

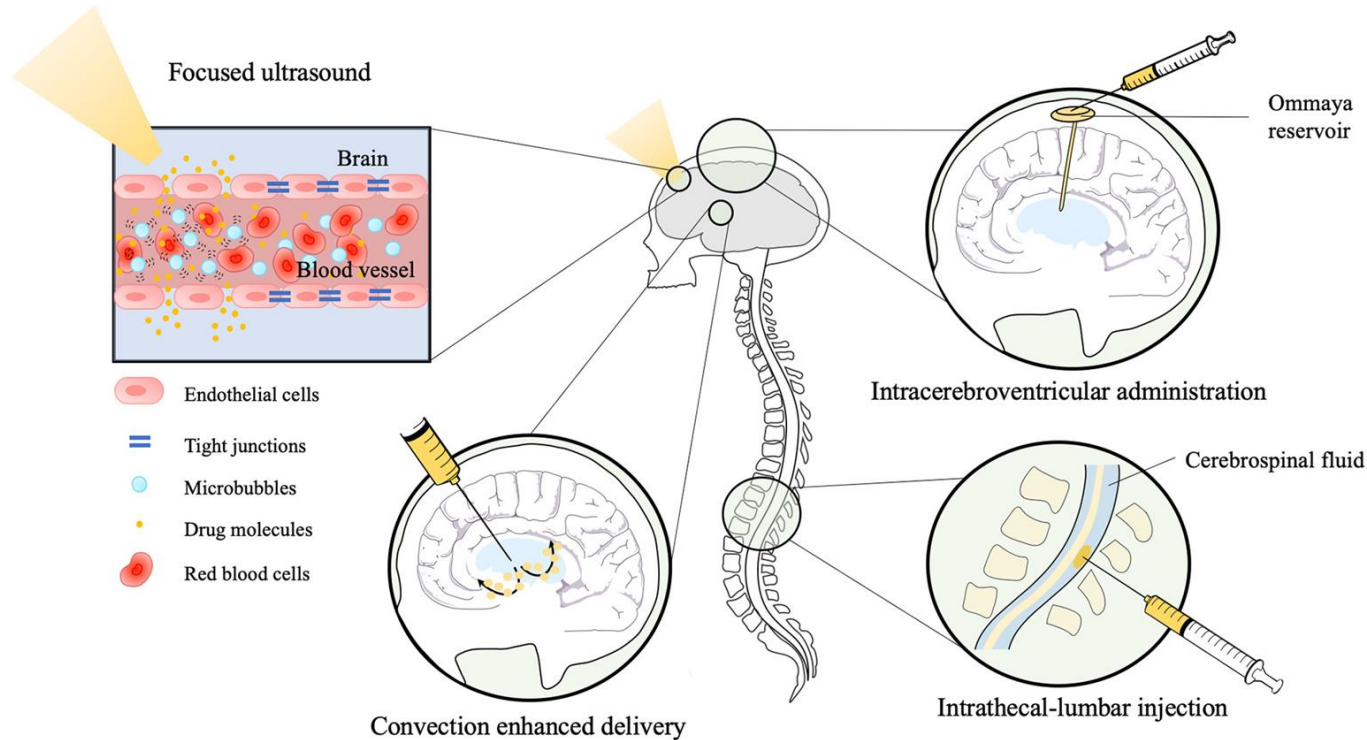
Peptide-functionalized lipid nanoparticles for targeted systemic mRNA delivery to the brain

Emily Han, Sophia Tang, Dongyoon Kim, Amanda Murray, Kelsey Swingle, Alex Hamilton, Kaitlin Mrksich, Marshall Padilla, Rohan Palanki, Jacqueline Li, Michael J. Mitchell

