


INTRACEREBRAL DELIVERY OF CYTOKINE IMMUNOTHERAPY WITH HYDROGEL ACCELERATES RECOVERY POST-ICH IN RATS

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CRS 2025 ANNUAL MEETING & EXPOSITION

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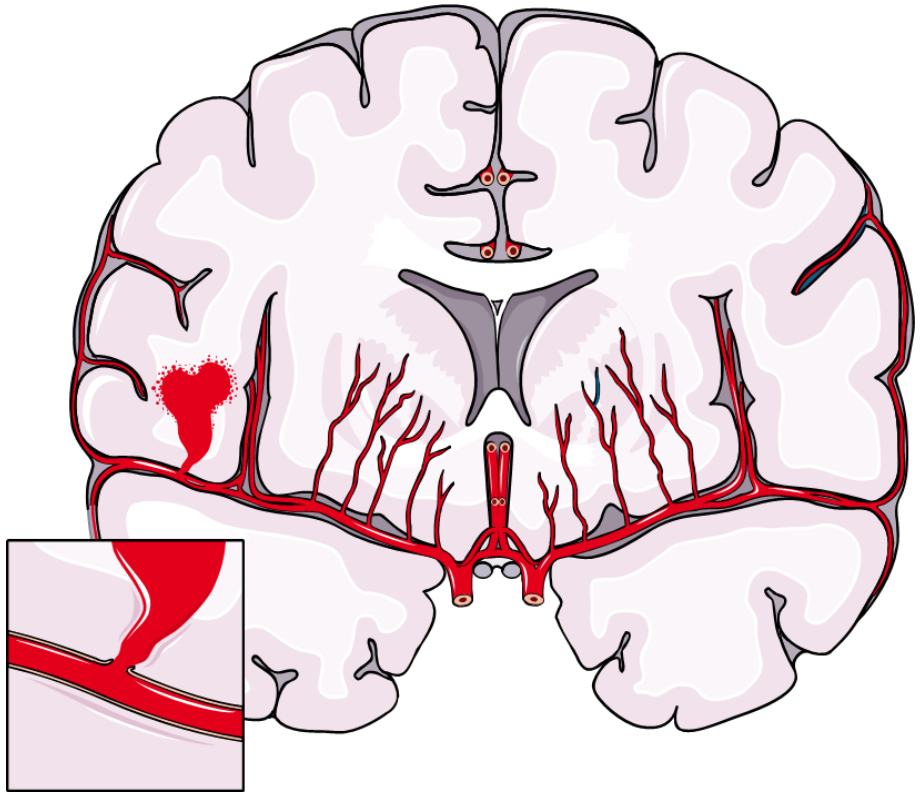
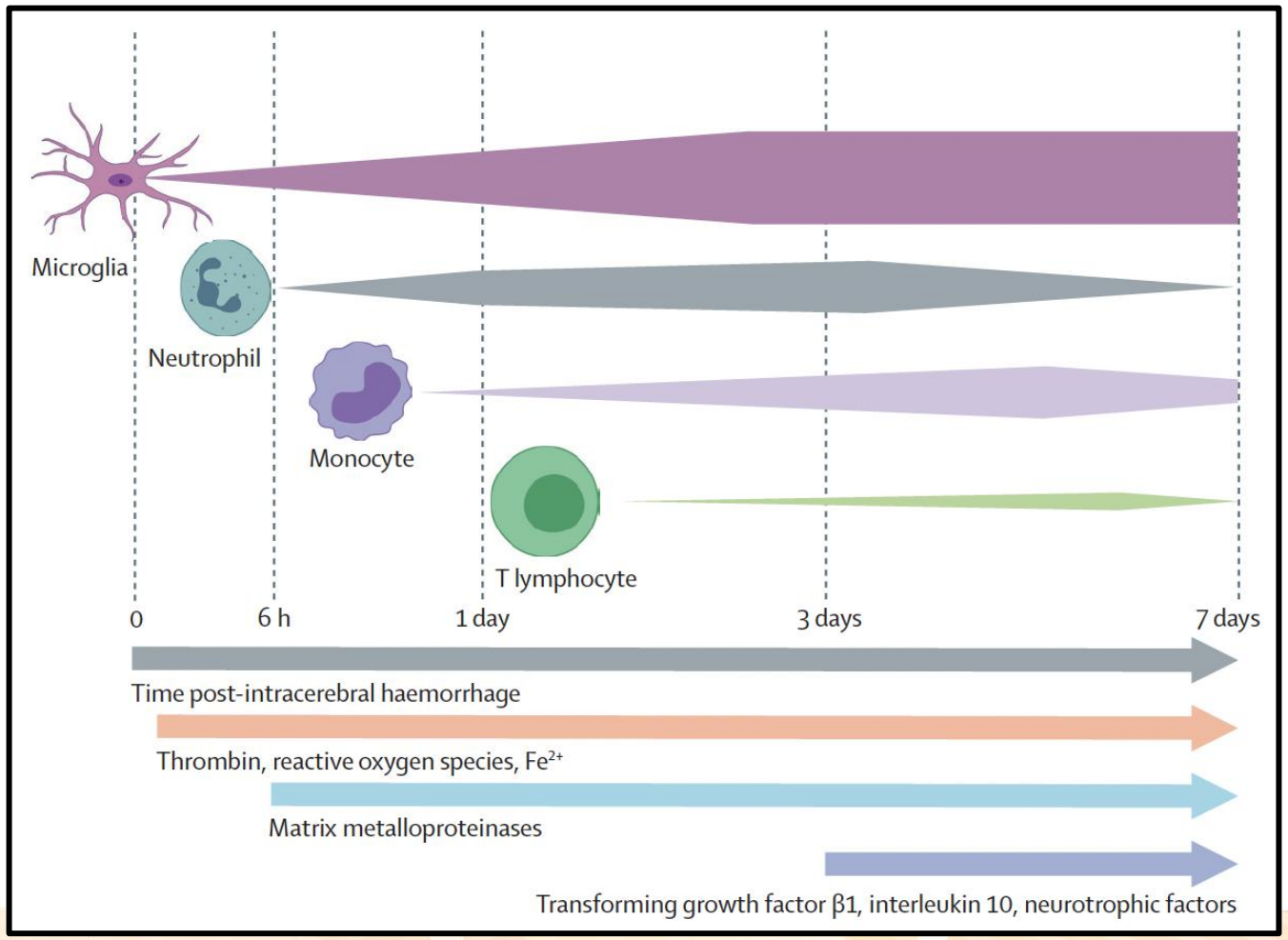
NEXT-GENERATION DELIVERY INNOVATIONS

Significance: Lack of disease-modifying solutions for Intracerebral Hemorrhage (ICH) survivors with progressive neurological deficit



1. 200,000 Americans affected by ICH per year, primarily hypertensive.
2. ~30-80 mL clots in humans. Mechanical disruption to neurons and other cells of the CNS parenchyma causes permanent damage.
3. High mortality (40 - 50%).
4. RBC debris, cellular debris, immune cell infiltration induces acute inflammation. This is ***secondary damage*** post-ICH.
5. No current treatments address inflammatory and cytotoxic reactions post-ICH.

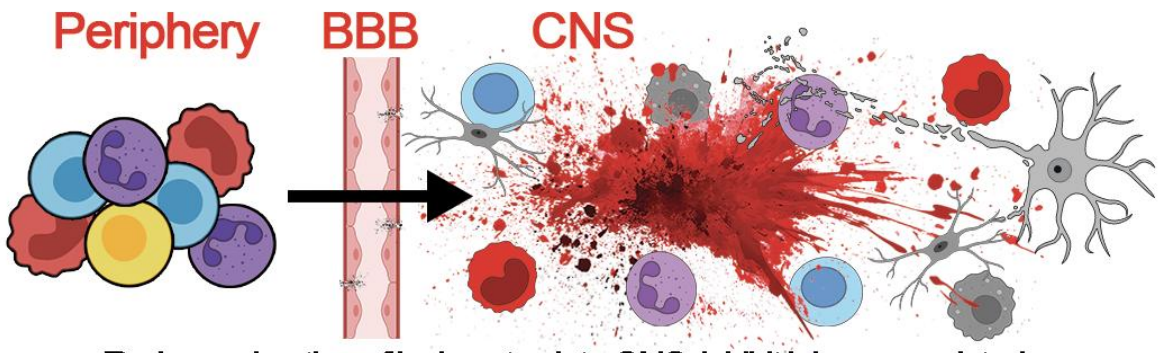
Premise: The inflammatory milieu and associated sequelae of ICH. “What is inflammation” in this context?



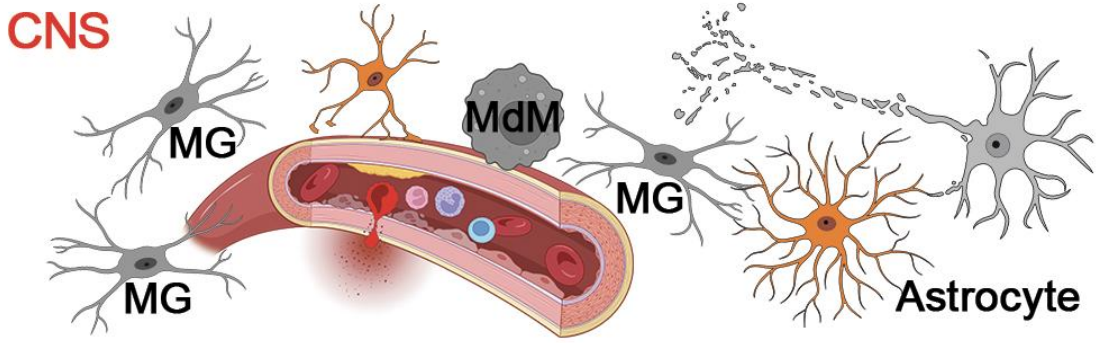
- Vascular changes, permeability
- Edema, intracerebral pressure.
- Recruitment of monocytes, neutrophils, T cells.
- Elevated levels of IL-6, TNFa, IL-1b.
- Oxidative Stress
- Potential for cytotoxicity, via apoptosis, excitotoxicity, and cellular toxicity mechanisms.

Xue et al. Lancet Neurology (2020) 19 (12) 1023 - 1032

Proposed interventions to attenuate ***chronic inflammation*** post-ICH



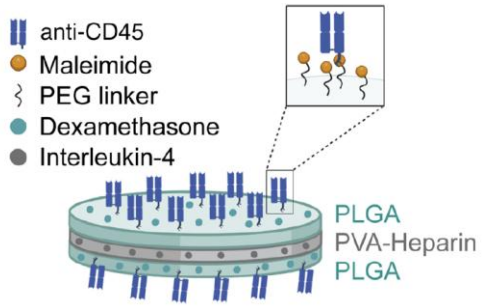
Reduce migration of leukocytes into CNS; inhibit injury-associated microglia with CNS-penetrant drugs

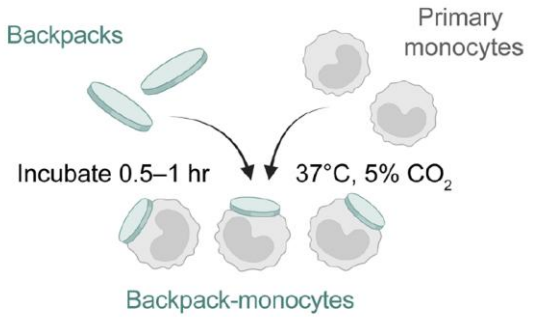


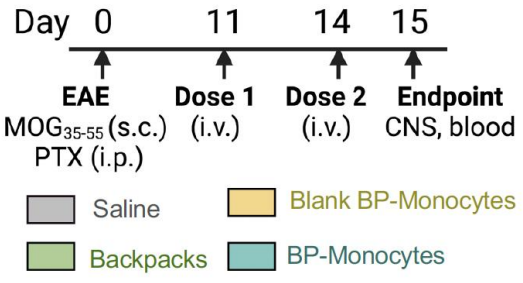
Reduce intravascular inflammation; inhibit injury-associated microglia and astrocytes with CNS-penetrant drugs; counter spread of focal to global neurolinflammation

