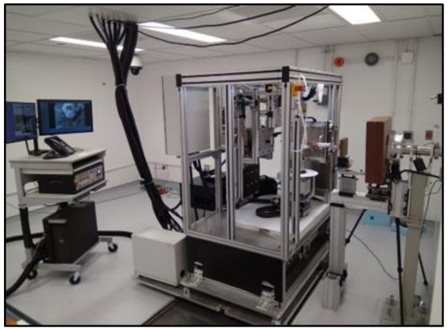
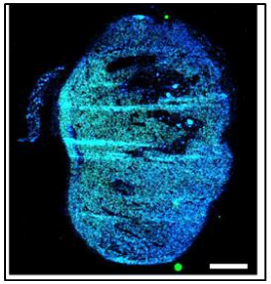
FLASH Proton Experiments at Penn

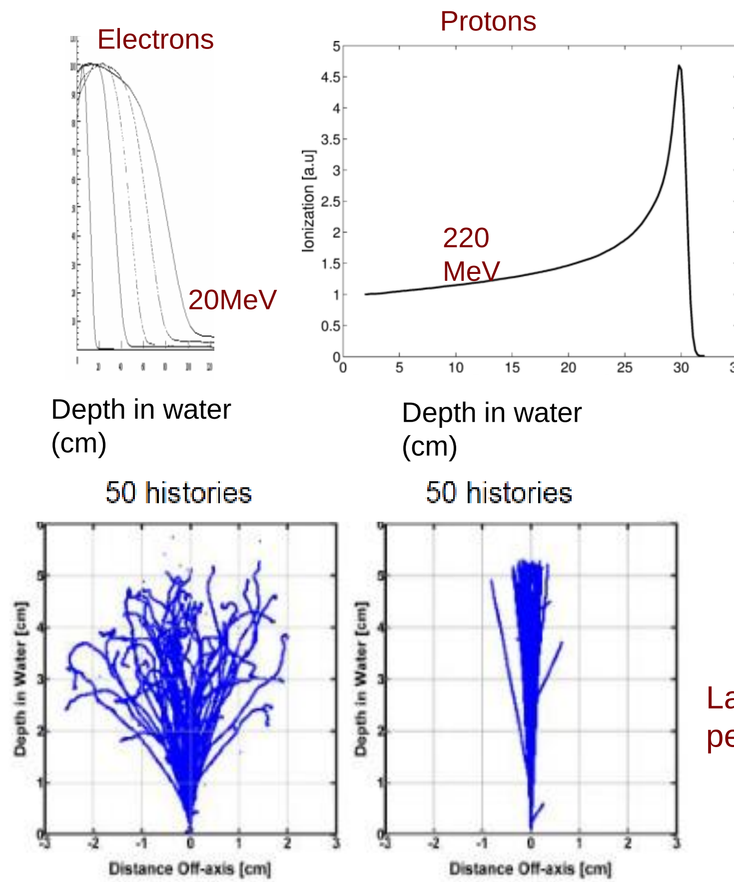
- **Eric S. Diffenderfer, Ph.D.**




Beam Characteristics: Protons vs. Electrons

- **Treating deep-seated tumors**
- **Better dose conformality (small lateral penumbra)**
- **Easier to upgrade from commercial systems (cyclotron-based)**
  - Already at high dose rate
  - Pencil beam scanning
  - Record & Verification



Depth Dose Curves

Lateral penumbra

Courtesy L. Dong

How do we determine the biological effects of proton FLASH?

Measuring in-vivo RBE with proton beams is technically challenging and highly variable.

Reducing the uncertainty in physical beam parameters can improve the variability and reproducibility of radiobiology dose rate experiments.

Our goals for implementing pFLASH

1. Reduce uncertainty due to beam delivery and positioning

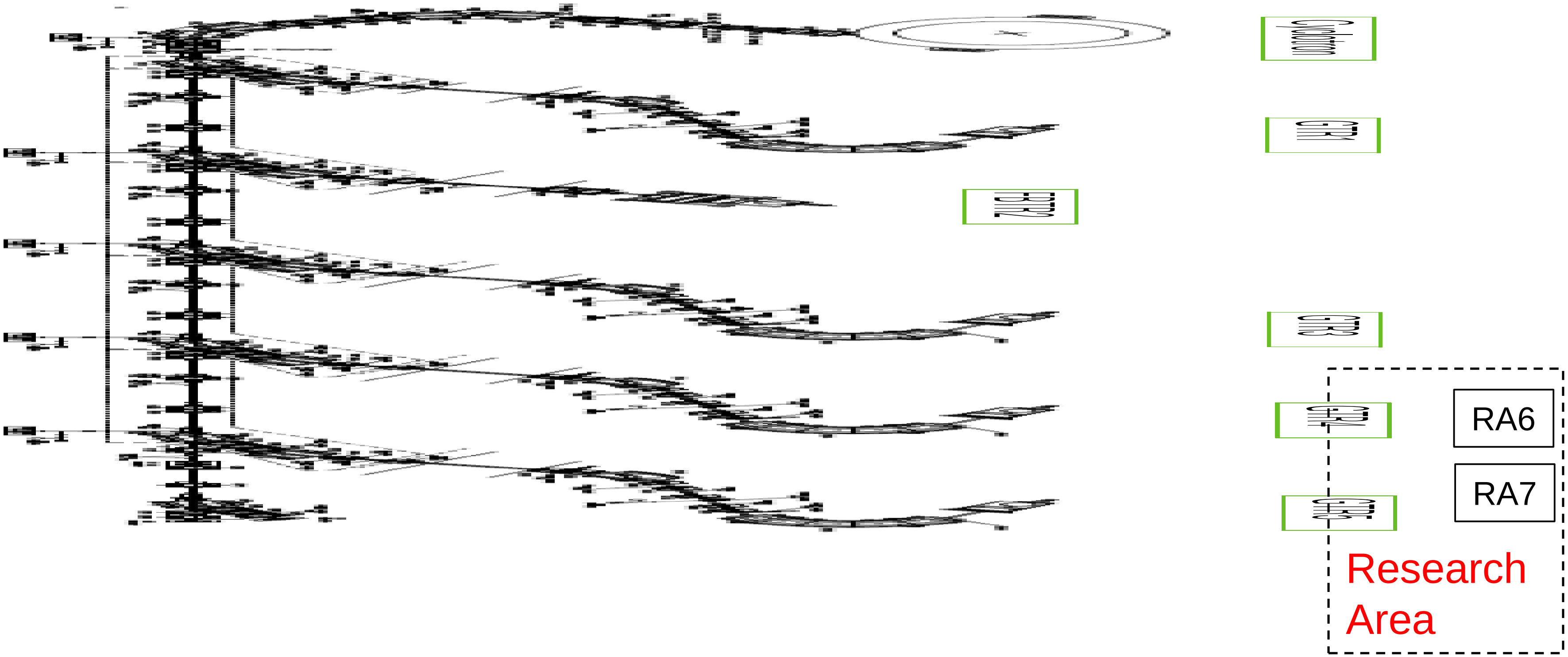
2. Reduce uncertainty due to dosimetry at high dose rates

3. Reduce uncertainty due to dose rate variation

1. Reduce uncertainty due to beam delivery and positioning

Proton Research Room at Penn

- **The Robert's Proton Center includes a fixed beam room with 2 beam lines dedicated for research.**

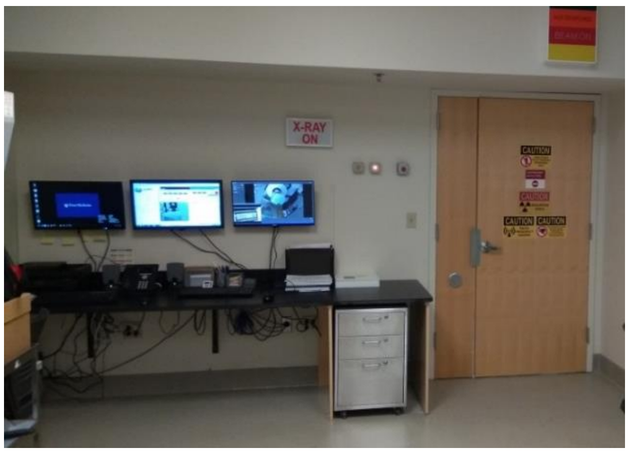


Proton SARRP

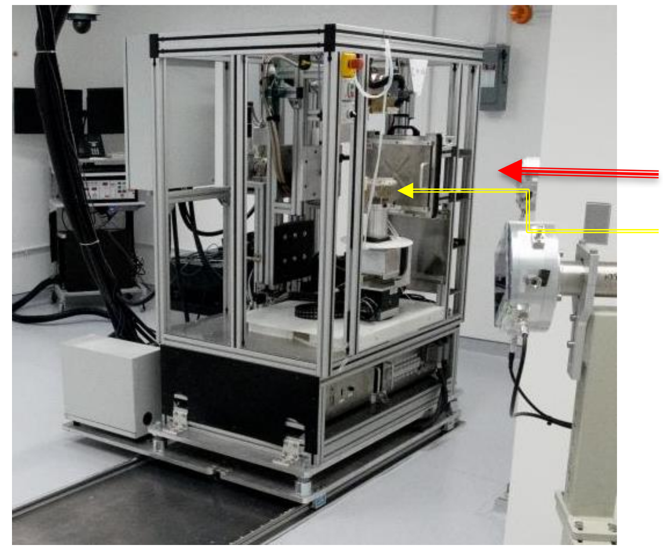
- Roberts Proton Therapy Center
  - IBA Proteus Plus C230 Cyclotron
  - 5 clinical treatment rooms (4 gantry and 1 fixed beam)
- Dedicated research room
  - Small Animal Radiation Research Platform (SARRP) on rails

Small Animal Radiation Facility-SARRP with proton beam layout

Prep/Control room with enclosed Photon SARRP,
remote anesthesia/proton beam operations



Vault with Image-Guided Proton/Photon irradiator

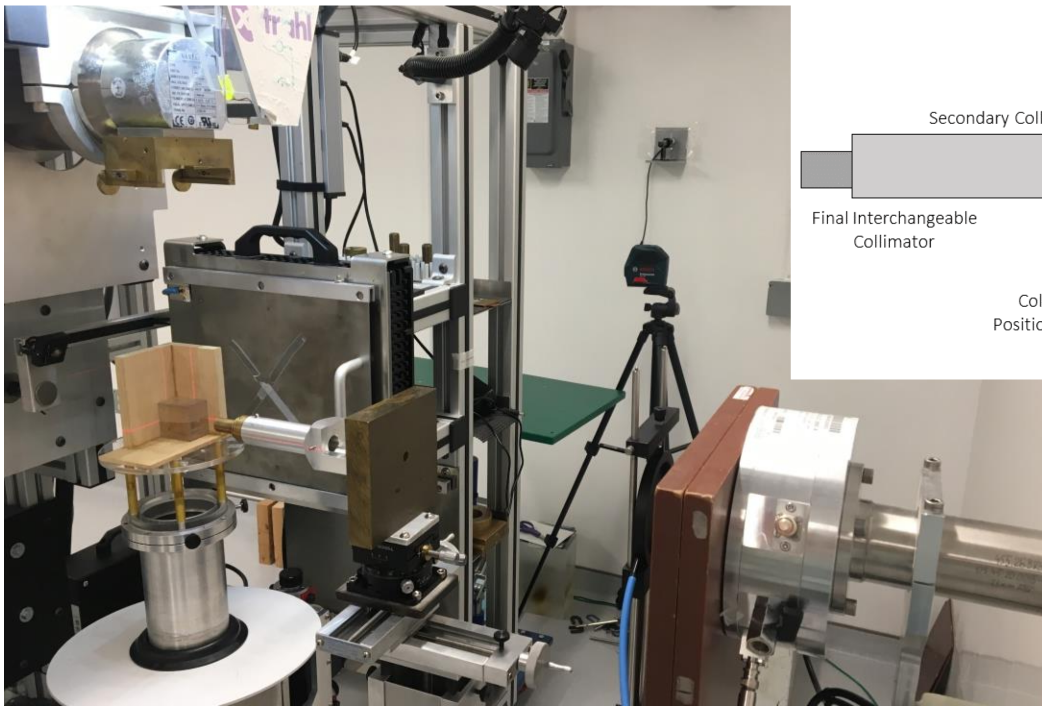


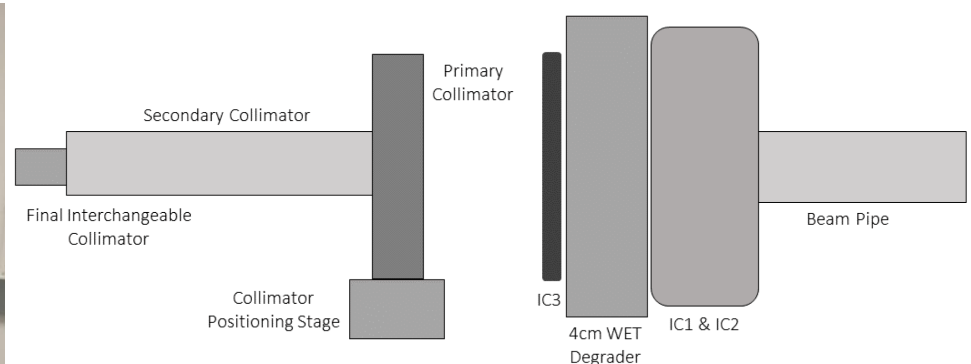
<u>Facility supports</u>:

- 23 Penn investigators for animal RT
- Core Facility for P01 “Immune Checkpoints and Radiation in Cancer”
- Current FLASH RT efforts

Collimation and on-line dose monitoring

- **Collimation system designed for proton field sizes appropriate for small animals**
  - Interchangeable brass collimators
  - Field sizes of 0.5-10 mm width achievable



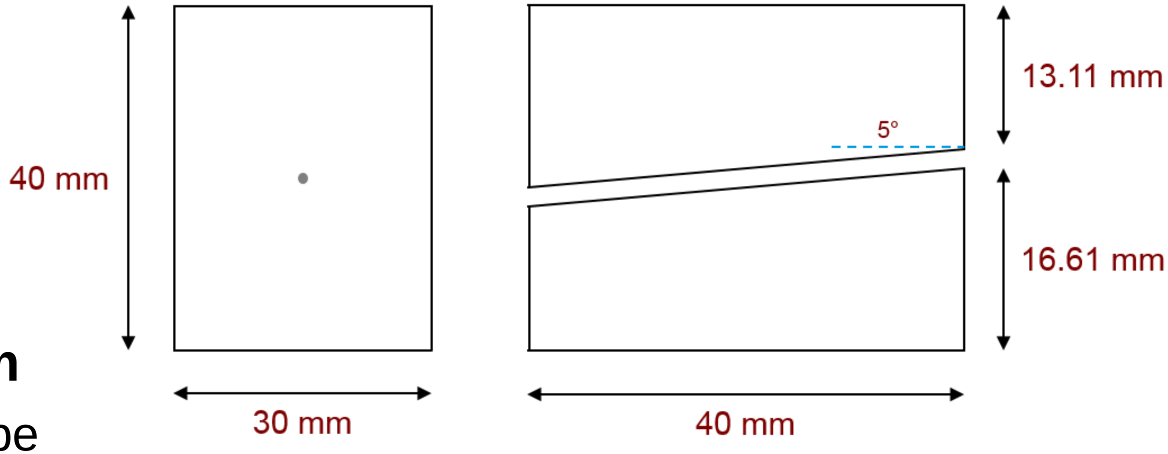


- On-line monitoring with IC2 and IC3
  - IC2 with dual channel readout electrometers
  - IC3 (thin window Bragg peak chamber)

Baseline and QA System

- **A QA program developed to help maintain reliability**
  - Alignment between SARRP/imaging isocenter and proton isocenter
  - Energy/PDD verification
  - Beam profile
    - Flatness
    - Symmetry

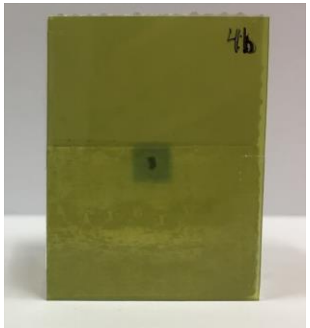
- **3D printed QA phantom**
  - 3 cm x 4 cm x 4 cm cube
  - EBT3 Gafchromic film

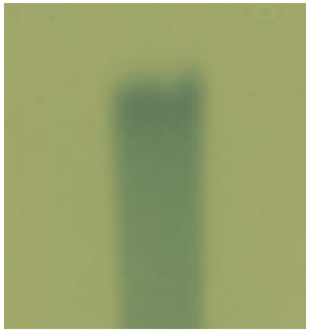


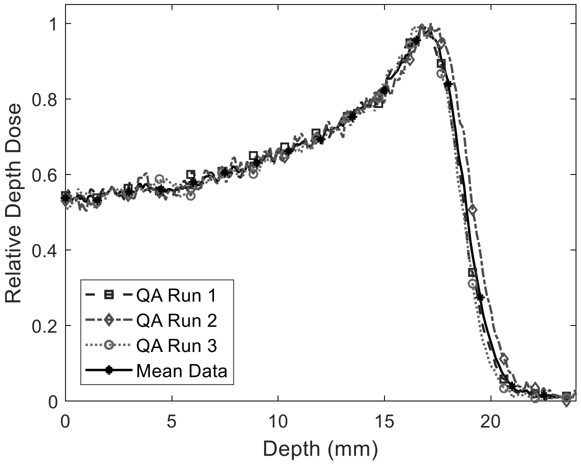
Kim MM, Irmen P, Shoniyozov K, et al., Phys Med Biol (2019)

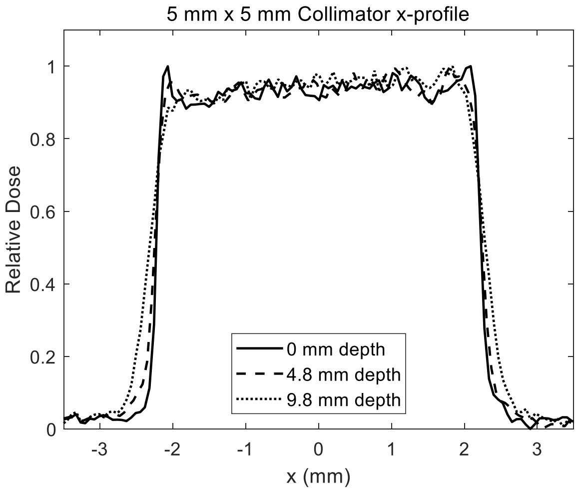
QA Phantom Results

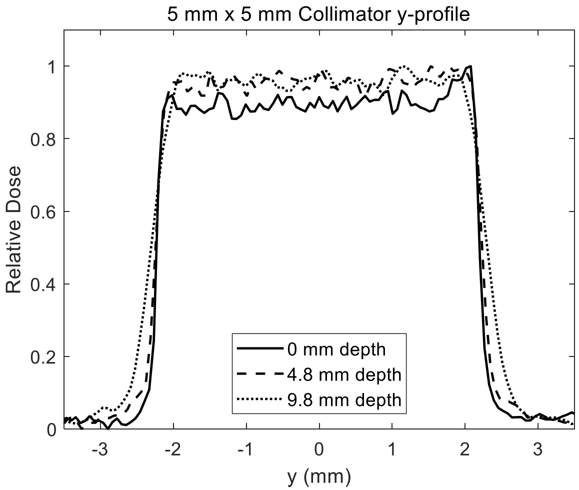
- **Isocenter alignment within 0.12±0.04 mm between SARRP/imaging isocenter and proton beam isocenter**
- **Flatness and symmetry < 6%**
- **Range variations < 1 mm**







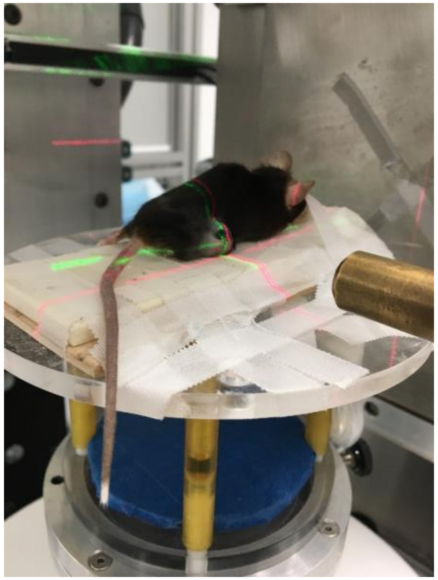


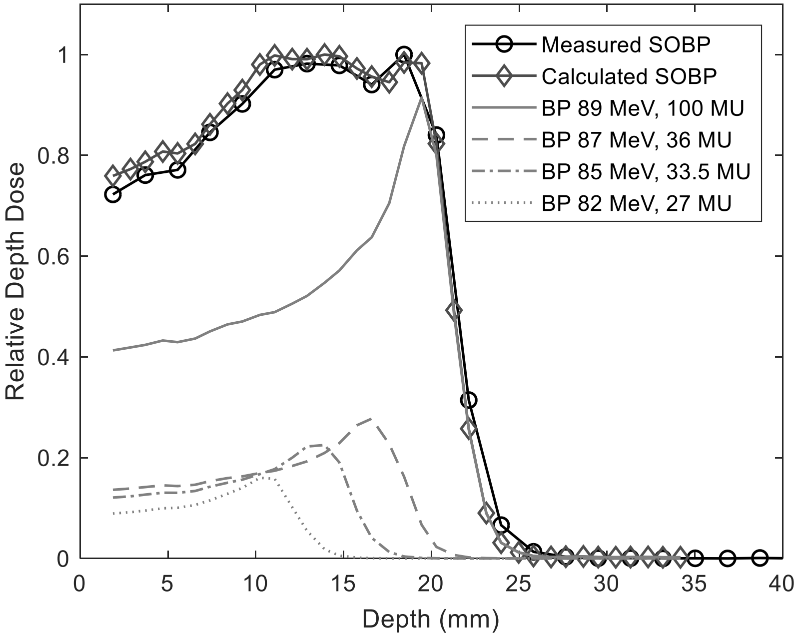


Kim MM, Irmen P, Shoniyozov K, et al.,
Phys Med Biol (2019)

Spread Out Bragg Peak (SOBP)

- **Using measured monoenergetic beam characteristics, SOBPs can be generated**

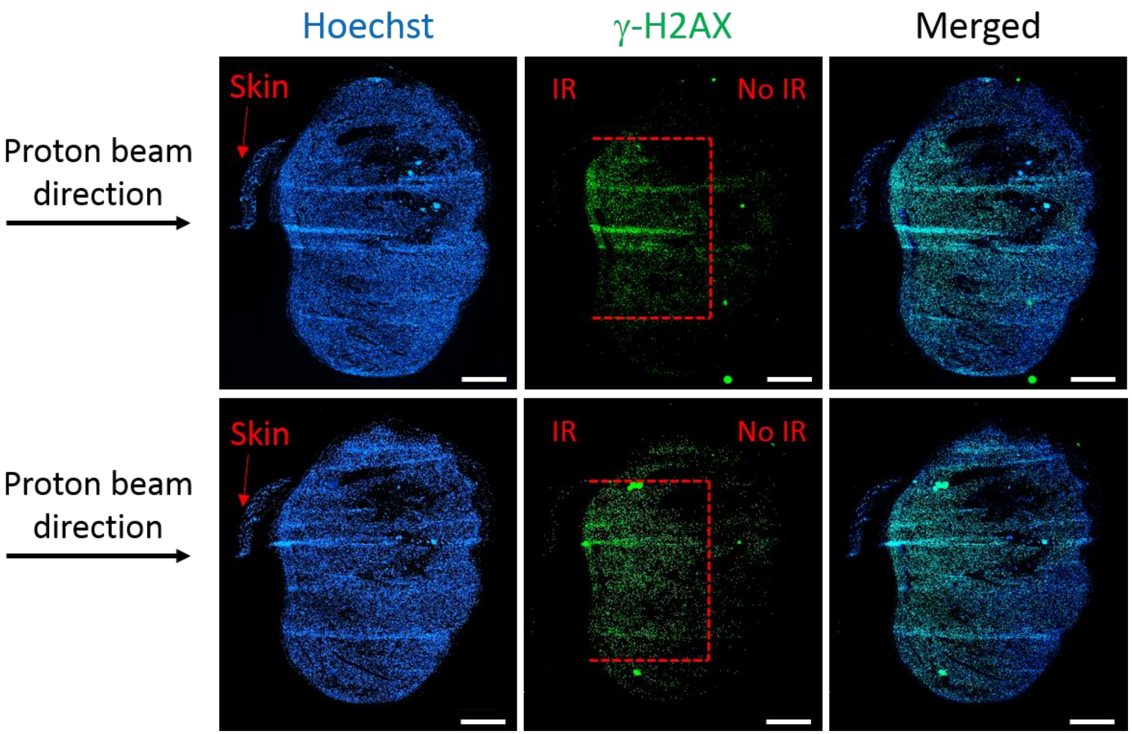




Kim MM, Irmen P, Shoniyozov K, et al.,
Phys Med Biol (2019)

