Chameleon Nanocarriers for RNA Delivery and Genome Editing

3-6-2026

Dresden

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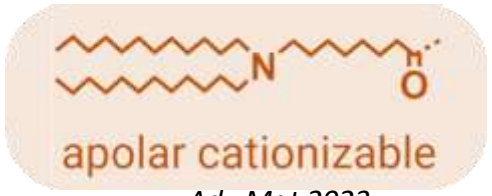
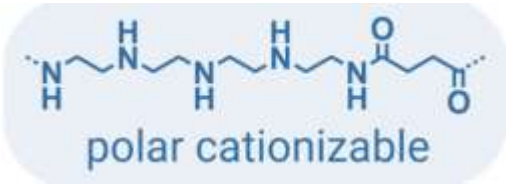
Molecular Chameleons by Chemical Evolution of RNA Carriers

Solid-phase synthesis of xenopeptides

LAF



Adv Mat 2023

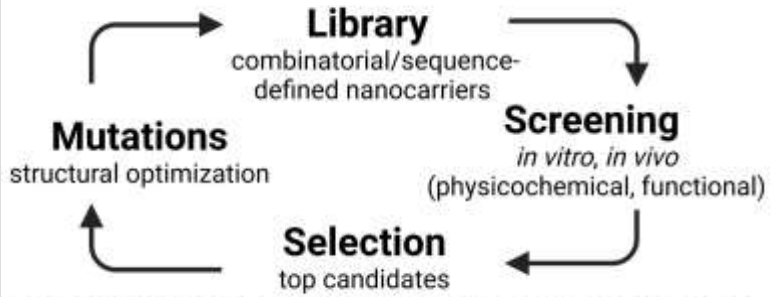


Angew Chem 2011

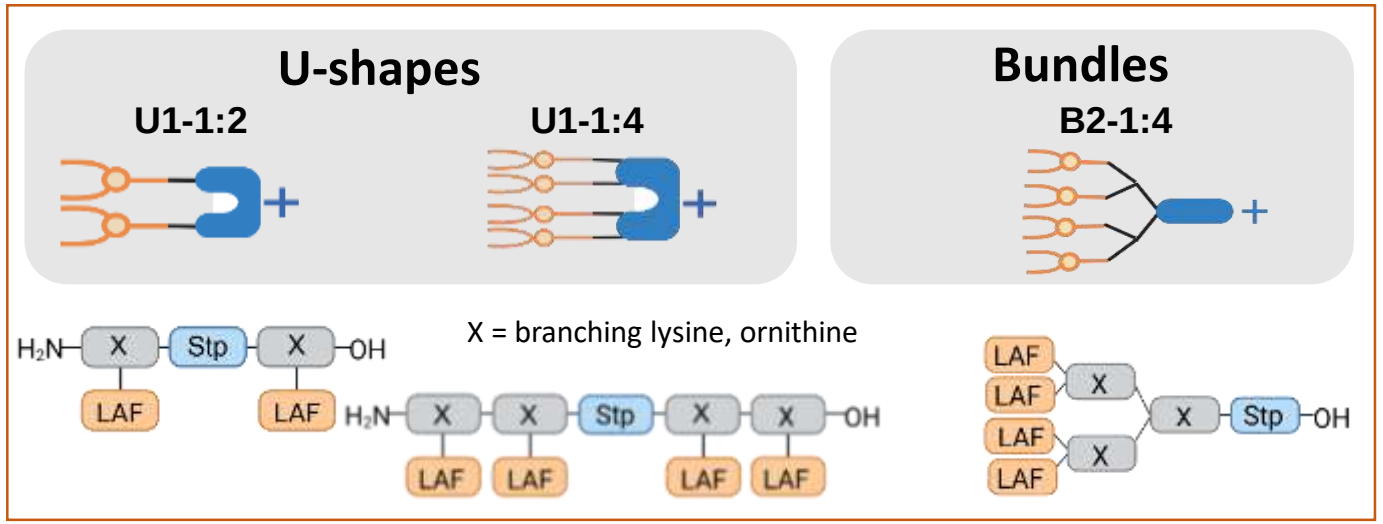
Stp

Evolution cycles of lipo-xenopeptides (XPs)
(>2000 sequences, >10 topologies)

Chemical evolution strategy



➢ **Small highly efficient LAF-XPs** , easy synthesis (4-6 couplings)

