Childhood Cancer Data Initiative Webinar Series

Developing Translational and Predictive Imaging Biomarkers of Radiotherapy-Induced Brain Injury in Preclinical Models

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NIH NATIONAL CANCER INSTITUTE

May 12, 2026

Today's Speaker

Ethel J. Ngen, Ph.D.

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- Director of the Responsive Imaging BioSensor and BioEngineering (RISE) Lab

Johns Hopkins University School of Medicine

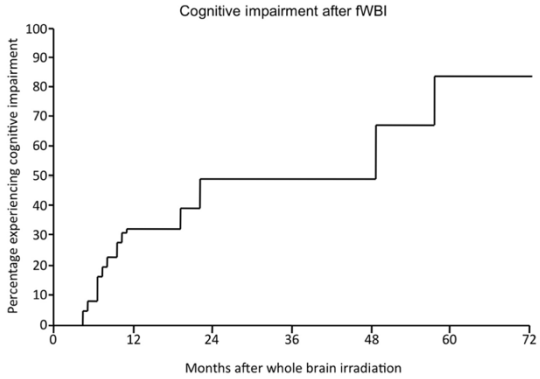
Agenda

1. *Radiotherapy-induced brain injury in pediatric brain tumor survivors*
2. *Developing longitudinal MRI biomarkers of RIBI in a preclinical mouse model*
3. *Utilizing the developed MRI biomarkers to evaluate potential RIBI therapies in preclinical rodent models*
4. *Utilizing the developed MRI biomarkers to evaluate potential RIBI therapies in a tumor-bearing preclinical rodent model*
5. *Q&A*

Radiotherapy-induced Brain Injury in Pediatric Brain Tumor Survivors

Radiotherapy-Induced Brain Injury (RIBI) Incidence

- RIBI occurs in 50-90% of brain tumor survivors treated with radiotherapy
- RIBI increases in incidence and severity over time
  - Detected in some cases, as early as 6 months, or decades post-radiotherapy
- RIBI is a chronic, progressive, neurodegenerative, and debilitating side effect
  - RIBI progresses to dementia in ~5% of cases
- No FDA-approved RIBI therapies
  - Memantine (approved for Alzheimer's disease) shows modest promise



Greene-Schloesser D. et al. 2012, Front. Oncol. 2(73) 1-18

RIBI Risk Factors

Clinical characteristics of RIBI

- Changes in short-term memory
- Executive function
- Attention
- Processing speed

Risk factors associated with developing RIBI

- Age at time of irradiation (> in younger patient)
- Radiation doses and dose fractions (> with high doses and fractions)
- Brain volume irradiated (> with large volumes)
- Brain regions irradiation (> for hippocampus and left frontal lobe)
- Patient gender (> in female patients)

The Need for RIBI Diagnostic Biomarkers and Therapies

- Pediatric patients are surviving childhood cancer and growing into adulthood
  - 5-year progression free survival ≥ 80%
- There is a growing need for RIBI prophylactic and therapeutic strategies

The need for noninvasive imaging biomarkers for RIBI

- Early injury (RIBI) detection
- Injury (RIBI) progression or remission following therapeutic interventions

Limitations of current methods to detect RIBI

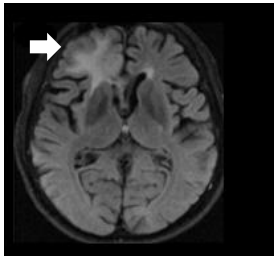
- Neuropsychological evaluations:
  - Late detection – already symptomatic
- Histopathological evaluations:
  - Invasive and can't be used longitudinally

MRI provides a noninvasive means to detect and longitudinally monitor RIBI

Advantages of MRI for Pediatric Brain Tumor Patients

No ionizing radiation

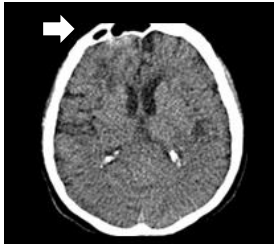
Magnetic Resonance Imaging (MRI)



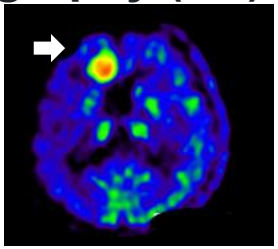
T_2–weighted FLAIR MRI

Ionizing radiation

Positron Emission Tomography (PET) & Computed Tomography (CT)



No contrast CT



^{11}C-methionine PET

MRI Advantages

- No exposure to ionizing radiation
- High spatial resolution
- Multi-parametric (T_2, T_1, diffusion, etc.)
- Longitudinal imaging

MRI Disadvantage

- Lower sensitivity (μM)

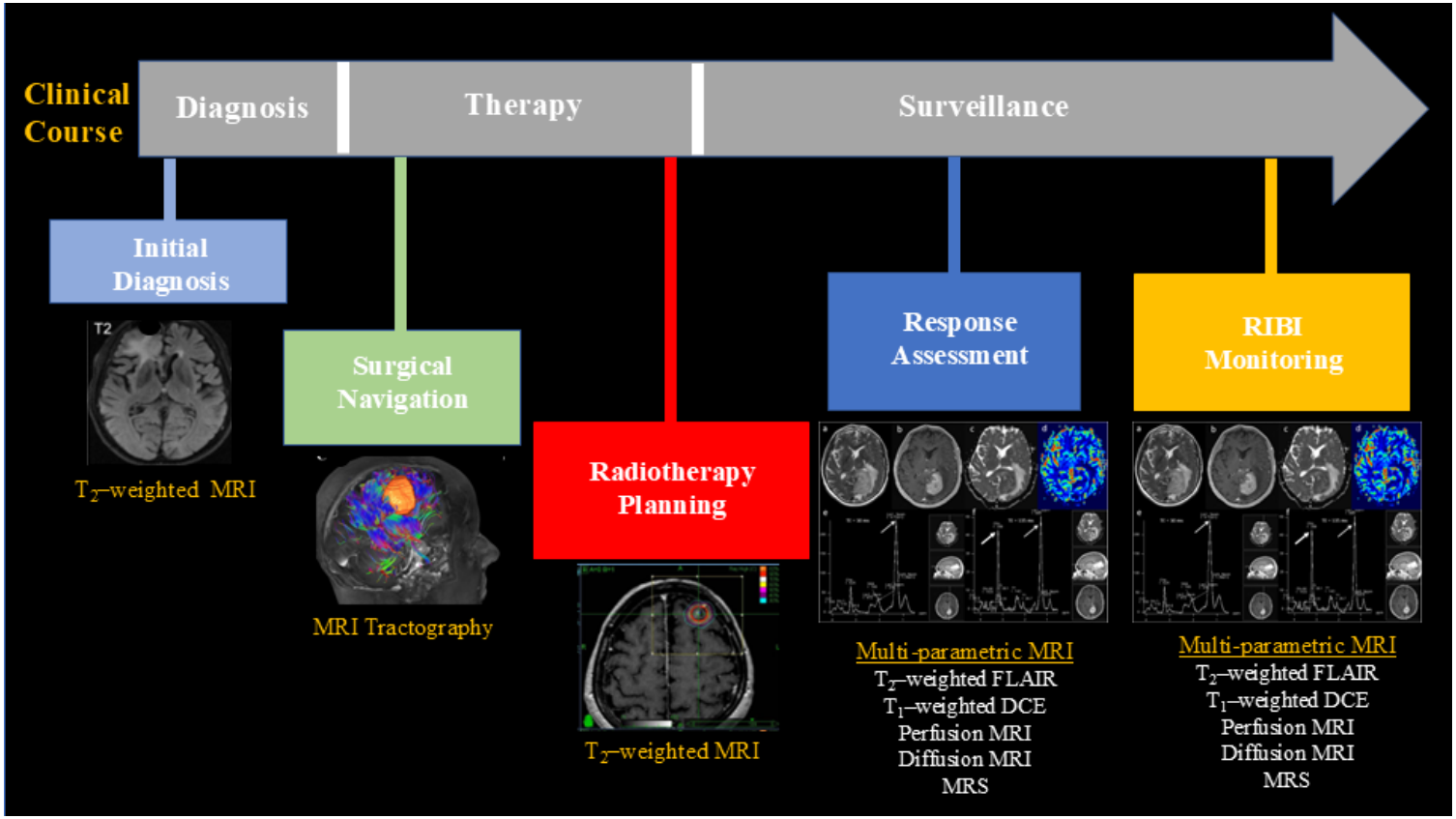
CT & PET Disadvantages

- Exposure to ionizing radiation
- Low spatial resolution
- Short tracer half-life (PET)

PET Advantage

- PET - higher sensitivity

Integration of MRI in Pediatric Patient Care



The Promise of Noninvasive MRI Biomarkers of RIBI

- **Early Detection.** To detect the on-set of injury early on

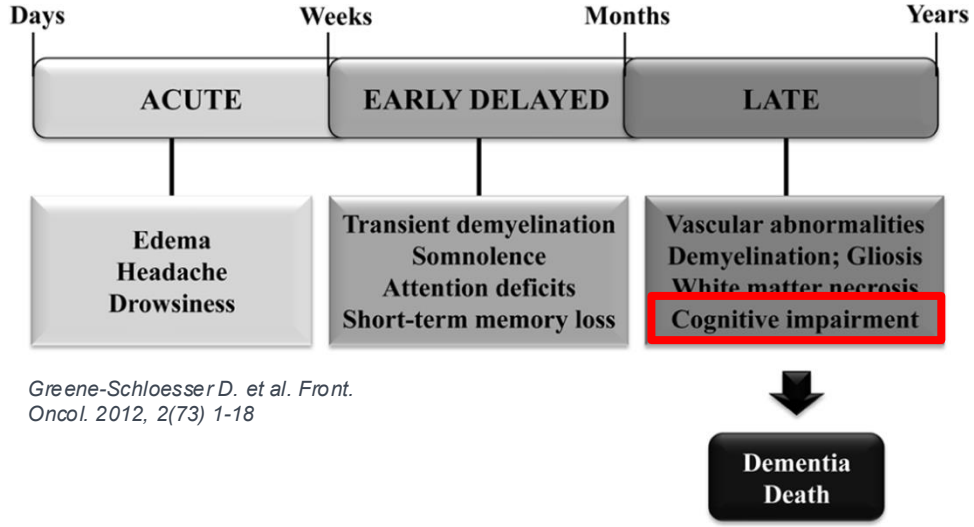
- **Patient Stratification.** To stratify patients based on the severity of injury
  - Mild Injury (RIBI)
  - Moderate Injury (RIBI)
  - Severe Injury (RIBI)

- **Responses assessment.** To monitor tissue responses to therapy
  - To monitor RIBI progression or remission

The need for preclinical models of RIBI for MRI biomarker development

Identifying Potential MRI Biomarkers of RIBI

Pathogenesis of RIBI



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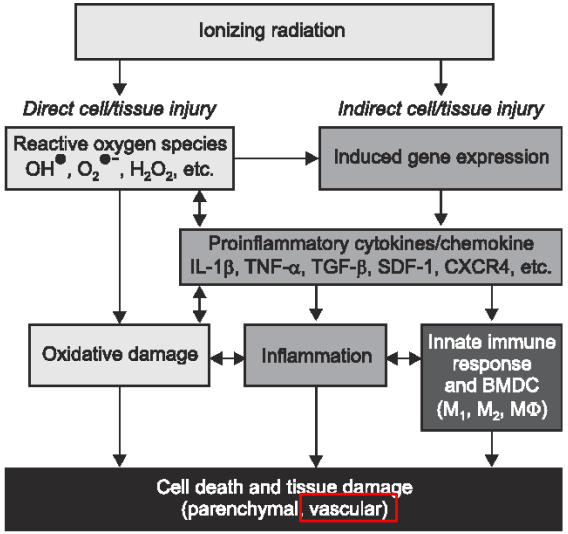
Key Drivers of RIBI

- Oxidative stress
- Neuroinflammation



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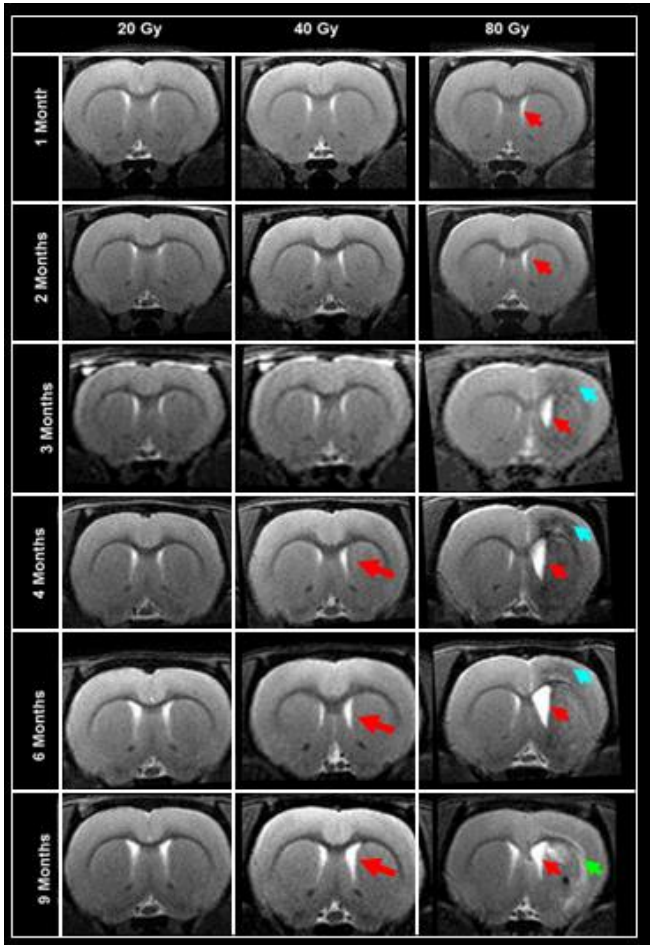
Correlation in several neurodegenerative diseases:

- Blood brain barrier (BBB) permeability changes = Short-term memory loss changes

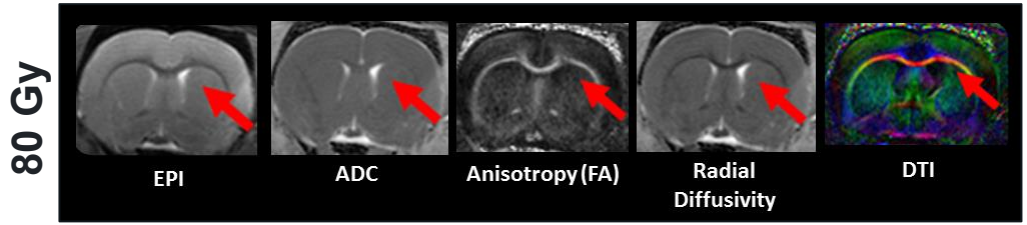
Evaluating the Effect of Radiation Dose on the Rate of Injury Induction



