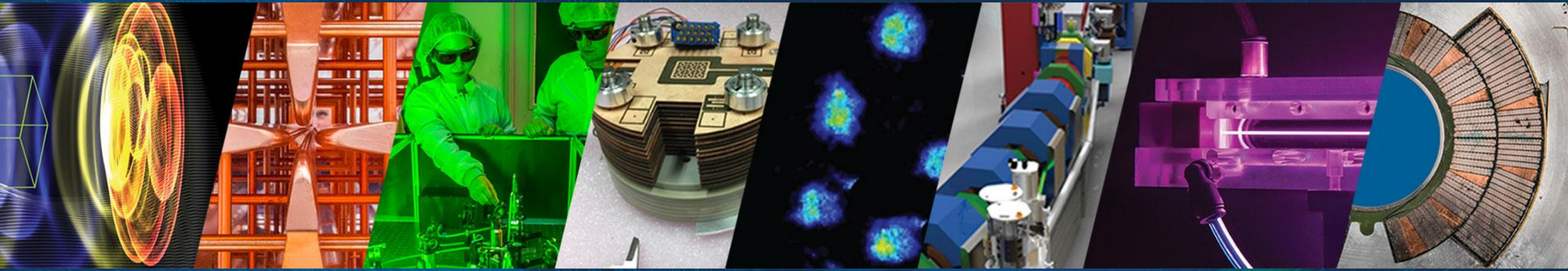
Exploration of ultra-high dose rate radiobiology with laser-driven protons at BELLA

K. Nakamura, BELLA Center

ATAP Division, Lawrence Berkeley National Laboratory



NN2024: 14th International Conference on Nucleus-Nucleus Collisions

August 21, 2024, Whistler, BC Canada

BSE LaserNetUS

BERKELEY LAB ACCELERATOR TECHNOLOGY & APPLIED PHYSICS DIVISION ATAP

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Acknowledgement: Muti-Team Collaboration

BELLA Center

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Anthony Gonsalves	Chetanya Jain
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Eric Esarey	Thorsten Stezelberger
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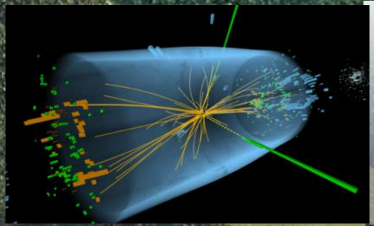
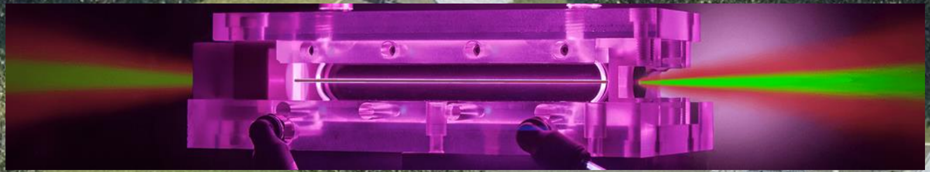
BELLA Center: one of the three major accelerator facilities at LBNL

BELLA (Berkeley Lab Laser Accelerator) Center houses multiple laser systems enabling a wide range of LPAs and their applications[1]

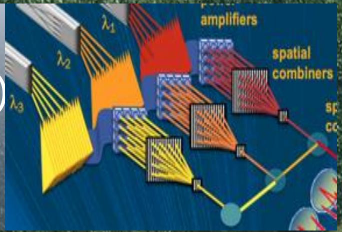


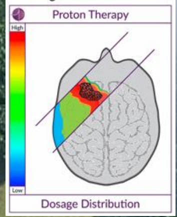
BELLA-PW (iP1)
40 Joule in 40fs (1 PW)
GeV acceleration, Staging
Proton & ion acceleration



BELLA-HTT
3 Joule in 30fs (100 TW)
Mono-chromatic gamma rays

BELLA FIBER
100s mJ in <100fs (>1kHz)
- Laser R&D
- Light sources at >1kHz

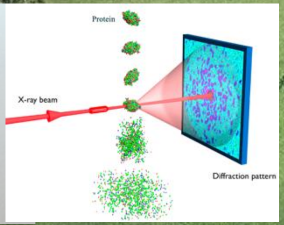




BELLA-iP2 at BELLA-PW
40 Joule in 40fs (1 PW)
Proton & ion acceleration

BELLA-KHz
A few mJ in 5fs (TW)
MeV Acceleration

BELLA-HTU
3 Joule in 30fs (100 TW)
X-ray laser



[1] K. Nakamura et al., Journal of the Particle Accelerator Society of Japan 19, 205 (2023)

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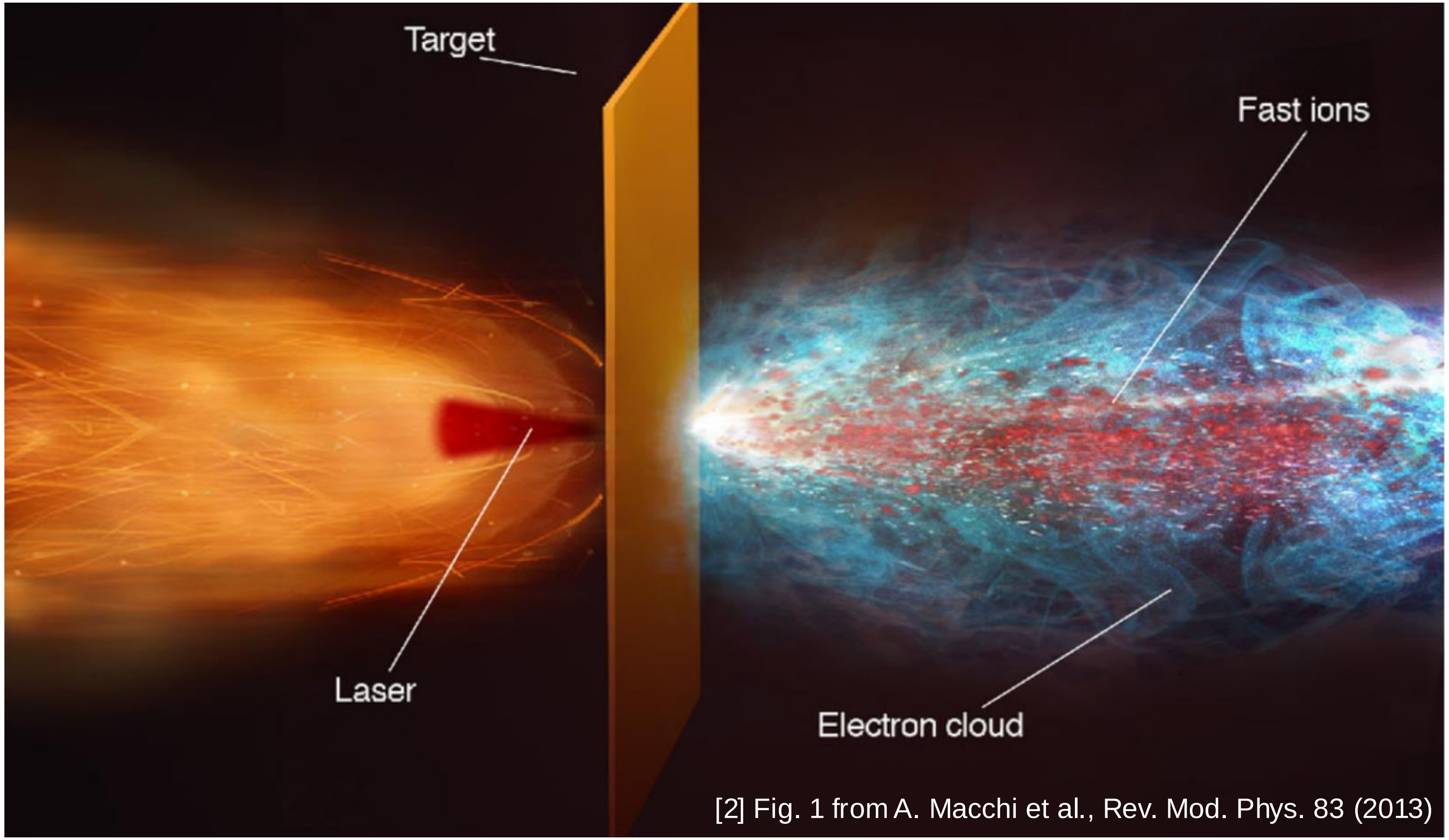
Laser-driven (LD) ion acceleration[2]: compact, pulsed, high-charge ion beam source

nm – μm scale targets



[2] Fig. 1 from A. Macchi et al., Rev. Mod. Phys. 83 (2013)

meter scale accelerator

Characteristics

- Ps pulse length at source
- Small source size
- Broadband
- Protons and other ion species in one bunch

Applications

- Warm Dense Matter research[3]
- Defect engineering[4]
- Pulsed neutron driver[5]
- Radiobiological research

[3] P. Patel et al., PRL 91 (2003) 125004, S. Malko et al., Nature Communications 13 (2022) 2893.
[4] W. Redjem et al., Communications Materials 4 (2023) 22.
[5] M. Roth et al., PRL 110 (2013) 044802.

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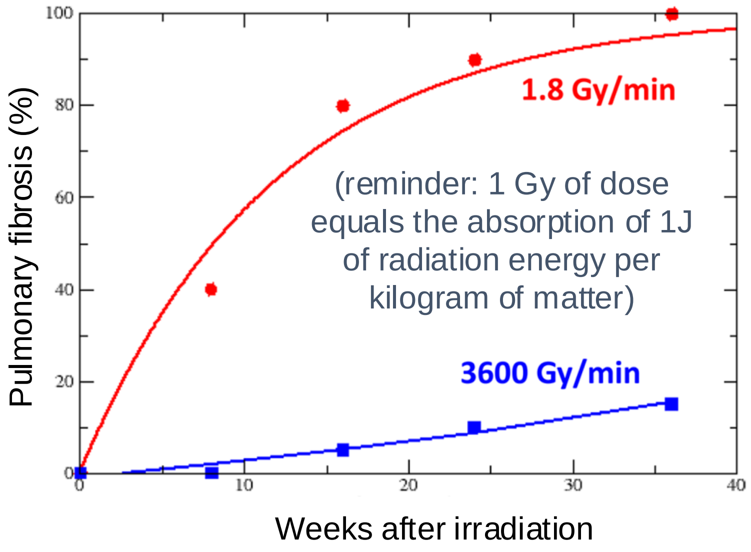
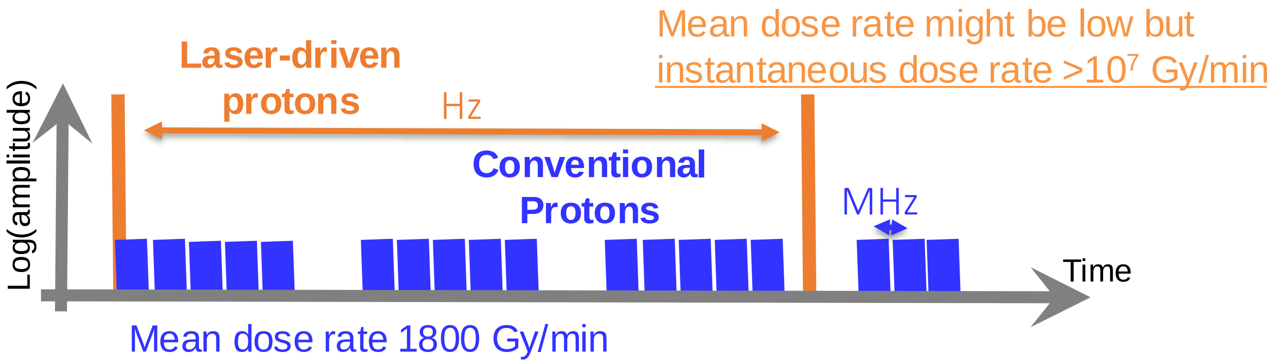
Laser-driven proton pulses are uniquely short and intense and are therefore of interest to study radiobiological/radiotherapeutical effects induced by ultra-high dose rates

FLASH effect: the differential **sparing of healthy tissue** under irradiation at **ultra-high dose rates**

- In-vivo study on mice irradiated with electrons
- Constant **total dose** but different **(mean) dose rates** (blue vs. red)





Mechanism of FLASH effect is not well understood

→ Laser-driven radiation sources provide uniquely high intra-pulse ("instantaneous") dose rates and are increasingly available in university-scale laser labs

→ They can contribute to FLASH research by complementing conventional accelerator facilities

Durante et al., Br Radiol 2018 10.1259/bjr.20170628.,
Favaudon et al: Sci Transl Med. 2014 10.1126/scitranslmed.aba4525

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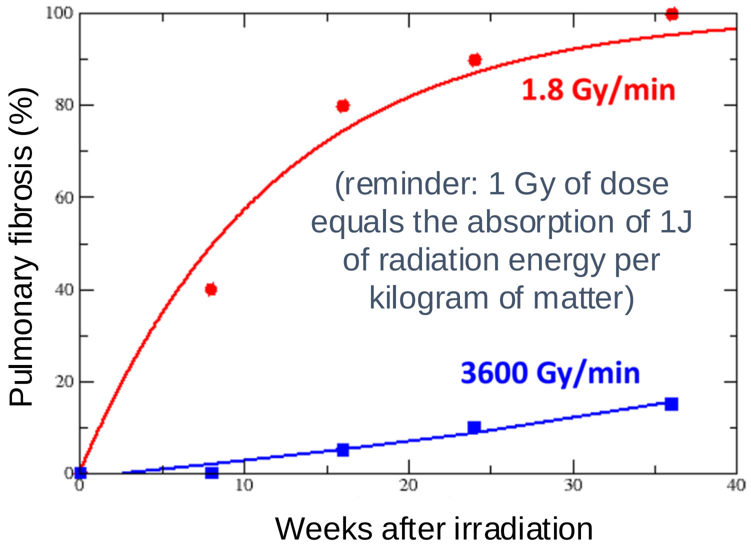

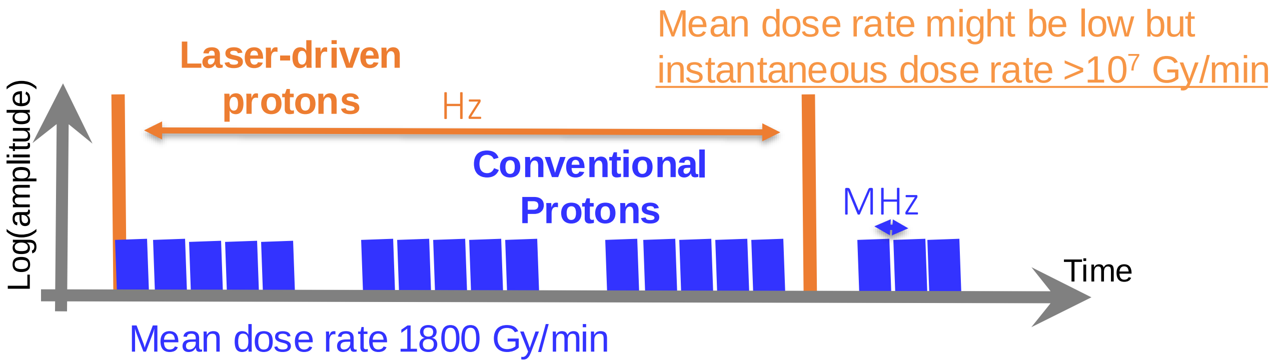

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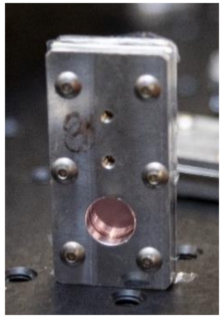
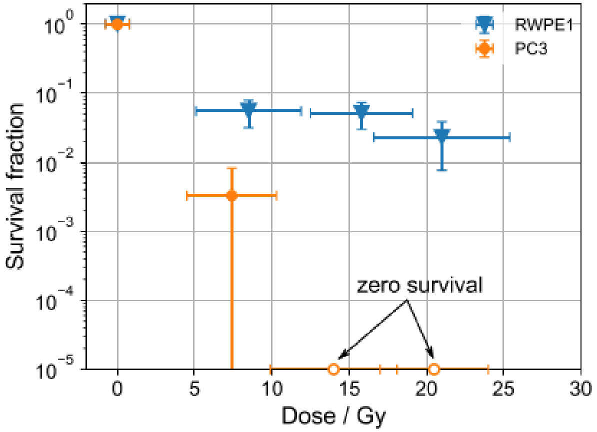
Continuous growth of radiobiological research with laser-driven proton beams: A. Yogo et al., Appl. Phys. Lett. 94:181502 (2009), S. Kraft et al., New J. Phys. 12:085003 (2010), D. Doria et al., AIP Advances 2:011209, **E. Bayart et al., Sci. Rep. 9:10132 (2019), F. Hanton et al., Sci Rep. 9:1-10 (2019)**, F. Kroll et al., Nat. Phys. 18:316-322 (2022), **J. Metzkes, et al., Sci. Rep. 13:20611 (2023)**, Snowmass/Journal article: **R. Schulte et al., Transformative Technology for FLASH Radiation Therapy, Appl. Sciences 13:5021 (2023)**