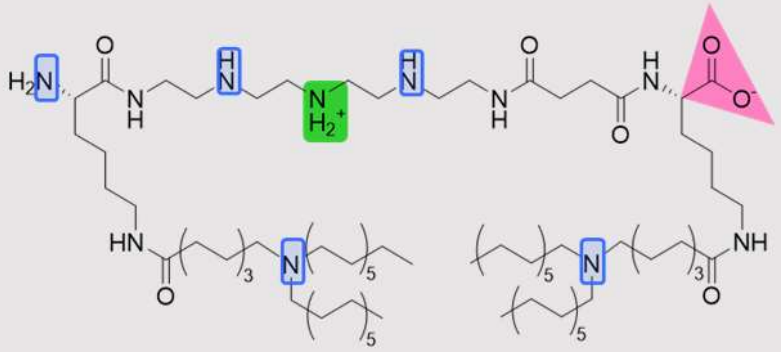


- Dynamic (‘Chameleon‘)
- Superior endosomal escape

S. Thalmayr, M. Grau, L. Peng et al *Adv Mat* 2023

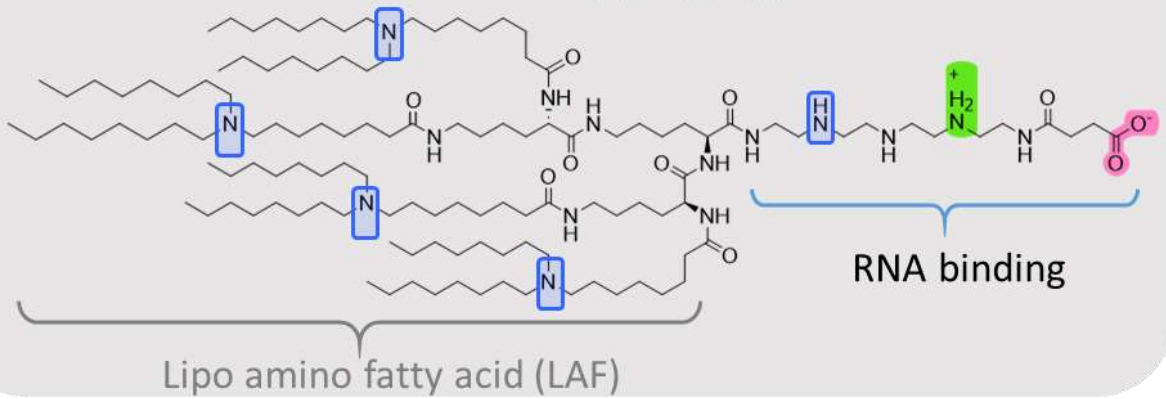
LAF-XP Structure Activity Relationships

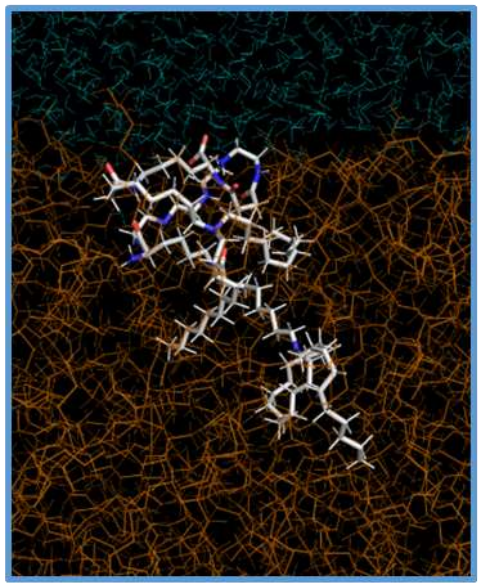
U-shapes



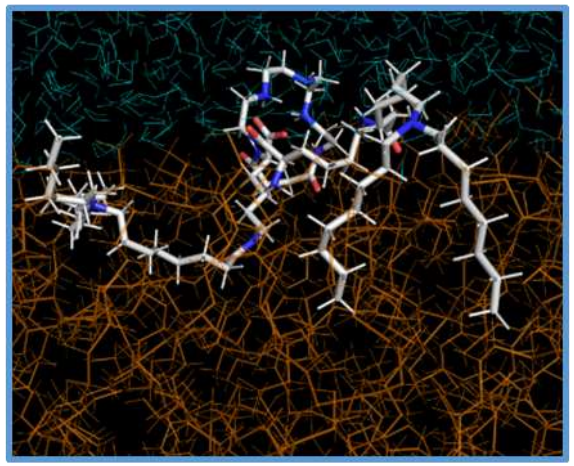
strongly pH dependent logD

Bundles





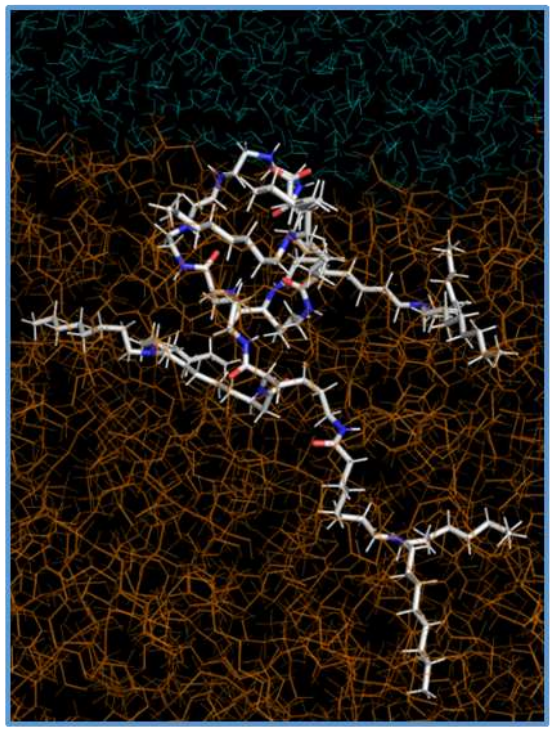
zwitter ion
logD [pH 7.4]: **0.61**



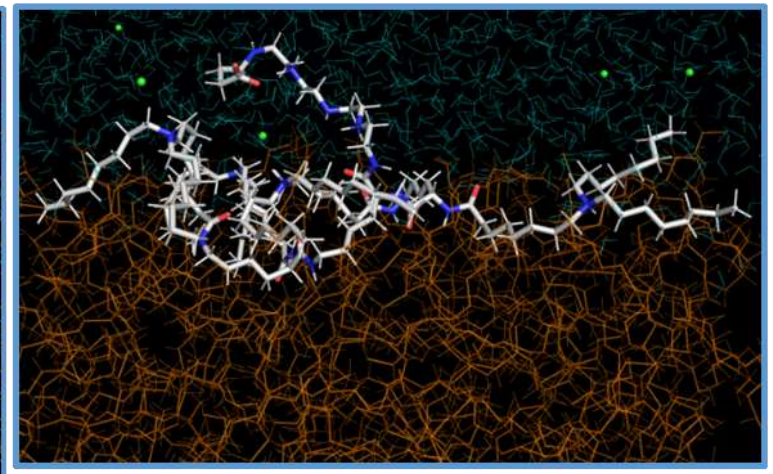
protonated
logD [pH 5.5]: **-1.16**

water

octanol

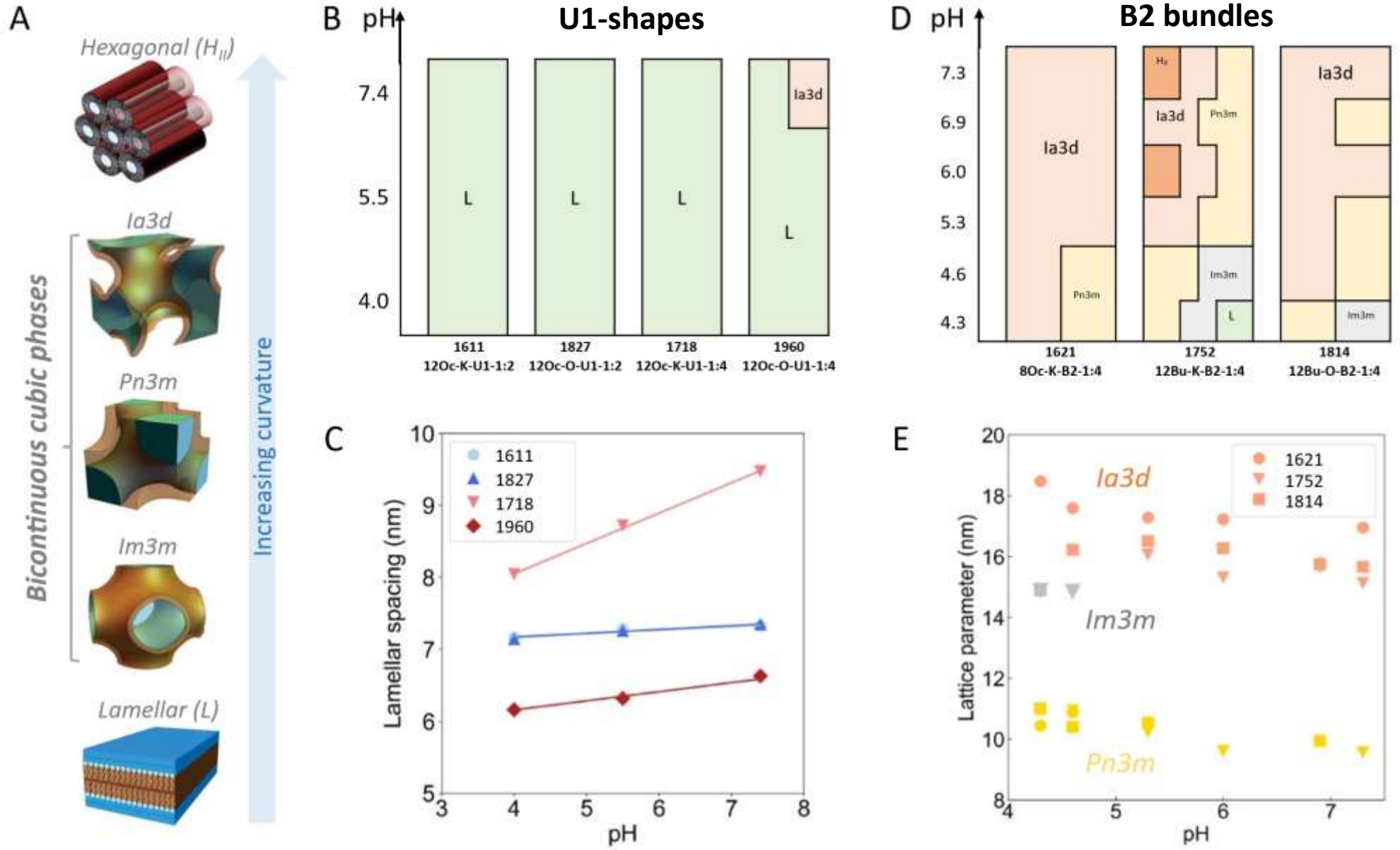


zwitter ion
logD [pH 7.4]: **0.83**



protonated
logD [pH 5.5]: **-1.14**

Interaction with lipids: SAXS study of LAF-XP/cholesterol bulk phases