Detection of atrophy by T_2-W MRI

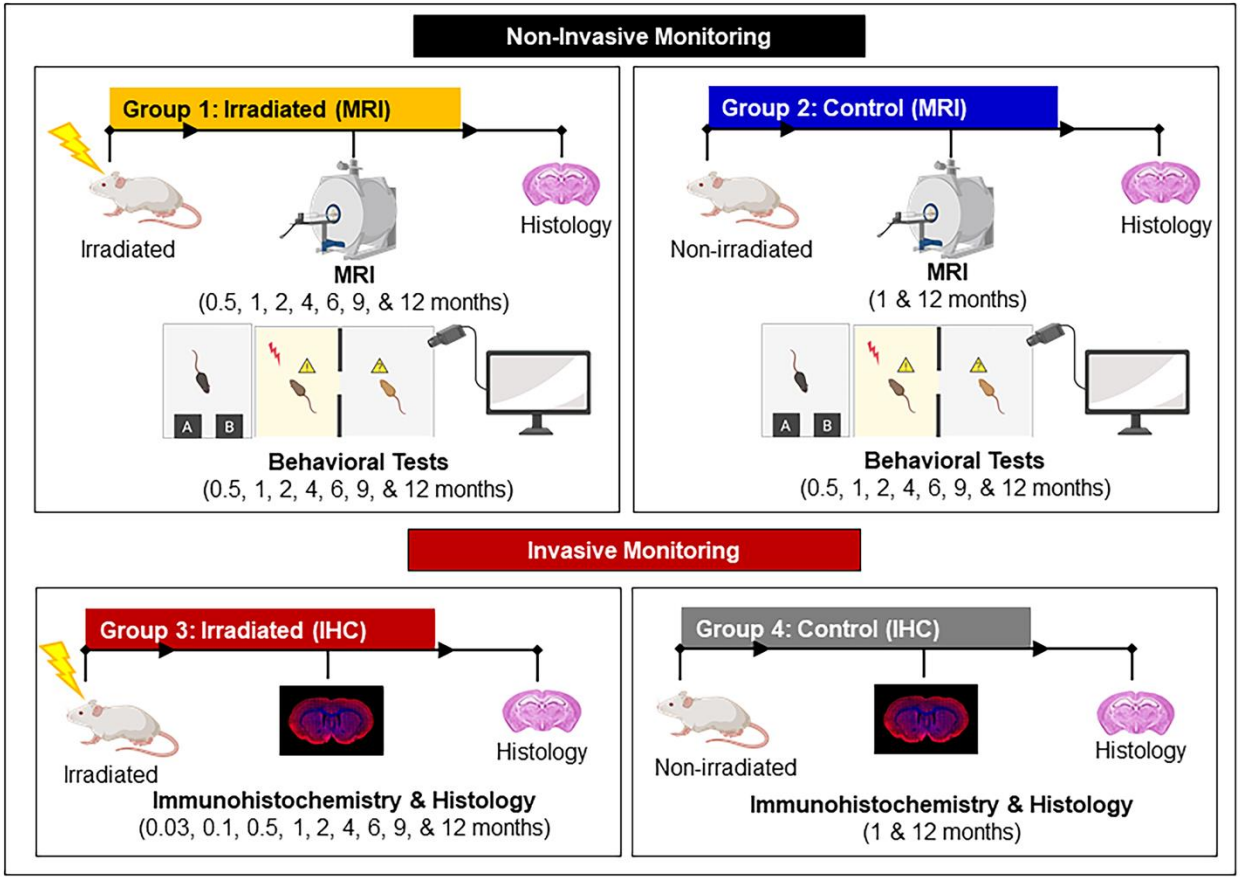
- High dose, without fractionation was used to induce injury at a faster rate
  - Within the lifespan of the mice

Diffusion MRI at 3 months post-irradiation

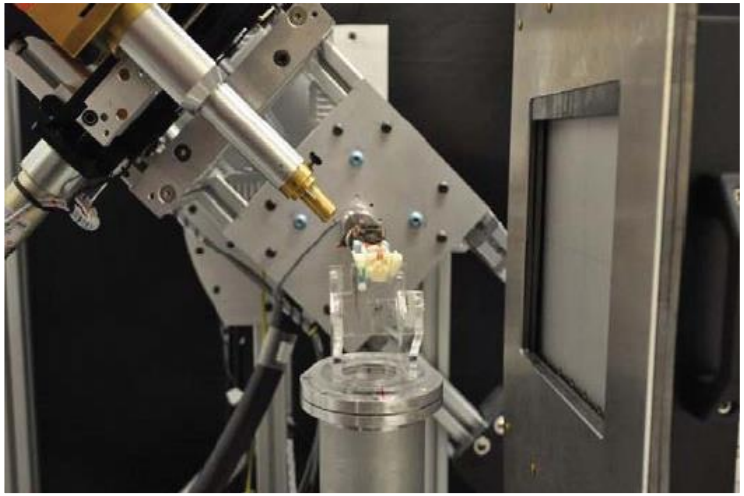


Developing Longitudinal MRI Biomarkers of RIBI in a Preclinical Mouse Model

Experimental Design



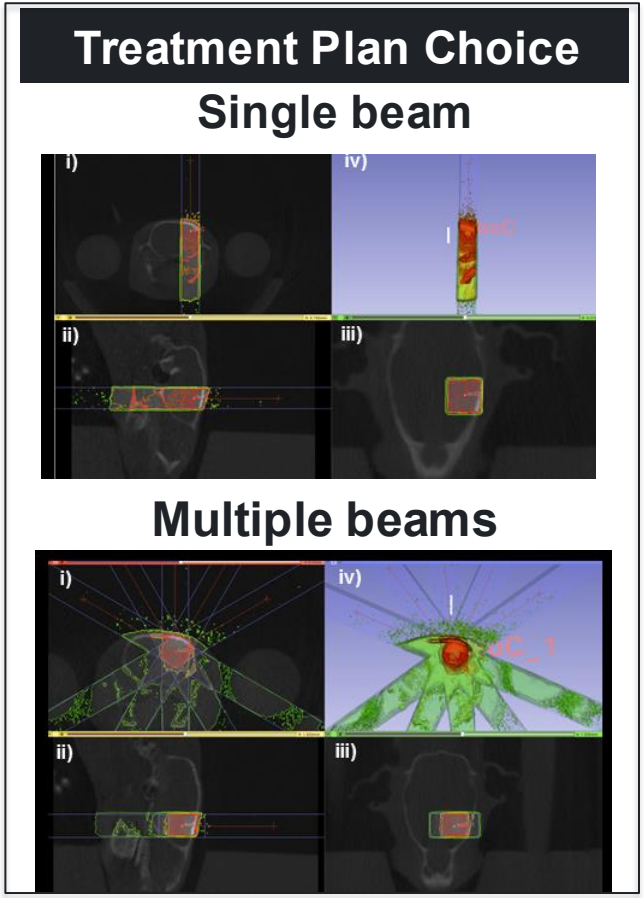
Computed Tomography (CT)-guided Radiotherapy-induced Brain Injury



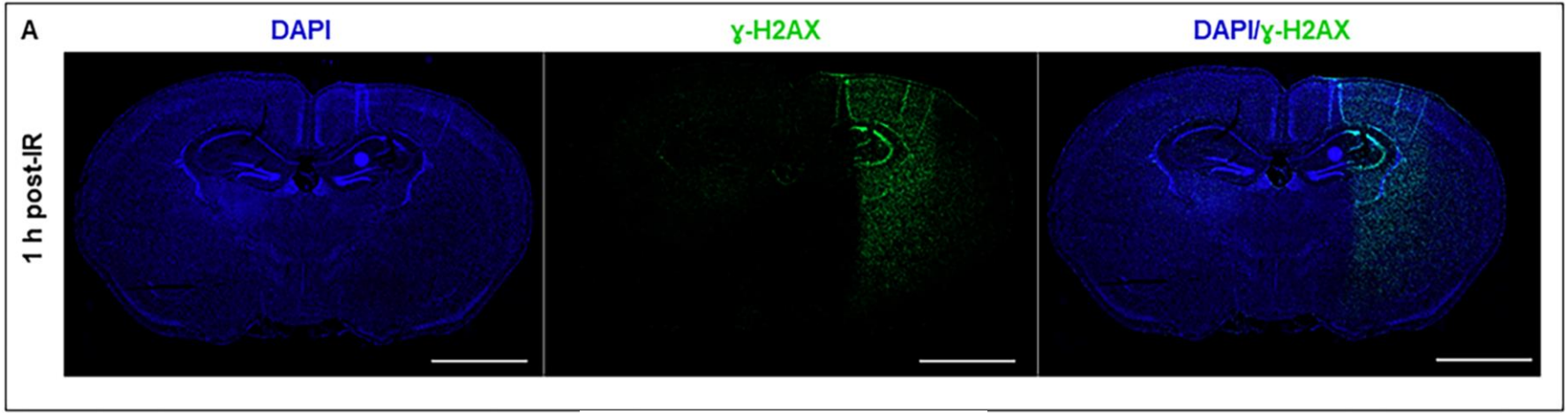
Small animal radiation research platform

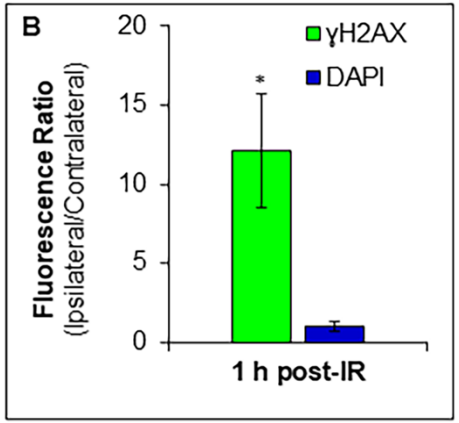
Single dose x-ray irradiation:

- Irradiation sites: hippocampus
- Beam size: 3 x 3 mm
- Beam type: Single (vertical)
- Dose delivery rate: 1.7 Gy/min
- Total dose: 80 Gy

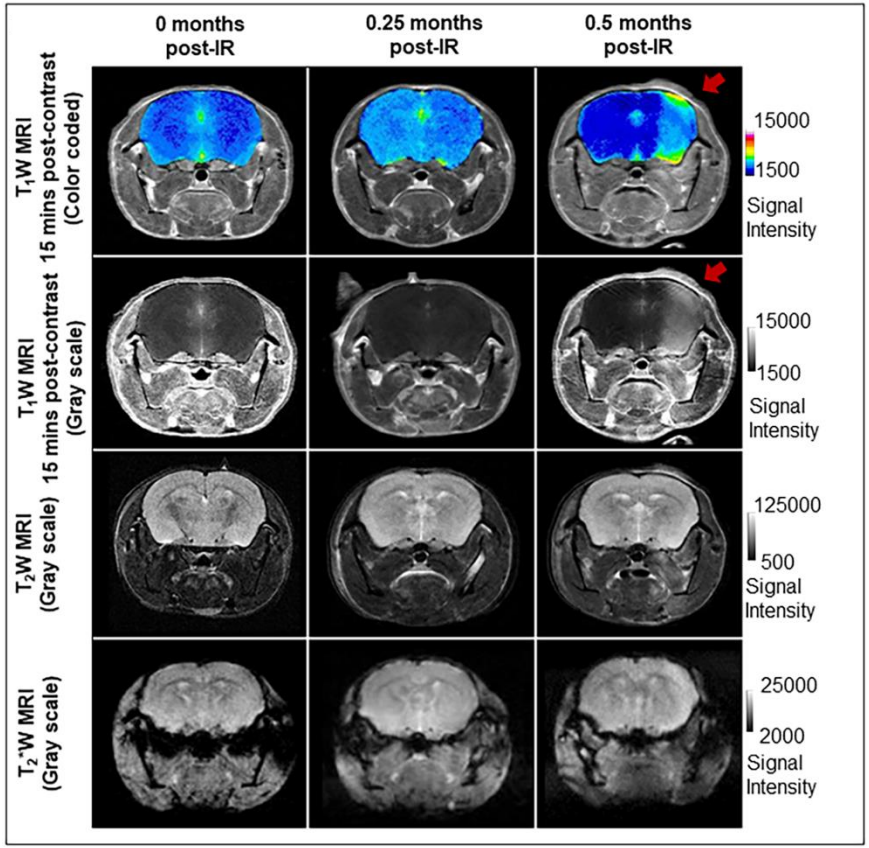


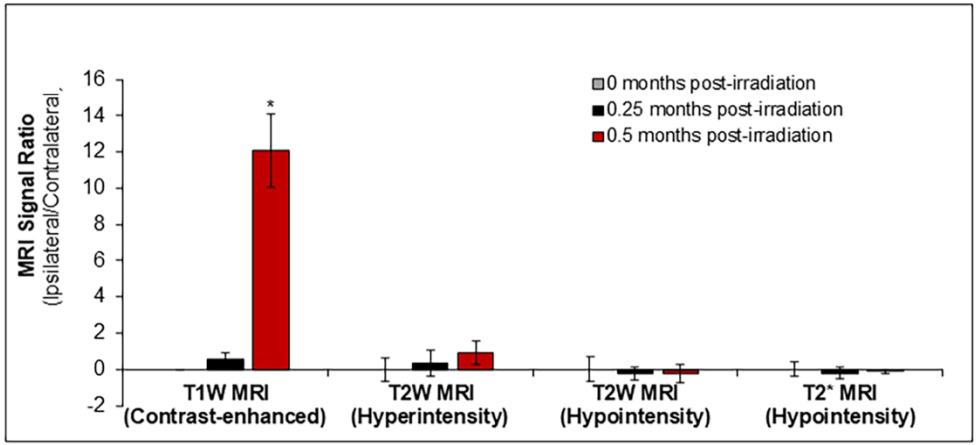
Immunohistochemistry Detects DNA Double Strand Damage 1h After Irradiation



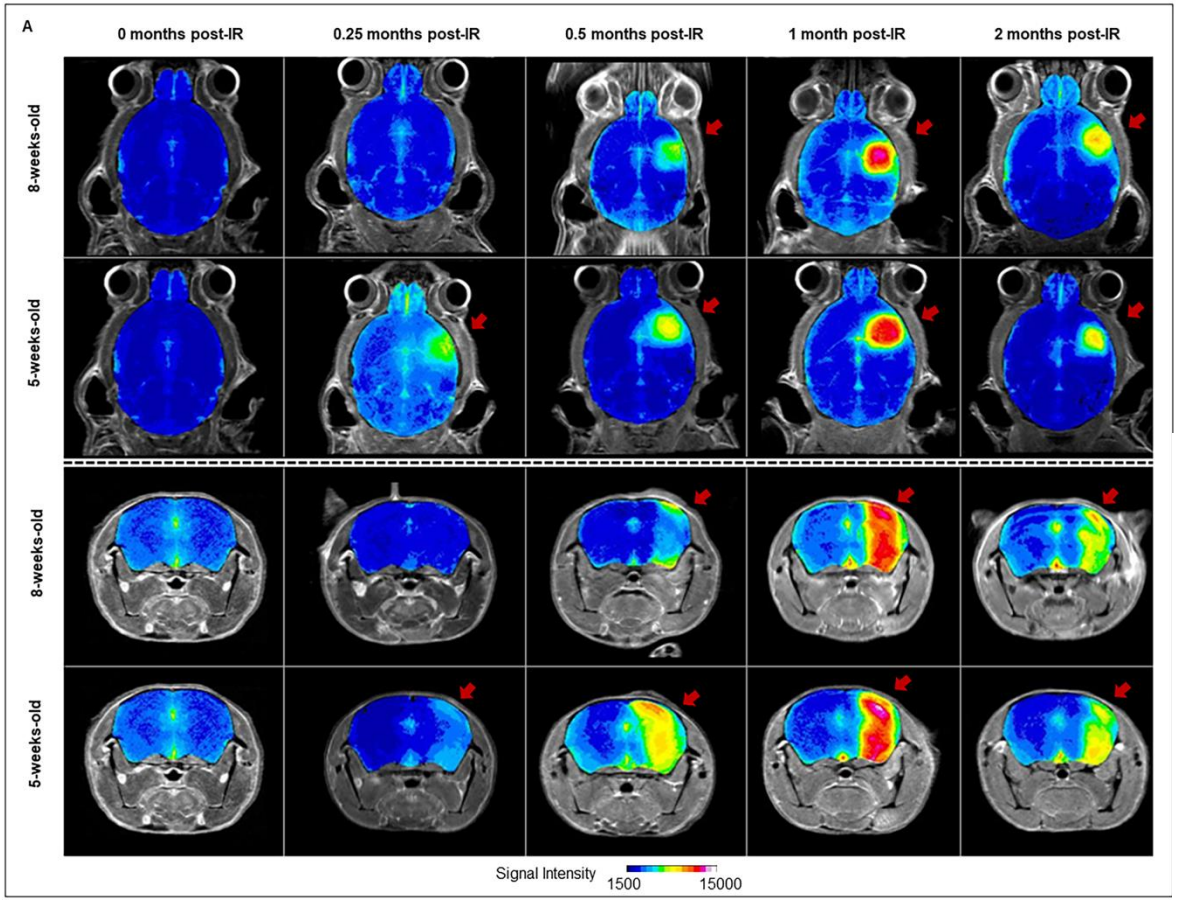


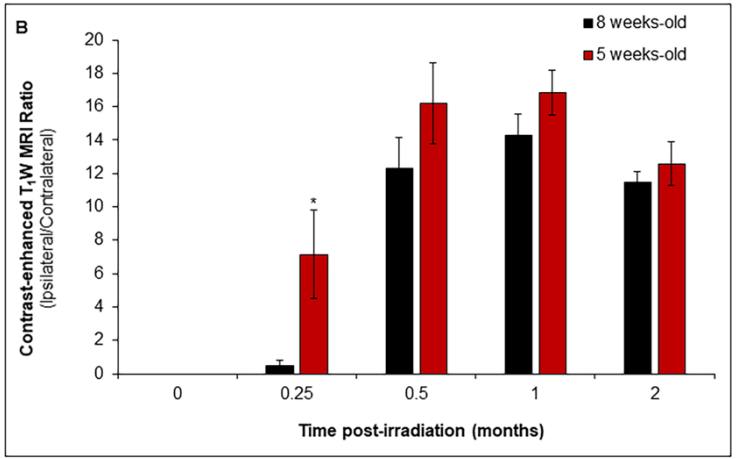
Contrast-enhanced T_1-weighted MRI Detects RIBI Early On



