2024

Enabling Intramuscular Injections for Nerve Regeneration In Vivo

Jessica Larsen

Carol and John ‘63 Cromer Family Endowed Associate Professor
Chemical and Biomolecular Engineering
Bioengineering

Center for
NANOTHERAPEUTIC STRATEGIES IN THE CENTRAL NERVOUS SYSTEM
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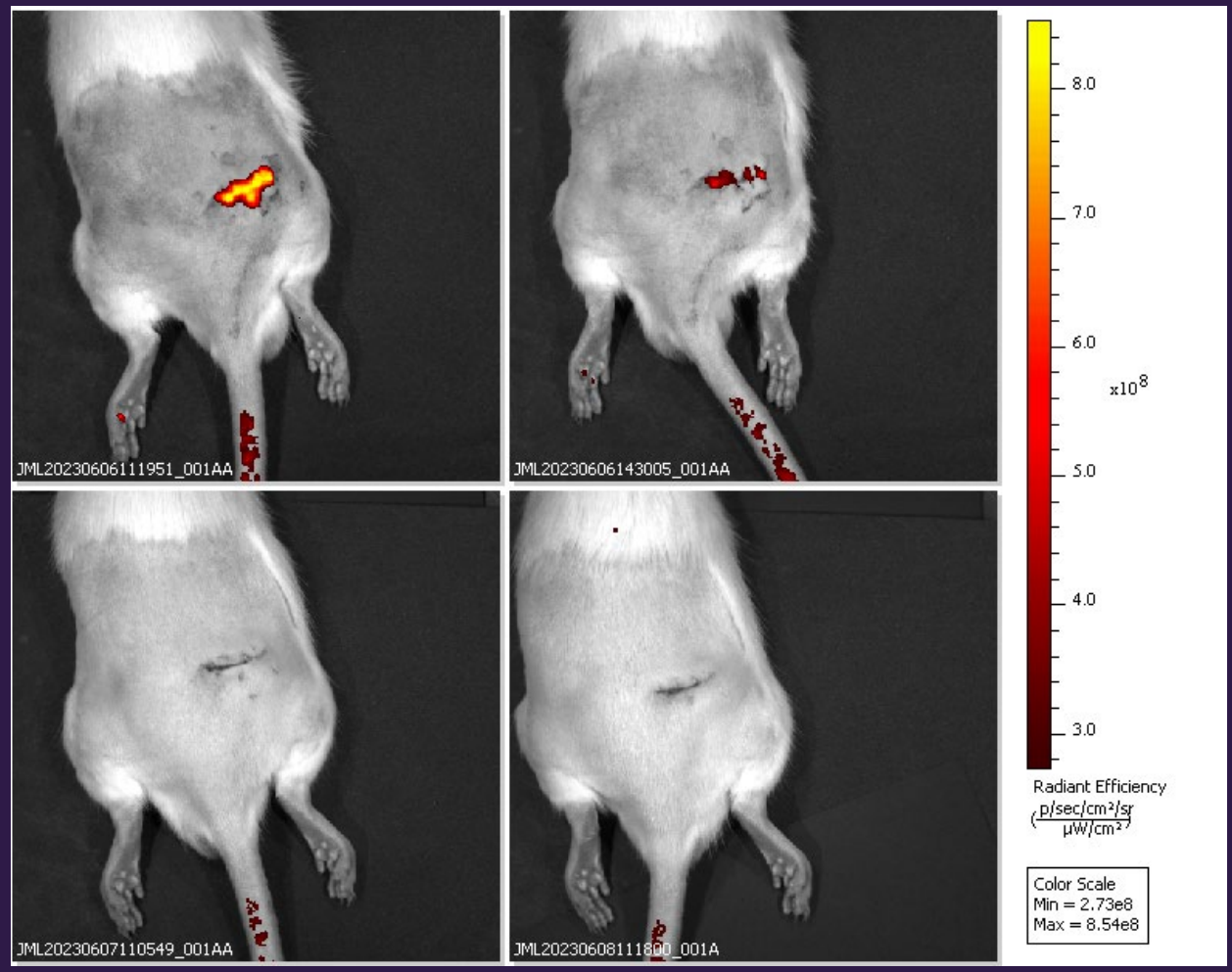
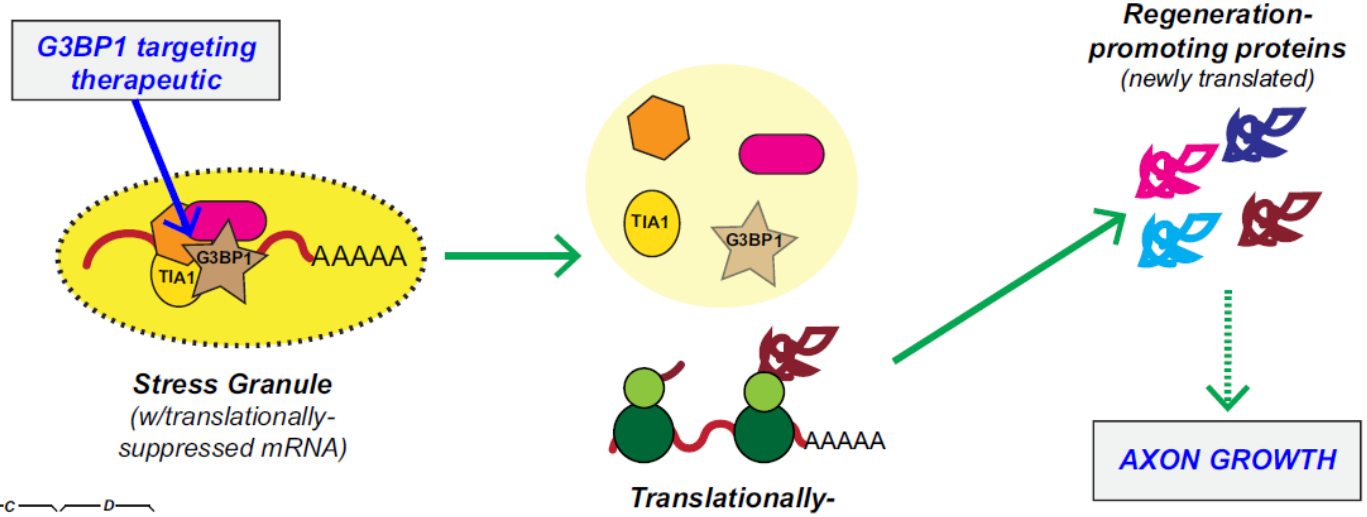
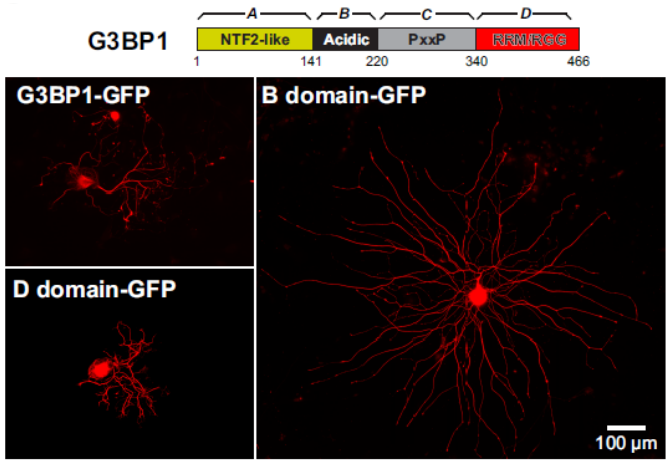


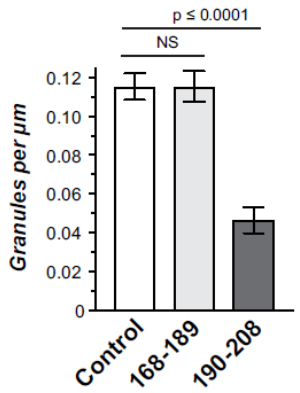
G3BP1 peptide accelerates nerve growth after injury.