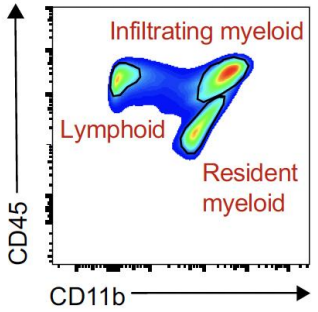
Shi and Yong. Science (2025) *adx0043*

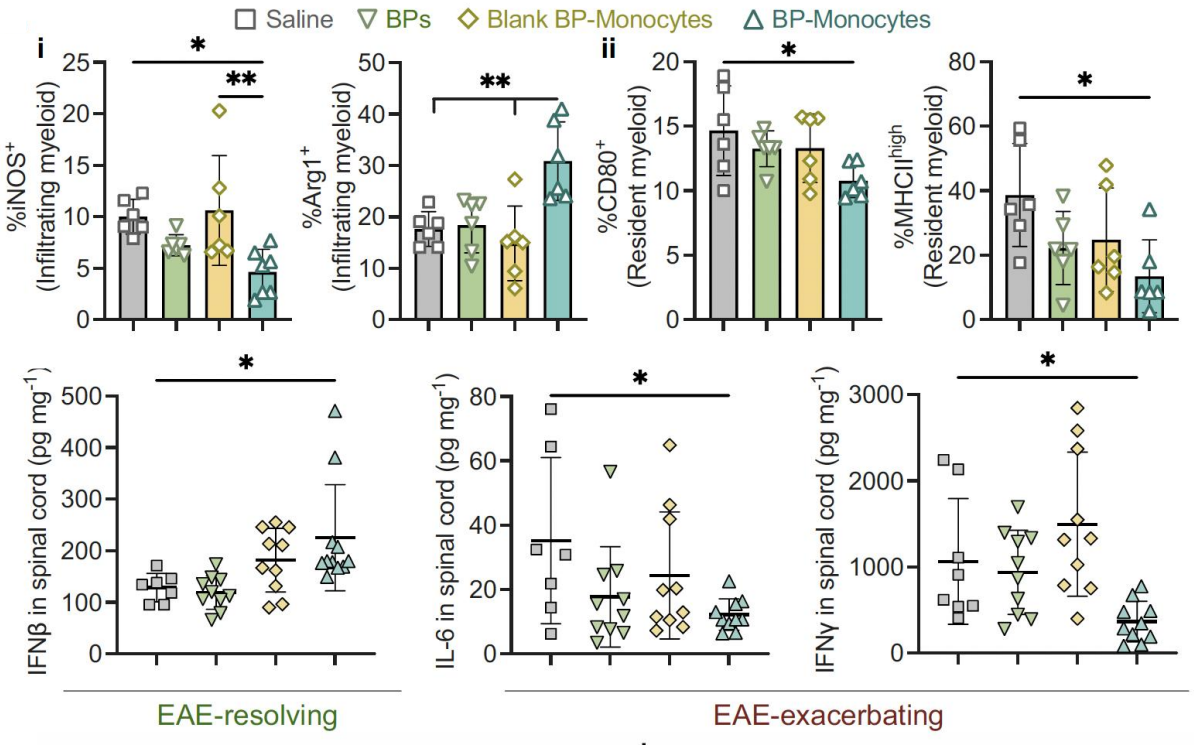
Previous work: Modulation of adoptively transferred monocytes/macrophages in periphery with central invasion to attenuate disease in neuro-inflammatory models: ***Mouse EAE***







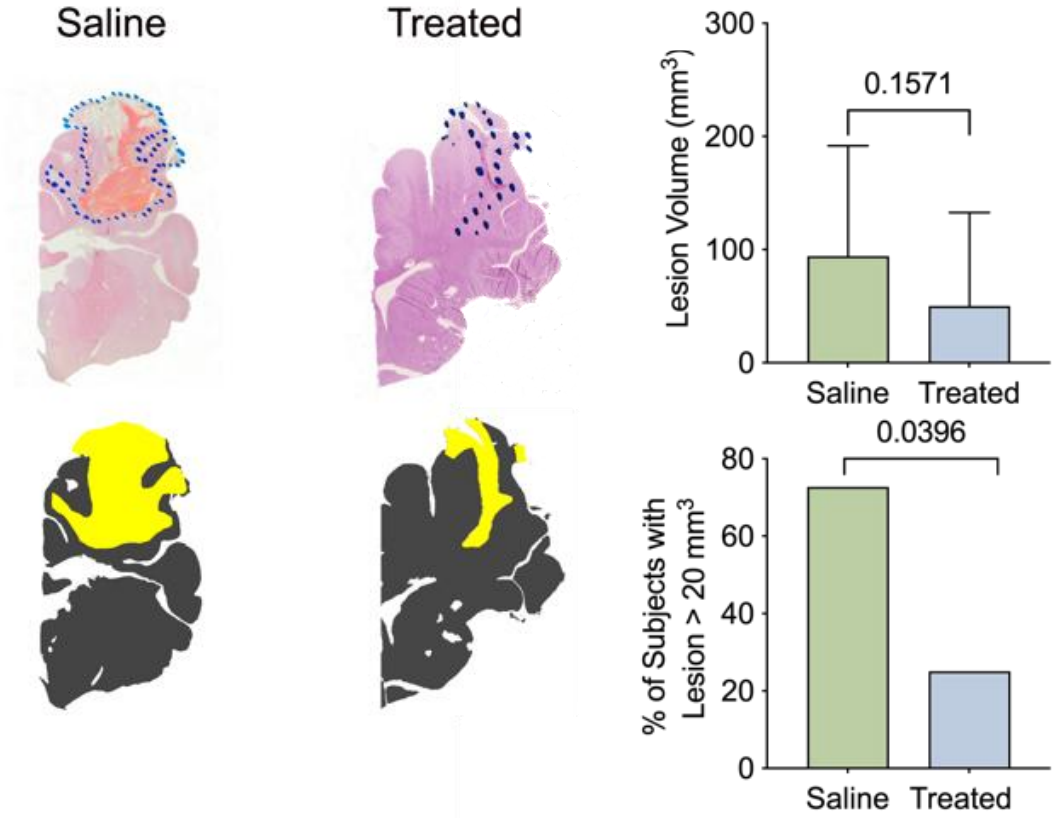


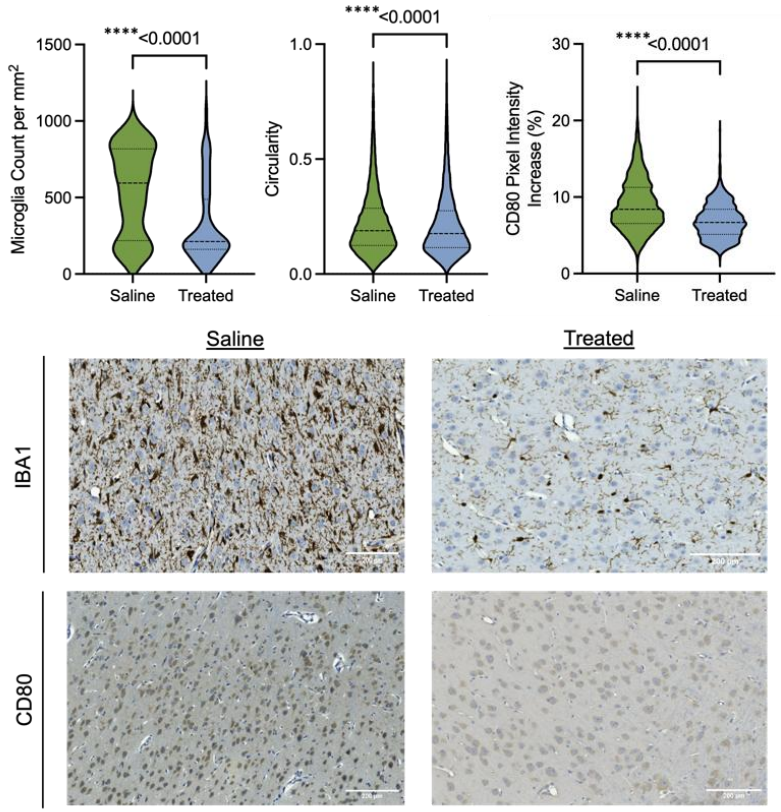


Adoptive transfer of monocytes + M2-instructive backpacks with IL4 + Dexamethasone ***attenuates EAE*** *(phenotype + inflammatory biomarkers) via* ***modulation of endogenous microglia/brain-infiltrating macrophages***

Kapate, Mitragotri, et al. (2023) PNAS *120 (17) e2221535120.*

Previous work: Modulation of adoptively transferred monocytes/macrophages in periphery with central invasion to attenuate disease in neuro-inflammatory models: ***Porcine cortical impact TBI***



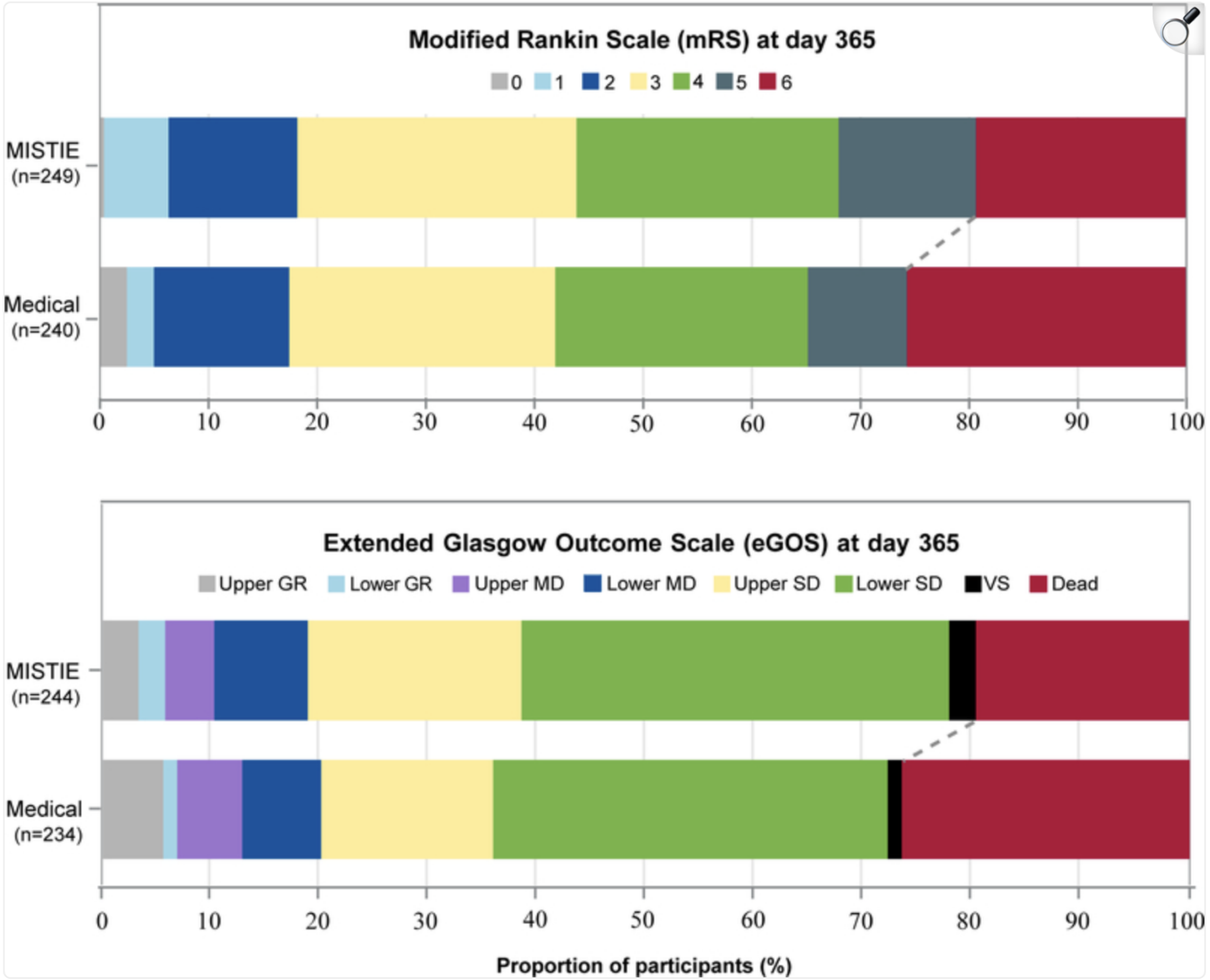


Adoptive transfer of M2 macrophages in cortical impact TBI reduce lesion volume / edema, number, and activation of IBA1+ microglia/macrophages in pigs.

Overarching Rationale:

- Inflammatory sequelae of ICH (and other brain injuries) can produce progressive, secondary damage. It involves microglia, infiltrating innate cells, and potentially infiltrating lymphocytes.
- Chronic inflammation and neurodegenerative consequences can be attenuated through targeted intervention at key moments (~hours to days).
- IL-4 + dexamethasone immunotherapy, with adoptively transferred macrophages, have previously resolved disease in MS and TBI context.
- Intervention can be localized to the CNS parenchyma or can act in the periphery. Peripheral interventions need to modulate cells that infiltrate the CNS or impact the blood-brain-barrier in a therapeutic way.
- Great and unmet opportunity in ***intracerebral hemorrhage*** treatment context.

