Carbon minibeams: An experimental method of radiosurgery

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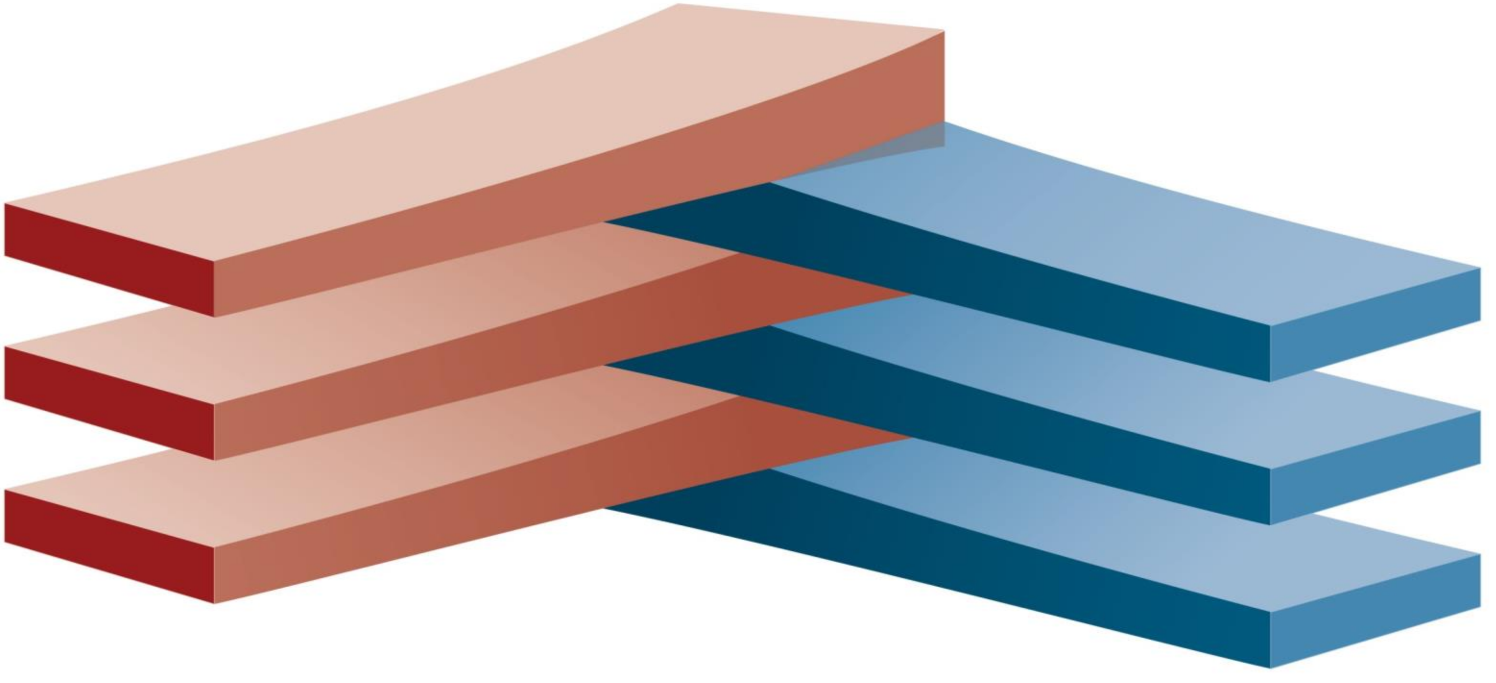
Two-directional Interleaved carbon minibeams



Dilmanian et al, IJROBP, 2012

Physics Contribution

Interleaved Carbon Minibeams: An Experimental Radiosurgery Method With Clinical Potential

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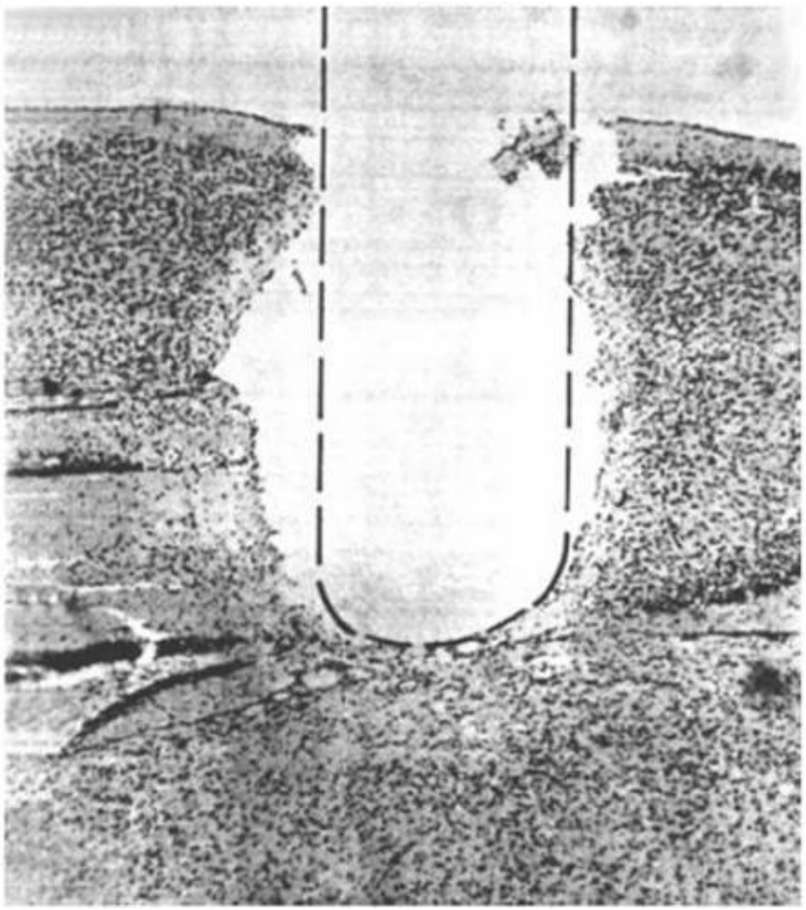
International Journal of Radiation Oncology, Biology, Physics, 2012.

The first message: Arrays of parallel thin planes of radiation are tolerated by tissues at very high doses

The effect was first discovered at BNL in the 1950s with individual deuteron pencil beams of different diameters on the mouse cerebellum.

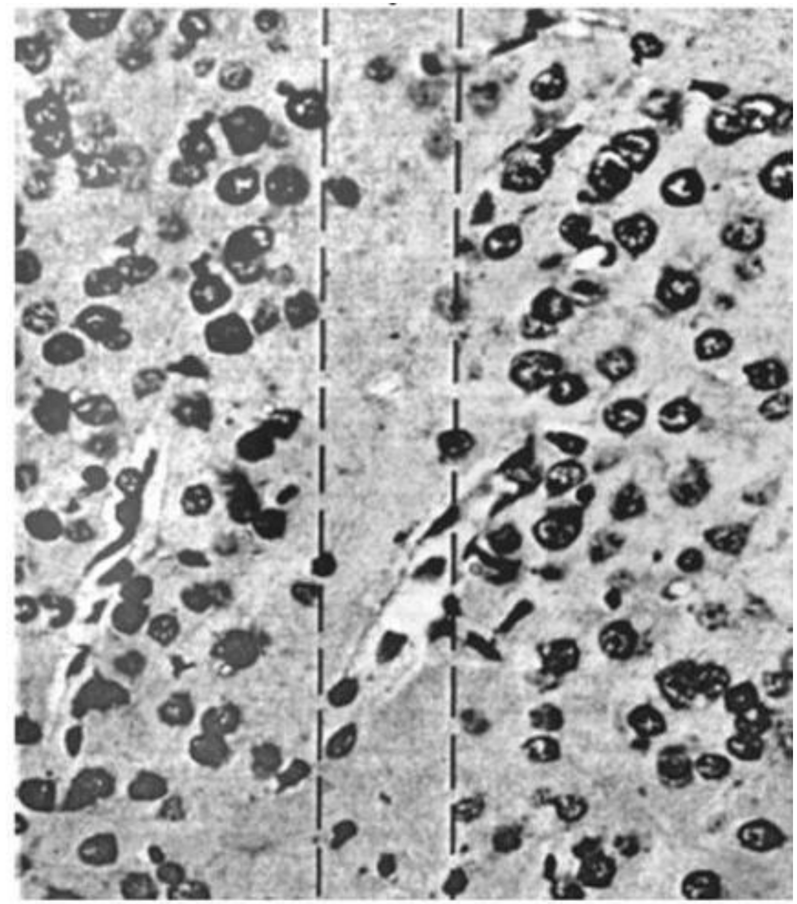
Mouse cerebellum irradiated with 25-MeV deuteron pencil beams