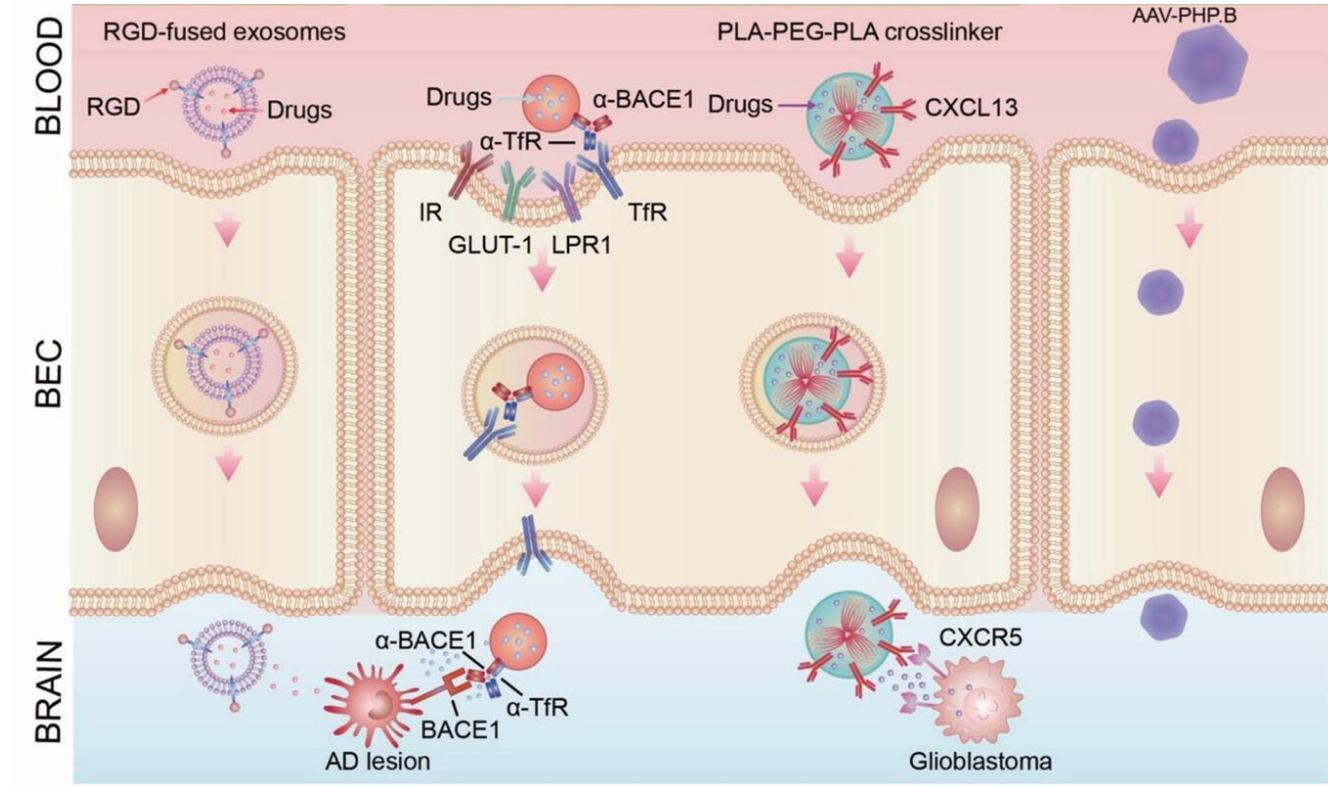
University of Pennsylvania

Drug delivery to the brain remains a great challenge

especially for large nucleic acid therapeutics!



BBB targeting can enhance drug carrier transcytosis



Can targeting peptides enable systemic mRNA LNP delivery through the BBB, to neurons?

Targeting peptide

Target receptor

RVG29

Nicotinic acetylcholine receptor (nAChR)

T7

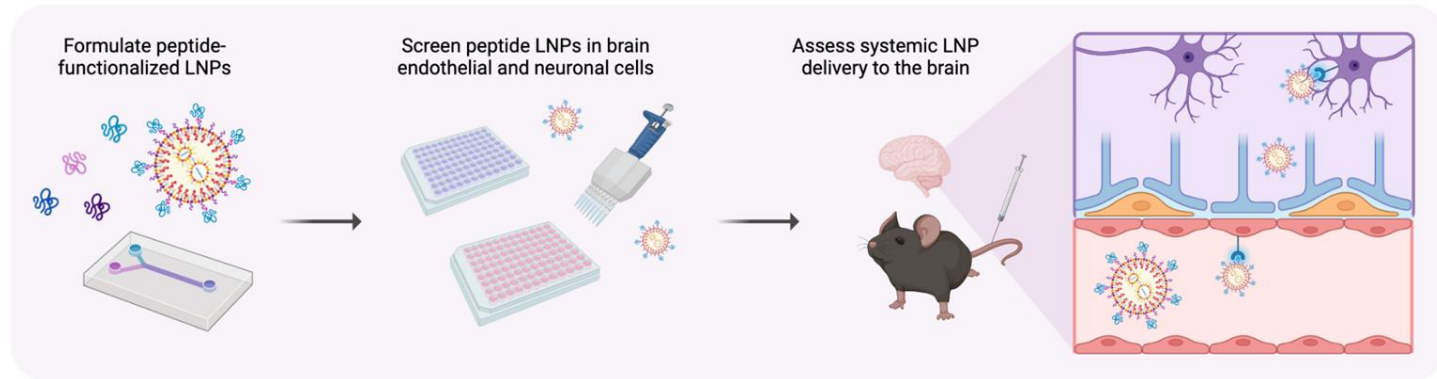
Transferrin receptor (TfR)