M. Grau, E. Kostyurina, J. Seidl, N. Martini, B. Winkeljann, O. Merkel, J.O. Rädler, E. Wagner, *Materials Today* 2026

LAF-XP Structure Activity Relationships

U-shapes

U1-1:2 ⟷ U1-1:4

shape: flexible

Lipid phase: *lamellar (L)*

pH dependent transfection:

→ **Bafilomycin** (endosomal vATPase inhibitor):
20-fold loss of efficiency (N2A cells)

strongly pH dependent logD

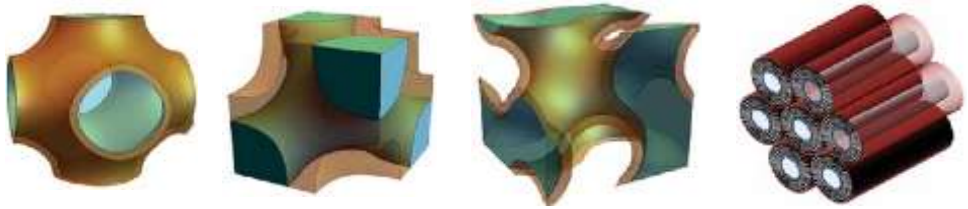
Bundles

B2-1:4

shape: dendritic

Lipid phase: *Bicontinuos cubic phase, fusogenic*

Im3m *Pn3m* *Ia3d* *Hexagonal (H_{II})*



pH independent transfection:

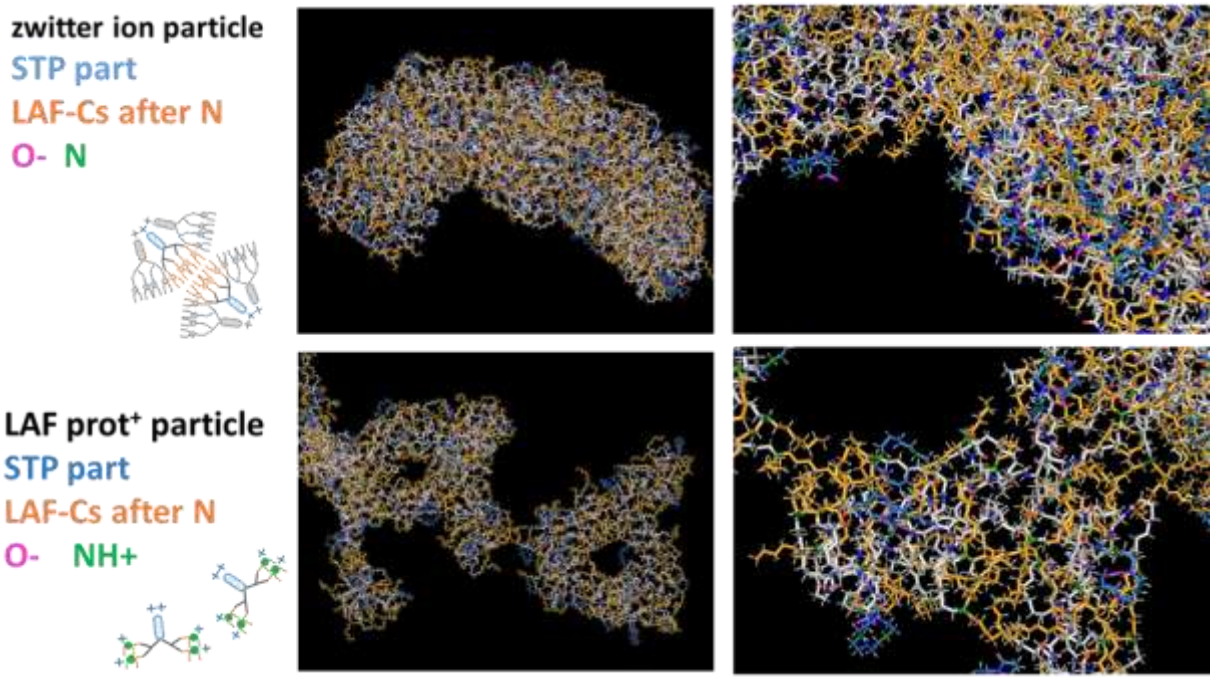
→ **Bafilomycin** only 1.5 to 4-fold reduction

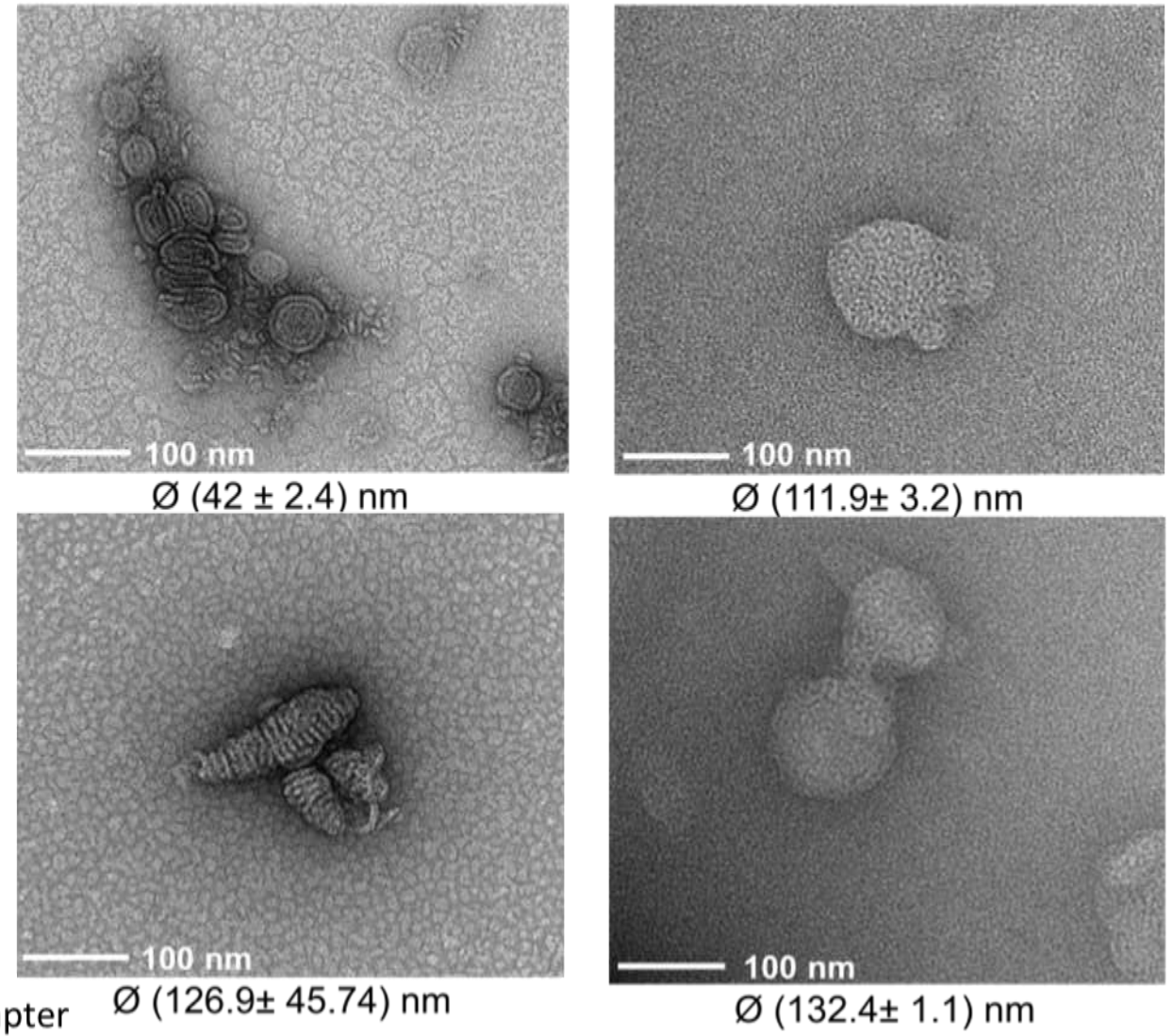
→ Very fast transfection kinetics (2 hrs)