1 mm



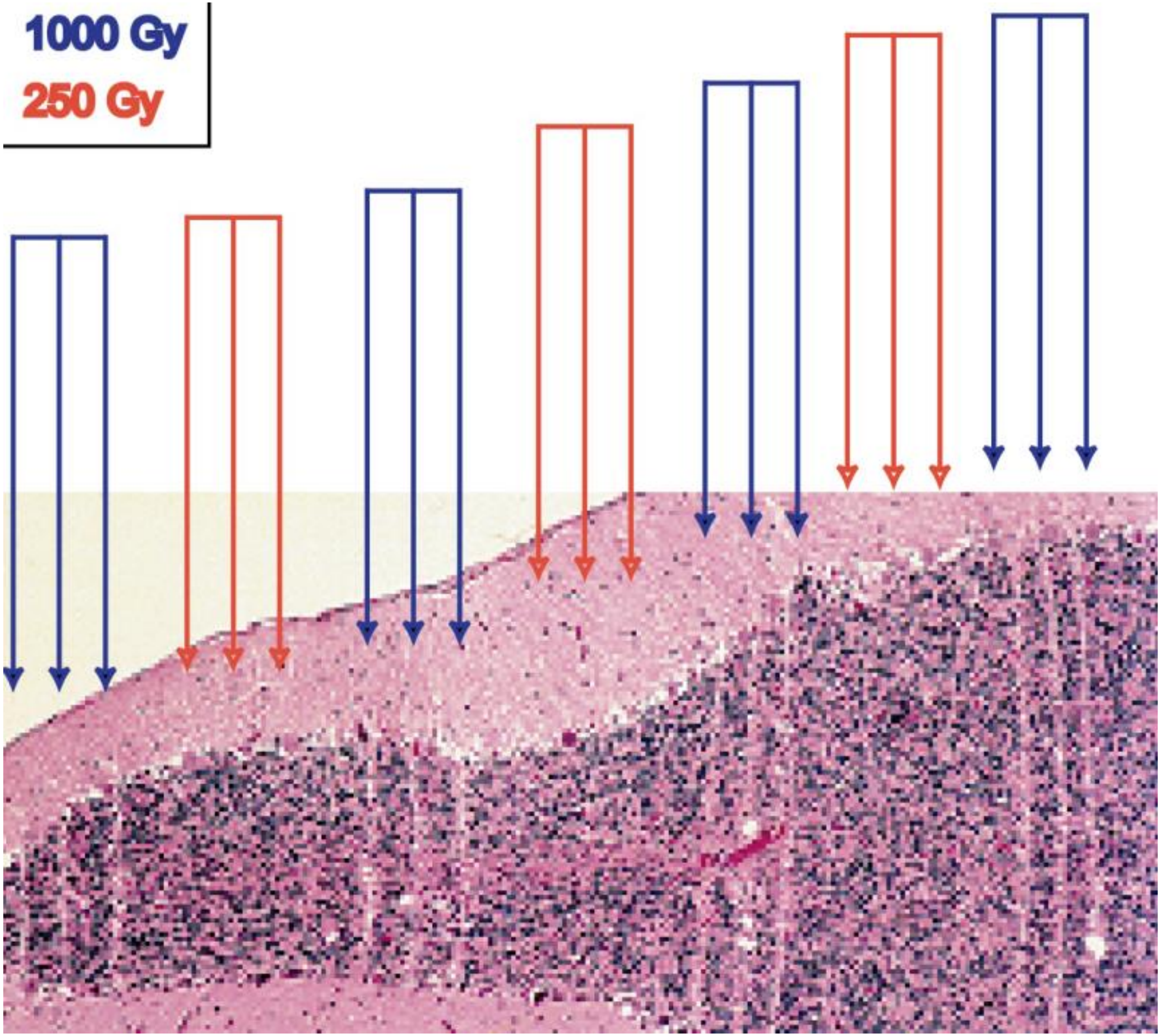
140 Gy

25 μm



4,000 Gy

Zeman W, Curtis HJ, et al., Rad. Res. 1961



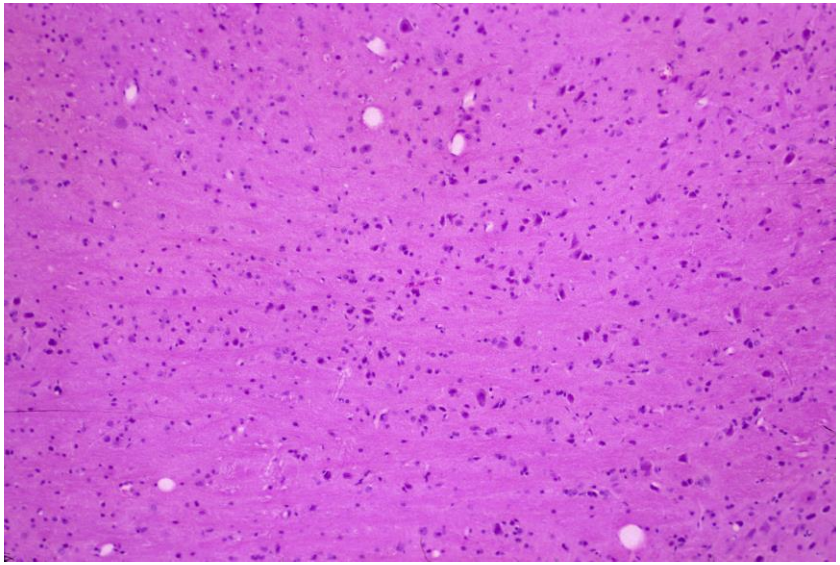
Rat cerebellum 3 months after irradiation with 37-µm x-ray microbeams spaced 75 µm.

Slatkin et al., Proc. Nat’l Acad. Sci. 1995

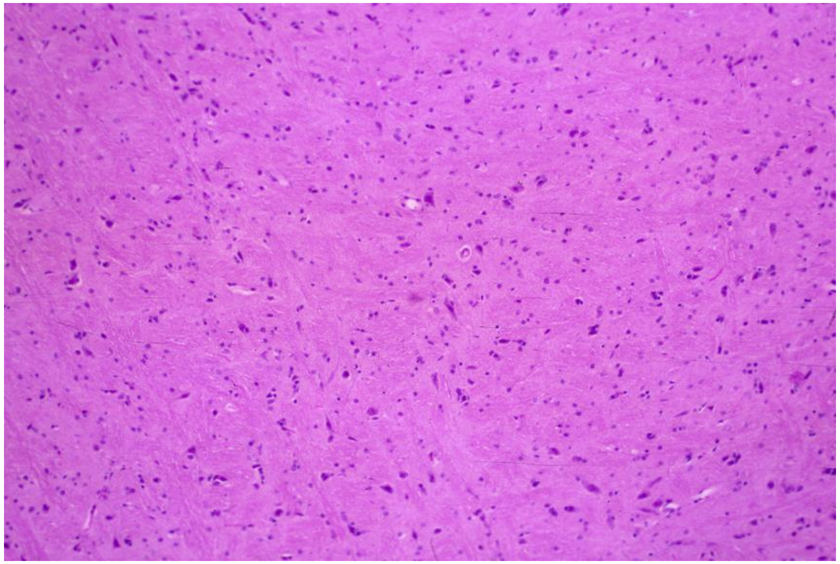
X-ray microbeam studies with very young CNS models at the NSLS and the European Synchrotron Radiation Facility (ESRF)

- Irradiating duck embryos at 120 Gy in-beam incident dose at the NSLS (Dilmanian et al., Cell. Molec. Biol. 2001)
- Irradiating the cerebella of suckling rats and piglets at ESRF at 300 Gy in-beam incident doses (Laissue et al., Dev. Med. Child. Neurol. 2007)

Comparing a rat brain irradiated with high dose microbeams with an unirradiated brain

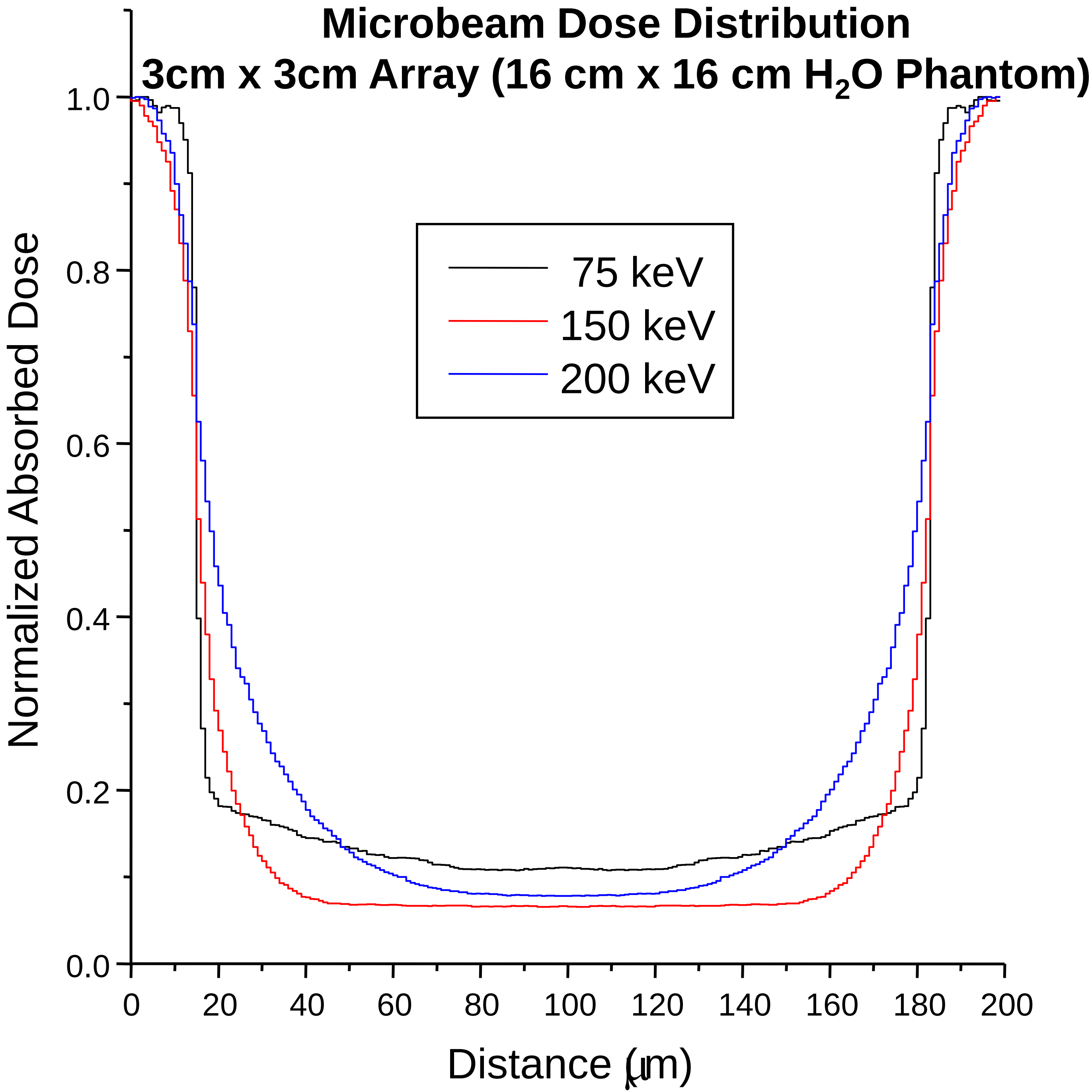


H&E-stained rat cerebrum 398 days after irradiation with a microbeam array with 27 μm beams, spaced 75 μm on-center at 250 Gy in-beam dose that cured its 9LGS tumor. The rat looked and behaved normally.

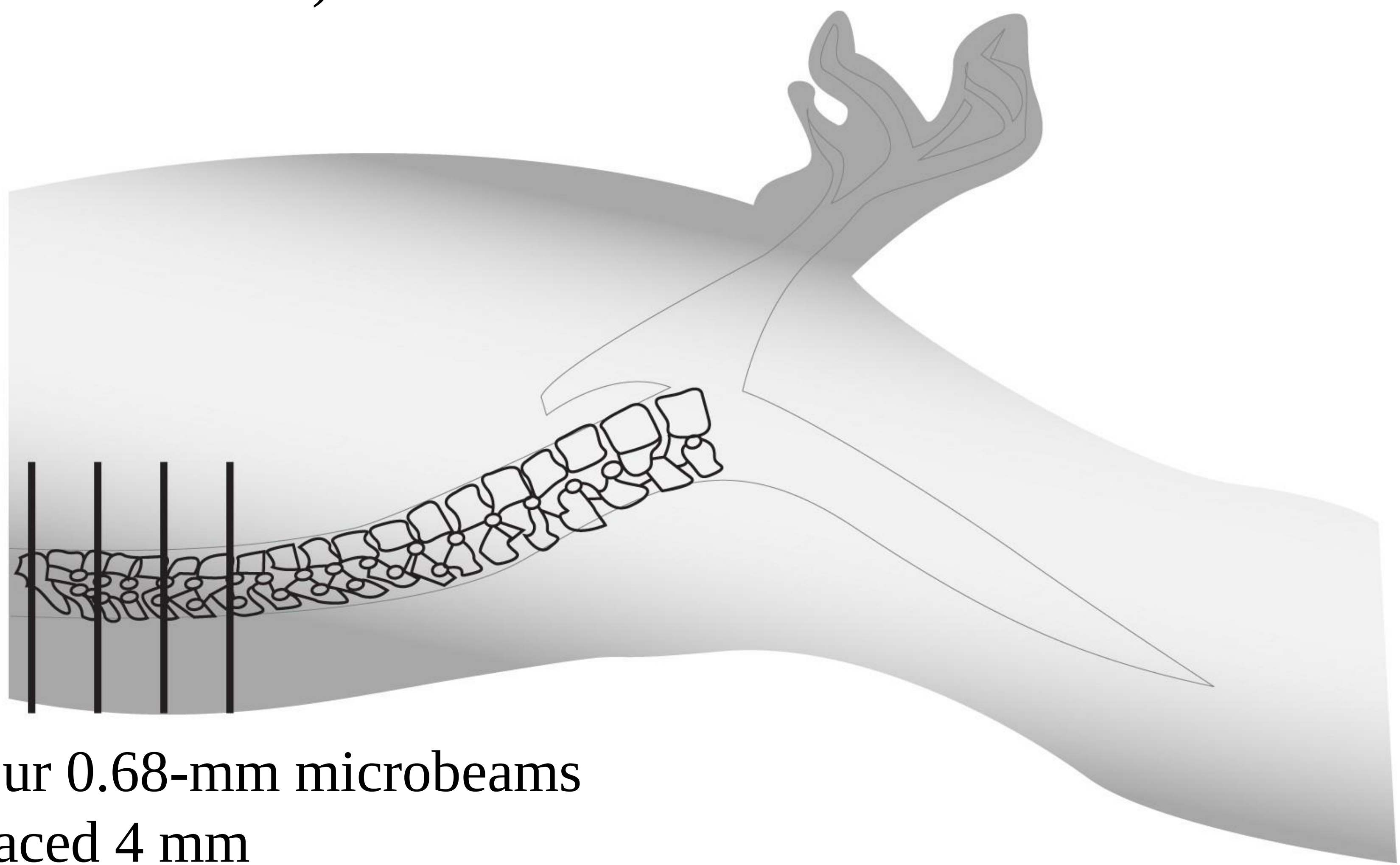


Similar to the image at the left for an age-matched unirradiated rat. The only visible differences are vacuoles in the right.

