A platform for radiobiology research using very-high energy (VHEE) laser plasma accelerated electrons at BELLA

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Lawrence Berkeley National Laboratory

Advanced Accelerator Concepts 2026, Los Angeles

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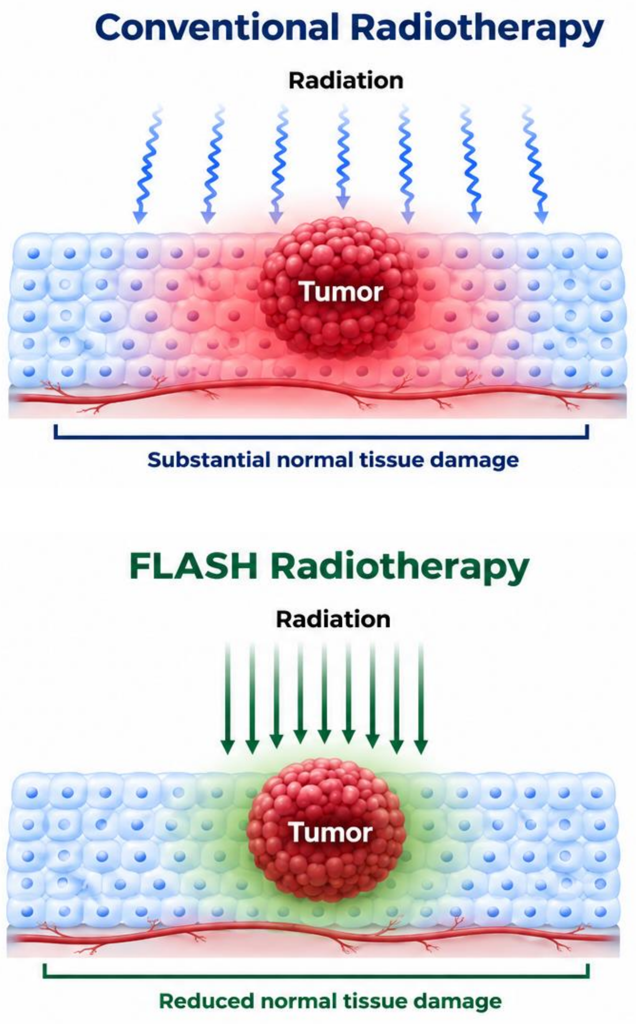
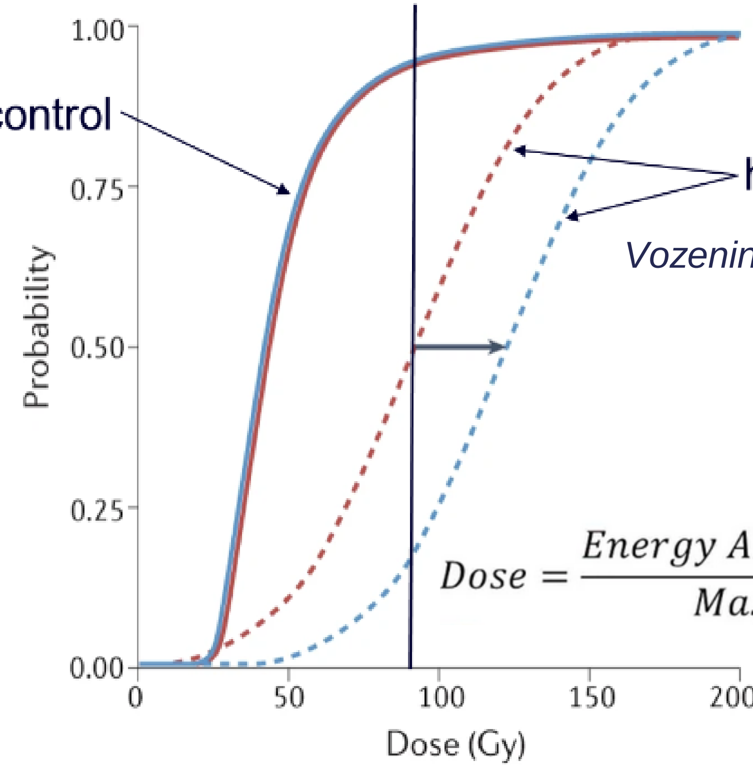
Ultra-high dose rate radiotherapy (FLASH-RT) demonstrates differential sparing of healthy tissue, but the underlying mechanism remains elusive





$$Dose = \frac{Energy\ Absorbed}{Mass}$$

Vozenin et al., Nature Reviews Clinical Oncology (2022); Esplen et al., Phys. Med. Biol. 65 (2020); Friedl et. al, Med. Phys. 49 (2022),…

TCP = tumor control probability
NTCP = normal tissue complication probability

Impact:

- Similar tumor control at reduced normal tissue damage (less follow-up cancer)
- Higher therapeutic doses in fewer fractions (fewer irradiation sessions)