M. Grau, E. Kostyurina, J. Seidl, N. Martini, B. Winkeljann, O. Merkel, J.O. Rädler, E. Wagner, *Materials Today* 2026

LAF-XP Structure & mRNA Polyplexes

Bundle LAF-XP in physiological salt
Molecular Dynamics: N. Martini, B. Winkeljann, O. Merkel





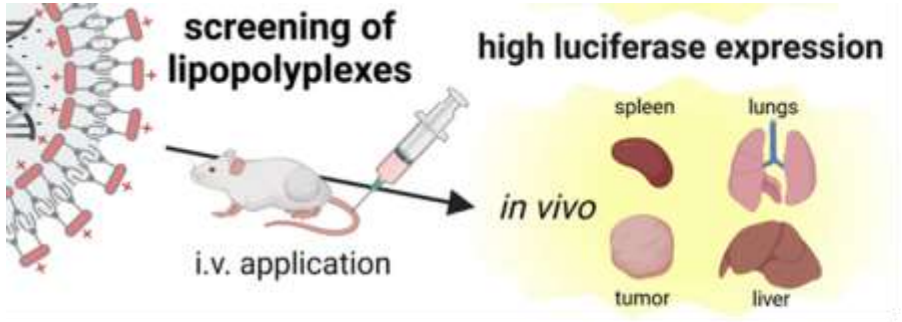
TEM: S. Kempter

M. Grau, E. Kostyurina, J. Seidl, N. Martini, B. Winkeljann, O. Merkel, J.O. Rädler, E. Wagner, *Materials Today* 2026

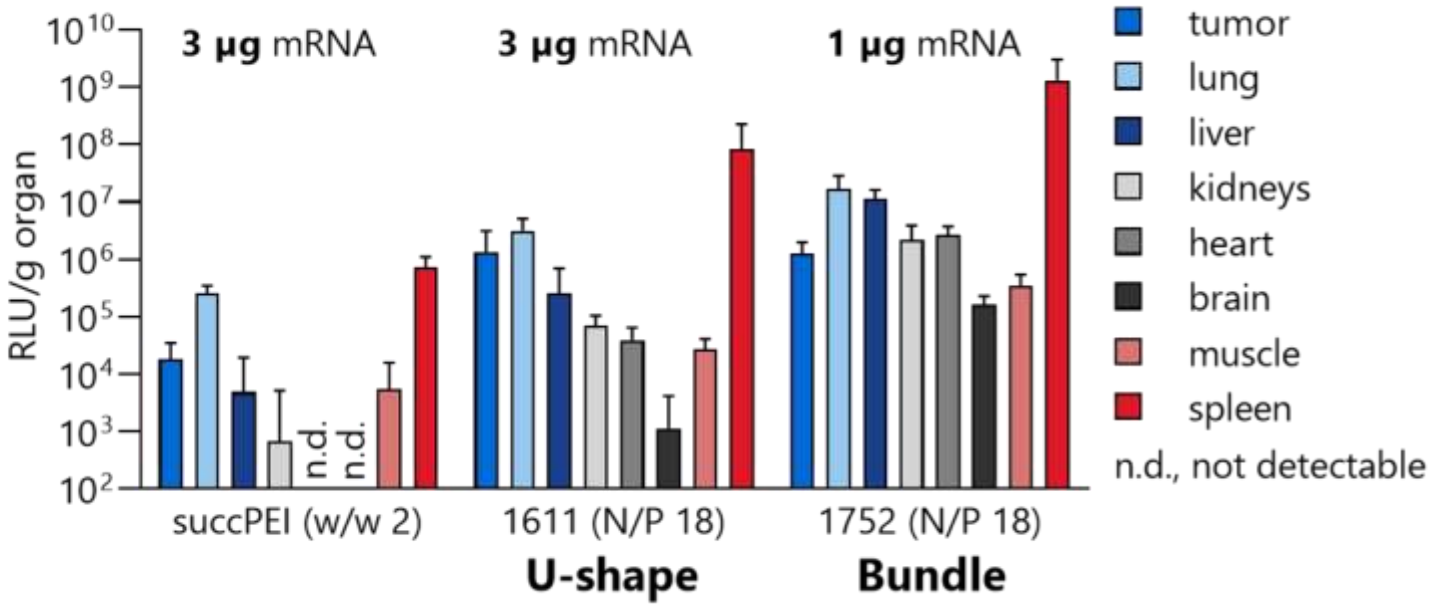
mRNA Polyplexes

in vitro:
Bundles superior, in **≥90% serum** at **ultra-low mRNA dose of 3 picogram** (≈**2 particles/cell**)

in vivo (i.v.):



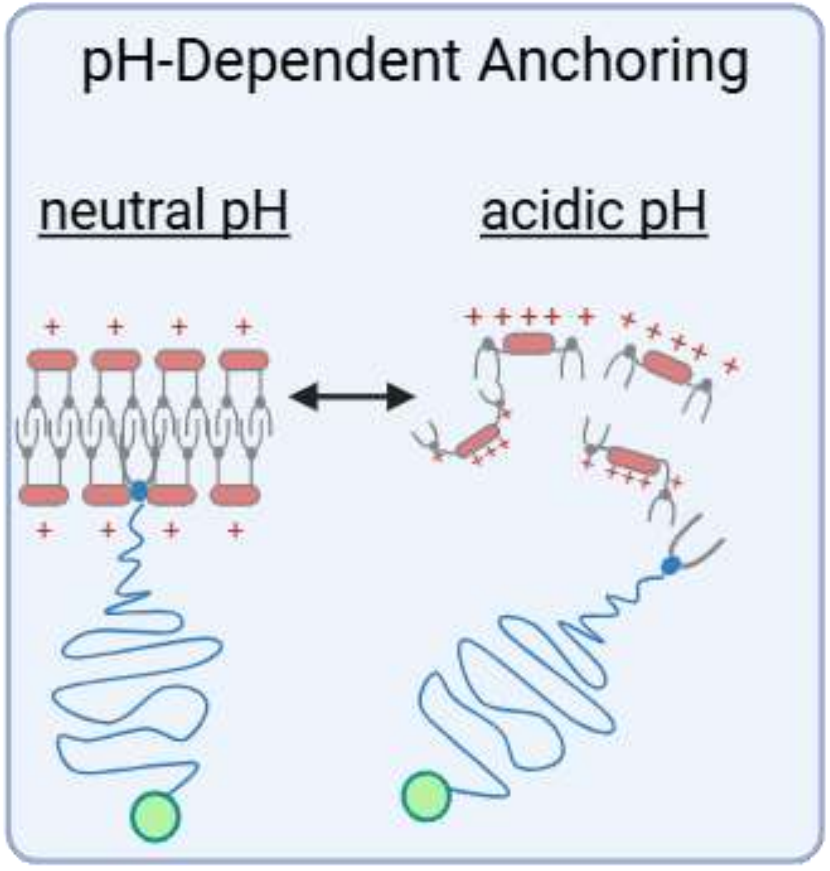
N2a tumor-bearing A/J mice (n=5);
Read-out at **6 h** after transfection