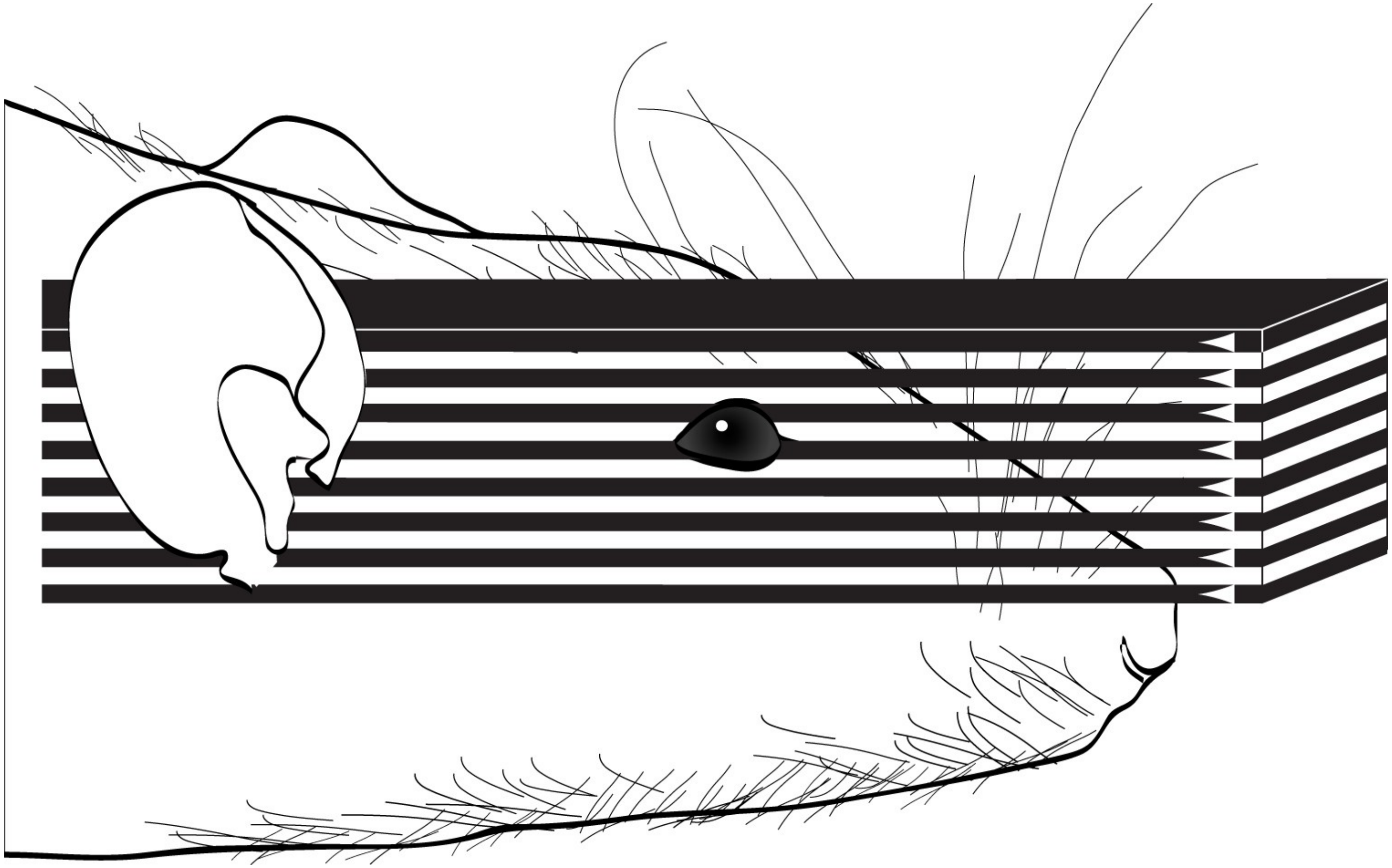
Dilmanian et al., Neuro-Oncology 4, 26-38, 2002.


Microbeam Dose Distribution
3cm x 3cm Array (16 cm x 16 cm H_2O Phantom)
75 keV
150 keV
200 keV
Normalized Absorbed Dose
0.0
0.2
0.4
0.6
0.8
1.0
0
20
40
60
80
100
120
140
160
180
200
Distance (μm)

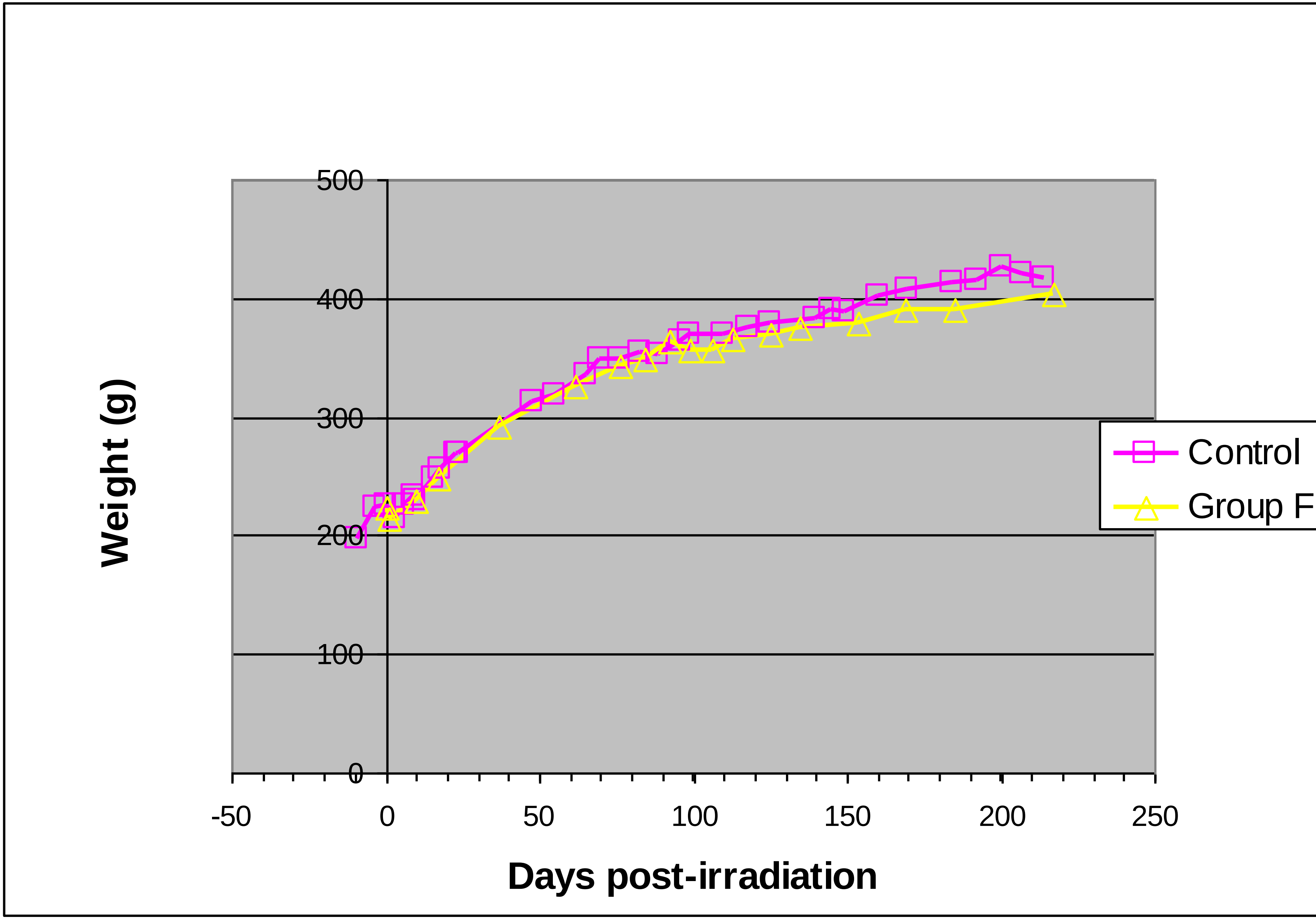
Evaluating the tissue-sparing effect of thicker x-ray microbeams (called minibeams)



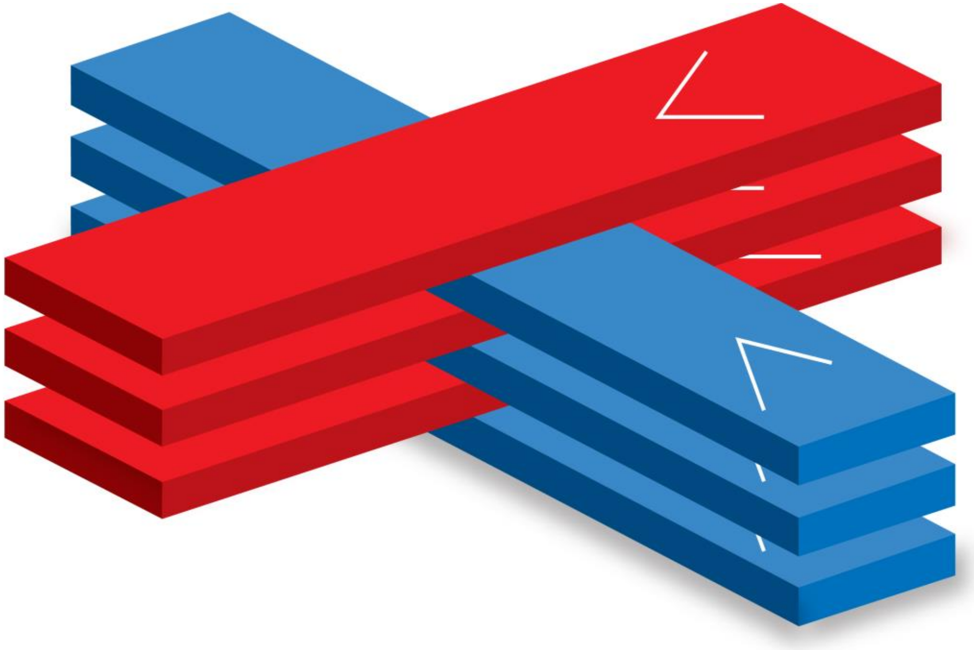
Four 0.68-mm microbeams
spaced 4 mm
400 Gy dose



Irradiation of nearly the entire rat brain irradiated with 0.68 minibeams spaced 1.32 mm on-center at 170 Gy incident dose did not produce any effects 7 months later. This puts the dose tolerance of the rats brain to these beam arrays 7-fold above that of single-dose-fraction broad beams.