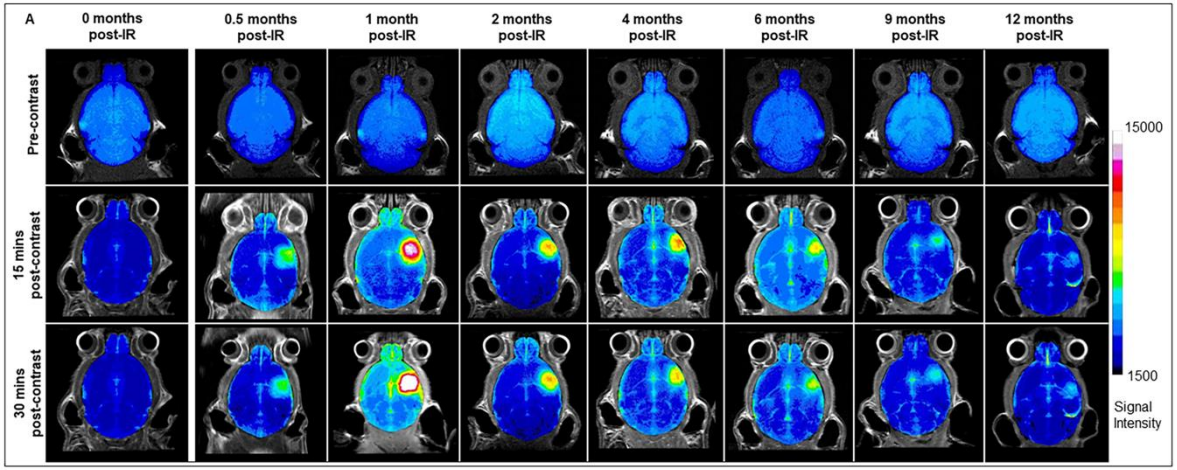


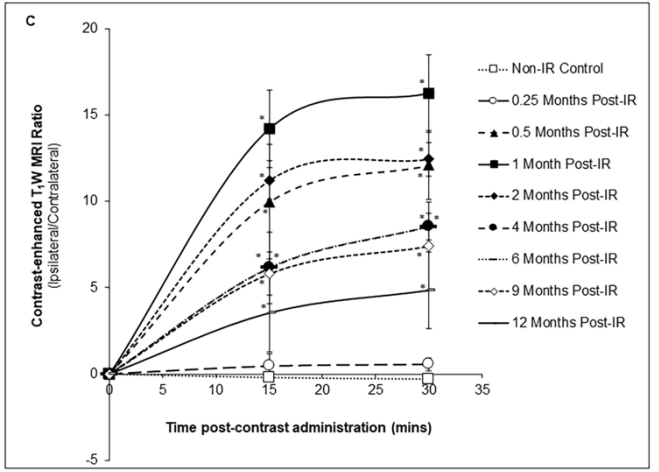
Contrast-enhanced T_1-weighted MRI Detects RIBI Earlier in Mice Irradiated at a Younger Age

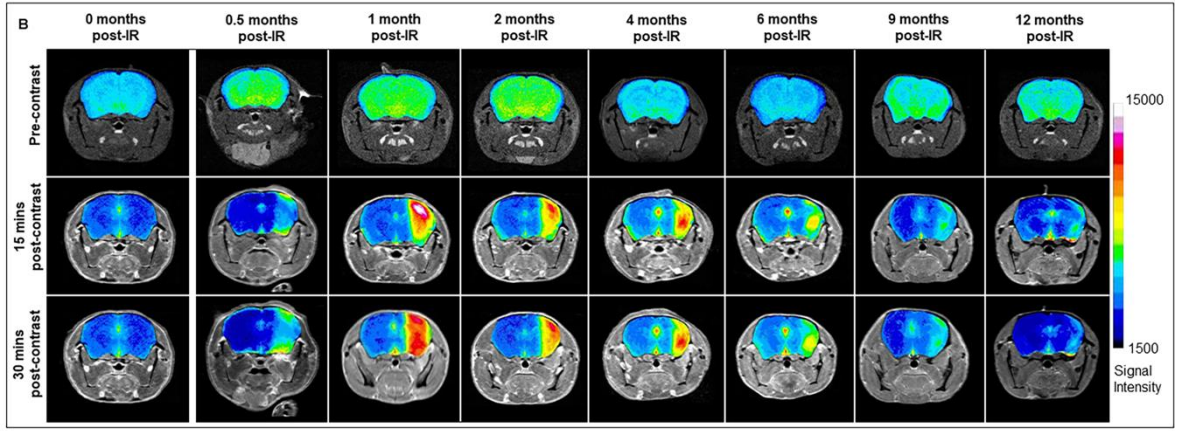


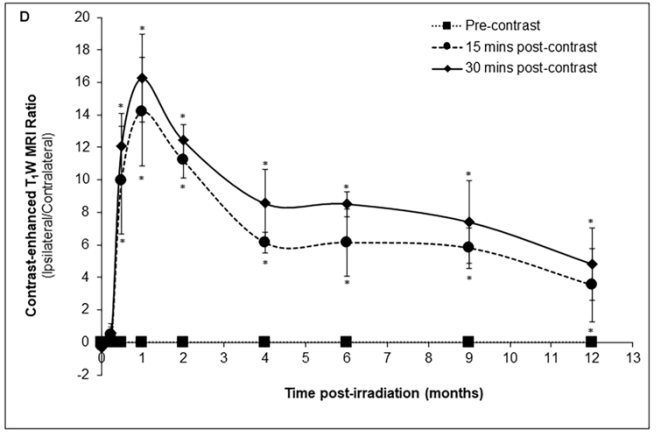


Contrast-enhanced T_1-weighted MRI Detects Changes in Blood Brain Barrier Permeability Post-IR

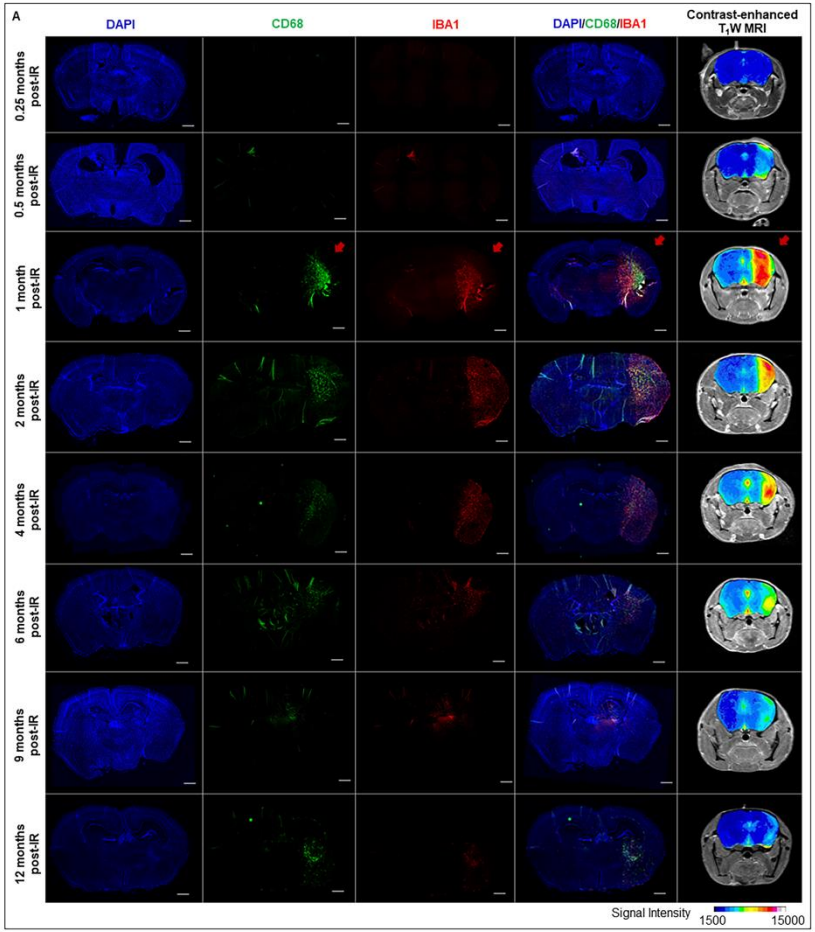


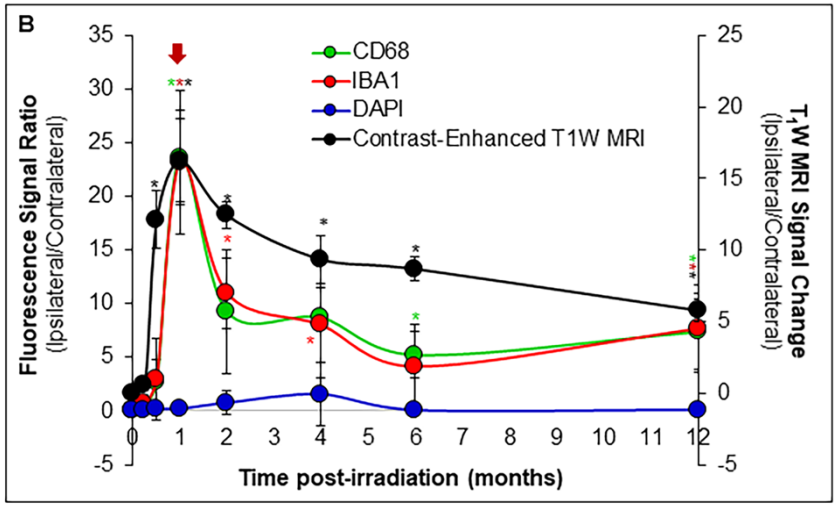




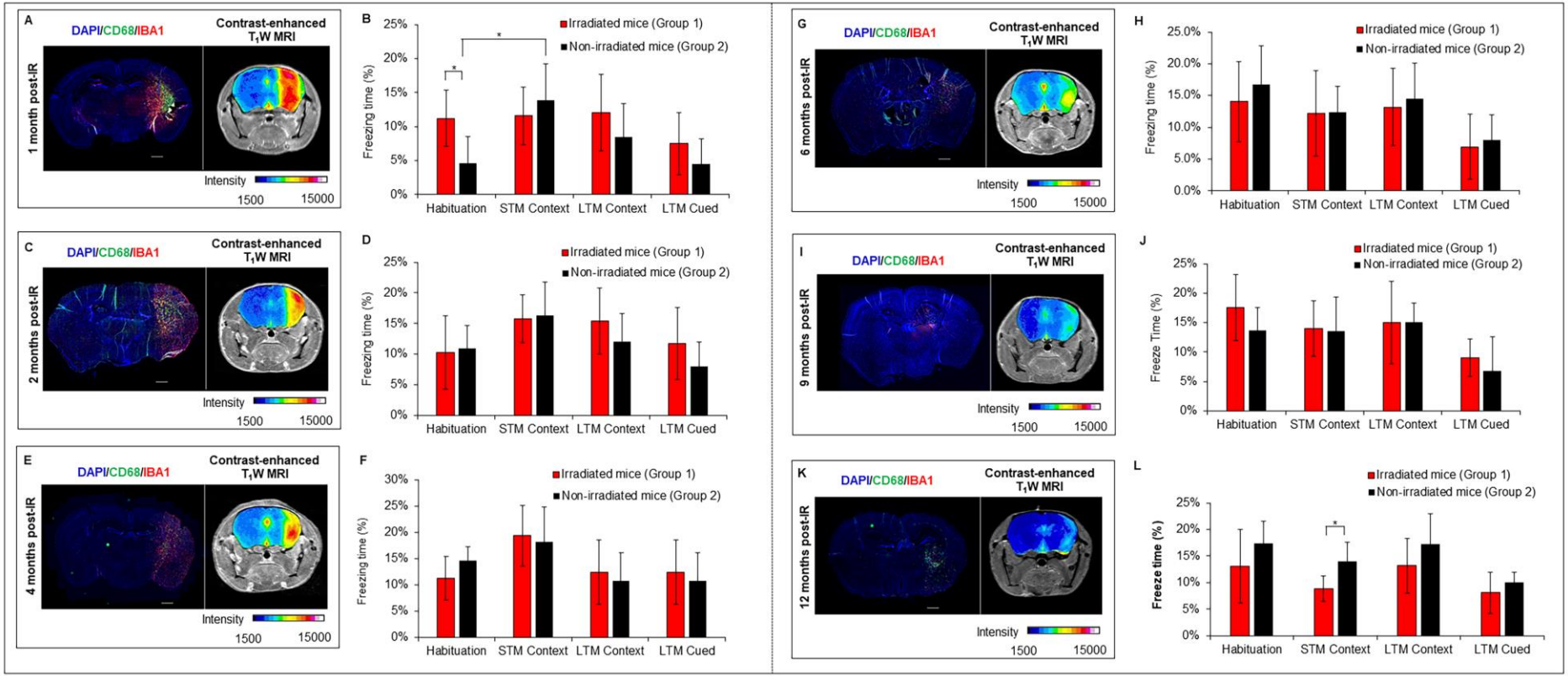


Neuroinflammation and BBB Permeability Peak at the Same Time (@ one-month post-irradiation)