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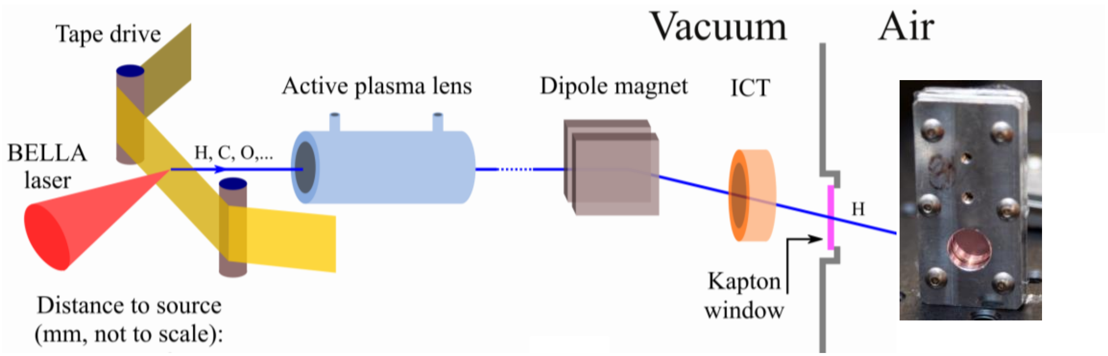
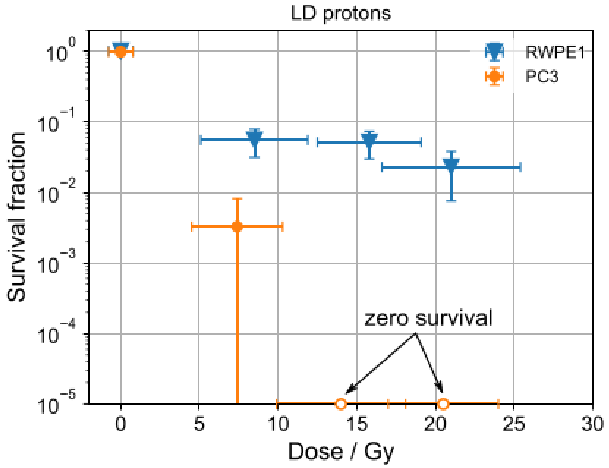
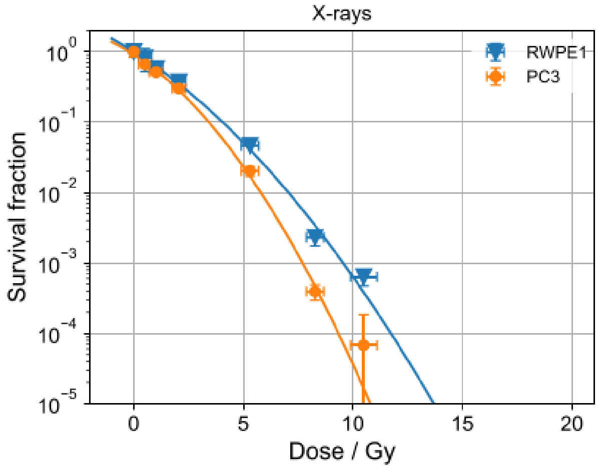
Sample exposures with laser-driven (LD) protons have shown differential tissue sparing, possibly due to ultra-high peak dose rate

Normal and tumor cell exposures with 2 MeV, 30 ns, 1 Gy/shot: higher normal cell than tumor cell survival

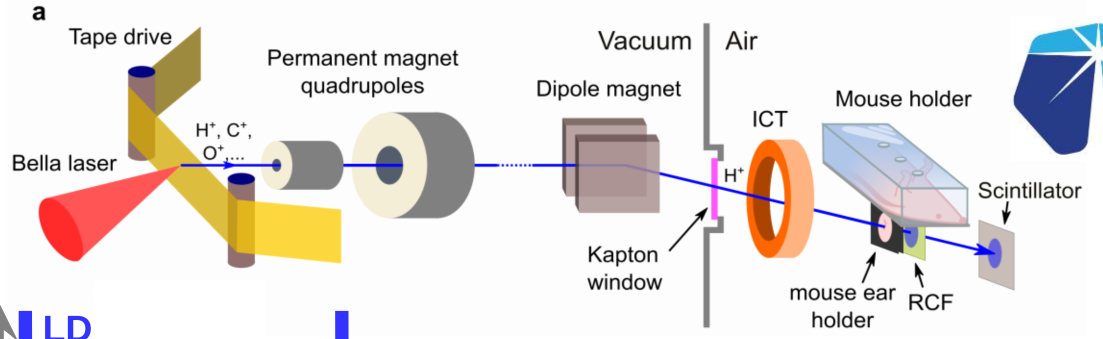


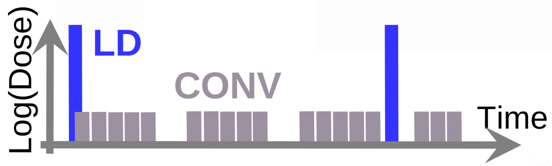


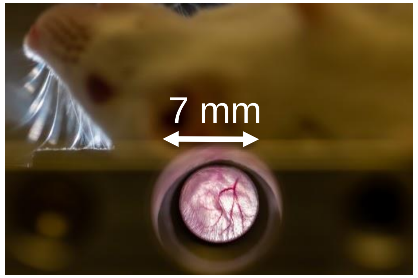


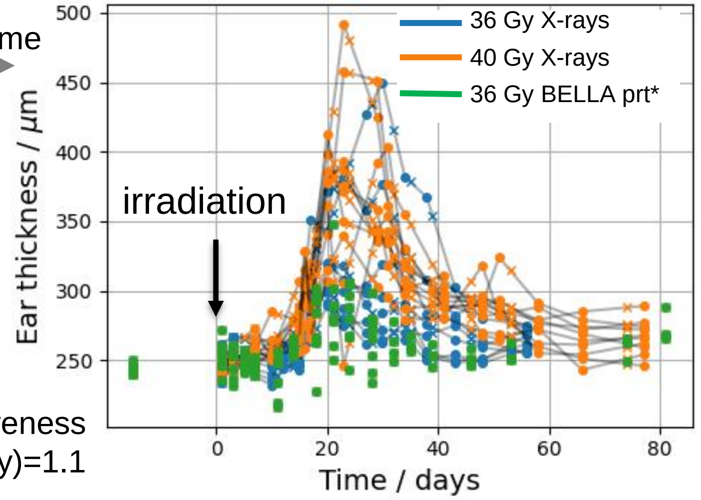
J. H. Bin et al., Sci. Rep. 12 1585 (2022); L. Geulig et al., Rev. Sci. Instrum., 93, 103301 (2022)

Normal mouse ear exposures with 8 MeV, 11 ns, 2 Gy/shot: Less ear swelling after LD proton than conventional X-ray