Dr. Jeffrey Twiss
University of South Carolina

PNS Regeneration slowed by LLPS/Stress Granule Formation







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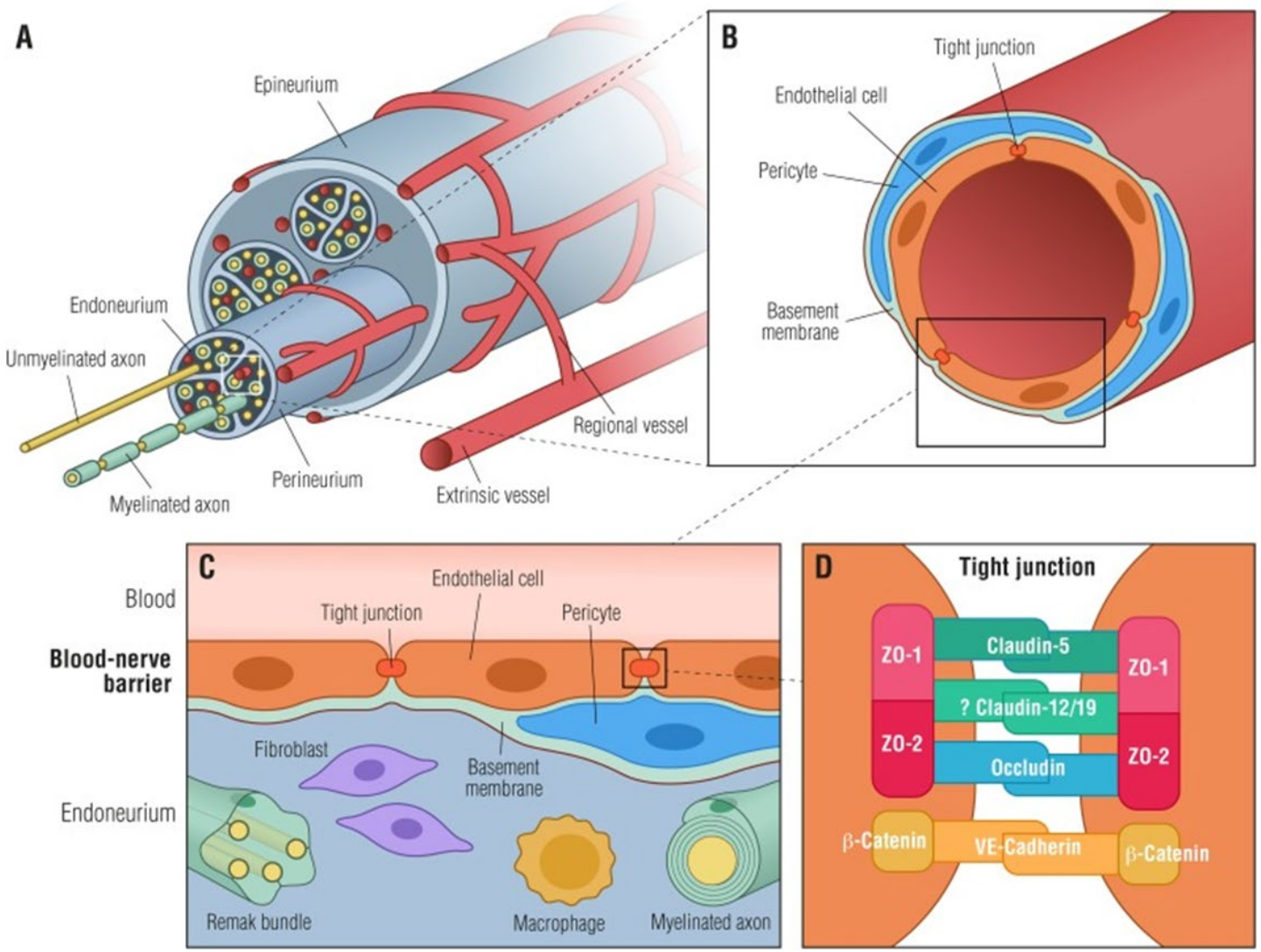
Sahoo, P., et. al, Nature Communications, 2018 DOI: 10.1038/s41467-018-05647-x

The BNB inhibits treatment of PNS conditions.



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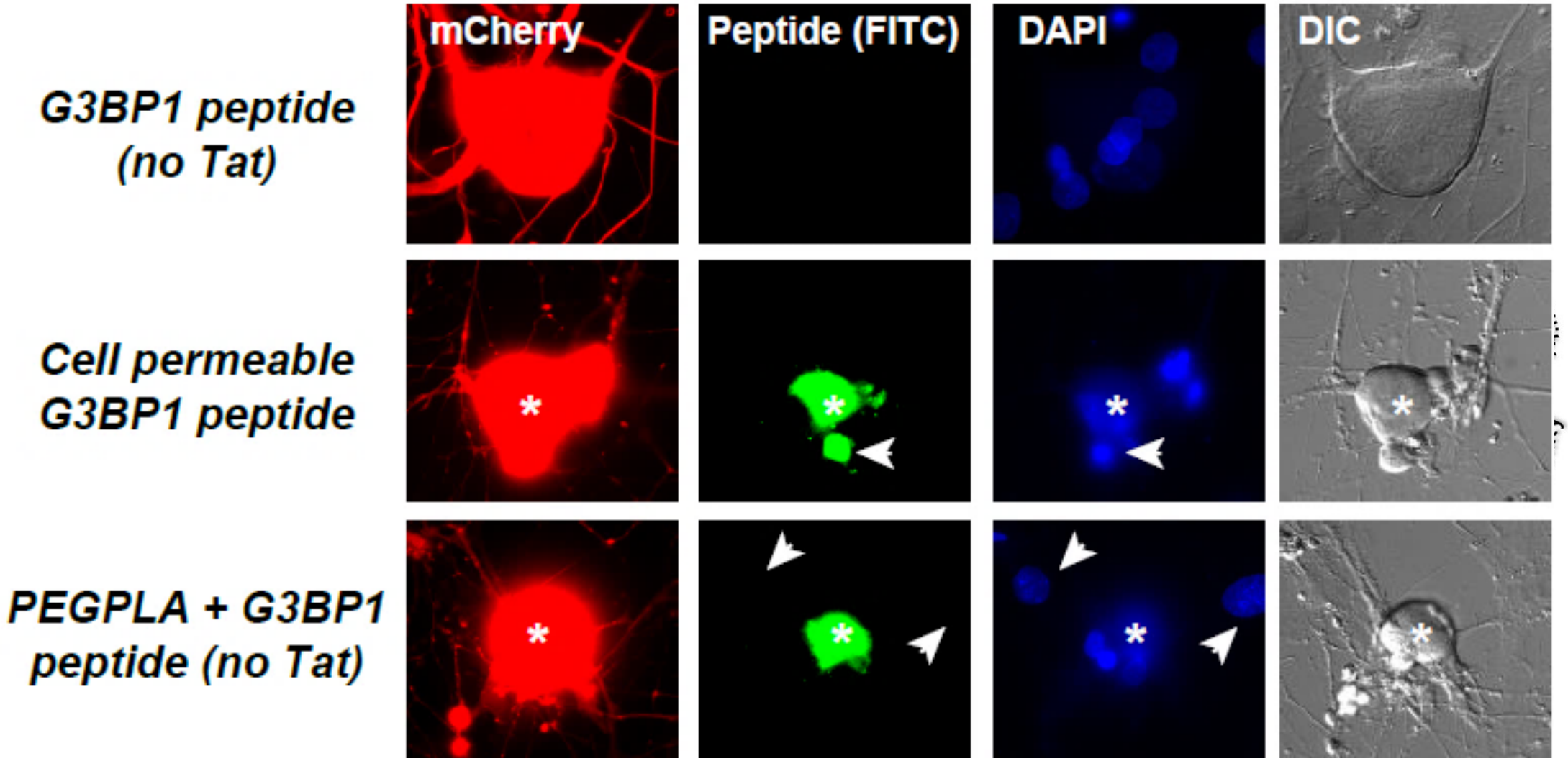
Faroni, A., et al., Advanced Drug Delivery Reviews, 2015, DOI:10.1016/j.addr.2014.11.010.