MISTIE - III



- Minimally invasive surgery with thrombolysis in intracerebral hemorrhage evacuation - Ph3
- Decrease >30 mL hematomas to less than 15 mL
- Median time to intervention ~2 days
- No improvement in outcomes, but also no difference in infection-related AEs

Hanley et al., Lancet. 2019; 393(10175): 1021–1032

ENRICH

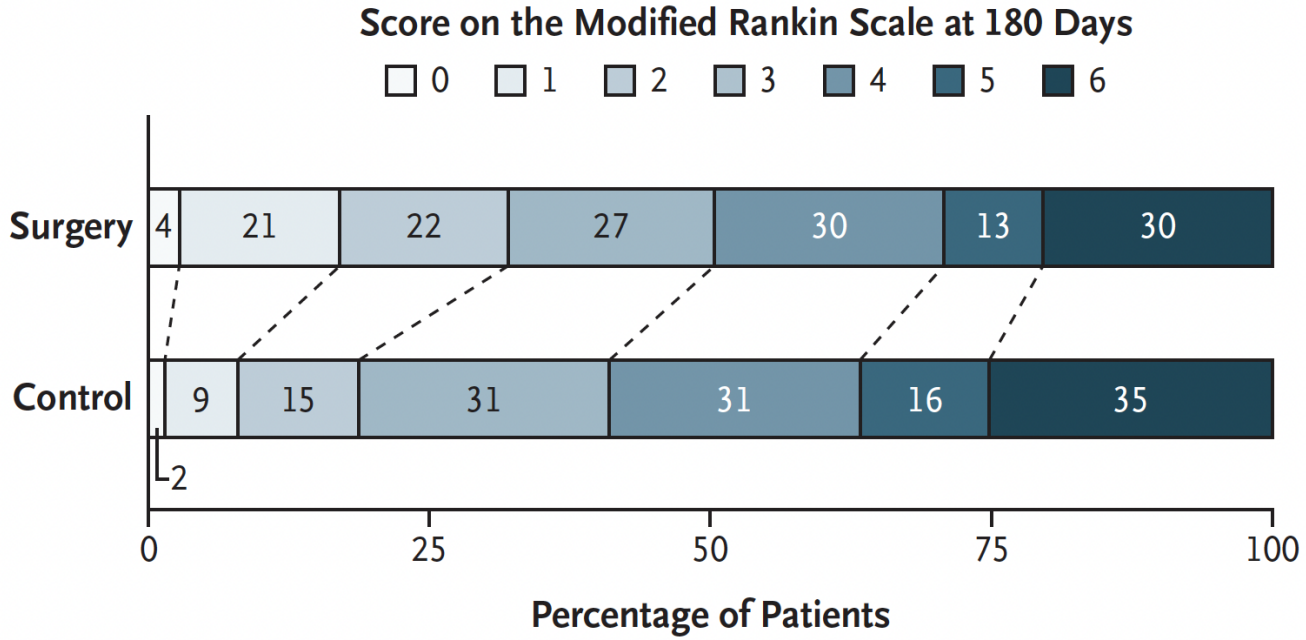


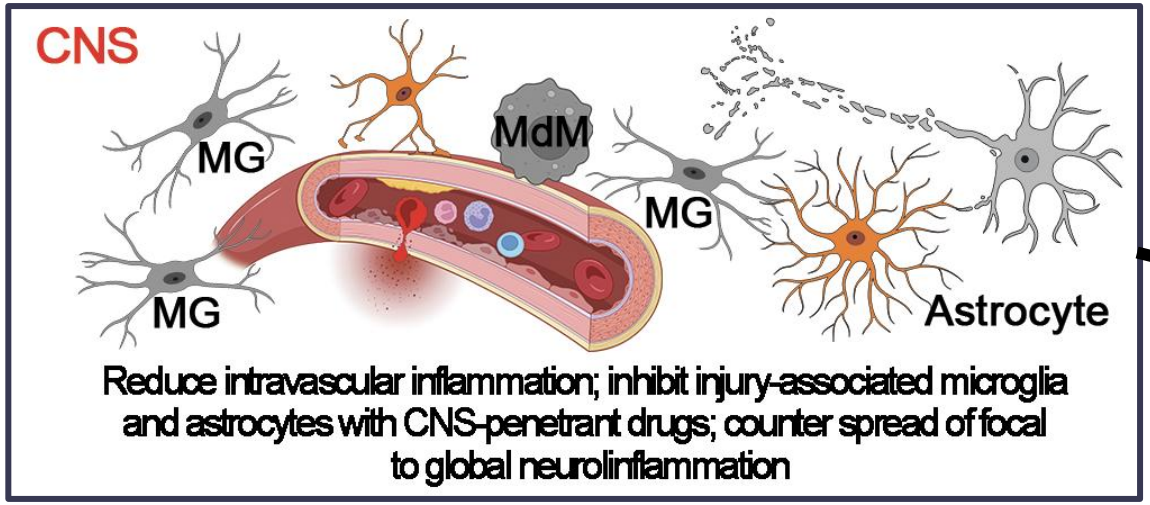
Figure 2. Distribution of Surgery Effect and Observed Scores on the Modified Rankin Scale.

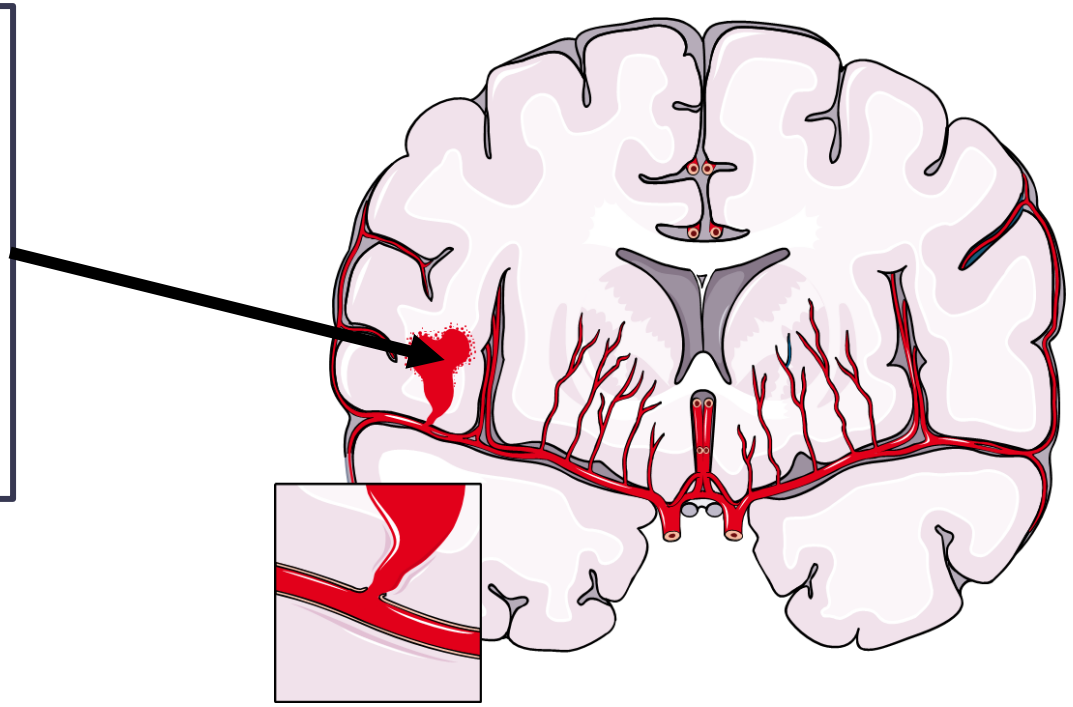
The raw distribution of scores for disability on the observed modified Rankin scale at 180 days is shown according to treatment group. Scores on the modified Rankin scale range from 0 to 6, with a score of 1 or lower indicating no or minimal deficit and 6 indicating death.

Early, minimally-invasive evacuation of lobar (but not basal ganglia) hemorrhages led to improved survival and reduced disease severity (disability) in human patients!

Pradilla *et al.* N Engl J Med 2024; 390: 1277-89.

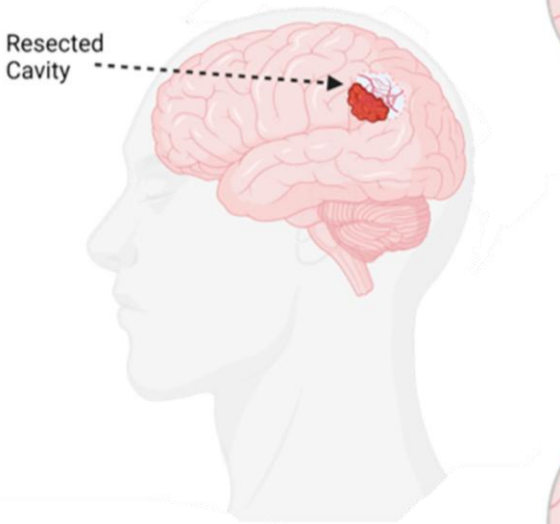
Proposed interventions to attenuate ***chronic inflammation*** post-ICH

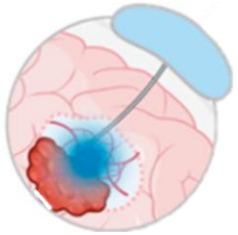




Shi and Yong. Science (2025) *adx0043*

Predicate Device-Based Approaches for Localized Brain Delivery

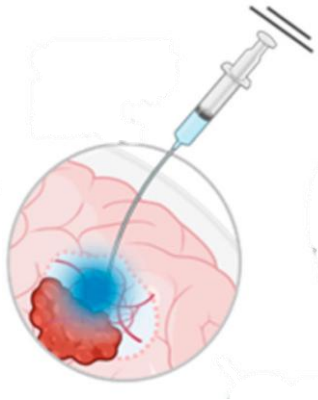




Ommaya Reservoir

Drug diffuses in via catheter

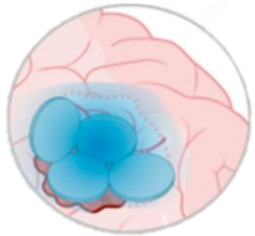
- ❌ Poor drug distribution
- ✅ Implanted during resection surgery
- ✅ Easy refill
- ❌ Relies on catheter placement. Permanent device.



Convection Enhanced Delivery

Drug pumped in via catheter

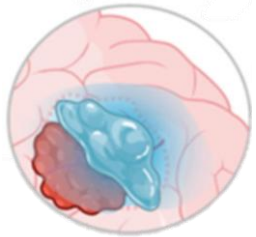
- ✅ Improved drug distribution
- ❌ Separate procedures after resection for insert/removal
- ❌ Relies on catheter placement
- ❌ Non-refillable



Polymer Wafers

Biodegradable polymer wafers slowly releasing drug

- ✅ Sustained release
- ✅ Implanted during resection surgery
- ❌ Infection risk, hydrocephalus risk
- ❌ Limited range of loaded drugs. Non-refillable

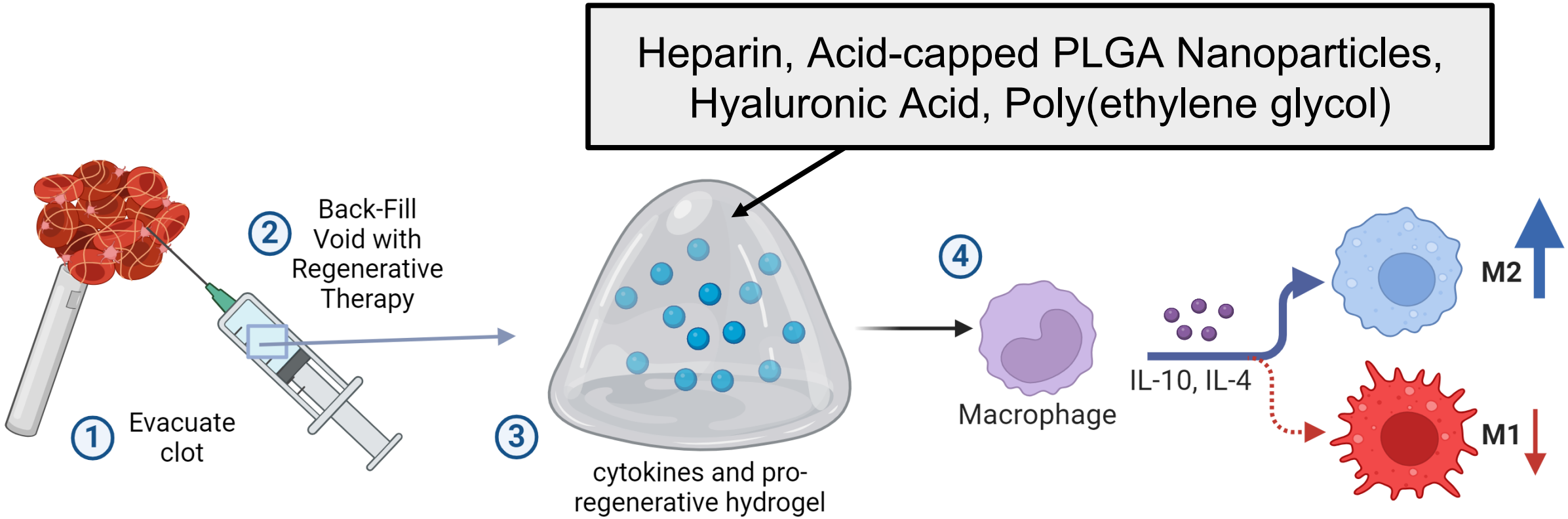


Hydrogel (or similar)