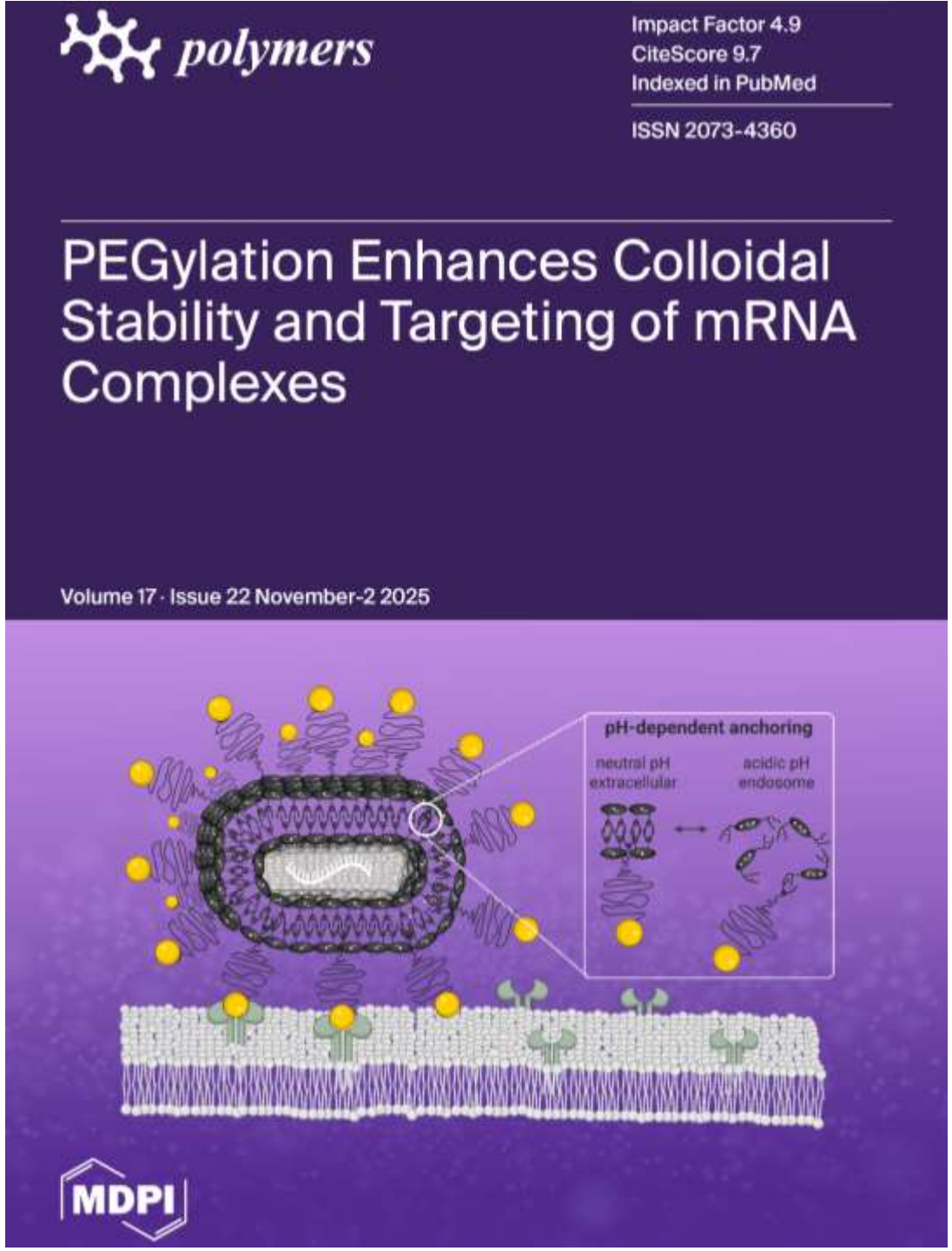
S. Thalmayr, M. Grau, L. Peng et al *Adv Mat* 2023

Solving the ‘PEG-dilemma’

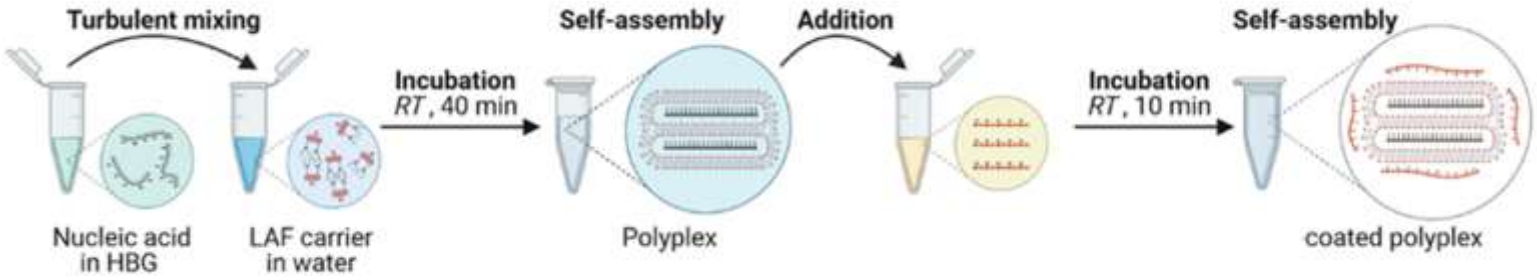
- Polyethylene glycol (2 – 20%) stabilizes
- GE11 provides EGFR-targeted delivery
- pH-sheddable in endosomes

