Imaging organ injury
Planning Radiation Protection Clinical trials

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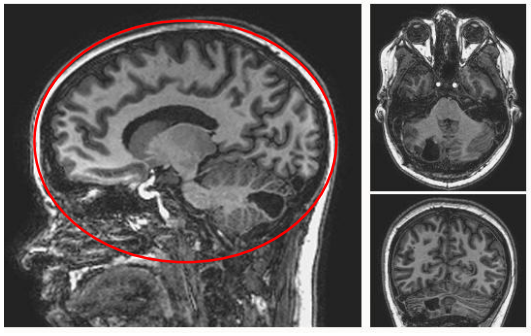
Stem cell cell depletion

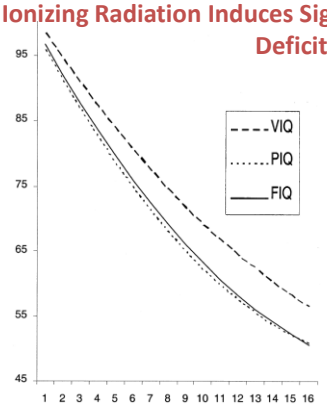
- Hair follicle vs basal layer
- Intestinal crypts
- Brain: hippocampal neuronal progenitors
- Salivary
- T cells including Treg
- Hematologic

Medulloblastoma

Whole Brain irradiation



Ionizing Radiation Induces Significant Neurocognitive Deficits



Estimated decline in full-scale, verbal and performance IQ (FIQ, VIQ, and PIQ, respectively) over time after childhood cranial radiation.

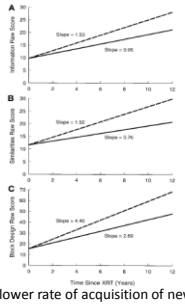
J Clin Oncol 22:4, 706-713,2004

Pattern of Intellectual Dysfunction

Fund of Factual Knowledge

Verbal Abstract Thinking

Nonverbal Abstract Thinking

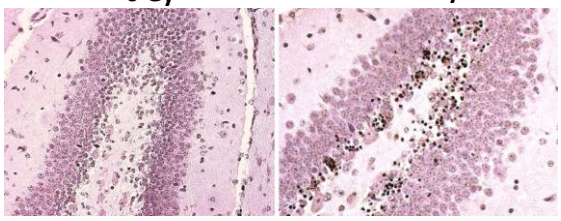


Conclusion: Decline in IQ may be 2/2 to slower rate of acquisition of new skills and info compared with healthy peers.

Palmer *JCO* 20

Radiation-induced apoptosis in neuronal progenitor cells: SGZ

0 Gy **7 Gy**



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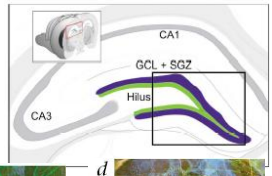
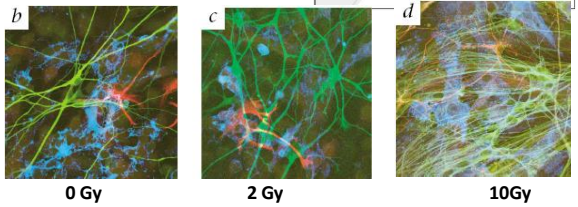
Siteman Cancer Center

Hippocampal neuronal apoptosis Neurocognitive deficit

β-tubulin (immature neurons, green), GFAP (astrocytes, red) and NG2 (immature oligodendrocytes, blue)