Outline

1) *Cell irradiations* with TNSA protons ~2 MeV





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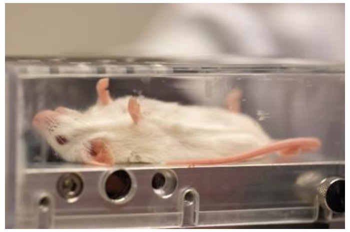
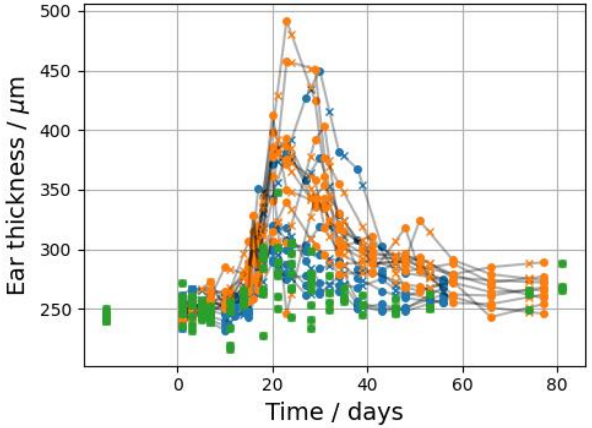
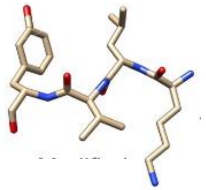
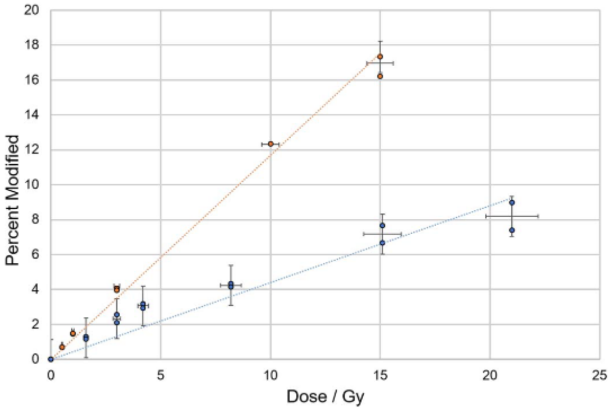


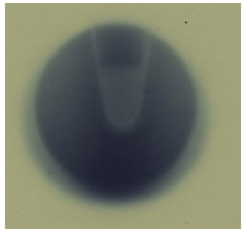


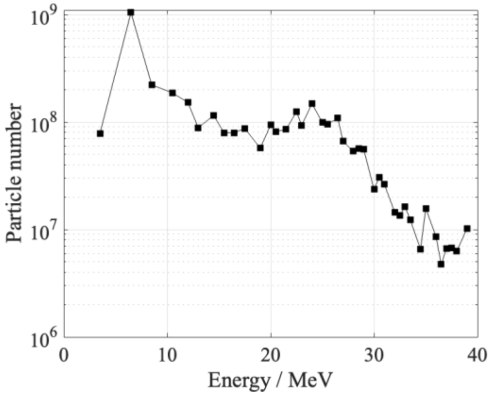
3) *Peptide irradiations with* synchrotron x-rays (ALS)





4) *Peptide irradiations* with TNSA protons ~7-30 MeV





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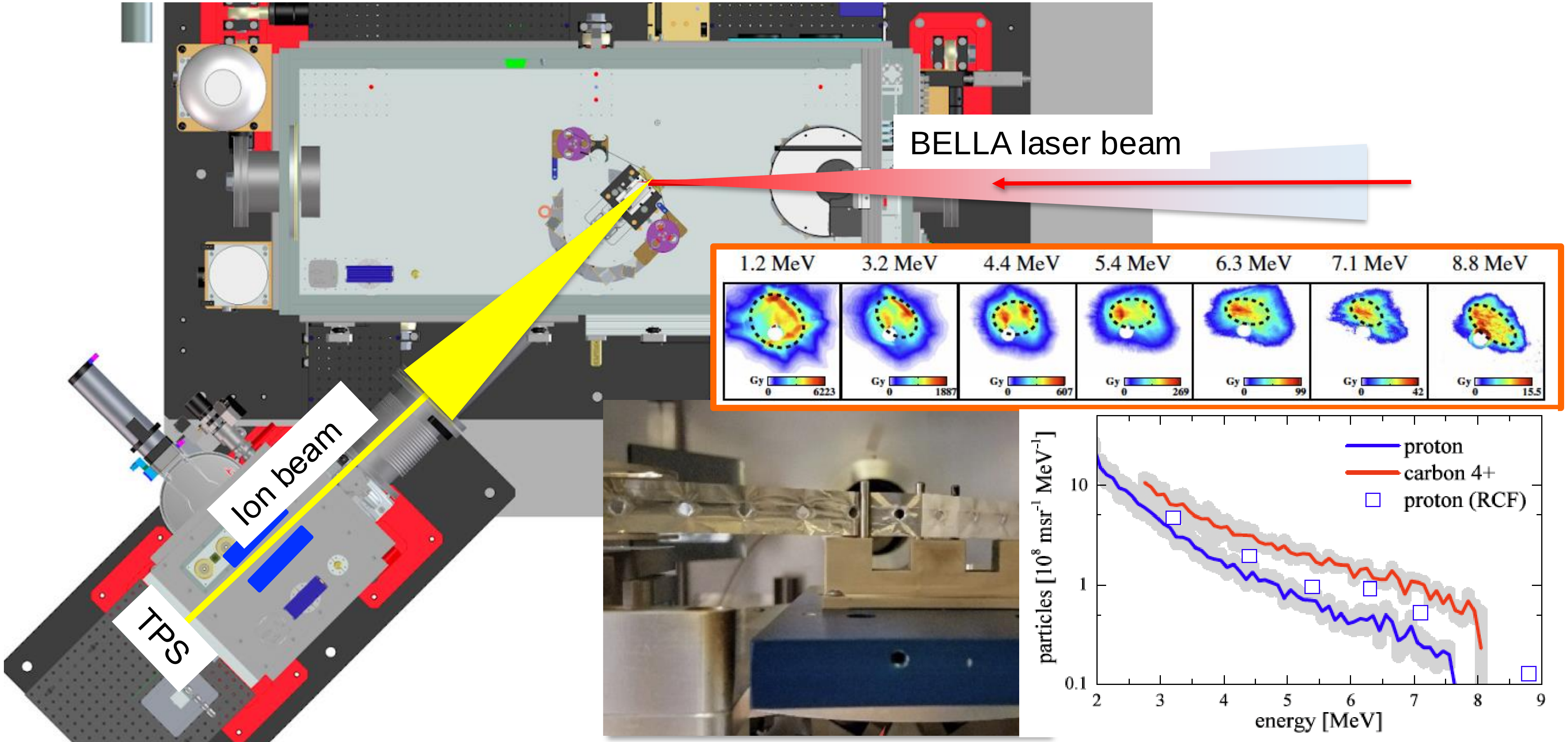
Long focal length (F/65) BELLA PW beamline allows for acceleration of low divergence, high charge, < 10 MeV proton beams



Tape drive target

*Steinke et al., PRAB **23**, 021302 (2020),*

*J.H. Bin et al., Rev. Sci. Instrum. **90**, 053301 (2019)*

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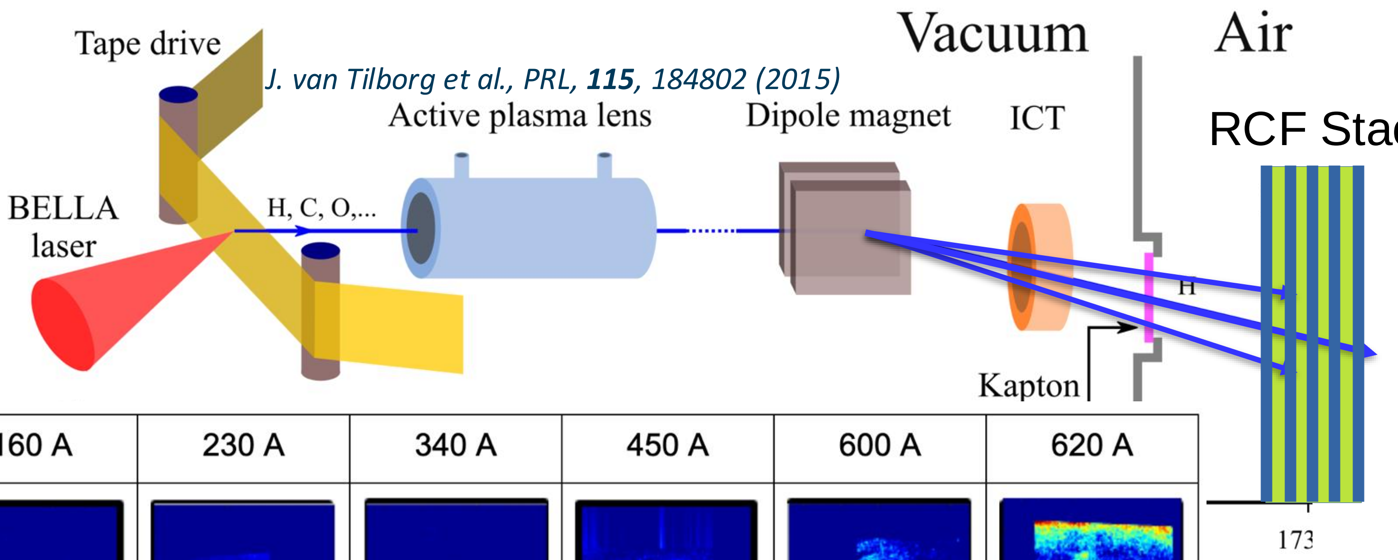
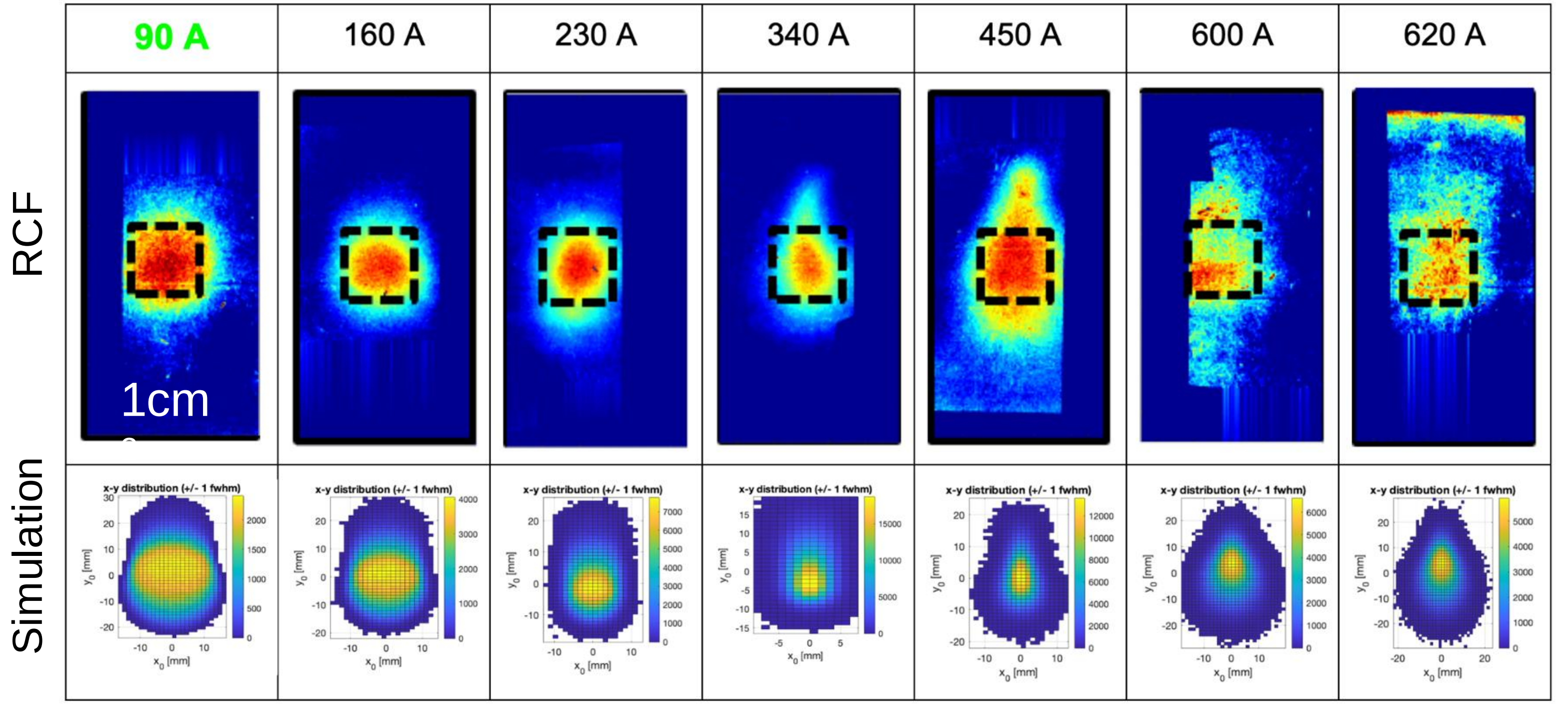
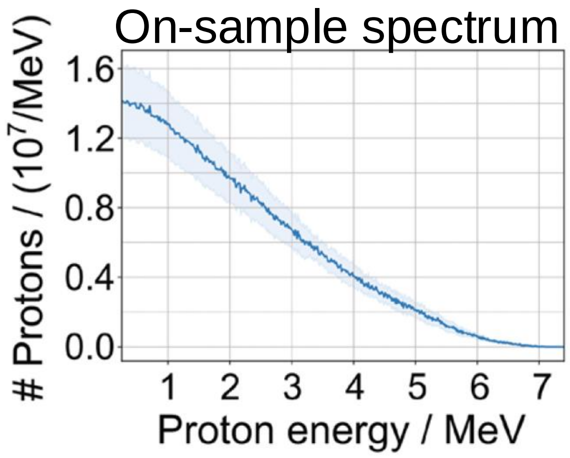
Active plasma lens transport: Experiment/Simulation showed good agreement, providing ~1 cm beam for radiobiology application

*J. van Tilborg et al., PRL, **115**, 184802 (2015)*







*L. Geulig et al., Rev. Sci. Instrum., **93**, 103301 (2022)* *J.H. Bin et al., Rev. Sci. Instrum. **90**, 053301 (2019)*

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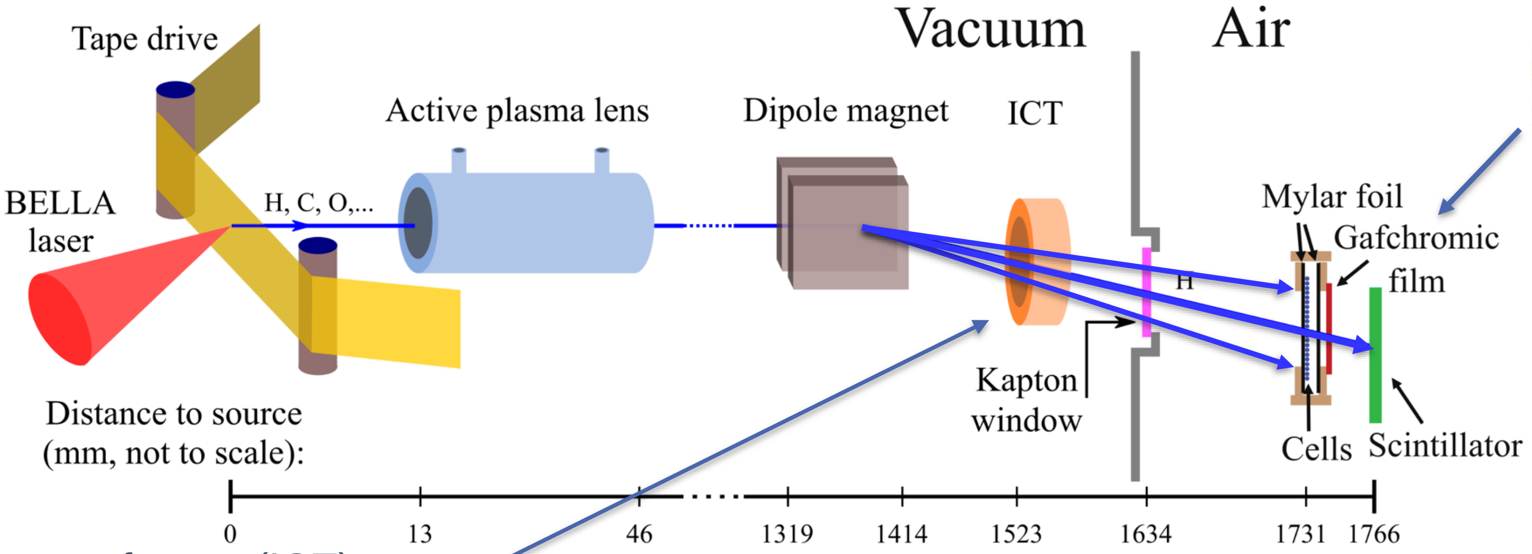
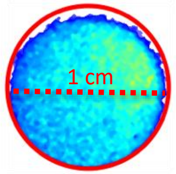
Offline/absolute (RCF) and online/relative (ICT) diagnostics are used to determine the dose applied to every irradiated cell sample