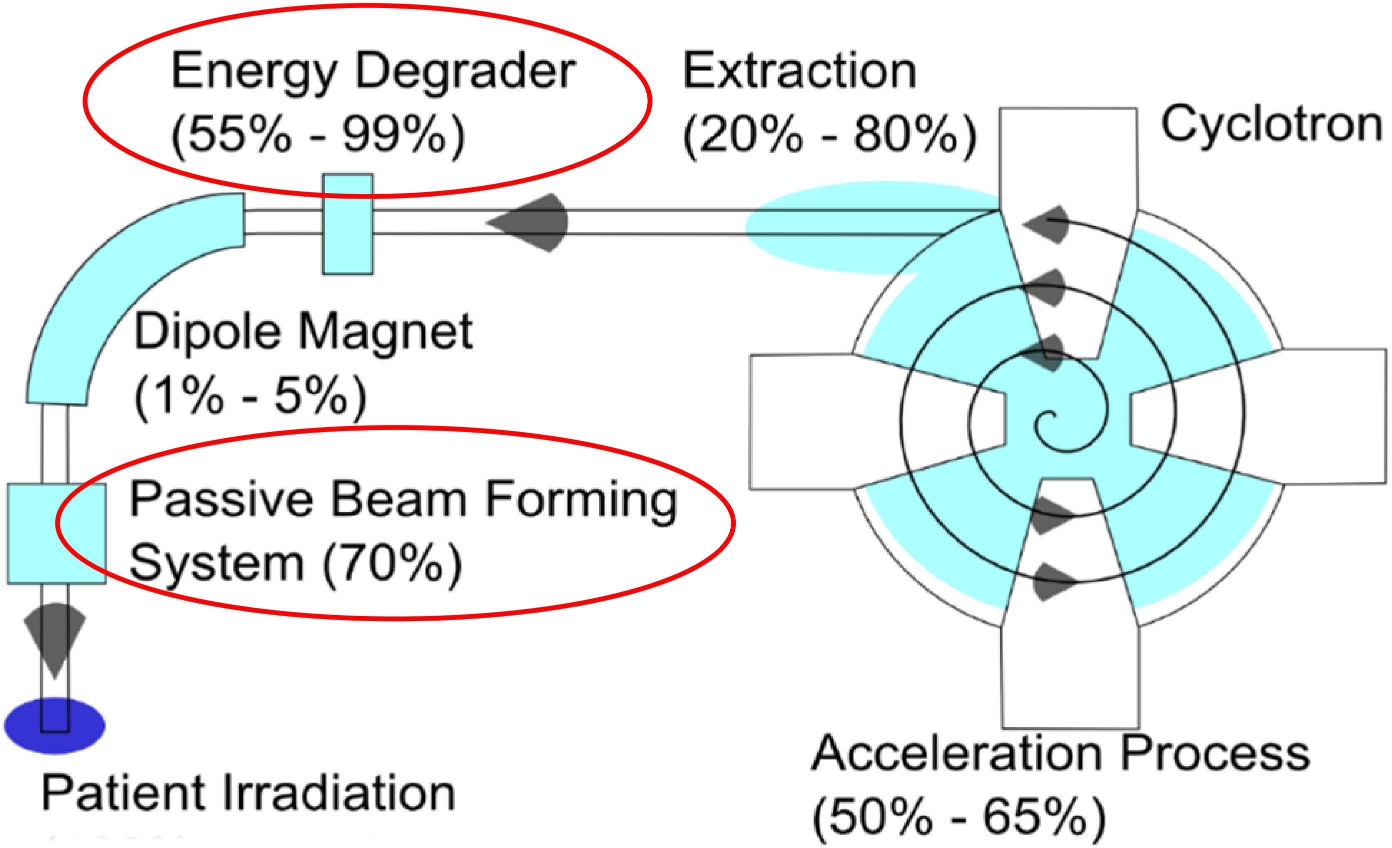
Low energy, low dose rate mouse Study

- **DNA double strand breaks shown with γH2AX staining in a mouse tumor model**
  - C57BL/6 mouse with flank tumor
  - 89 MeV (6.3 g/cm^2 range)
  - 5 x 5 mm^2 collimator
  - 2 cm WET bolus for Bragg Peak at 3 mm depth



Kim MM, Irmen P, Shoniyozov K, et al.,
Phys Med Biol (2019)

Beam Loss in Typical Proton Therapy Systems

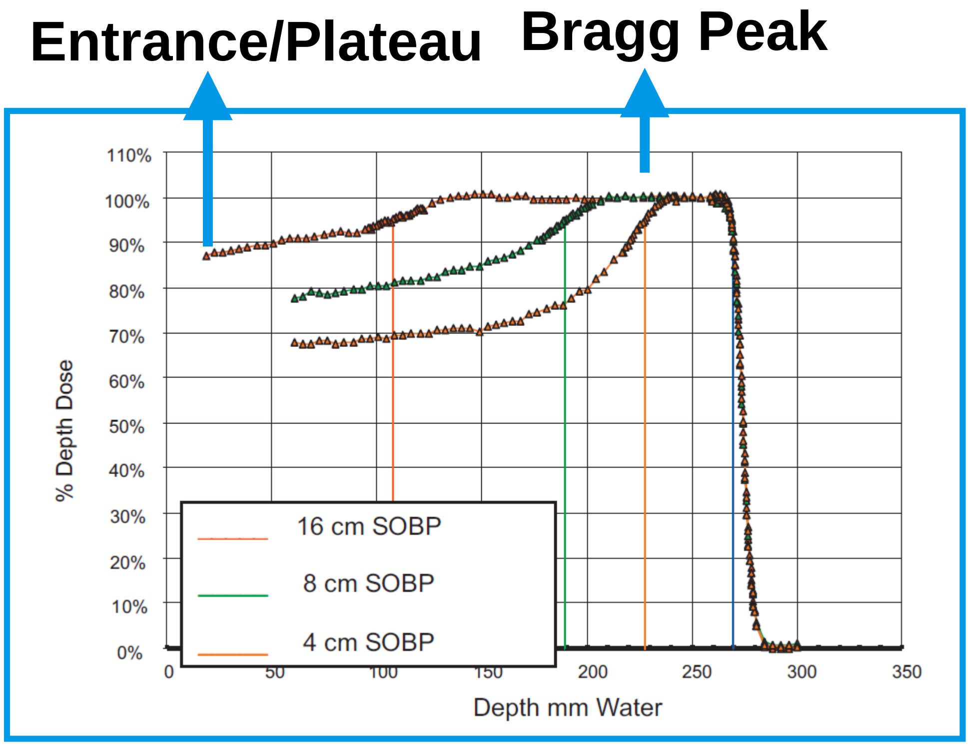


Courtesy L. Dong

Achieving FLASH dose rates

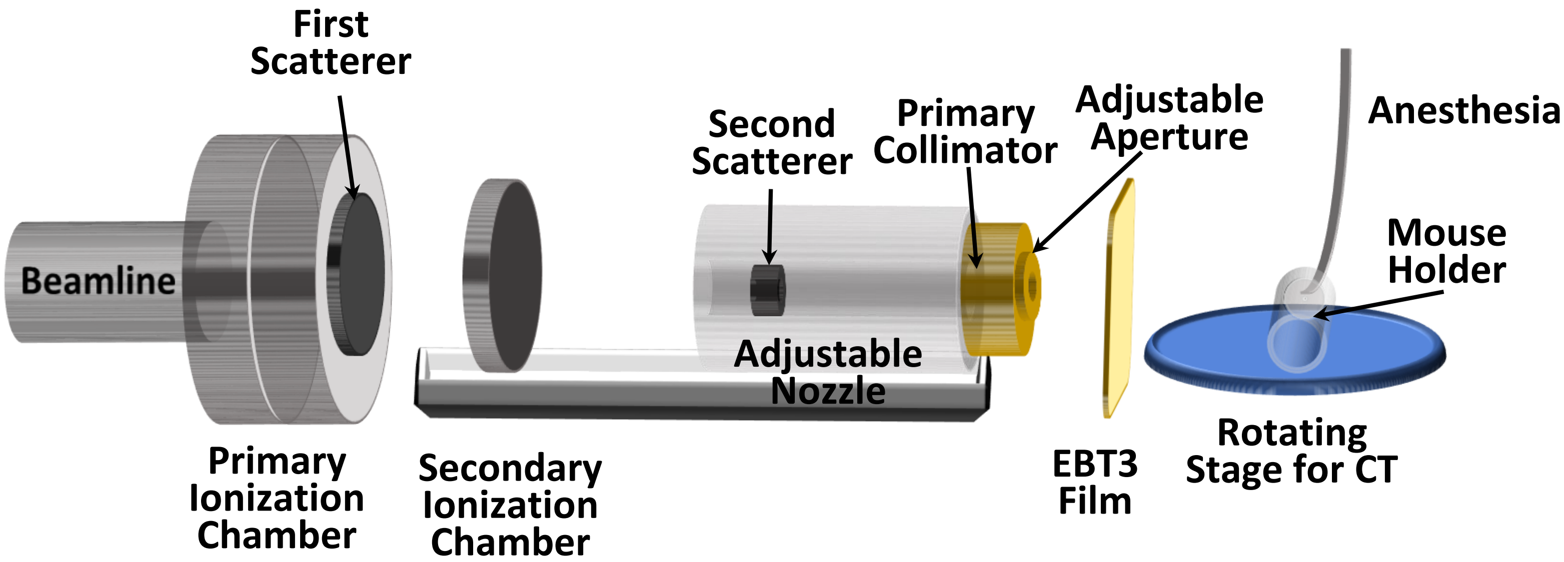
- Beam utilization efficiency drops with range in water, field size, nozzle design, and cyclotron extraction efficiency
- Bragg Peak enhancement is less than a factor of 3

Energy /MeV	Total Beam Loss
230	25%
215	53%
195	75%
175	87%
155	93%
135	96%
115	98%
95	99%
75	99.4%



Courtesy L. Dong

We implemented a double scattering system to efficiently increase the field size



Diffenderfer *et. al.* IJROBP 2020

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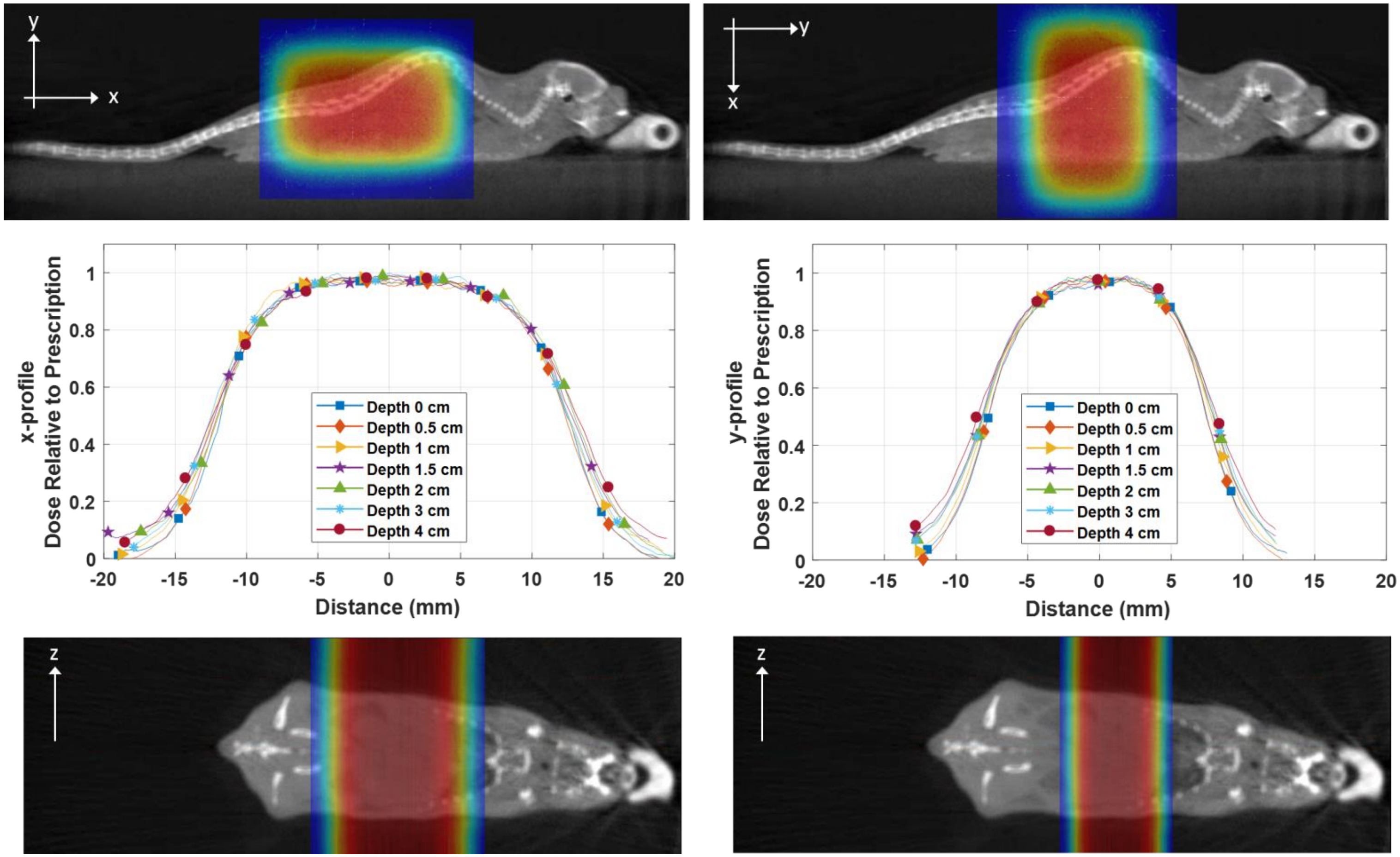