Polymers in Nanotechnology



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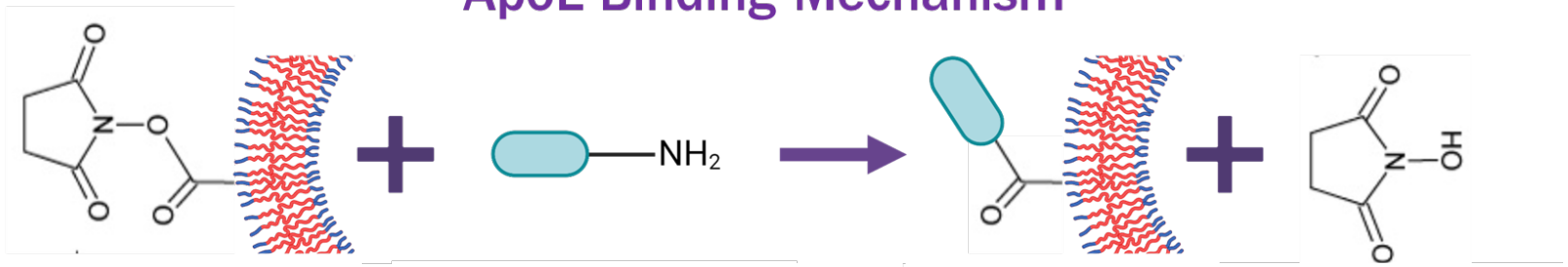
Iqbal, S.; Blenner, M.; Alexander-Bryant, A.; **Larsen, J.** ACS Biomaterials Science and Engineering. 2020. DOI: 10.1021/acs.biomac.9b01754

Polymersomes bind targeting ligands using different bioconjugation chemistries.

ApoE Binding Mechanism

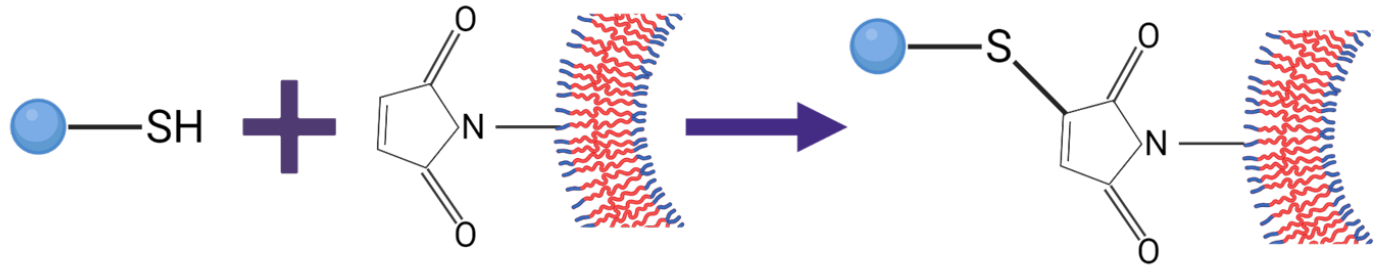


NHS Ester Derivative | ApoE + reactive amine | ApoE-conjugated polymersome | NHS leaving group

Targets:

- Low-density lipoprotein receptors (LDLR)

RVG-Cys Binding Mechanism



RVG + reactive thiol | Maleimide-conjugated polymer | RVG-conjugated polymersome

Targets:

- Nicotinic acetylcholine receptors
- Neural cell adhesion molecule (NCAM)

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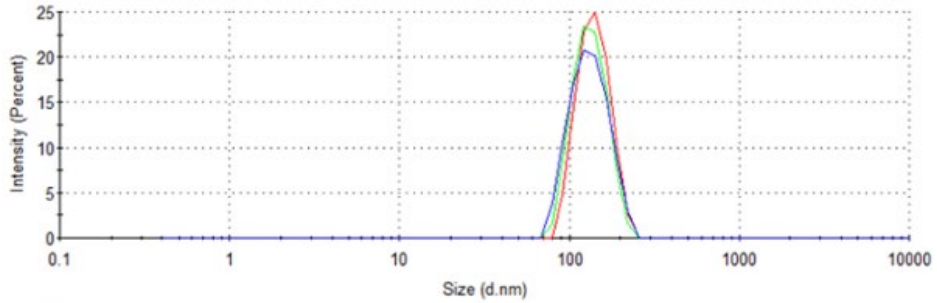
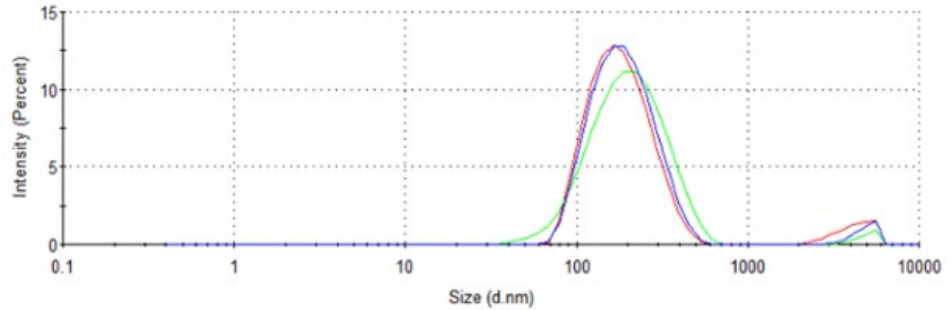
PEG-PLA polymersomes are characterized and ligand attachment is confirmed.