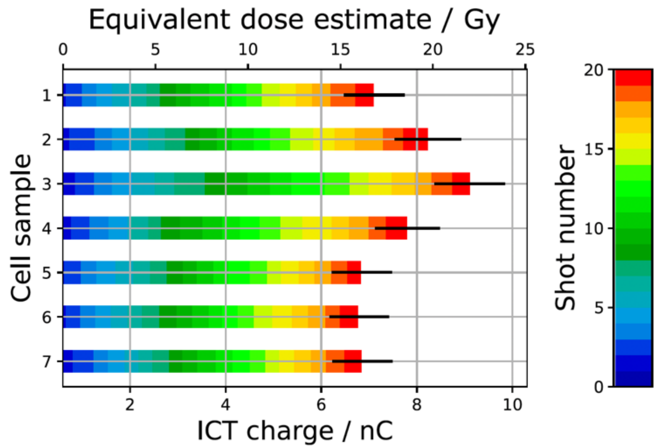


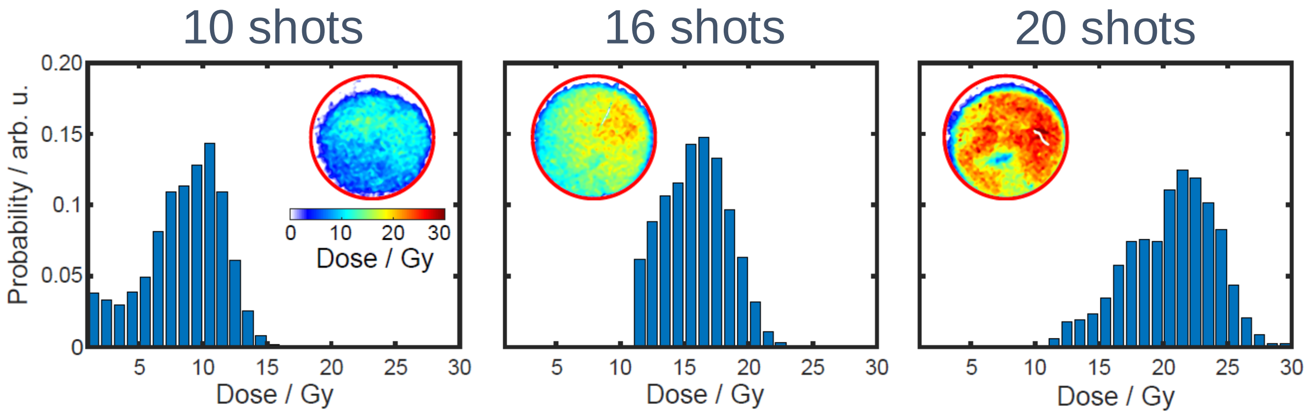


Dose on cells:
1 Gy per shot

Variation across sample:
20 % due to beam profile
non-uniformity

Integrating current transformer (ICT)
fielded for online dosimetry

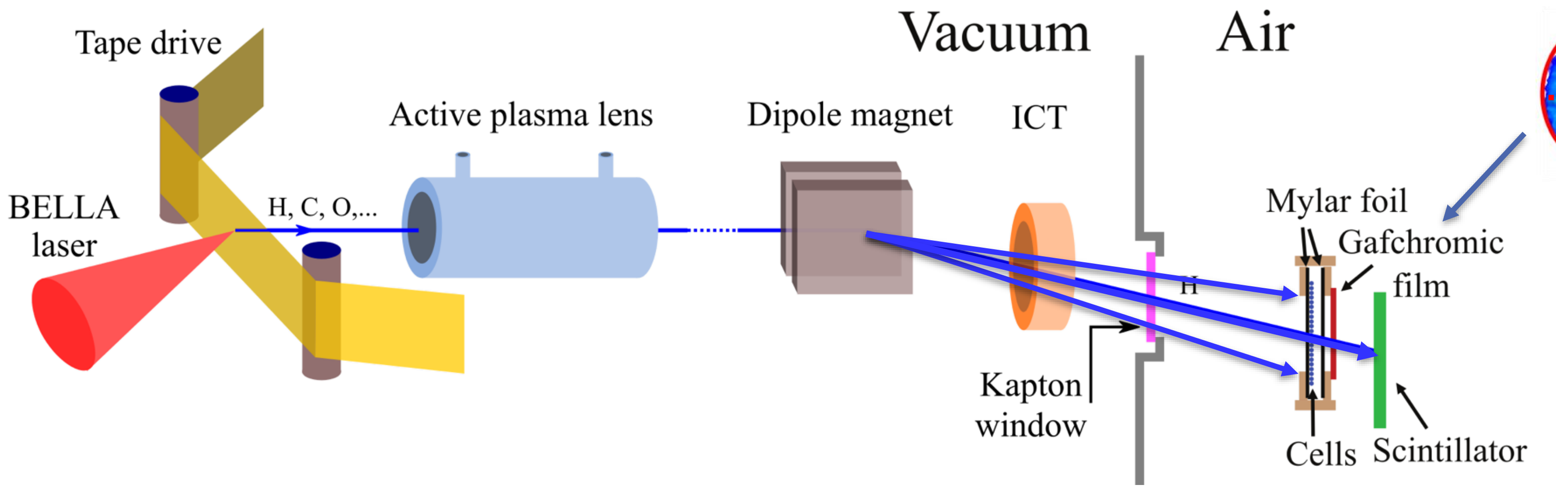


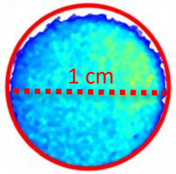


→ Proton pulse length ~30 ns → **instantaneous dose rate of 4×10^{7} Gy/s**
mean dose rate: 0.5 Gy/s (pulse separation 5 s)

L. Geulig et al., Rev. Sci. Instrum., ***93****, 103301 (2022)* *J.H. Bin et al., Rev. Sci. Instrum.* ***90****, 053301 (2019)*

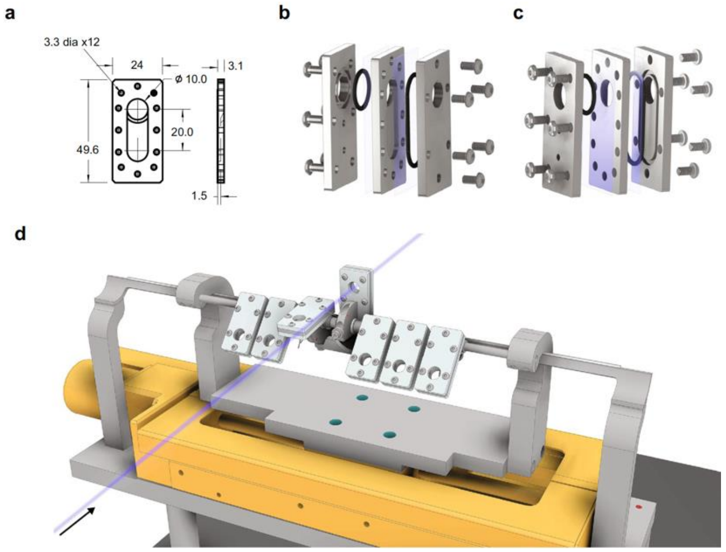
Laser accelerated ions delivered by active plasma lens to cell sample - differential sparing between normal and tumor cells observed



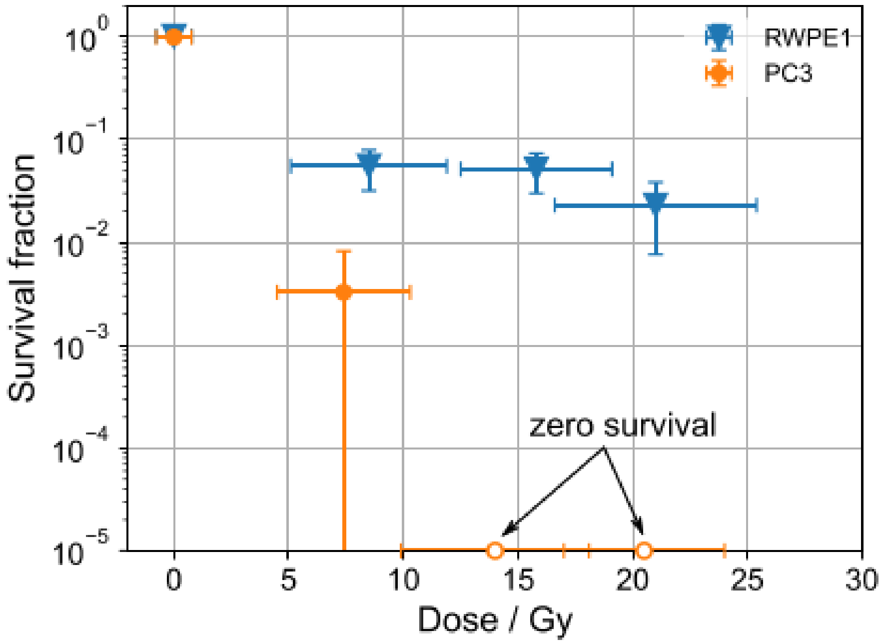


Dose on cells:
1 Gy per shot

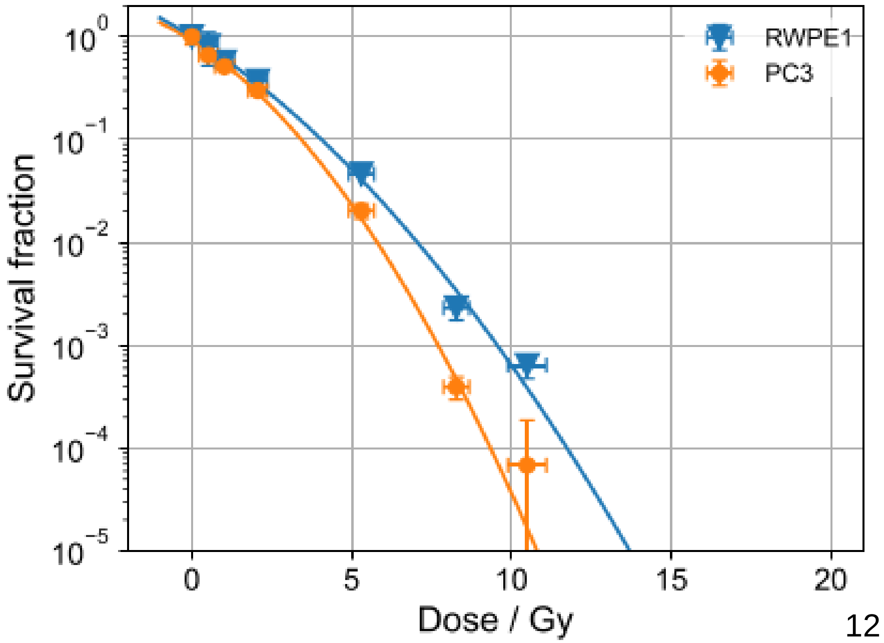
- PC3 prostate tumor cells
- RWPE1 normal prostate cells



LD protons: ultra-high instantaneous dose rate



X-rays: clinical dose rate



J. H. Bin et al., Sci. Rep. ***12*** *1585 (2022)*

In general, the literature recognizes that oxygen concentration may play an important role in the FLASH effect

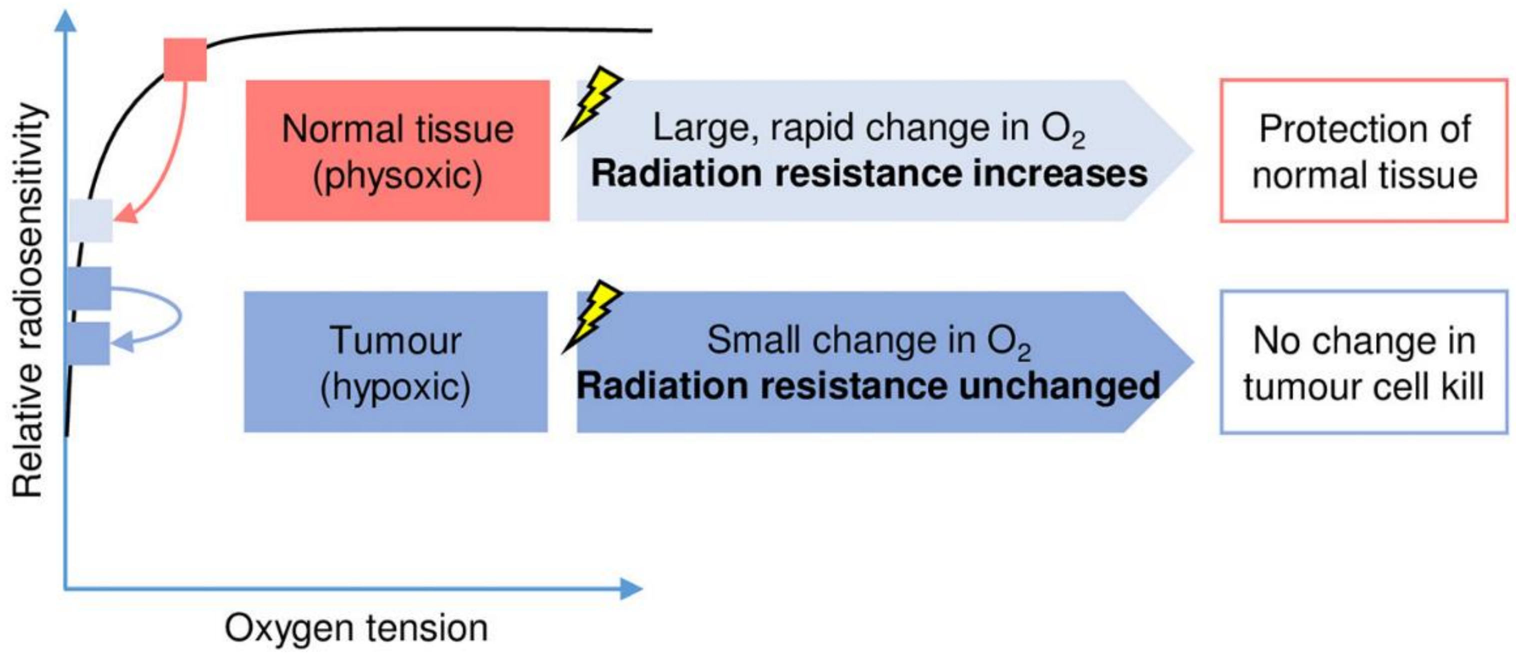
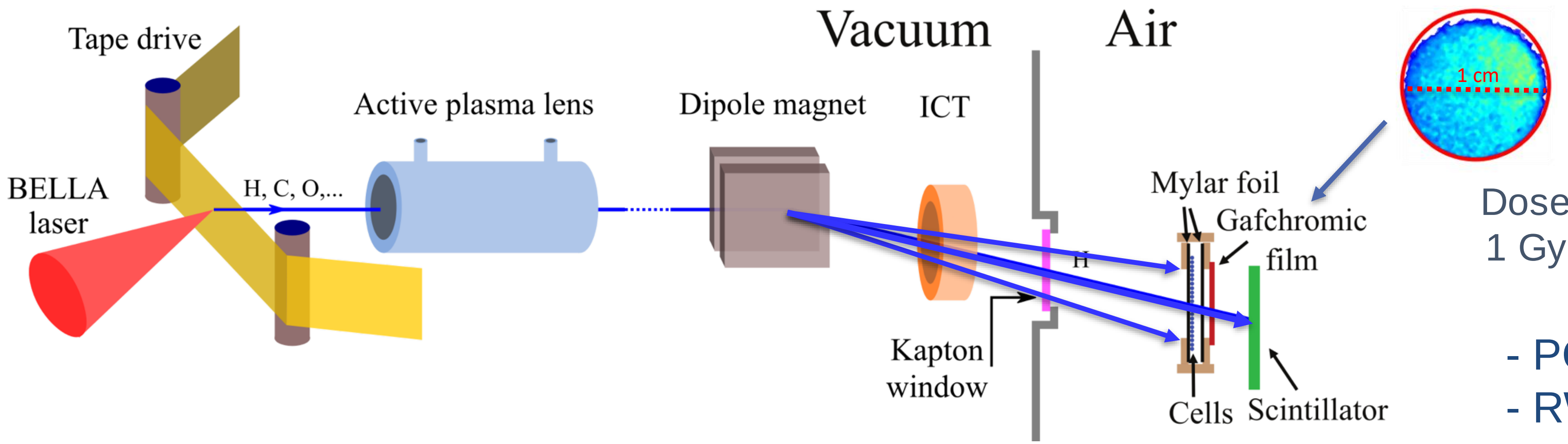


FIGURE 2 | The oxygen depletion hypothesis. The relationship between oxygen tension (horizontal axis) and radiation sensitivity (vertical axis) is shown schematically and has been widely reported (40, 41). In response to FLASH-RT, the physiological level of oxygen (physoxic) found in normal tissues decreases rapidly (pink arrow) and has an important impact on radiation sensitivity. This temporary or transient hypoxia protects the normal tissues as radiation resistance increases. In contrast, oxygen levels are low (hypoxic) in tumor tissues and consequently FLASH-RT has less of an impact on radiation sensitivity.

Wilson et al. Frontiers in Oncology 2020 10.3389/fonc.2019.01563

RNA sequencing of cell samples suggests a possible role of different responses of normal versus tumor cells to oxidative stress



Dose on cells:
1 Gy per shot

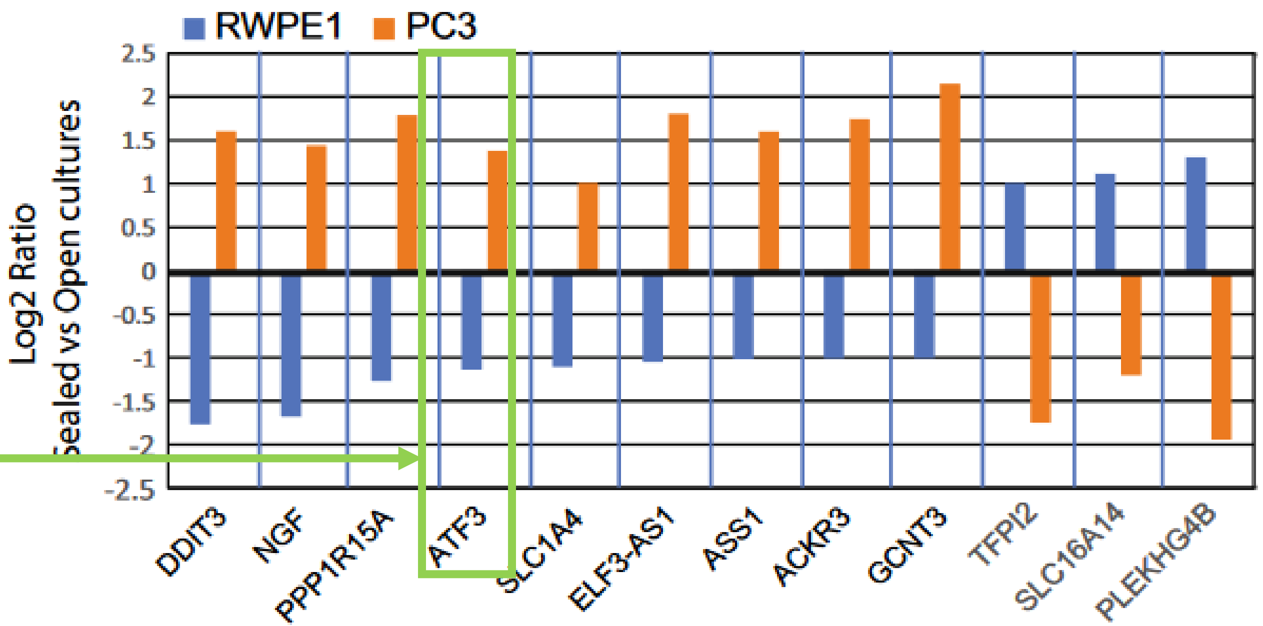
- PC3 prostate tumor cells
- RWPE1 normal prostate cells

- Cell samples were sealed off from air 24 hrs prior and 24 hrs after irradiation

→ Artificially reducing oxygen concentration to be more similar to *in vivo* conditions

- RNA sequencing of cell samples showed differential expression of genes responsible for dealing with oxidative stress.