Angiopep-2 (AP2)

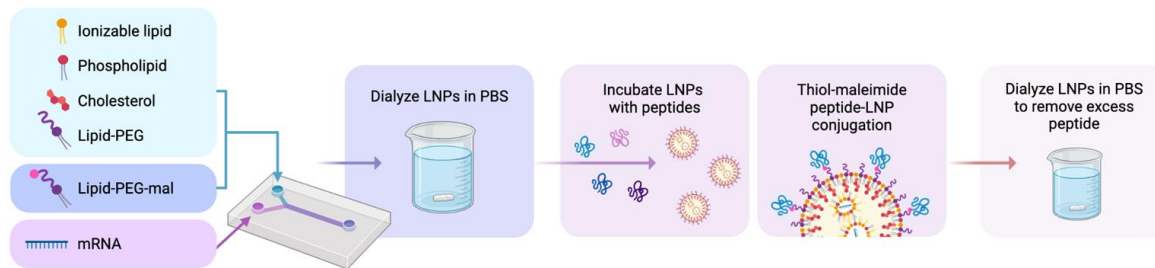
Low density lipoprotein receptor-related protein 1 (LRP-1)

mApoE

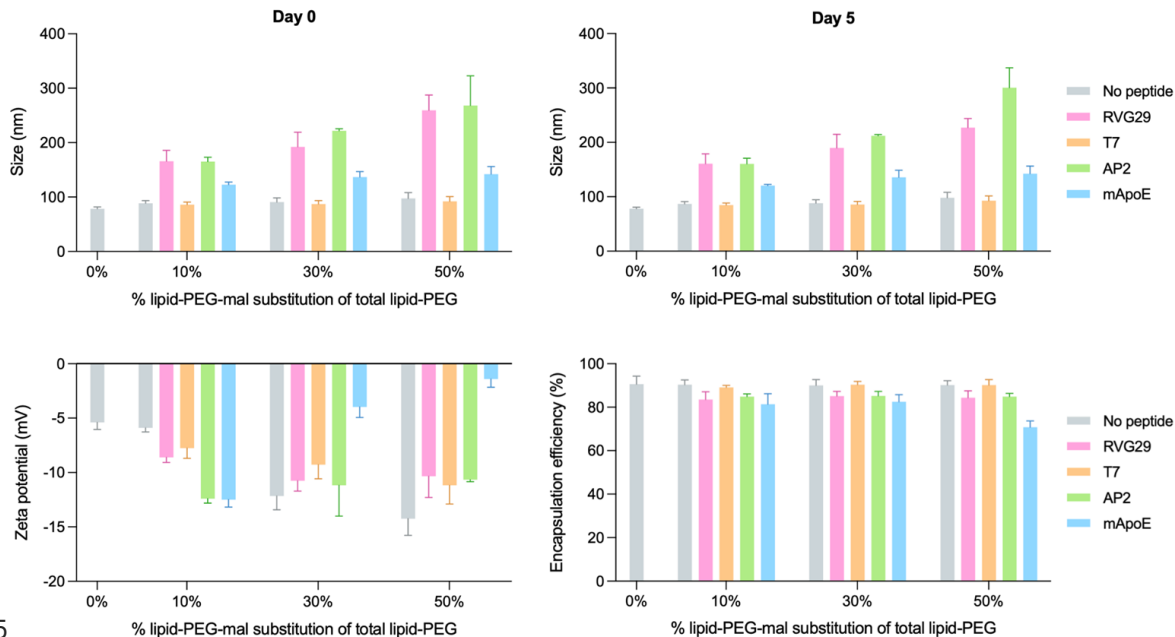
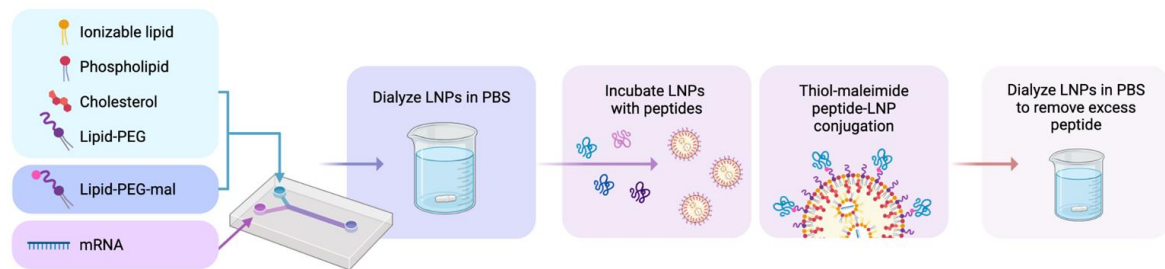
Low density lipoprotein receptor (LDLR)