*Radiobiological effectiveness RBE(proton/x-ray)=1.1

J. De Chant et al., PRAB 28 (2025); L. Obst-Huebl et. al. (in review, 2026), arXiv:2602.20460

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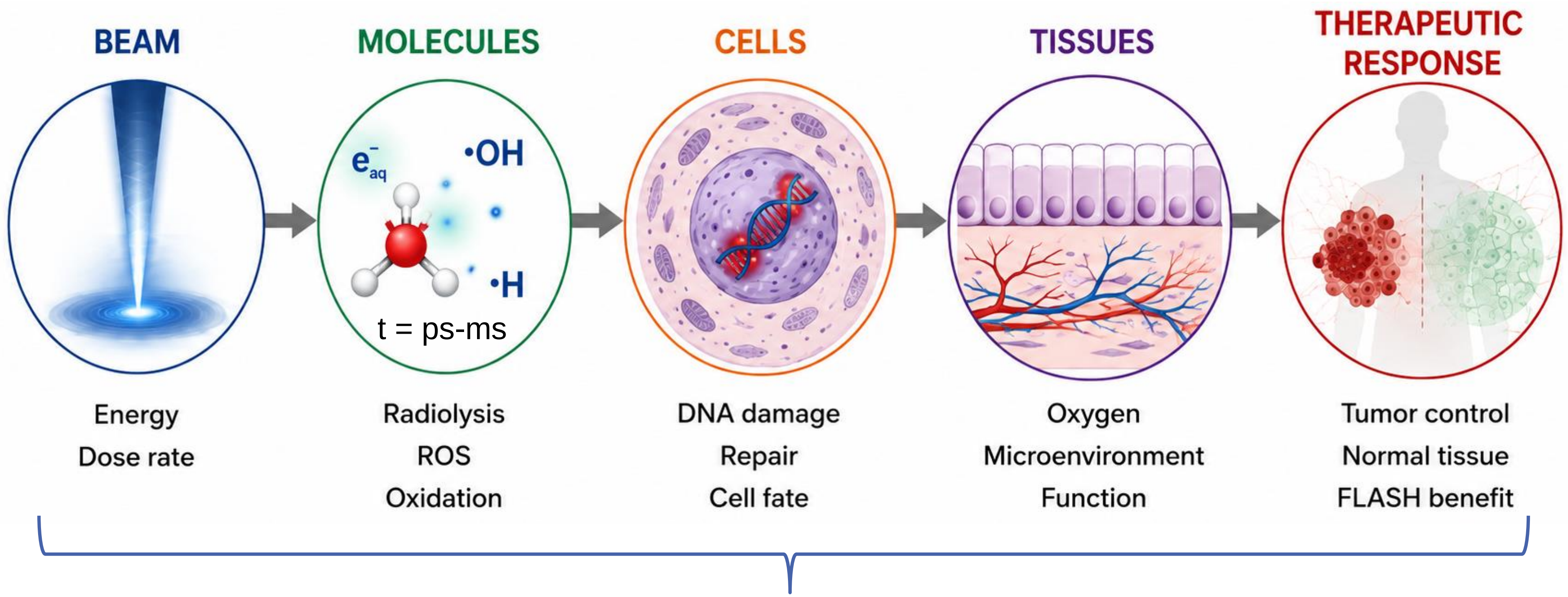
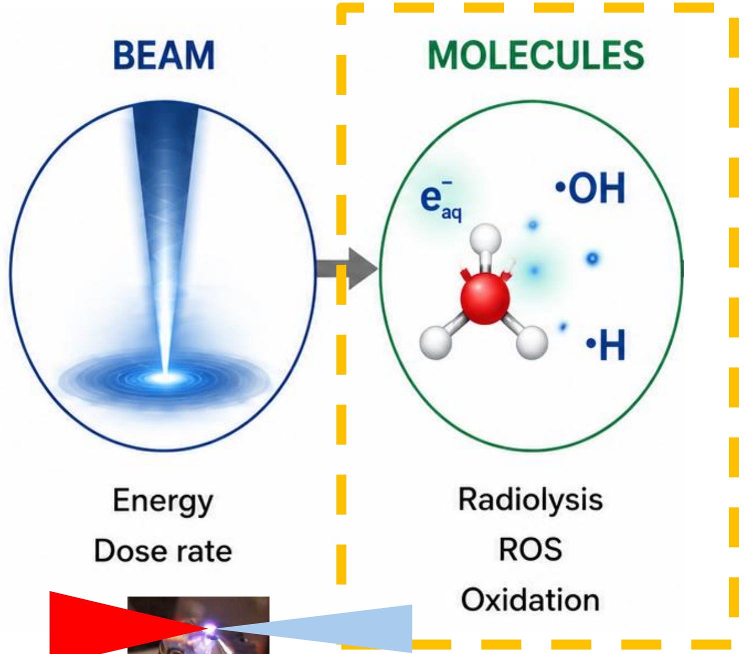
Exploring the mechanism of the FLASH effect requires connecting physical beam properties to biological outcomes across multiple scales

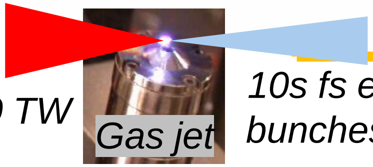


Various hypotheses to explain the FLASH effect address different parts of this process, but none have been confirmed

Vozenin et al., Nature Rev. Cancer (2026)

Ultrafast laser-driven radiation sources can be tools to elucidate early radiochemical processes