Biodegradable hydrogels slowly releasing drug

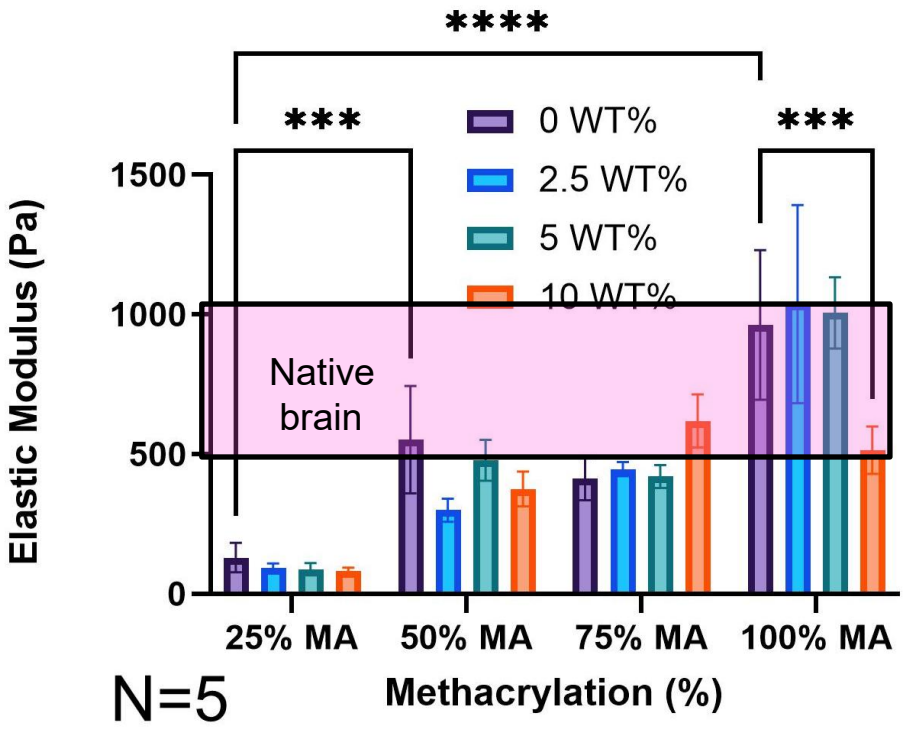
- ✅ Sustained multi-day release
- ✅ Implanted during resection surgery
- ✅ Fills any size cavity
- ❌ Non-refillable

Formulation and administration of a cytokine-stabilizing hydrogel (**ParenchyGel**) for brain delivery

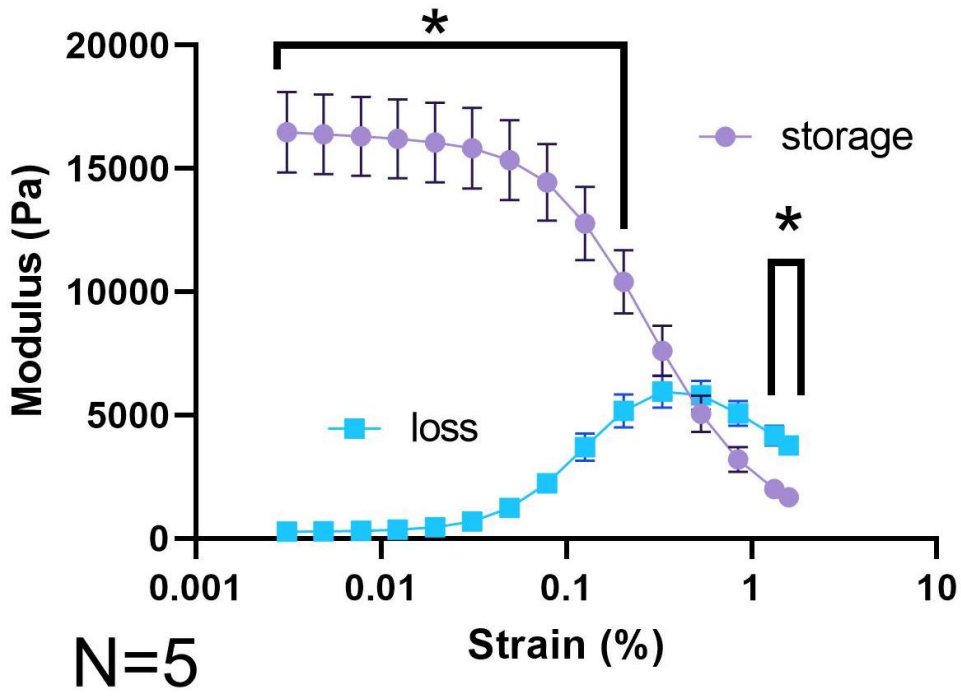


ParenchyGel is **Injectable and Mimics Brain Stiffness**

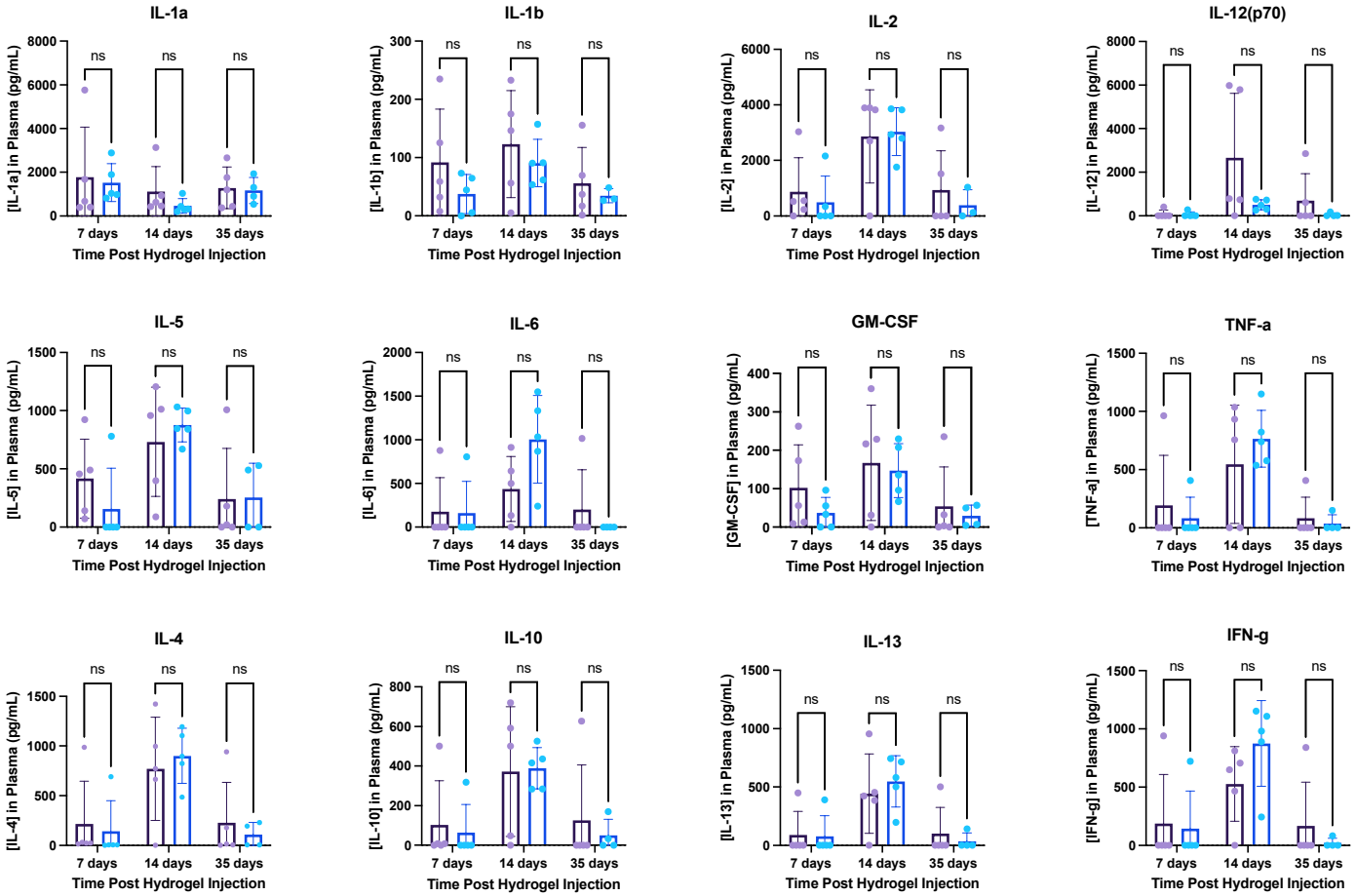
Compression:

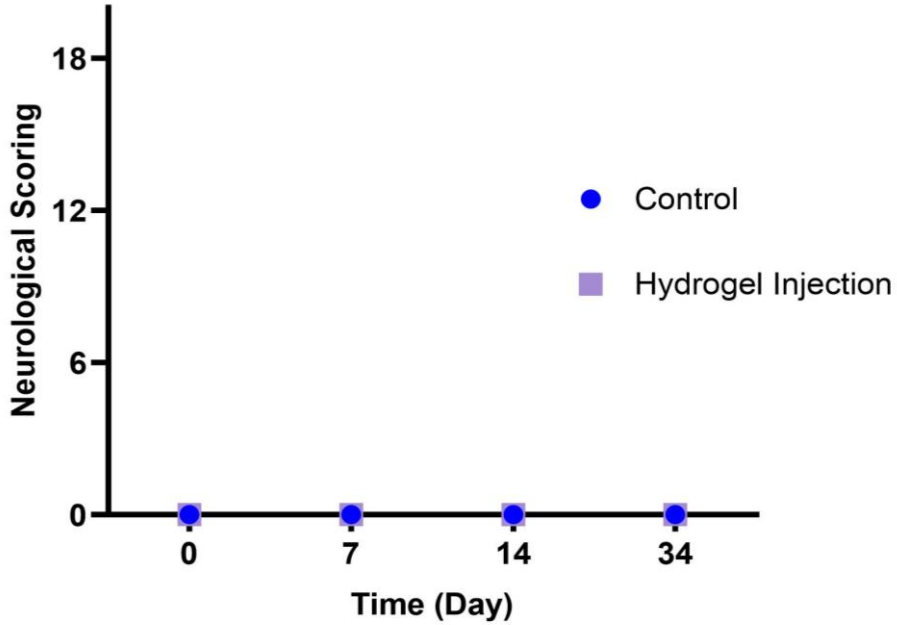


Shear w/ Amplitude Ramp

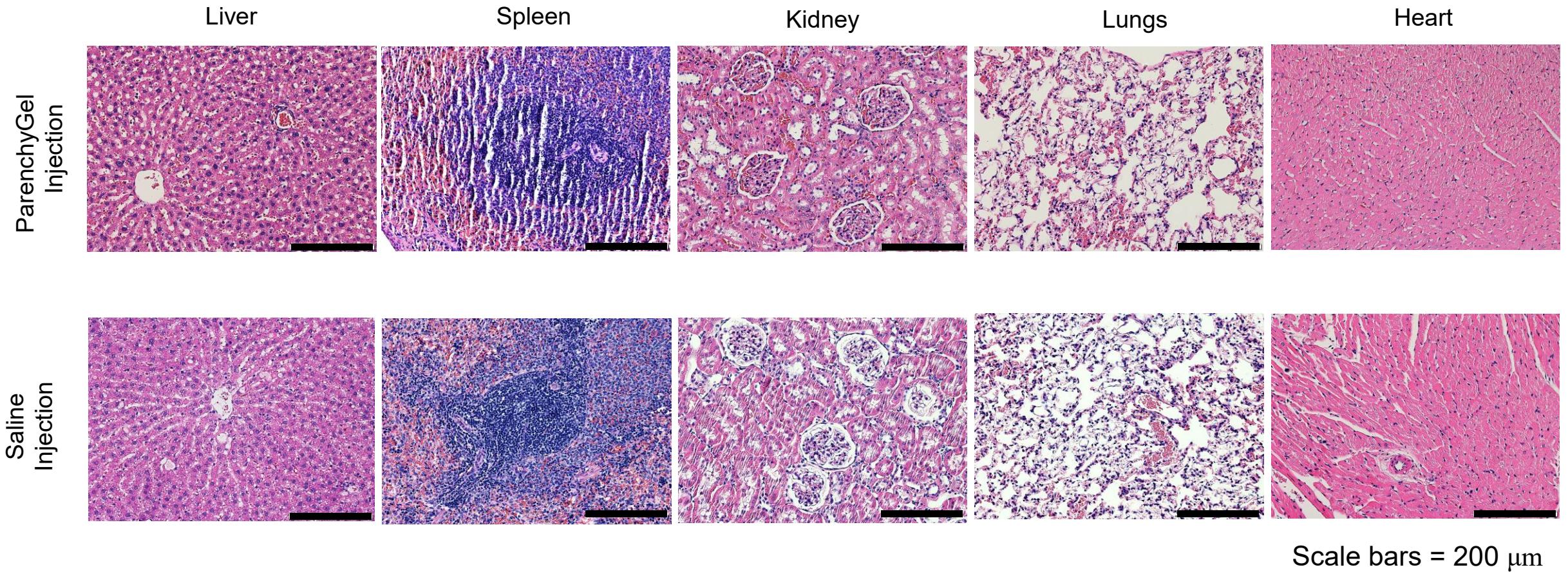


ParenchyGel does not elicit a systemic immune reaction or affect rats' motor/sensory function