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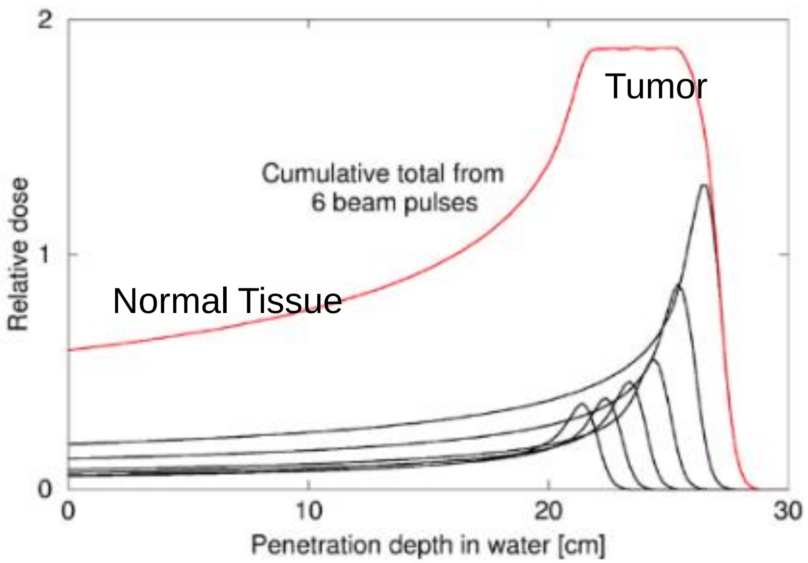
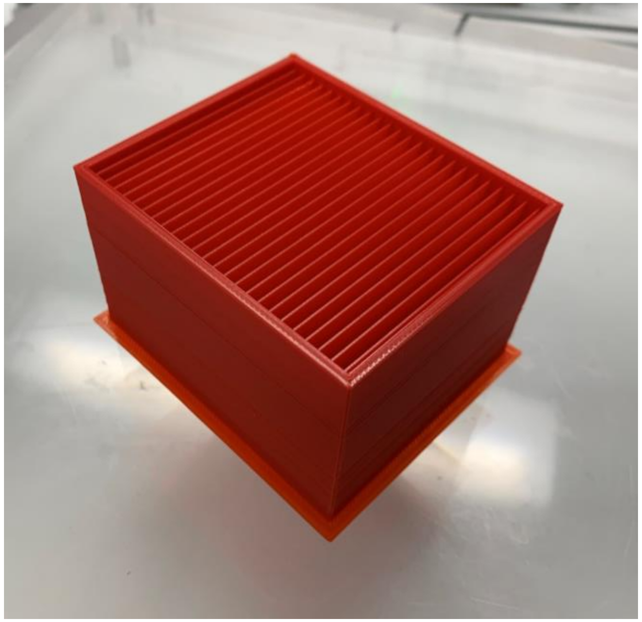
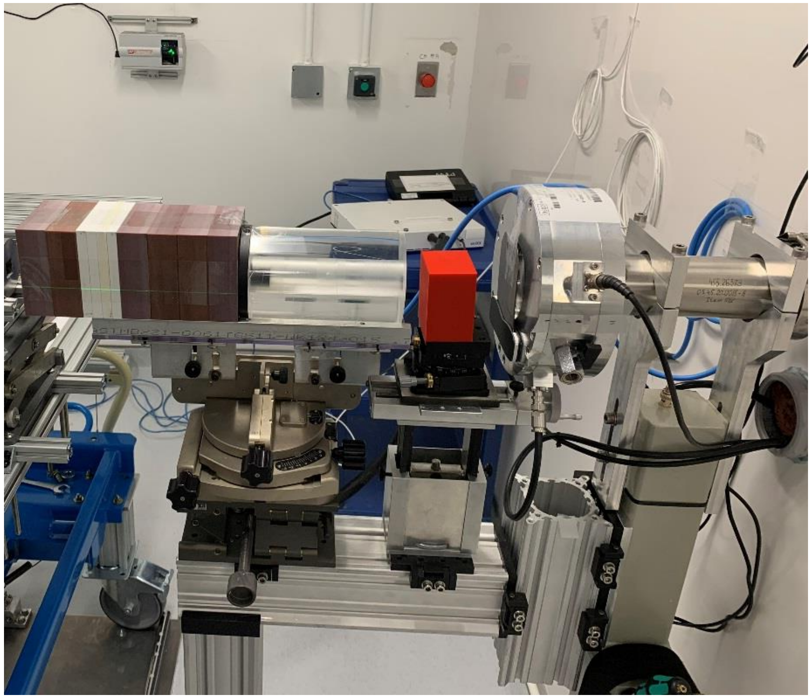
Plateau vs. Bragg Peak

- **Bragg Peak**
  - High LET
  - Higher ionization density
  - Is there a FLASH effect at the Bragg Peak as in the plateau region?

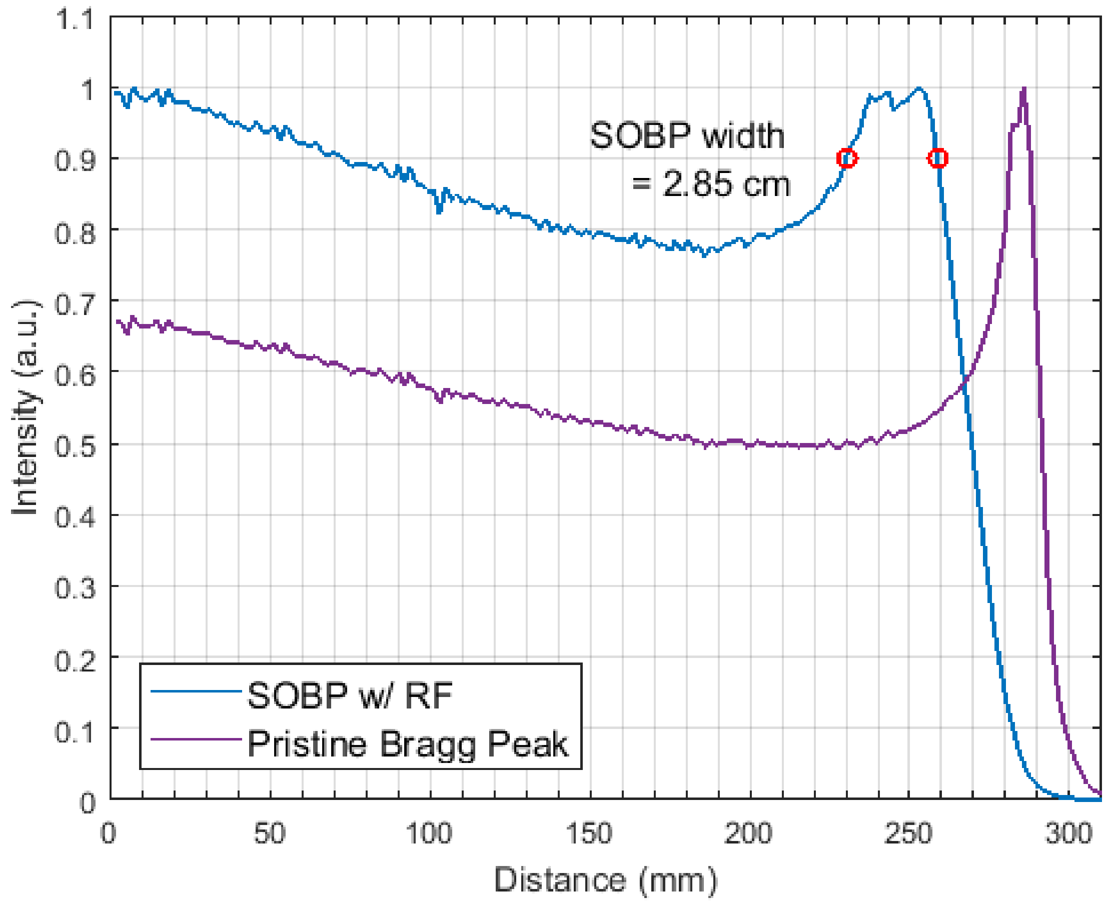


We implemented a ridge filter to efficiently generate an SOBP





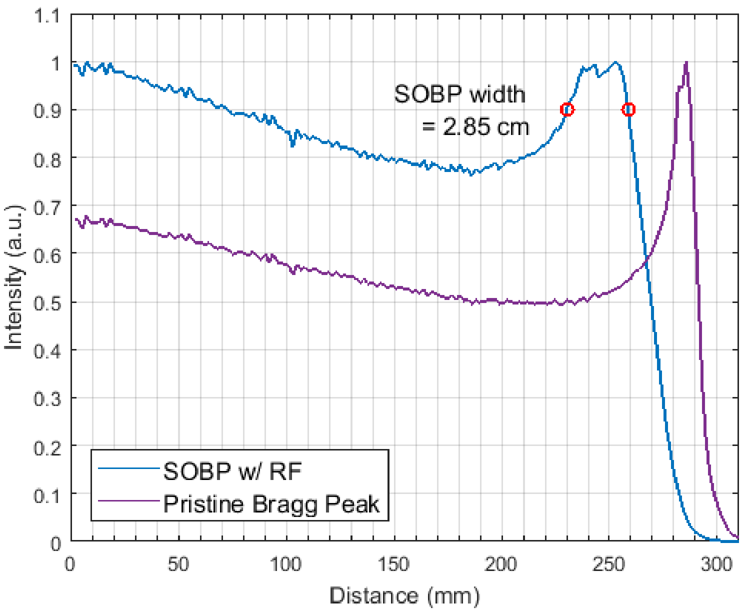
Double scattered Bragg Peak + ridge ridge filter

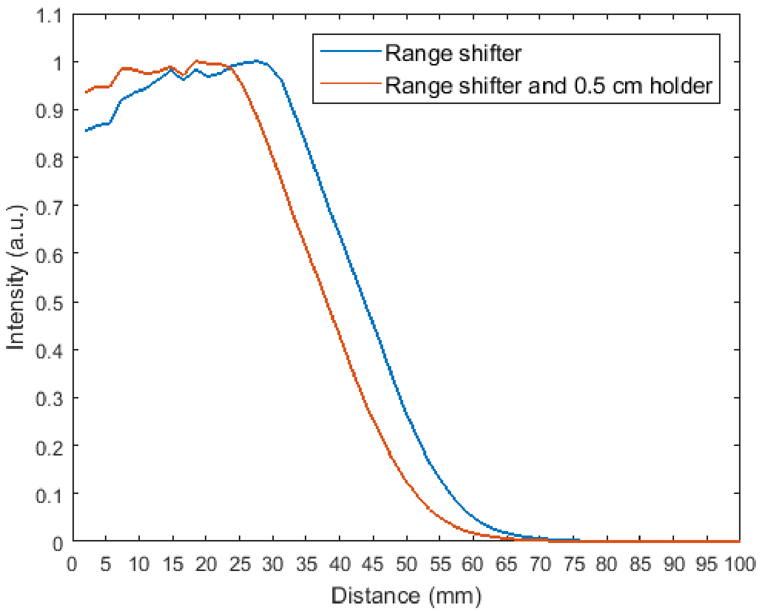


We implemented a ridge filter to efficiently generate an SOBP

Add range shifter for treating shallow targets.

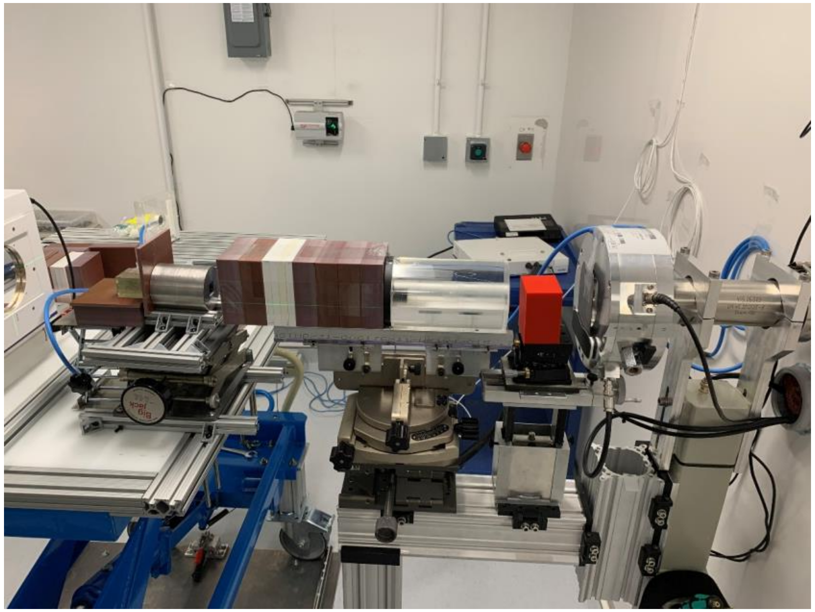
Lots of scattering/range straggling leads to long distal falloff.