Weight (g)
500
400
300
200
100
0
-50
0
50
100
150
200
250
Days post-irradiation
Control
Group F

Interleaved x-ray minibeams



Dilmanian et al., PNAS 2006

Mechanisms of microbeams' tissue-sparing effect

The underlying effects are "the dose-volume effect" and "the prompt microscopic biological repair effect".

The “Dose-volume Effect”

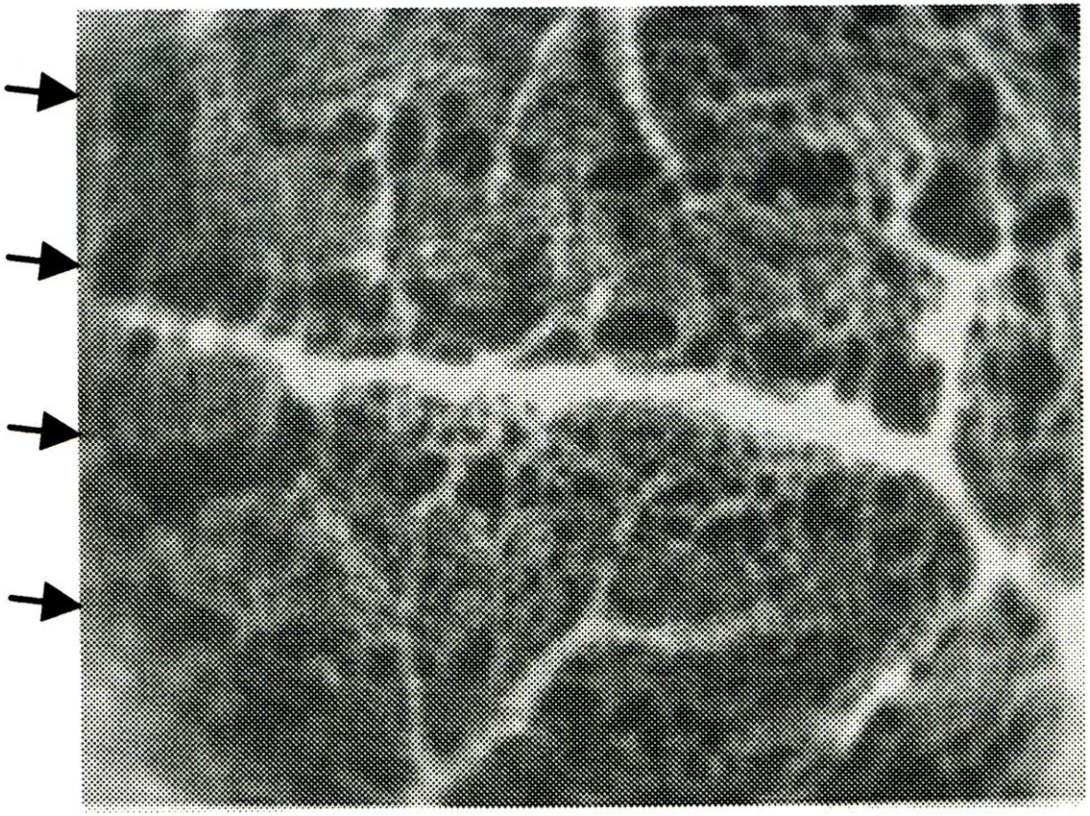
- The threshold dose for radiation damage to tissues in an organ increases as the number of exposed functional sub-units in that organ decreases. Therefore, in a uniform organ such as the brain, the threshold dose for tissue damage increases as the exposure volume decreases.
- The effect is the basis for the high tissue tolerance in grid therapy and in stereotactic radiosurgery.

The Prompt microscopic biological repair effect

However, for very small exposures, i.e., below ~700 μm, the capillary blood vessels seem to repair themselves promptly, i.e., within half a day.

This is the second component of the mechanisms underlying the tissue-sparing effect of x-ray microbeams and minibeams.

Microbeam irradiation of chicken chorio-allantoic membrane (CAM)



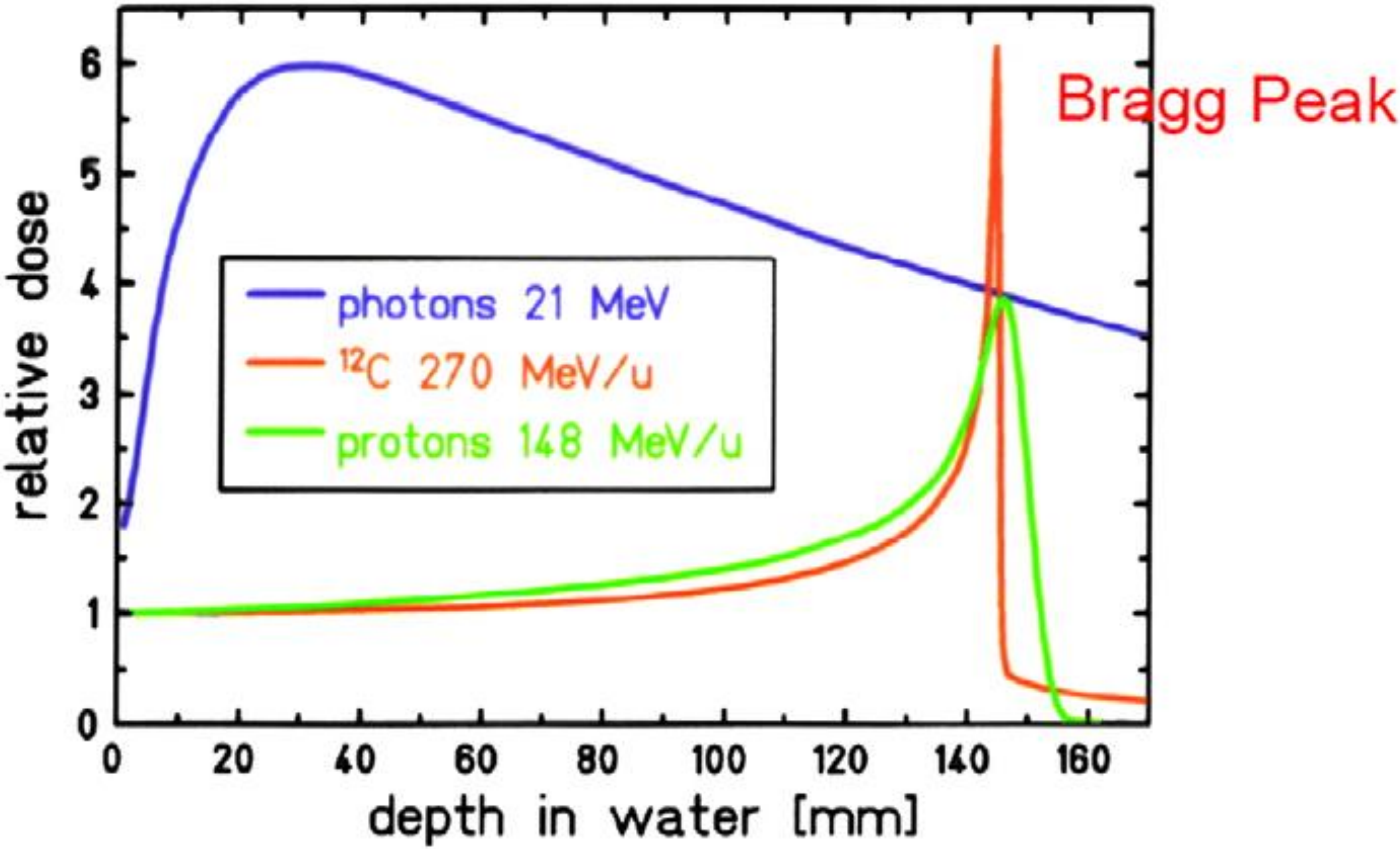
CAM picture 24 hours after irradiation with 300 Gy microbeams (25-μm beam width/200 μm spacing) showing re-appearance of new capillaries (Blattmann, et al, Paul Scherrer Institute, Scientific Report 2001).

Prompt recovery of the microvasculature

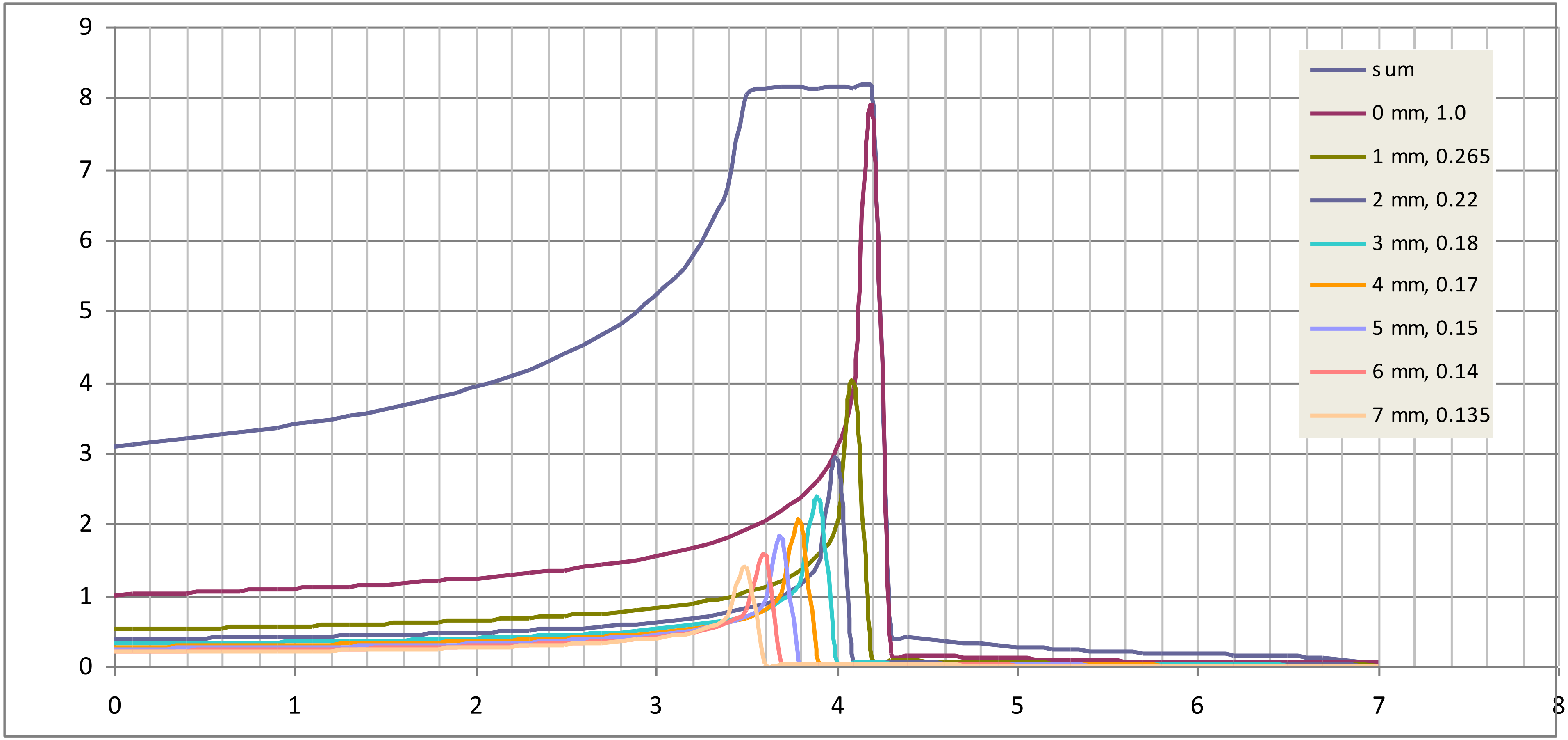
At ESRF mice were irradiated in their cerebrum with arrays of 25-μm microbeams 312 and 1,000 Gy doses. Using intravital two-photon microscopy after injection of FITC dextran, no FITC leakage outside the vessels were found at either dose between 12 hours and 1 month.

