Dexamethasone Nanotherapeutics for Traumatic Brain Injury

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Disclosure and Disclaimer

- Dr. Ken Webb and Dr. Jeoung Soo Lee: Equity ownership in NeuroHope Therapeutics, a private company engaged in the development of nanoparticle-based drug delivery systems.

- Any opinions, findings, and conclusions or recommendations expressed in this material are those of the author and do not necessarily reflect the views of the Department of War, DHA, SBIR/STTR Programs, WRAIR, or DHACA.

Traumatic Brain Injury

- A large unmet medical need
  - 400,000 confirmed cases during OEF, OIF, OND[1]
- Increased incidence in military service members
- Severe / penetrating TBI
  - Acute emergency care
- Mild / moderate TBI (90% of cases)
  - Long-term consequences[2-4]
    - Increased mortality, incidence of neurodegenerative disease, adverse impact on mental health
- No effective therapy

[1]Phys Med Rehab Clin NA 2024; 35: 559
[2]Trans Neurodegener 2017; 6:20
[3]Public Health Rep 2017; 132:251
[4]Mil Med 2023; 188:199

Therapeutic Development

✓ **Mechanism and Target Identification**

Altered signaling pathways, neuro-inflammation

✓ **Therapeutic Availability**

Phosphodiesterase (PDE) inhibitors

Corticosteroids

✗ **Toxicity and side effects**

- Rolipram-severe GI side effects (nausea / vomiting)[1]

- Methylprednisolone

NASCIS-increased risk of sepsis / pneumonia [2]

CRASH-increased mortality [3]

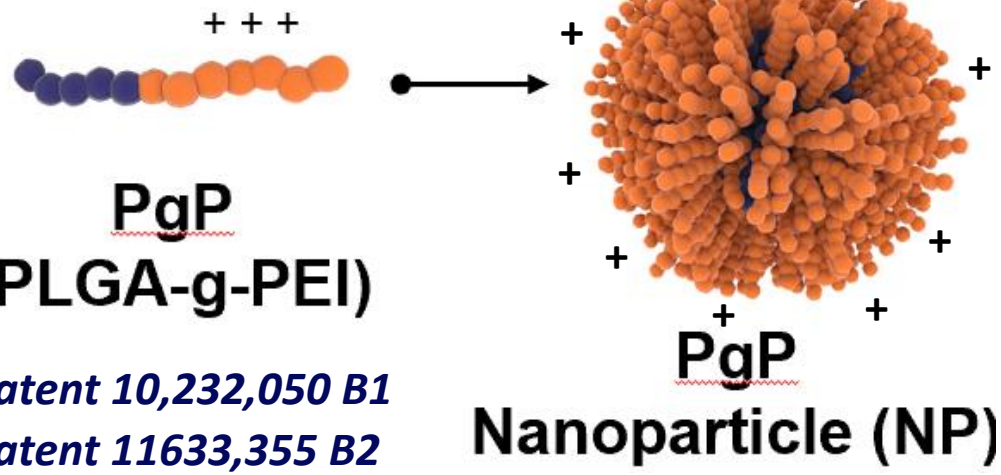
Root Cause? Prolonged, high-dose, systemic administration

1. Curr Opin Chem Biol 1999; 3: 466

2. JAMA 1997; 277: 1597

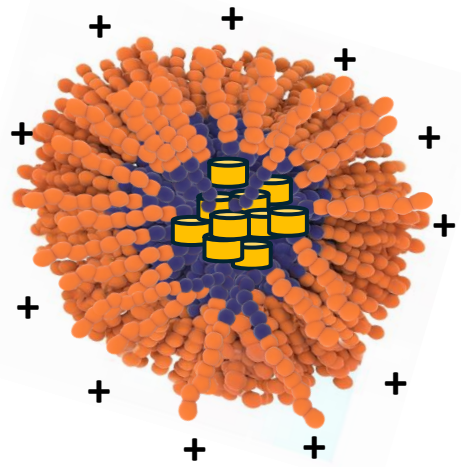
3. Lancet 2004; 364: 1321

Solution: Local, sustained delivery to CNS

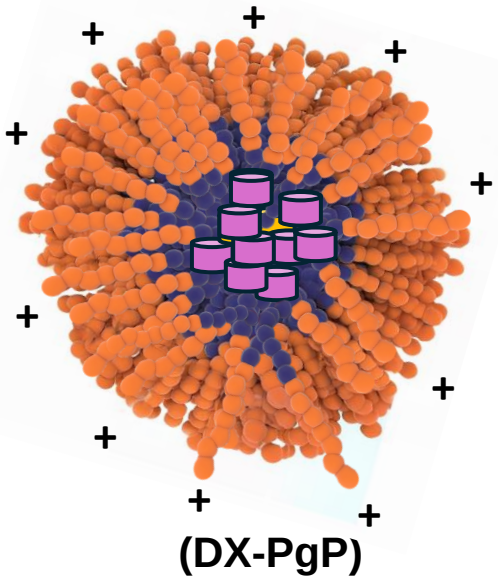


US patent 10,232,050 B1
US Patent 11633,355 B2

Rolipram
(Rm)

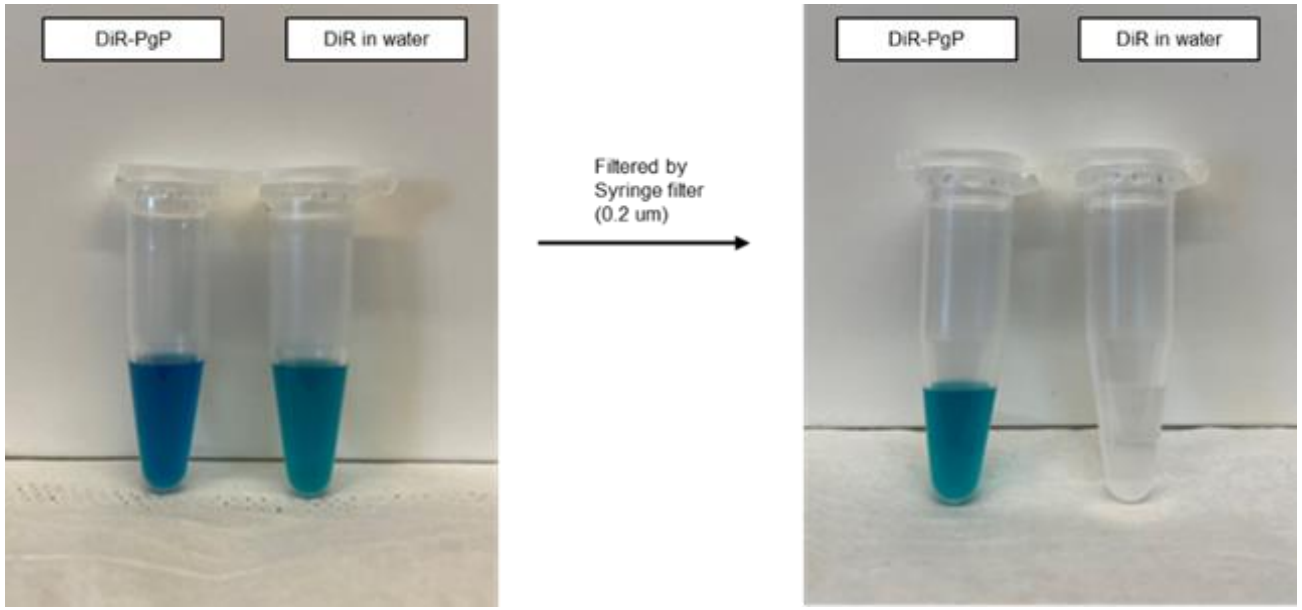


Dexamethasone
(DX)



Benefits of Polymeric Micelle NPs: Drug Solubility

Polymeric micelle hydrophobic core increases aqueous solubility of nonpolar drugs

