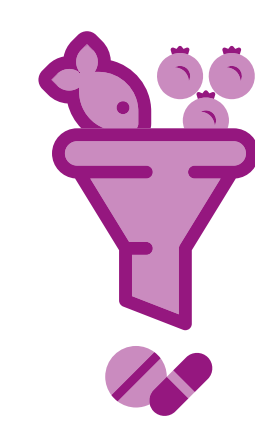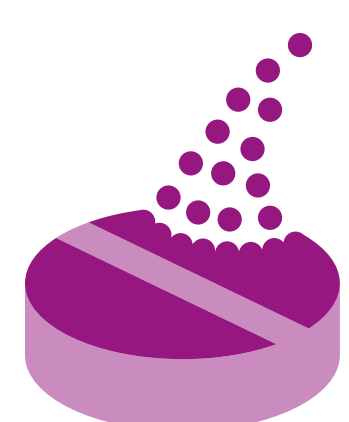Prof. H. Frey (University of Mainz)

APIs, HPAPIs & Intermediates

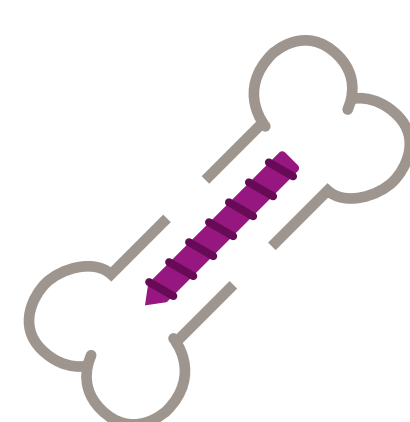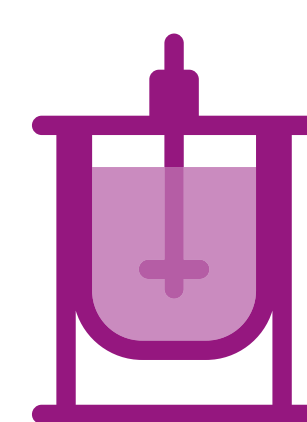Oral drug delivery

Complex parenterals
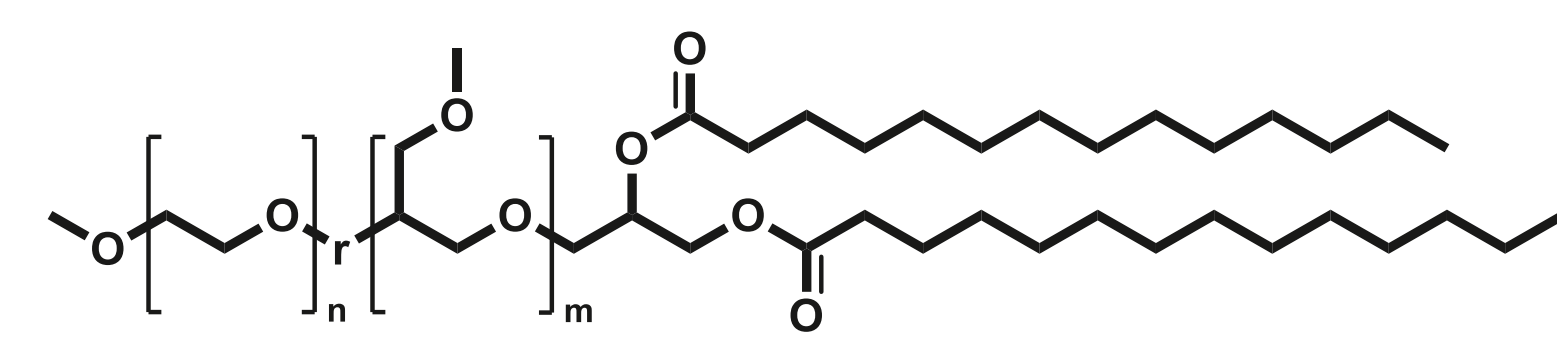
Nutraceuticals

Pharmaceutical ingredients

Amino acids

Implantable medical devices
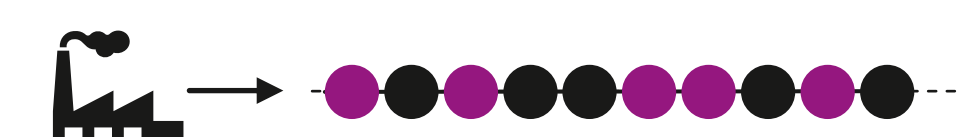
Cell culture