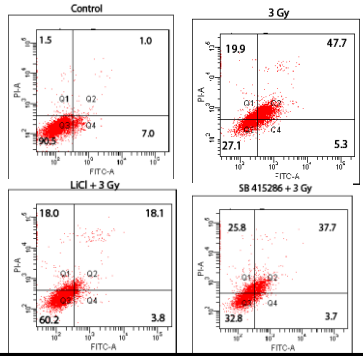
FIKE & PALMER Nature Medicie, 2002



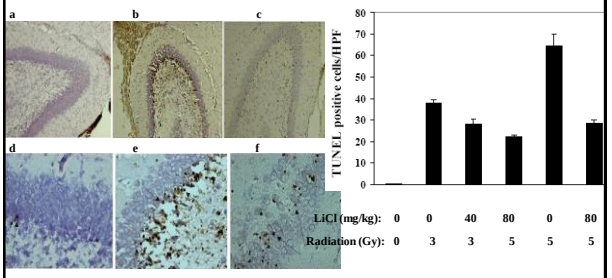


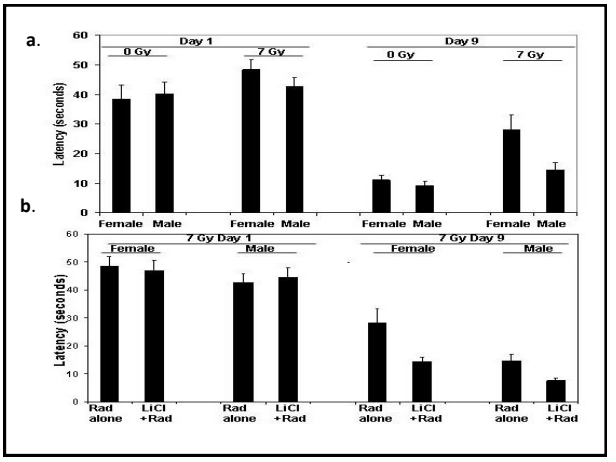
0 Gy **2 Gy** **10Gy**

Neuronal apoptosis

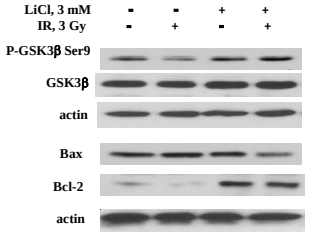


TUNEL staining of hippoampal neurons

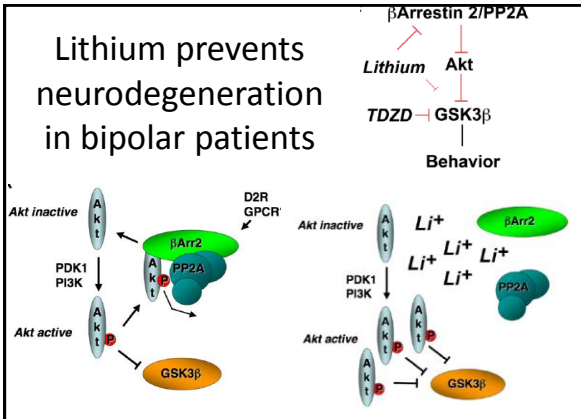




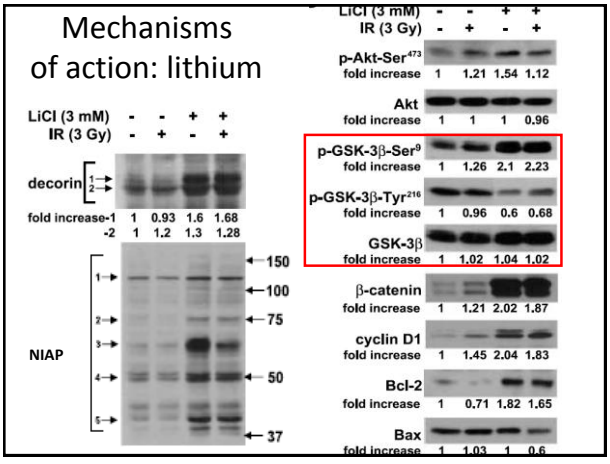
Lithium increases phospho-GSK3 And alters expression of bax & Bcl2