→ E.g., down/up regulated in RWPE1/PC3:
  - ATF3: responsive to reactive oxygen species (ROS), which induce permanent damage in cells



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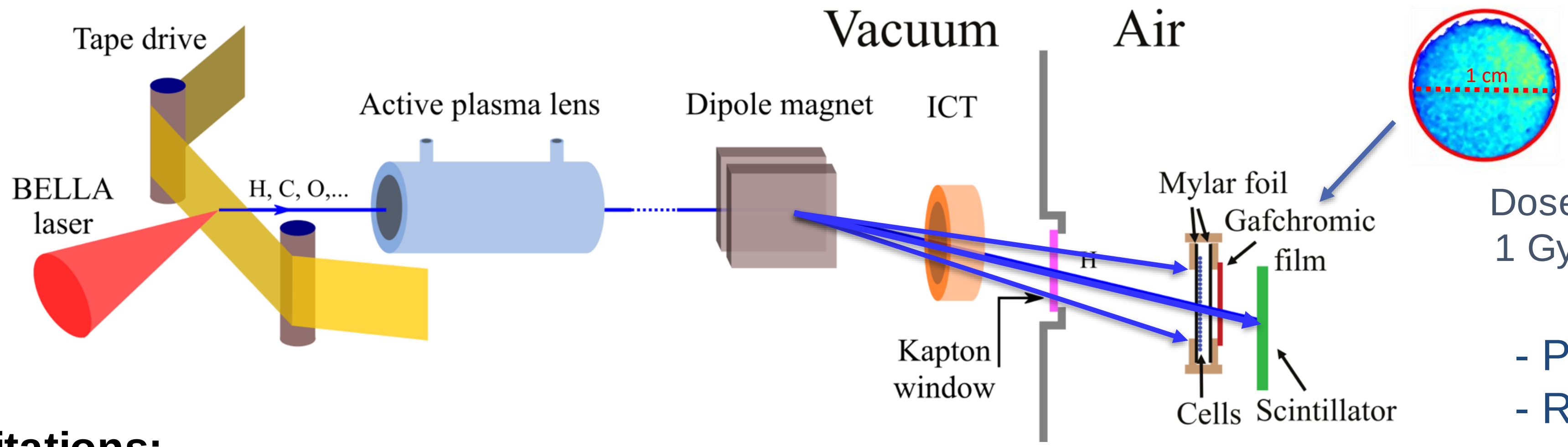

Dose on cells:
1 Gy per shot

- PC3 prostate tumor cells
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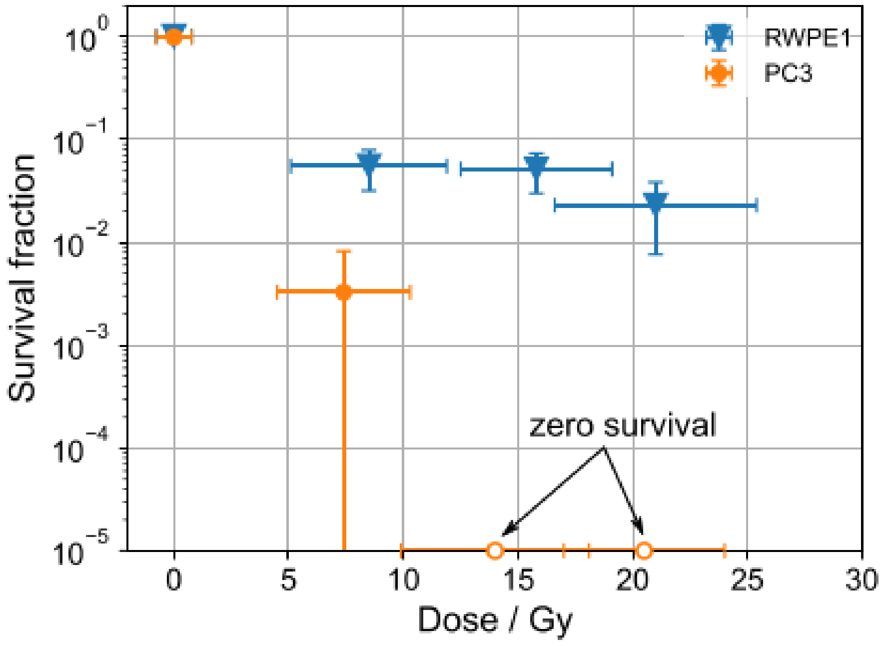
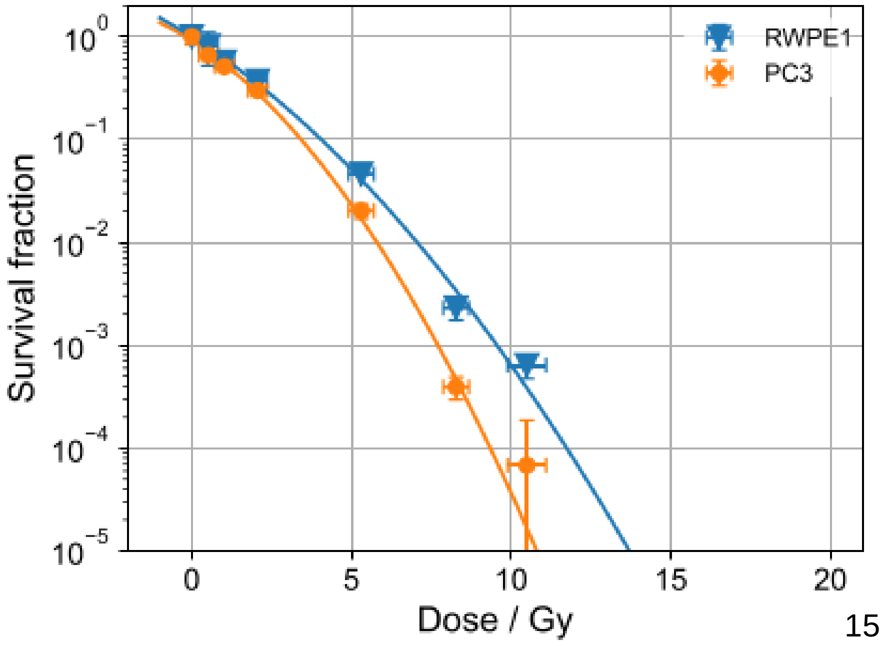
Limitations:

- Dose homogeneity and shot to shot fluctuations
- Clinical proton dose rate reference is missing (X-ray radiobiological effectiveness is different) → *influence of LET?*
- Oxygen tension is unknown
- More cell types needed
- In vivo study needed

LD protons: ultra-high instantaneous dose rate



X-rays: clinical dose rate



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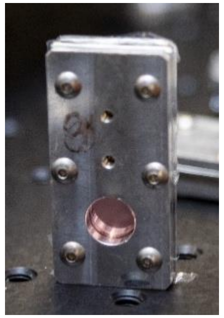

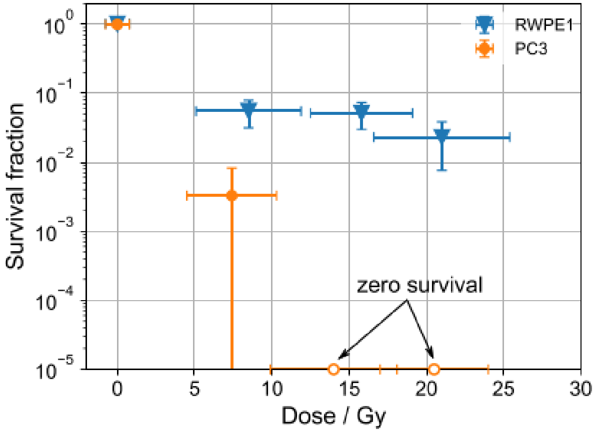

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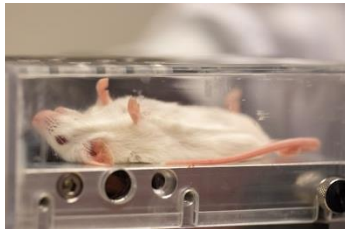

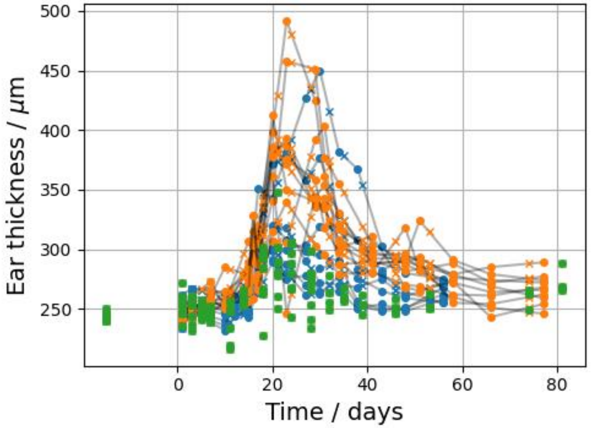

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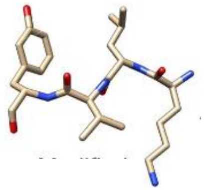

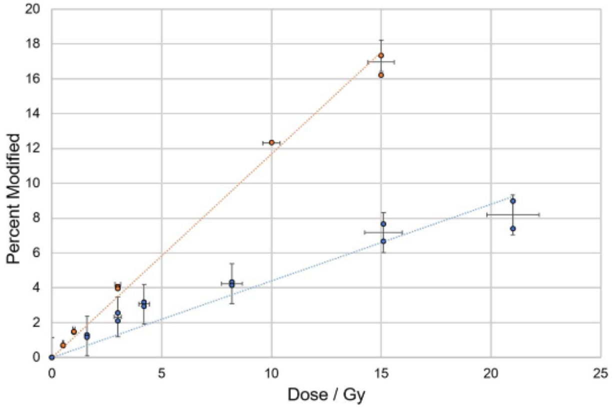

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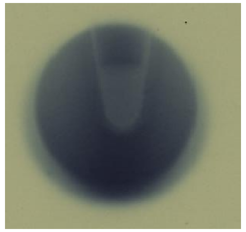
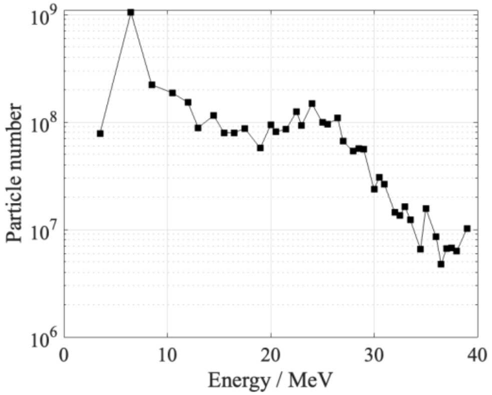
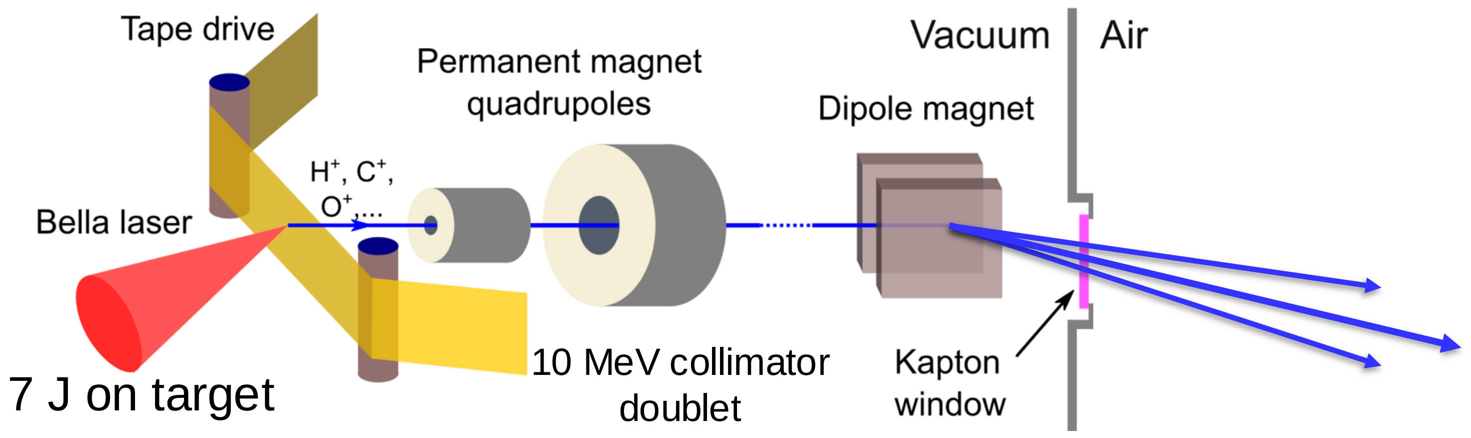
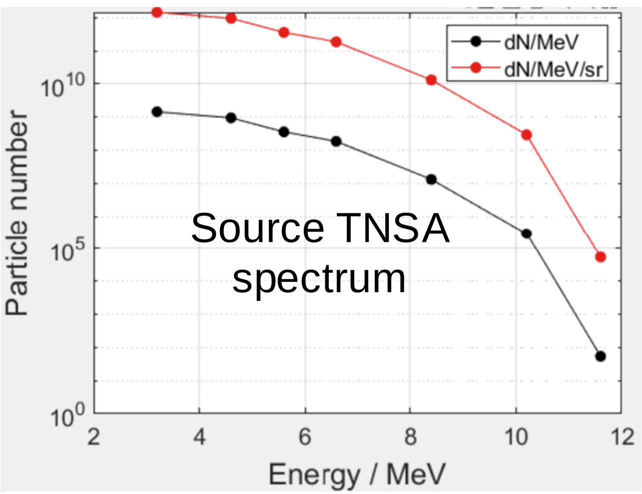




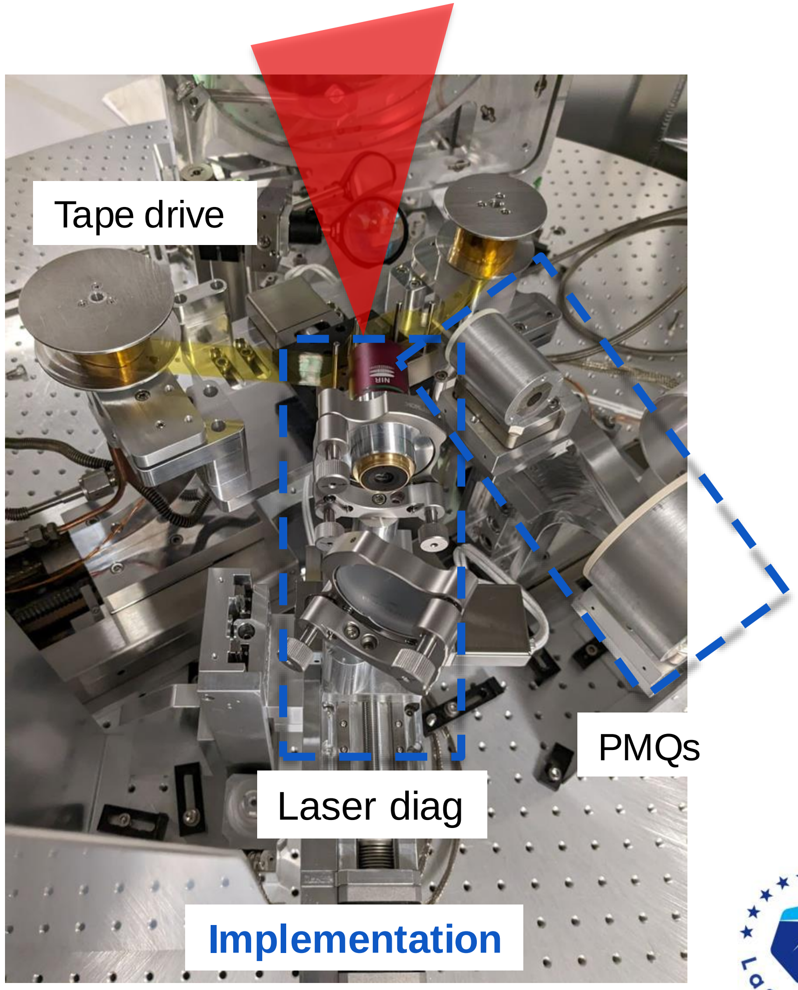
Beamline preparations for volumetric (few mm-thick) sample irradiations at BELLA iP2

New high intensity setup (F/2.5 “iP2”) for several 10 MeV TNSA beams → deeper penetration into tissue