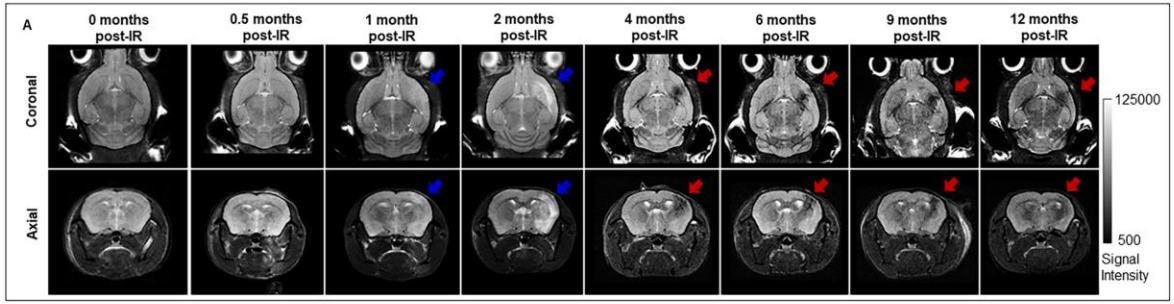


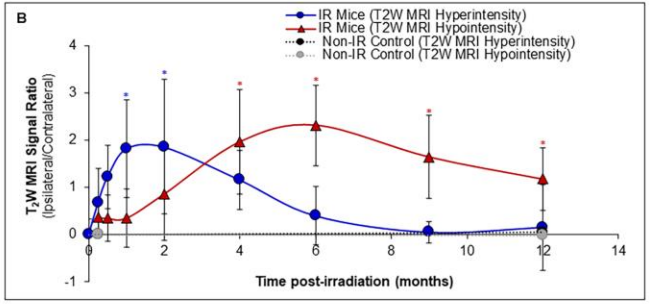


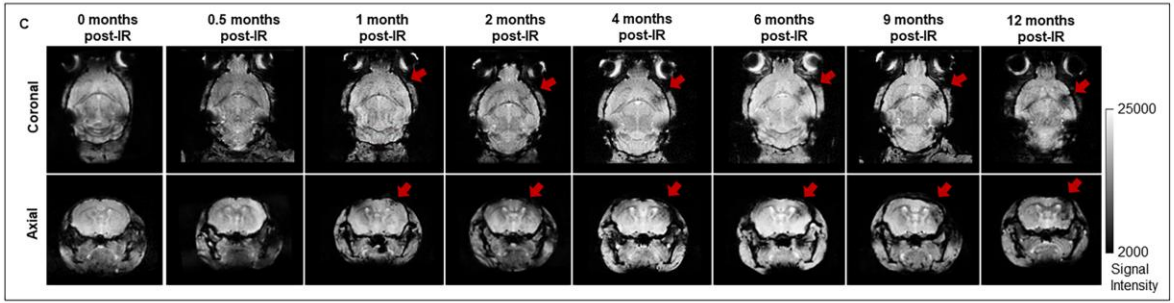
The Onset of Transient Cognitive Impairment Correlates with Peak BBB Permeability and Neuroinflammation

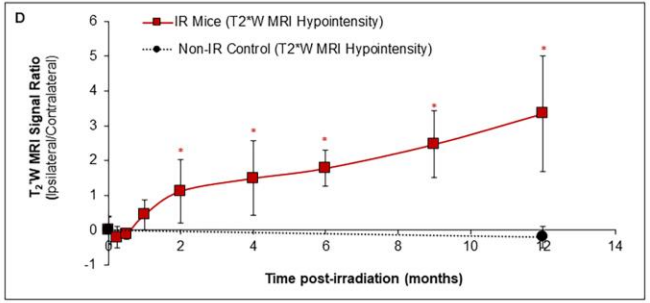


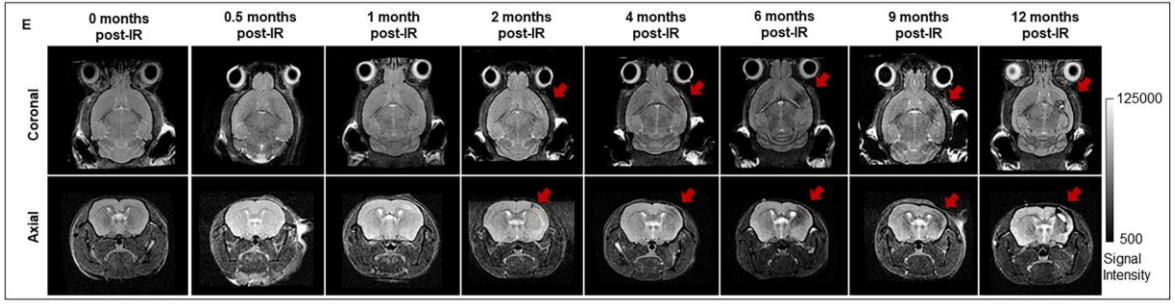
Anatomical (T_2W) & Susceptibility (T_2*W) MRI Detection of Late RIBI

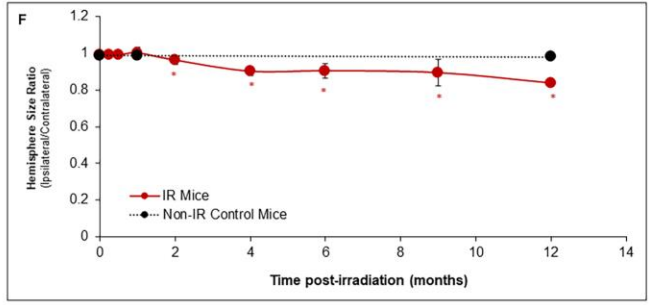




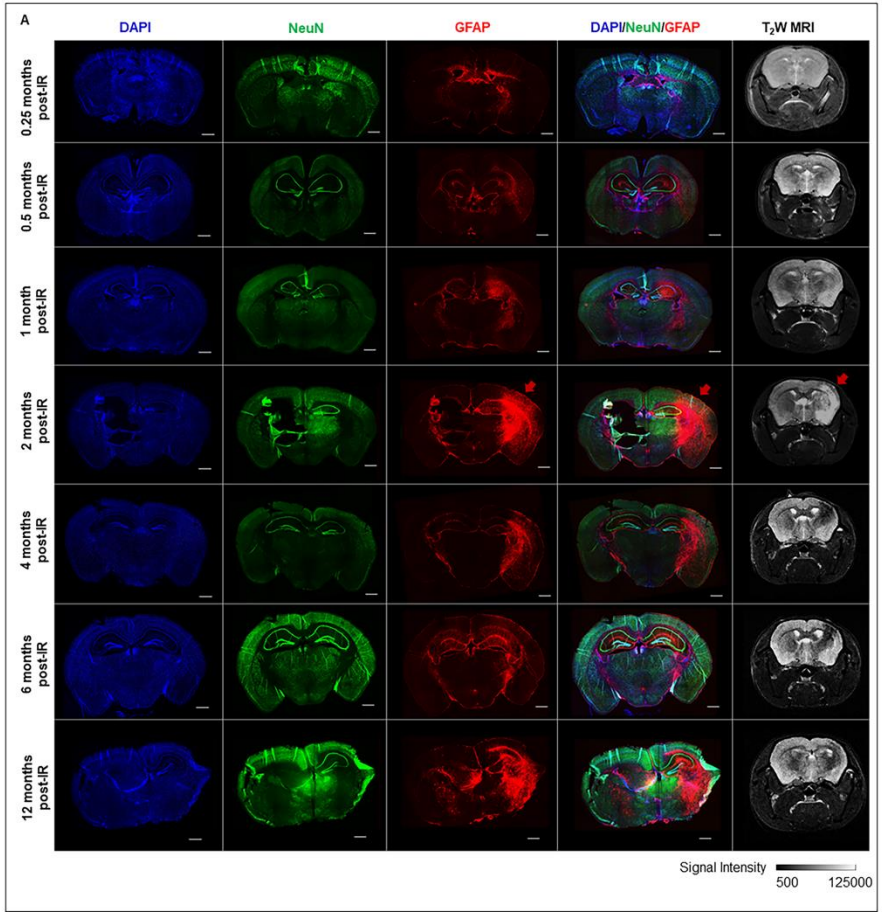


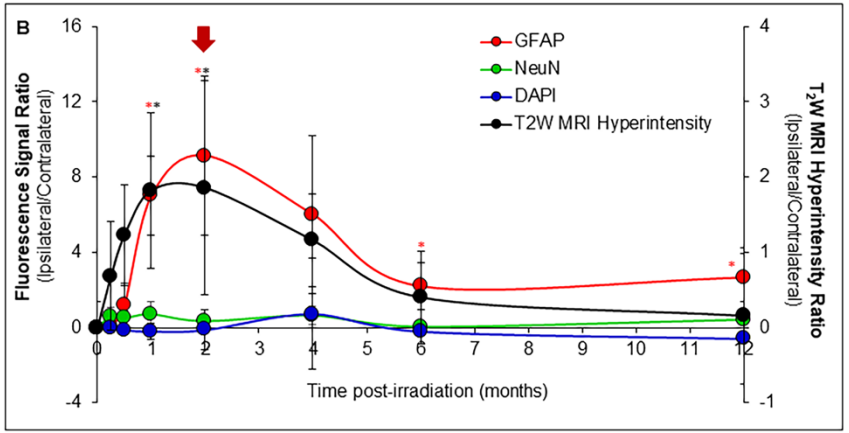




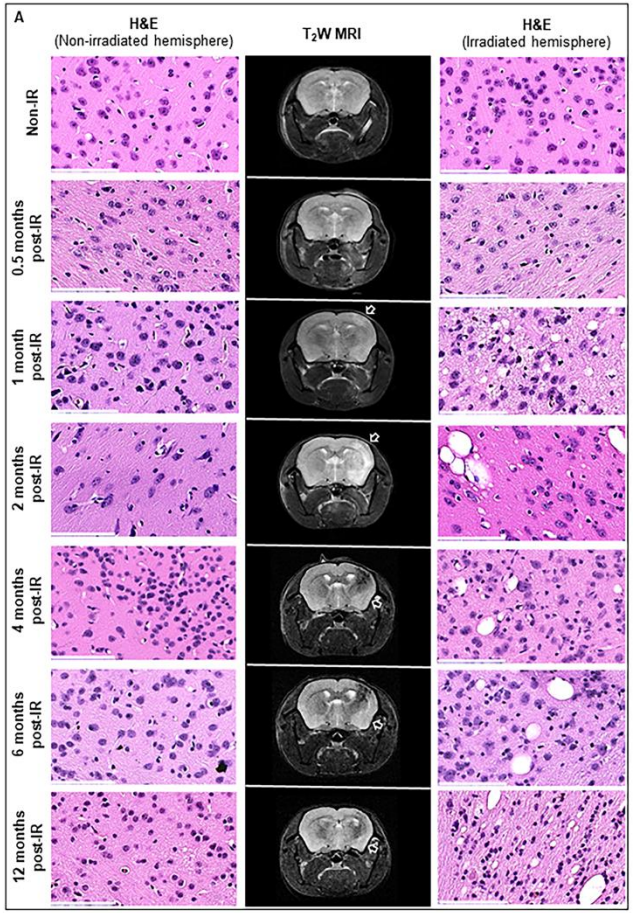


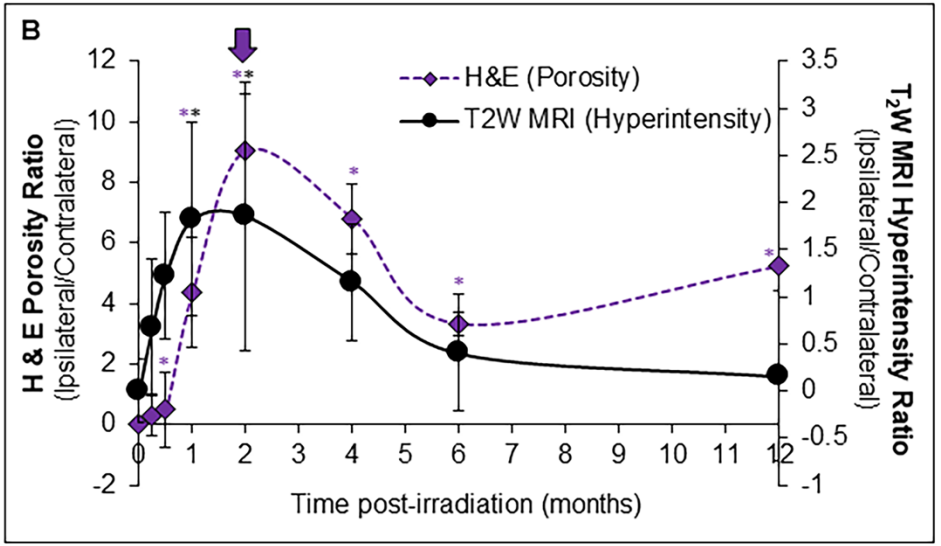
T_2-weigted MRI Hyperintensity Biomarker Correlates Strongly with Astrogliosis



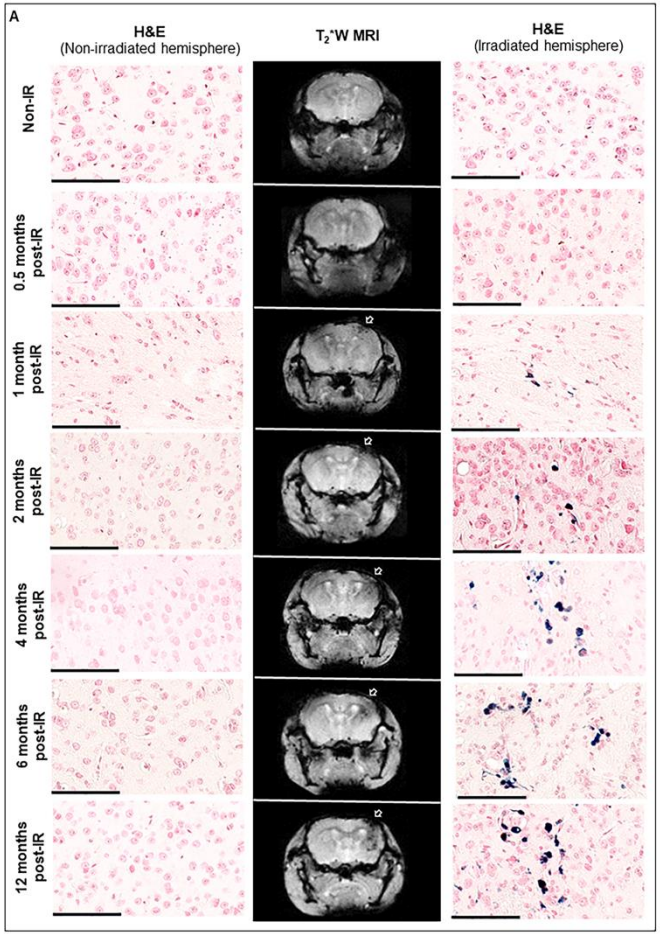


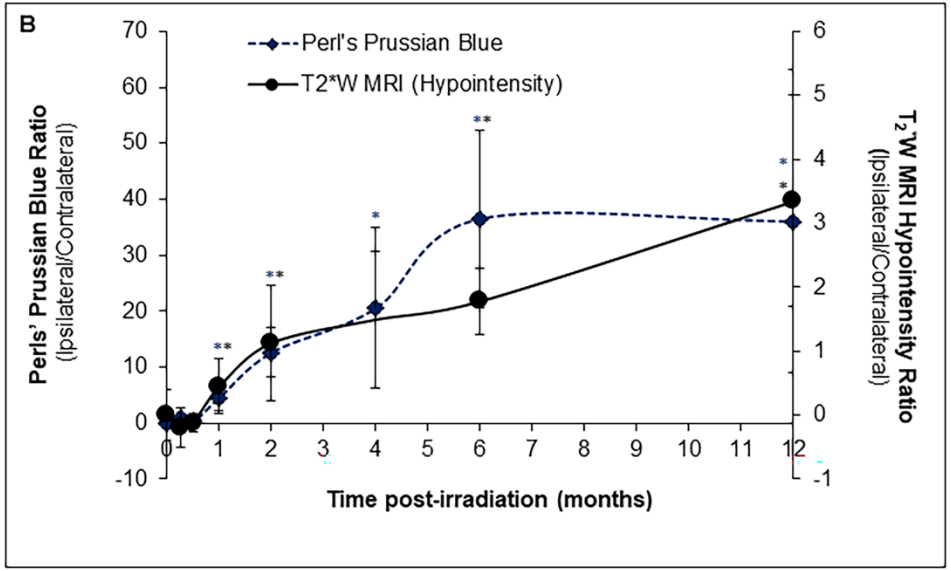
T_2-weigted MRI Hyperintensity Biomarker Also Correlates Strongly with Edema