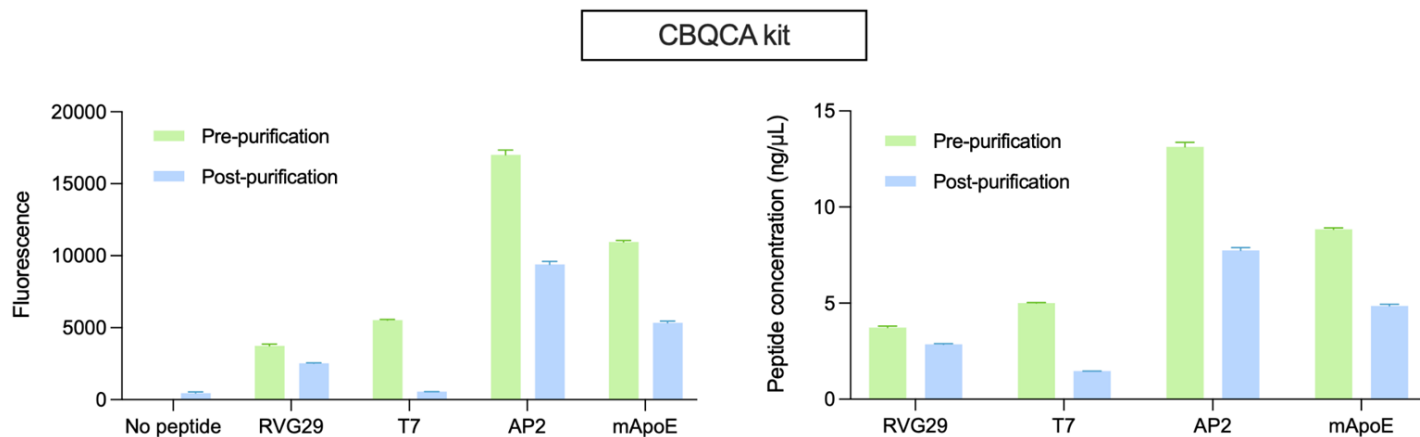
Peptides are stably conjugated to LNPs via thiol-maleimide reaction



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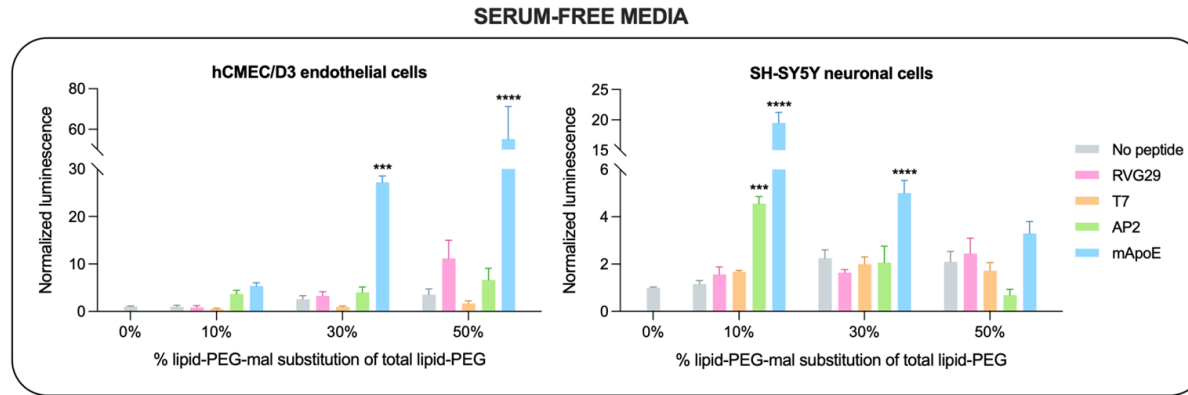
Protein quantification kits confirm peptide-LNP conjugation



LNPs have a 10% lipid-PEG-mal substitution.