DMG-rPEG - our frontrunner rPEG-lipid

Well-defined random copolymers with controlled topology

EO — GME — EO — GME — GME — EO

Established conjugation chemistry

Lipid ●●●●●●●

Scalable in existing Evonik Pharma-PEG assets

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%
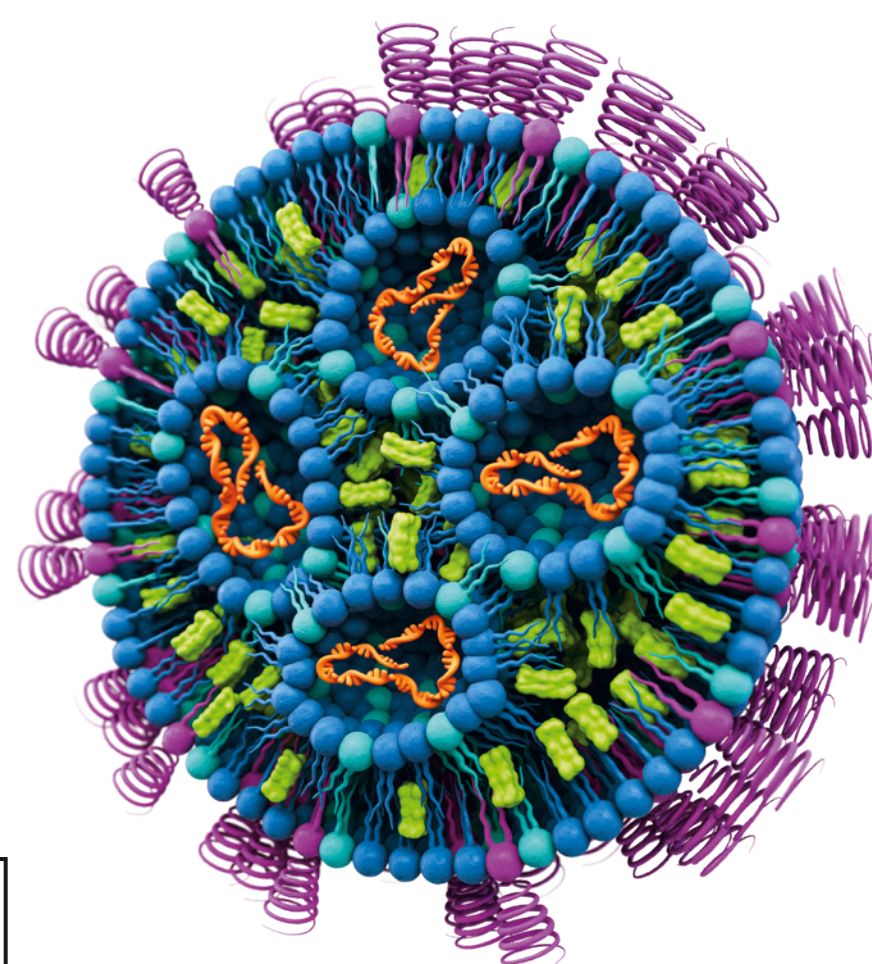- Particle stability, encapsulation efficiency

Helper Lipid
- ~10%
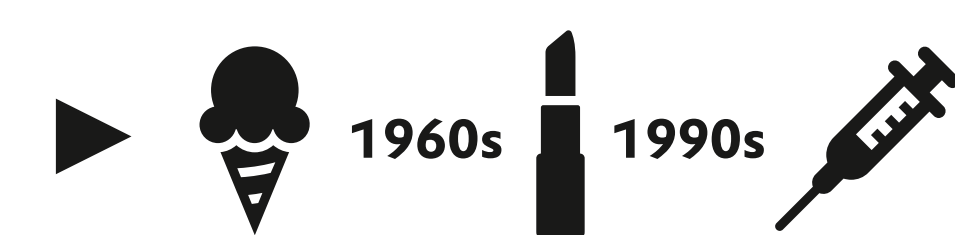- Stability and particle morphology