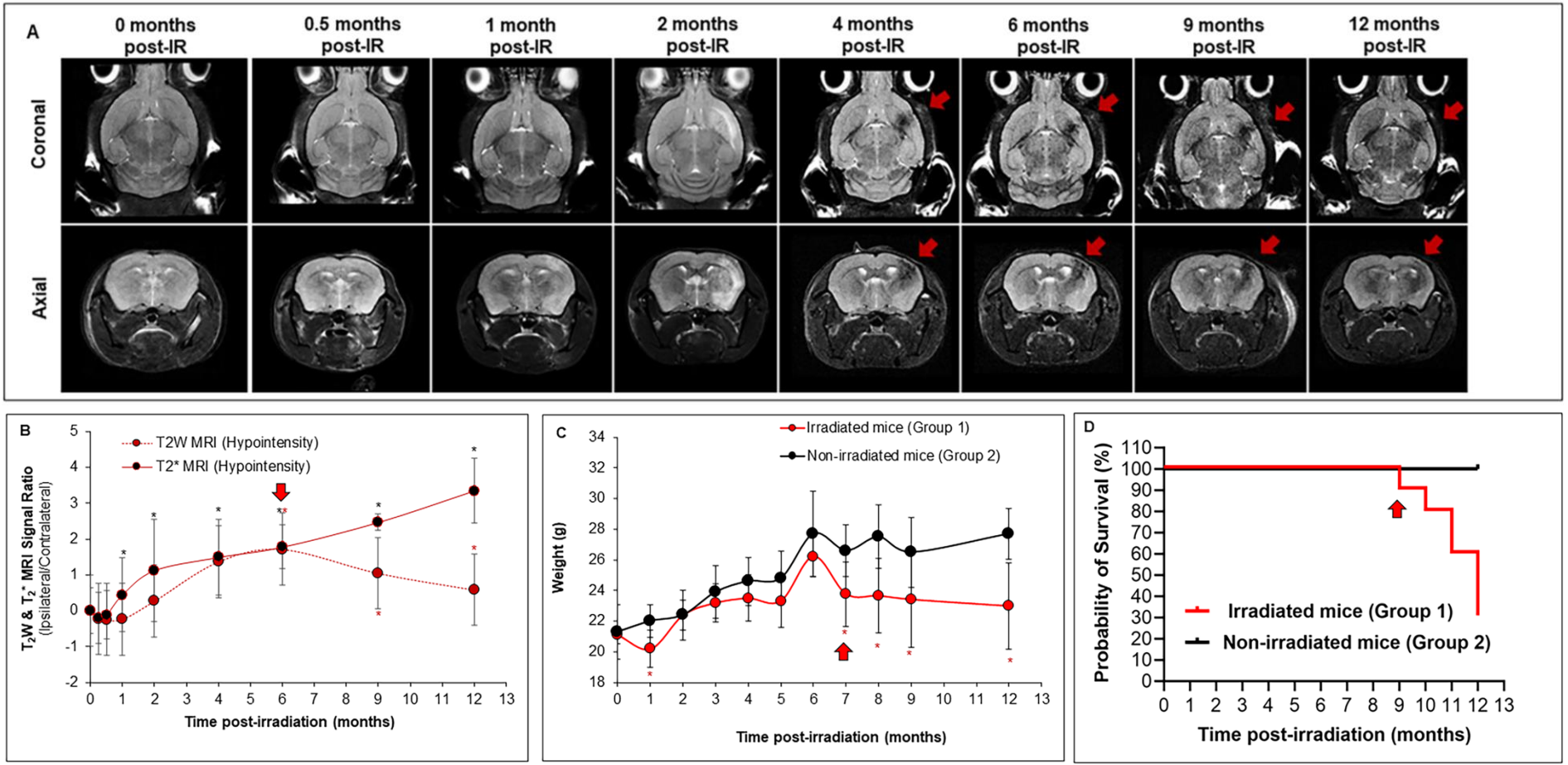


MRI Hypointense Biomarkers Correlate with Iron Deposits From Late Vascular Damage

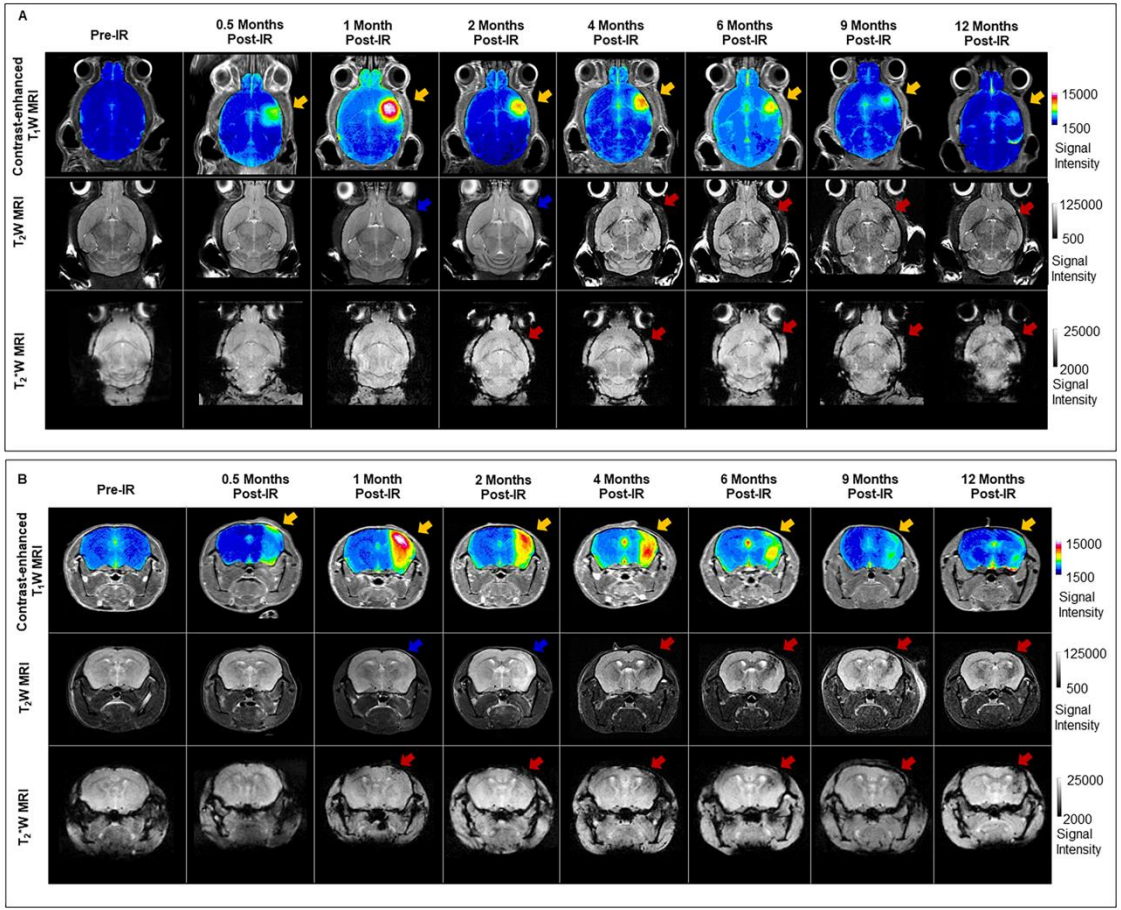


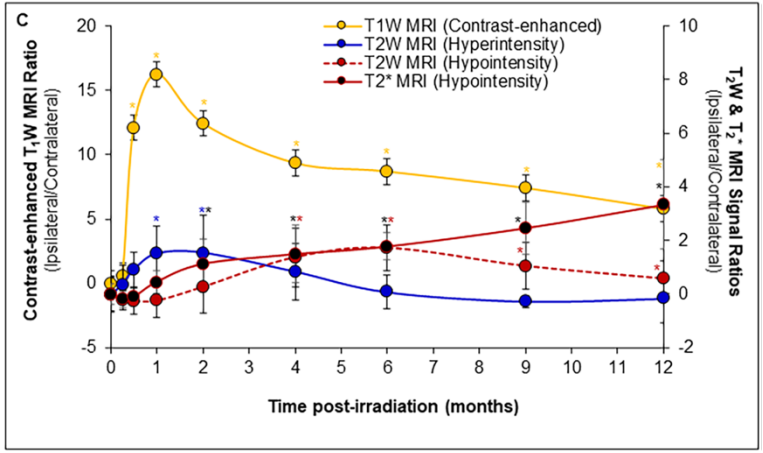


T_2-weighted MRI Hypointense Biomarker Predicts Poor RIBI Outcomes

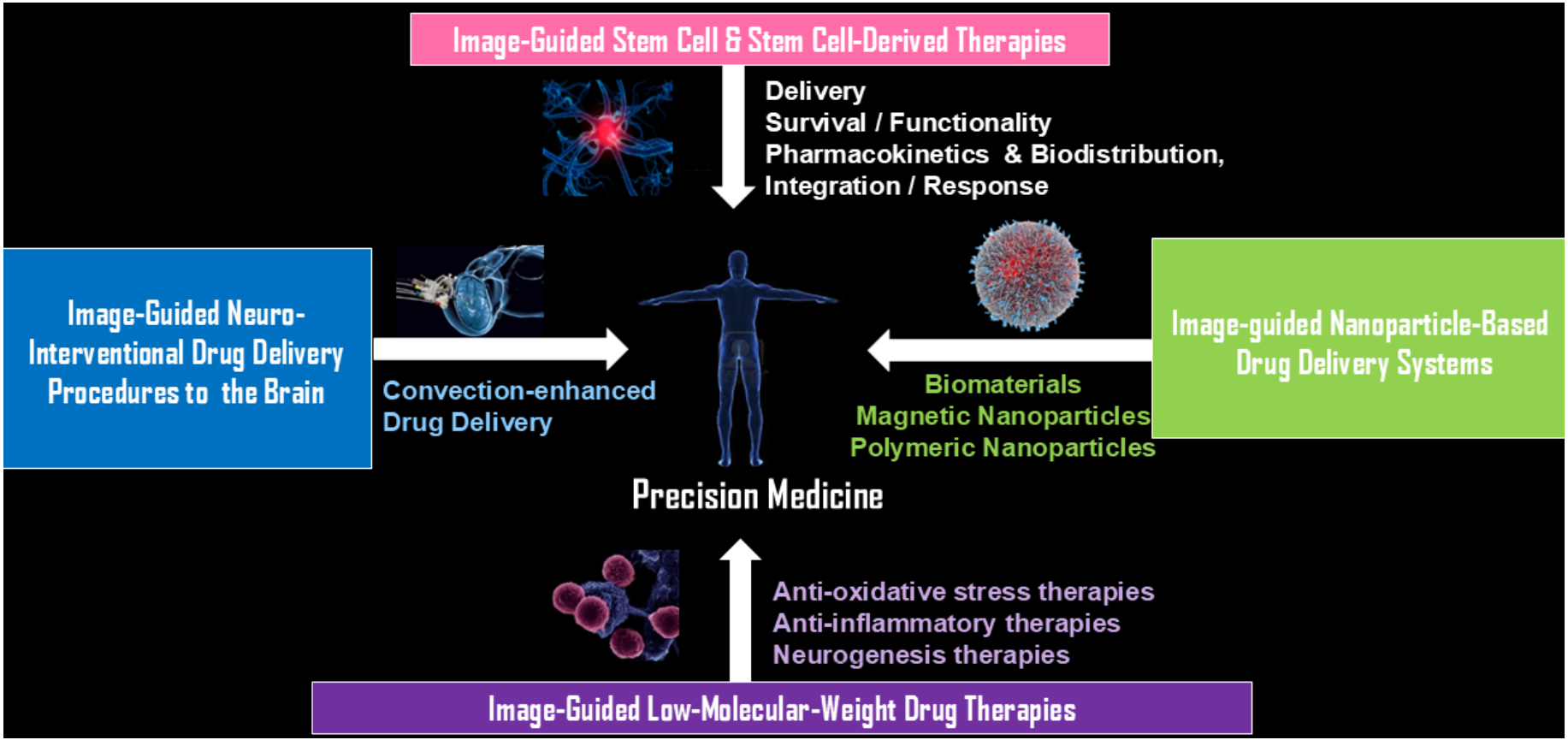


MRI Biomarker Summary





Using MRI Biomarkers to Evaluate Potential RIBI Therapies



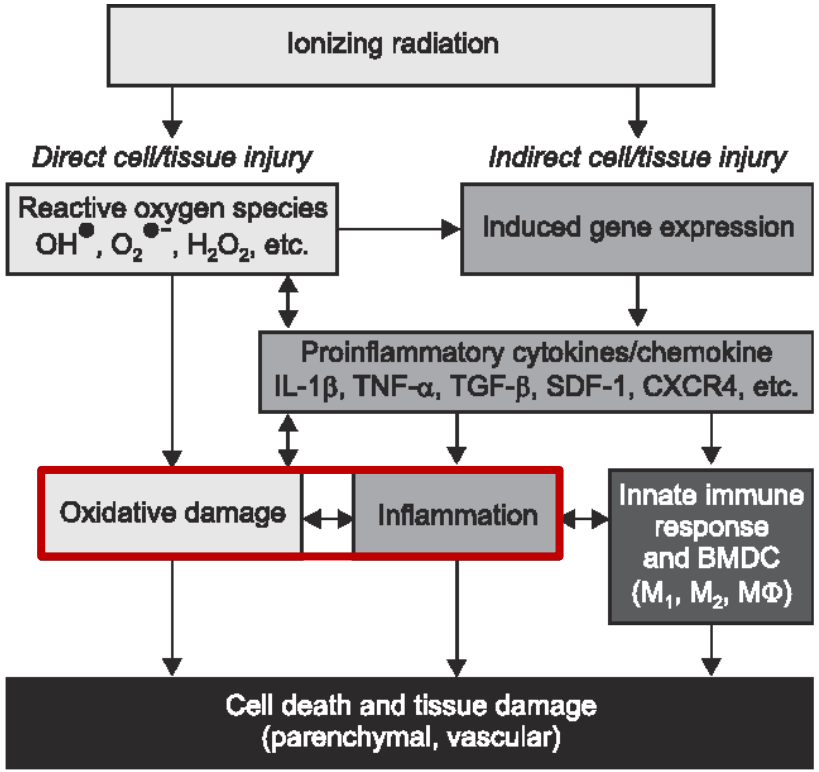
Utilizing the Developed MRI Biomarkers to Evaluate Potential RIBI Therapies in Preclinical Rodent Models

Oxidative stress-responsive nanotheranostic agents

Identifying Potential Therapeutic Targets of RIBI

Key Drivers of RIBI

- Oxidative stress
- Neuroinflammation



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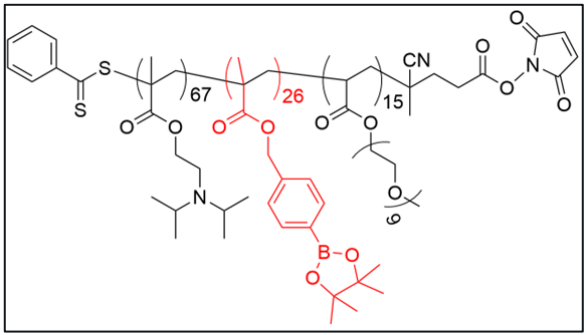
Developing Oxidative Stress-responsive Neuroprotective Agents

Objective: To develop oxidative stress-responsive neuroprotective agents:

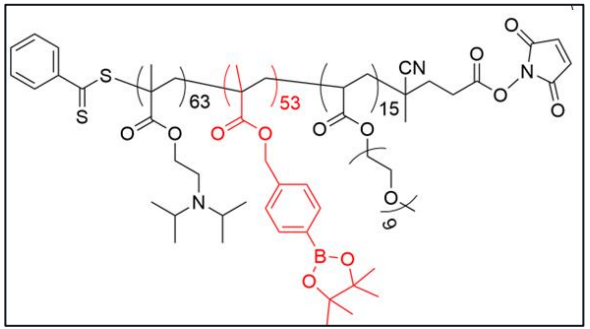
1. To reduce chronic oxidative stress and neuroinflammation;
2. To improve RIBI outcomes

