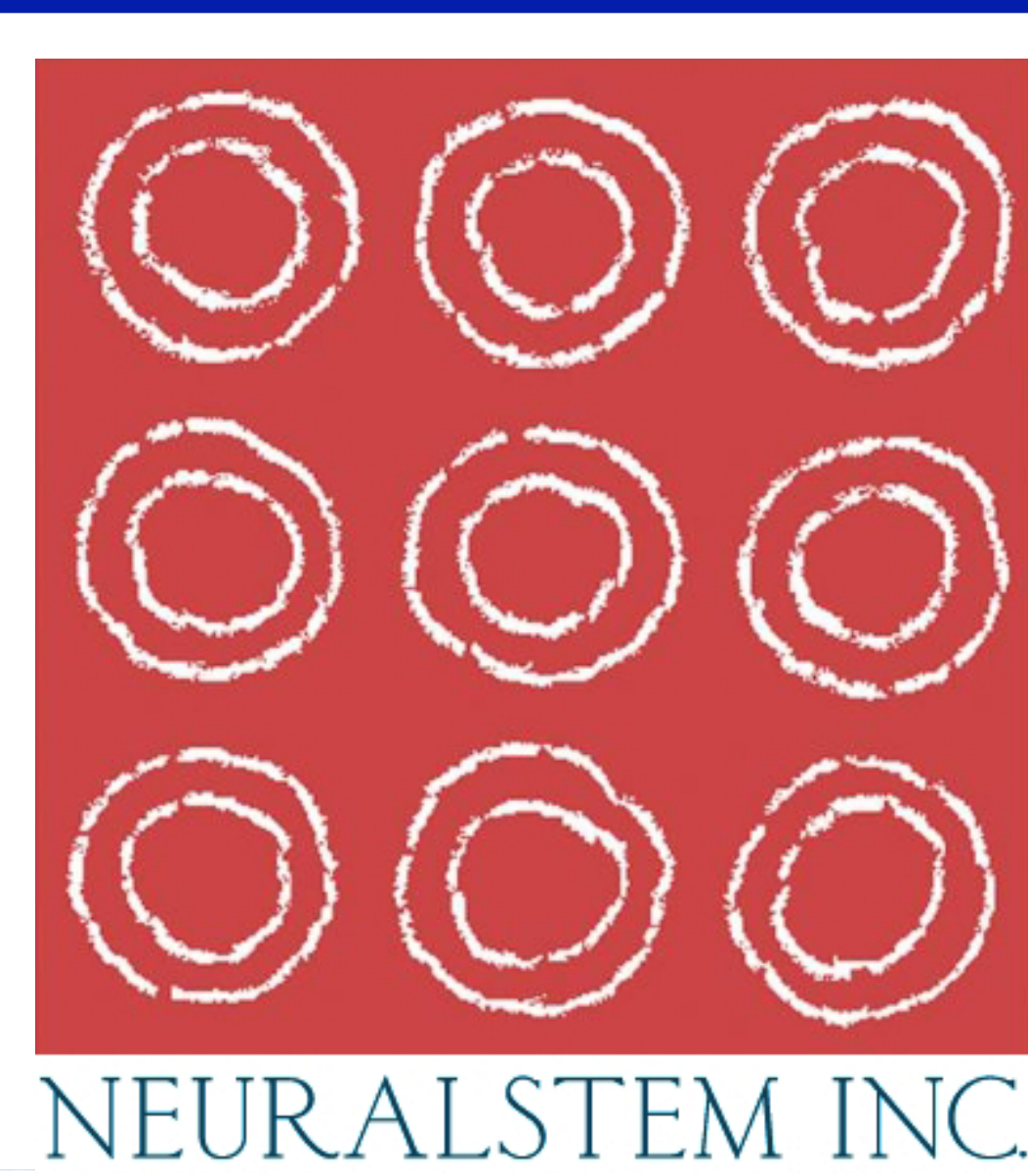




Reversal of radiation-induced cognitive impairment by oral administration of neurogenic small molecule compound NSI-189

Barrett D. Allen¹, Munjal M. Acharya^{*,1}, Celine Lu¹, Erich Giedzinski¹, Vipin K. Parihar¹, Mike Heffran², Karl K. Johe² and Charles L. Limoli¹

¹Dept. of Radiation Oncology, Univ. of California, Irvine, CA 92697, ²Neuralstem Inc., Rockville, MD 20850, USA.