Stealth Lipid
- ~1.5%
- Colloidal stability and size regulation

The PEG dilemma

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

▶ 1960s | 1990s

▼

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

▶
- Hypersensitivity reactions
- Complement activation
- Accelerated blood clearance
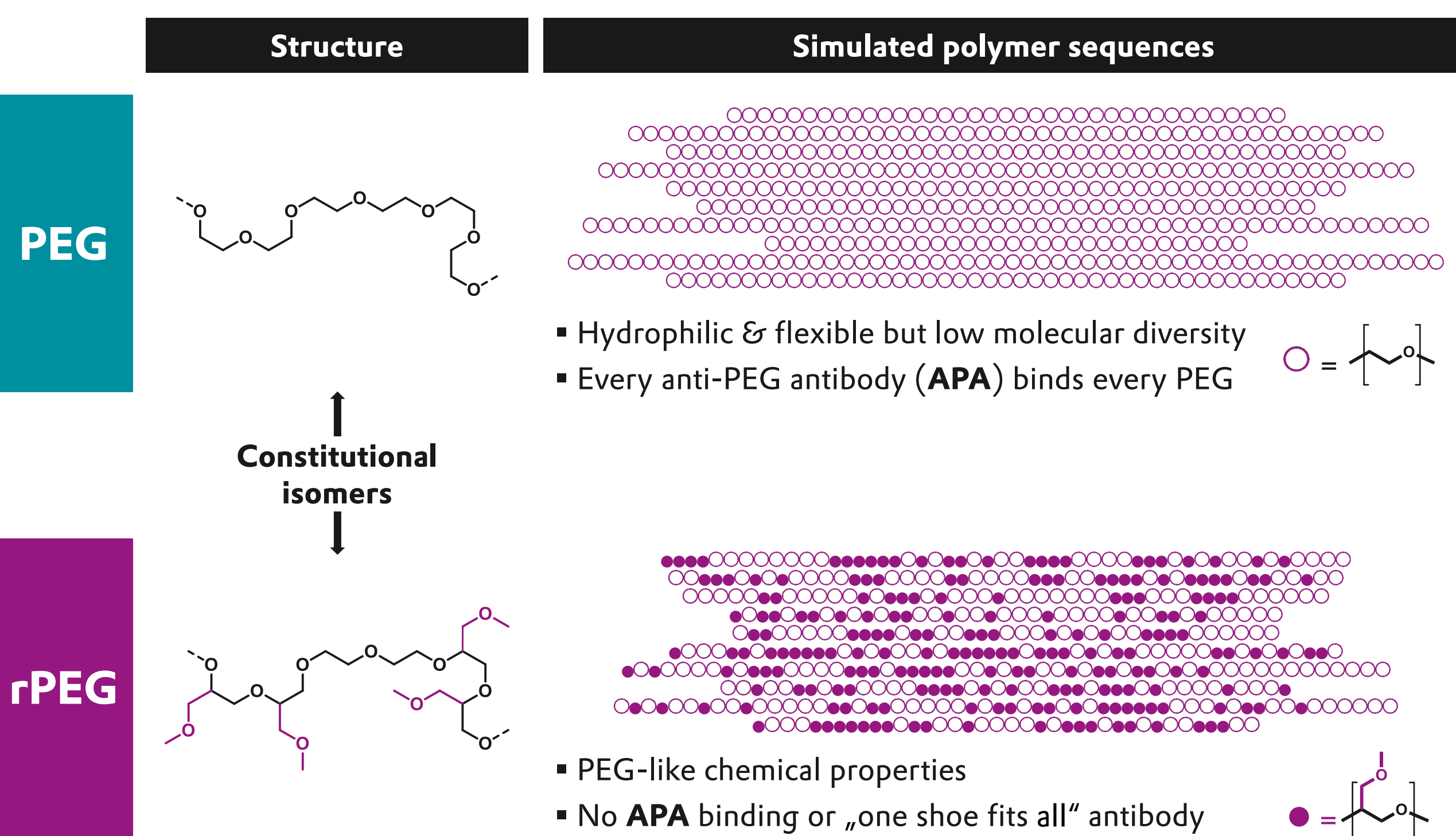- Σ The PEG dilemma