Serduc et al, IJROBP 2006

Comparing dose distributions produced in water by x rays, protons, and carbon ions

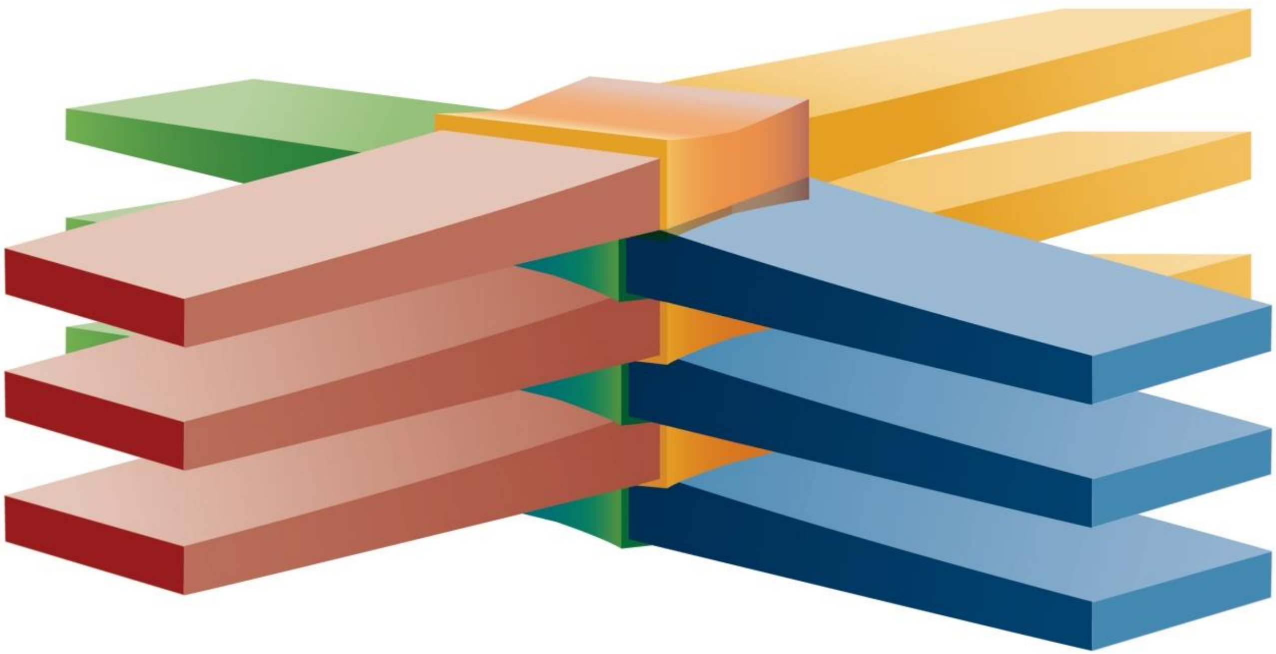


Carbon Bragg-peak spreading at the NASA Space Radiation Laboratory (NSRL), BNL

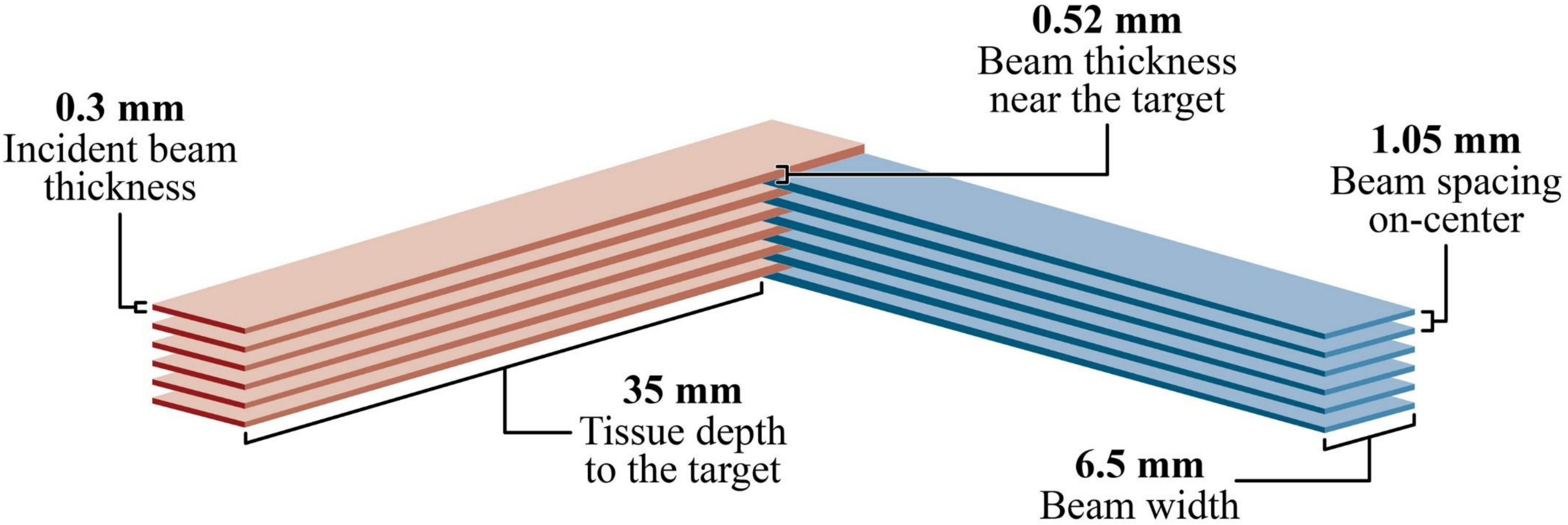


Work in collaboration with Dr. Adam Rusek of BNL

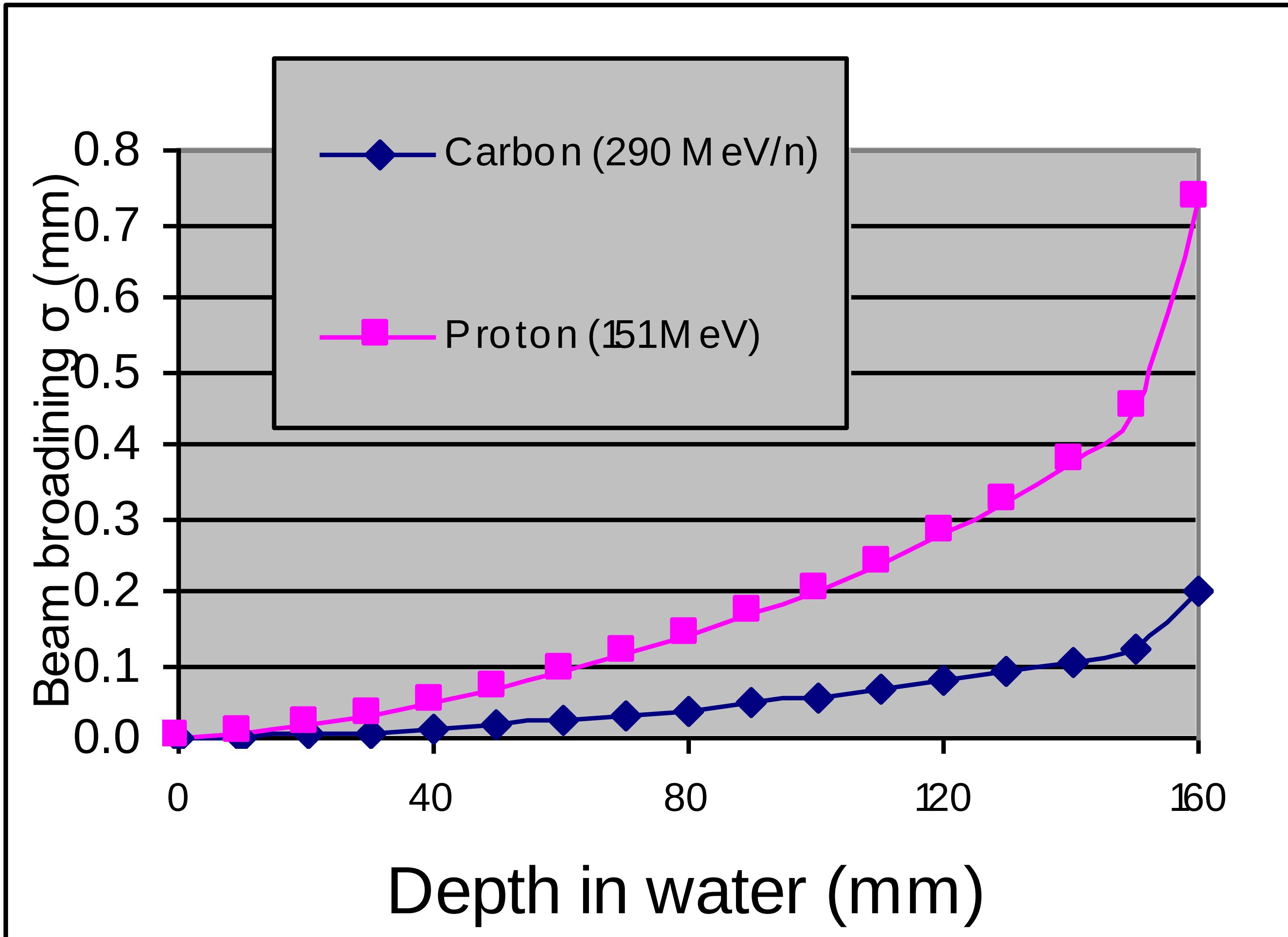
Four-directional interleaved carbon minibeams



Two-directional interleaved carbon minibeams to the scale



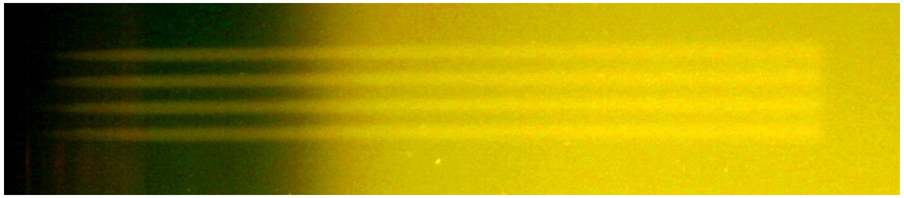
Beam broadening in protons and heavy ions