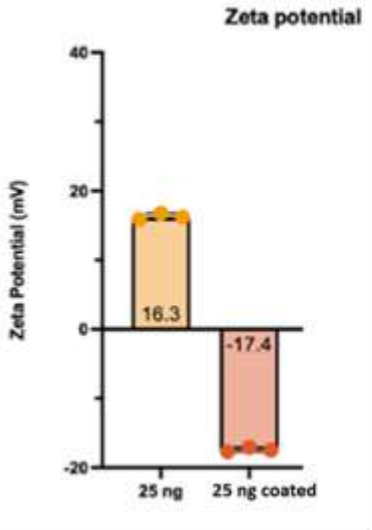


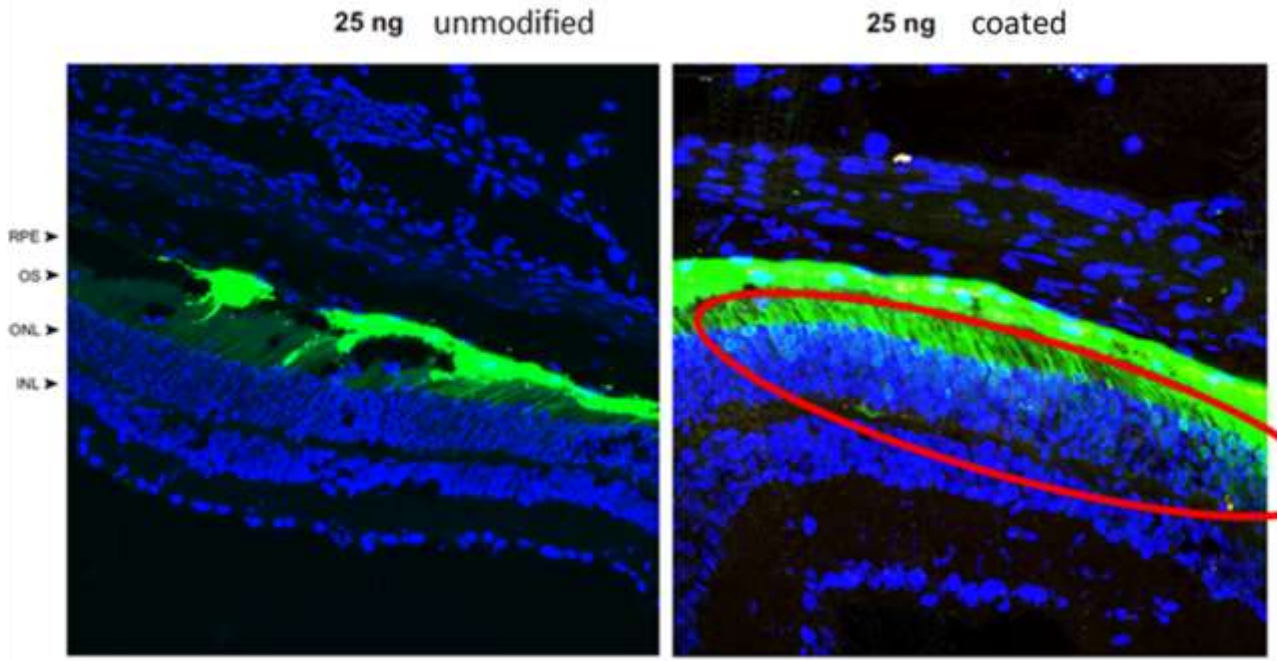
P. Folda et al. *Polymers* 2025 (cover story)



in vivo: Subretinal Injection of Coated mRNA Polyplexes







Effective **photoreceptor targeting**

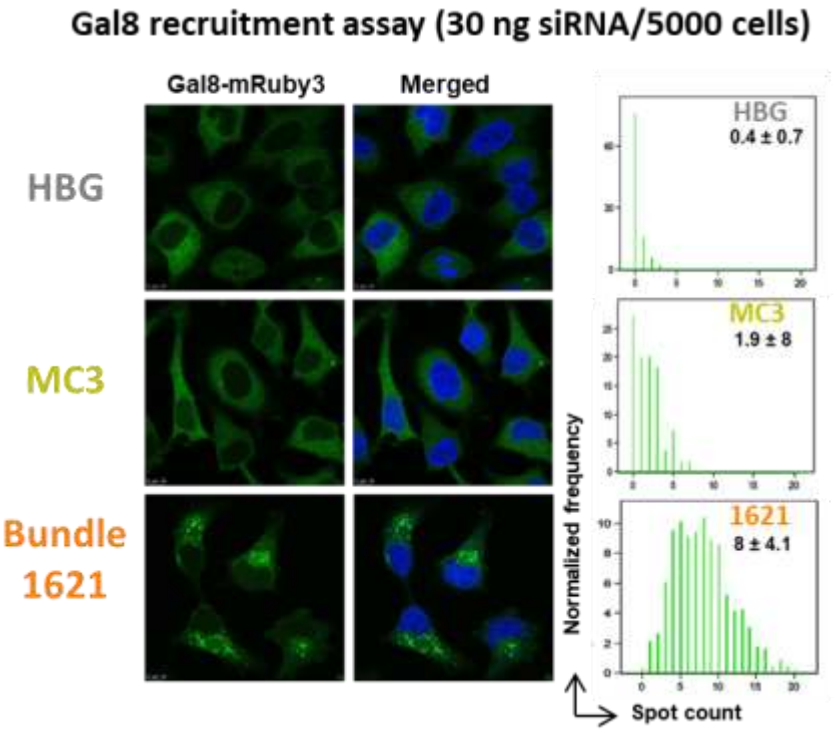
at just **25 ng mRNA**/per mouse eye

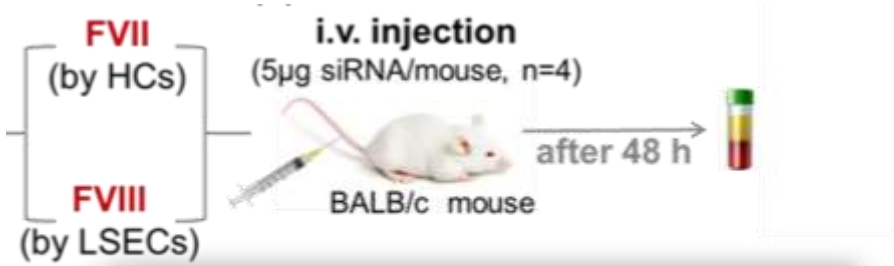
Desired target site:
Photoreceptors!

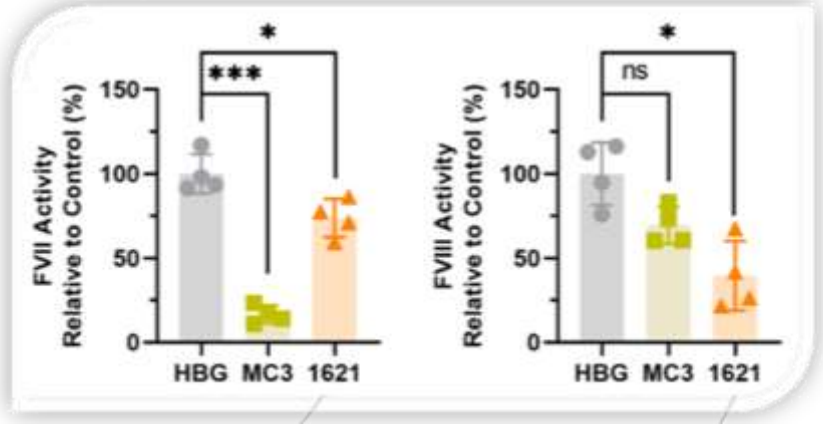
R. Di Cunto, E. Weidinger, S. Thalmayr, J. Seidl, E. Wagner, A. Auricchio (TIGEM Naples /LMU)