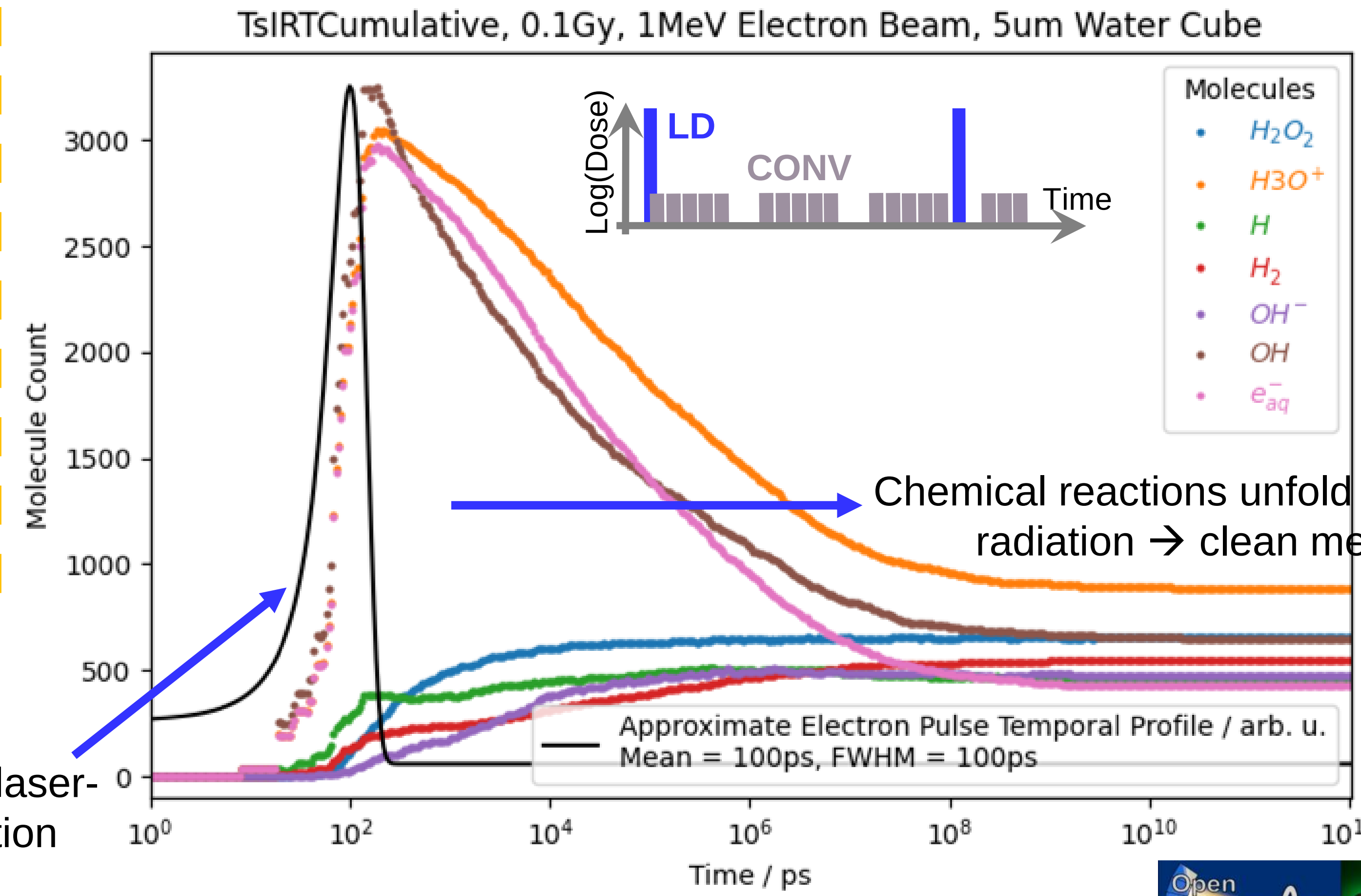




~100 TW

10s fs e⁻ bunches

Short burst of laser-driven radiation



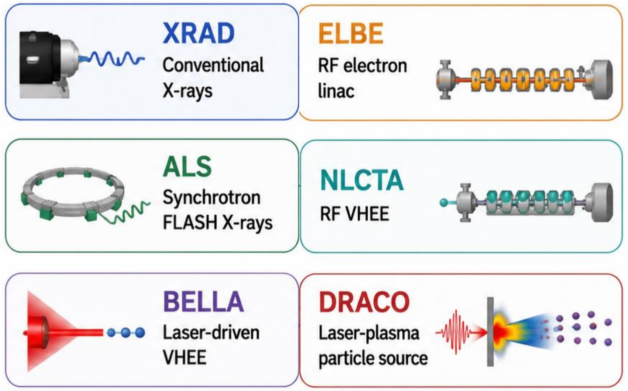
Chemical reactions unfold without continued radiation → clean measurements

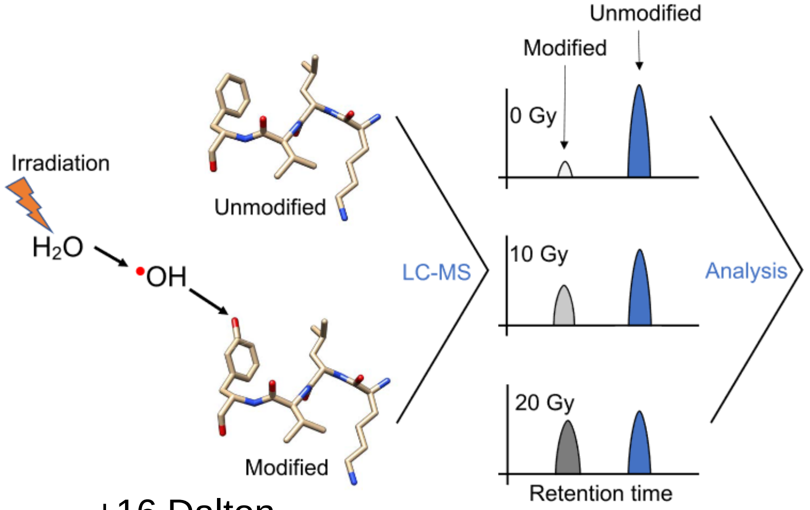
<u>Growing body of radiobioly literature using LPA electrons:</u> Laschinsky *Journal of Rad. Research* **53** (2012), Oppelt *Radiat. Environ. Biophys.* **54** (2015), Andreassi *Rad. Research* **186** (2016), Labate *Sci. Rep.* **10** (2020), Cavallone *Appl. Phys. B* **127** (2021), Guo *Nat. Commun.* **16** (2025), McAnespie *Phys.Med.Biol.* **70** (2025), *eBeam4Therapy*,…