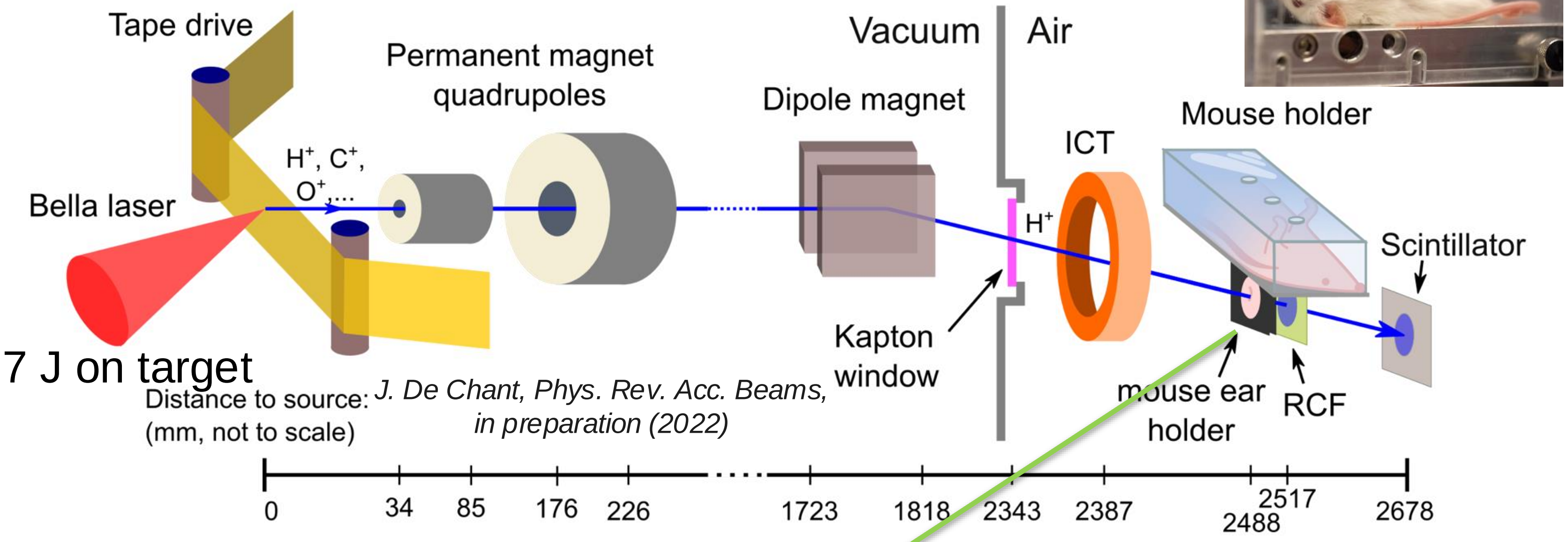


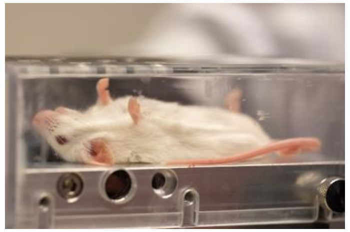
(target location selected away from best focus to increase shot to shot stability, I_{peak} ~ 2×10^{19} W/cm^2)

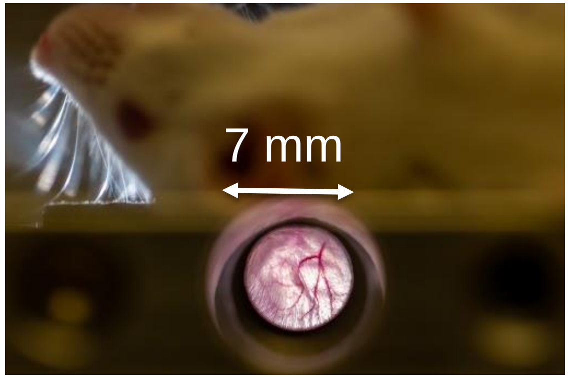


L. Obst-Huebl, Proc. SPIE 12583 (2023) S. Hakimi et al., Phys. Plasmas. 29, 083102 (2022)

Beamline preparations for volumetric (few mm-thick) sample irradiations at BELLA iP2

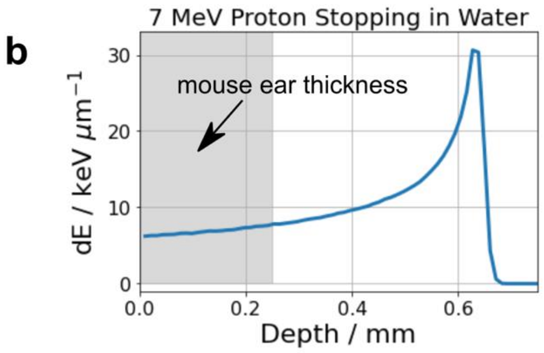


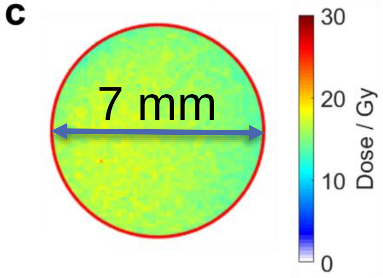




7 J on target

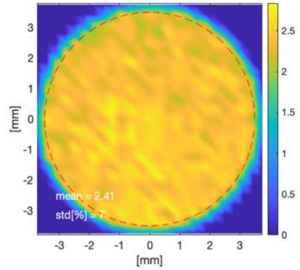
J. De Chant, Phys. Rev. Acc. Beams, in preparation (2022)





Dose on ear (RCF)

1.5 Gy/shot, lateral variation < 10 %, $1x10^8$ Gy/s



Simulated beam profile (Cosy infinity + Matlab/MC integration)

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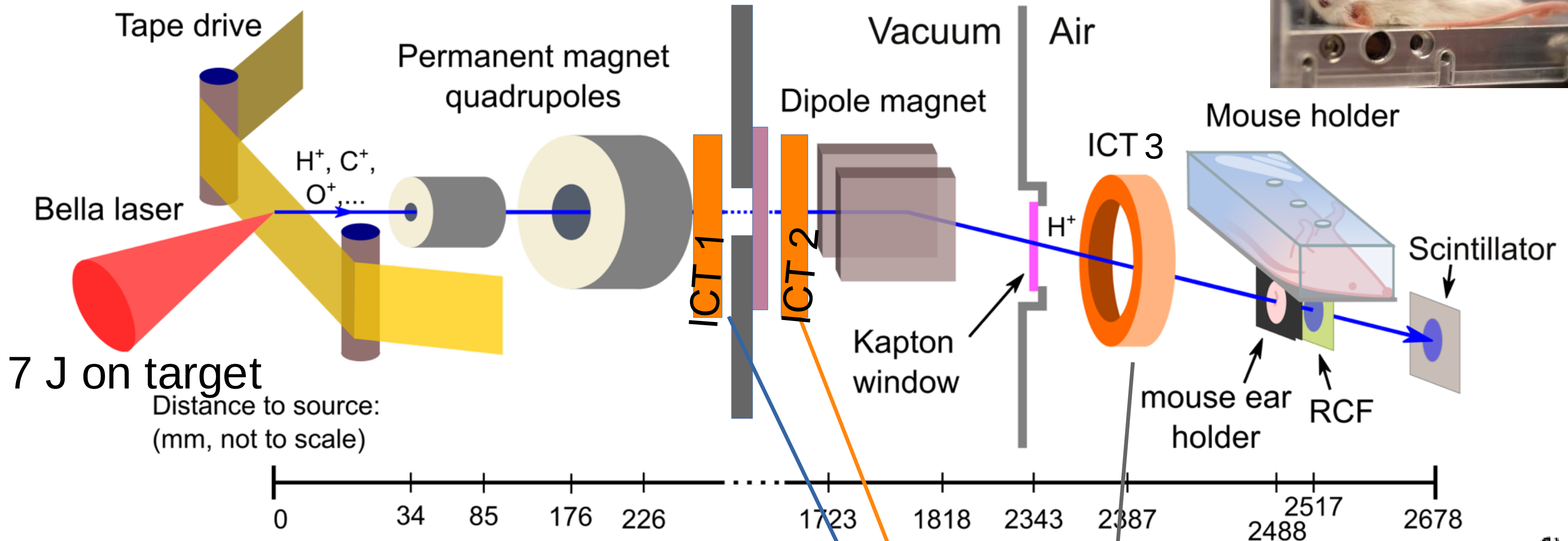
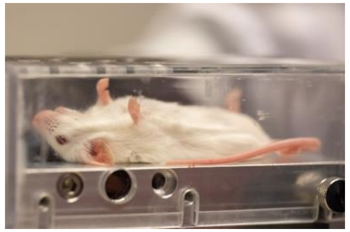
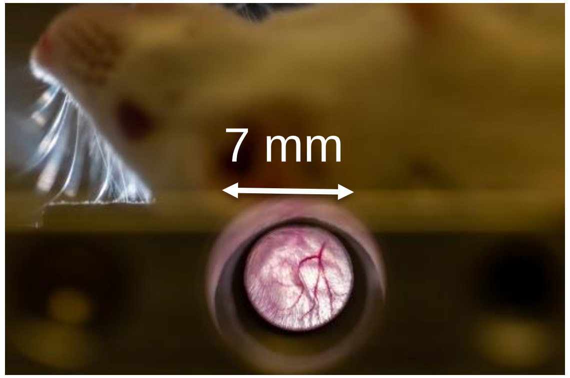
LaserNetUS

Continued development of online beam monitoring with ICTs allowed for precise application of prescribed dose



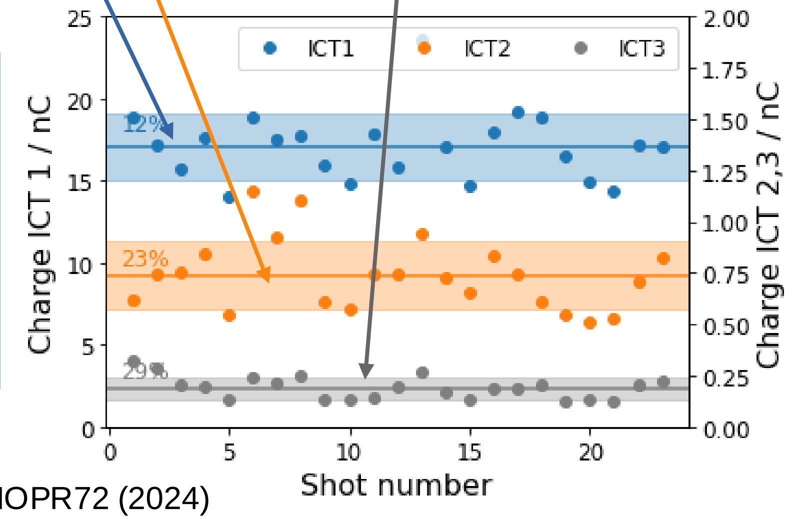


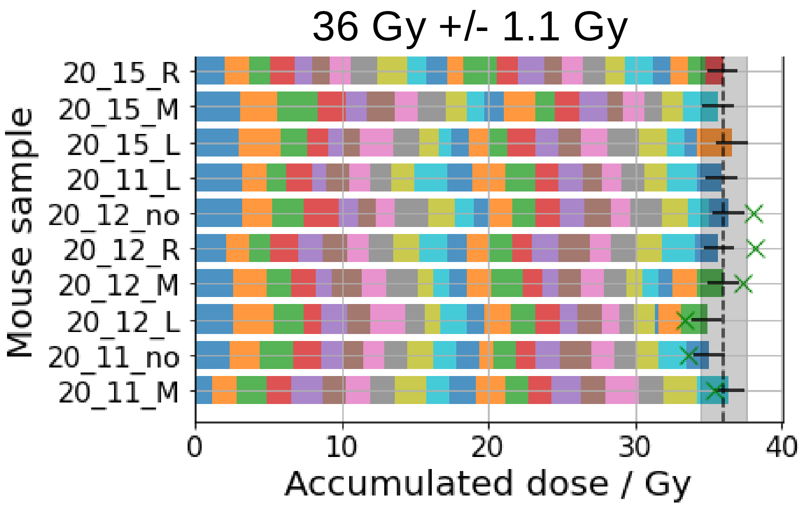


Preliminary data

4 shot days, total of 1220 shots & 60 irradiated animals with prescribed doses of 10 – 40 Gy

Bio endpoints: ear thickness and reddening

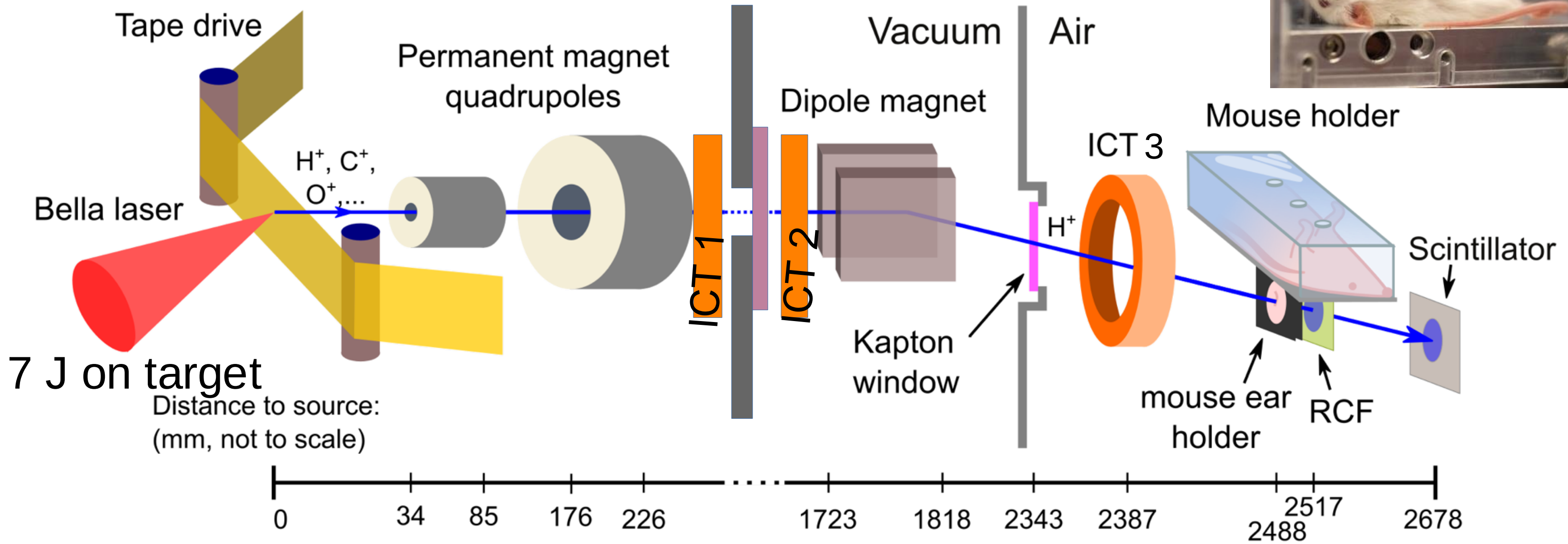


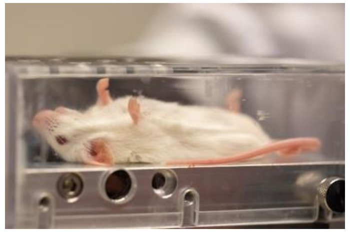


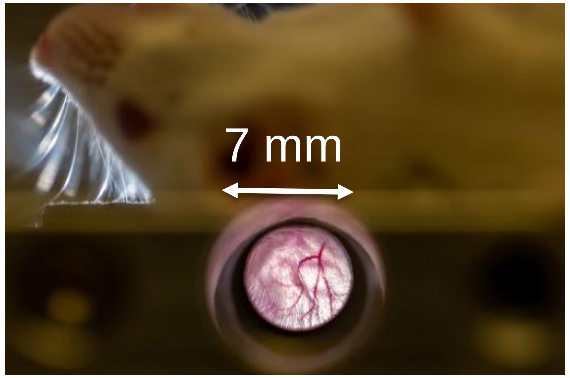
L. Geulig et al., Rev. Sci. Instruments 93 (2022) 103301.
J. De Chant et al., Journ. of Acc. Conferences, IPAC'24 MOPR72 (2024)

U.S. DEPARTMENT OF ENERGY | Office of Science

First animal irradiation at BELLA with 7 MeV laser-driven protons to investigate radiation damage to mouse ear tissue in vivo shows sparing compared to x-rays

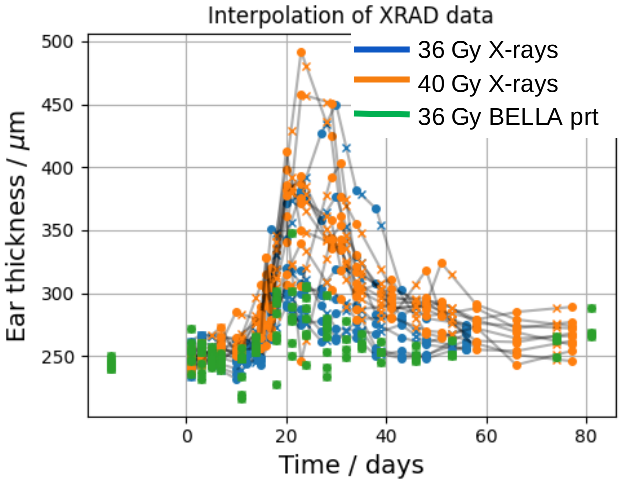


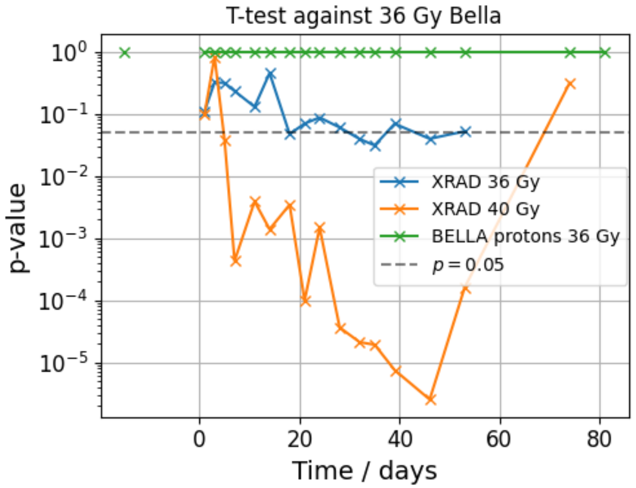


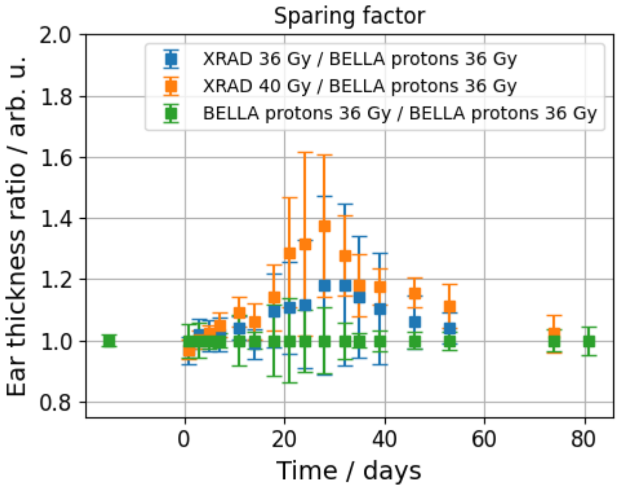


Preliminary data

L. Obst-Huebl, J. Inman, et al., in preparation





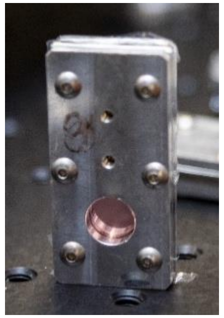


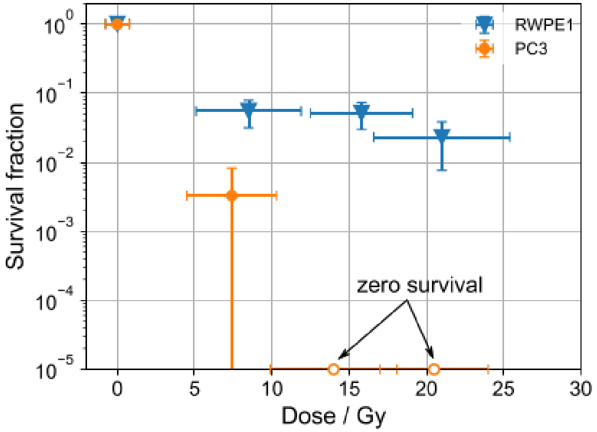
Ongoing:

- Biological tissue staining methods and transcript sequencing
- *Is RBE (proton/x-ray) = 1.1 valid?* → Seeking proton reference irradiation opportunities

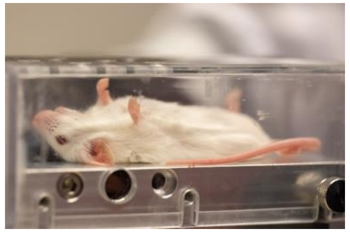
Outline

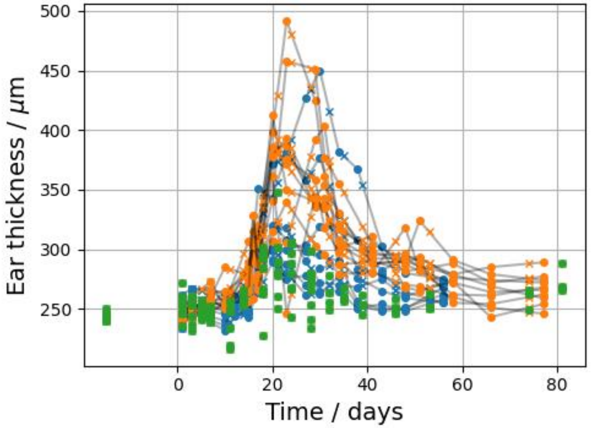
1) *Cell irradiations* with TNSA protons ~2 MeV



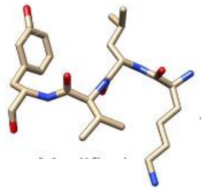


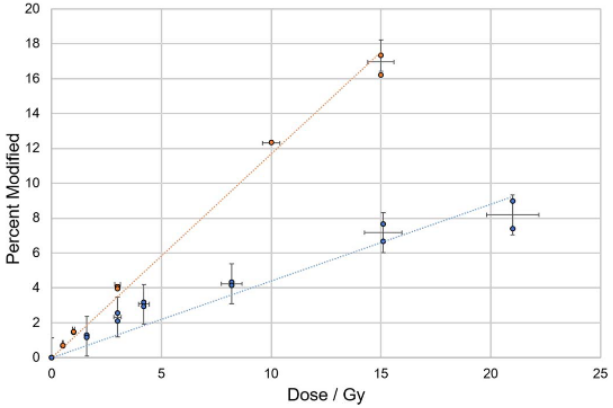
2) *Mouse ear irradiations* with TNSA protons ~7 MeV



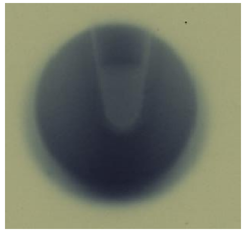


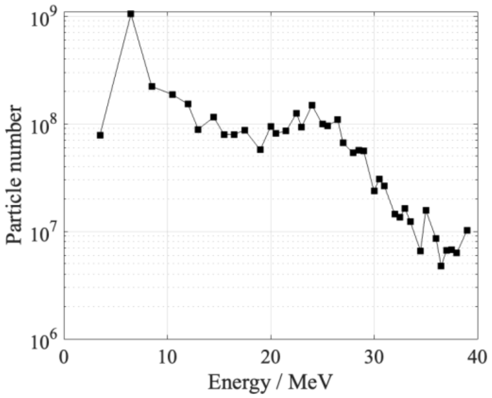
3) *Peptide irradiations with* synchrotron x-rays (ALS)





4) *Peptide irradiations* with TNSA protons ~7-30 MeV





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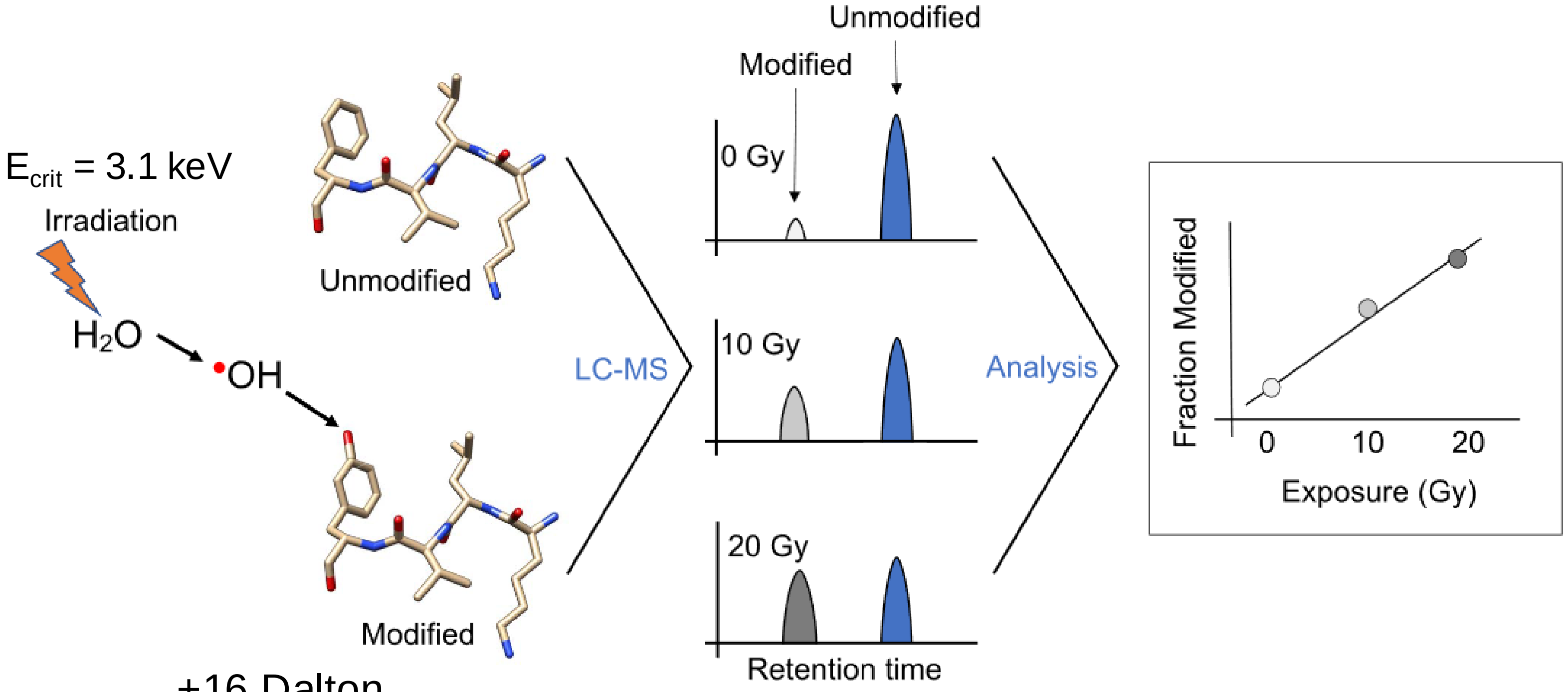
A peptide irradiation platform was established at the Advanced Light Source (ALS) to study dose rate effects on oxidative damage to peptides

X-ray footprinting mass spectrometry used with a reductionist approach (peptides in vitro) to isolate individual components of the FLASH effect



+16 Dalton oxidative modification

Liquid Chromatography Mass Spectrometry (LC-MS)

S. Gupta et al., Radiation Research 200(6), 523-530 (2023)

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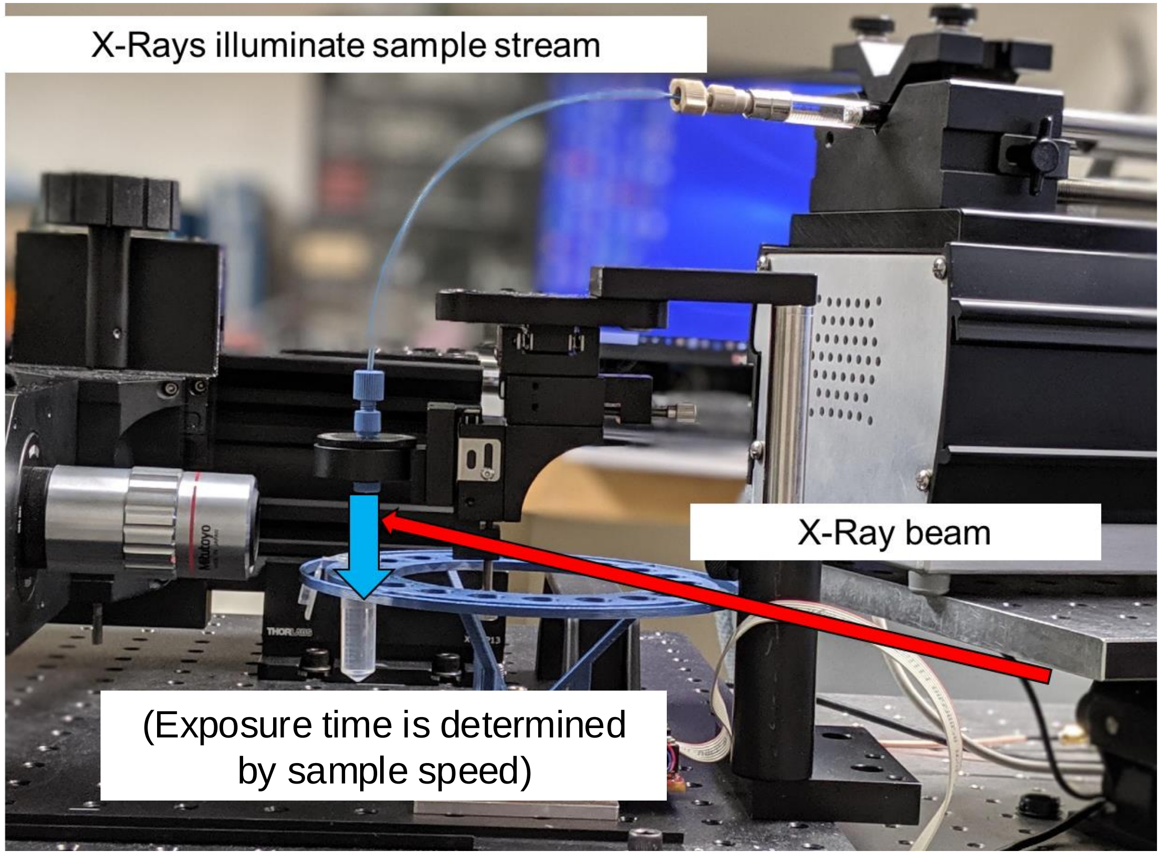
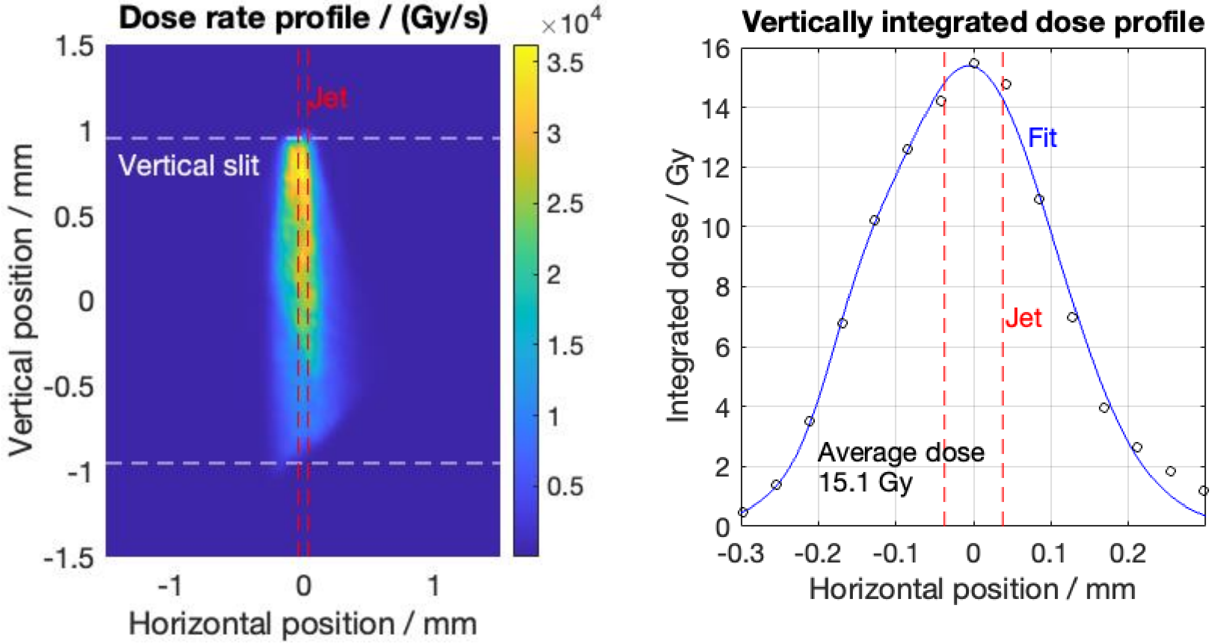


Dosimetry was conducted with radiochromic film

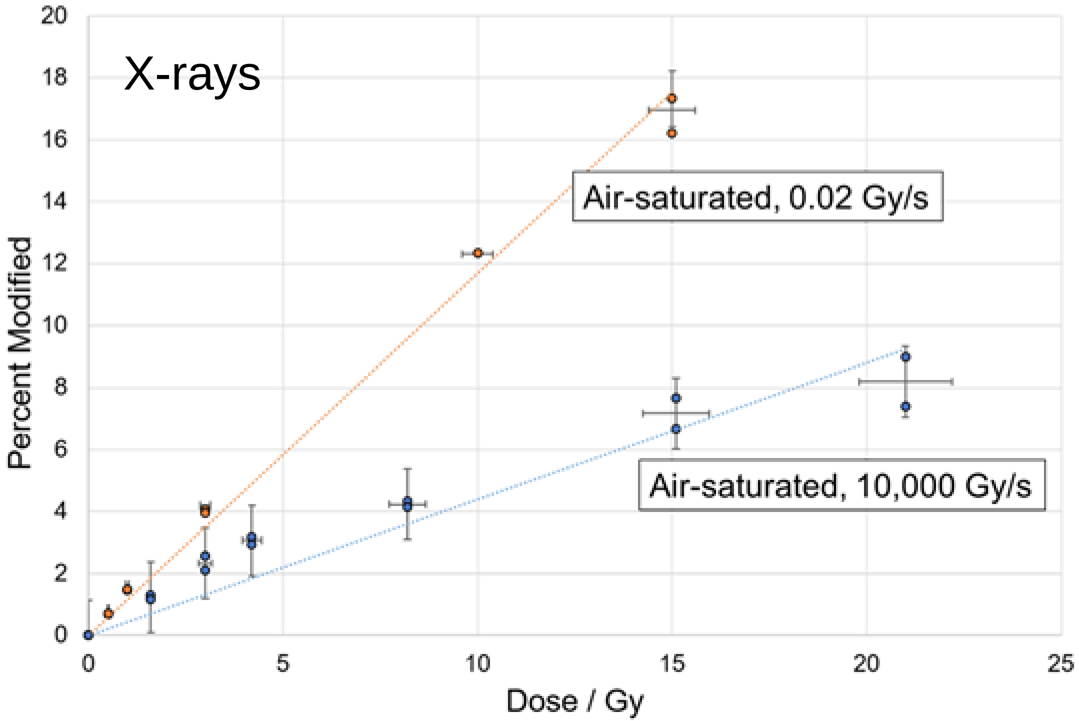


S. Gupta et al., Radiation Research 200(6), 523-530 (2023)

U.S. DEPARTMENT OF ENERGY | Office of Science

The dose rate and oxygen dependent modification of peptides is confirmed in x-ray irradiations at the ALS versus at a conventional x-ray tube