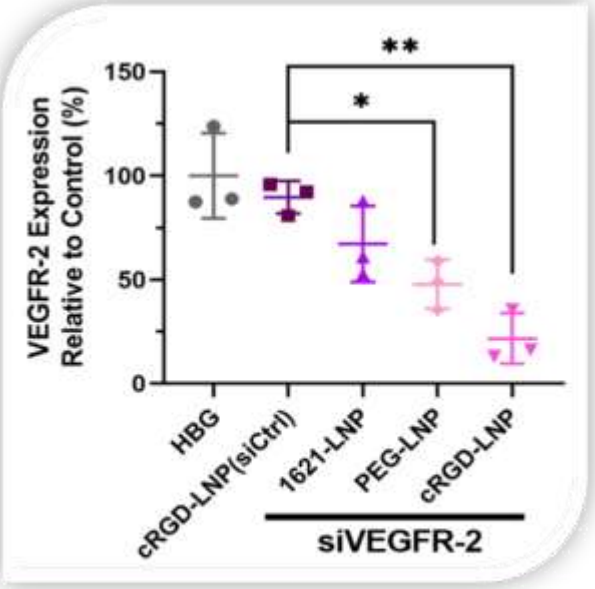
siRNA LNPs

siRNA LNPs: Endosomal Escape – Endothelial Targeting in Liver / Tumor

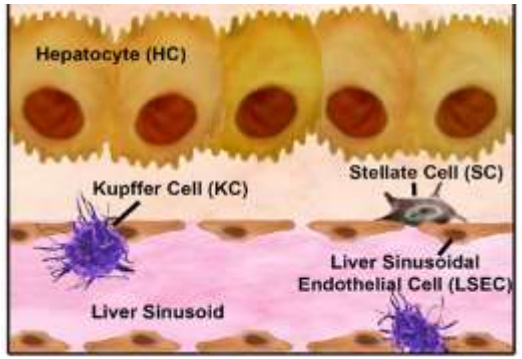






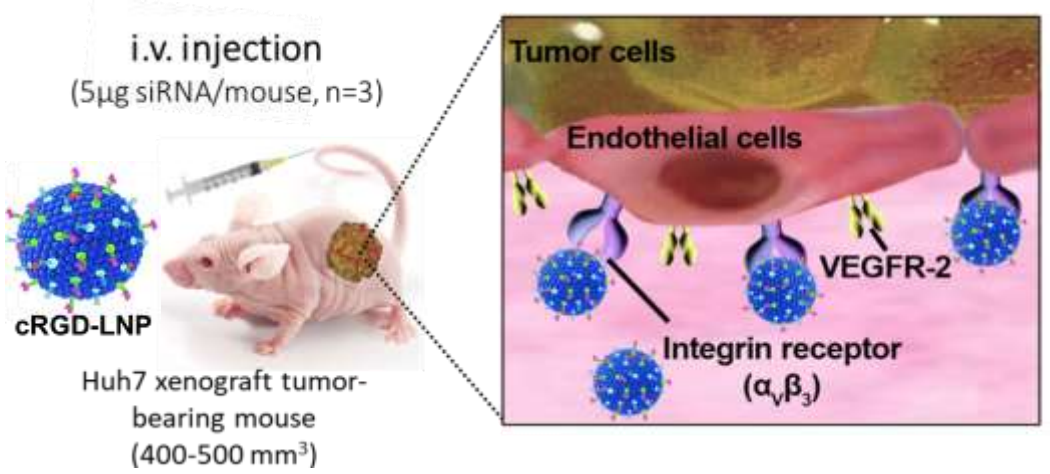


High knockdown of VEGFR-2 in integrin-overexpressing TECs



Onpattro
(siRNA LNP with MC3)
Hepatocyte targeting, FVII knockdown

siRNA LNP with XP 1621
LSEC targeting, FVIII knockdown

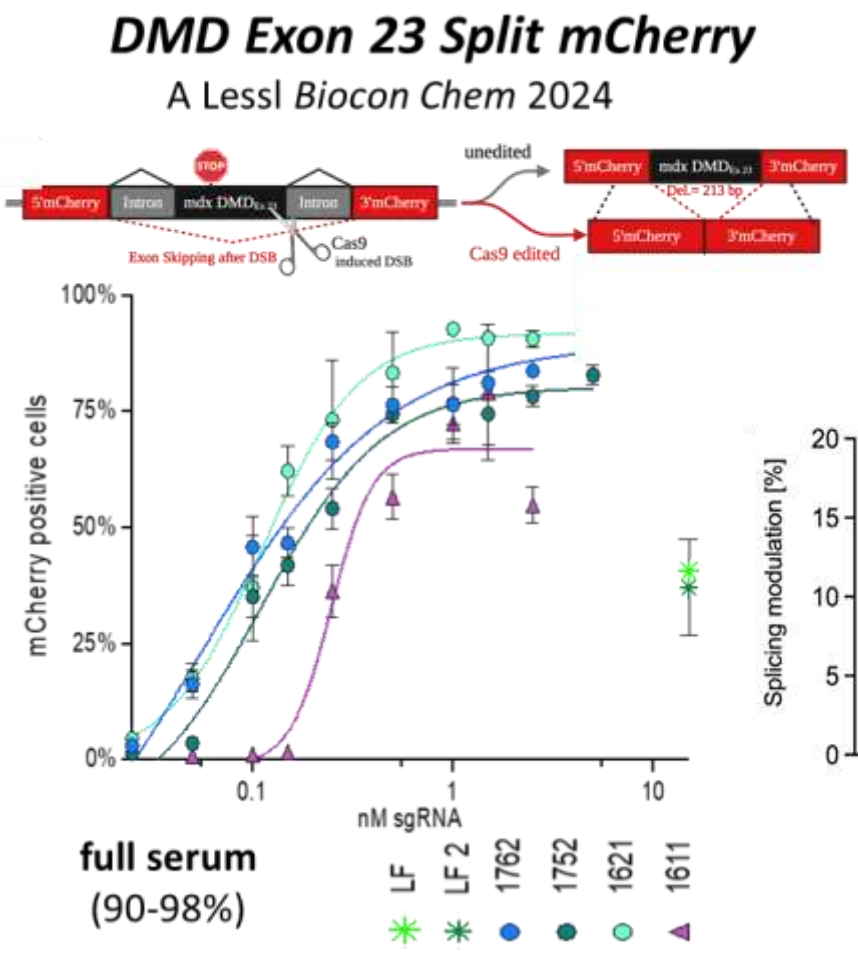


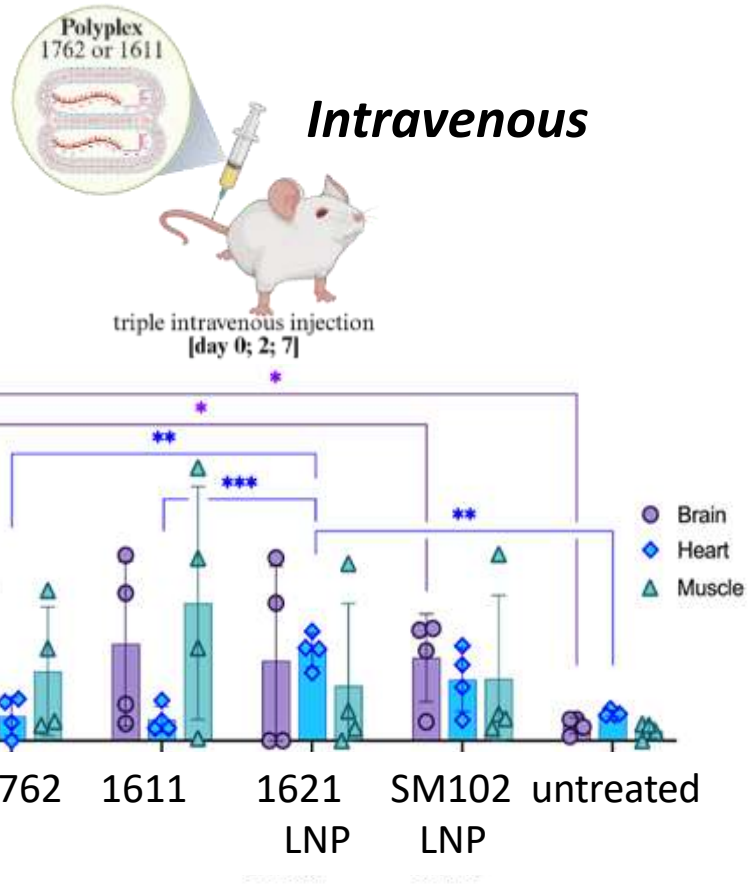
M. Yazdi et al *Small* 2024

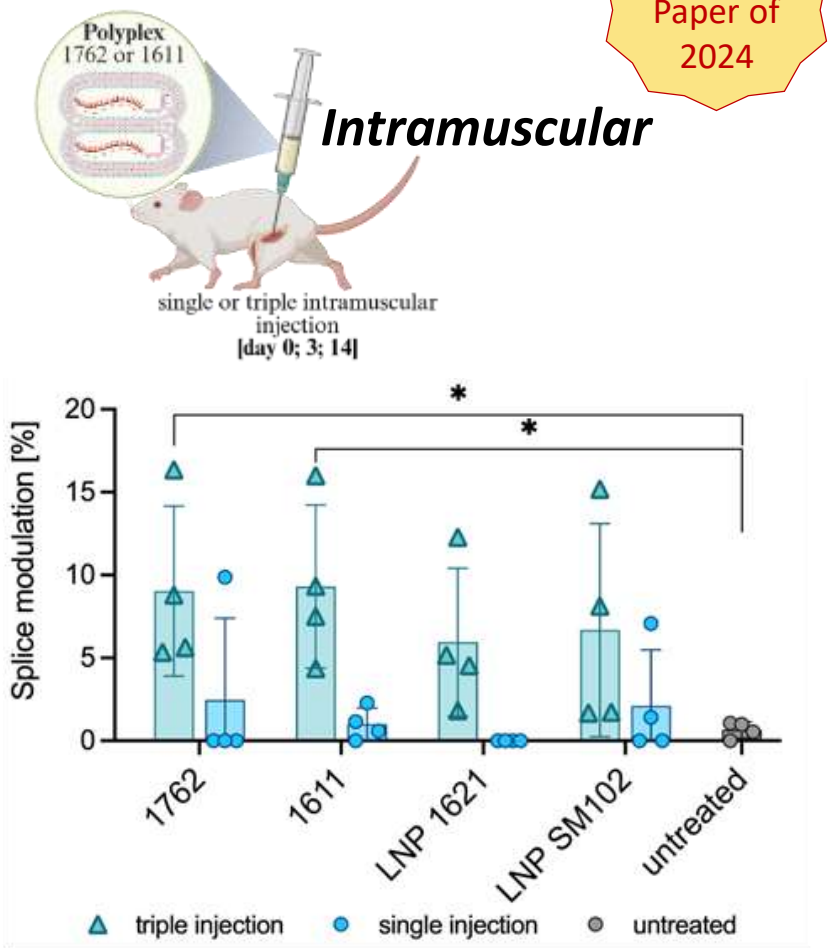
CRISPR Cas9 mRNA / sgRNA

Duchenne Muscle Dystrophy (DMD) Exon23 Skipping by Gene Editing

Best *JCR* Paper of 2024







***In vivo* gene-editing** after **intravenous** and **intramuscular** application effective at 3µg RNA/dose:
Exon 23 splicing modulation in dystrophin-expressing **cardiac muscle**, **skeletal muscle** and **brain tissue**

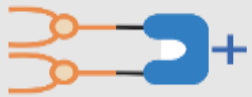
J. Germer, A. Lessl, J. Pöhmerer et al *JCR* (2024)

Chemical Evolution of RNA carriers continues

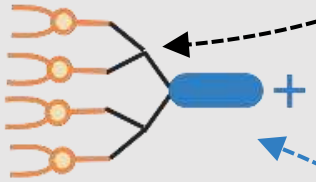