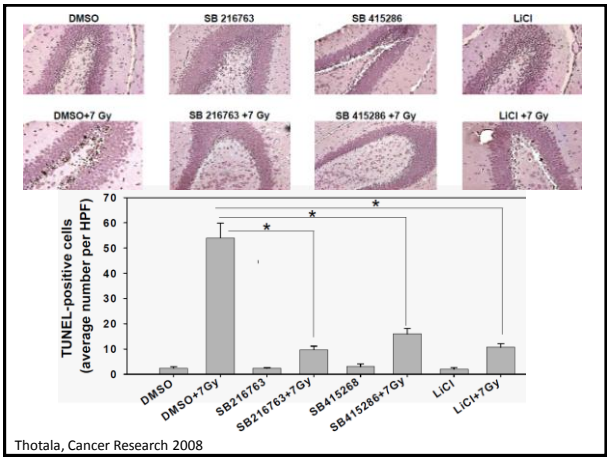


Lithium prevents neurodegeneration in bipolar patients

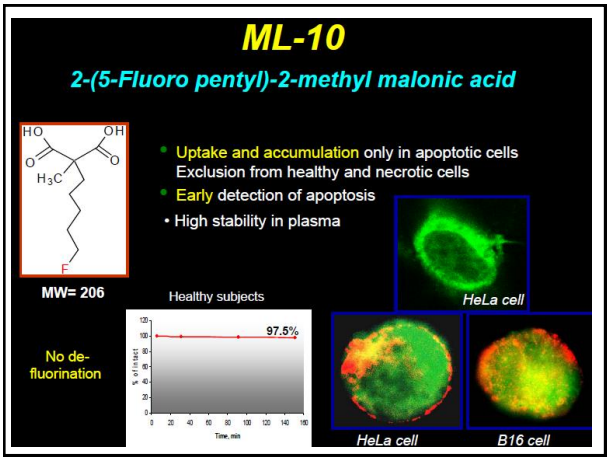


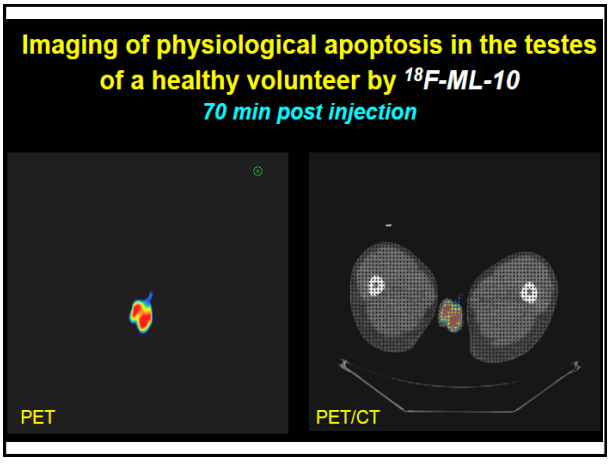
Beaulieu,and Caron, Cell 2008

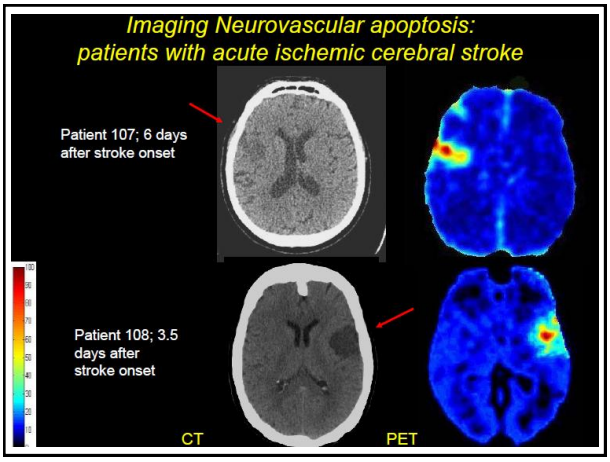


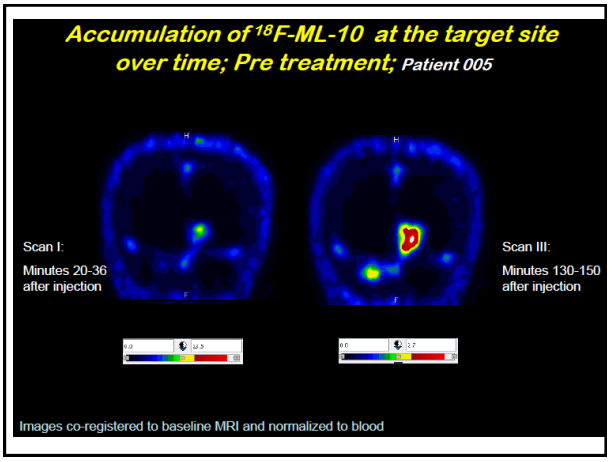


Thotala, Cancer Research 2008

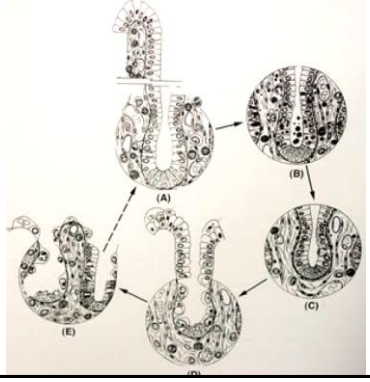








Intestinal crypts

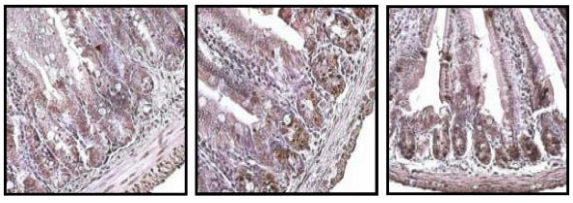


Apoptosis in intestinal crypts
TUNEL staining

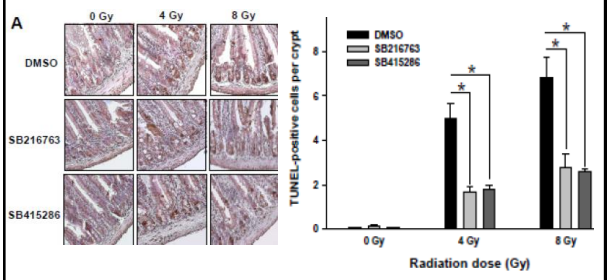
- 0 Gy

4 Gy

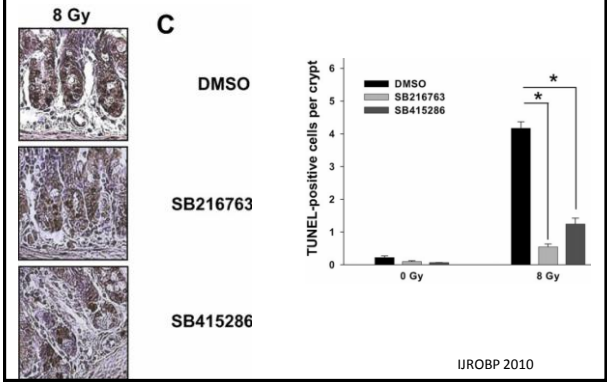
8 Gy



GSK3 inhibitor prevents intestinal injury