Agent Design: Two oxidative stress-responsive biocompartible polymers:

- Possessing varied phenylboronic acid pinacol ester (BAPE) moieties
- To scavenge reactive oxygen species (ROS) were developed



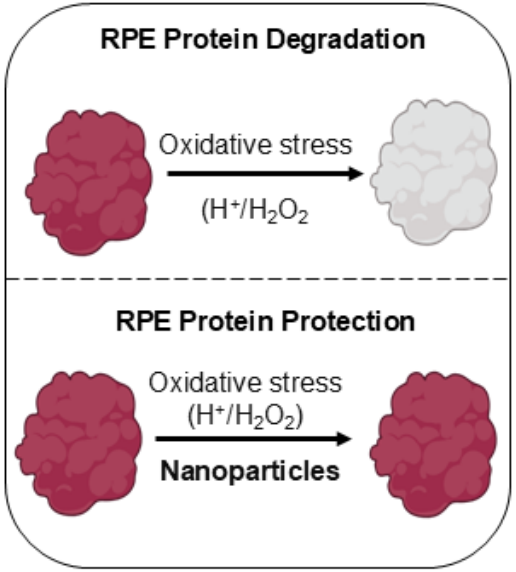
P2a



P2b

Both Agents Protect R-phycoerythrin Protein from Degradation Under Oxidative Stress

a



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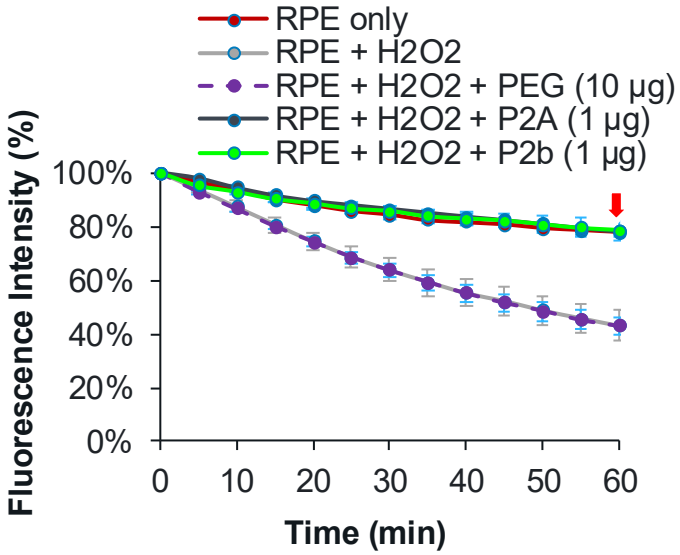

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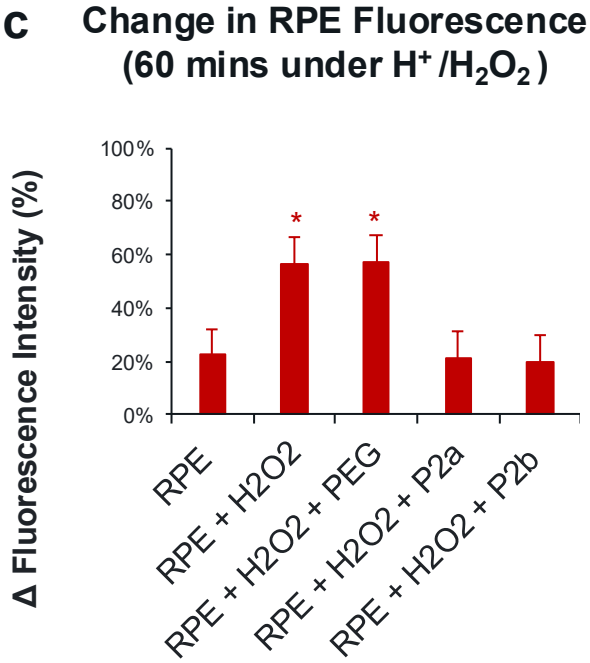
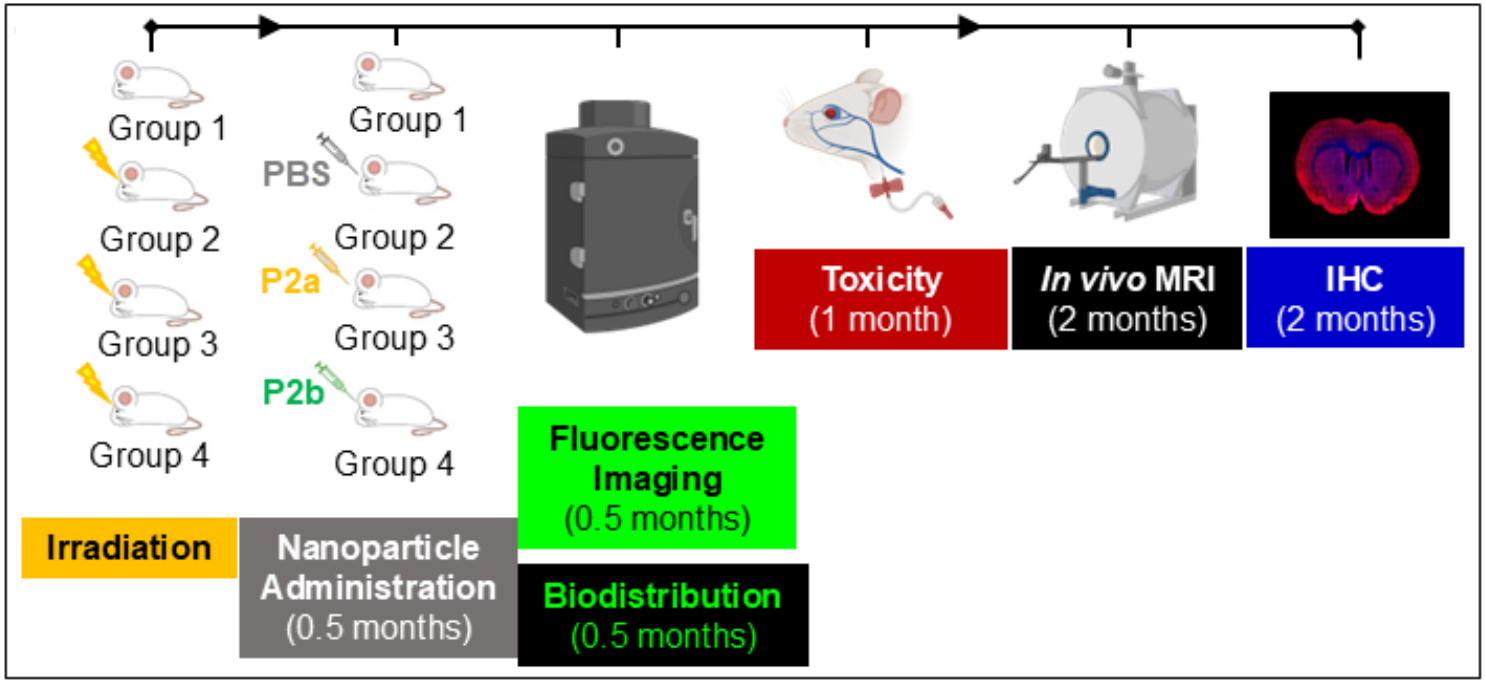
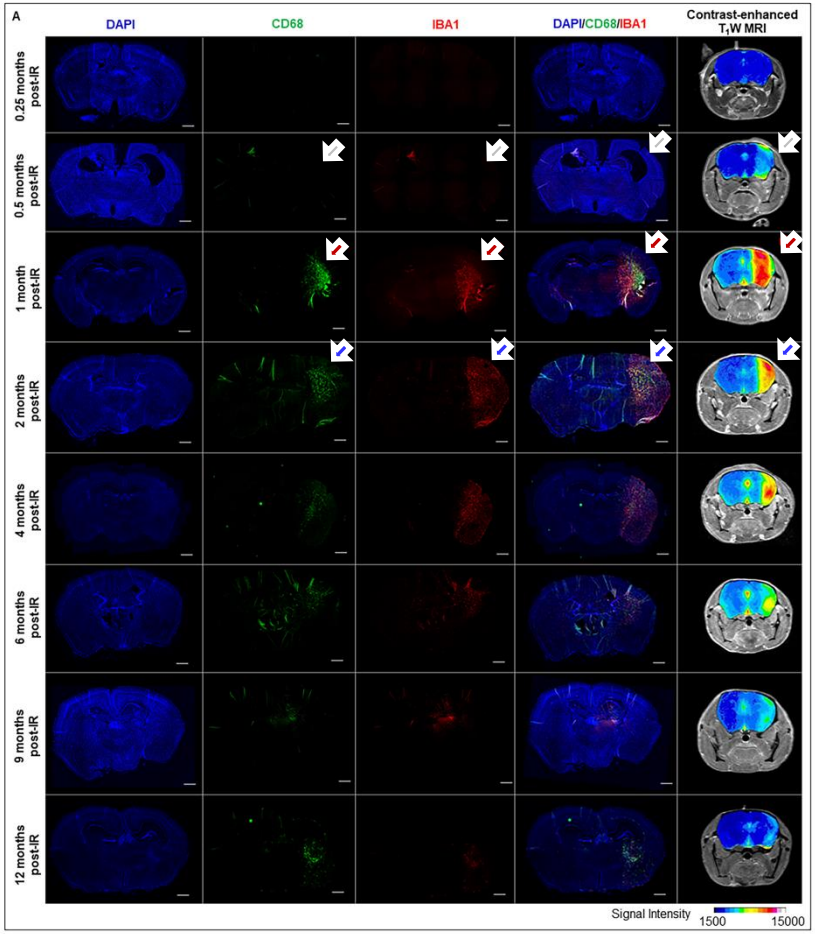


Evaluating Nanoparticle Efficacy in a Preclinical Mouse Model of RIBI Using the MRI Biomarkers



Determining the Best Time Points to Administer the Nanoparticles and to Evaluate Their Efficacies



Best NP administration time point

- 2 weeks post-irradiation

Rationale:

- BBB permeable for NP delivery
- No inflammation detected until later

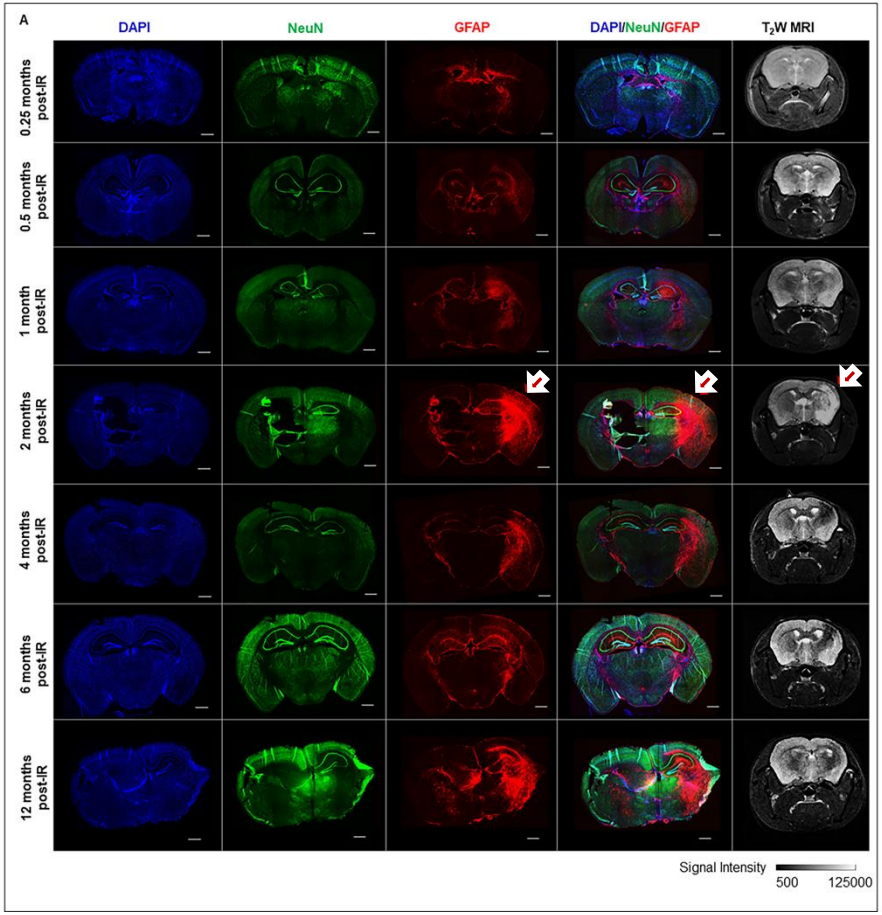
Best NP evaluation time point

- 2 months post-irradiation

Rationale:

- Neuroinflammation still detected

Determining the Best Time Points to Evaluate Nanoparticle Early Efficacies



Astrogliosis is induced by neuroinflammation

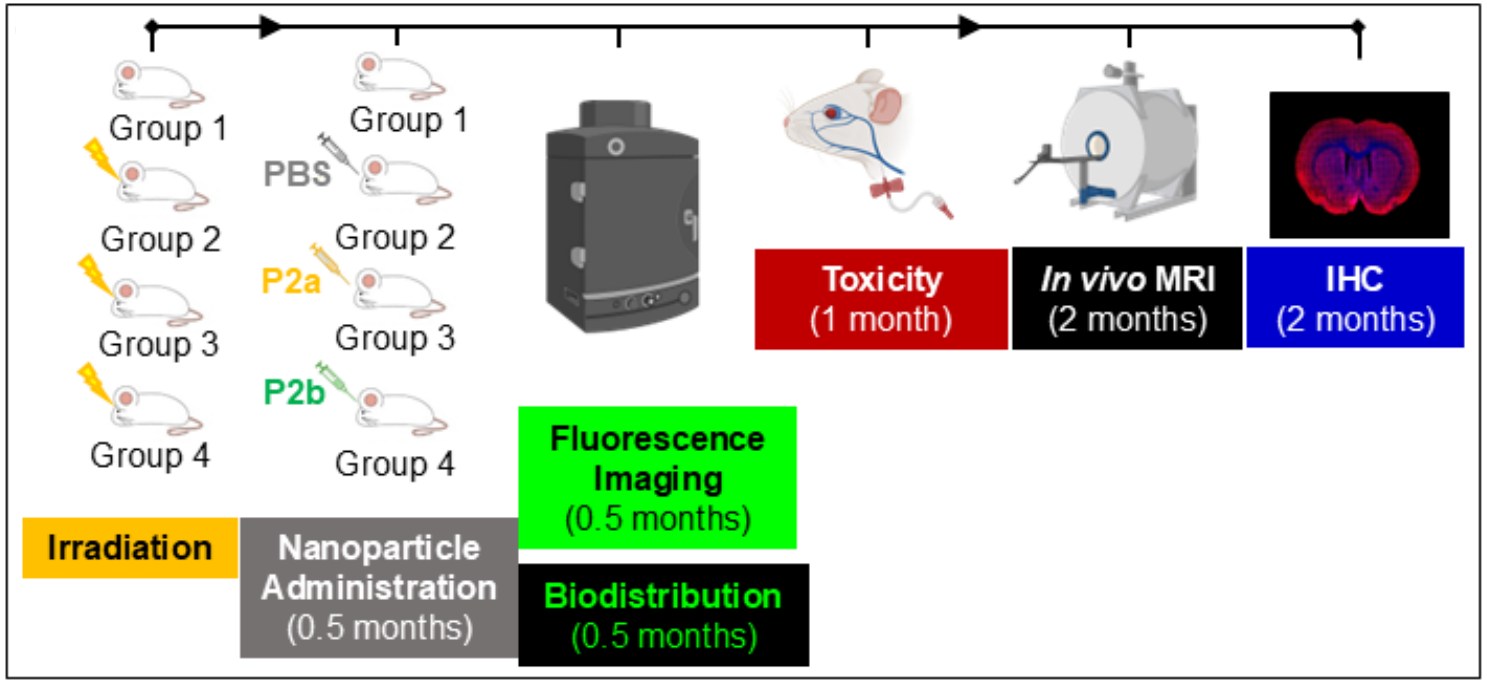
Best NP evaluation time point

- 2 months post-irradiation

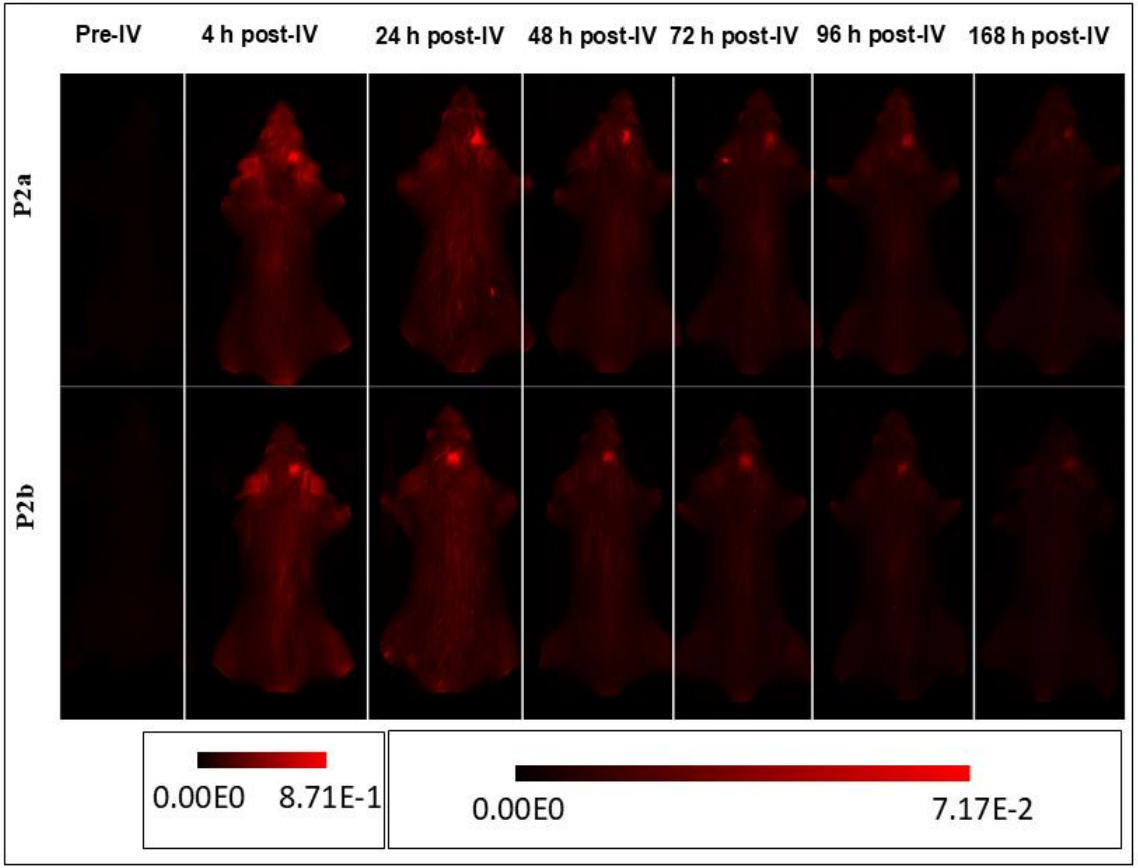
Rationale:

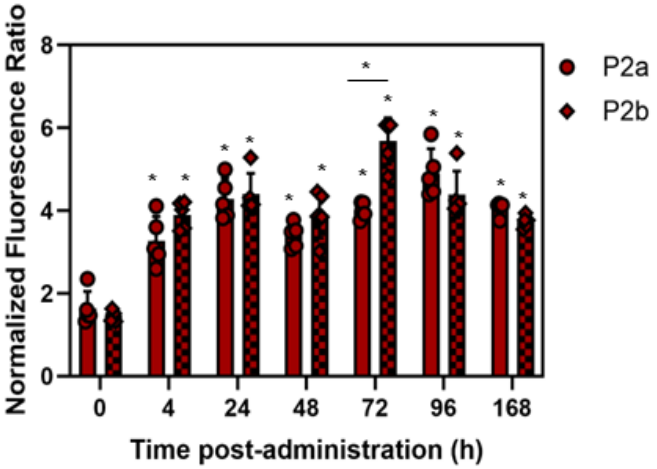
- Maximum astrogliosis detected

Evaluating Nanoparticle Efficacy in a Preclinical Mouse Model of RIBI Using the MRI Biomarkers

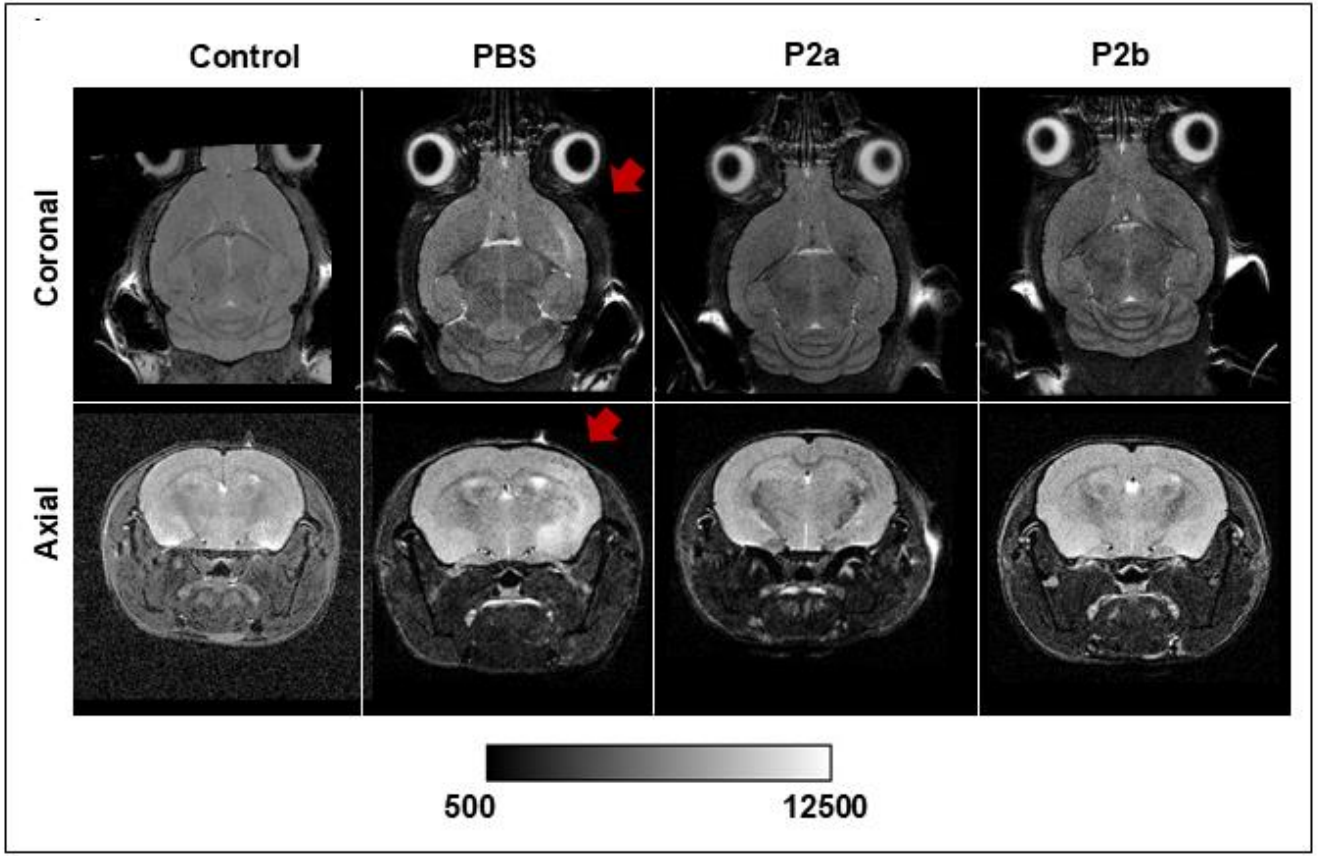


Nanoparticles Accumulate Specifically at the Site of Brain Injury (2 Weeks Post-Irradiation)

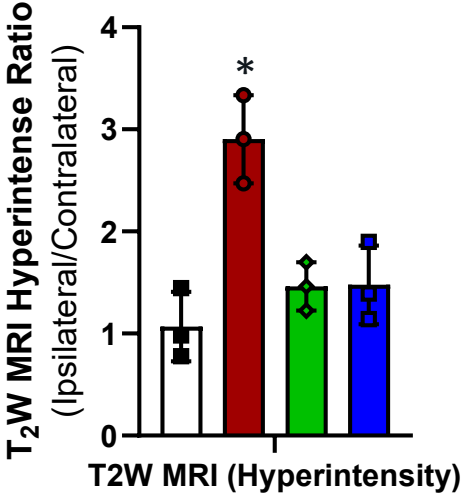




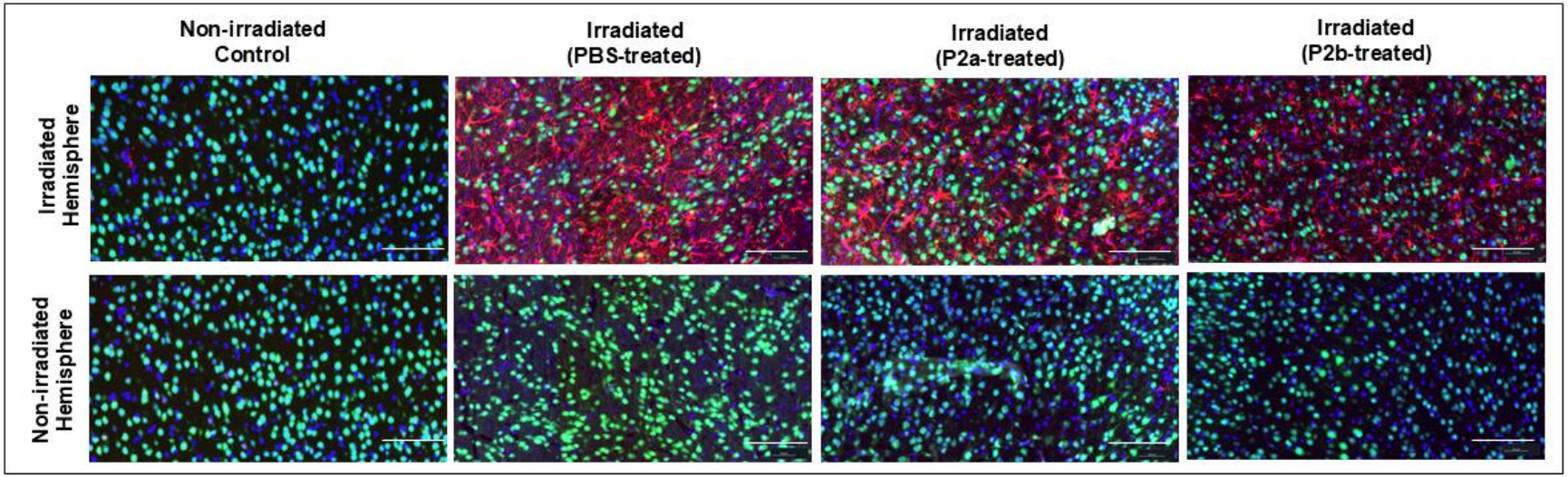
Nanoparticles Reduce Edema at 2 Months Post-Irradiation

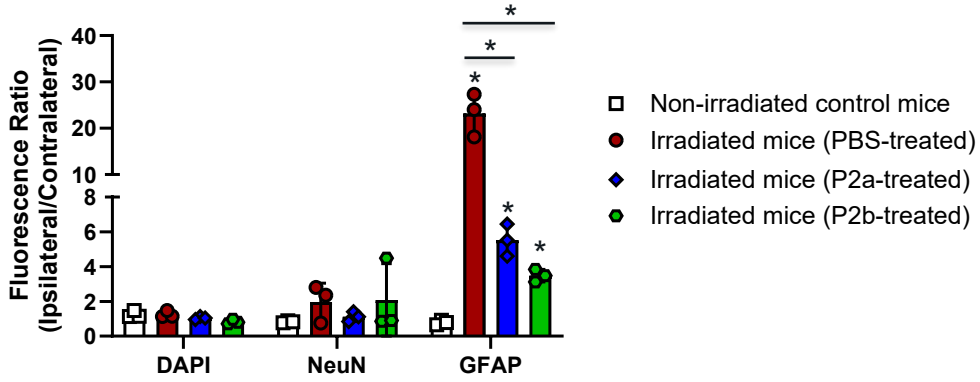


- Non-irradiated control mice
- Irradiated mice (PBS-treated)
- Irradiated mice (P2a-treated)
- Irradiated mice (P2b-treated)

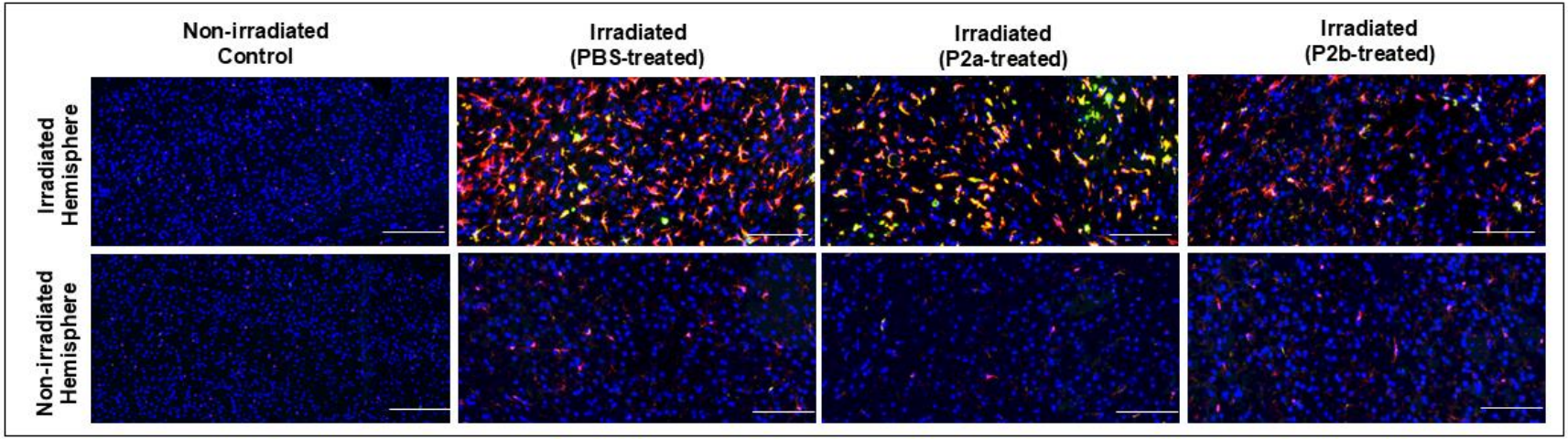


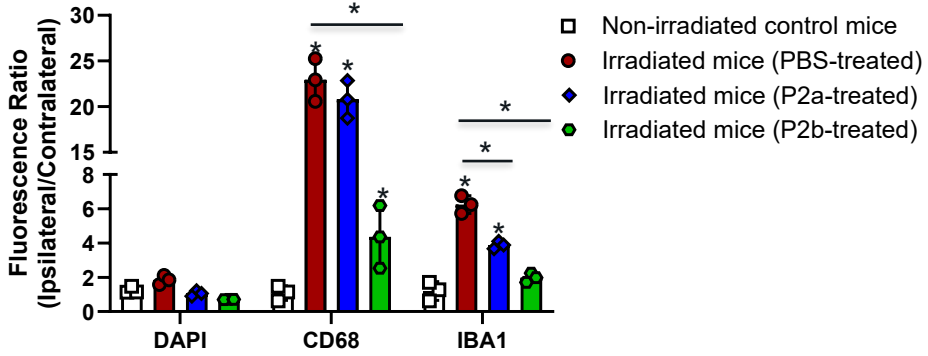
Nanoparticles Reduce Astrogliosis at 2 Months Post-Irradiation