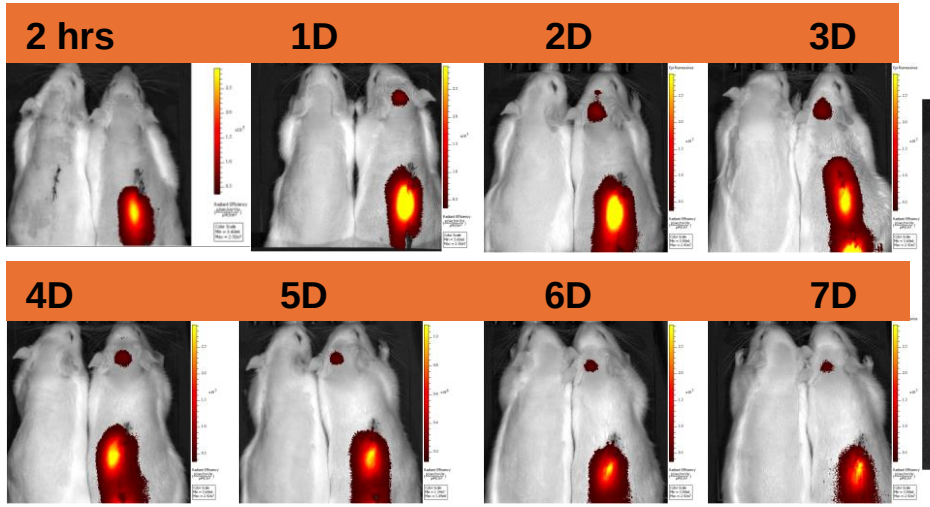


- Eliminates need for organic solvents / emulsifiers that often increase toxicity

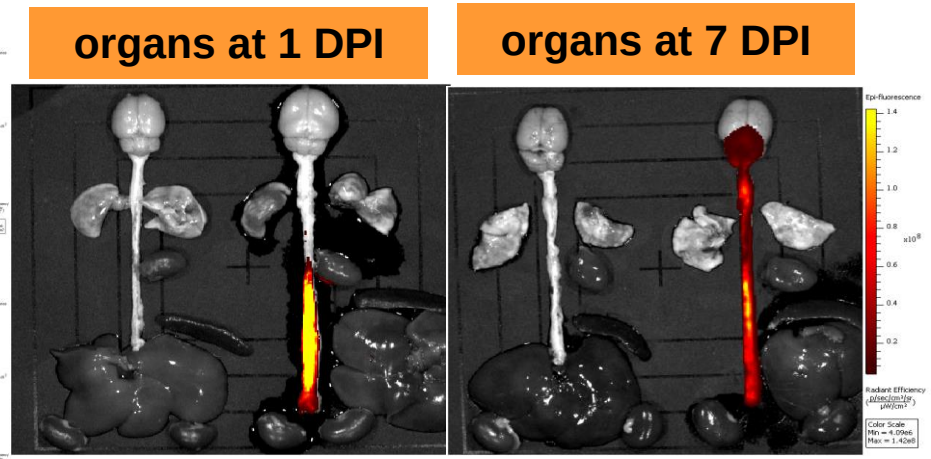
Benefits of Polymeric Micelle NPs: Prolonged CNS Residence Time

Polymeric micelle cationic shell binds anionic cell membrane macromolecules

Live animal imaging



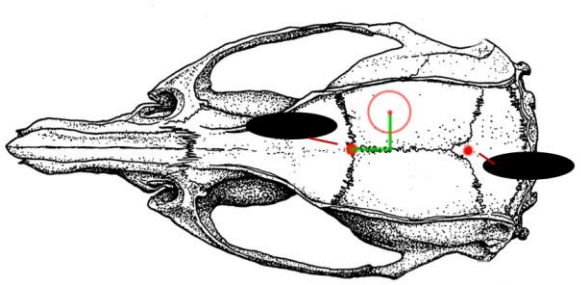
Ex vivo organ imaging



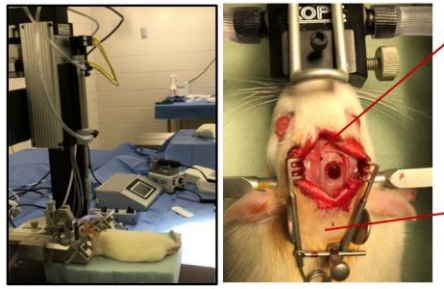
- Single administration achieves prolonged residence time (>7 days) in CNS
- No distribution to peripheral tissues / organs

J Neurosci Res 2025; 103: e70091

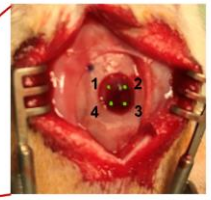
Preliminary Study 1:
Rm-PgP Improves Motor Outcome in CCI TBI Model



- Craniotomy (4 mm diameter)
- Impact tip diameter 3 mm
- Location centered at 1.0 mm posterior and 3.5 mm lateral (right) from bregma



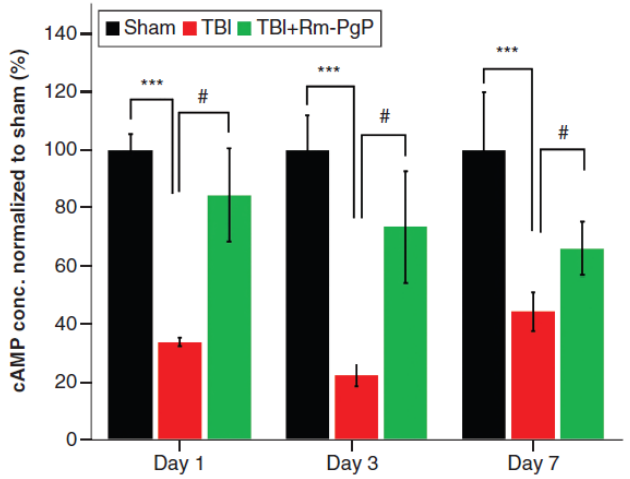
Impact Speed: 3.5 m/s
Impact Depth: 2 mm
Dwell Time: 250 msec



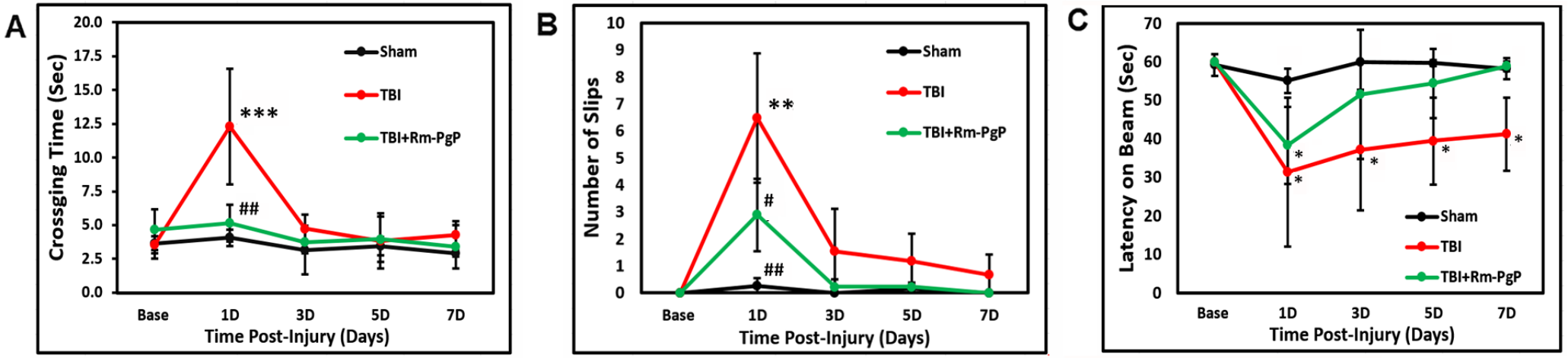
5µL Intraparenchymal injections (4x)

Injection Positions

	A/P	M/L
(1)	-3	3
(2)	-3	4
(3)	-4	4
(4)	-3	3

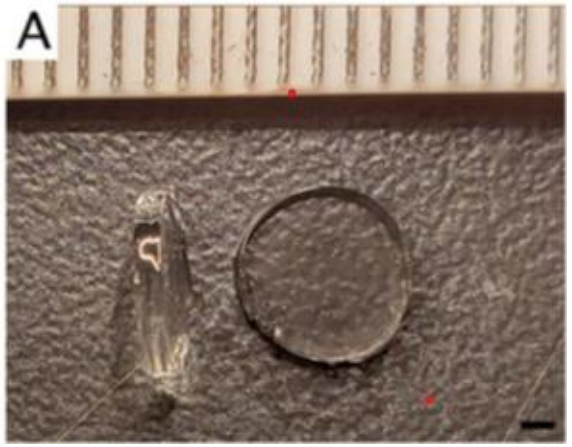


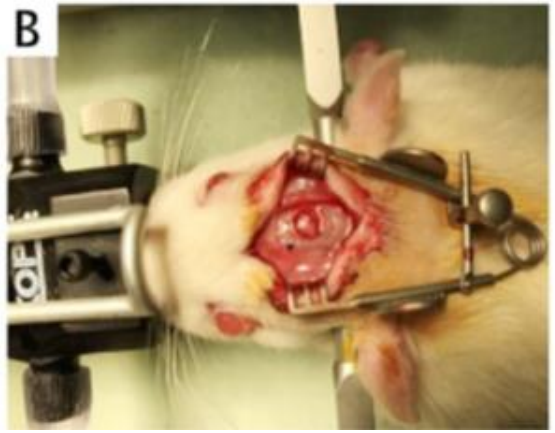
Beam walk (Crossing) **Beam walk (foot slip)** **Beam balance**