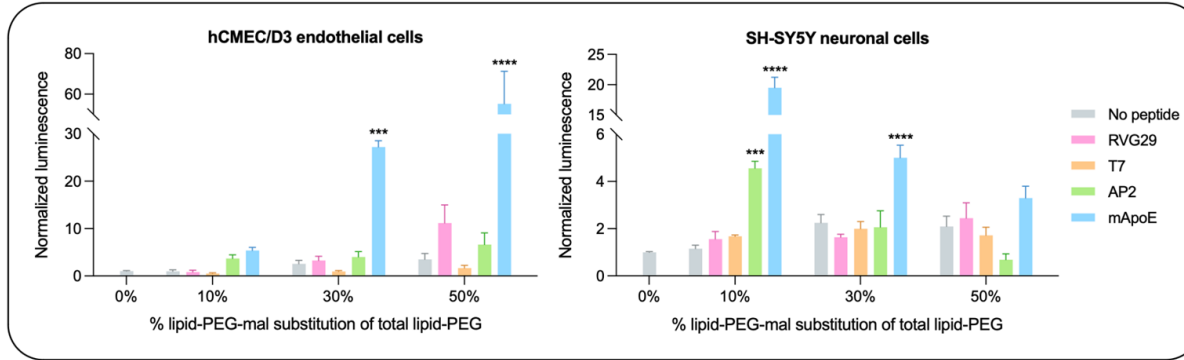
Han et al., *Nano Lett.*, 2025

Peptide targeting enhances mRNA transfection of brain endothelial and neuronal cells *in vitro*