▼

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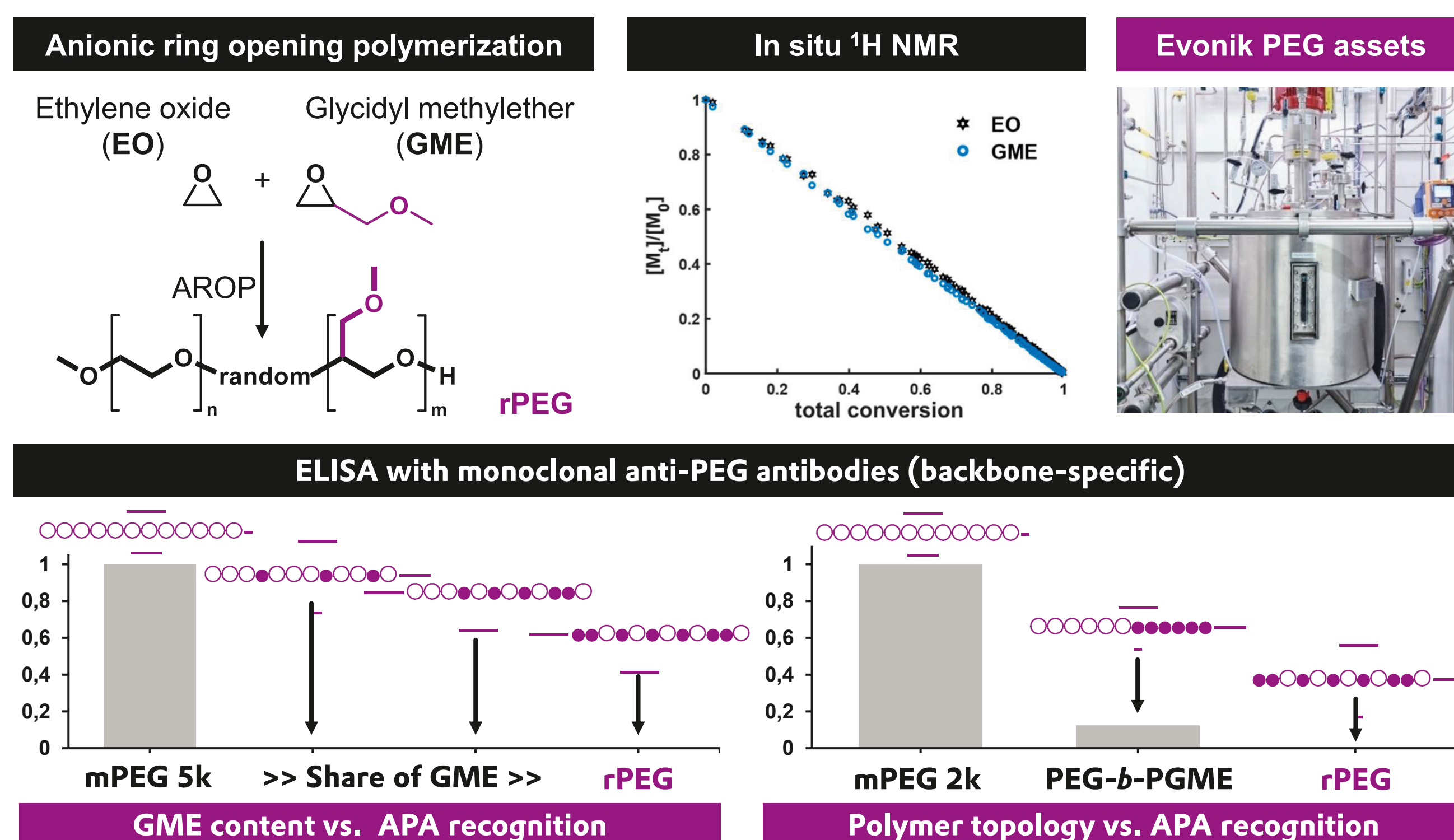e.g., the Covid-19 vaccines use of PEG lipids

▶ **PEG-related immunogenicity** is a concern for RNA medicines.