Visualizing dose distributions from carbon microbeams

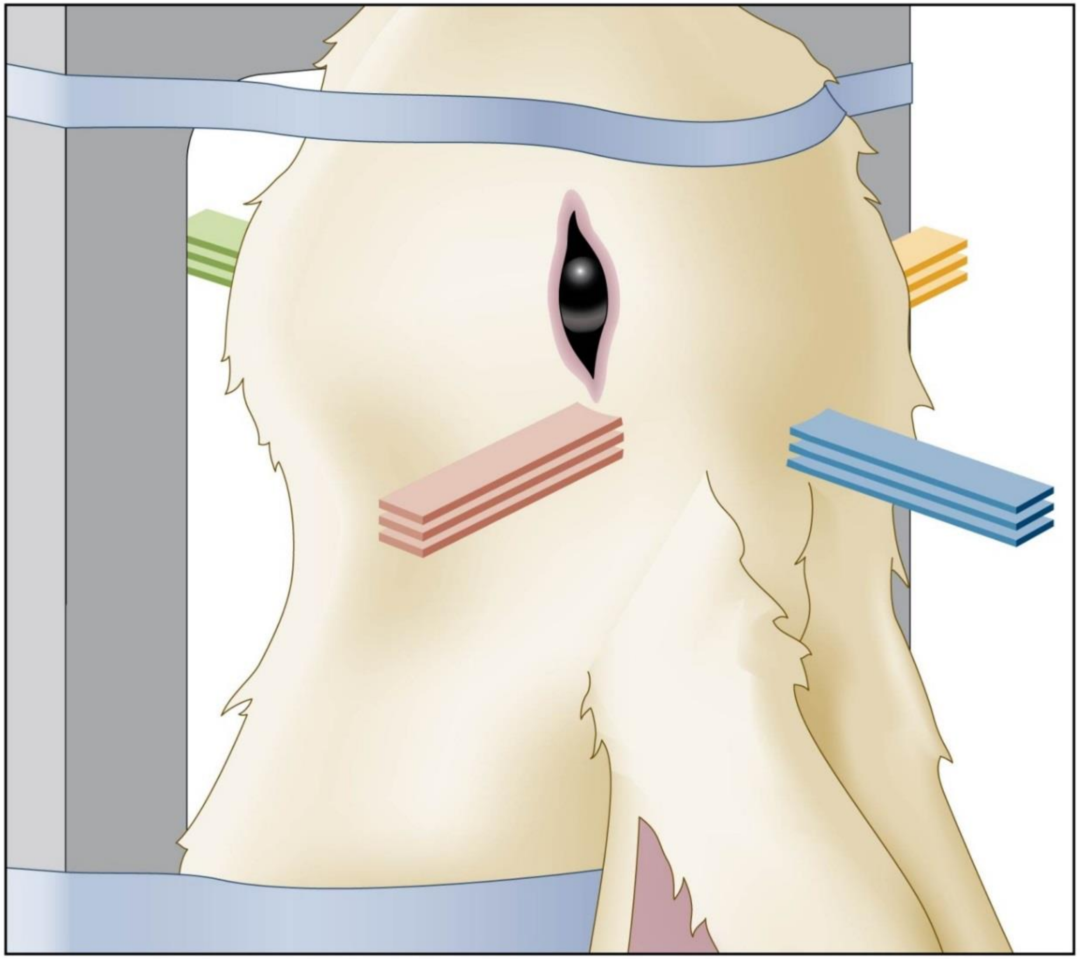
250 MeV/nucleon carbon microbeams (11.8 cm range)
at 1.2 mm beam spacing on-center and 5 Gy incident dose.

203 MeV/nucleon carbon beam (8.3 cm range)
at 1.3 mm beam spacing on-center.



148 MeV/nucleon carbon beams (4.8 cm range)
at 1.3 mm beam spacing.

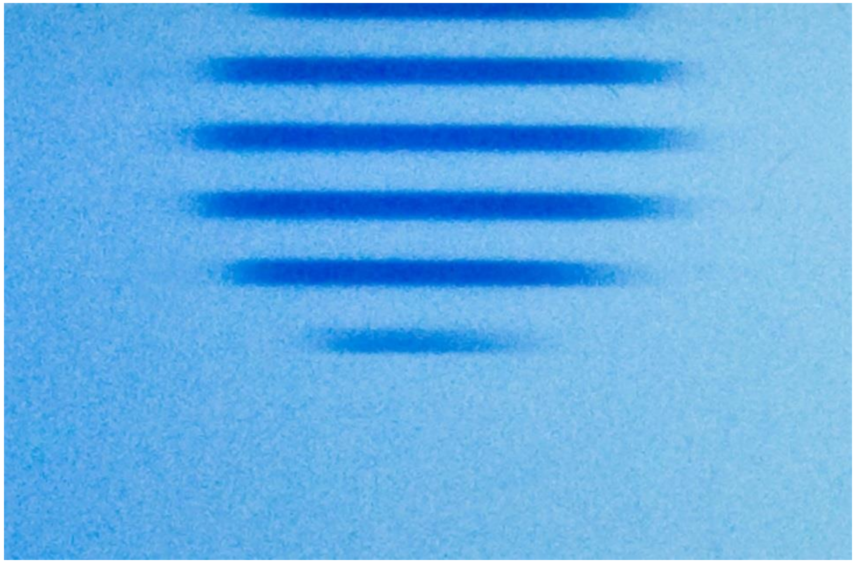
Four-directional interleaved carbon minibeams to ablate a target in the rabbit brain



Exposure parameters

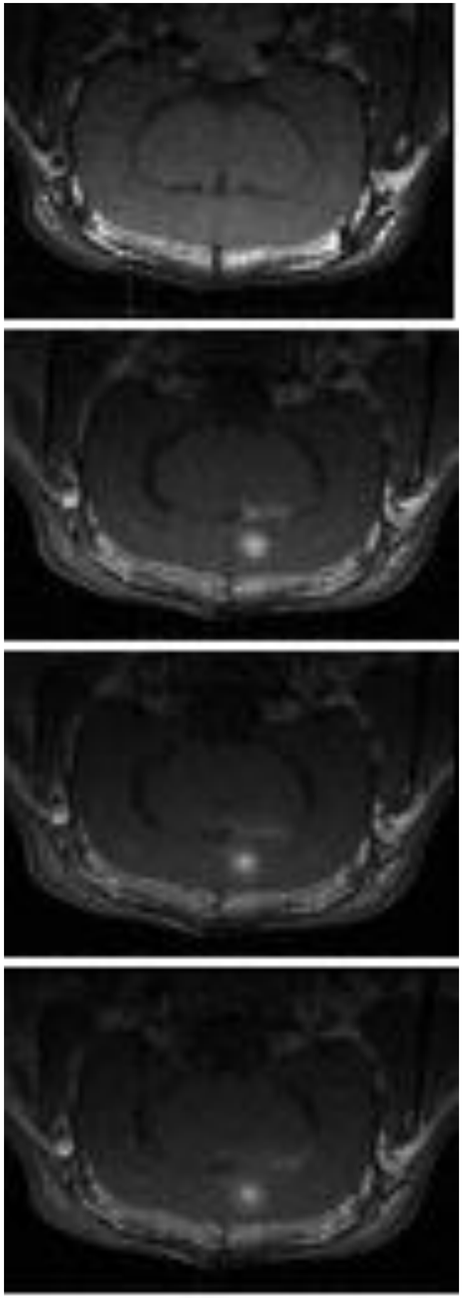
- 6.5-mm target volume
- 0.3-mm incident carbon minibeams, spaced 1.05 mm on-center
- Bragg-peak spreading over 124-135 MeV/nucleon beam energy.
- 40 Gy target absorbed dose, which is 120 photon-equivalent Gy (GyE) using RBE of 3.0. This is a very high dose for single-dose fraction radiation.

The minibeam array captured on a chromographic film



This film, positioned 10 cm downstream of the multislit collimator, is an indication that the array was parallel.