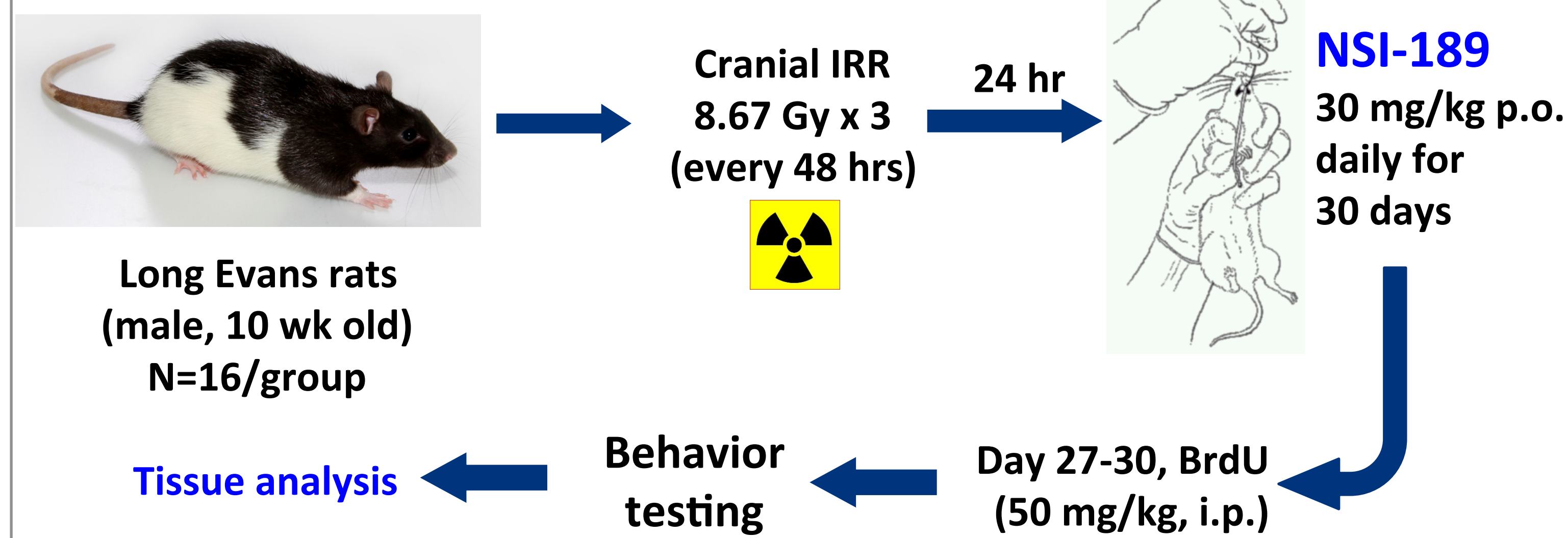


INTRODUCTION

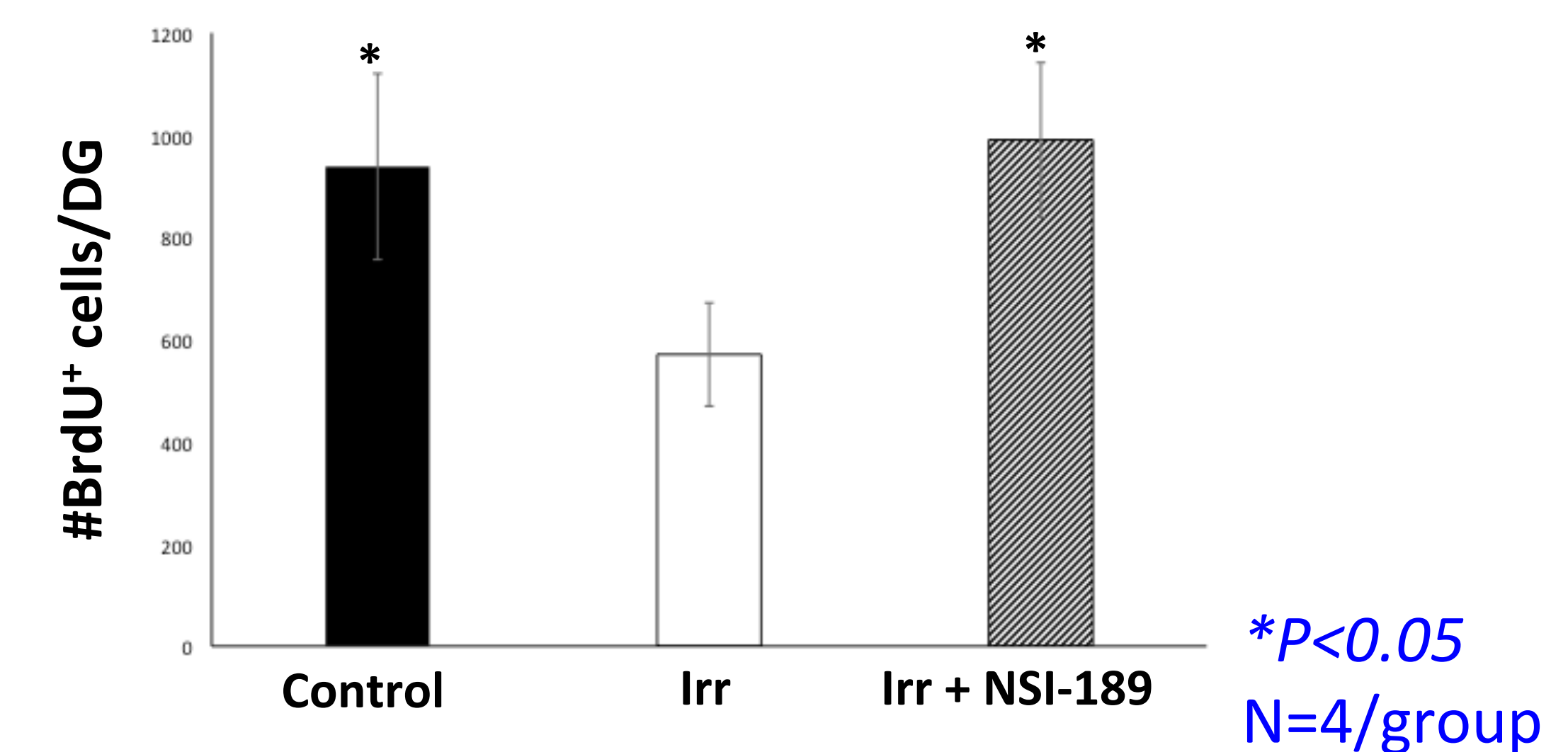
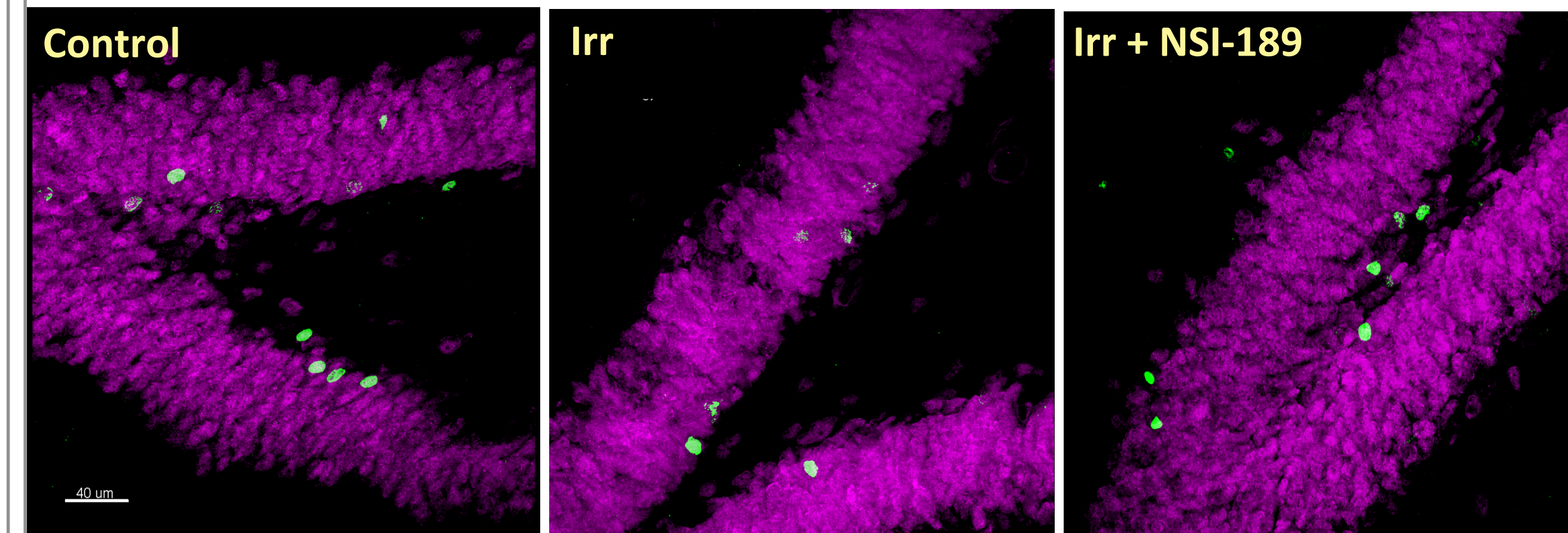
- More than 1.68 million new cases of cancer expected to be diagnosed in 2016. About 60% of patients survive >20 years. 1/3rd of the 1.68 million diagnosed will develop brain mets.
- For many of these metastatic lesions, along with primary tumors (25,000 new cases/yr), **radiotherapy** remains a primary treatment modality involving 200,000 patients/yr that receive partial or whole brain irradiation (IRR).
- Cranial IRR is shown to be associated with **progressive dementia** and hippocampal-dependent **cognitive dysfunction**, especially in pediatric cases. Persistent cognitive decrements adversely affect **quality of life with little or no clinical recourse**.
- Anti-oxidant and anti-inflammatory strategies have shown marginal benefit for improving cognition after irradiation.
- NSI-189** is novel BBB permeable small molecule shown to increase neurogenesis and hippocampal volume.
- Importantly, NSI-189 has shown **behavioral benefits** in a mouse model of **depression** and **considerable promise in a Phase 1B clinical trial for the treatment of major depressive disorder (MDD)**, Fava *et al.*, *Mol. Psych.*, 2016).
- Using clinically-relevant fractionated whole brain IRR, we show beneficial neurocognitive effects of orally administered NSI-189 on hippocampal- and frontal cortex-dependent behavior tasks 1 month post-irradiation in rats.