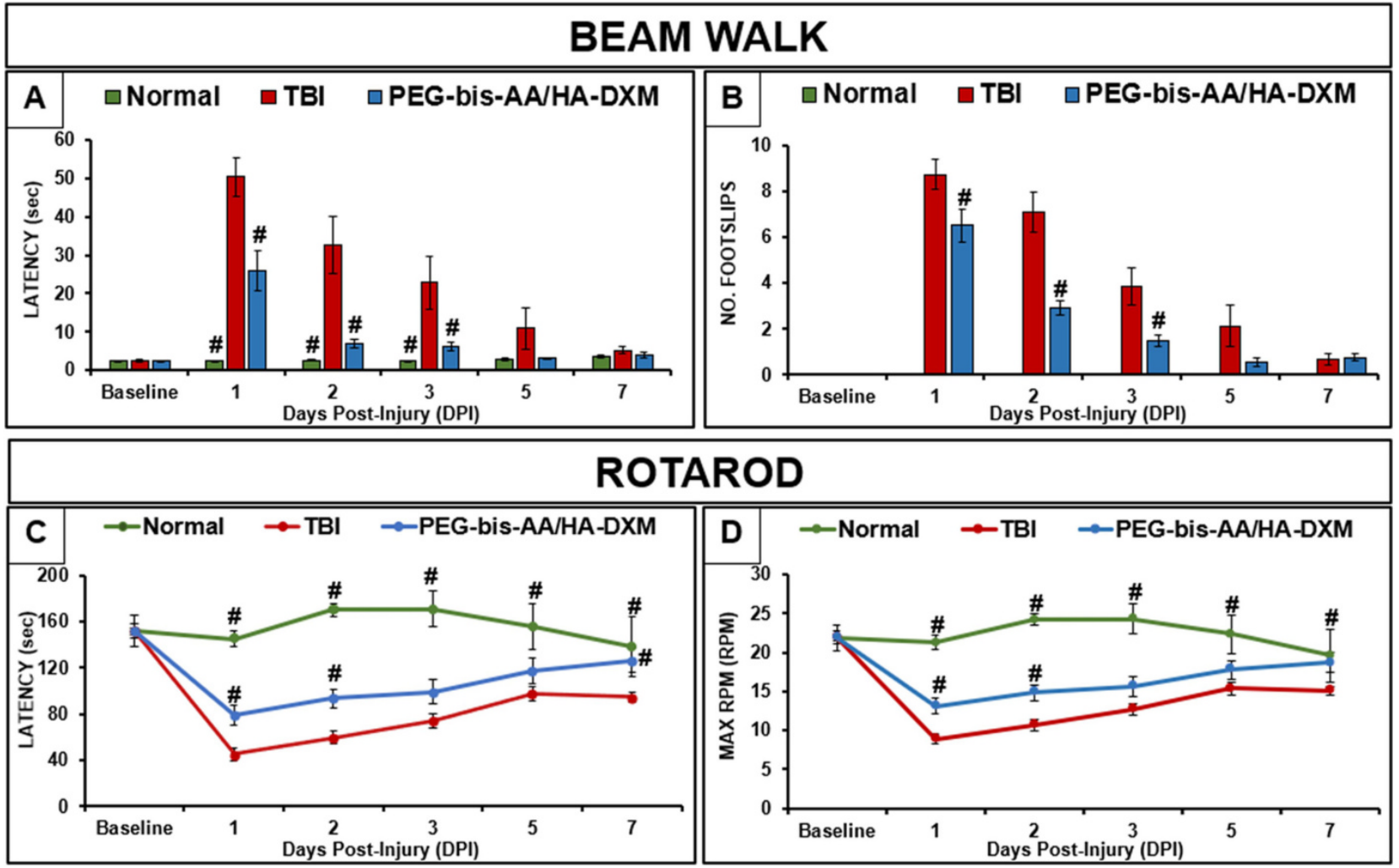


Nanomedicine 2022; 17:431

Preliminary Study 2: (Collaboration with WRAIR) Hydrogel-based Local DX Delivery Improves TBI Recovery

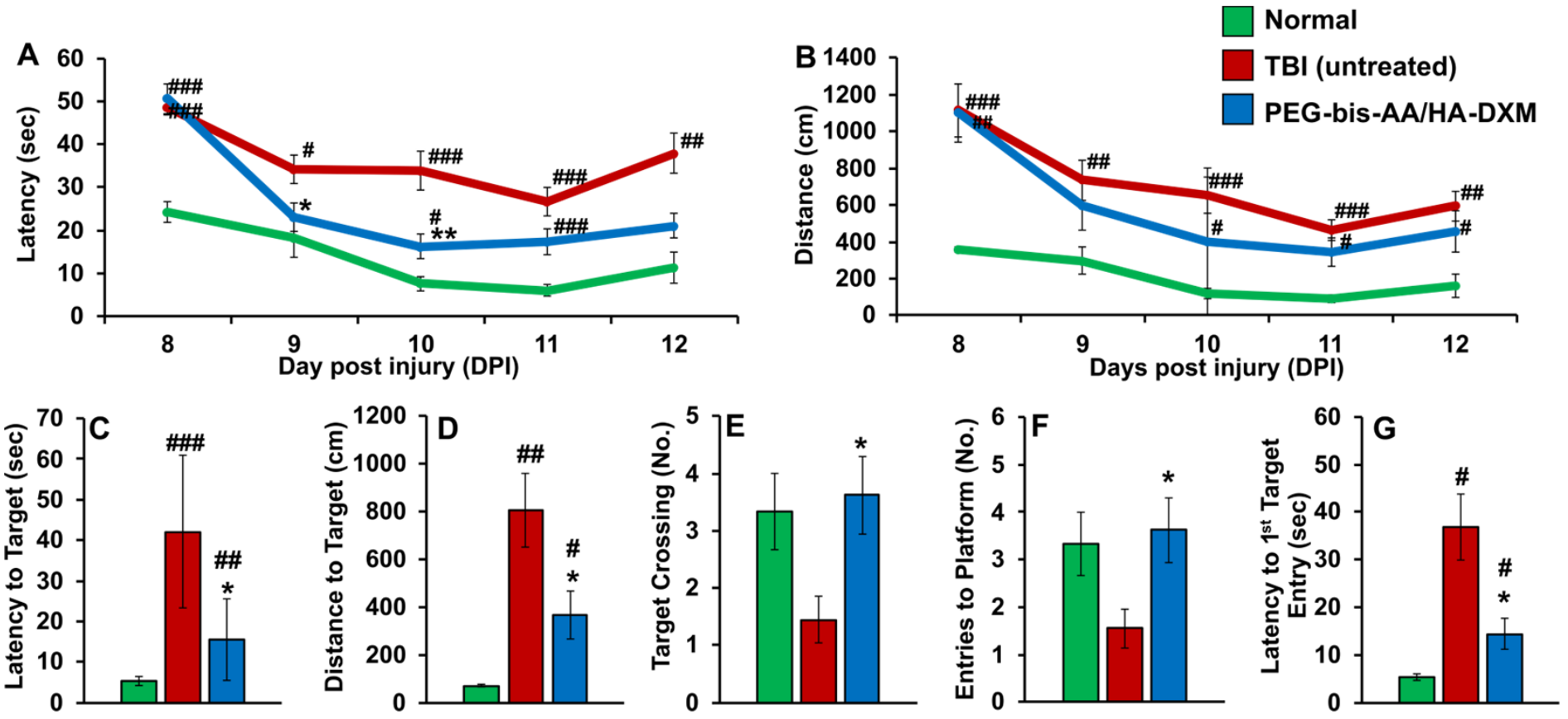






Exp Neurol 2023; 369:114533

Local DX Delivery Improves Cognitive Recovery after TBI



Gels 2025; 11:600

Dexamethasone-based Nanotherapeutics for TBI (DoW SBIR Phase I grant)

Goal: To address the military need for acute TBI treatment

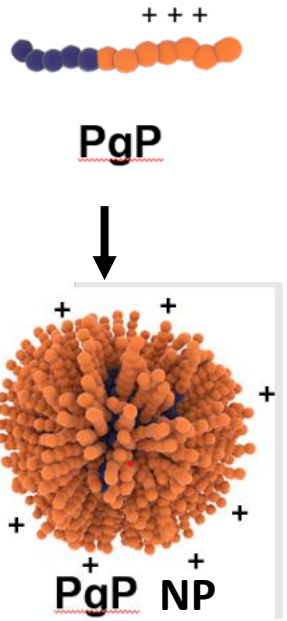
- Can be administered in austere, far-forward positions by personnel without specialized medical training or access to advanced healthcare facilities.
- Provide acute stabilization during prolonged evacuation.
- Shorten time for recovery and return to service.
- Ensure long-term well-being.