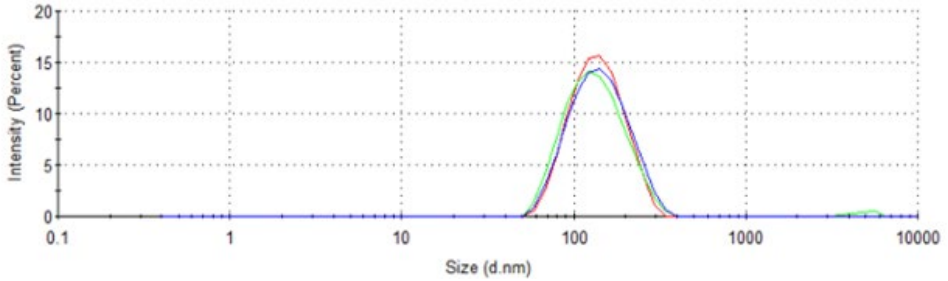
Untagged



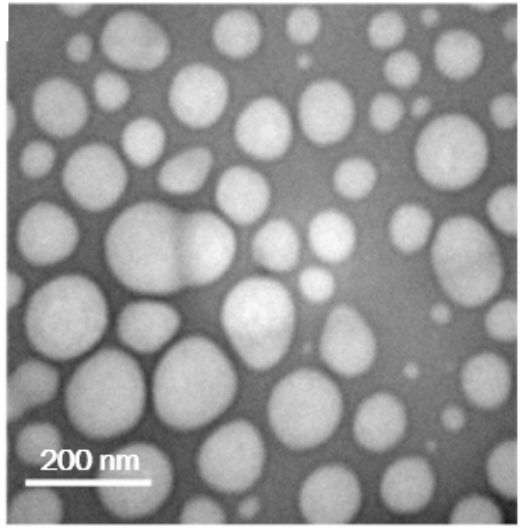
ApoE

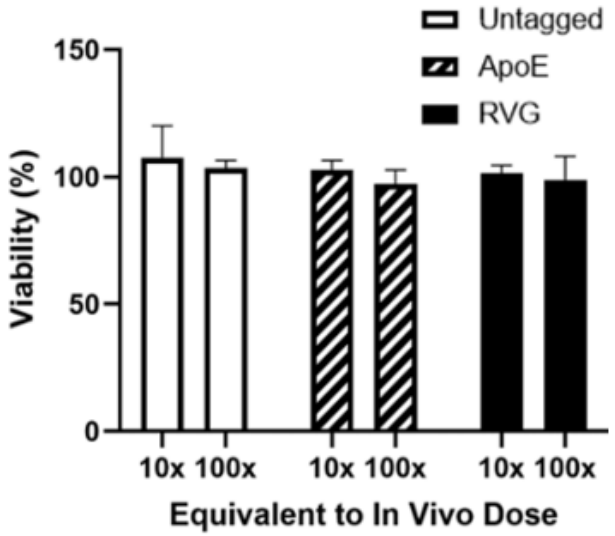


RVG



Ligand	Z-Avg. Diameter [nm]	PDI	ζ-Potential [mV]	Loaded Content [mg AF647 · 10^{-5} / mg PS]
-	136 ± 5.9	0.04 ± 0.017	-26.3 ± 4.5	13.9 ± 3.5
ApoE	181 ± 47.6	0.19 ± 0.15	-7.67 ± 4.9	7.75 ± 1.4
RVG	128 ± 41.5	0.20 ± 0.092	4.29 ± 0.6	9.97 ± 10





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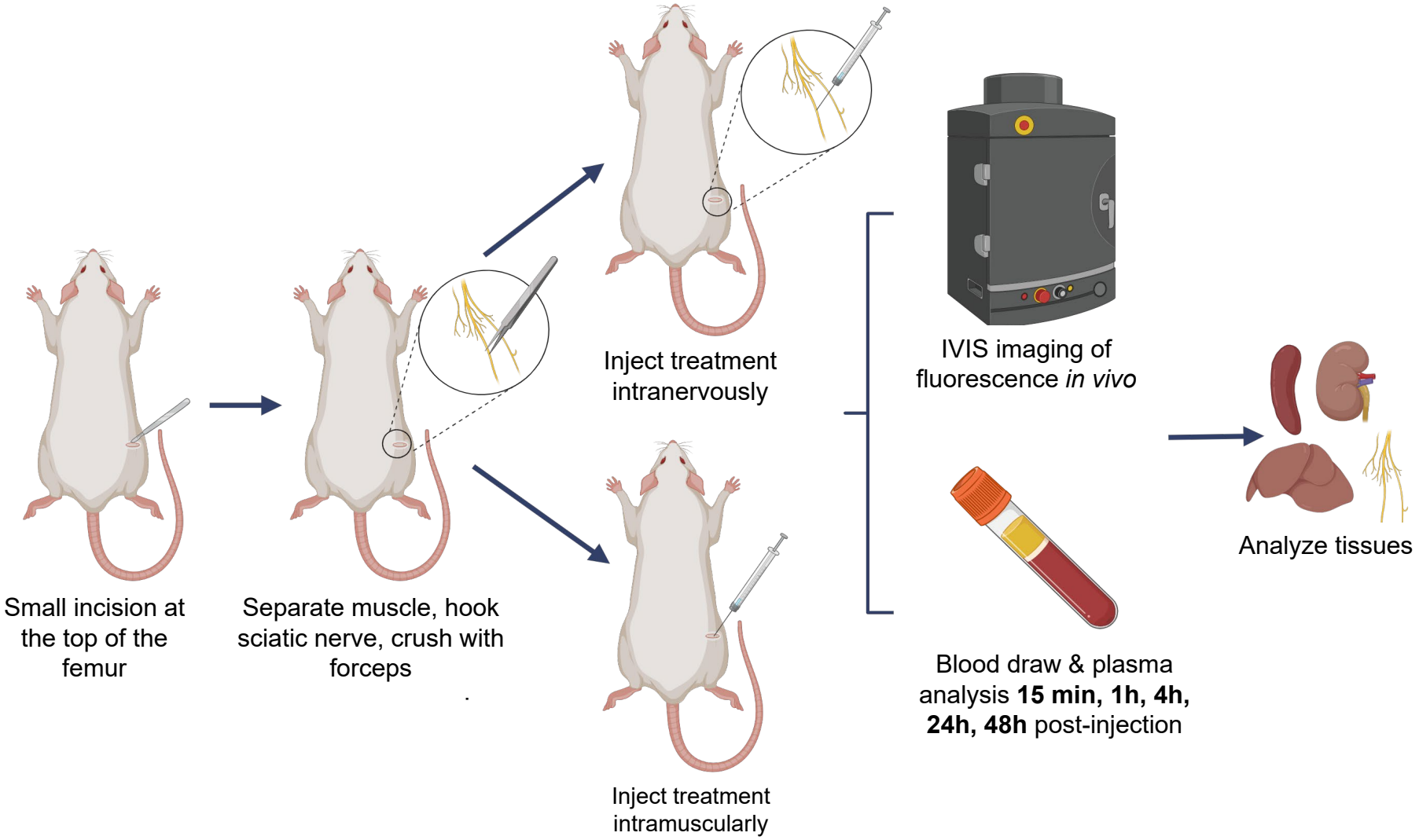
Sciatic nerve injury model on Sprague Dawley rats