J. Schuemann et al., Medical physics 46 (2019)

We are establishing a standardized peptide oxidation assay to probe ultrafast radiochemical processes

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

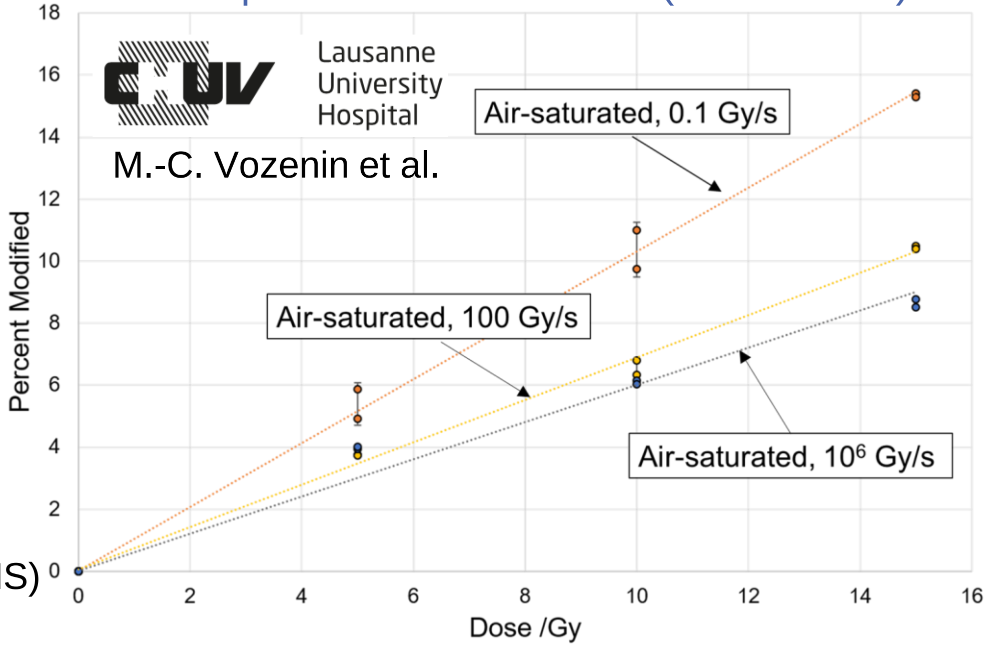




+16 Dalton oxidative modification

Liquid Chromatography Mass Spectrometry (LC-MS)

6 MeV pulsed electron beam (CHUV linac)



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Peptide oxidative damage mirrors normal tissue sparing trends observed in FLASH and is a compelling reductionist approach to study the early dynamics of radiation damage*

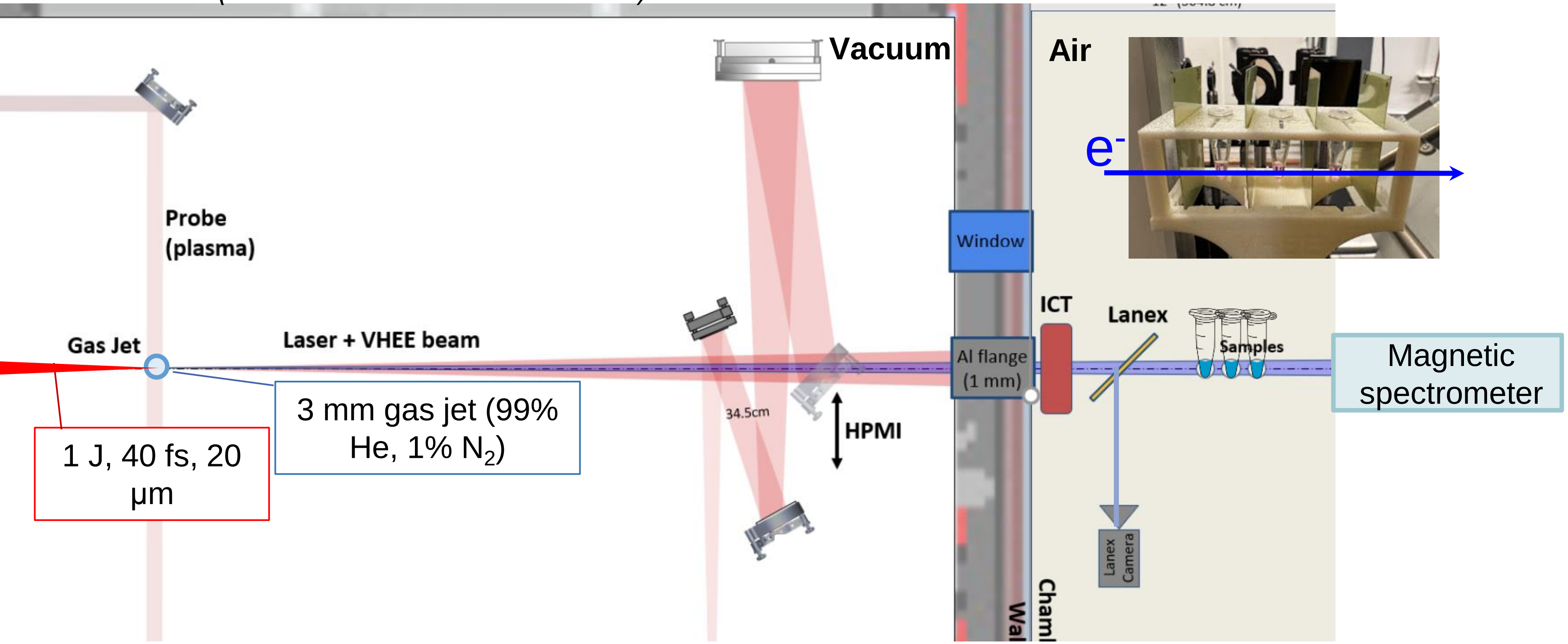
*although not distinguishing normal versus tumor