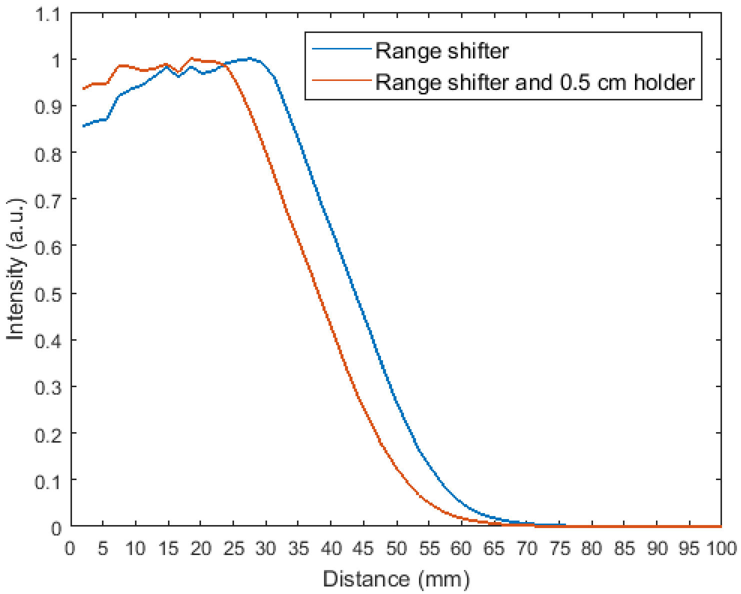




In a mouse sized phantom

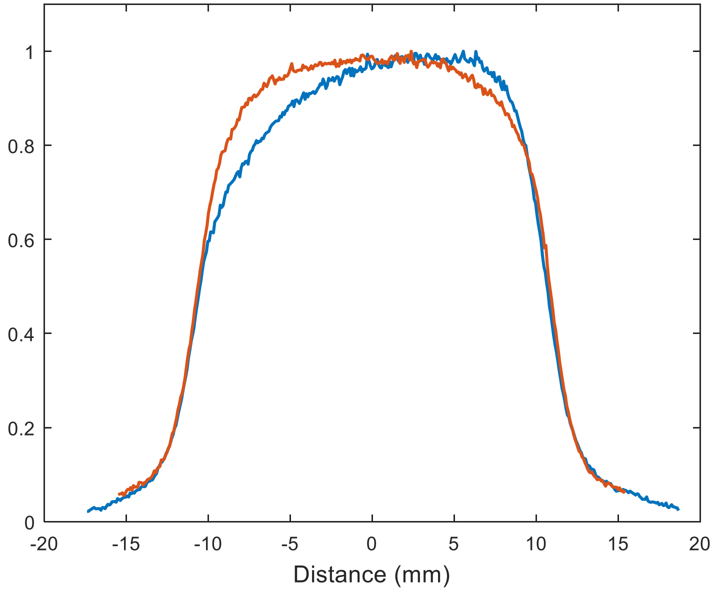
- 22 cm SW range shifter
- Mouse holder has 0.5 cm WET

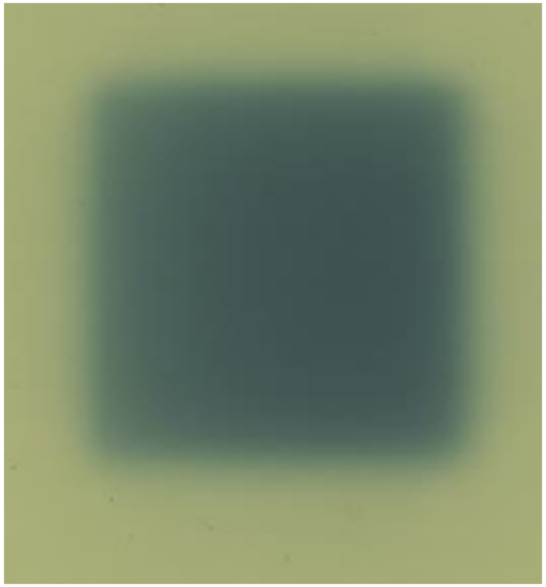




Film profile at Bragg Peak

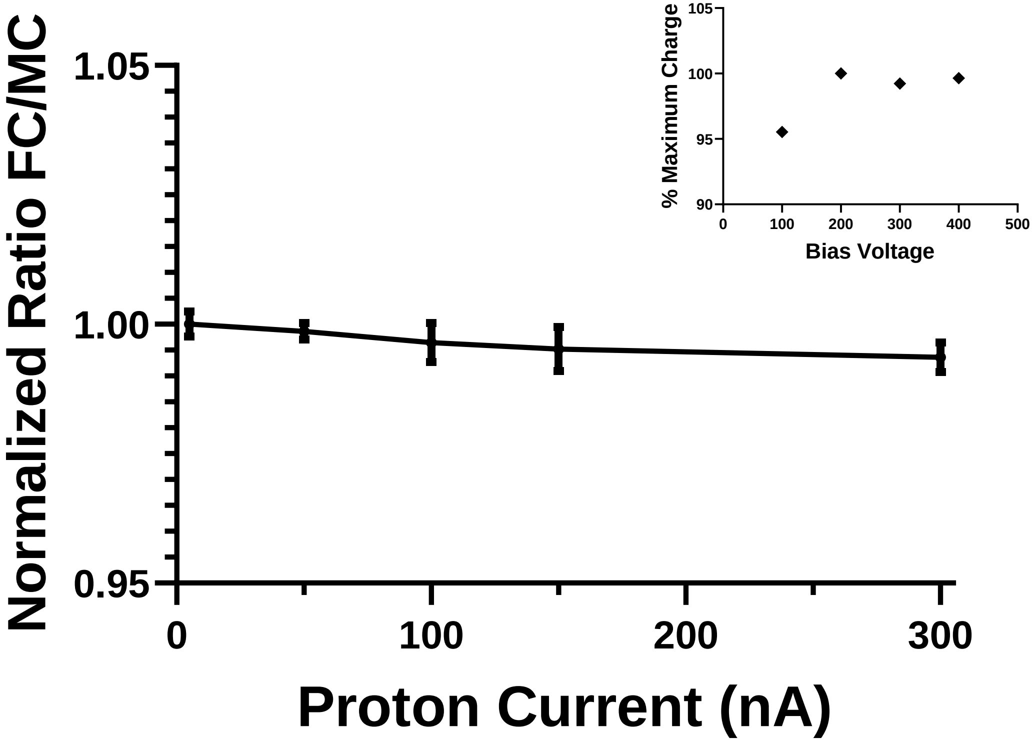
- 2 cm x 2 cm collimator
- Uniform field with double scatterer





2. Reduce uncertainty due to dosimetry at high dose rates

We measured voltage saturation curves and recombination factors for the PTW Advanced Markus chamber.



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We verified results with a simple Faraday Cup.

- Ion collection efficiency should be verified, independent of dose rate

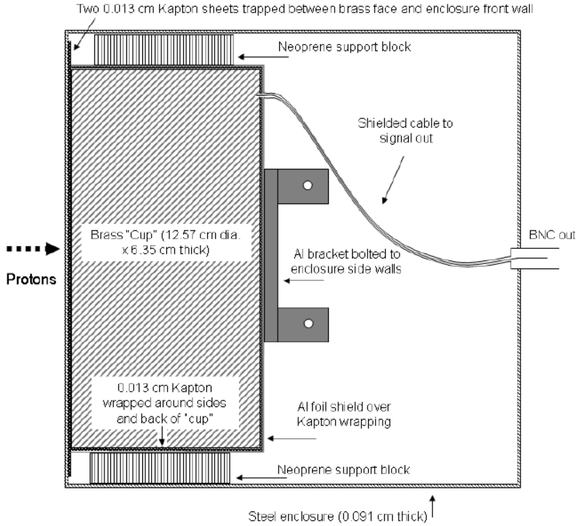
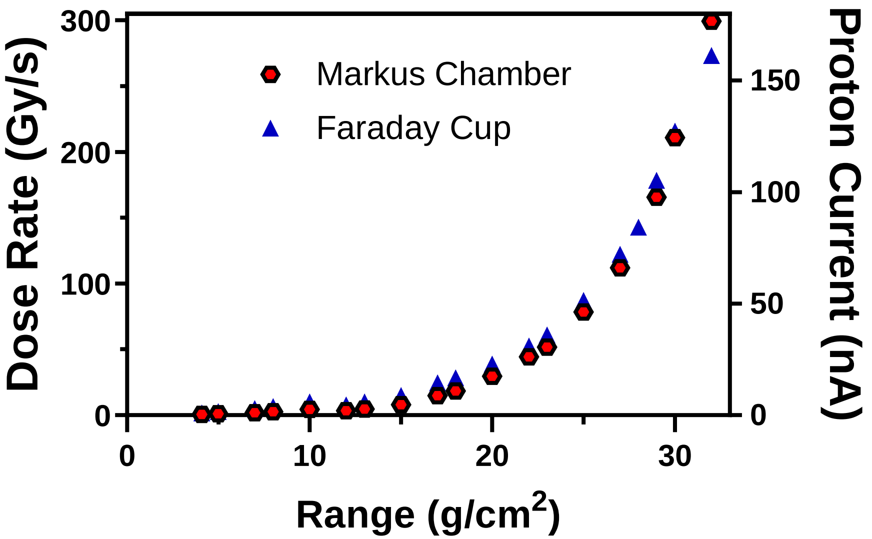


Fig. 4. A diagram of the EMC-2 vacuumless Faraday cup (the thickness of the Kapton and Al foil layers are exaggerated for clarity).



Cascio and Gottschalk IEEE 2009

Diffenderfer *et. al.* IJROBP 2020

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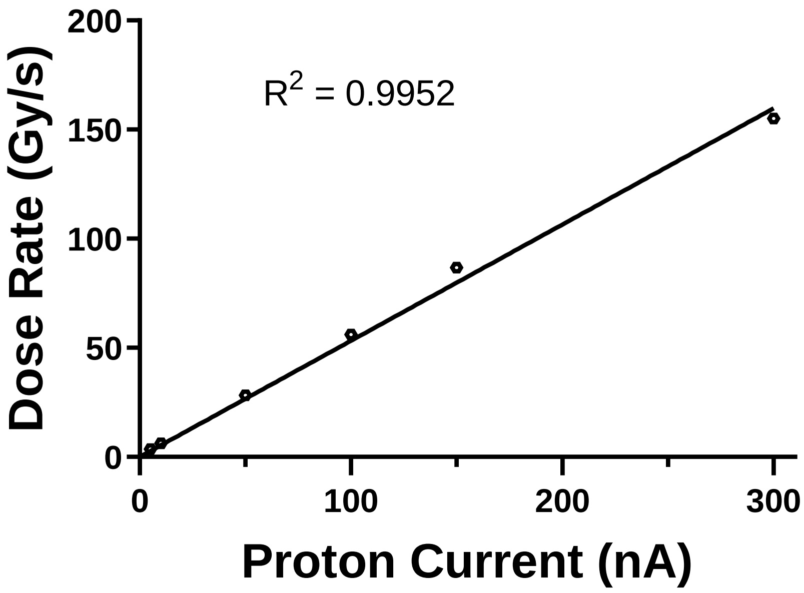