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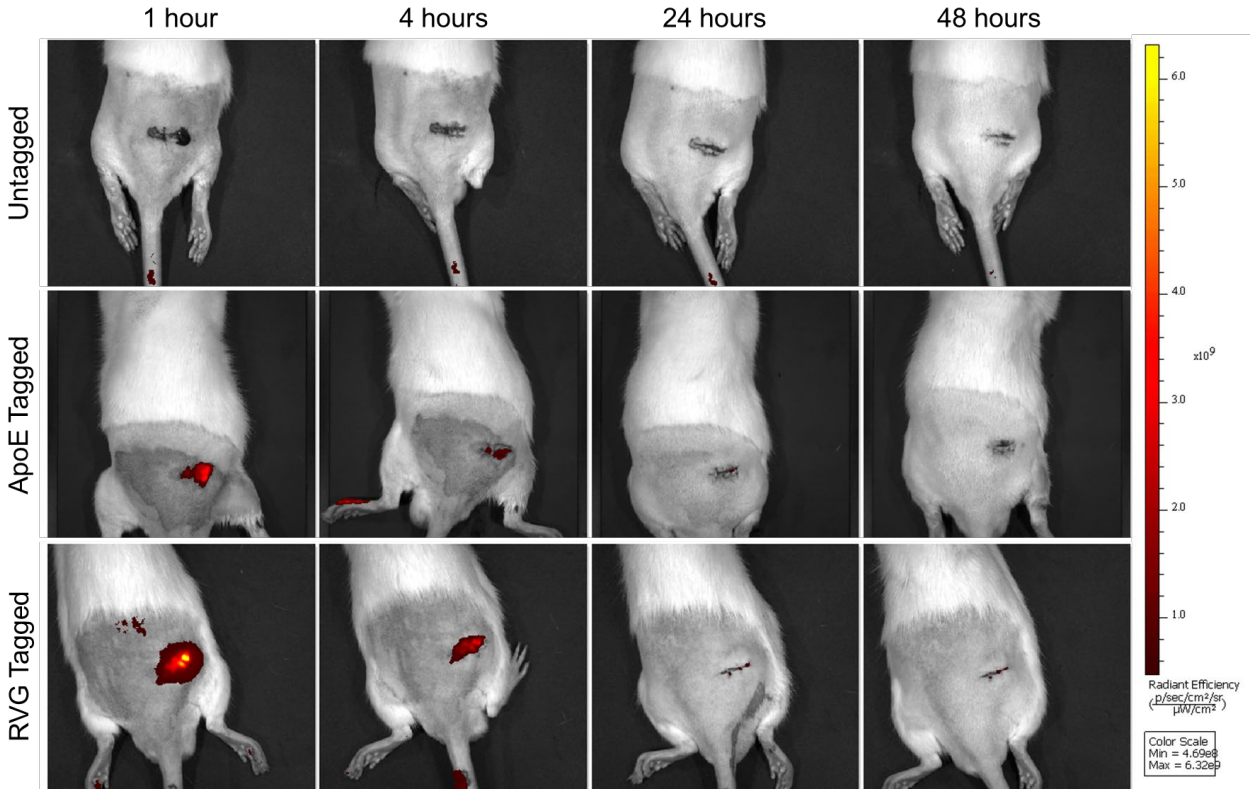
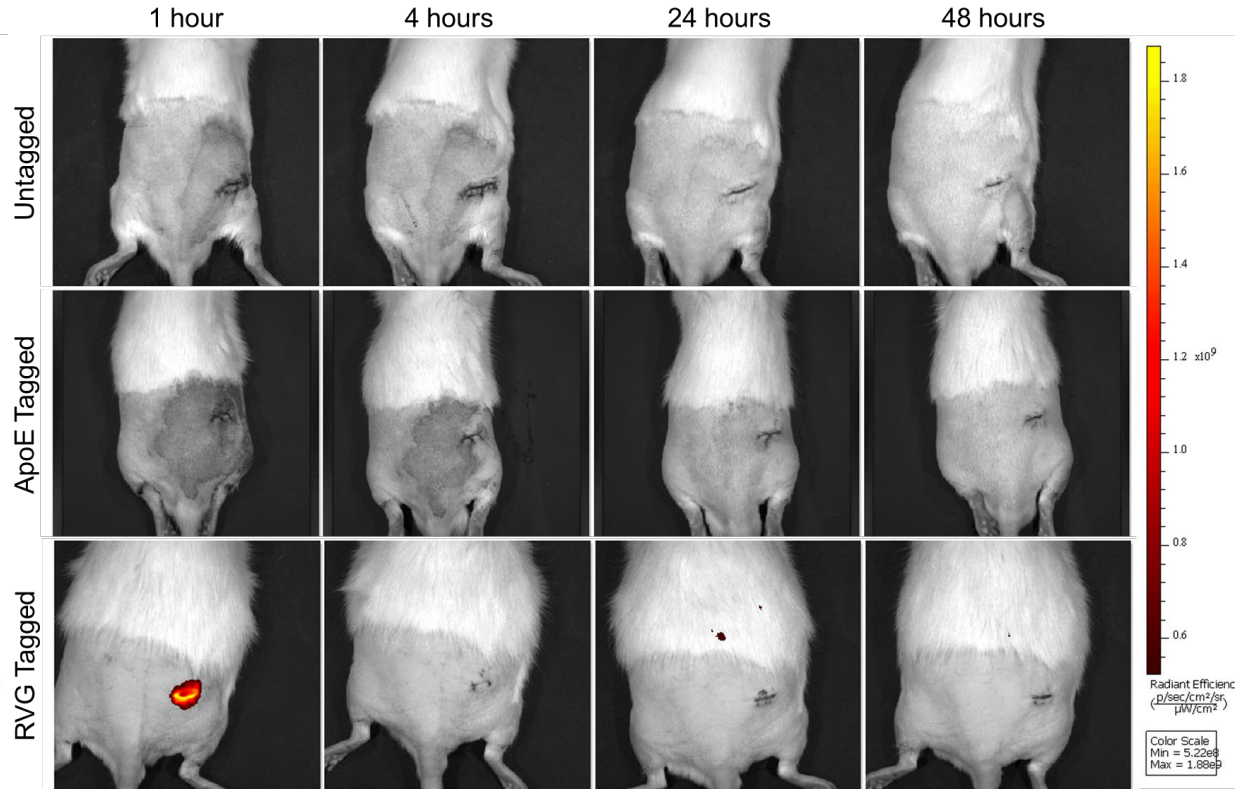
ApoE and RVG-tagged polymersomes are retained for extended period when administered via IN injection.

Intranerve Injection



Intramuscular Injection



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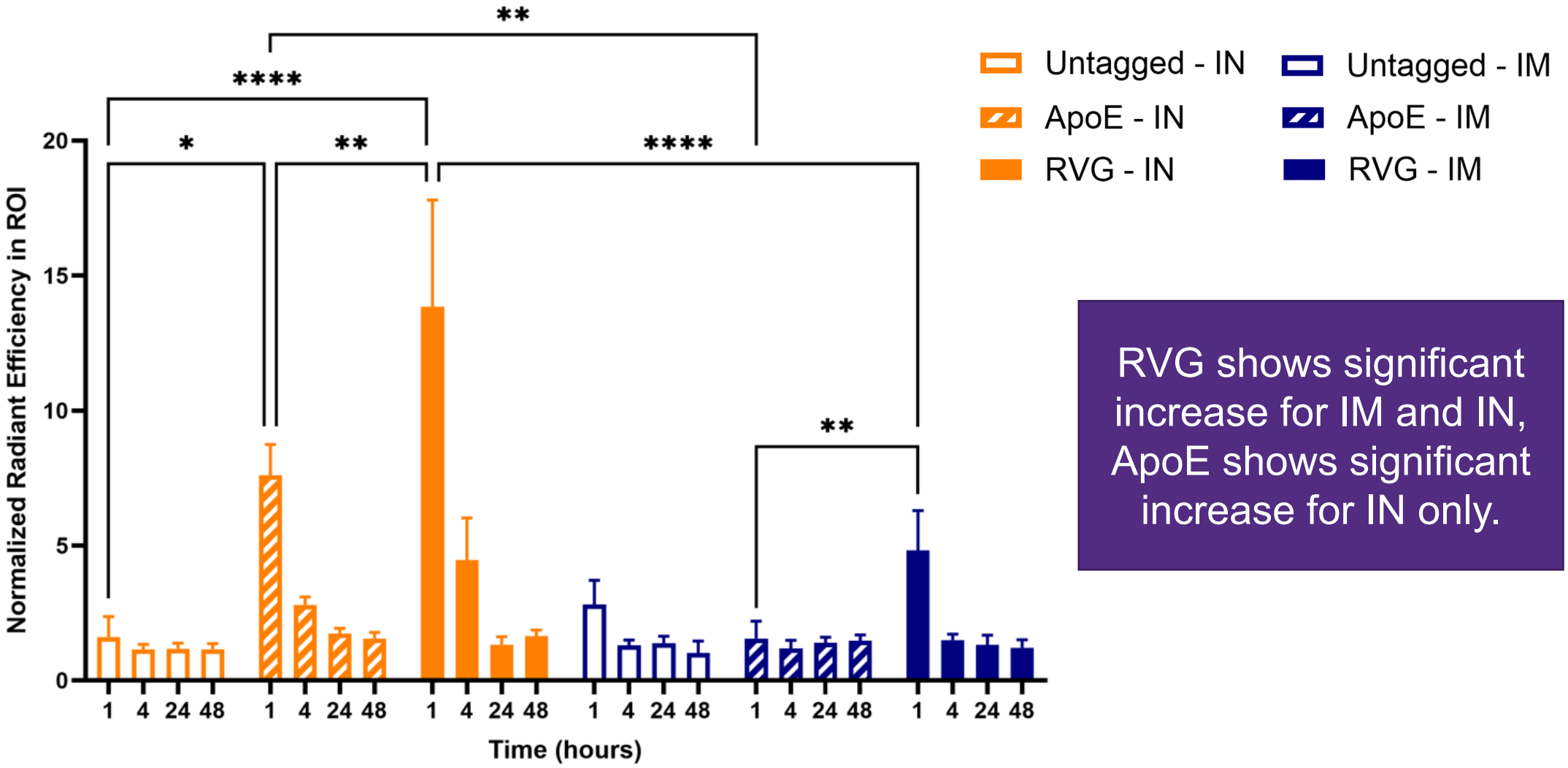
Normalized radiant efficiency significance only occurs at 1-hour timepoint.