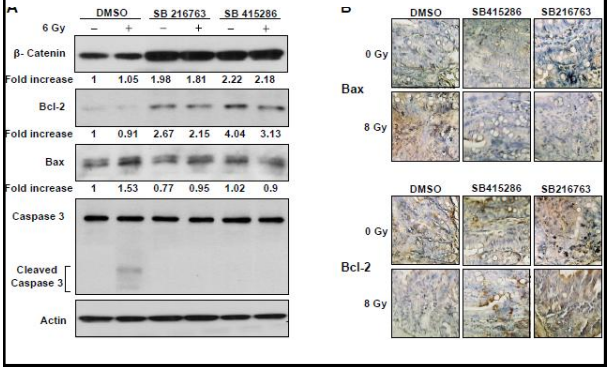


Cytoprotection: GSK3 inhibition

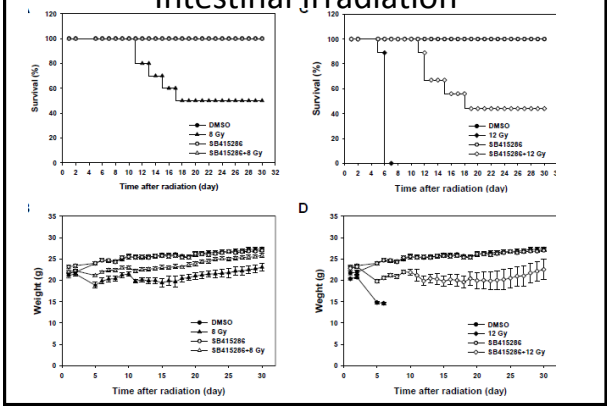


IJROBP 2010

GSK3 inhibition alters Bax & Bcl2 in intestinal crypt cells



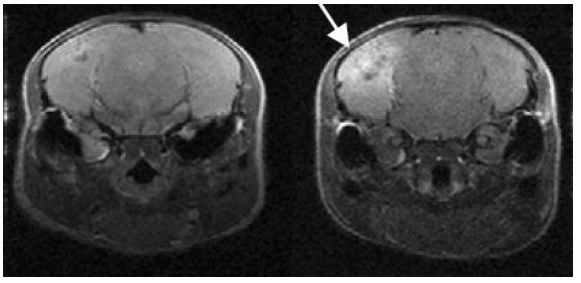
Intestinal Irradiation



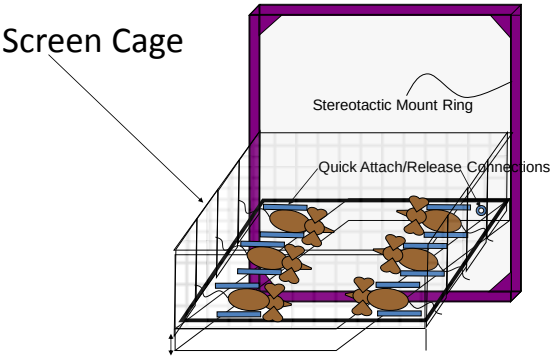
Prevention of brain necrosis

- Prevention vs. Mitigation
- Gammaknife on mouse models

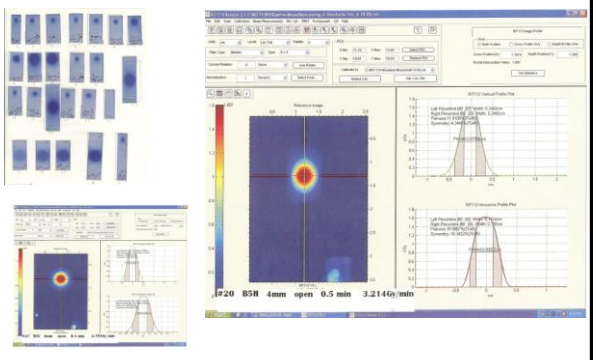
Mouse models of brain necrosis



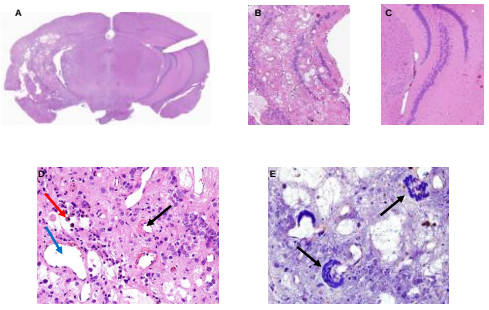
Screen Cage



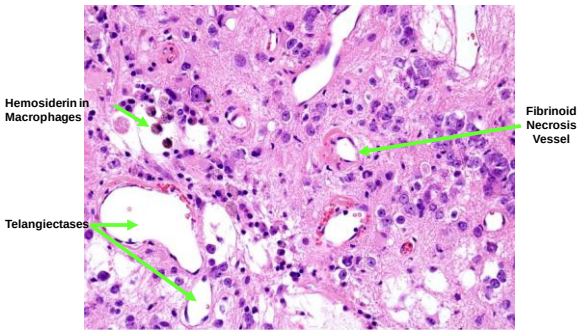
Film Dosimetry



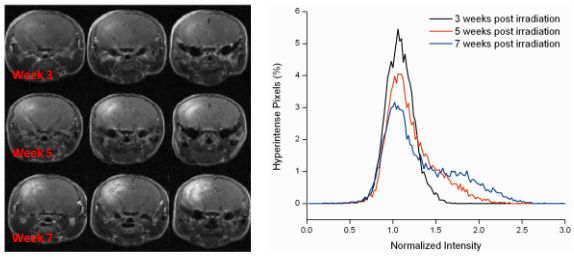
Histology of Irradiated Mouse Brain