T1-weighted Gd-enhanced 4T MRI images 6 months after the irradiation

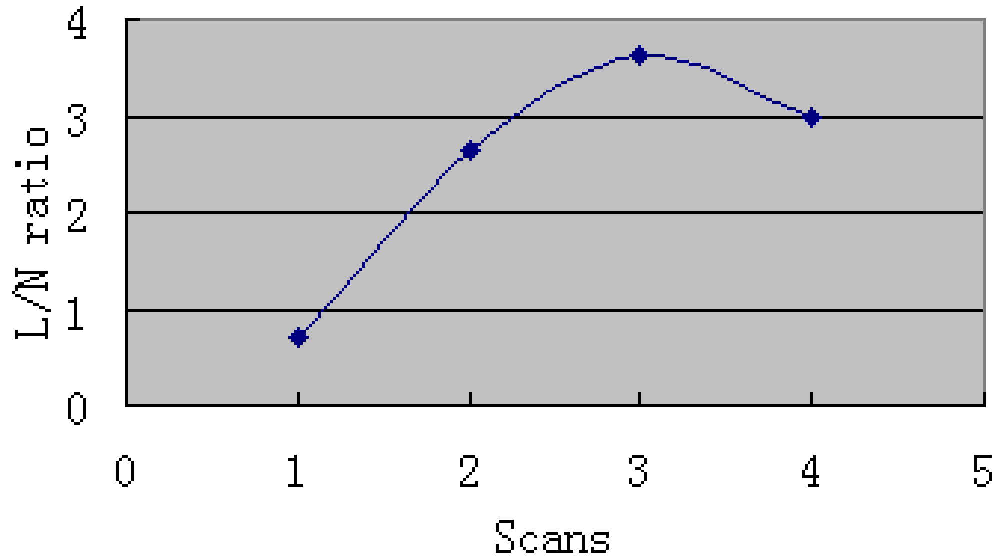


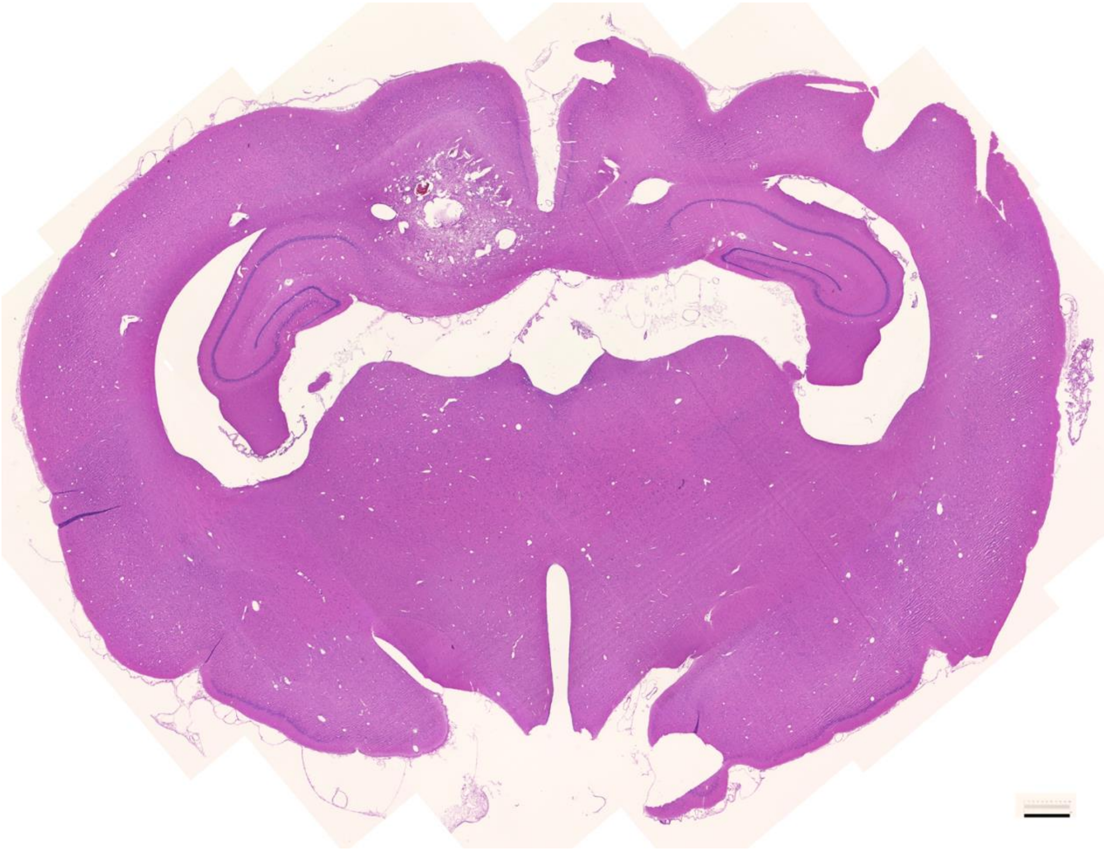
PreGD

GD1 0-12 min

GD2 12-24 min

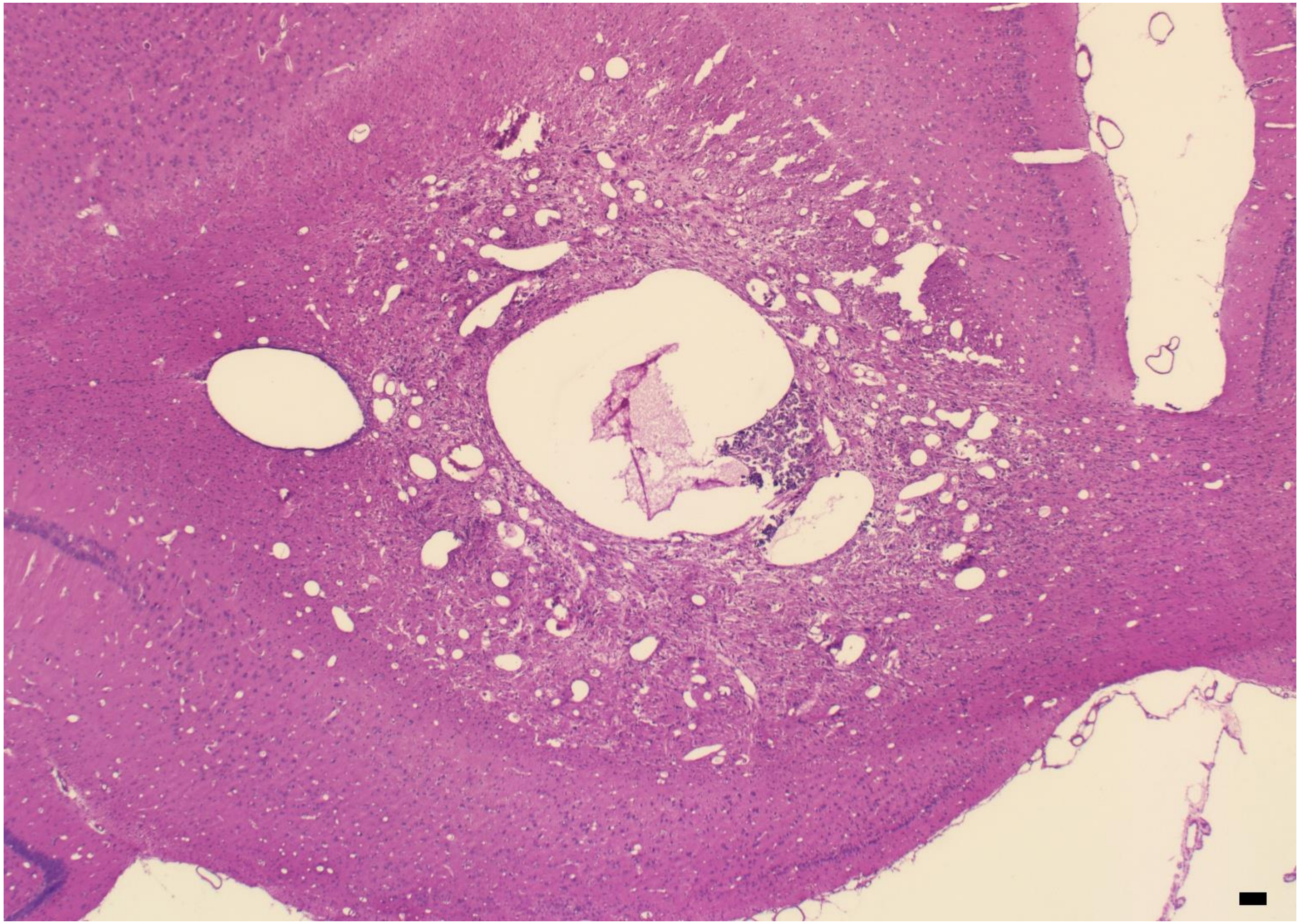
GD3 24-36 min



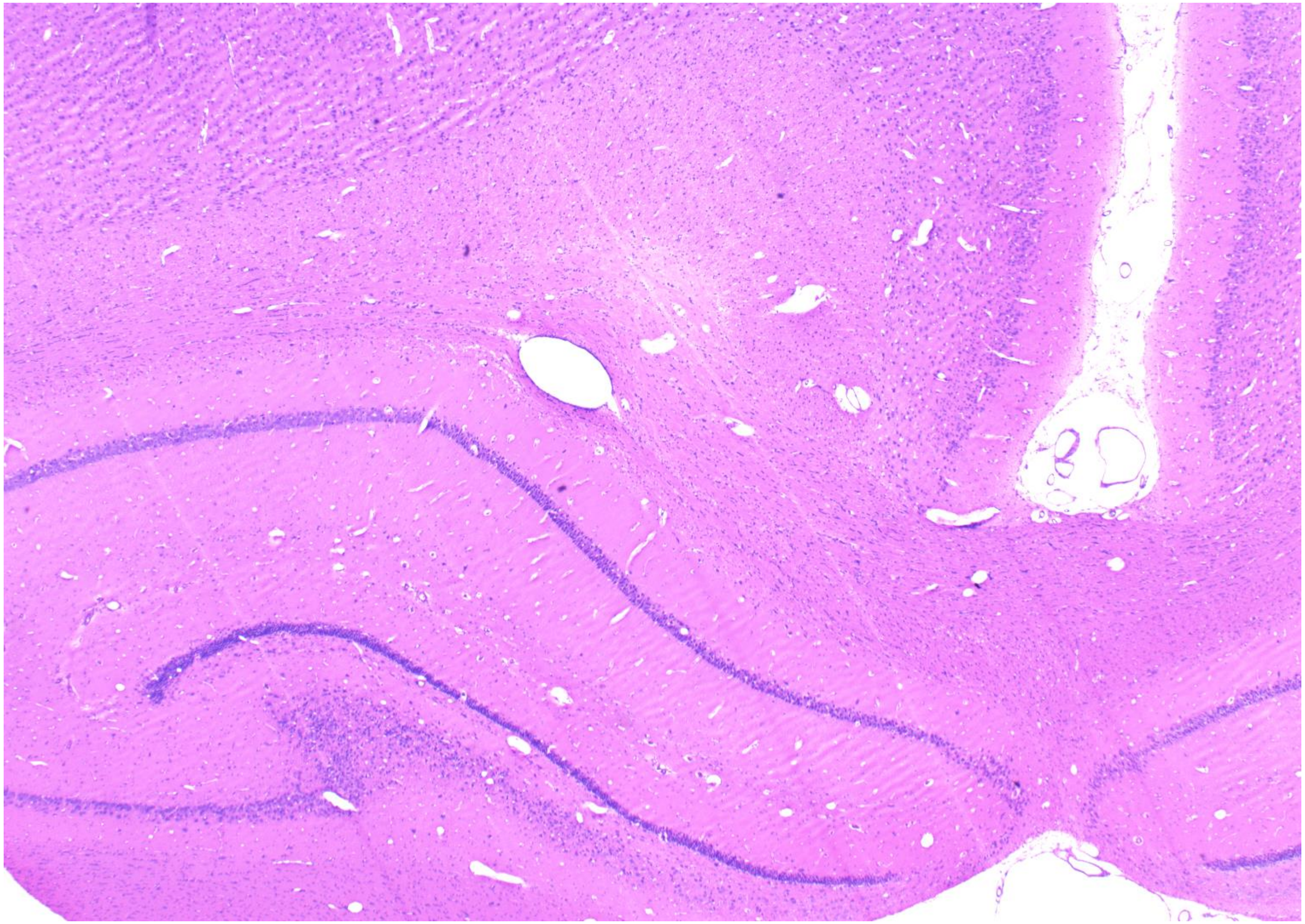


Work in collaboration with Kerry O'Banion
and Sean Hurley of University of Rochester

The higher magnification of the previous slide

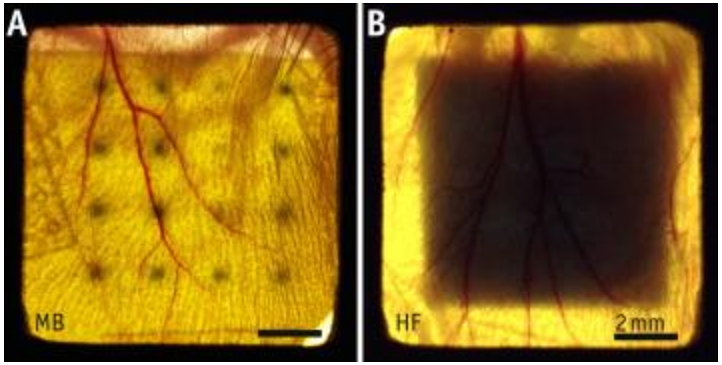


A slide 5.6 mm deeper than the central slide



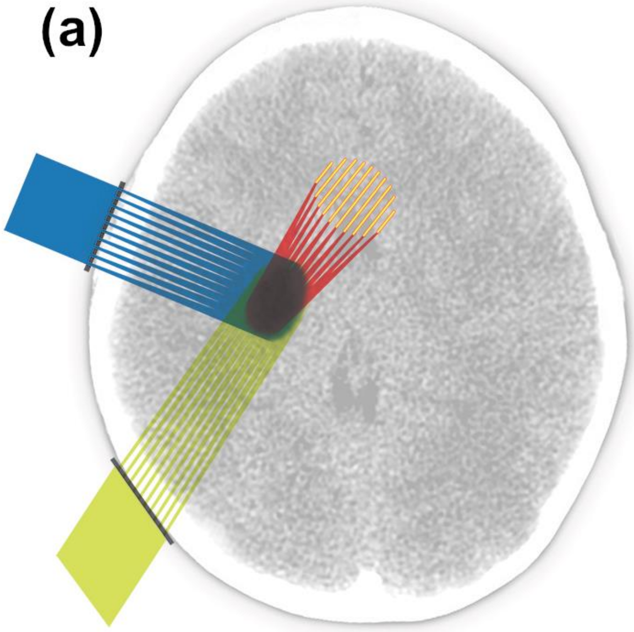
Tissue sparing of proton minibeams

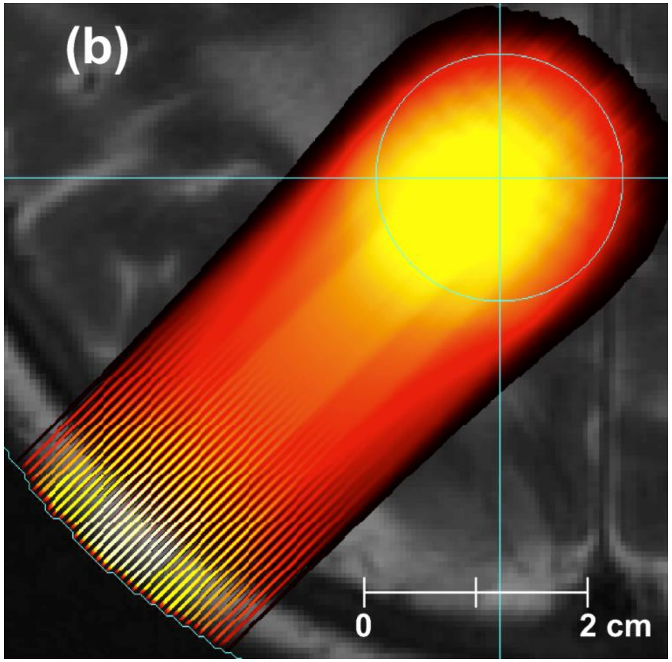
- Stefanie Girst, et al. of University of Munich have studied the tissue sparing of proton minibeams in the mouse ear (Radiation Oncology 2016) using 0.18 x 0.18 mm beams at 6,000 Gy. Solid beam irradiation at the same 60 Gy average dose produced tissue necrosis.