Approach: DX-PgP nanotherapeutics for intranasal administration

Objective: *In vitro* assessment of physico-chemical properties and activity

- DX loading, particle size, and stability
- Cellular uptake and cytotoxicity of DX-PgP
- Anti-inflammatory bioactivity of DX-PgP

Characterization of DX-PgP: Loading Efficiency, Particle Size, and Stability



DX Loading Efficiency

unt of DX added (µg)	Amount of DX loaded (µg)	Amount of PgP (mg)	Loading efficiency (%)	sample size
100	98.34 ±1.1	1	98.34 ±1.1	6
250	101.93 ±13.02	1	40. 77 ± 5 .21	4
500	87.93 ± 5.7	1	17.59 ± 1.14	4

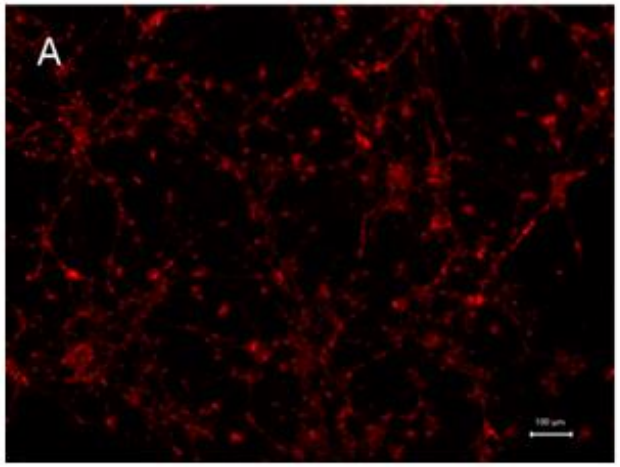
DX-PgP Particle Size and Charge

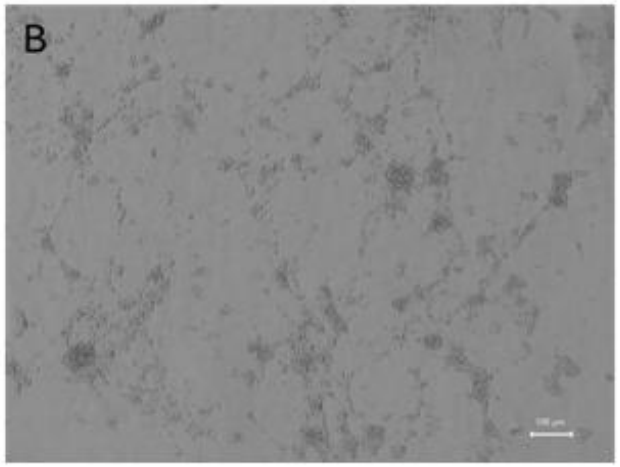
	Particle size (nm)	PDI	ξ-potential (mV)
PgP	148.3	0.46	+46.9
DX-PgP	130.3	0.5	+51.6

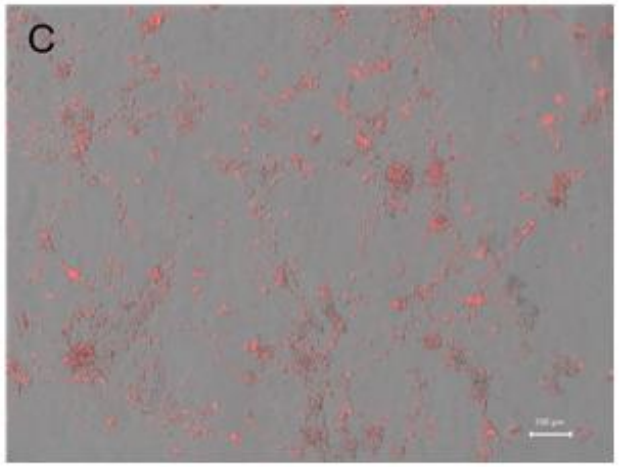
DX-PgP Stability during Storage

	0 M	1 M	2M	3M	4M
Condition	% Initial DX loading	% DX remaining	% DX remaining	% DX remaining	% DX remaining
RT	95 +/- 3.35	99.45± 1.98	96.62± 1.95	95.3± 3.35	86.15±2.5
4C	95 +/- 3.35	92.99± 1.66	94.49± 2.84	92.50± 2.89	69.11±10.15
-20	95 +/- 3.35	65.39± 2.95	71.03± 2.26	66.23± .82	41.57±4.37