M. Grau, E. Kostyurina et al, **Chemical topology** of lipo-amino fatty acid mRNA carriers triggers distinct lipid bulk phases and endosomal escape mechanisms. *Materials Today* **2026**

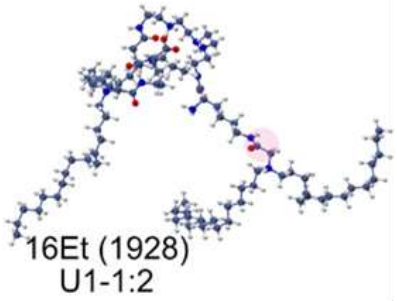
Steffens RC, S. Thalmayr et al, Modulating efficacy and cytotoxicity of lipoamino fatty acid nucleic acid carriers using disulfide or hydrophobic **spacers**. *Nanoscale* **2024**

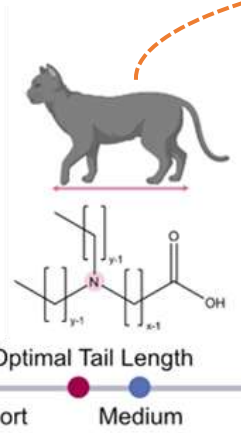
U-shapes

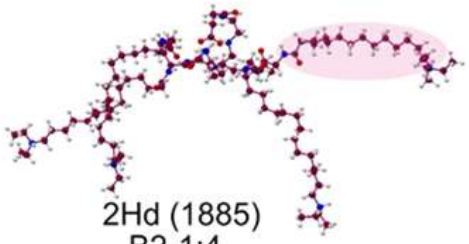


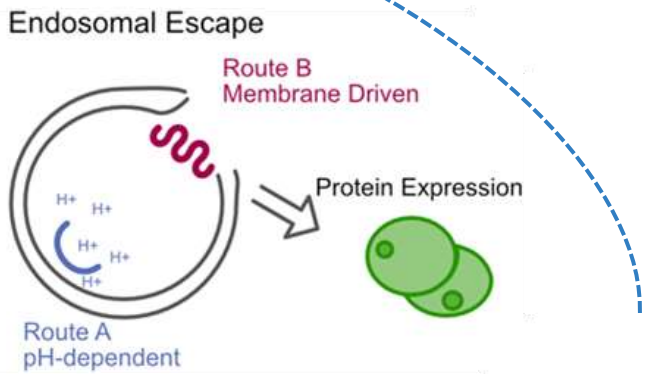
Bundles











M. Grau, N. Martini et al, Modulating mRNA carrier efficacy through the molecular **catwalk of ionizable nitrogens** in lipidic domains. *J. Colloid Interface Sci.* **2026**

T. Burghardt, S. Thalmayr et al, **Hydrophobic refinement** of polarity-switchable lipo-xenopeptides modulates endosomal escape and enhances mRNA delivery in vitro and in vivo. *J. Am. Chem. Soc.* **2026**

RNA Delivery - Chemical Evolution of Vectors

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Franziska Haase
Ulrich Lächelt *(now @ Vienna U)*
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evoVect