Less damage after ultra-high dose rate than conventional dose rate irradiations



S. Gupta et al., Radiation Research 200(6), 523-530 (2023)

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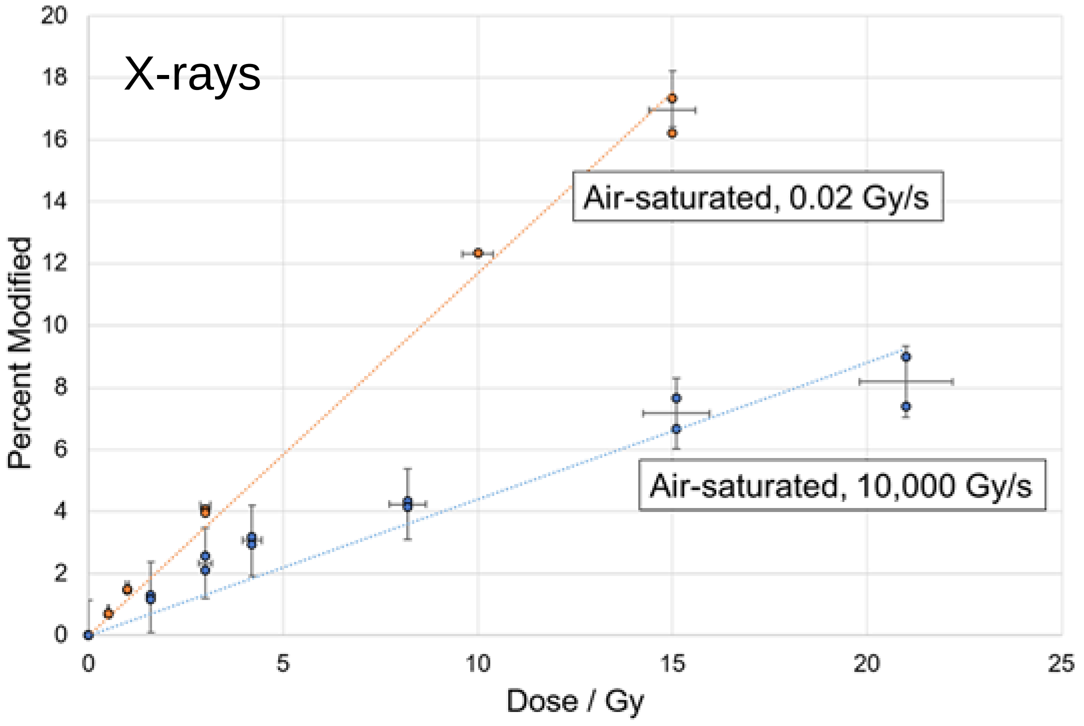
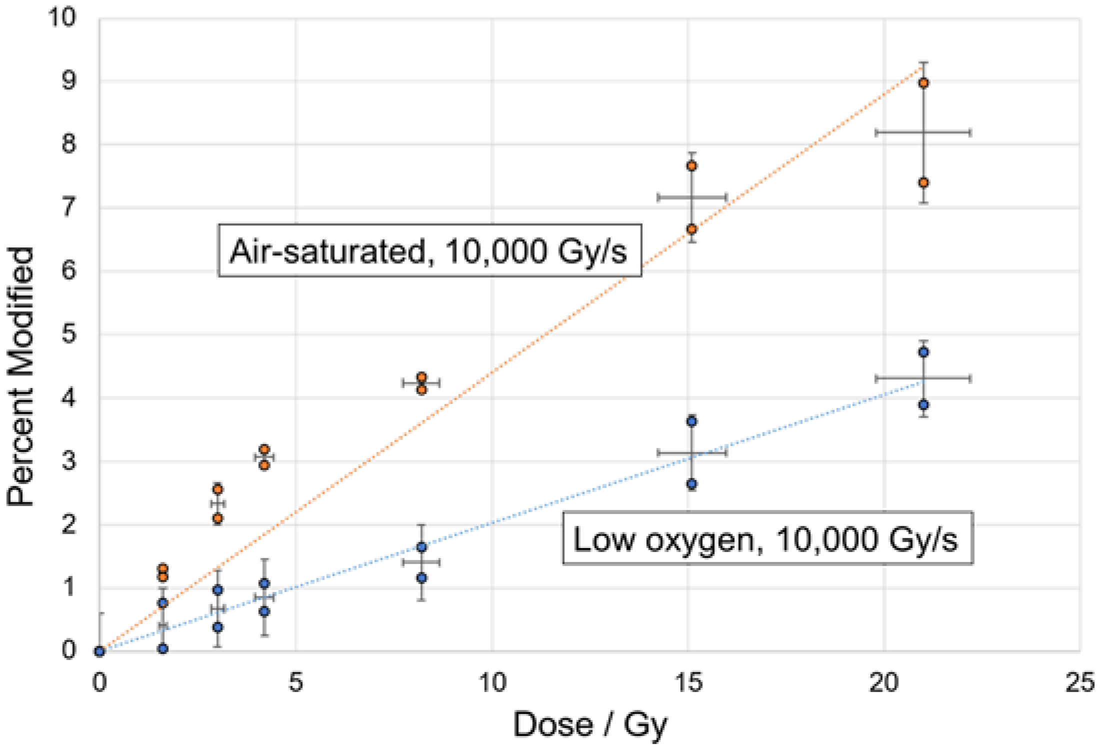


Less damage at lower than atmospheric oxygen content



S. Gupta et al., Radiation Research 200(6), 523-530 (2023)

U.S. DEPARTMENT OF ENERGY | Office of Science

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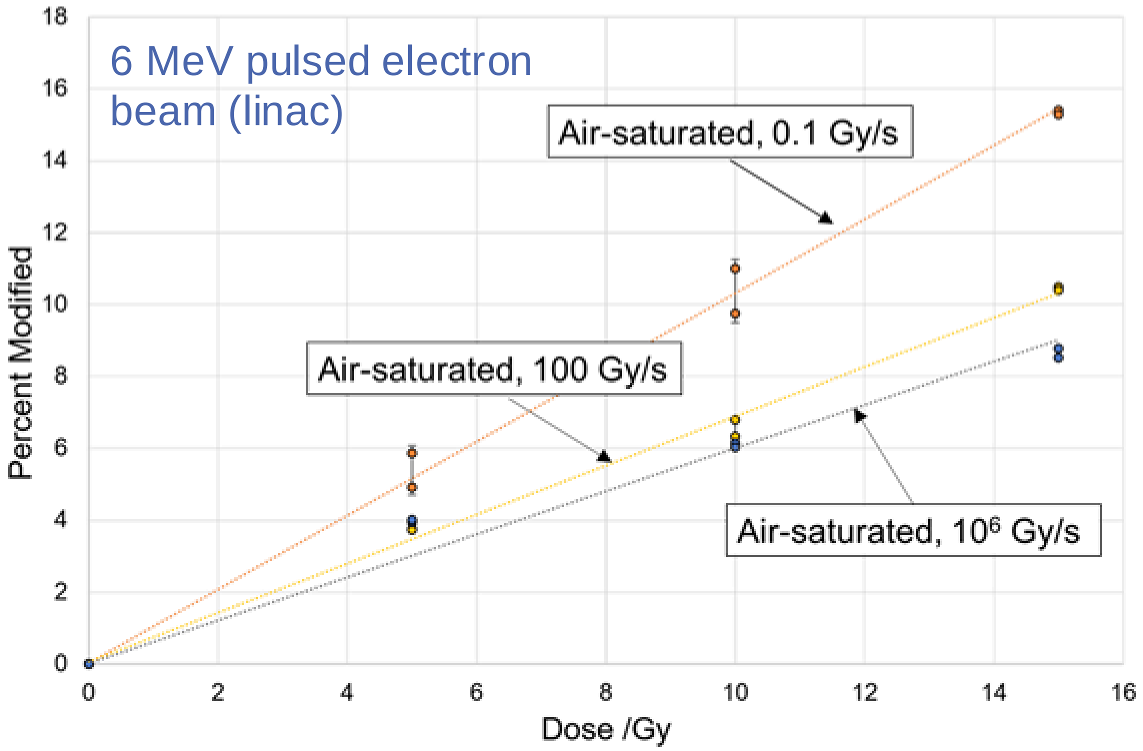
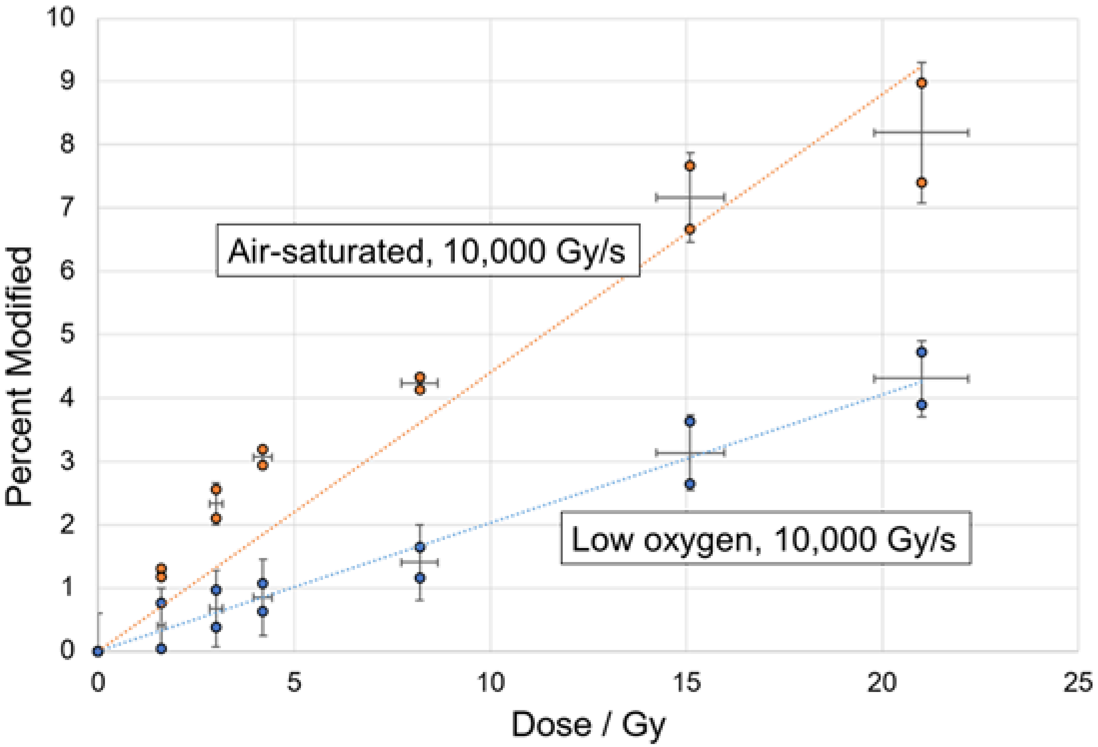


Less damage at low than atmospheric oxygen content



S. Gupta et al., Radiation Research 200(6), 523-530 (2023)

U.S. DEPARTMENT OF ENERGY | Office of Science

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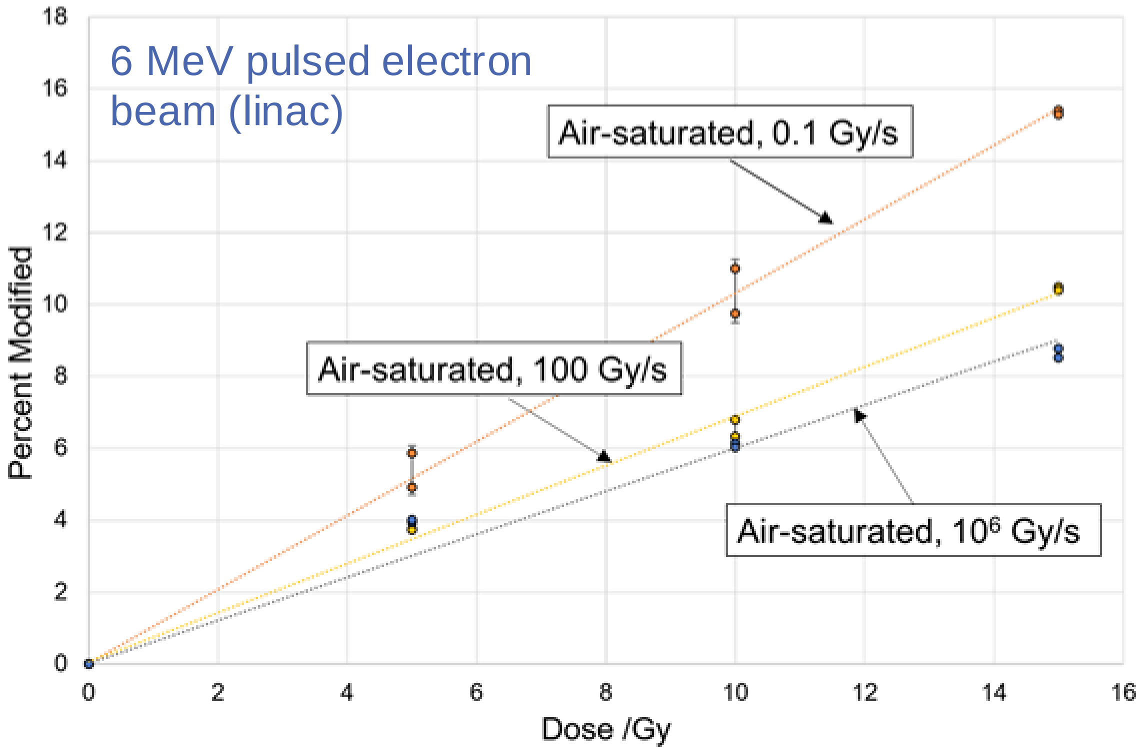

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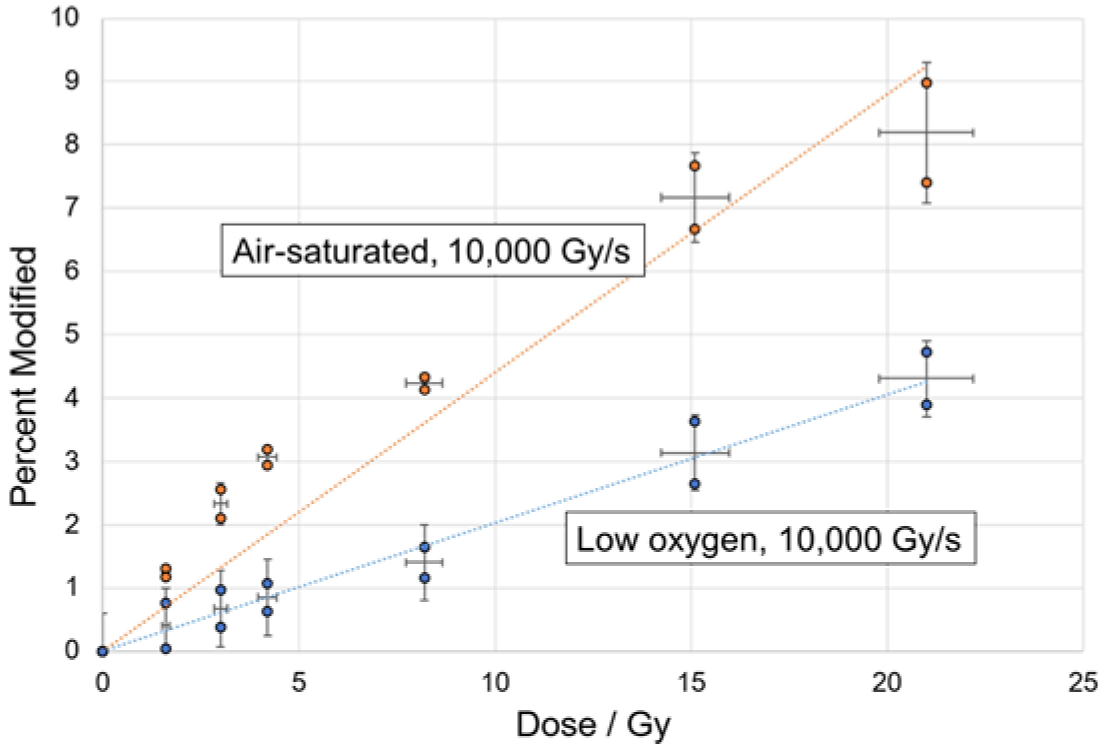

Result: peptides can be used in a reductionist approach to study the damage by OH radicals under different radiation regimes and sample conditions

S. Gupta et al., Radiation Research 200(6), 523-530 (2023)

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Outline

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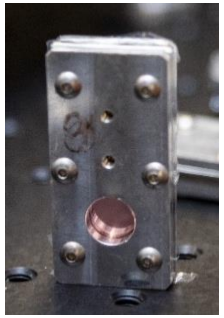

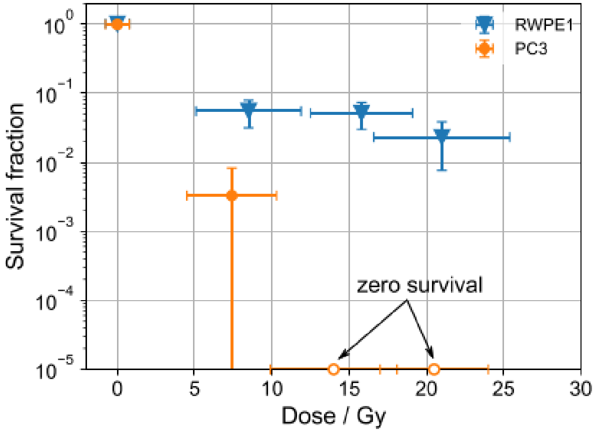

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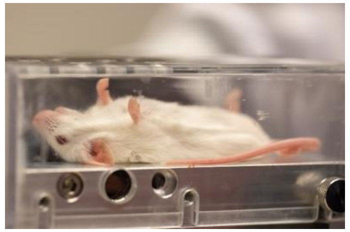

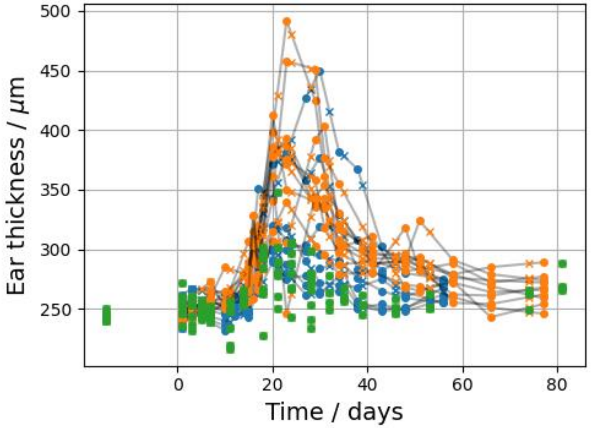

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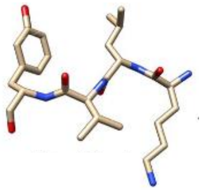