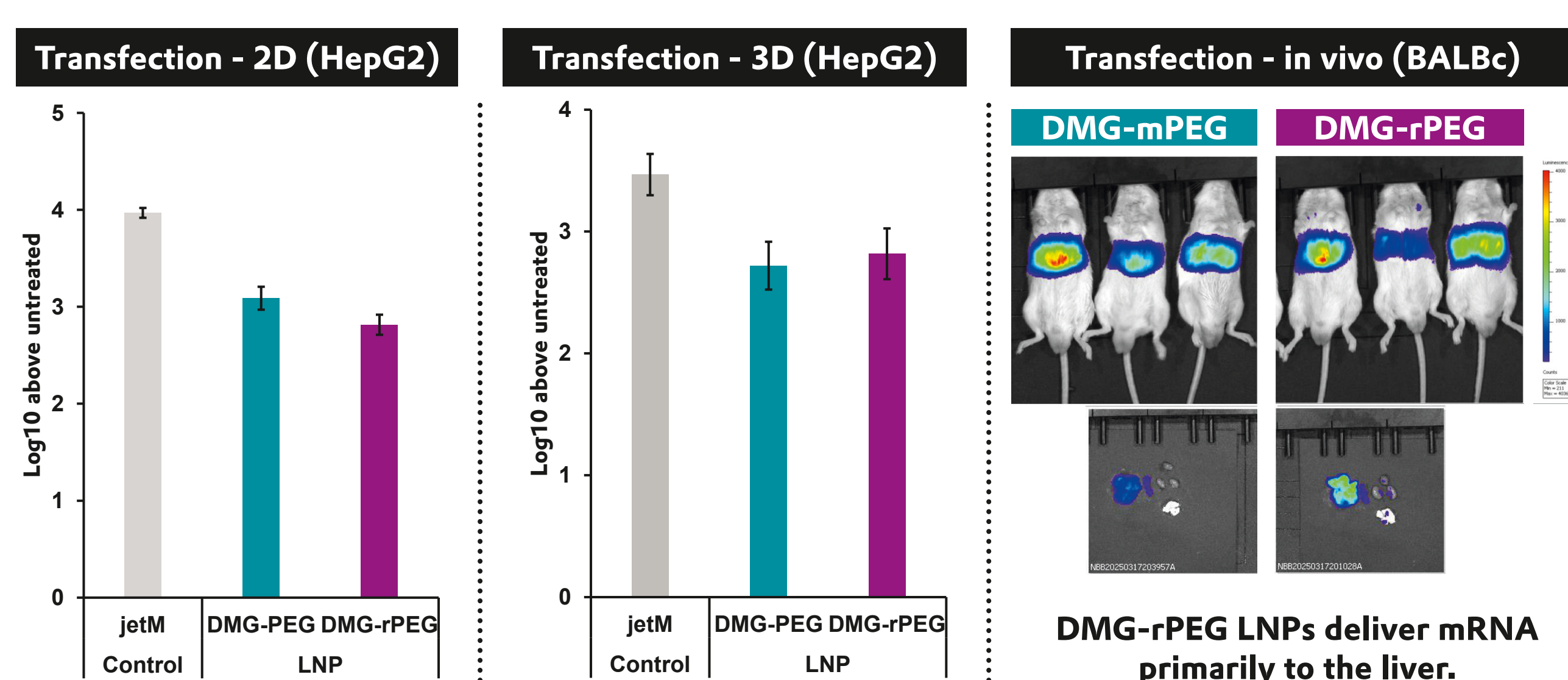*Average of four studies from 2011 – 2019, n=2431 blood donors.

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rPEG: Hydrophilic units randomly distributed along a PEG backbone

Structure	Simulated polymer sequences

PEG

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

Constitutional isomers

rPEG

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

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

Anionic ring opening polymerization

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

AROP → random → rPEG

In situ ¹H NMR

total conversion

Evonik PEG assets

ELISA with monoclonal anti-PEG antibodies (backbone-specific)

mPEG 5k >> Share of GME >> rPEG

GME content vs. APA recognition

mPEG 2k | PEG-*b*-PGME | rPEG

Polymer topology vs. APA recognition

DMG-rPEG transfection in vitro and in vivo

Transfection - 2D (HepG2)

Log10 above untreated

jetM Control | DMG-PEG | DMG-rPEG LNP

Transfection - 3D (HepG2)

Log10 above untreated

jetM Control | DMG-PEG | DMG-rPEG LNP

Transfection - in vivo (BALBc)

DMG-mPEG | DMG-rPEG

DMG-rPEG LNPs deliver mRNA primarily to the liver.