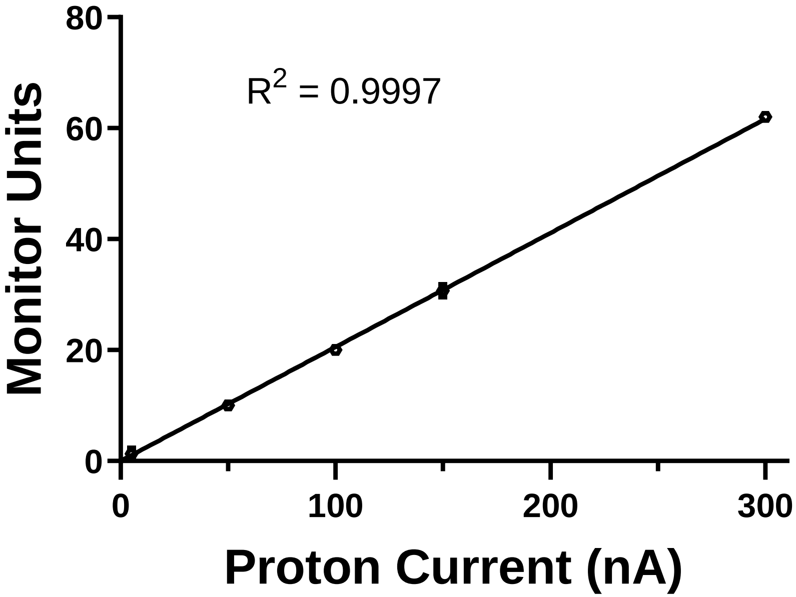

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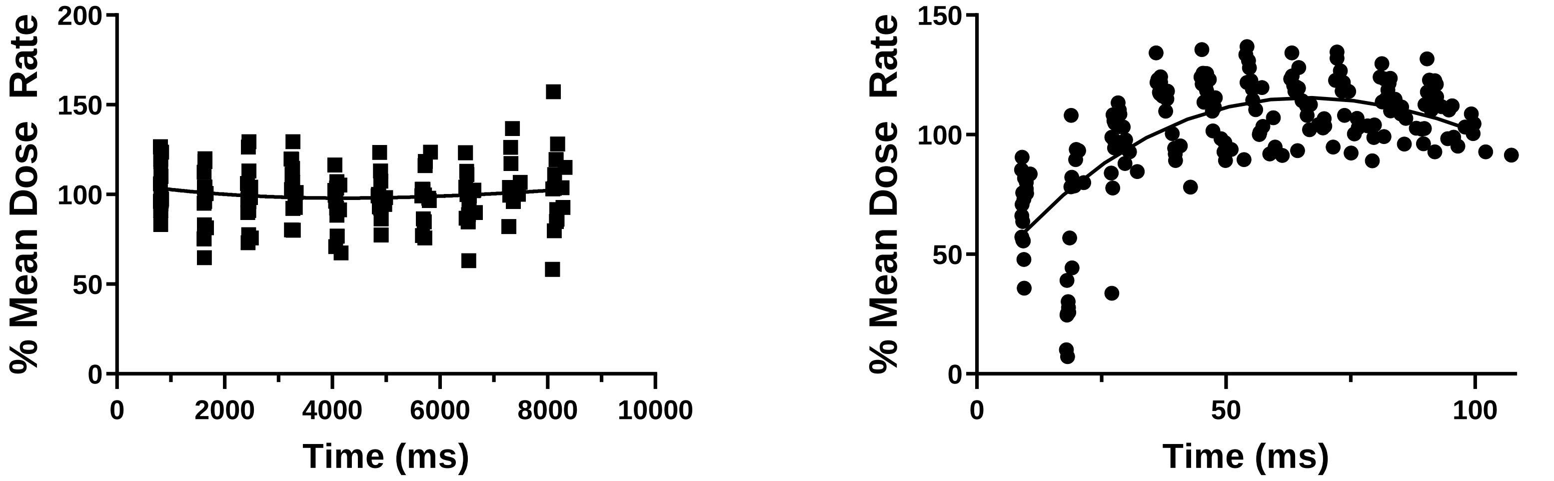
3. Reduce uncertainty due to dose rate variation

The proton beam current from the cyclotron exhibits variation over time.



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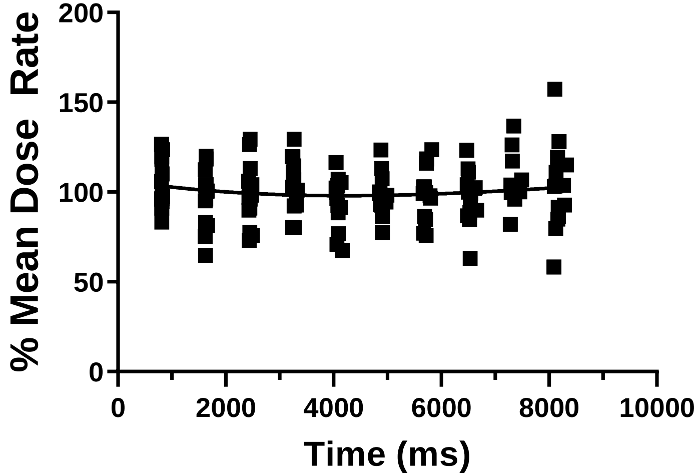
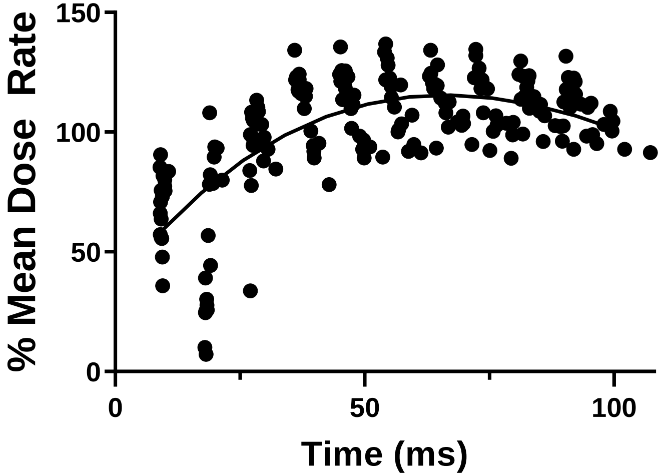
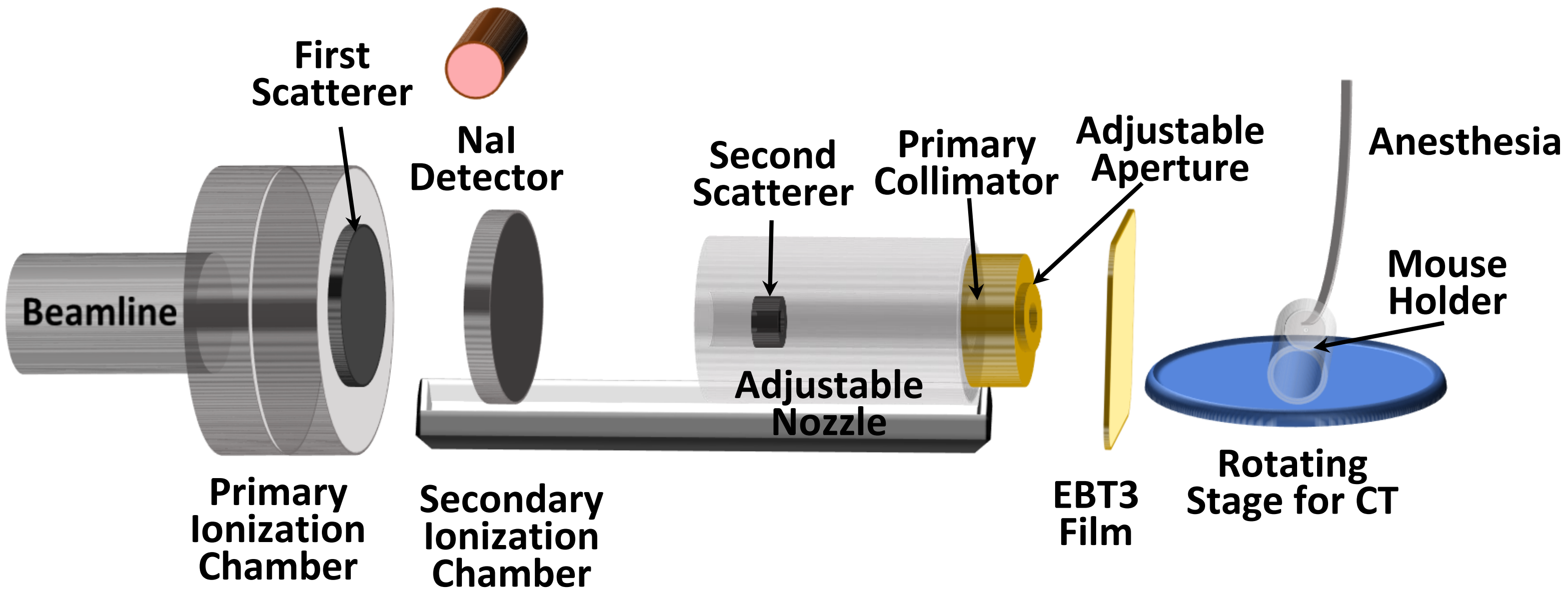
We measure the prompt gamma emission time trace to monitor intra beam dose rate variation.







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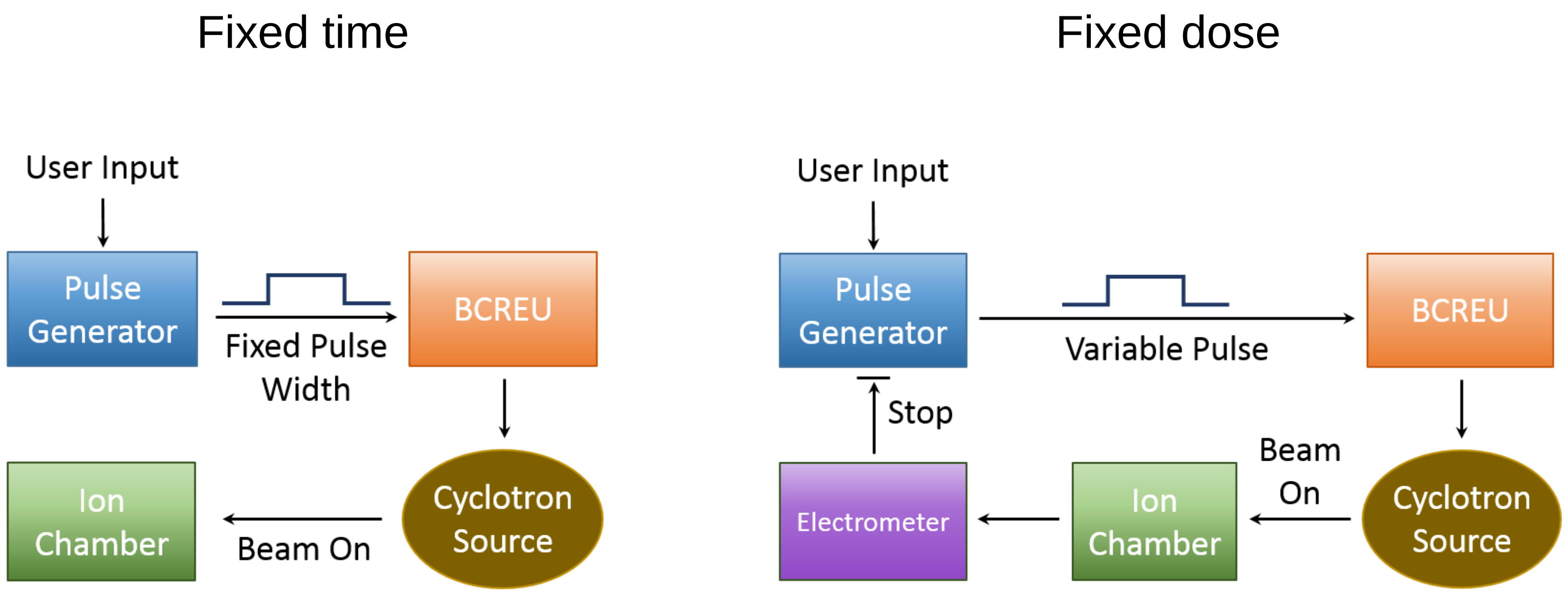
We implemented a dose counter with preset to control total dose delivery.



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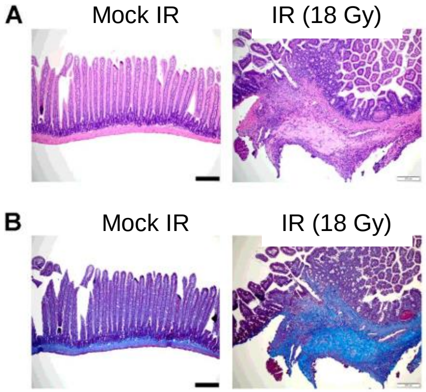
Measuring in-vivo RBE with proton beams is technically challenging and highly variable.

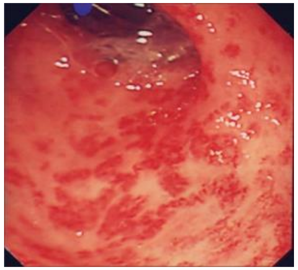
Reducing the uncertainty in physical beam parameters can improve the variability and reproducibility of radiobiology dose rate experiments.