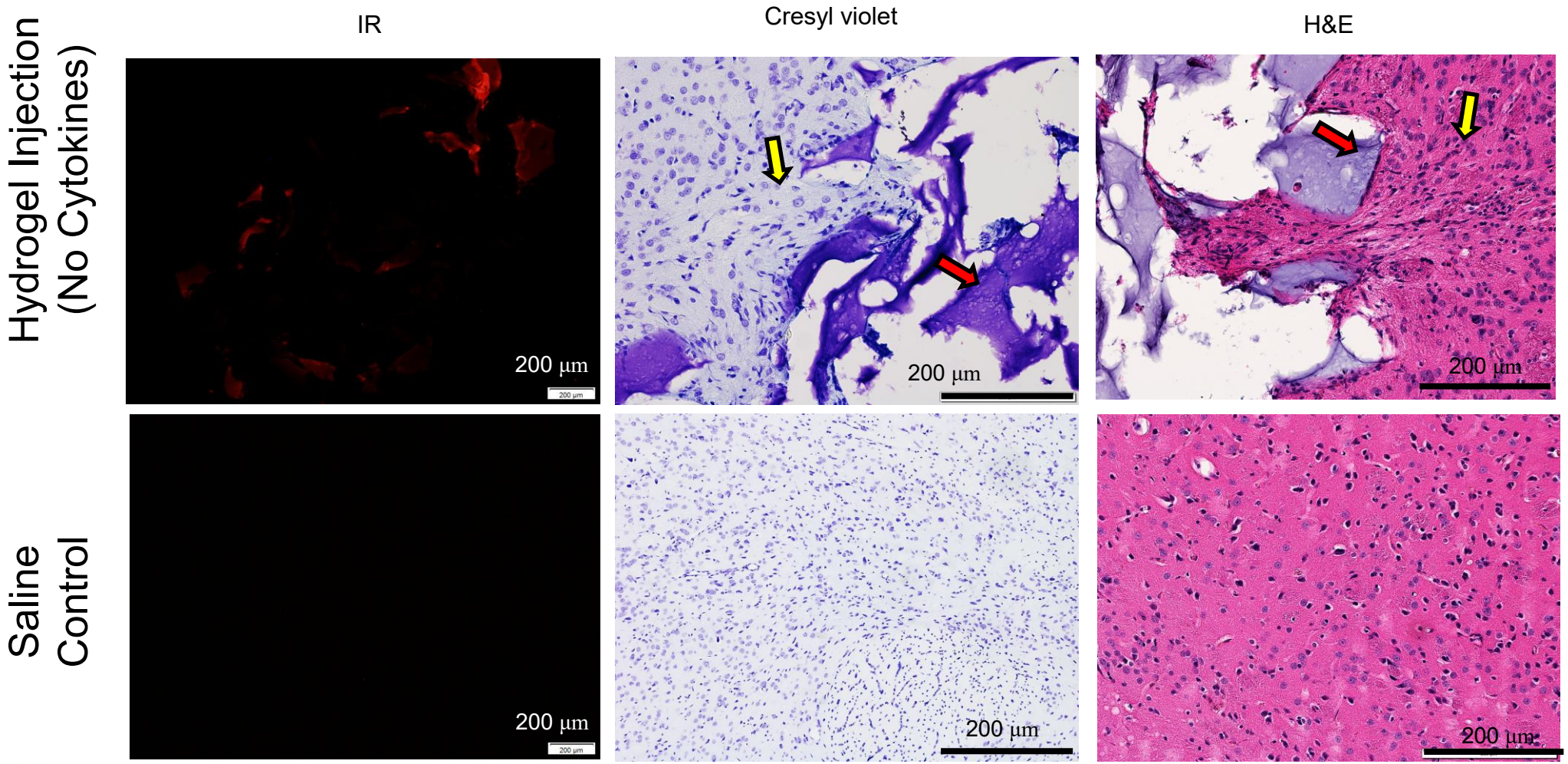


Peripheral Organ Histology Exhibited Negligible Cytotoxicity

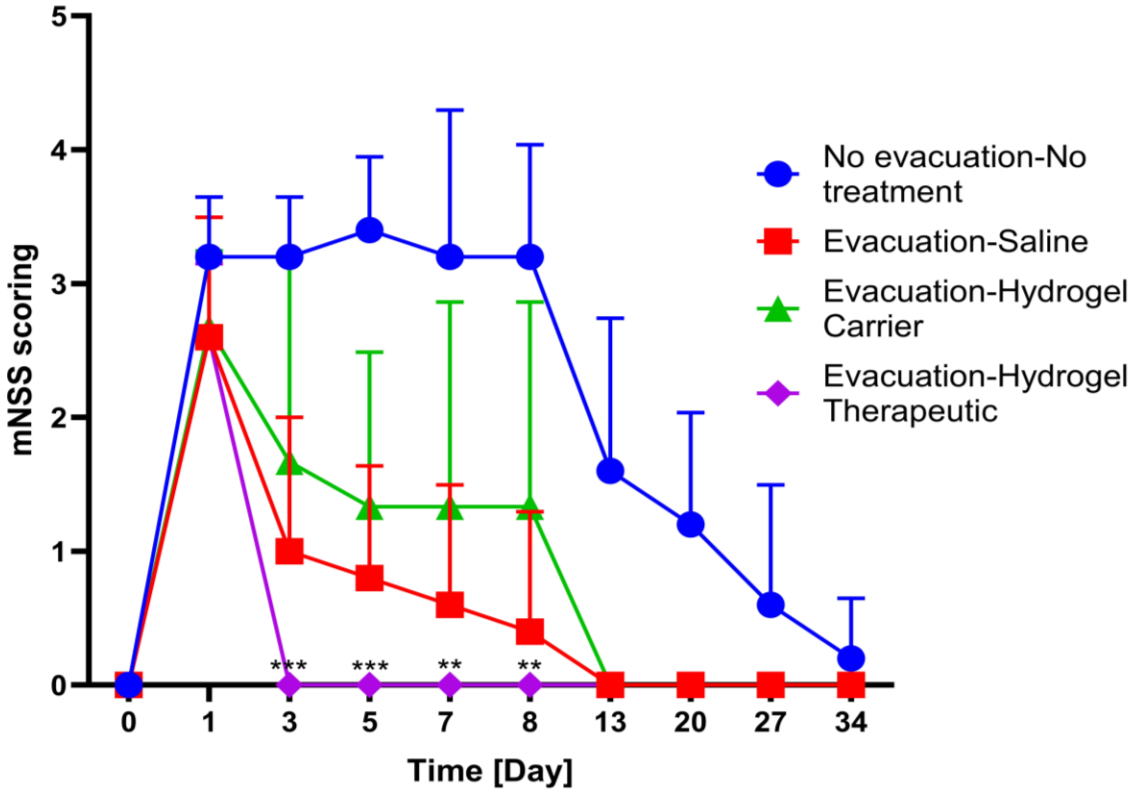


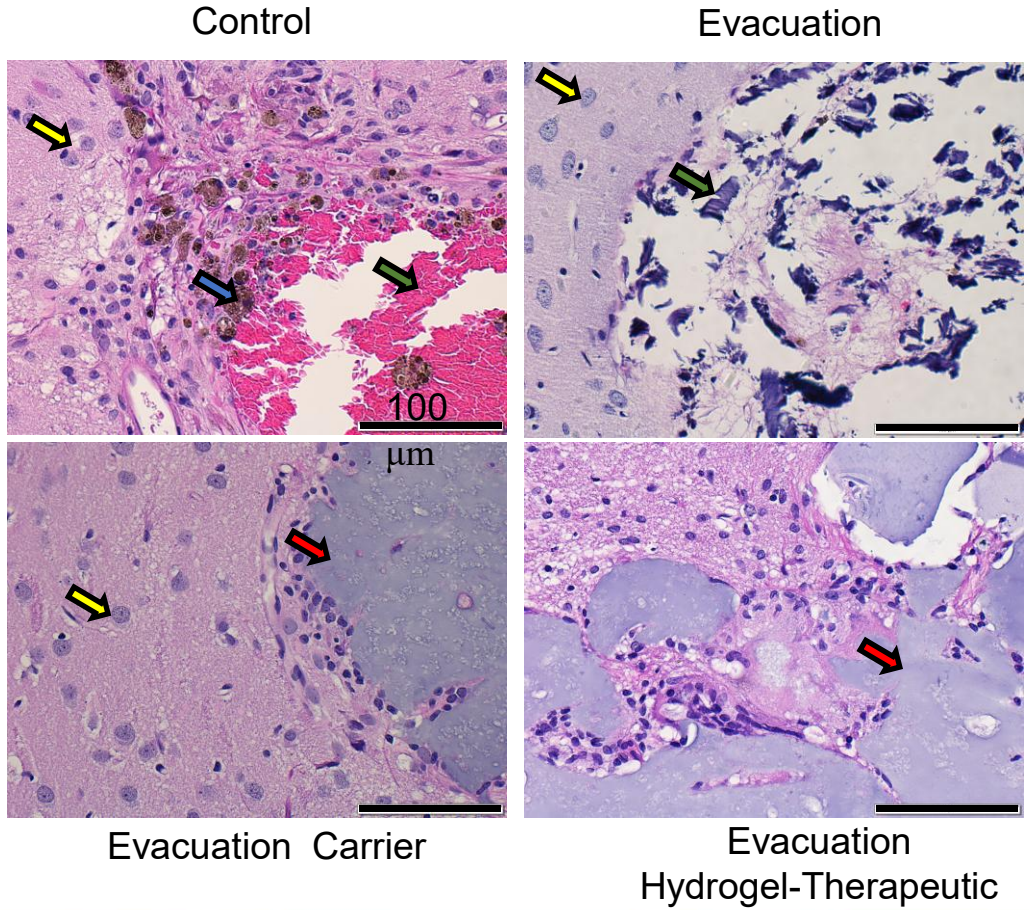
Scale bars = 200 μm

ParenchyGel (SD Rats) Integrates with Brain Tissue interface without significant inflammation, neurotoxicity



ParenchyGel loaded with IL-4 and IL-10 accelerated motor and sensory recovery following ICH in Rats





Summary (ICH)

- Intracerebral ParenchyGel is safe in healthy rats and in rats after ICH (with hematoma evacuation).
- ParenchyGel injection did not produce systemic immune reactions or toxicity.
- ParenchyGel integrates within the CNS parenchyma, based on tissue and neuron staining.
- Hematoma evacuation produced the most marked reduction in disease severity.
- Most rapid resolution of disease occurred in ParenchyGel + Immunotherapy group.

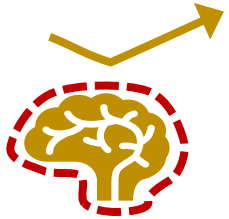
The Problem: Glioblastoma

No cure

Glioblastoma (GBM) is the fastest growing, most aggressive tumor of all nervous system tumors. Median survival is **12–15 months**, and less than **7% survive beyond five years**.

Recurrence

Cancer cells **infiltrate past the resected tumor margins**, making **complete surgical removal impossible.** Residual cancer cells contributes to **90% of patients recurring.**