Cellular Uptake of DX and DX-PgP

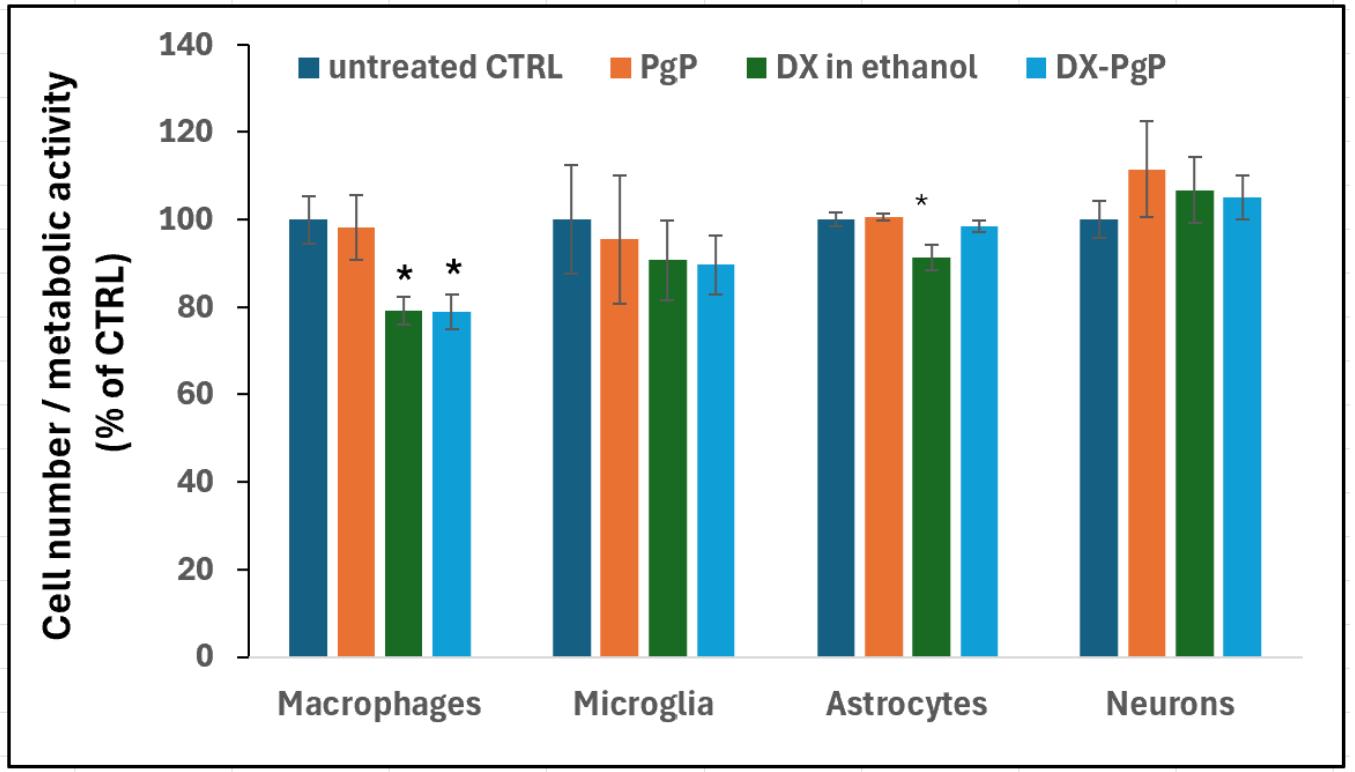


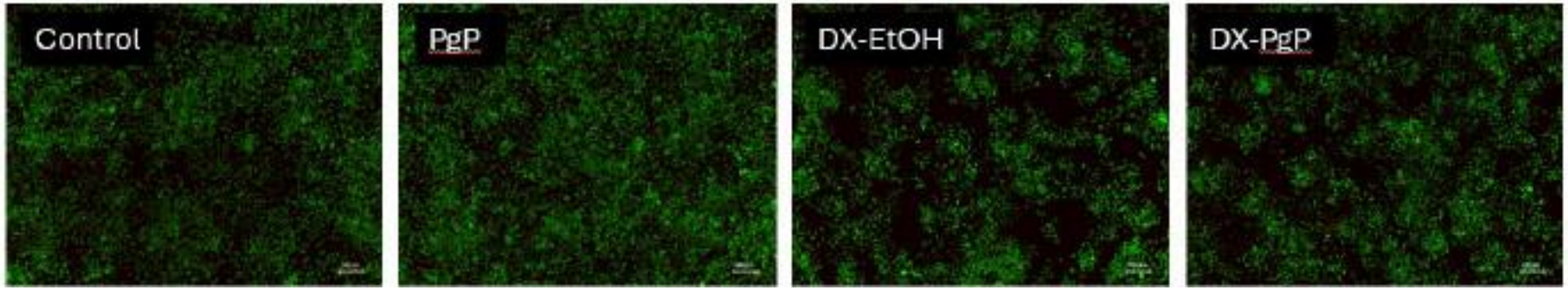




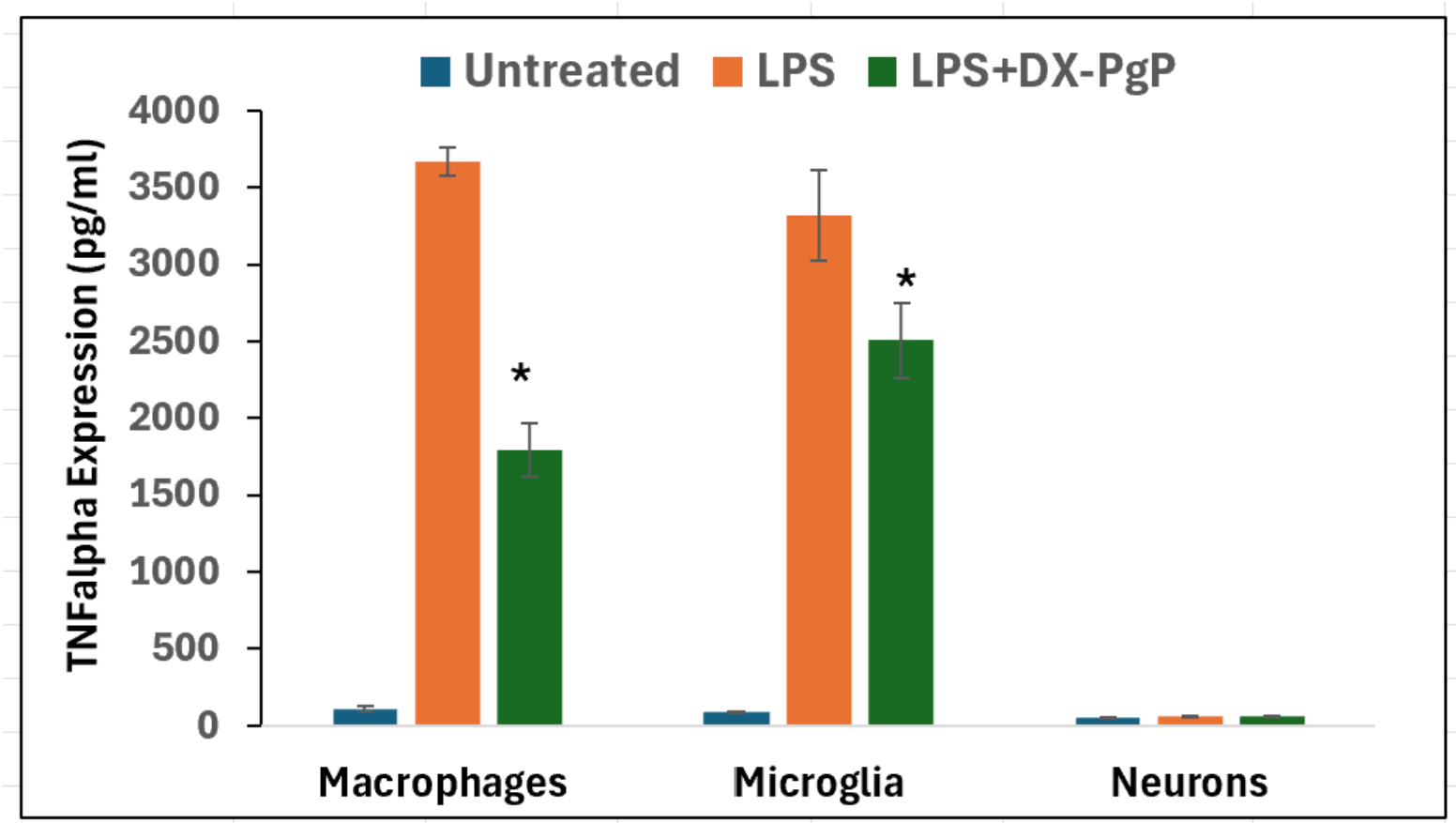
Cell Types	Samples	% uptake by cells
CGN (Cerebellar granular neuron)	DX-EtOH	45.14±5.07
	DX-PgP	41.26 ± 2.39
RAW 264.7 (Macrophage)	DX-EtOH	51.38 ± 3.84
	DX-PgP	42.67 ±5.06
BV2 (Microglia)	DX-EtOH	52.85 ± 5.48
	DX-PgP	28.04 ± 5.99
Astrocyte	DX-EtOH	59.30 ± 2.58
	DX-PgP	42.67 ± 5.06