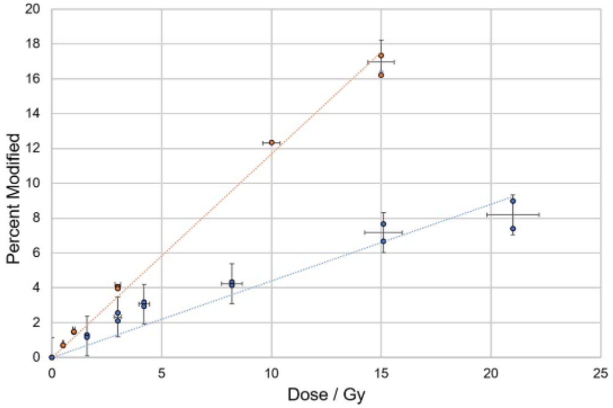

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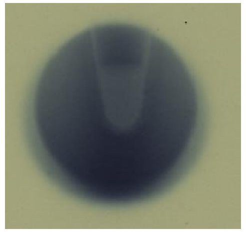
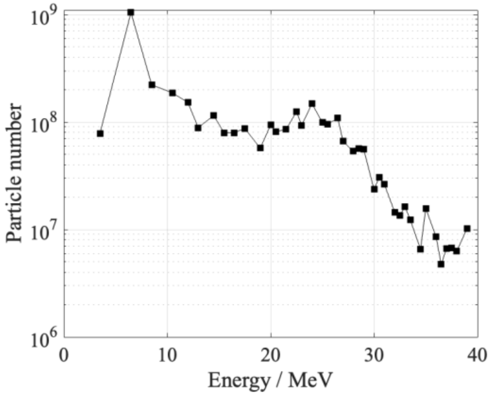
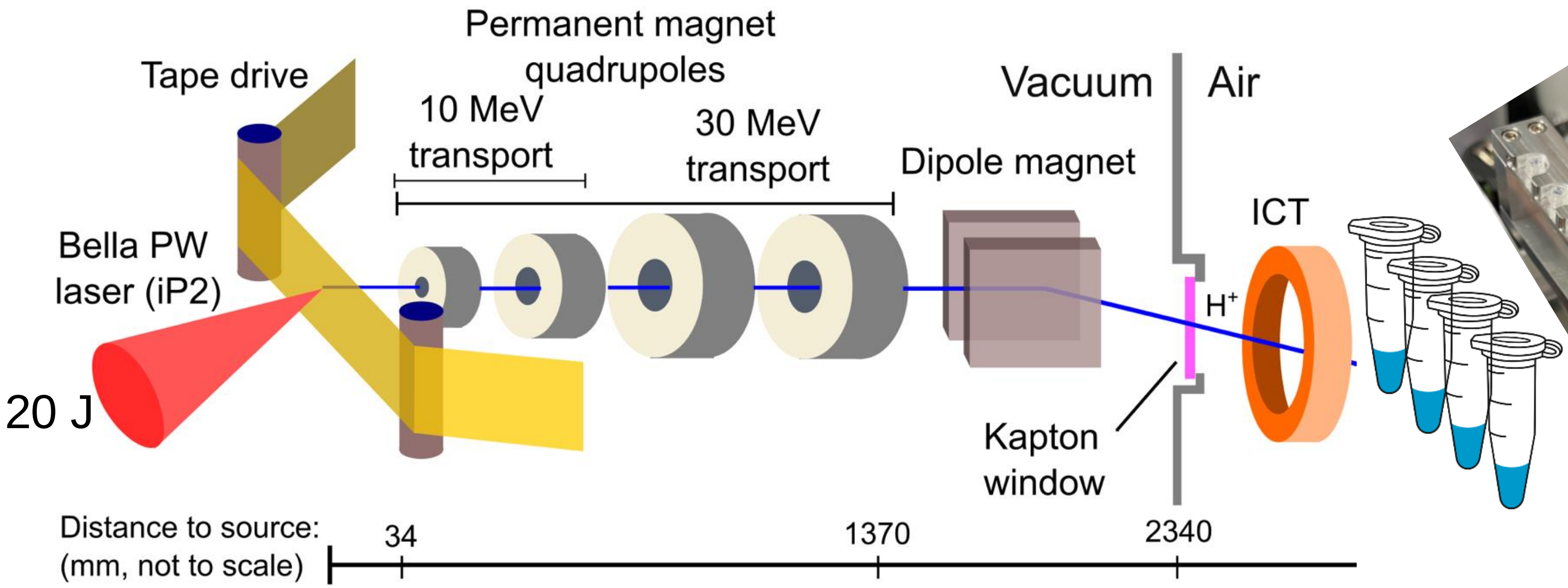
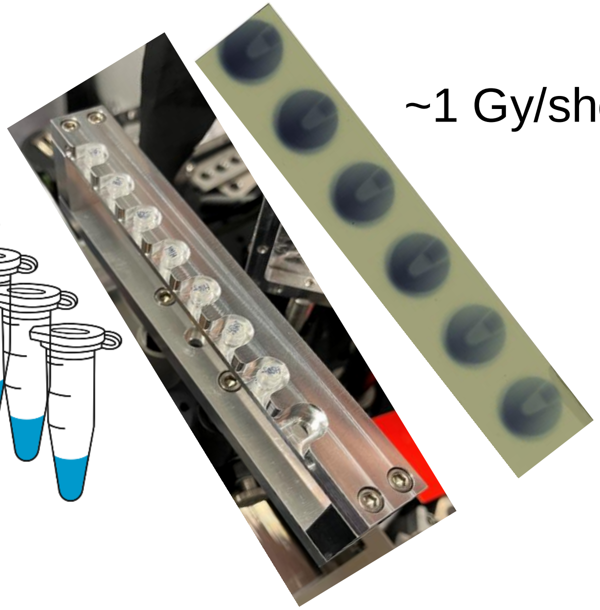




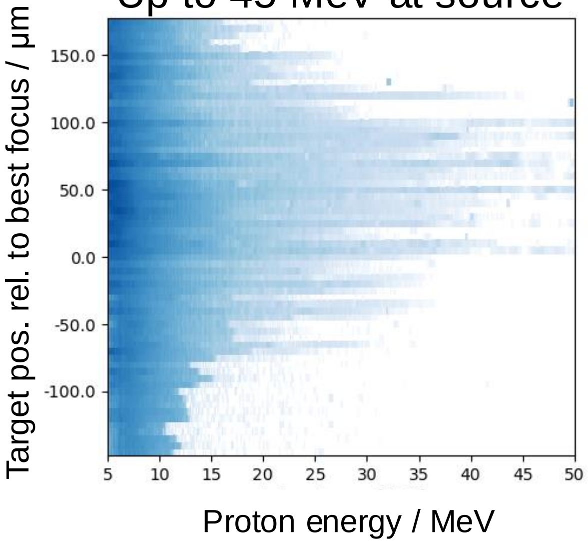
First peptide experiments at BELLA iP2 with ~7-30 MeV protons were conducted in April 2024



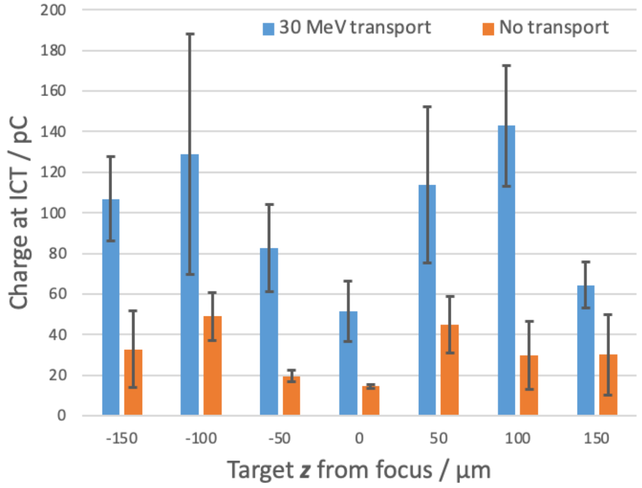


~1 Gy/shot

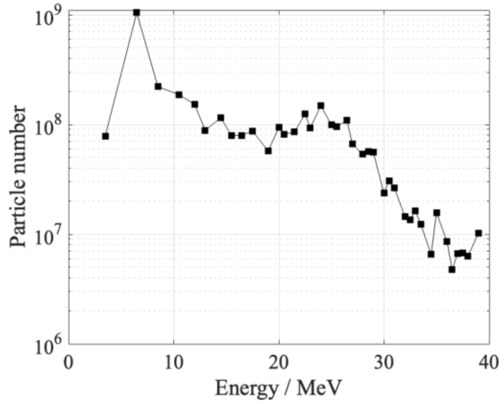
Up to 45 MeV at source



3x improved transport with 4 quadrupoles



Broad spectrum delivered to sample



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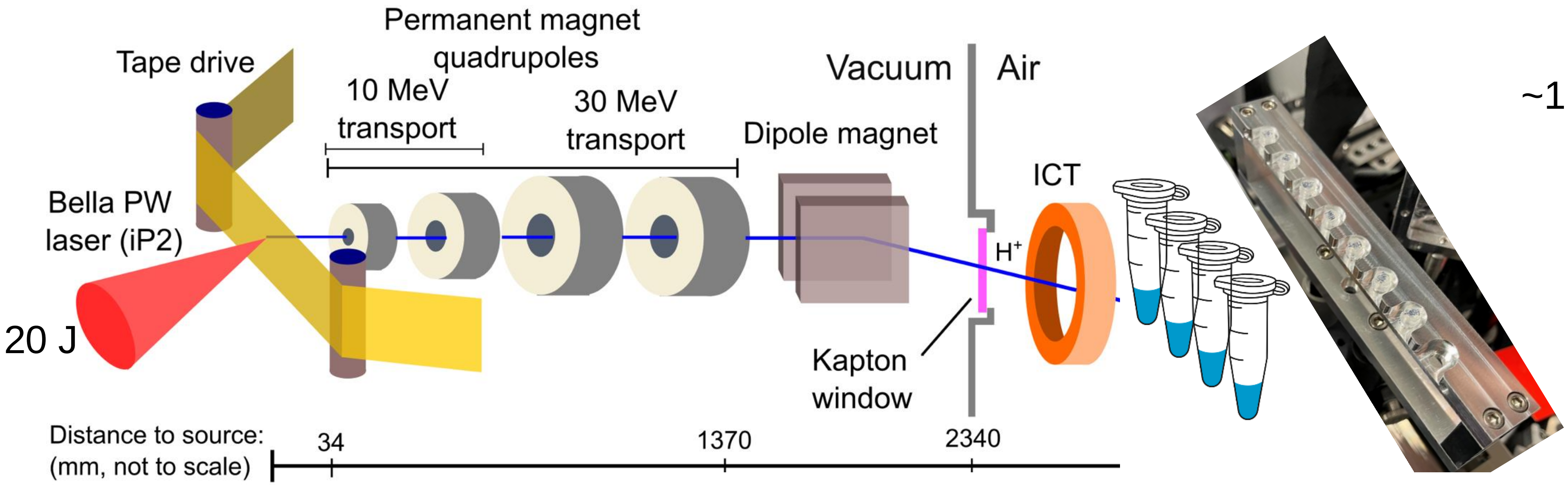
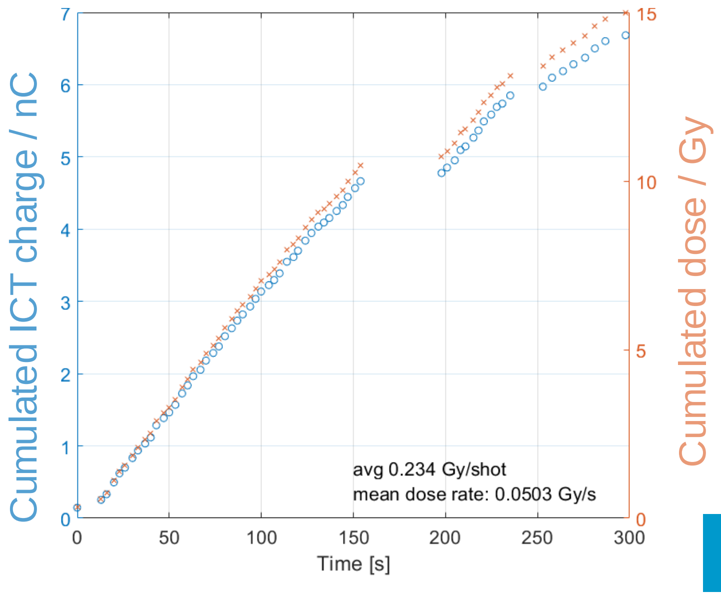
The stability of the higher energy TNSA source needs further improvement for systematic radbio studies





Proton dose and spectrum *declined over the course of sample irradiations* due to a drift in the system when shooting the laser continuously every ~5-10 seconds
→ Finding the source of this drift + implementing online spectral measurements are work in progress

Sample # 1 2 3 4 5 6

LC-MS results are pending – stay tuned!

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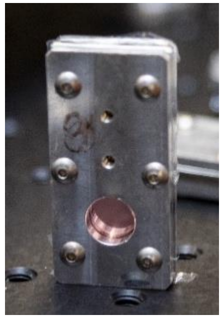
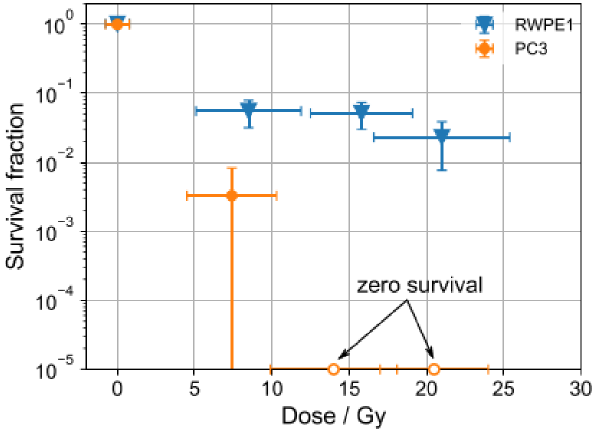
Outline

1) *Cell irradiations* with TNSA protons ~2 MeV





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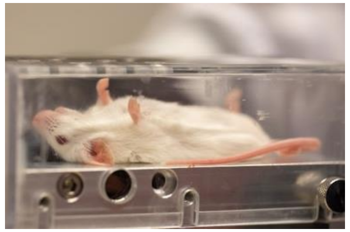

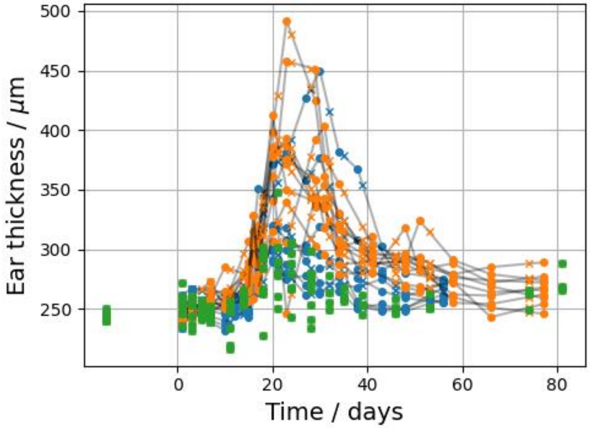

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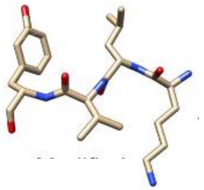

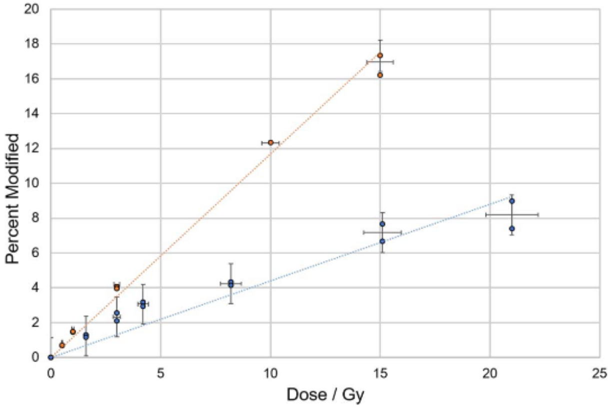

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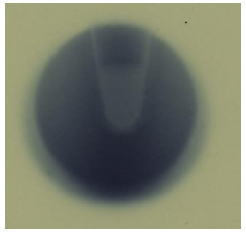

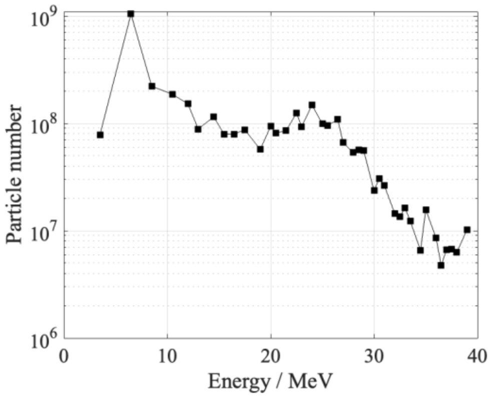

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Summary

1) *Cell irradiations* with TNSA protons ~2 MeV

- **Differential sparing of normal versus tumor tissue observed** *in vitro* when irradiated with ultra-high instantaneous dose rate laser-driven protons
- RNA sequencing of cell samples suggests a possible role of **different responses of normal versus tumor cells to oxidative stress in ultra-high dose rate regime**

2) *Mouse ear irradiations* with TNSA protons ~7 MeV

- **Reduced damage to normal tissues confirmed *in vivo*** comparing irradiations with laser-driven proton beams to conventional dose rate x-ray
- Ongoing analysis of results aims to investigate underlying mechanisms of the sparing observed

3) *Peptide irradiations with* synchrotron x-rays (ALS)

- The **dose rate and oxygen dependent modification of peptides was confirmed** in x-ray irradiations at the ALS versus at a conventional x-ray tube
- Peptides can be used in a **reductionist approach to study the damage by OH radicals** under different radiation regimes and sample conditions

4) *Peptide irradiations* with TNSA protons ~7-30 MeV

- First peptide irradiation experiments at BELLA iP2 with ~7-30 MeV protons were conducted in April 2024, the analysis of the results is currently underway
- The **stability of the higher energy TNSA source needs further improvement** for systematic radbio studies