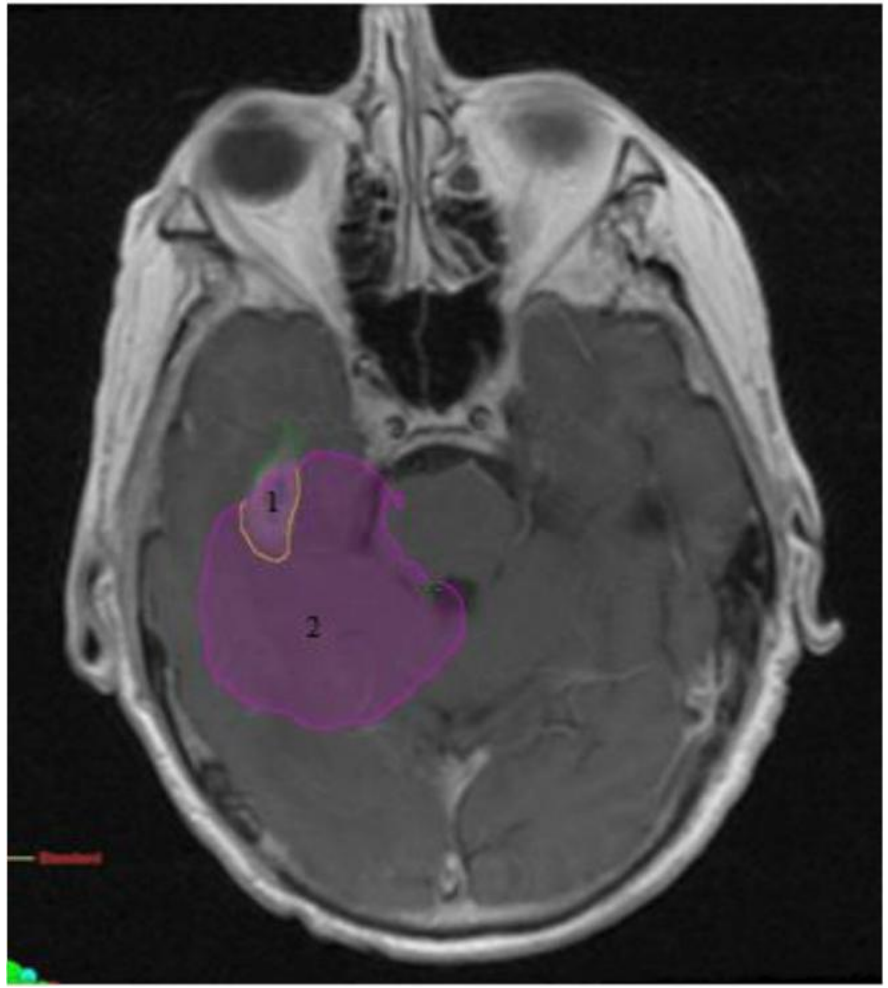
Few treatments

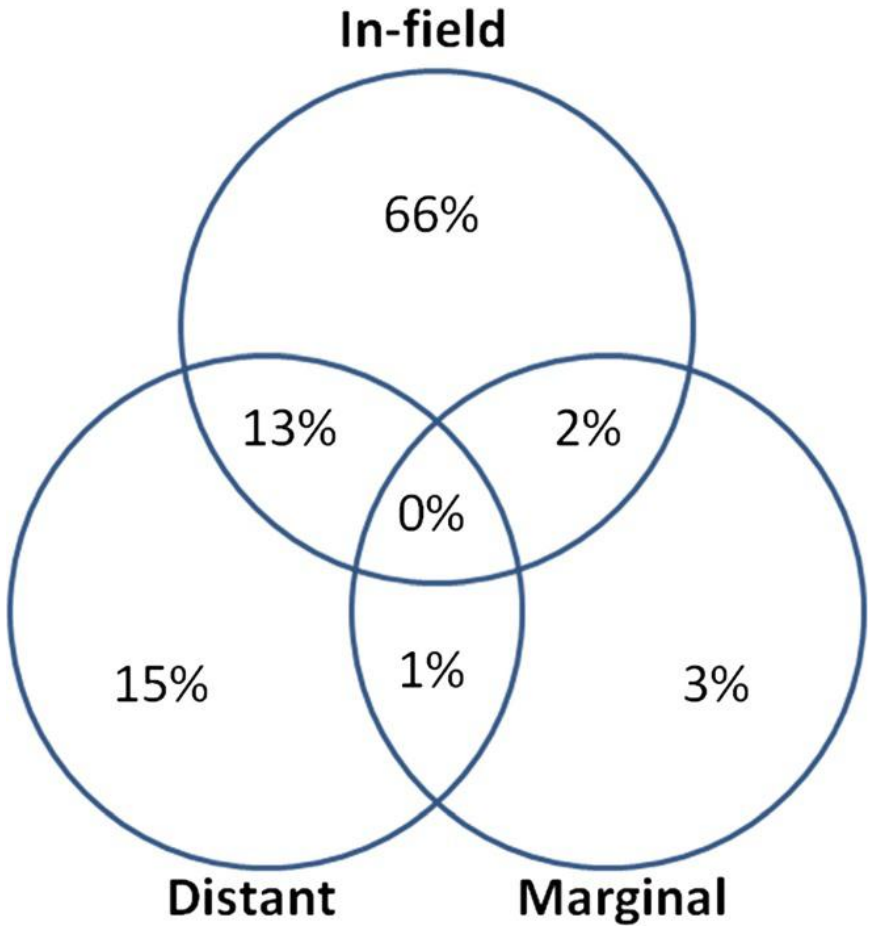
Most chemotherapy drugs are **unable to penetrate** the blood-brain-barrier, limiting treatment options for GBM to only **6 FDA-approved treatments**.

Ineffective Local Drug Delivery

The Gliadel® wafer locally delivers a chemotherapy but has **poor tissue coverage and penetration into the margins**. Limited advancements in the last 20 years.

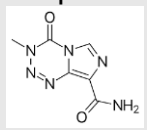
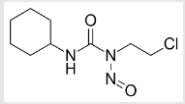
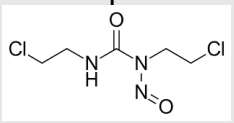
Pattern of Failure in GBM Patients Receiving TMZ + Radiation





Gebhardt, B.J., Dobelbower, M.C., Ennis, W.H. *et al.* Patterns of failure for glioblastoma multiforme following limited-margin radiation and concurrent temozolomide. *Radiat Oncol* **9**, 130 (2014). https://doi.org/10.1186/1748-717X-9-130

Approved treatments for Glioblastoma **Last new approval was in 2011**

	Temodar® (Temozolomide)	Gleostine (lomustine) Capsules	BiCNU (carmustine for injection)	AVASTIN bevacizumab 100 MG/4 ML INJECTION FOR IV USE	GLIADEL® WAFER (carmustine implant)	OPTUNE GIO®
	Drugs				**Drug-Device**	**Device**
Company	Merck	Alembic Pharmaceuticals	Emcure Pharmaceuticals	Genentech	Azurity Pharmaceuticals	Novocure
Type	Compound 	Compound 	Compound 	Monoclonal antibody 	Chemotherapy device 	Tumor Treating Fields 
Mechanism of Action	Chemotherapy ✅ Crosses BBB	Chemotherapy ✅ Crosses BBB	Chemotherapy ✅ Crosses BBB	Targets VEGF ✅ Does not need to cross BBB	Biodegradable polymer + carmustine ✅ Does not need to cross BBB	Low-intensity electric fields on scalp to inhibit cell division ✅ Does not need to cross BBB
Patients	✅ Newly diagnosed ✅ Recurrent	❌ Newly diagnosed ✅ Recurrent	❌ Newly diagnosed ✅ Recurrent	❌ Newly diagnosed ✅ Recurrent	✅ Newly diagnosed ✅ Recurrent	✅ Newly diagnosed ✅ Recurrent
Dosing	✅ Oral Daily, then 5 days / mo	✅ Oral Every 6 weeks	❌ IV Every 6 weeks	❌ IV Every 2 weeks	✅ Wafer (up to 8) During resection surgery	✅ Wear 18 h/day
Cost	100 mg: $2-5k	100 mg: $7k	100 mg: $3k	$4-10k/month	8 devices: $10-20k	$27k/month
Patent exp.	2014 (no generics)	2009	2007	2019	2020 (no generics)	~2030
% of market	40-50%	20-25%	5-10%	5-10%	5-10%	5-10%

ParenchyGel – GBM: Team and Technology

John Clegg, PhD
Assistant Professor of Biomedical Engr.

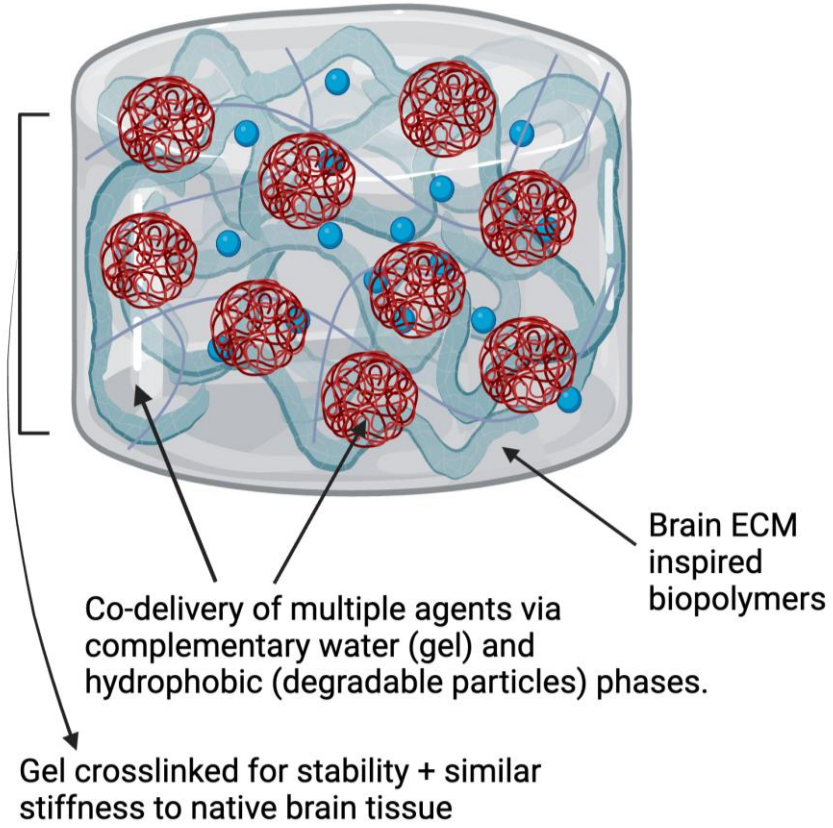
Kar Ming Fung, MD, PhD
Histology collaborator
Pathologist, OU Medical Center

James Battiste, MD, PhD
Glioblastoma Collaborator
Neuro-Oncologist
OU College of Medicine