Cytotoxic Assessment of DX-PgP

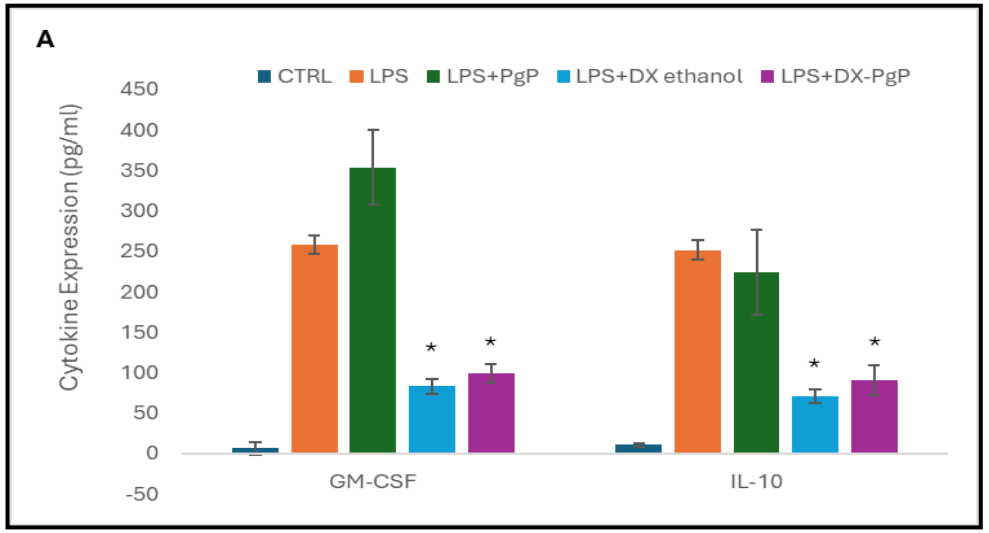


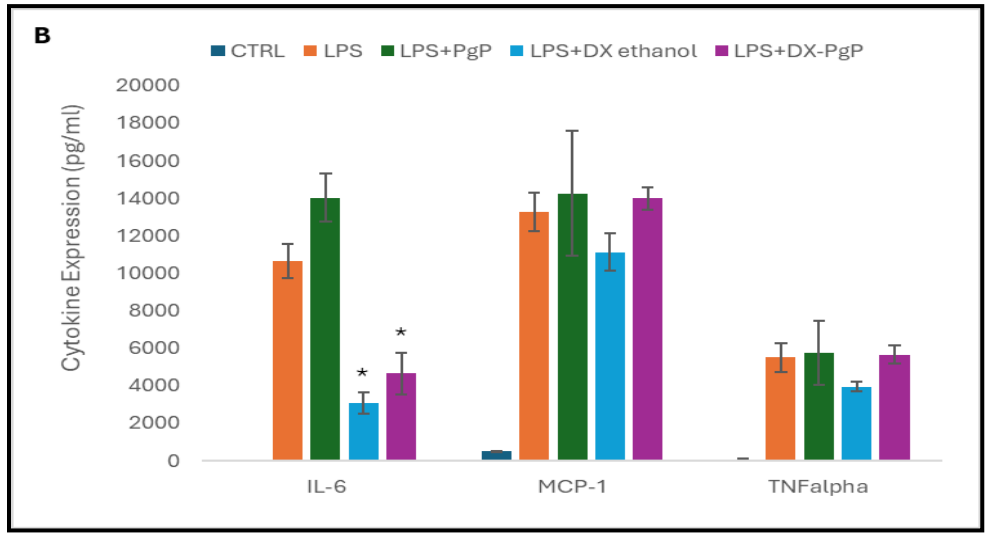


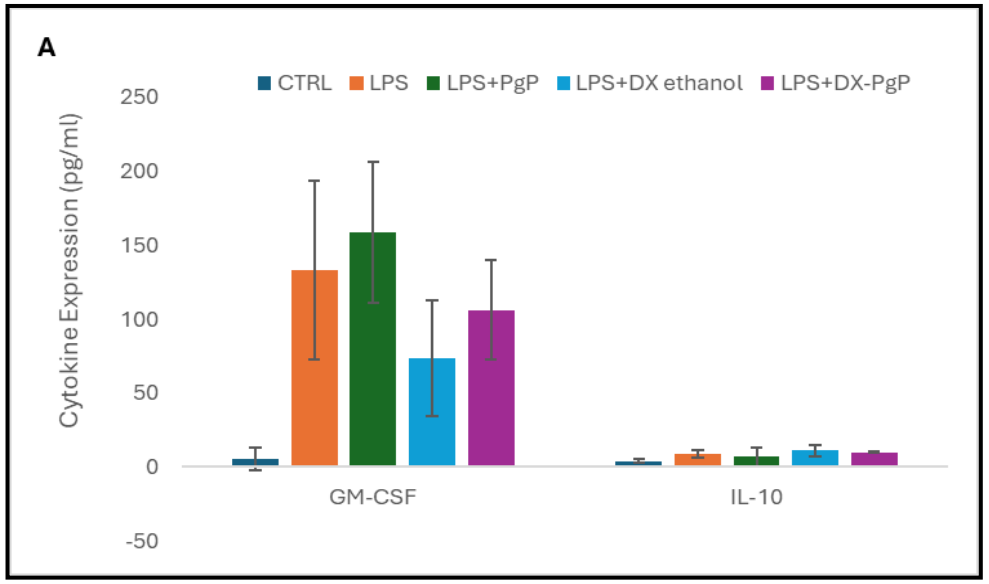
DX-PgP Mitigates LPS-induced TNFα Expression

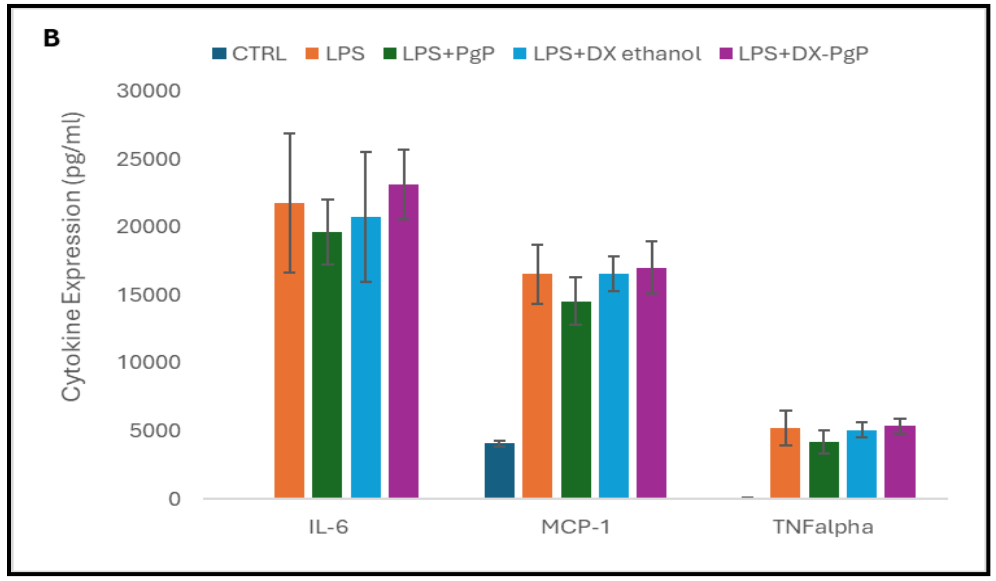


DX-PgP Modulates Cytokine Expression









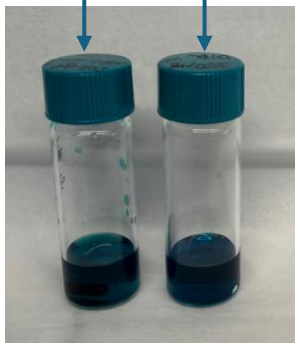
Dexamethasone-based Nanotherapeutics for TBI (DoW SBIR Phase II grant)

Objective: Pre-clinical assessment of DX-PgP in controlled cortical impact (CCI) and blast TBI models.

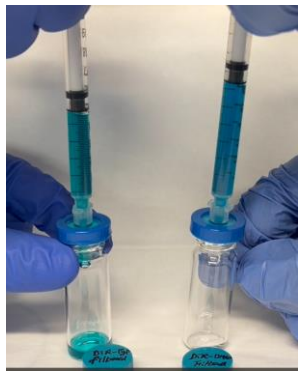
- Therapeutic Efficacy
  - Intracisternal administration
  - Intranasal administration
- Biodistribution
- Pharmacokinetics
- Toxicity

Biodistribution of DiR-PgP by Intracisternal administration in a rat blast TBI model in collaboration with Dr. Pam VandeVord (VT)