RVG shows significant increase for IM and IN, ApoE shows significant increase for IN only.

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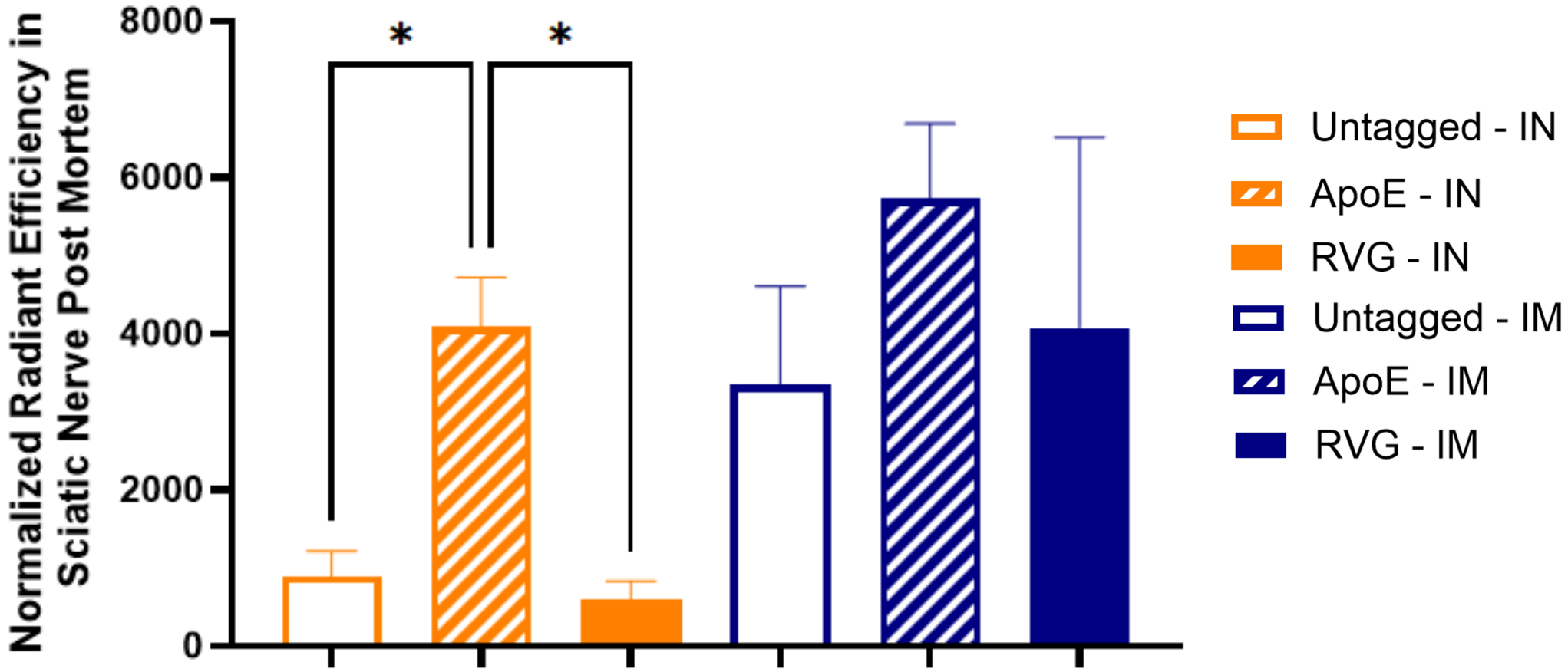
ApoE-tagged polymersomes are highly retained in the nerve.



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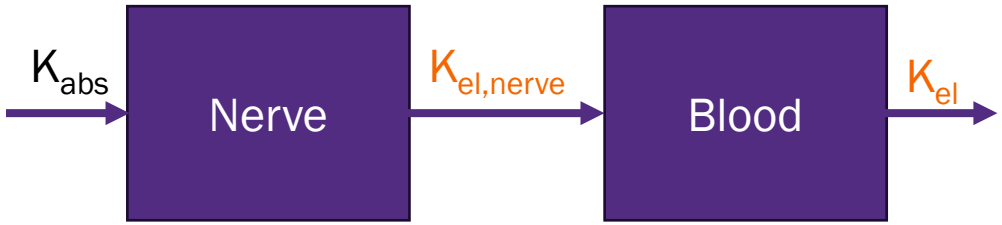
Pharmacokinetic Evaluation

Two Compartment Model



$$\frac{dC}{dt} = Kel_{nerve} \cdot (D - C) - Kel \cdot C$$

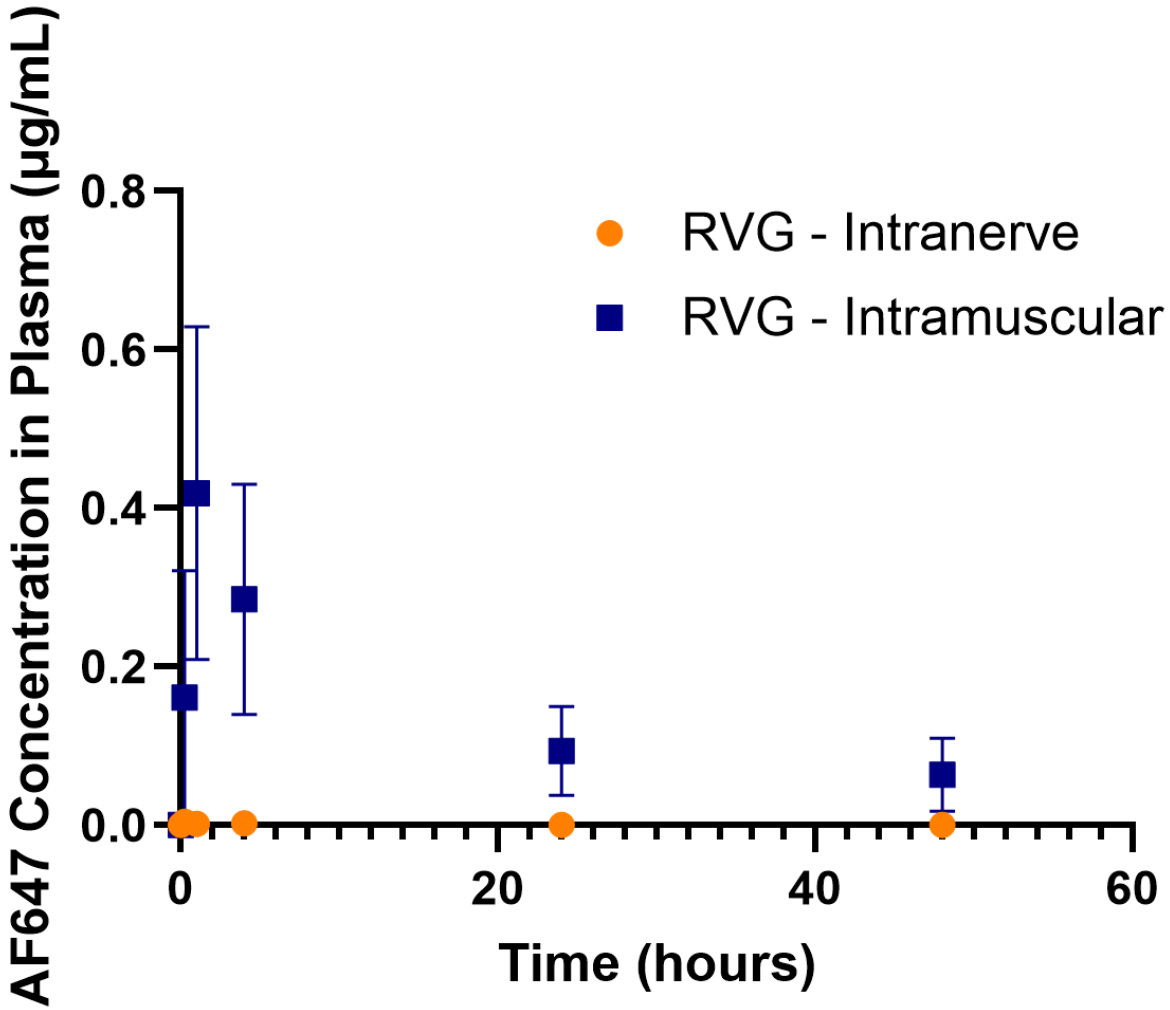
Where:

C is the plasma concentration at time t

D is the initial dose

Kel_{nerve} is the elimination rate from the nerve tissue

Kel is the elimination rate constant



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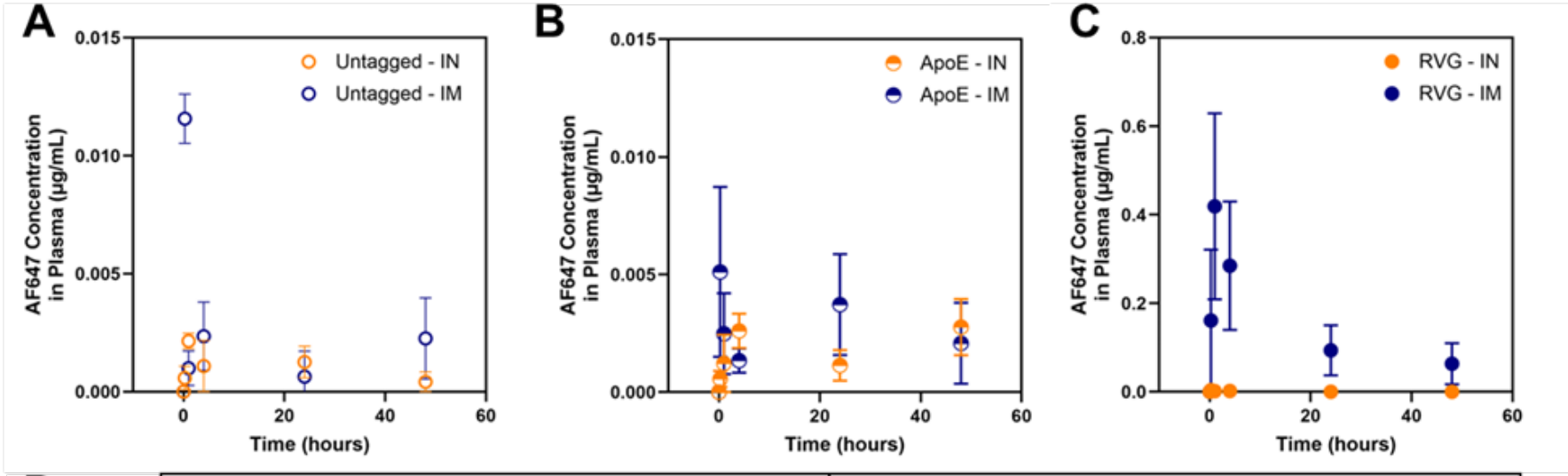
Pharmacokinetic Evaluation



D

	Intranerve (IN)			Intramuscular (IM)		
	Untagged	ApoE	RVG	Untagged	ApoE	RVG
AUC (µg*h/mL)	0.050 ± 0.028	0.091 ± 0.033	0.080 ± 0.084	0.076 ± 0.053	0.130 ± 0.069	6.97 ± 3.17
MRT (hr)	19.4 ± 16.3	25.5 ± 16.9	3.43 ± 1.41	23.1 ± 29.2	25.0 ± 21.6	14.3 ± 10.8
Vss (mL/µg)	2.94 ± 2.96	2.11 ± 1.60	0.870 ± 0.428	2.28 ± 3.29	1.44 ± 1.47	0.015 ± 0.014
Cl (mL/h)	0.151 ± 0.084	0.083 ± 0.030	0.253 ± 0.07	0.010 ± 0.068	0.058 ± 0.030	0.001 ± 0.0005

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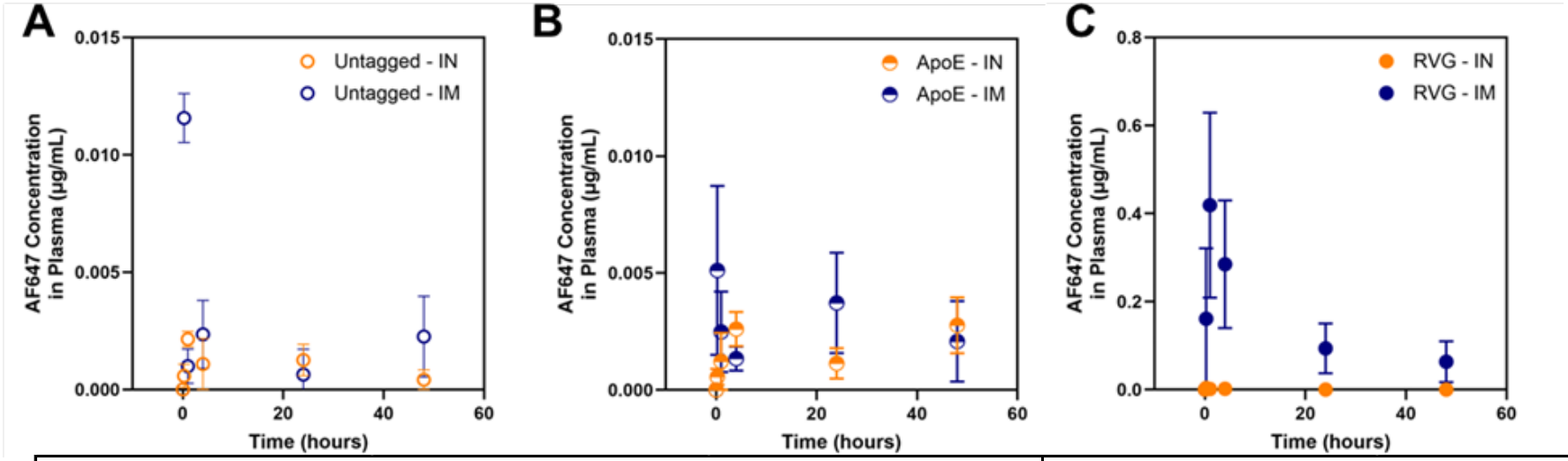

	Intranerve (IN)			Intramuscular (IM)	
	Untagged	ApoE	RVG	Untagged	RVG
k_a (1/hr)	0.009409 (0.001504 to 0.07900)	0.022647 (0.0005288 to 0.01248)	0.1713 (0.03574 to 1.381)	3.269 (1.439 to ???)	1.079 (0.3630 to 2.687)
k (1/hr)	4.886 (0.9312 to 42.17)	0.8645 (0.1721 to 4.714)	33.6 (8.955 to 183.8)	96.89 (67.41 to 128.2)	0.3132 (0.09897 to 0.8501)
$t_{1/2}$ (hr)	0.1398 (0.01620 to 0.7335)	0.79 (0.1449 to 3.967)	0.02033 (0.003715 to 0.07627)	0.007049 (0.005326 to 0.01013)	2.181 (0.8035 to 6.901)
R^2	0.2485	0.3045	0.5418	0.754	0.346

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Conclusions

PEG-PLA polymersomes are able to **encapsulate and deliver a peptide of the acidic domain of the G3BP1 protein**.

IVIS and pharmacokinetic analysis shows **ApoE-tagged polymersomes have high retention** in the body for the 48-hour study.

RVG-tagged polymersomes showed improved nerve penetration, with significantly increased fluorescent signal 1-hour post-injection over ApoE and untagged polymersomes.