Scientific Premise

- Radiation-induced intestinal injury (fibrosis, colitis, diarrhea, perforation) is a common side effect in patients with GI tumors.
- In cooperative group trials, using modest dose (40-50.4 Gy) chemoradiation after resection of pancreatic cancer,severe toxicities (grade 3 or higher) occurred in **~50%** of patients (Regine *et al., Ann Surg Oncol* 2011).
- This high rate of severe toxicity <u>limits the RT dose of abdominal radiotherapy to a low, ineffective dose</u>. Not surprisingly, local failure rates for PanCa in the postoperative setting often exceed 50%. (Neoptolemos *et al., N Engl J Med.* 2004).

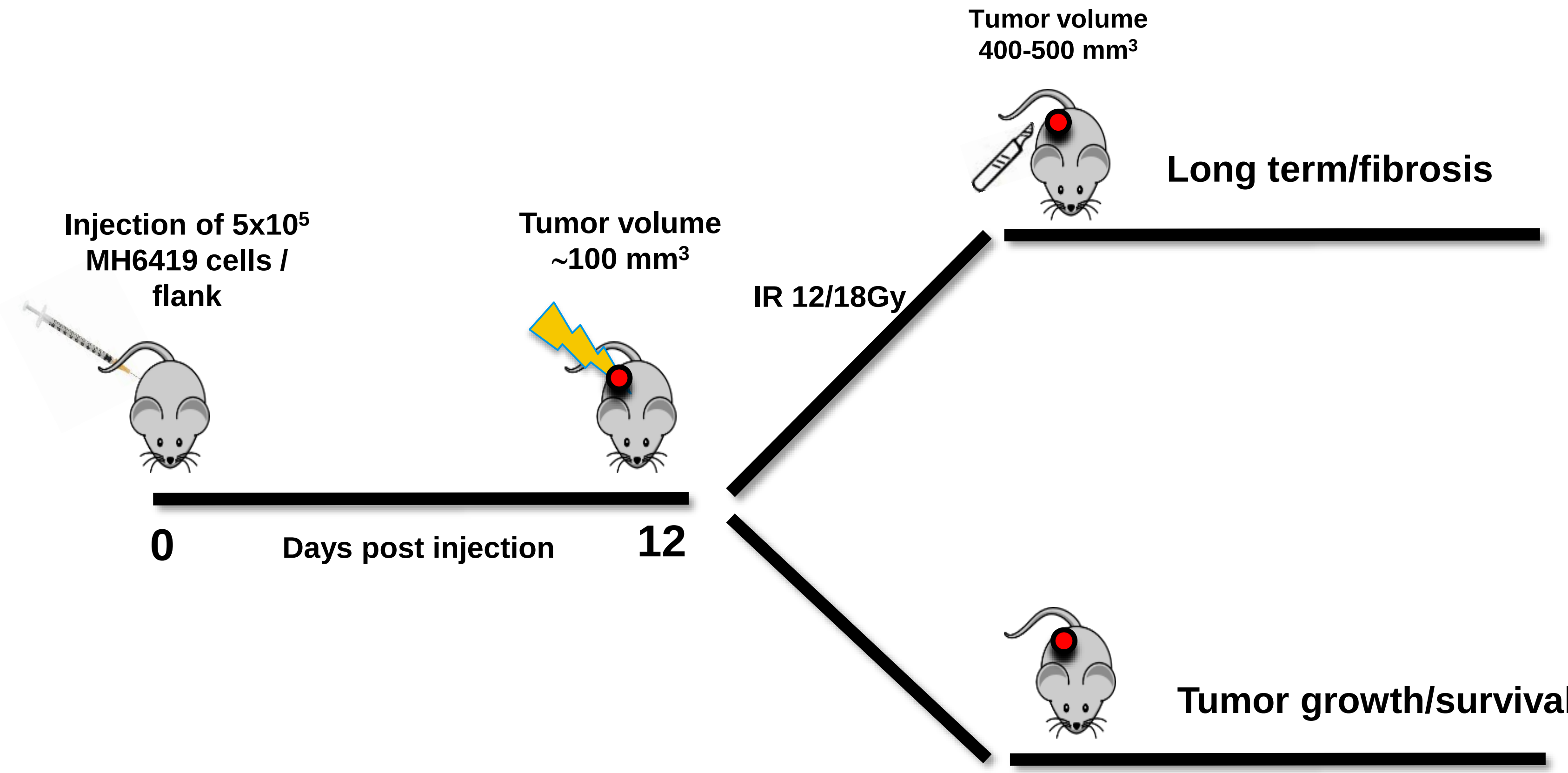


Verginadis *et al., Cancer Res.*, 2016

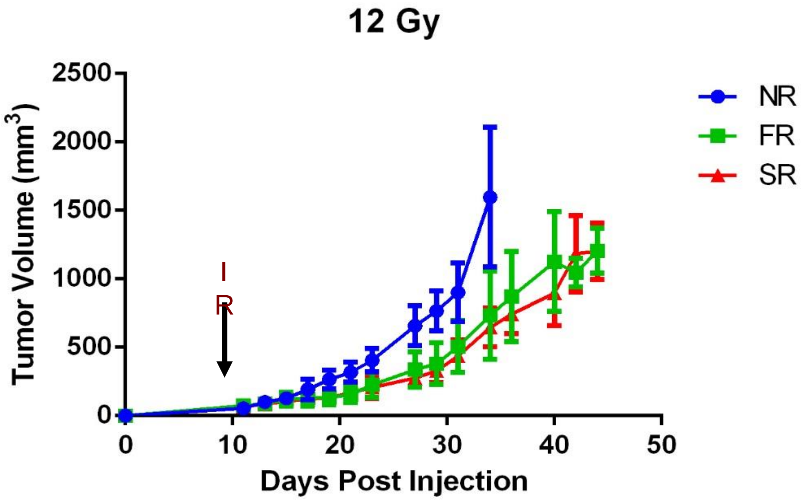


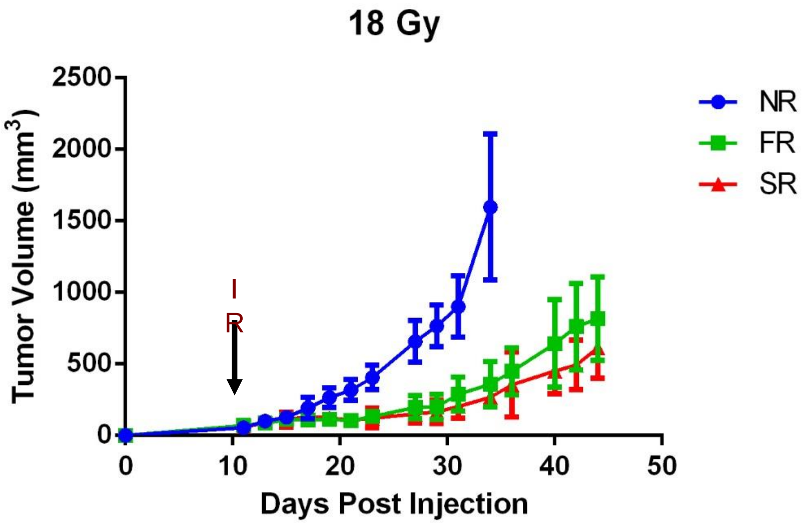
Andreyev, *Lancet Oncol.*, 2007

Initial proton studies: Focal Proton RT of PanCa and Small Intestine



Focal proton FR and SR of syngeneic KPC PanCa tumors

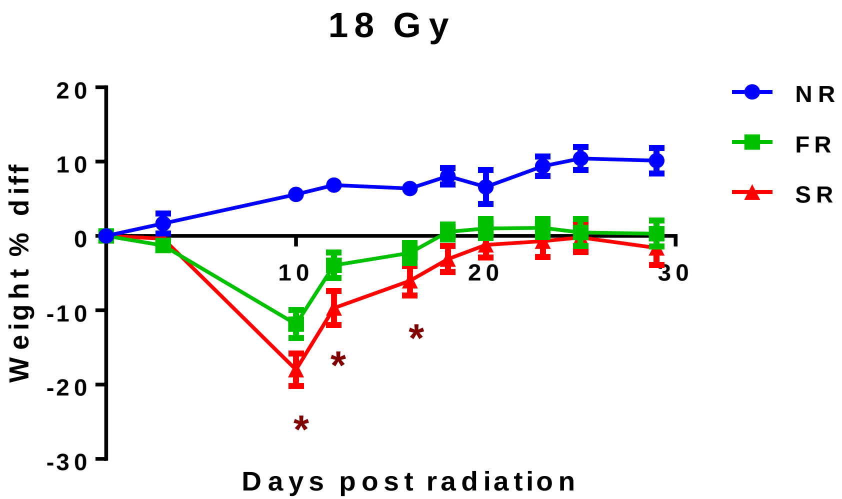




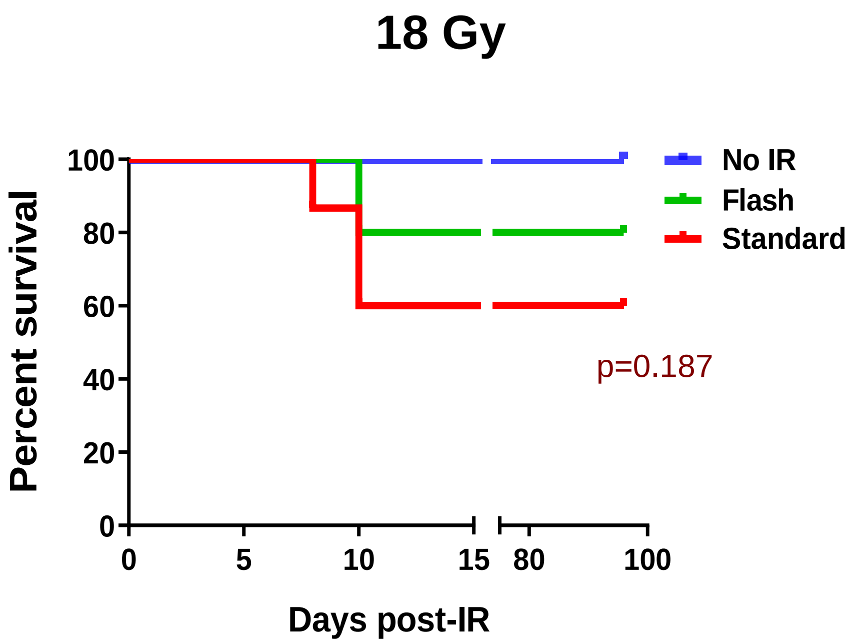
$5x10^5$ MH6419 cells injected on the flank; n=10 per group; Arrow indicates the time of PRT NR curve is the same for both graphs.