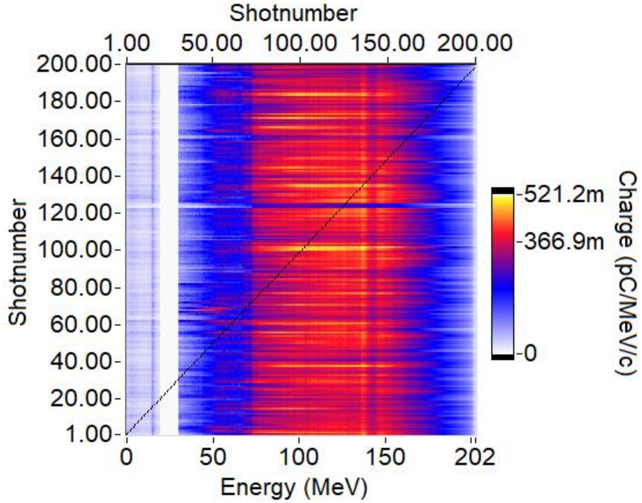
S. Gupta et al., Radiation Research 200(6), 523-530 (2023); *S. Kidd et al., Applied Science 16 (2026);*

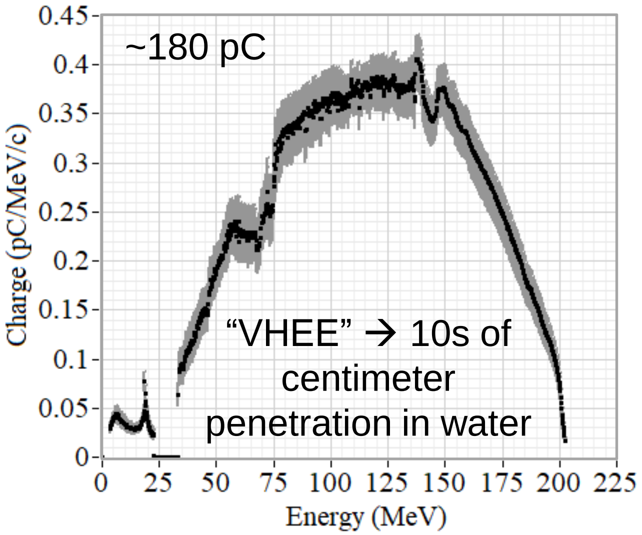
BELLA HTT Setup and Spectrum aimed at maximizing charge in 50-200 MeV (VHEE) range to deliver dose evenly to thick samples

Optimized LWFA beams for maximum charge in 50-200 MeV energy band using ionization injection