- John Eley of University of Maryland is carrying out studies with parallel planar proton minibeams on the rat's brain.

A second method of carbon-minibeam radiotherapy: Merging carbon minibeams at tissue depth





Dilmanian FA, Eley JG, Krishnan S. Int. J. Radiat. Oncol. Biol. Phys., 2015.

MCNPX simulation of the merging proton and lithium ion minibeams

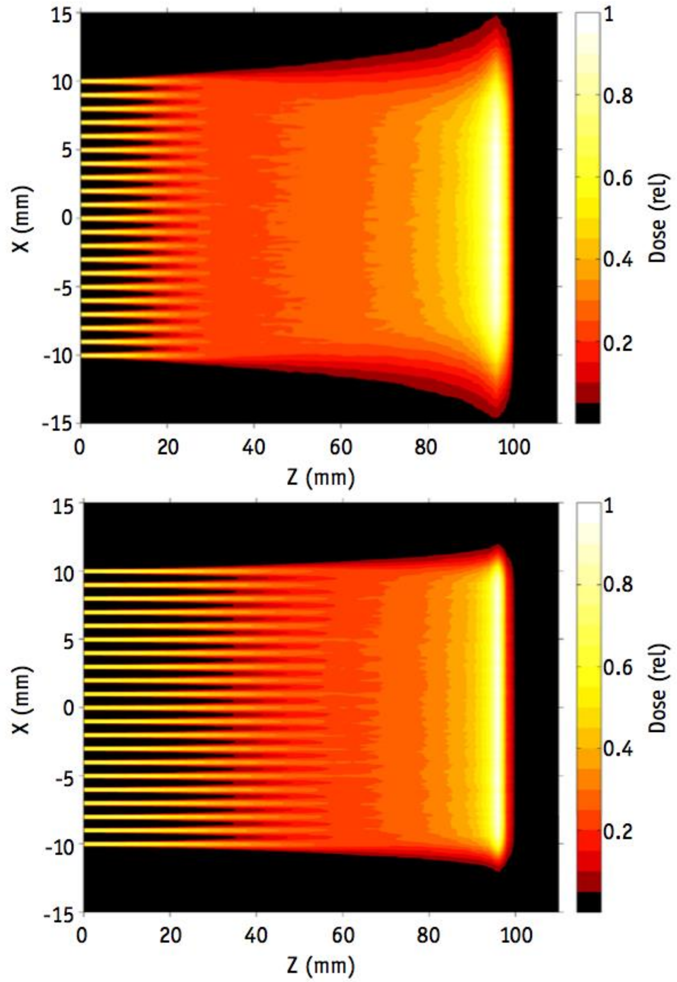
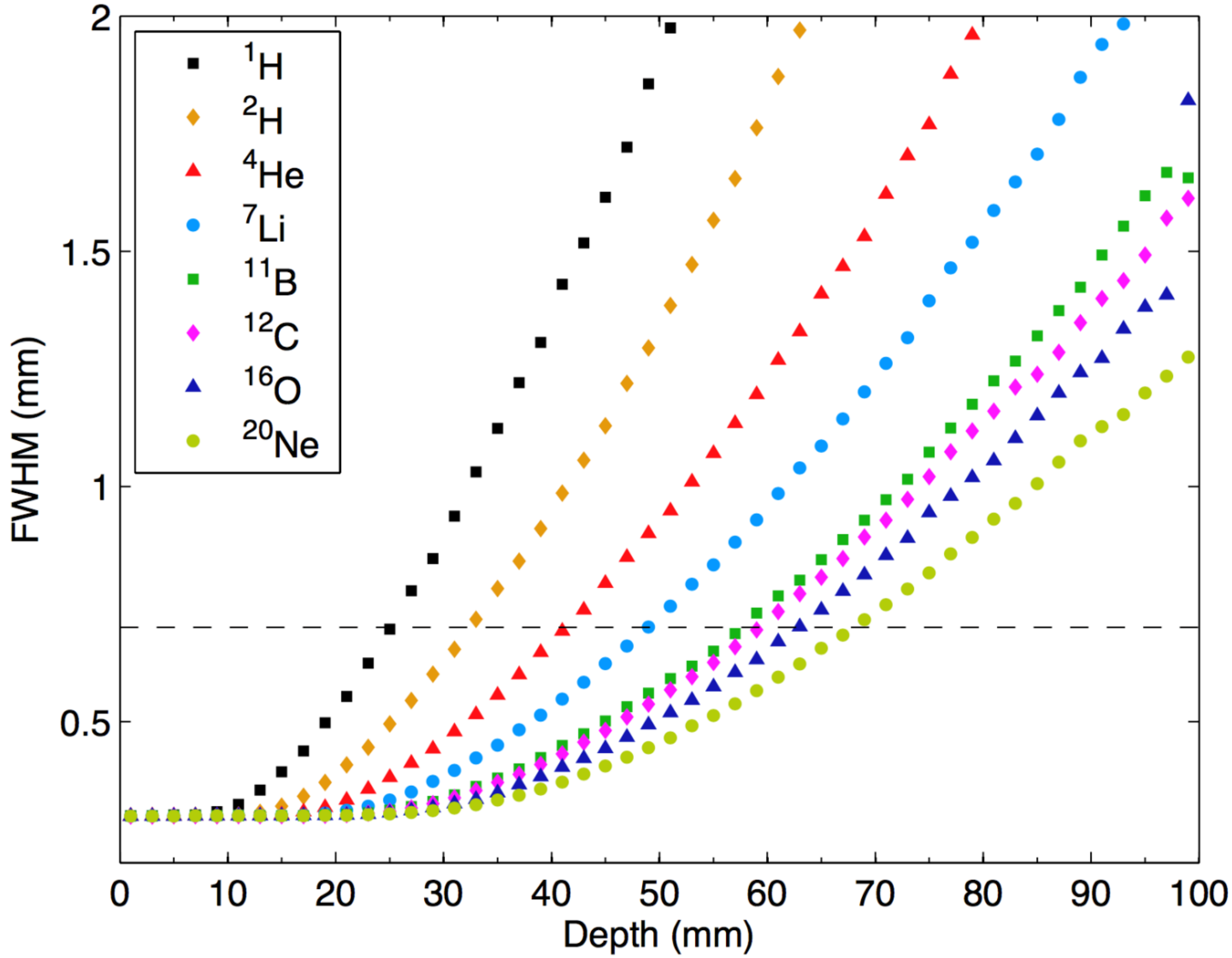
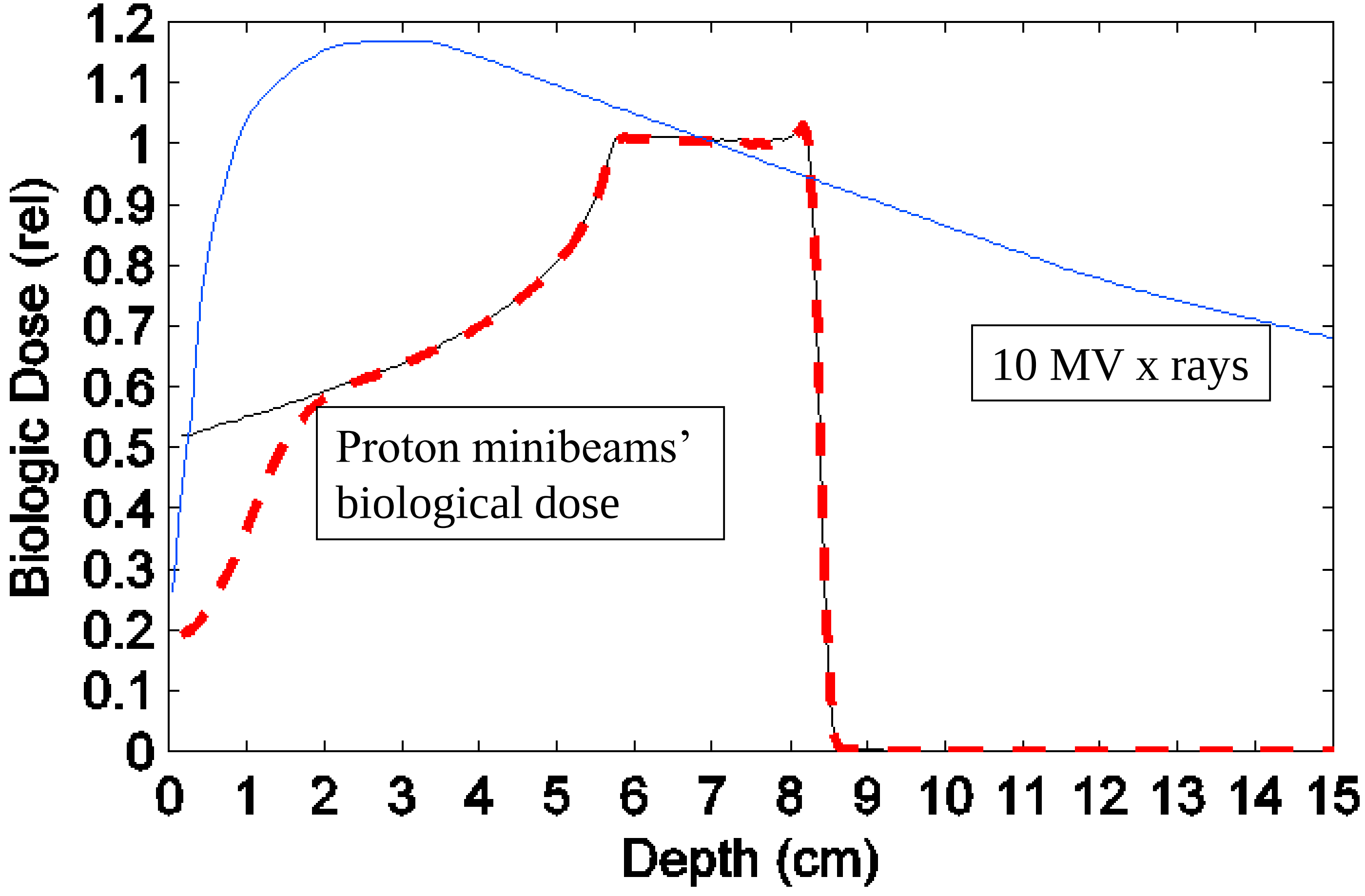


Fig. 5. MCNPX simulations of arrays of planar minibeams of 116-MeV protons (top) and 931-MeV Li-7 ions (bottom) of Figure 4. MCNPX = Monte Carlo N-Particle System.



MCNPX simulations of broadening in water of planar minibeams of protons and several light ions, and that for pencil minibeams of protons, all at energies producing 10 cm range in water.

Plateau dose for a 2.5-cm target in the brain



Advantages of the method over conventional carbon therapy

- Lower impact on the non-targeted tissues
- Possibly single-dose-fraction feature
- Possibly allowance for re-irradiation of recurrent brain tumors

Method’s main prospective applications as deduced from the clinical results coming out of Japan and Germany

- Radioresistant tumors and/or tumors residing among radiosensitive organs, in general.
- Specifically, tumors of the brain, spinal cord, spinal column, head-and-neck, and bone and soft tissue sarcomas.

Possible beam configurations in clinical implementation of the method

- Horizontal beam and a patient on a rotating chair.
- Gantry may not provide adequately parallel beam.

Acknowledgents

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- Voices against Brain Cancer.