Christopher Pierce
3rd year PhD Student

Chandra Kumar Elechalawar, PhD
Postdoctoral Researcher, OUHSC

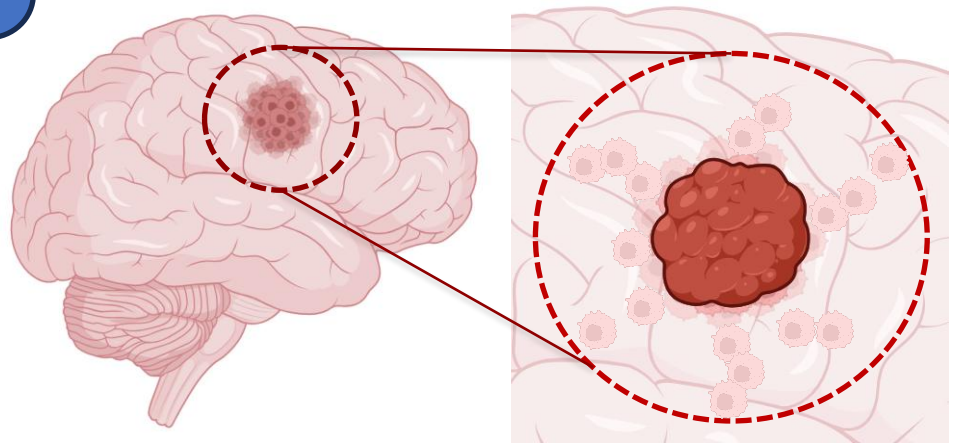
Brandon Bueltel
1st year PhD Student



Preclinical Data: ParenchyGel

1

Tumor removal

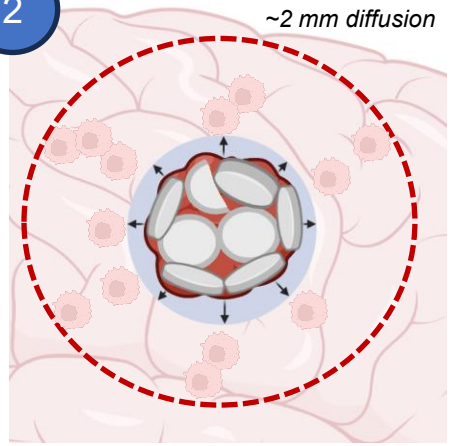


Surgery **removes as much of the tumor as possible** while preserving function

2

SOC

~2 mm diffusion

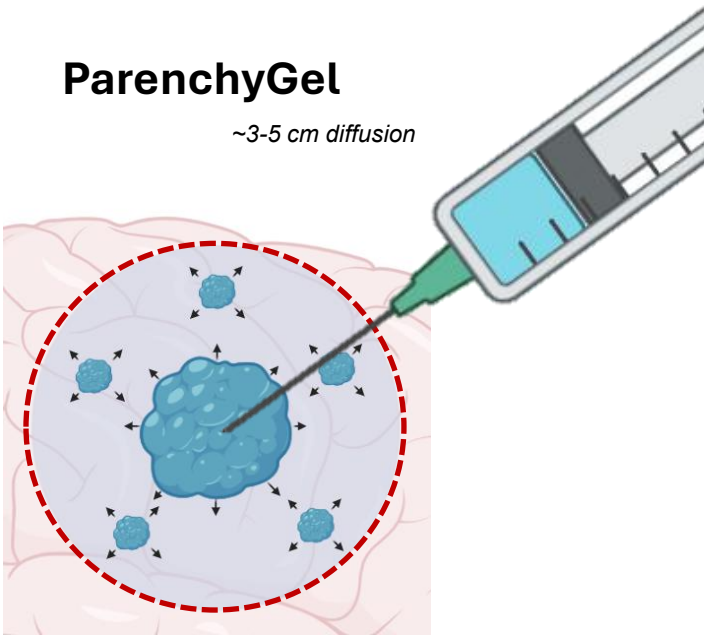


RT, TMZ, and wafers have **limited efficacy** in killing residual cancer cells

vs

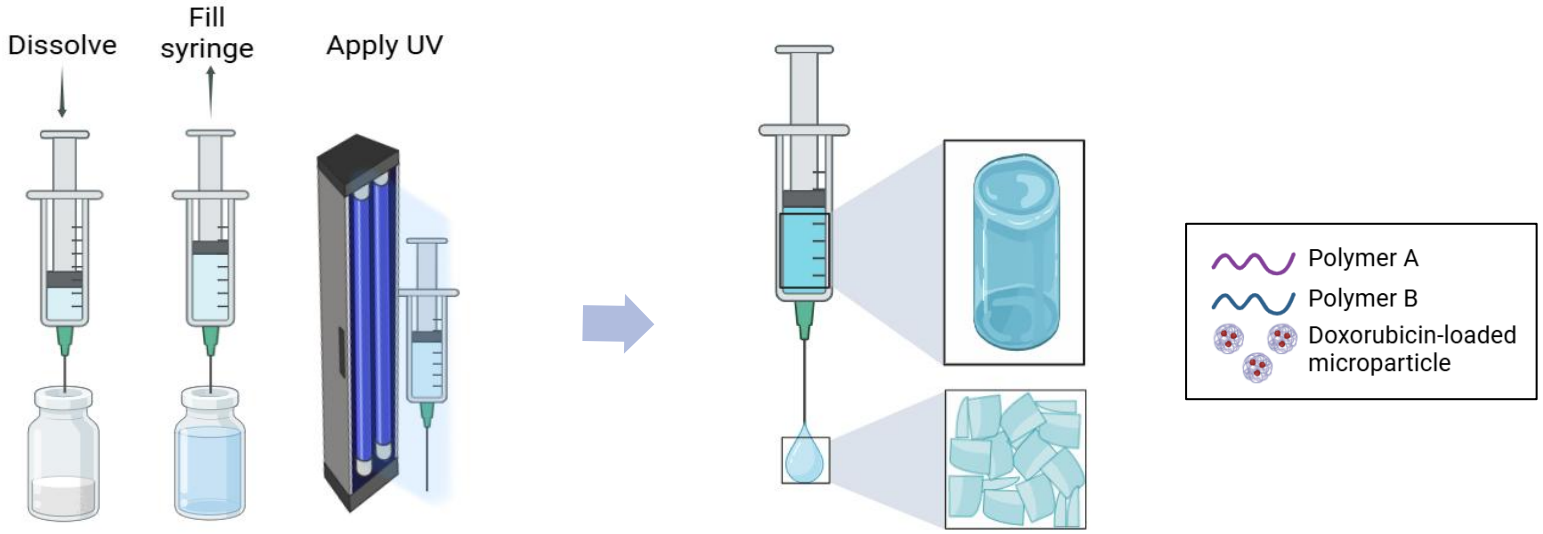
ParenchyGel

~3-5 cm diffusion



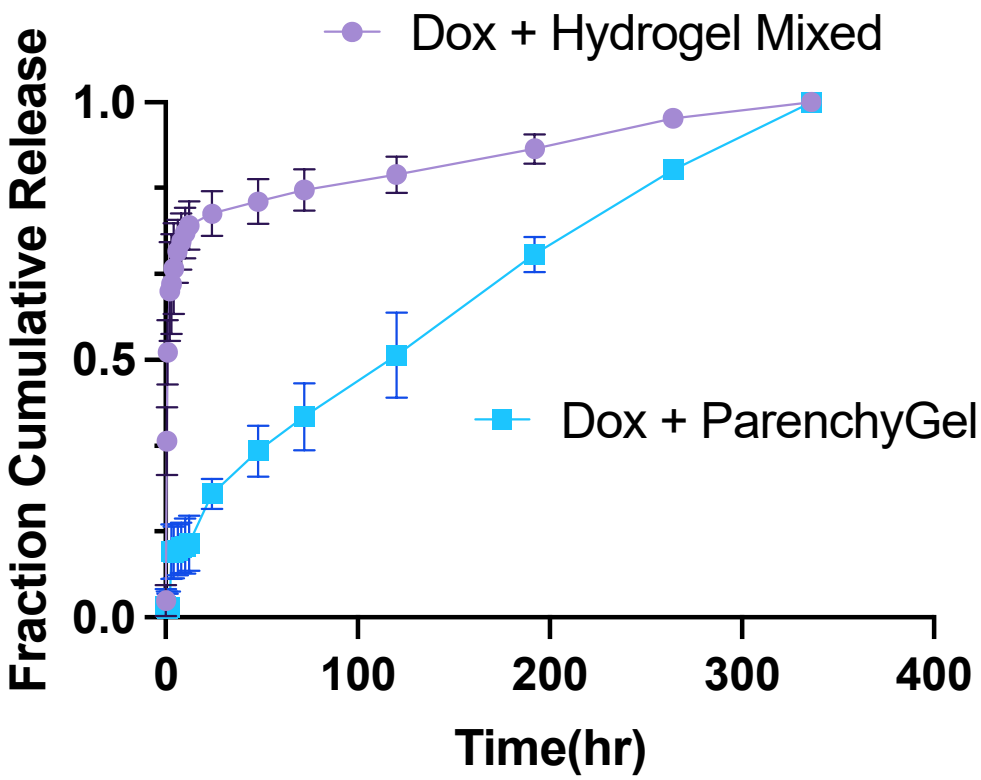
ParenchyGel may deliver more **potent chemotherapies** to an **expanded region**

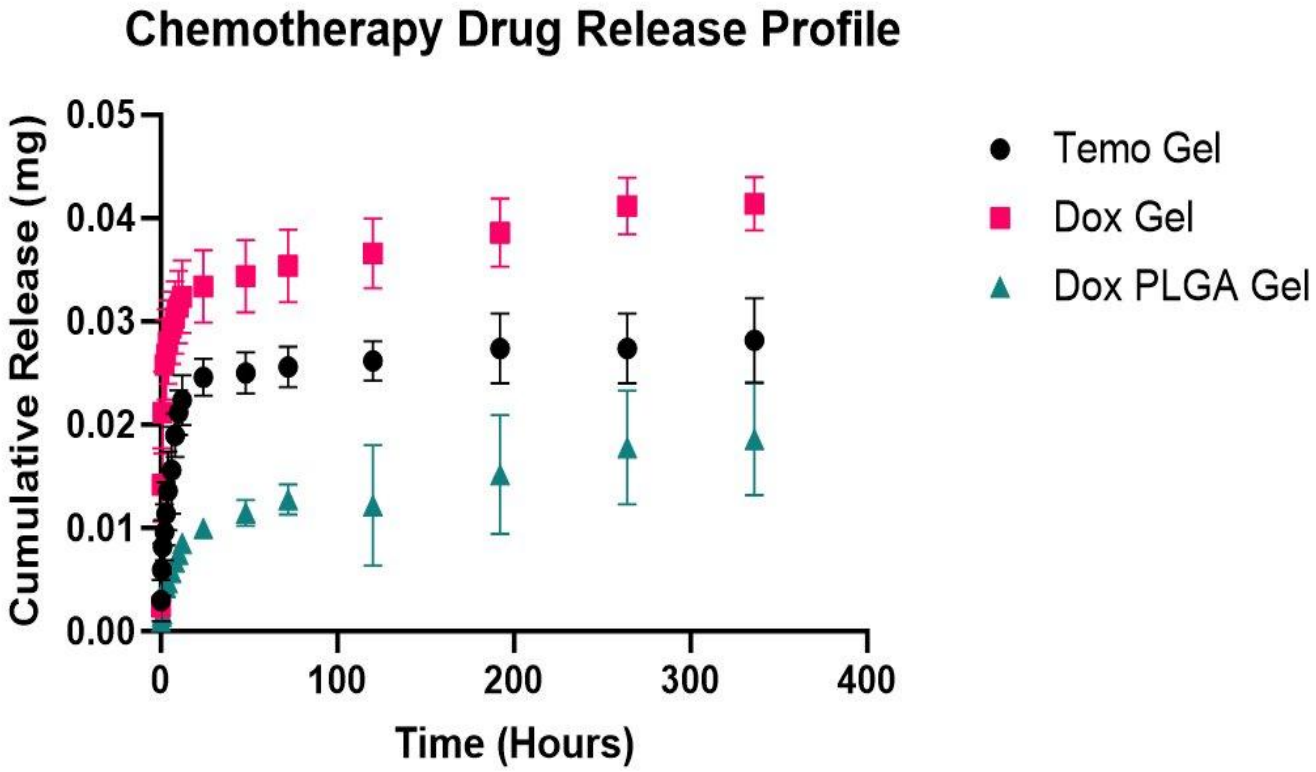
ParenchyGel Preparation



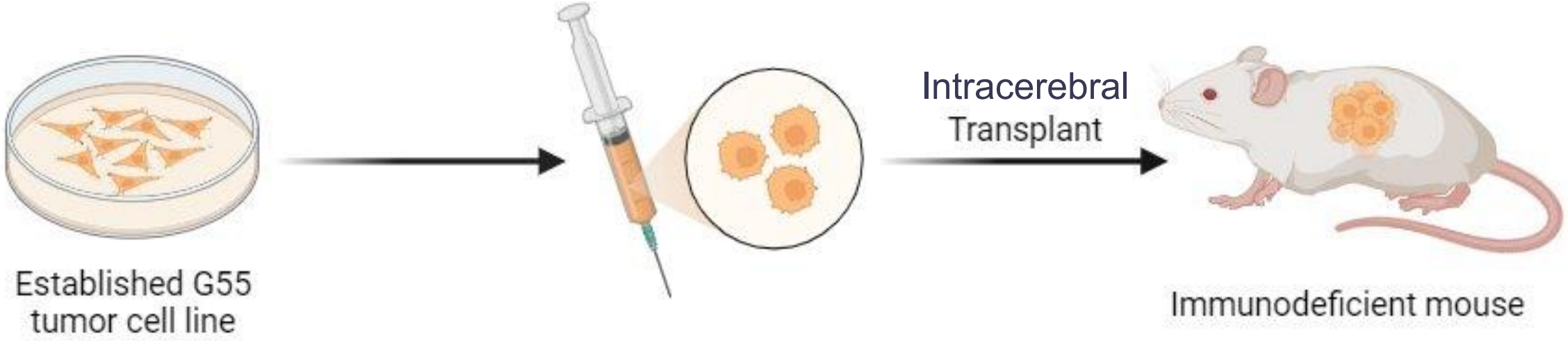
Standard of care (SOC), Radiotherapy (RT), temozolomide (TMZ)

Doxorubicin loading in PLGA nanoparticles (rather than bulk mixing) reduces burst release and achieves sustained elution.