BELLA HTT ("Hundred Terawatt Thomson") interaction chamber

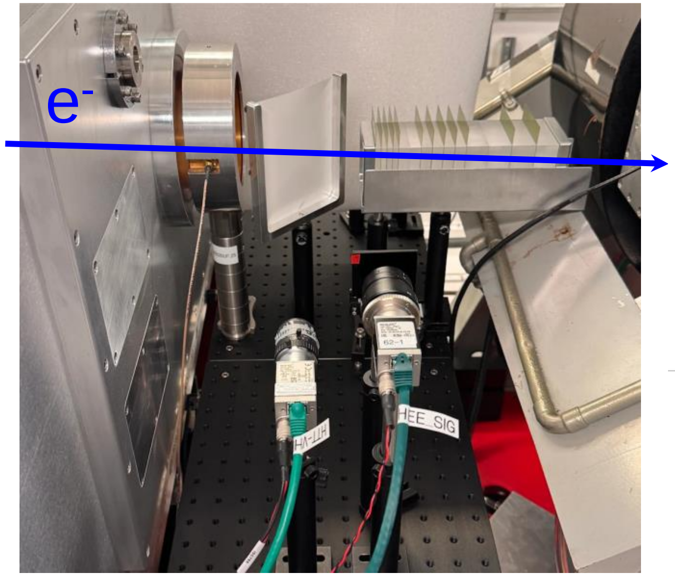




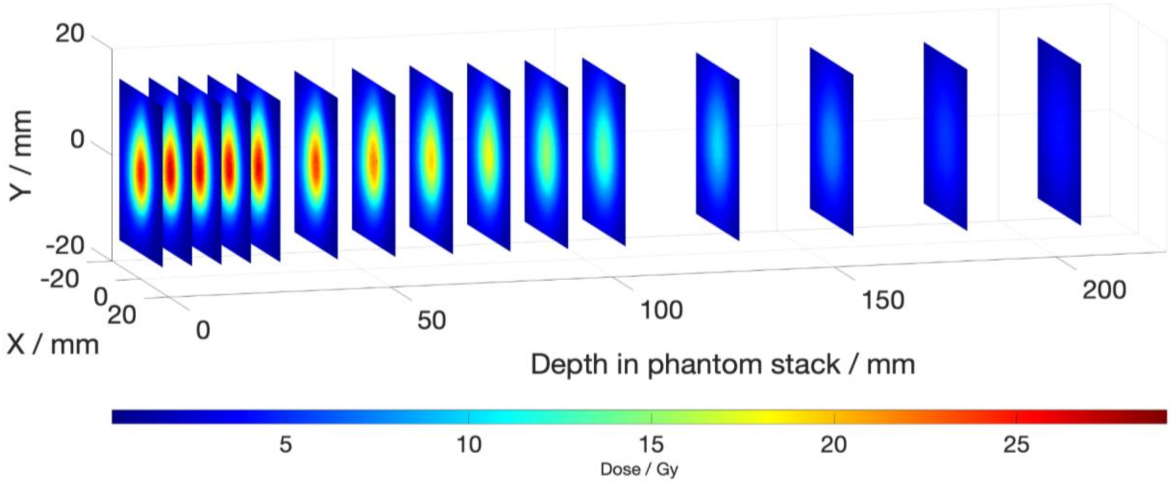


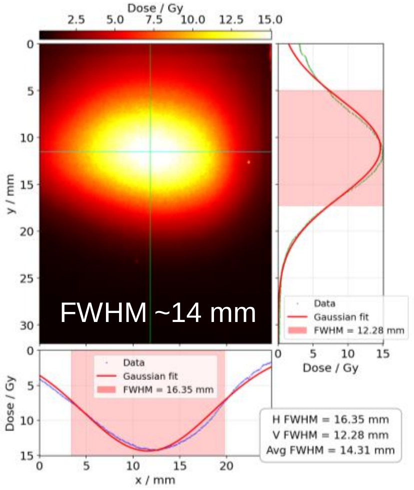
Chen et al., J. Appl. Phys. 99 (2006); McGuffey et al., Phys. Rev.Lett. 104 (2010); Pak et al., Phys. Rev.Lett. 104 (2010); Clayton et al., Phys. Rev. Lett. 105 (2010); Tsai et al., Sci. Rep. in press (2026) nature.com/articles/s41598-026-56639-7

BELLA VHEE depth dose profile was characterized using a phantom stack interleaved with radiochromic film, showing beam penetration up to 20 cm in plastic

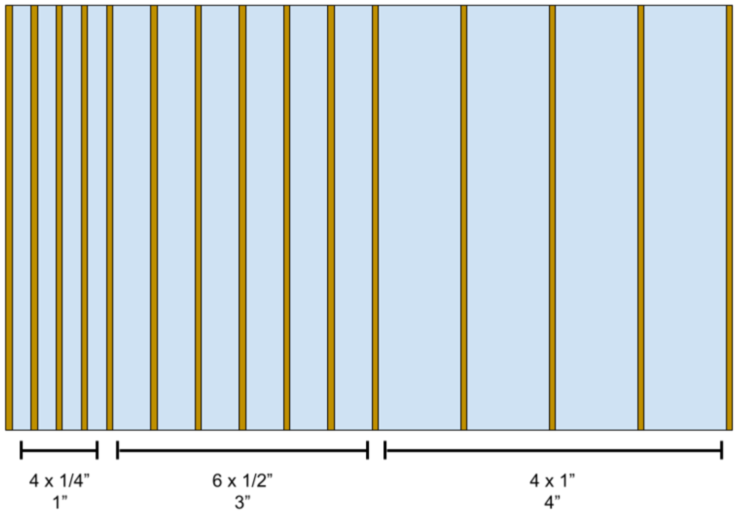


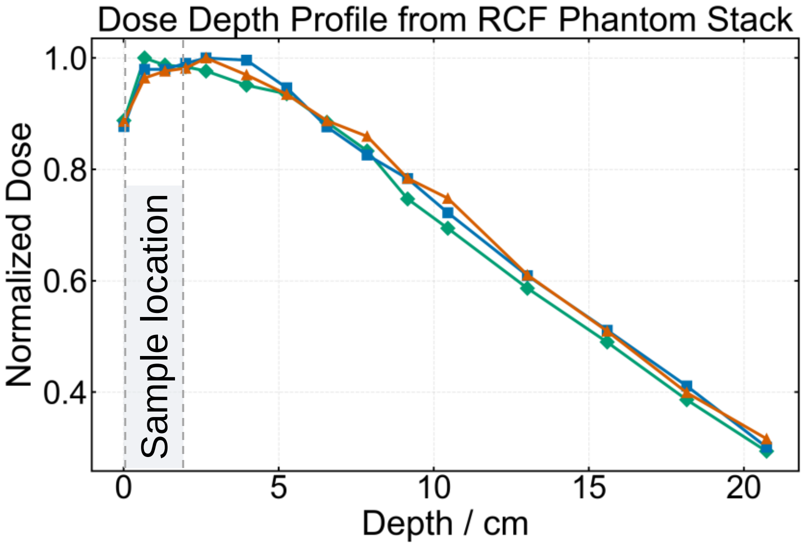
Sample area





3" x 3" cast acrylic (PMMA) sheets with radiochromic film between
14 PMMA sheets, 15 RCF total





Labate et al., Sci. Rep. 10 (2020);
Zhou et al., PRAB 28 (2025)

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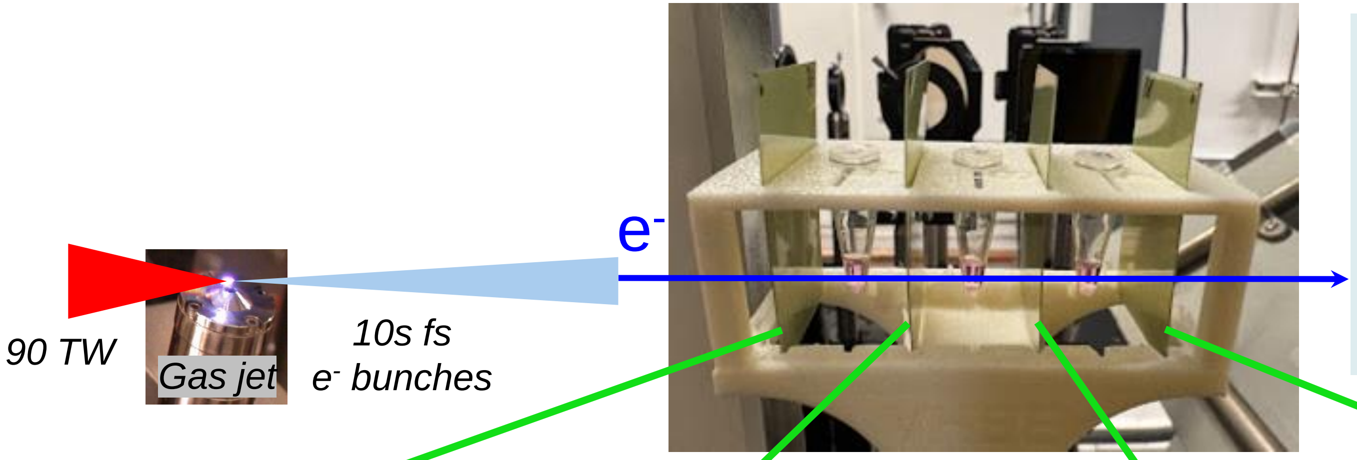
Absolute sample dosimetry was performed using calibrated radiochromic film (EBT)