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

Summary

DMG-rPEG

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

Partners

- Controllable size, e.g., **80 – 110 nm**
- Narrow PDI, e.g., **0.02 – 0.2**
- High cell viability **>70%**
- High encapsulation efficiency **>90%**
- Do **not** bind to anti-PEG antibodies
- High transfection **on par** with benchmarks

Safer and more efficient RNA therapeutics
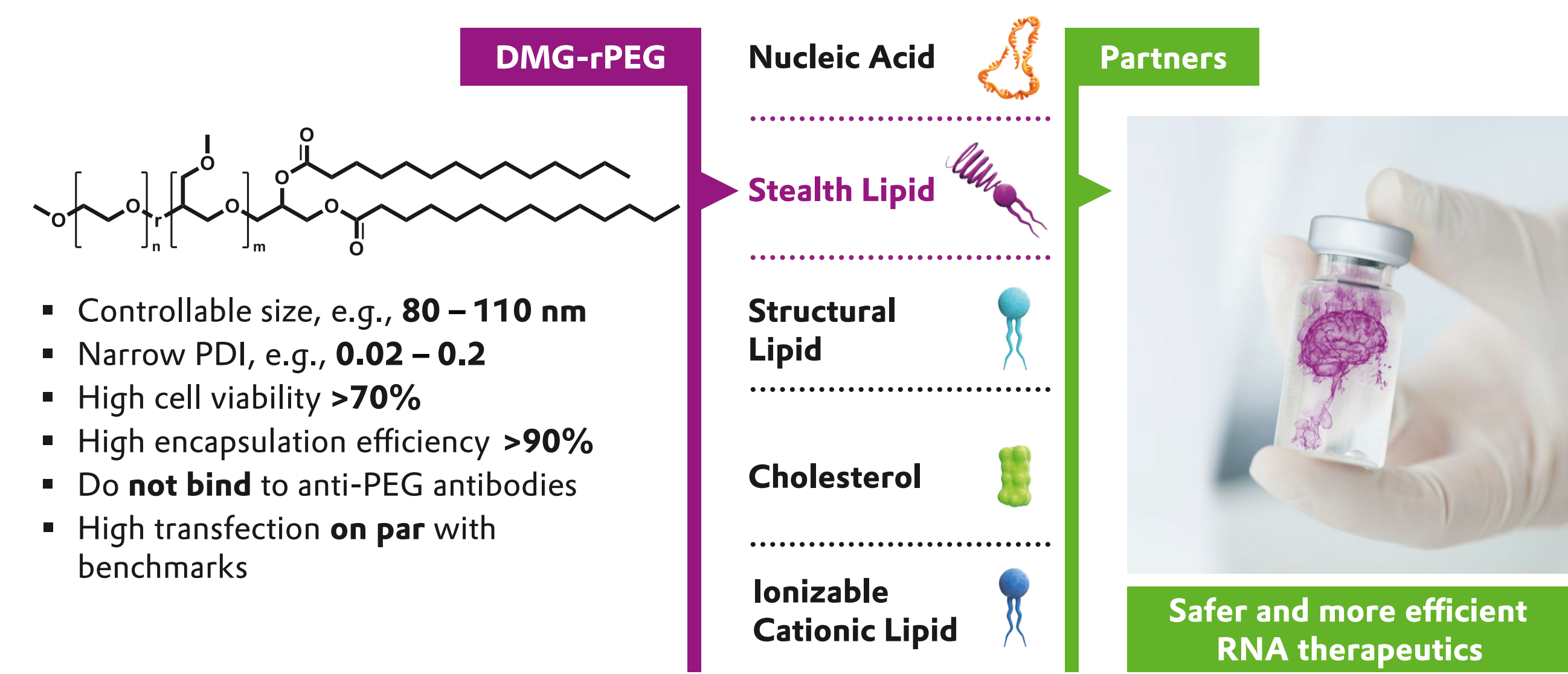
DMG-rPEG is a beyond-PEG stealth lipid to boost your formulation

EVONIK Leading Beyond Chemistry