DiR-PgP DiR-5% DMSO in Saline

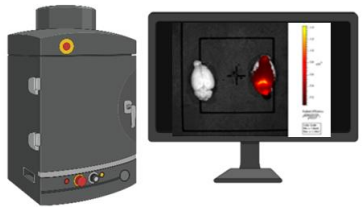


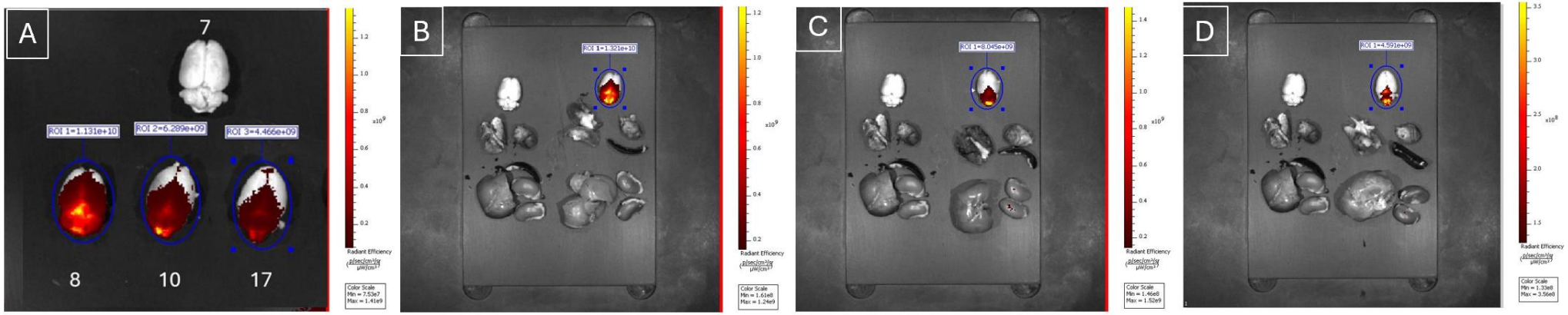
0.2 µm syringe filter



Blast TBI model generation

Ex Vivo organ imaging

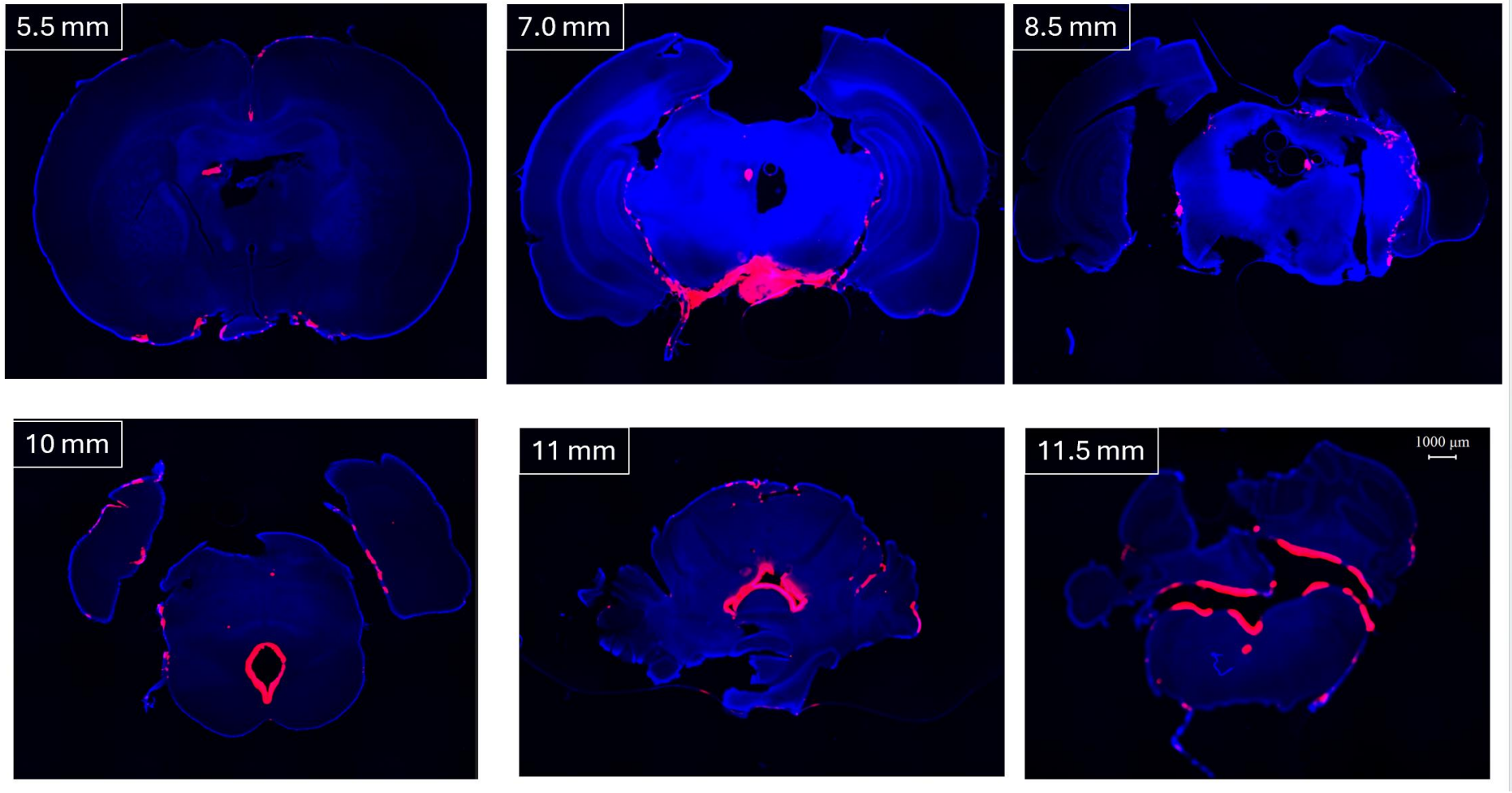




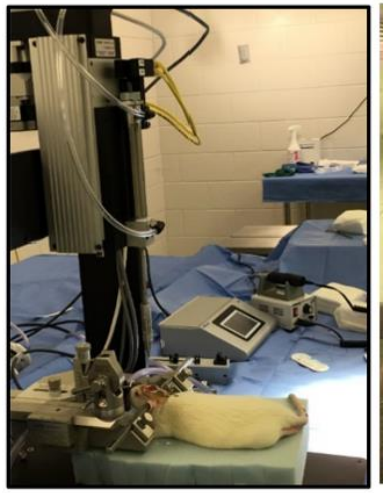
A) Brain (7: saline, 8, 10, 17: DiR-PgP, B) –D) All organs (left: saline, right: DiR-PgP)

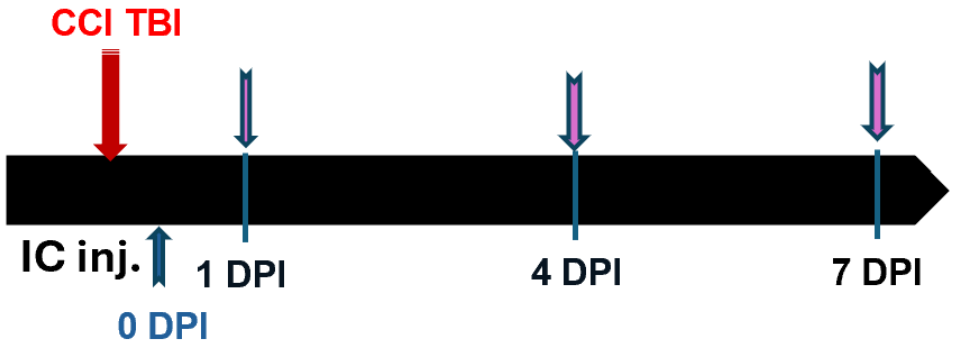
Localization of DiR-PgP in a rat brain (bTBI model)

Vibratome

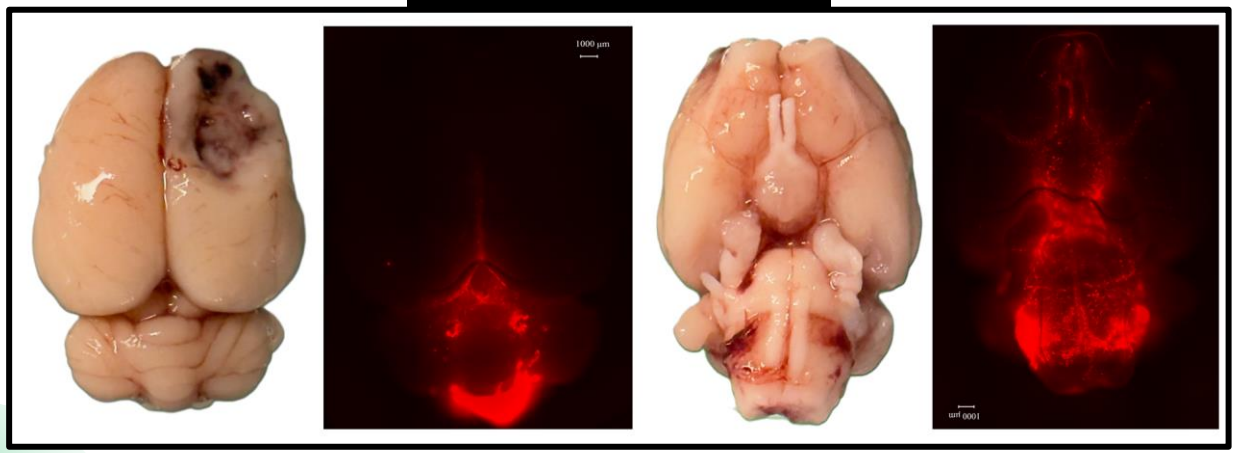


Biodistribution of DiR-PgP by Intracisternal administration in a rat CCI TBI model (Dr. Jeoung Soo Lee, Clemson)

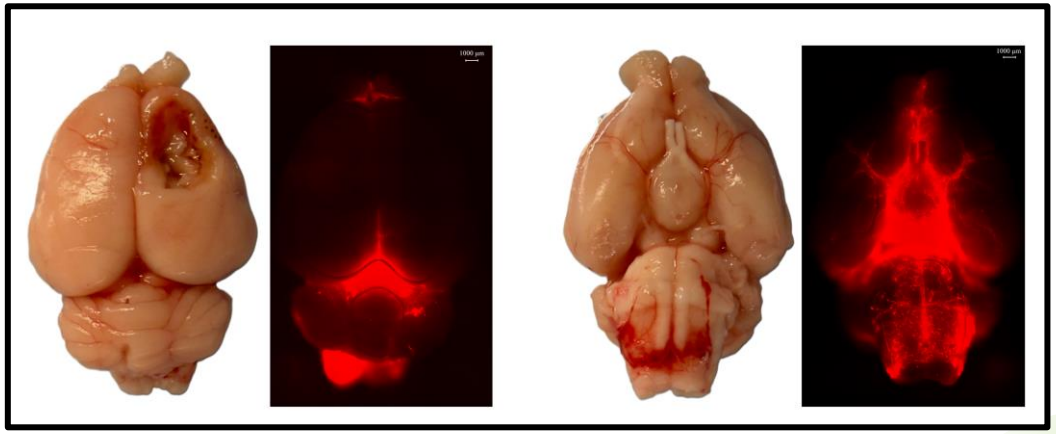




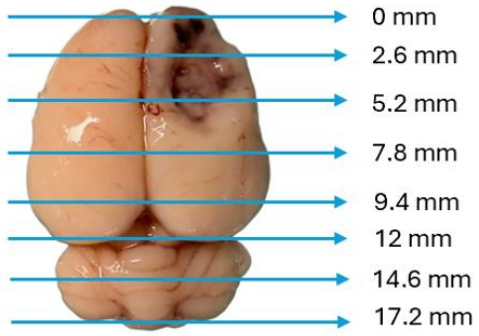
1day post- IC Inj.