ApoE-tagged polymersomes some improved nerve retention, with significantly increase fluorescence signal remaining in post-mortem nerves.

Polymersomes are capable of significantly improving penetration and retention of a potential therapeutic for peripheral nerve injuries.

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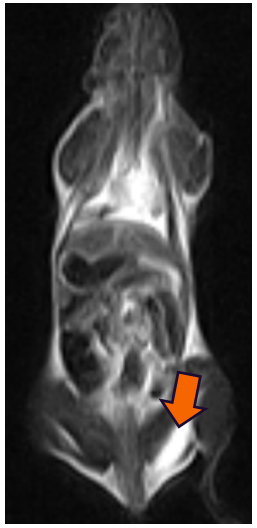
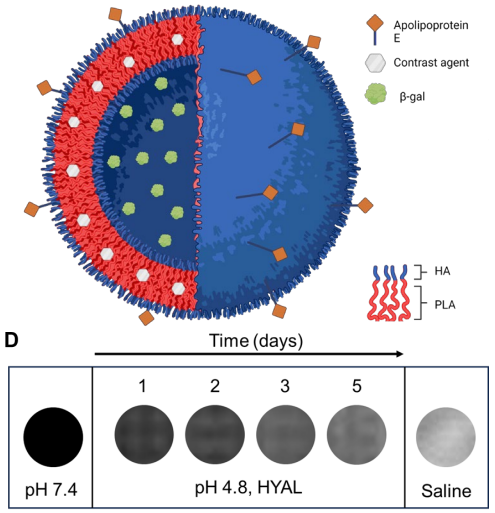
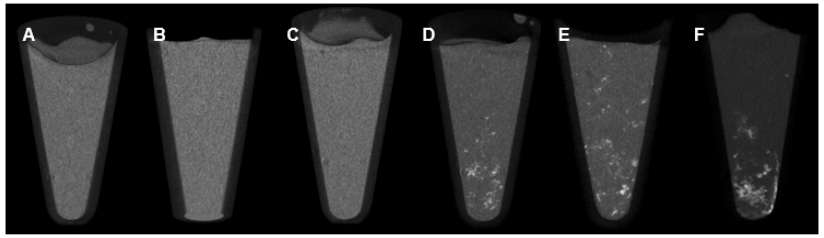




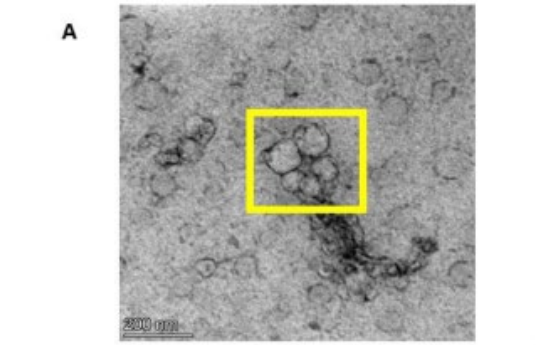
Enzyme Responsive Polymersomes as Theranostics

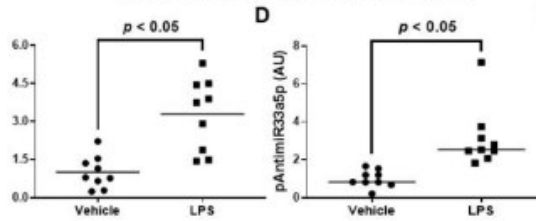
10.2217/nnm-2023-0300
10.1021/acsbiomaterials.2c01386
10.3389/fceng.2022.997607



Polymersome-Enhanced CT Imaging of Glioblastomas in Mice

Angela Alexander-Bryant, PhD, ClemsonU

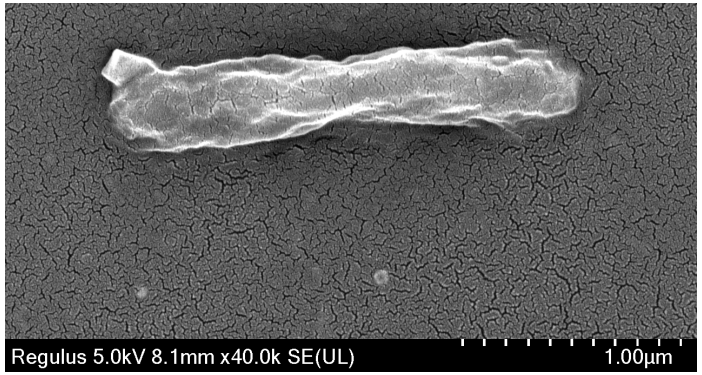




Delivery of Plasmids

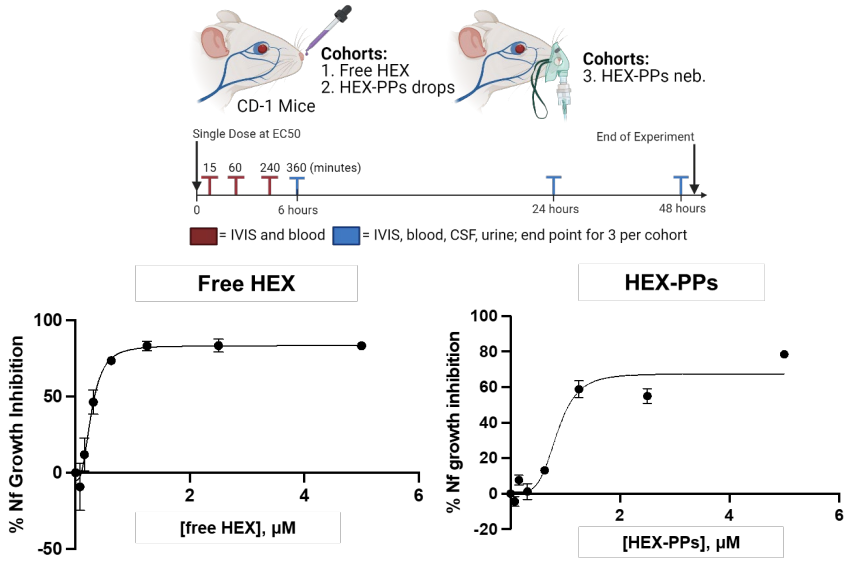
Alexis Stamatikos, PhD, ClemsonU

10.3390/diseases11030088



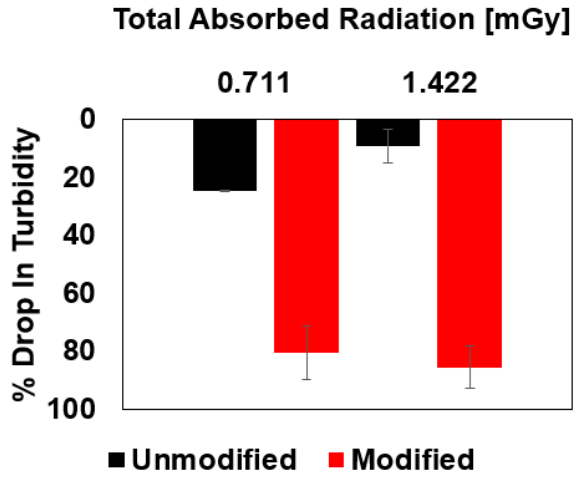
Elongation of Polymersomes for Improved Co-Drug Delivery

10.26434/chemrxiv-2022-2c8c2
10.3791/62548
10.1021/acsabm.1c00203
10.1088/1361-6528/ab6bf1



Intranasal Polymersomes to Treat Brain Eating Amoeba

Jim Morris, PhD, ClemsonU



Radiation-Responsive mRNA Delivery

10.1021/acs.molpharmaceut.3c00439
10.1016/j.freeradbiomed.2024.04.219

Acknowledgements

Graduate Students (8 Ph.D.)

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Nicholas Johnson
Sierra Niskanen
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Pranavi Thatavarthi
Alyson Schwartz
Sophia Fetten
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Kati Lorenz

Alumni

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