RESULTS

Experimental Design

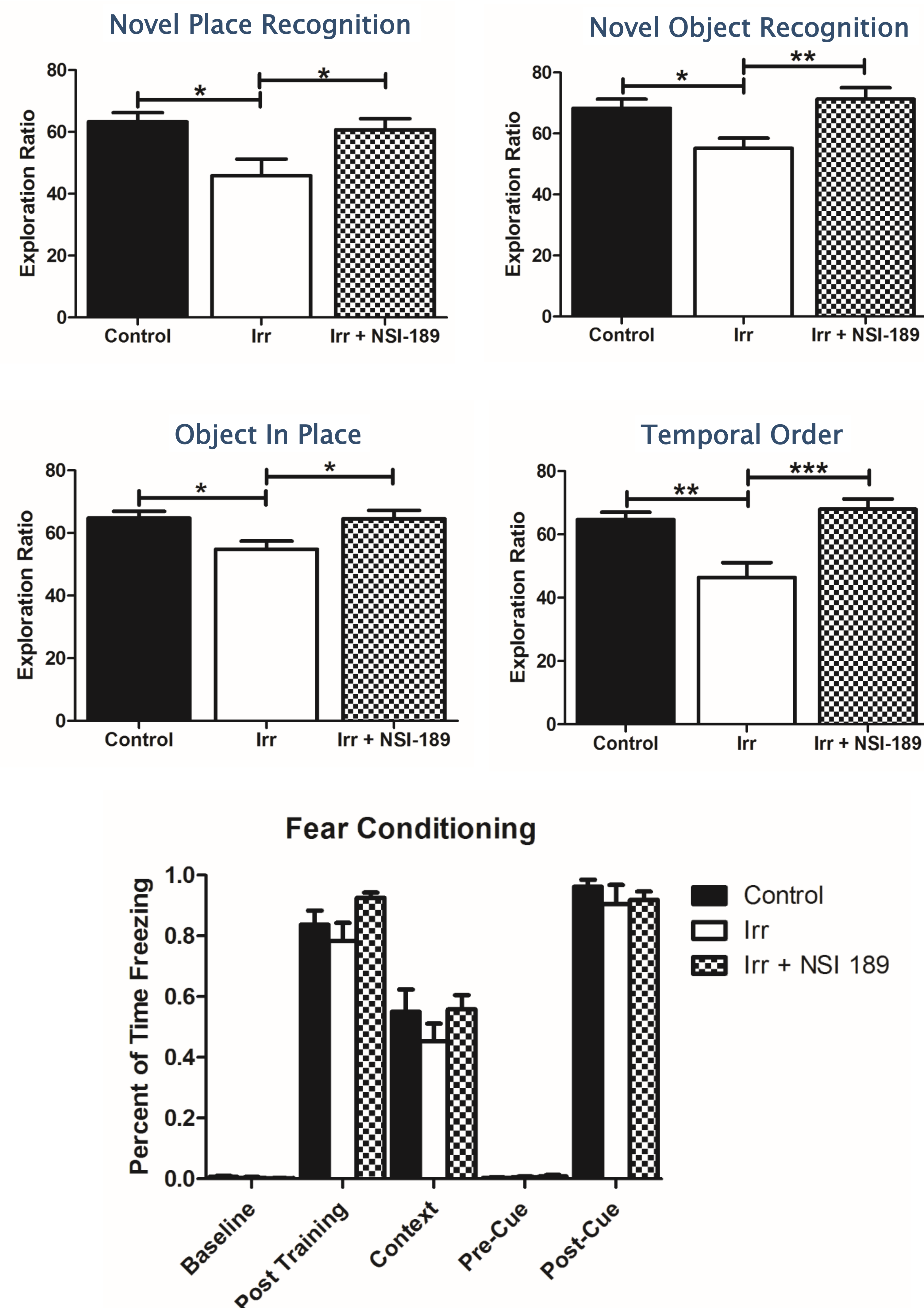


NSI-189 treatment preserve hippocampal proliferation

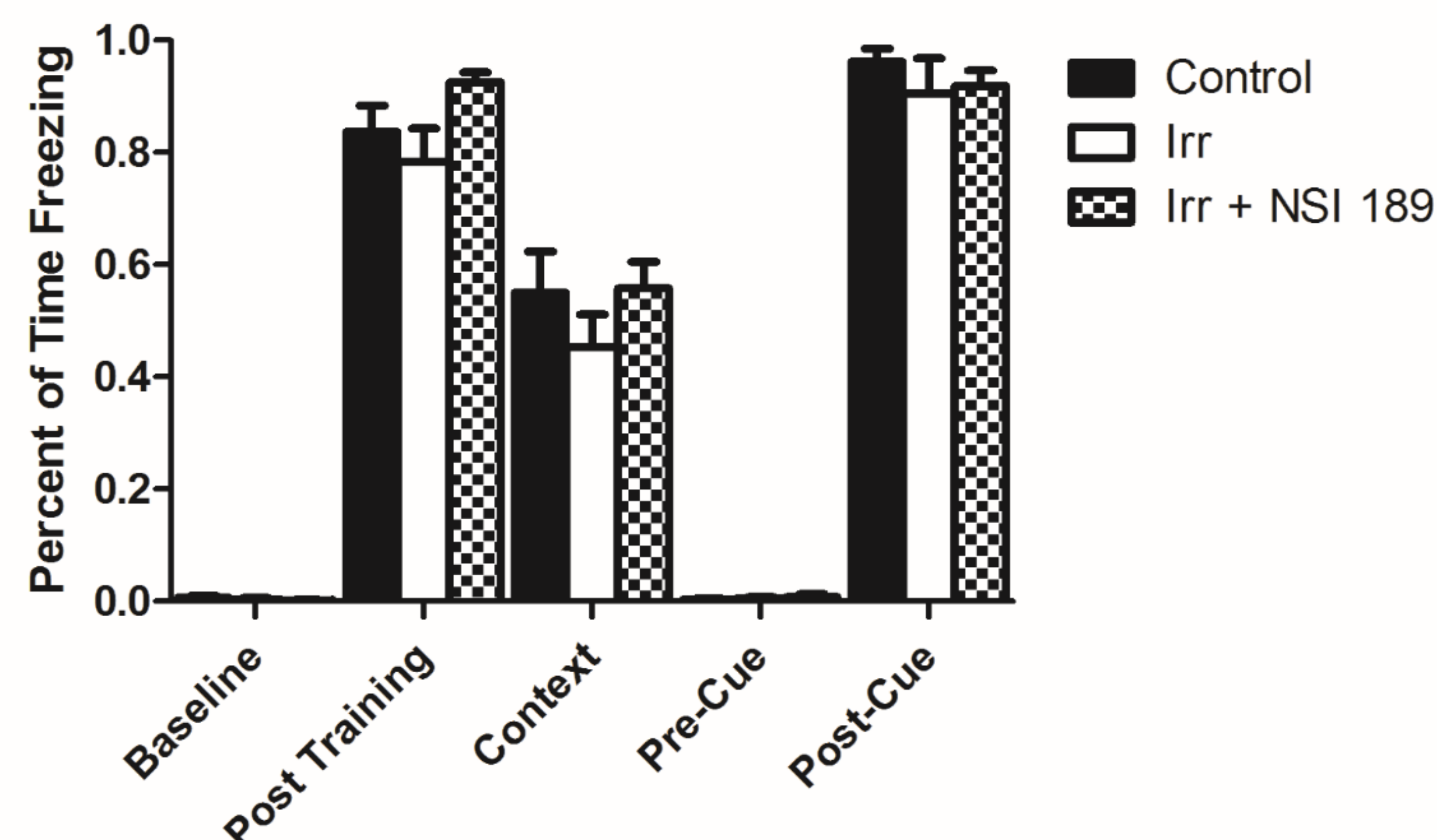


Cognitive function

NSI-189 treatment ameliorates radiation (27 Gy)-induced cognitive deficits



Fear Conditioning



*P<0.05, **P<0.01, ***P<0.001 (ANOVA, Bonferroni's correction, N=16/grp)

CONCLUSIONS

- Oral administration of NSI-189 mitigated radiation-induced behavior impairments.
- NSI-189 treatment ameliorated radiation-induced impairments in hippocampal- and frontal cortex-dependent episodic and spatial memory function as assessed by 4 spontaneous exploration tasks.
- Cranial irradiation showed a trend toward impaired contextual fear conditioning.
- Measurements of hippocampal volume did not show significant effects of cranial irradiation.
- NSI-189 treatment also preserved the number of proliferating cells within the hippocampal subgranular zone.
- In summary, the BBB permeable, small molecule compound NSI-189 shows promise as a potential **translational intervention** against radiation-induced cognitive dysfunction.

ACKNOWLEDGEMENTS

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