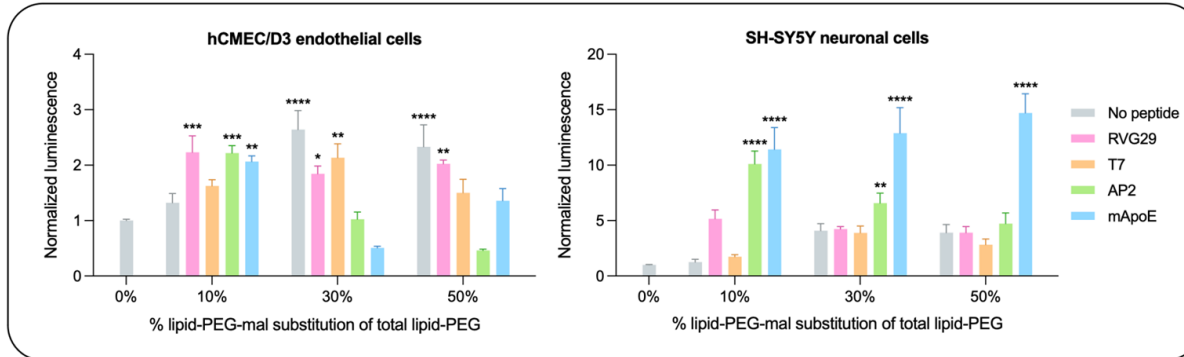


Peptide LNPs still enhance neuronal mRNA transfection in serum-containing media

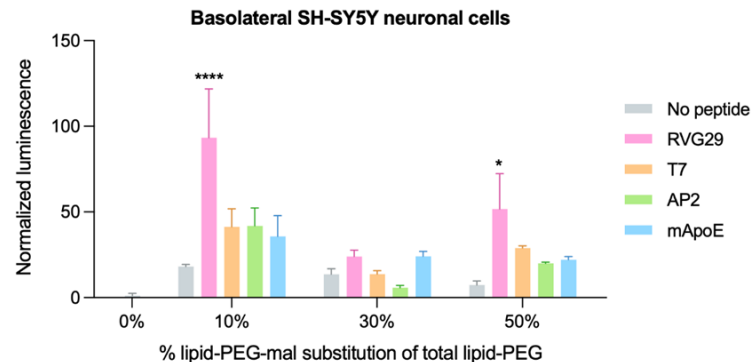
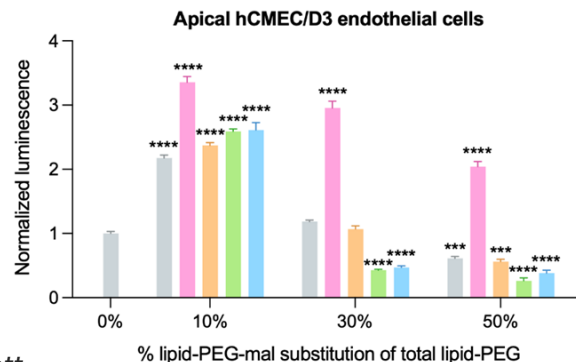
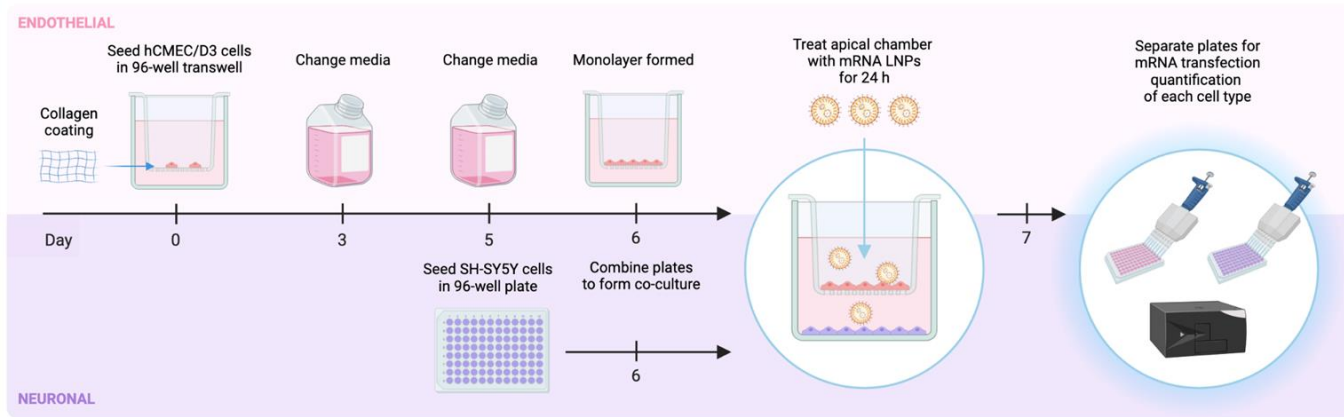
SERUM-FREE MEDIA



SERUM-CONTAINING MEDIA



Peptide targeting enhances transcytosis across a brain endothelial monolayer *in vitro*

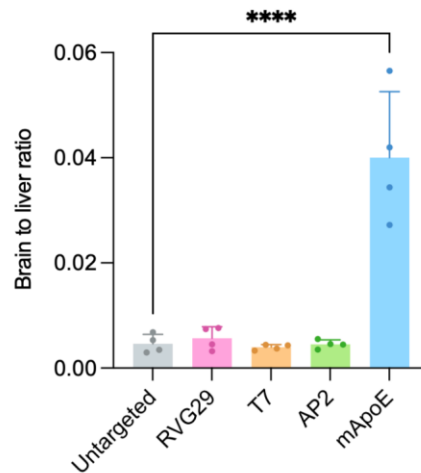
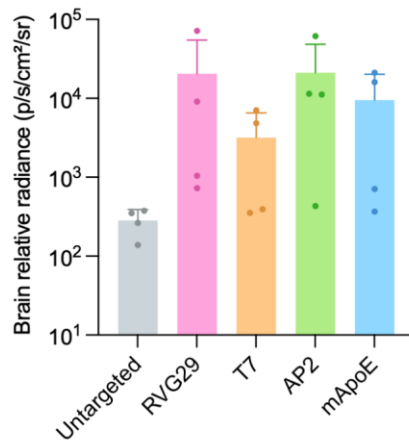
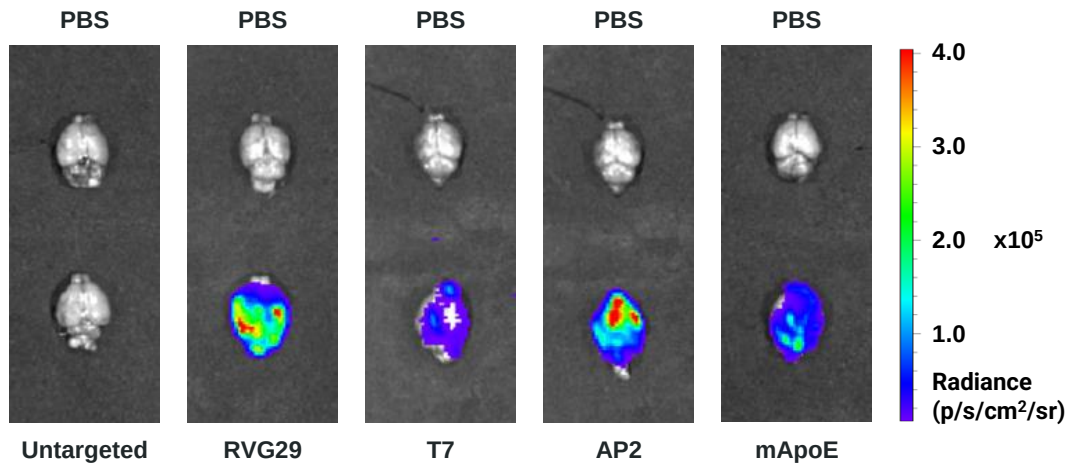