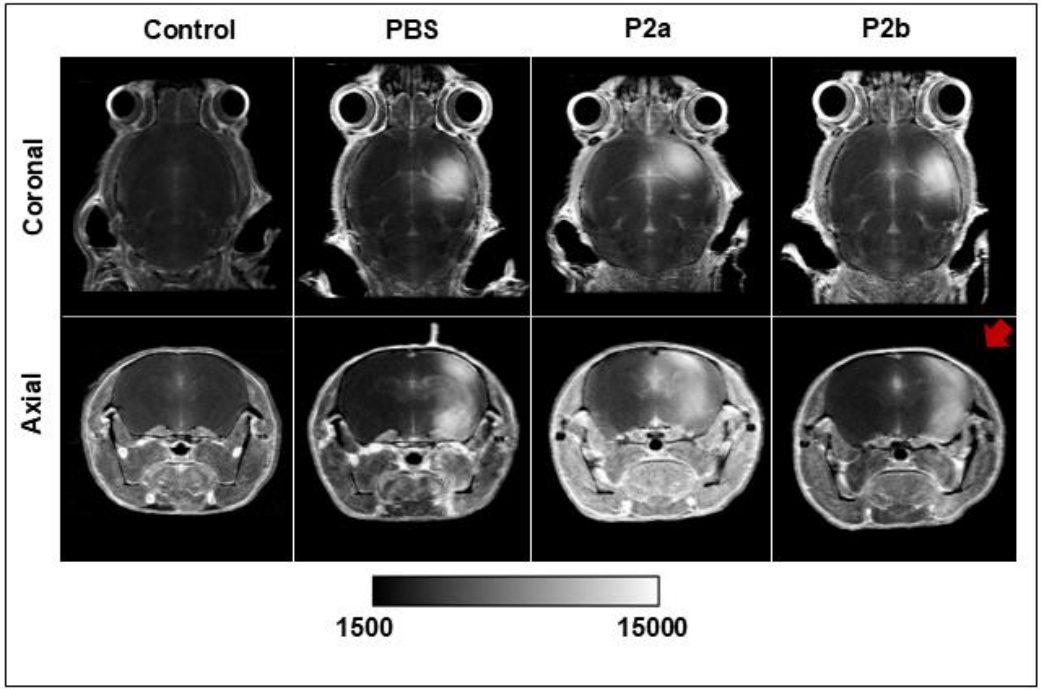


Nanoparticles Reduce Neuroinflammation at 2 Months Post-Irradiation

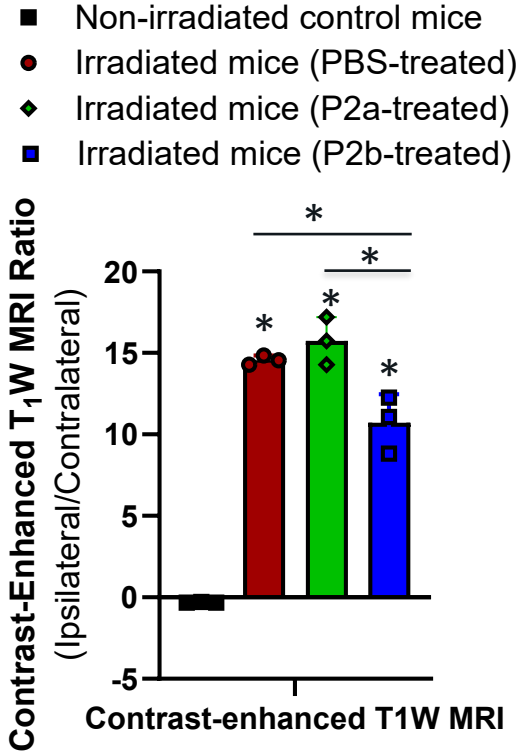




Nanoparticles Reduce BBB Permeability at 2 Months Post-Irradiation



- P2b had 53 ROS scavengers
- P2a had 26 ROS scavengers

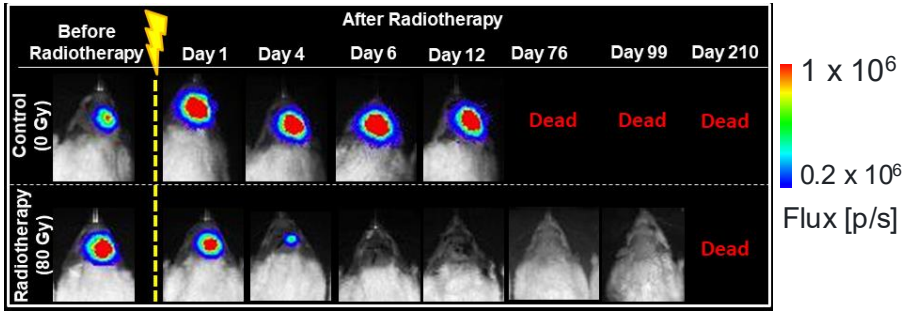


Utilizing the Developed MRI Biomarkers to Evaluate Potential RIBI Therapies in a Tumor-Bearing Preclinical Rodent Model

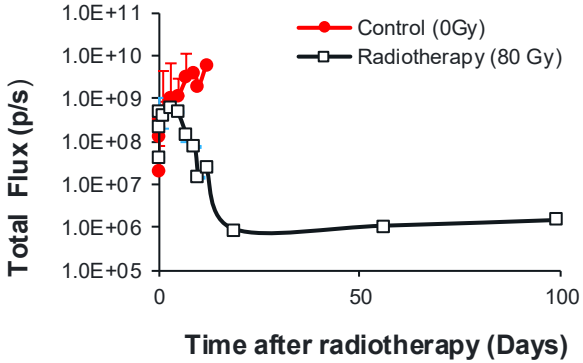
Stem cell therapies

Effects of Radiotherapy on Tumor Eradication

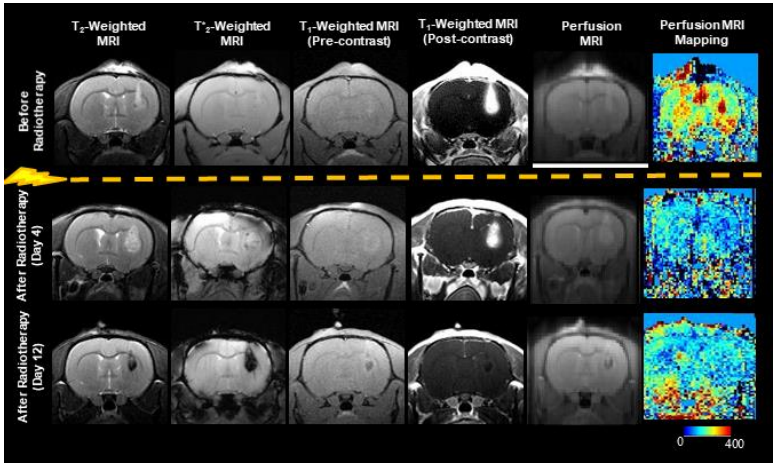
a Bioluminescence imaging (BLI)



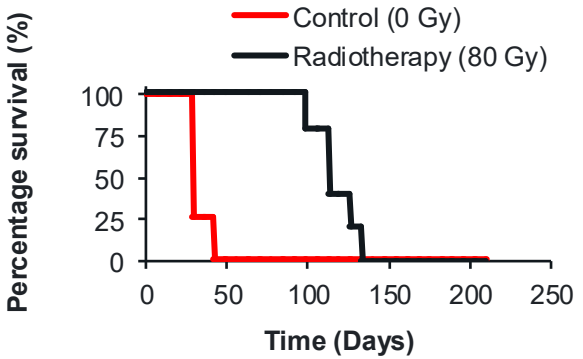
b



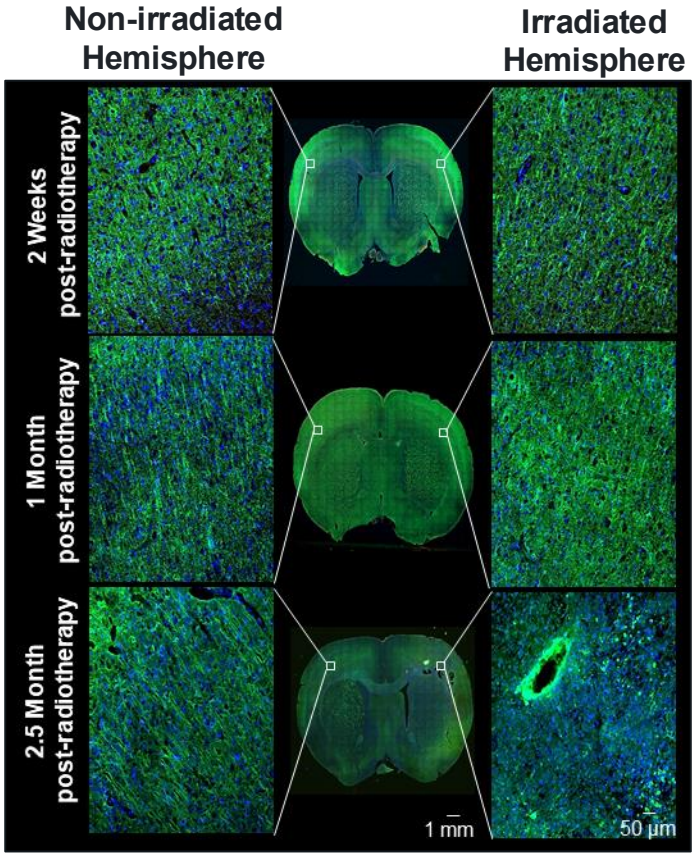
c Multi-parametric MRI



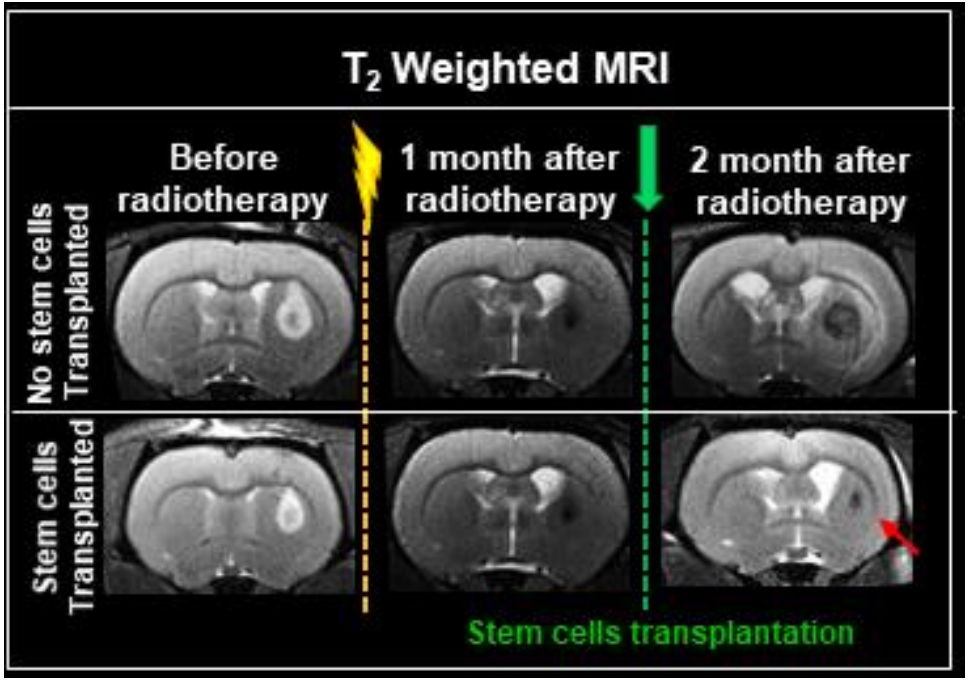
d

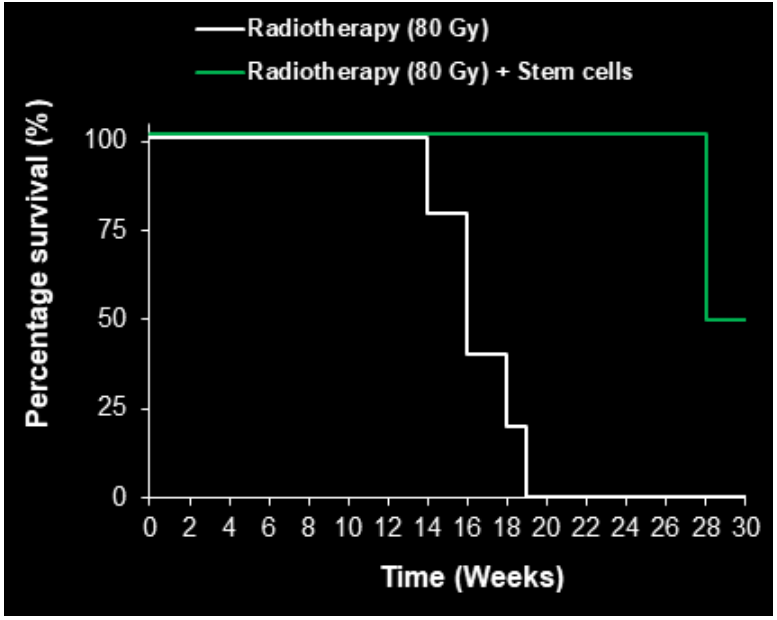


Effects of Radiation Dose on Injury Induction After Tumor Eradication



Effects of Stem Cell Therapies on Radiotherapy-Induced Brain Injury





Conclusion

- We have identified predictive and clinically translatable MRI biomarkers capable of:
  - Detecting the onset of radiotherapy-induced brain injury (RIBI)
  - Predicting neuroinflammation changes during RIBI
  - Predicting:
    - The onset of transient cognitive impairment
    - The onset of severe cognitive impairment
  - Predicting RIBI overall and survival outcomes

- Capable of monitoring tissue responses to a variety of potential RIBI therapies:
  - Biomaterial-based therapeutics
  - Stem cell-based and stem cell-derived therapies
  - Small molecular weight-based therapeutics

Future Direction

Clinically

- To evaluate the reliability of these MRI biomarkers in the clinical setting:
  - To detect RIBI early on in pediatric brain tumor survivors
  - To monitor responses to potential RIBI therapies in clinical trials

Preclinically

- To use the MRI biomarkers to evaluate newly developed
  - RIBI therapeutic agents
  - RIBI diagnostic agents

Acknowledgements

Key RISE Lab Members

Maya Teitz, B.Sc.
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(**MRI biomarkers**)

Saikat Maiti, Ph.D.
Post-doctoral fellow
(**nanotheranostic agents**)

Anupama Kumari, Ph.D.
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(**stem cells**)

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Esteban Velarde, B.Sc.
Xiaoju Yang, M.D.
Shana Lee, B.Sc.
Kristen Lecksell, B.Sc.
Chantelle Terrillion, Ph.D.

Funding Sources

NIH NATIONAL CANCER INSTITUTE

NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development

NIH National Institute of Mental Health

American Brain Tumor Association®
Providing and pursuing answers®

JAG JUNIOR FUND INC

Q&A

Join Us at Our Upcoming Events

June 9, 2026
1:00–2:00 p.m. ET

Longitudinal Studies in Genomically Defined Disease Cohorts

Dr. Smita Bhatia
University of Alabama at Birmingham

July 14, 2026
1:00–2:00 p.m. ET

CAR-NKT Cell Therapy for Neuroblastoma

Dr. Leonid Metelitsa
Texas Children's

Learn more and register at **events.cancer.gov/ccdi/webinar**

Also, save the date! CCDI Symposium on September 18, 2026

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