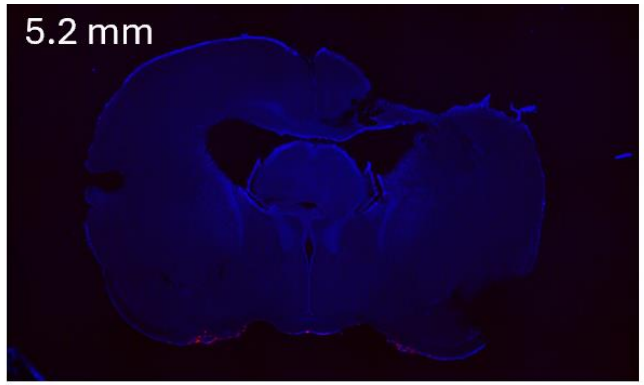


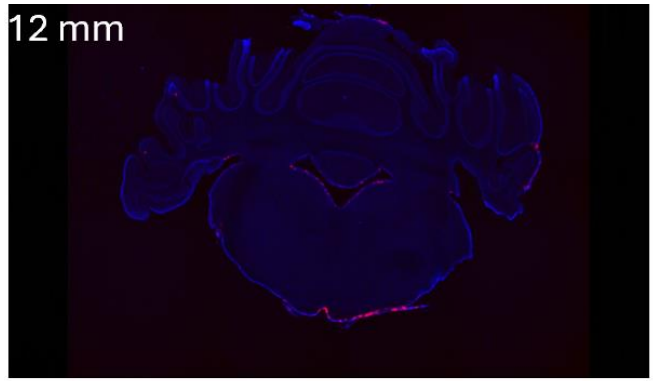
7Days post-IC inj

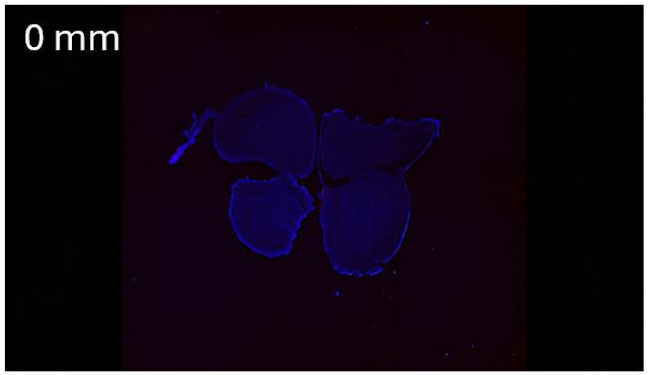


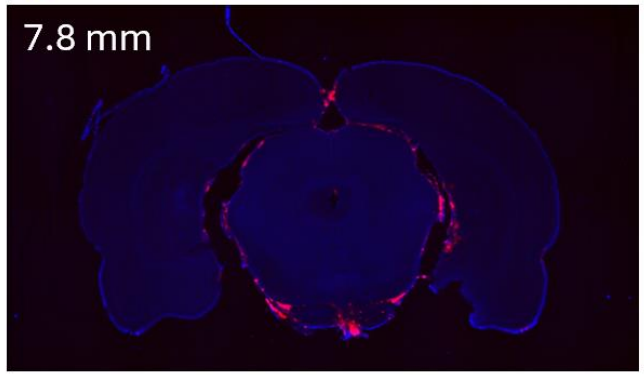
Localization of DiR-PgP in a rat brain (CCI TBI model)

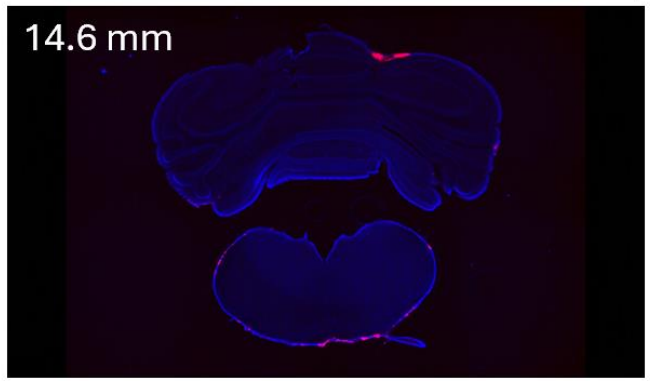


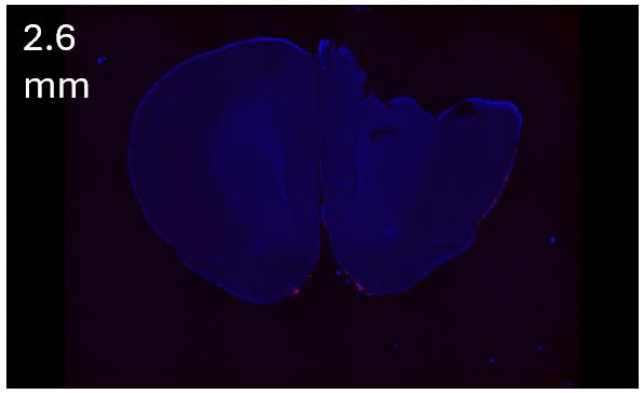


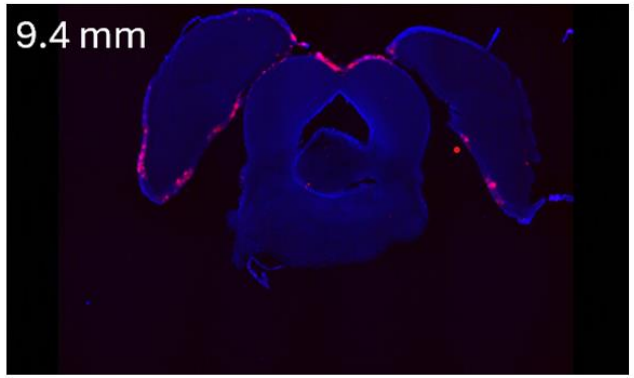


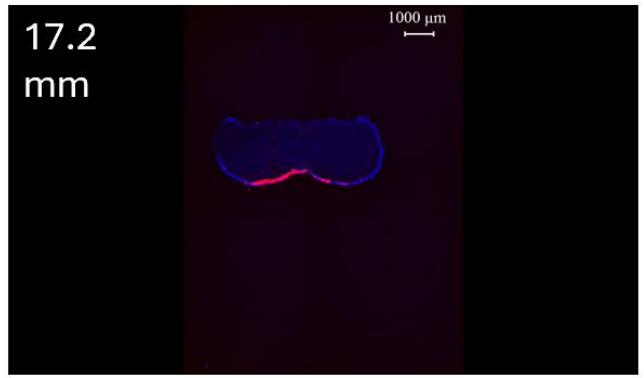












Summary / Conclusions

- Physico-chemical properties of PgP polymeric micelle nanocarrier enables drug solubilization and prolonged residence time.
- Local administration of rolipram and dexamethasone improve anatomical and functional measures of neurologic recovery.
- DX-PgP forms nanoparticles <200 nm, positive charge, stable up to 3 months storage.
- DX-PgP exhibits efficient uptake and is non-toxic in a wide range of CNS cell types.
- Intracisternal injection can effectively delivery DX-PgP to the brain in CCI and blast TBI models.

Acknowledgements

Team:

- Dr. Jeoung Soo Lee (co-Founder and CTO)
- Dr. Daniela Gonzalez
- Mr. Bradley Elliott
- Ms. Alex Vandenburg
- Mr. Greg Shin
- Mr. Miles Ware

Collaborators:

- Dr. Pamela VandeVord (Virginia Tech)
- Dr. Teresa Murray
- Walter Reed Army Institute of Research (WRAIR)
  - Dr. Zachary Bailey
  - Dr. Star Okada-Rising
  - Dr. Anke Scultetus
  - Dr. Deborah Shear

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South Carolina Research Authority

NIH NIGMS

CCCRP Combat Casualty Care Research Program

SCRA South Carolina Research Authority

DHA Defense Health Agency ®

THANK YOU

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