Peptides improve brain mRNA transfection after systemic administration

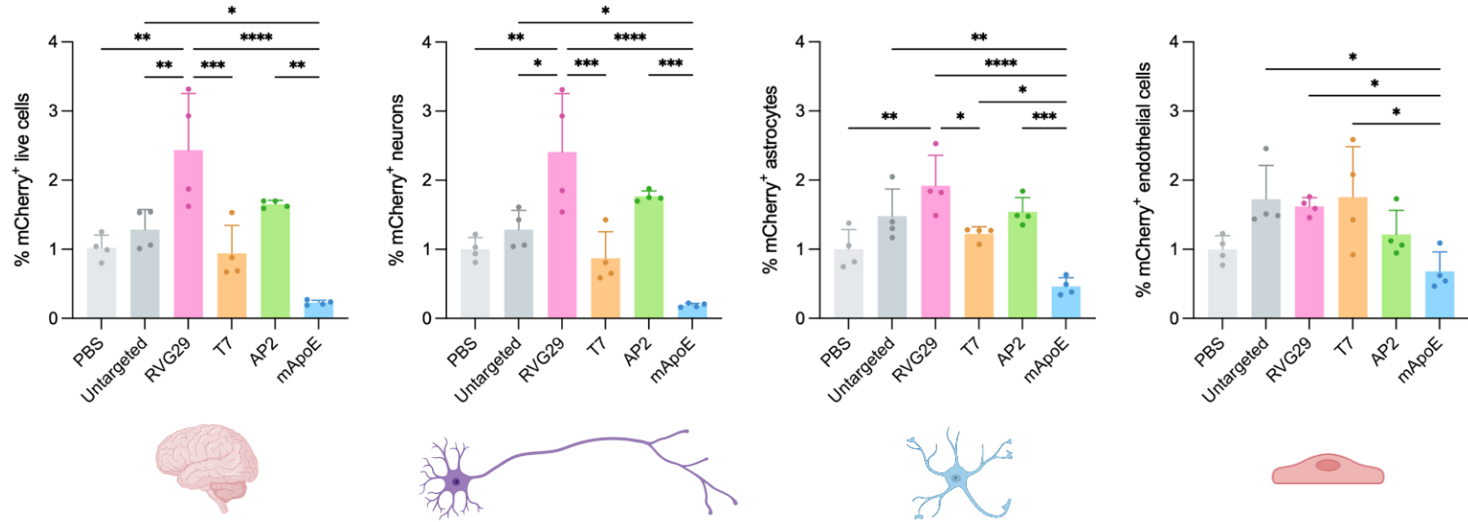
Targeted LNPs are made with 10% lipid-PEG-mal substitution.

Mice were treated with luciferase mRNA LNPs at a dose of 0.3 mg/kg for 6 h.