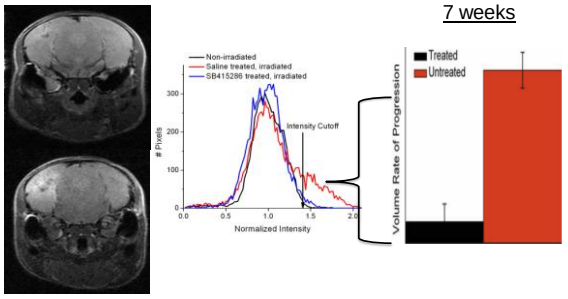
H&E Staining



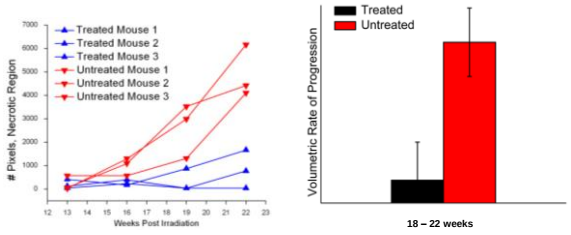
Development/Progression of Radiation Necrosis (60 Gy, single fraction GK irradiation)



Neuroprotection by SB415286 (60 Gy, single fraction GK irradiation)



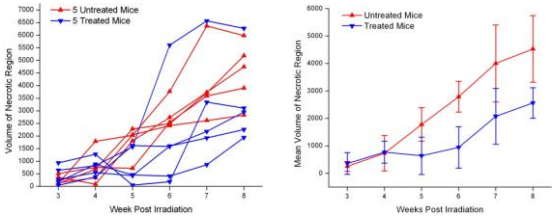
Neuroprotection by SB415286 (45 Gy, single fraction GK irradiation)



Mitigation: slowing progression of brain necrosis

- "Stroke patients on lithium showed less brain injury"
- Presently brain necrosis is treated with steroids
- GSK3 inhibitors could minimize (attenuate/mitigate) radiation induced necrosis

Mitigation of Radiation Necrosis by SB415286



Status

- Lithium Phase I: 3 patients accrued to half dose: advance to full dose
- fMRI & neurocognitive studies of irradiated children
- Aposense ML10 protocol for imaging radiation-induced apoptosis
- SBIR funding for topical formulations
- Noscira: oral cytoprotective agent

Conclude

- Inhibition of apoptosis within normal cells can reduce tissue injury
- Cytoprotection can mitigate brain necrosis
- Imaging is needed for clinical trials:
- MRI, PET/ML10

Acknowledgements

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- Xiaoyu Jiang

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