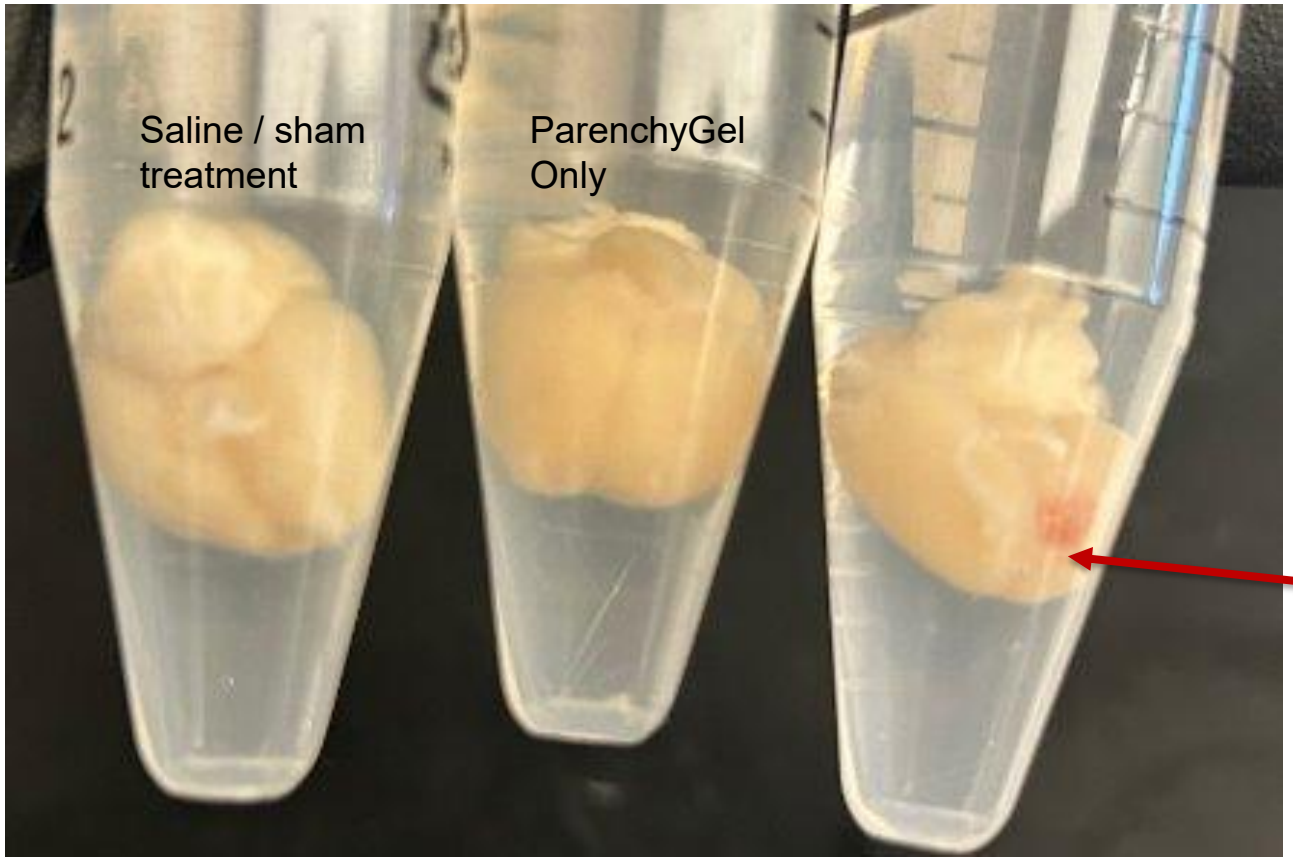




Orthotopic Xenograft model of Invasive Human GBM in Immunocompromised Mice

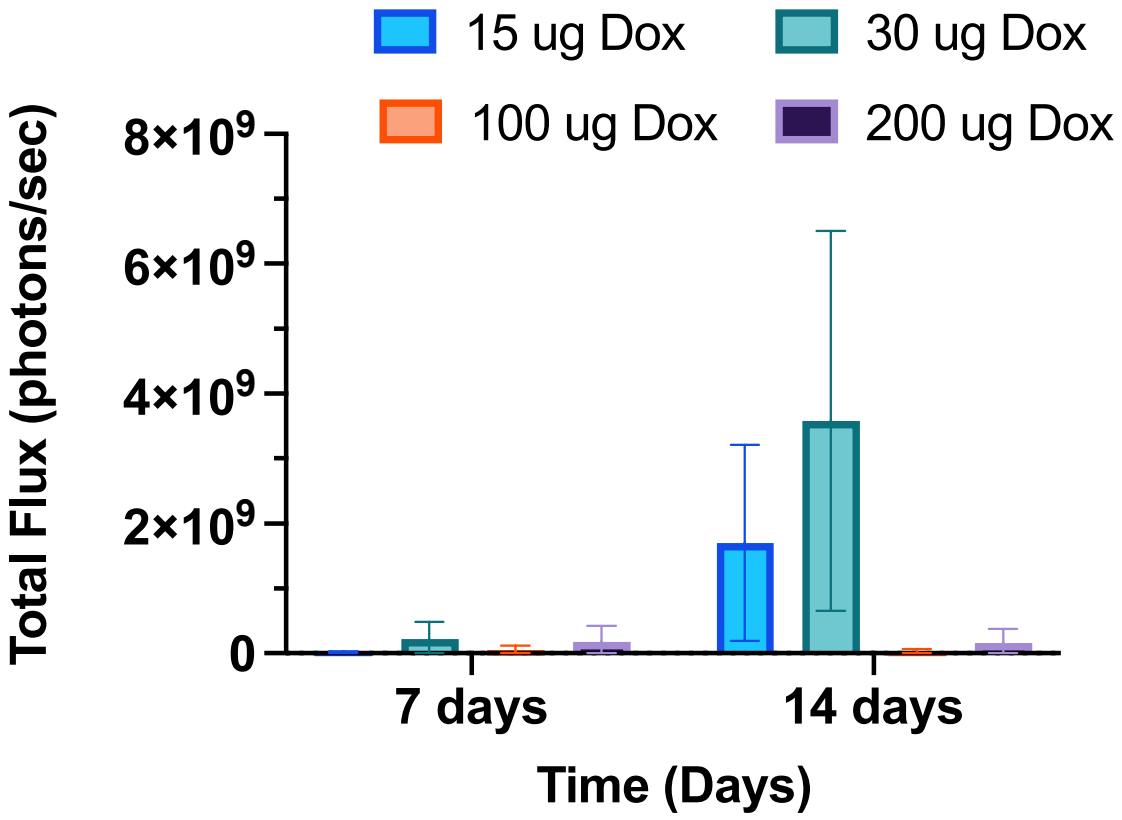


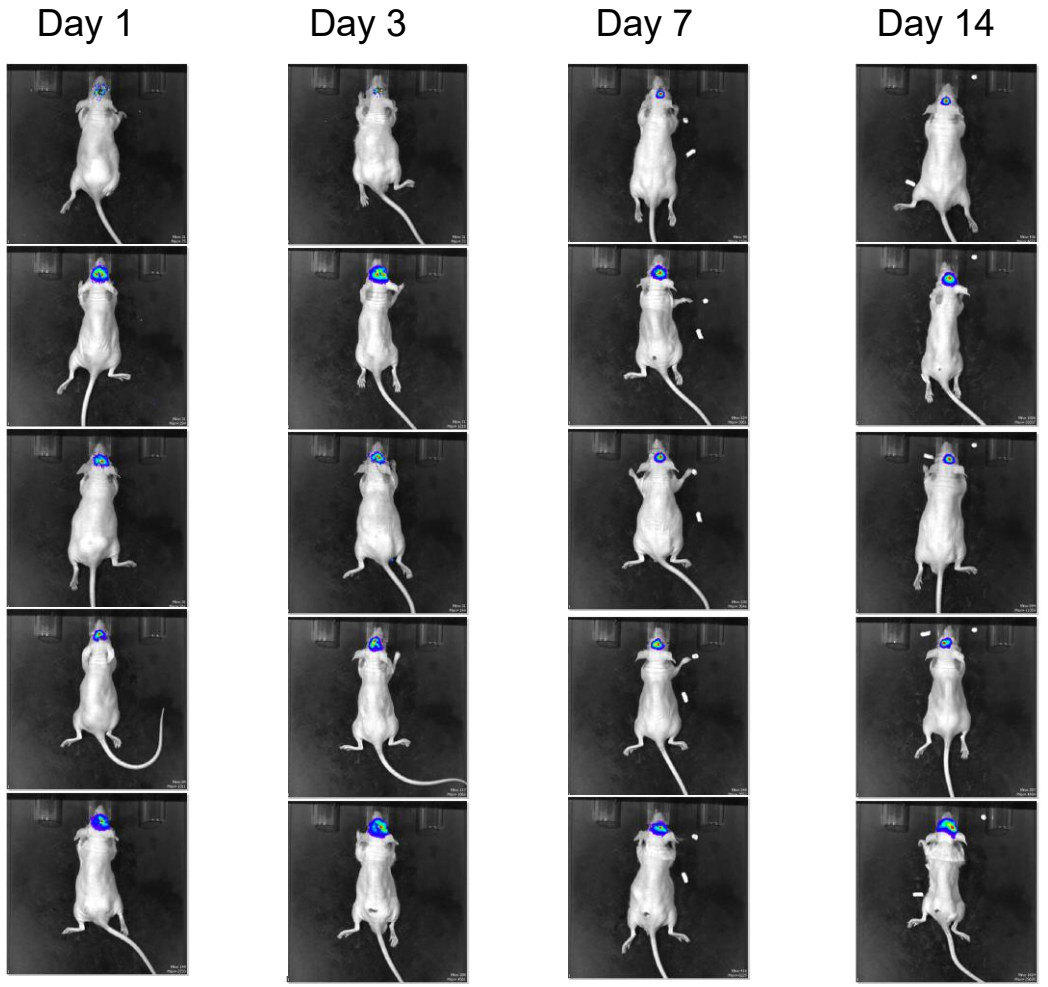
ParenchyGel-mediated DOX delivery IC spares peripheral organs from Dox exposure + concentrated dose in peri-tumor tissue



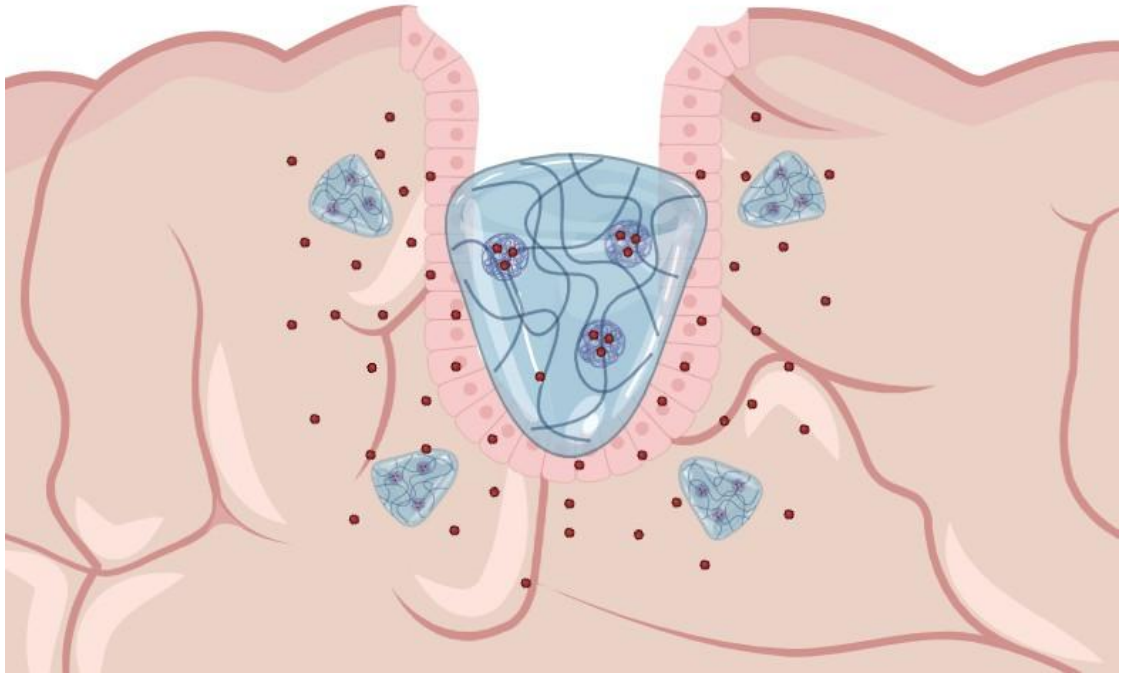
120 h
Post-injection

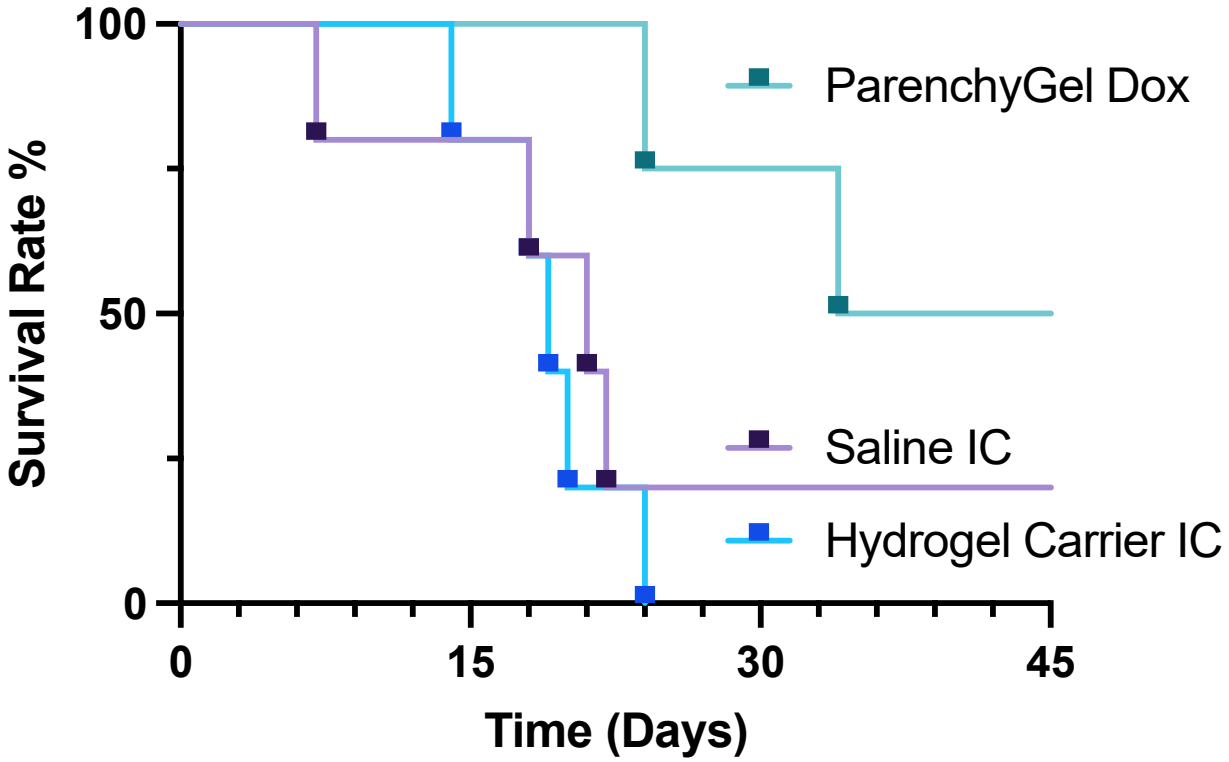
Dose escalation study (safety + pilot efficacy)





Intracerebral delivery of ParenchyGel Doxorubicin at time of tumor inoculation extends survival in mice





Conclusions

- Modulation of the brain tissue immune environment is a potentially useful strategy in treatment of a variety of CNS indications.
- We have invented a multi-phase drug delivery system that can deliver both small molecule and recombinant protein payloads over long durations.
- This allows for local delivery of drugs at therapeutic concentrations for sustained time (~weeks), even when those payloads have stability issues.
- Safety (local and systemic) appear favorable. Currently, the carrier device is designed to be permanent.
- We have demonstrated resolution of disease in rodent ICH and rodent GBM

Thank you! Please connect with us!

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NEURO IMMUNO ENGINEERING COLLECTIVE

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