Han et al., *Nano Lett.*, 2025



RVG29 LNPs transfected neurons *in vivo* after systemic administration

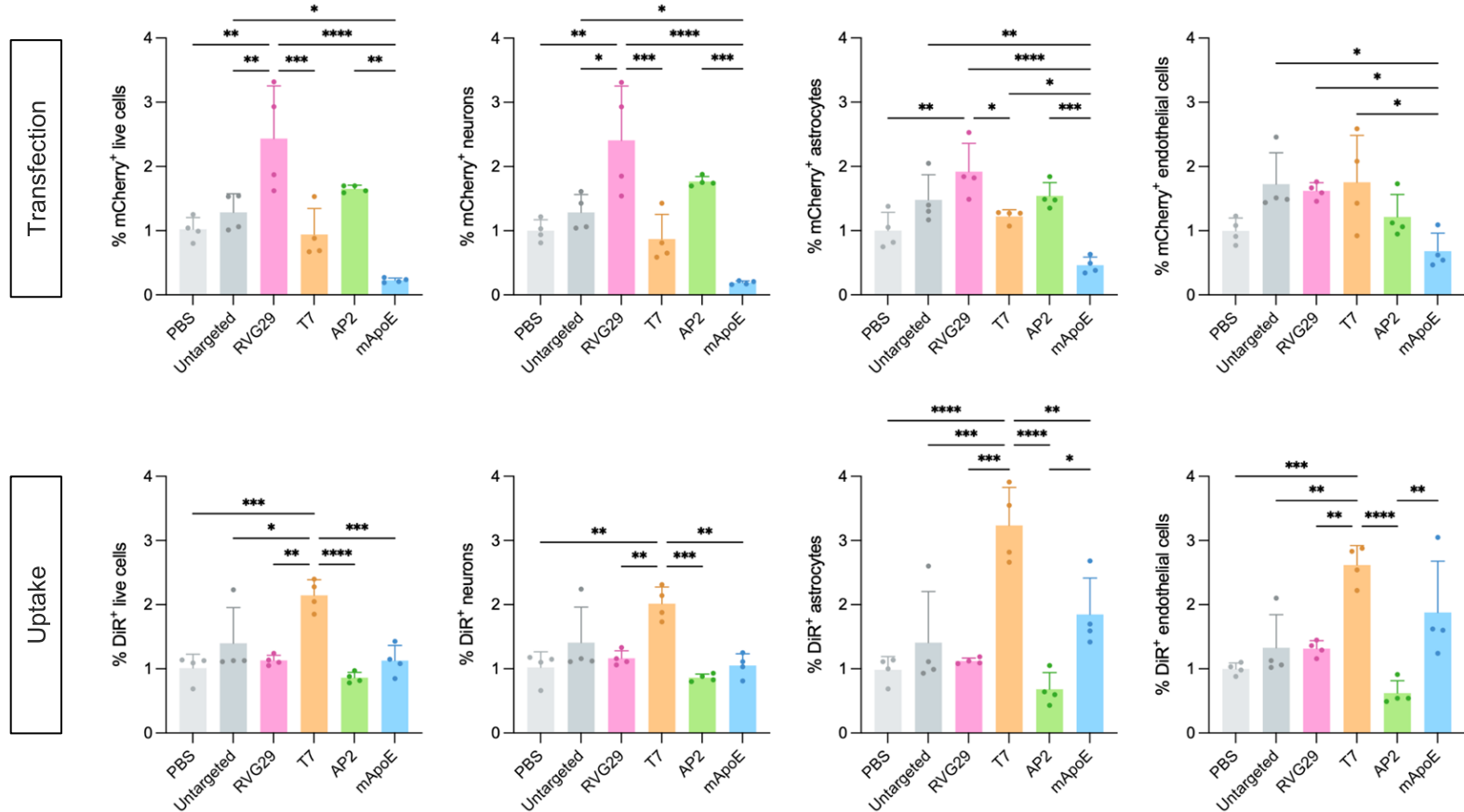


Targeted LNPs are made with 10% lipid-PEG-mal substitution.

Mice were treated with mCherry mRNA LNPs at a dose of 0.3 mg/kg for 12 h.

Han et al., *Nano Lett.*, 2025

Some peptides facilitate higher brain uptake, but not transfection

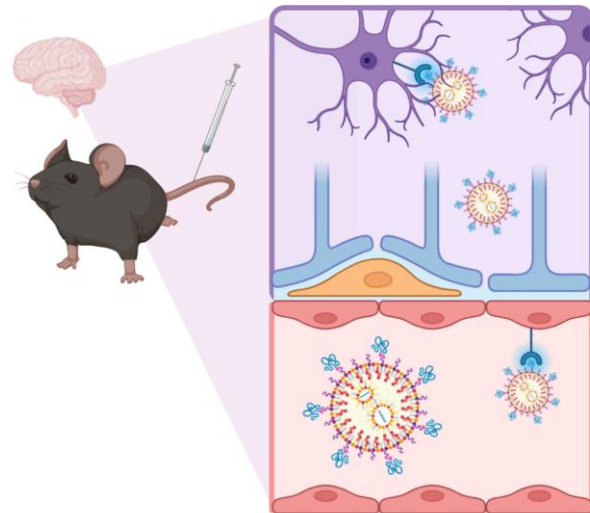


Conclusions

Peptide functionalization, especially with RVG29, can enhance mRNA transfection of neurons in the brain after systemic administration.

Ongoing work:

1. Investigate the precise BBB transcytosis mechanism of targeted LNPs
2. Assess LNP biodistribution in the mouse brain
3. Design peptides with higher brain specificity



Thanks!

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**NEXT-GENERATION
DELIVERY INNOVATIONS**