Diffenderfer *et al., IJRBOP, 2020.*

Body weight and overall survival following focal Proton FR and SR



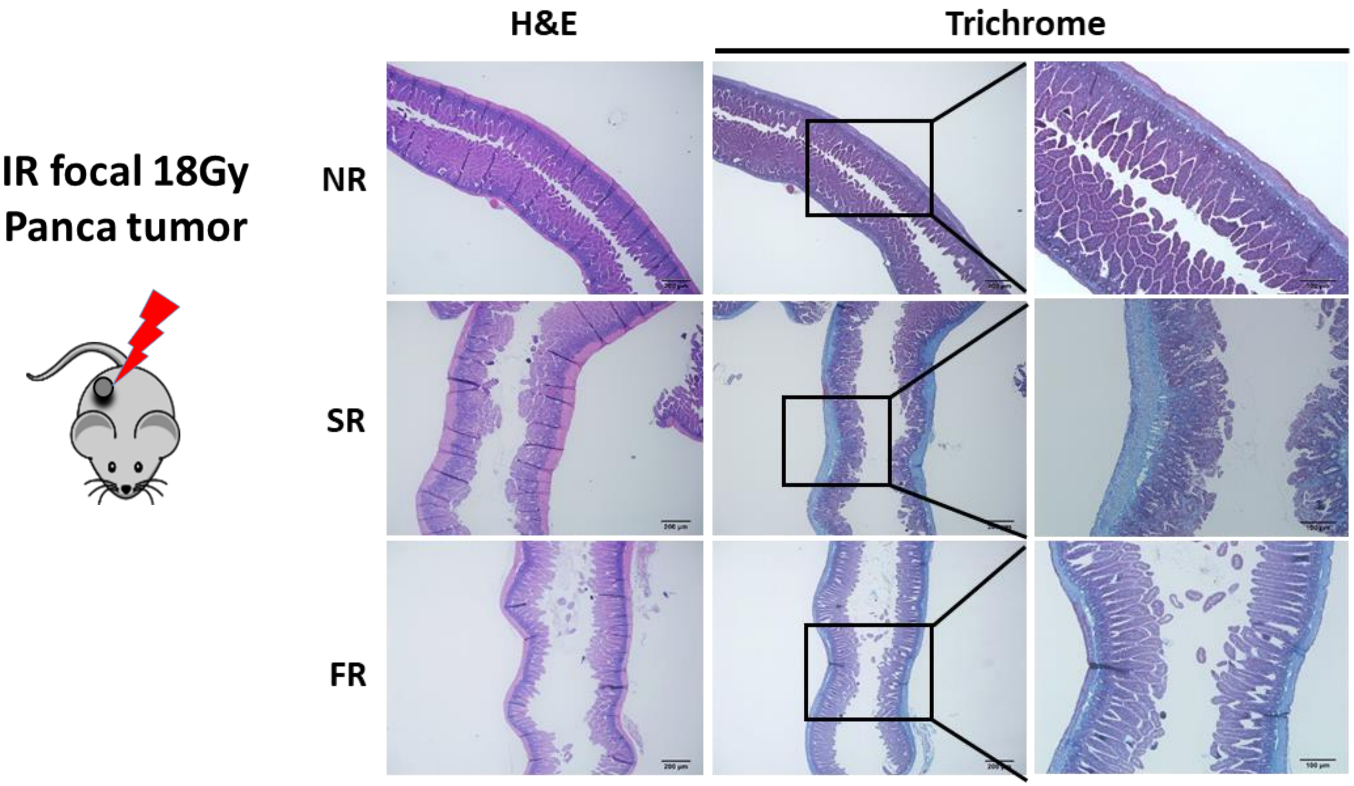
n=8 *P ≤0.05: SR vs FR, t-test

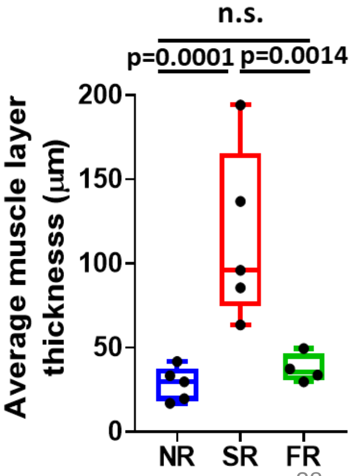


P value: SR vs FR, Gehan-Breslow-Wilcoxon test

Intestinal fibrosis following focal Proton FR and SR

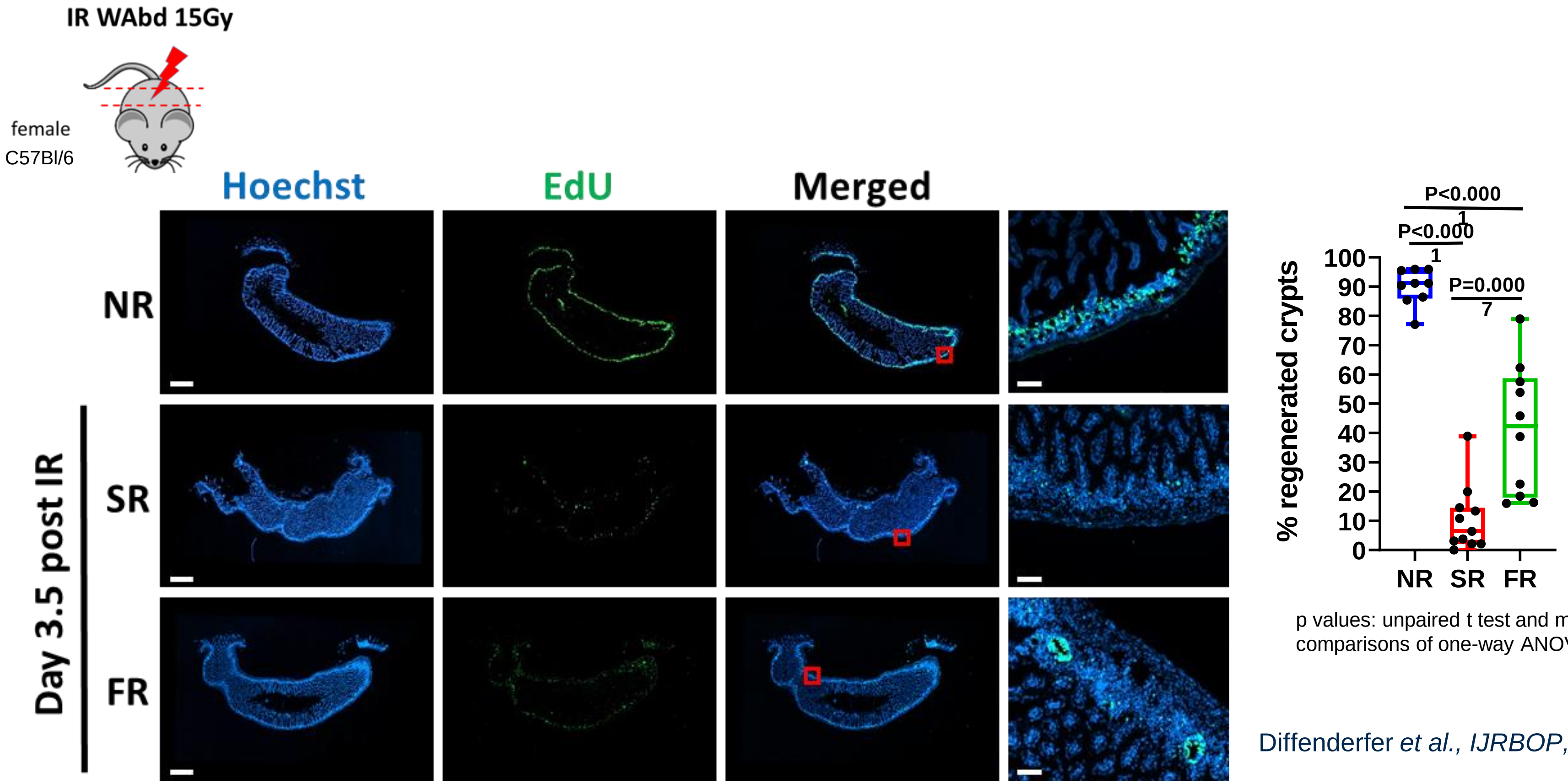
IR focal 18Gy
Panca tumor





Diffenderfer *et al., IJROBP 2020*

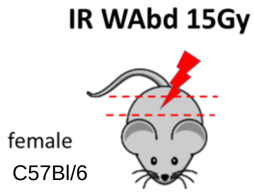
Crypt cell proliferation survival following W-abd proton FR and SR

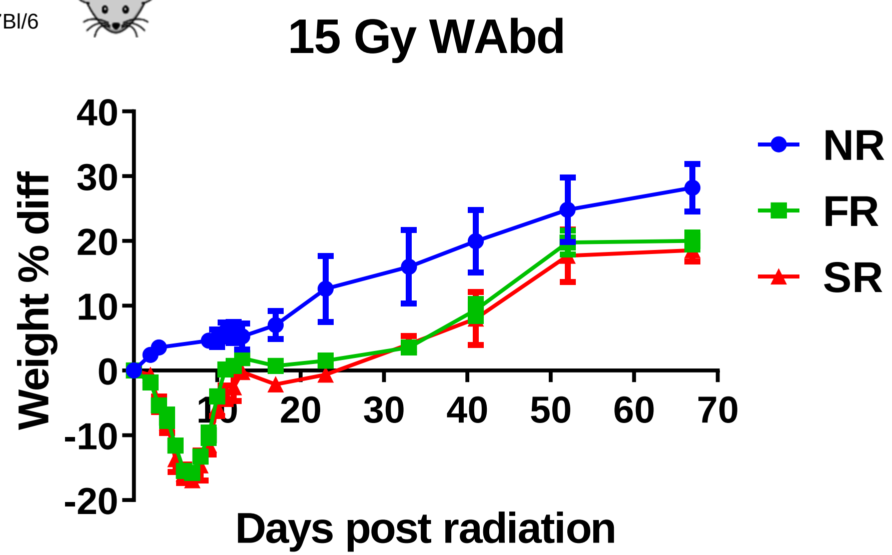


p values: unpaired t test and multiple comparisons of one-way ANOVA

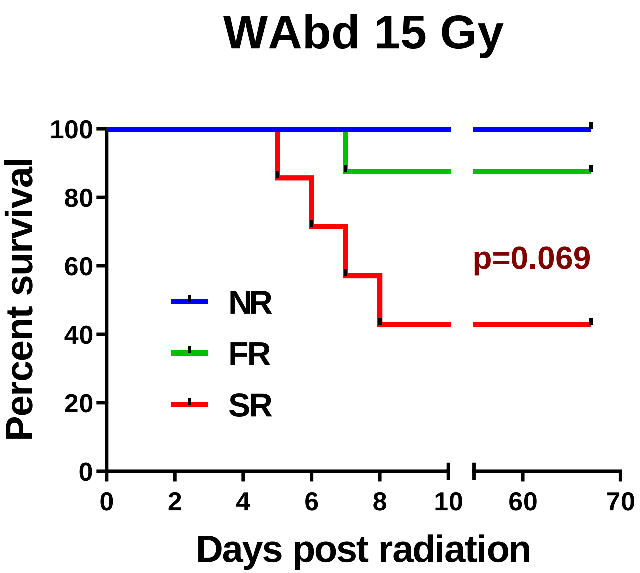
Diffenderfer *et al., IJRBOP, 2020.*

Body weight and overall survival following W-abd proton FR and SR



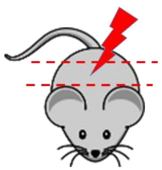


n= 7 mice

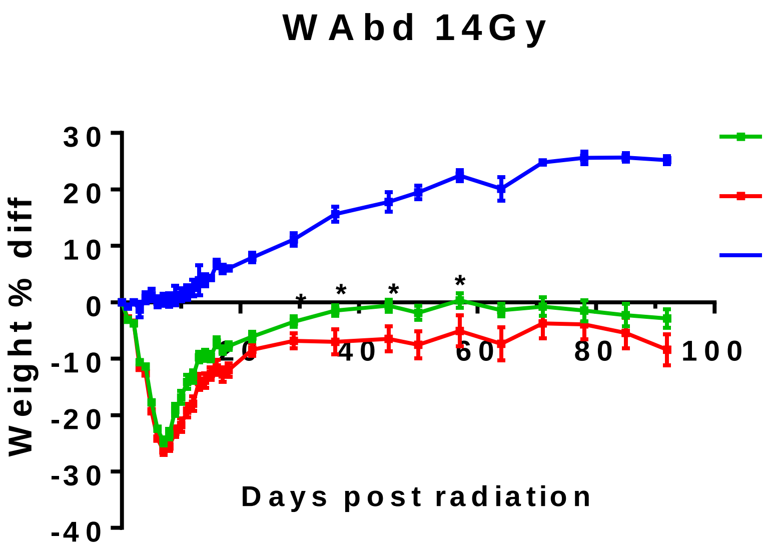


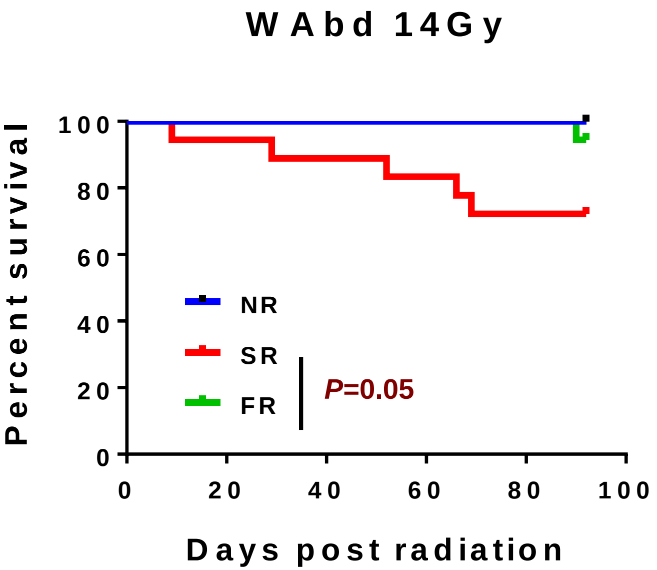
p value: ANOVA for NR, SR, FR

Body weight and overall survival of male C57Bl/6 mice following W-abd FR and SR



n=18





p value: ANOVA for NR, SR, FR

1. Reduce uncertainty due to beam delivery and positioning

We have implemented techniques to ensure the same radiation quality between FLASH and conventional dose rate proton radiation.

We have incorporated a small animal irradiator with imaging to minimize positioning uncertainty

We have implemented a method to treat with an SOBP using conventional and FLASH dose rate protons.

2. Reduce uncertainty due to dosimetry at high dose rates

We have validated ionization chamber dosimetry at FLASH dose rates.

We have designed our proton irradiation system to maintain consistent dosimetric parameters independent of dose rate.

3. Reduce uncertainty due to dose rate variation

We have implemented a method to monitor and record the time structure of FR

We have validated the Flash effect for protons in an in-vivo setting

FLASH Proton Experiments at Penn

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