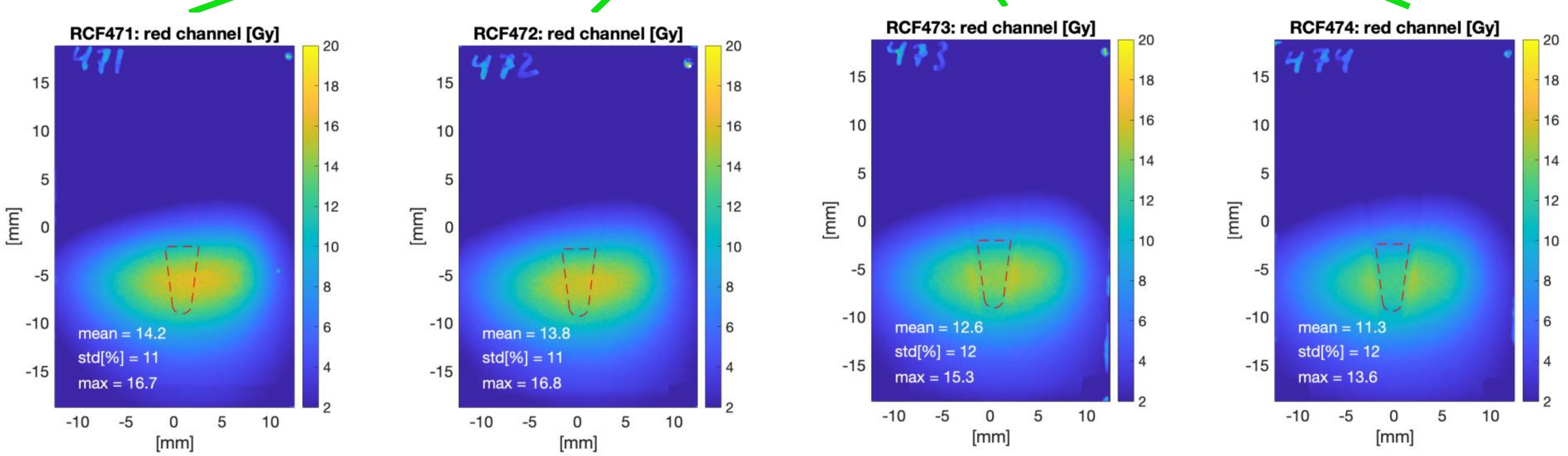


<u>Average dose rate to samples in stack</u>:

- 1st sample: (60 ± 12) mGy/shot
- 2nd sample: (55 ± 11) mGy/shot
- 3rd sample: (50 ± 10) mGy/shot

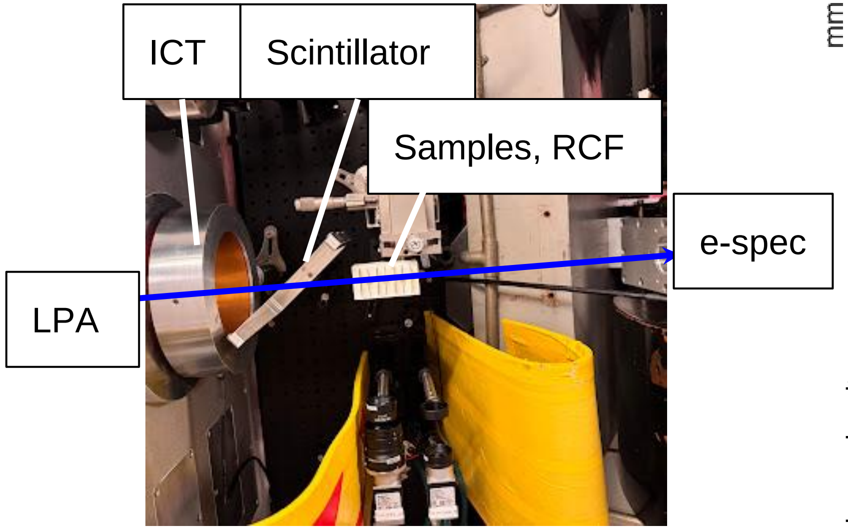
→ **Mean dose rate of 3-3.5 Gy/min** (1 Hz shot rate)

lateral dose uniformity: ~12%
depth dose uniformity: ~5%

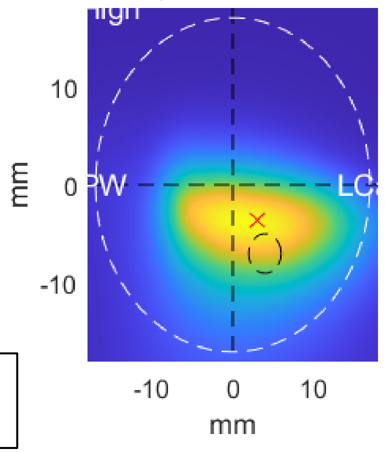


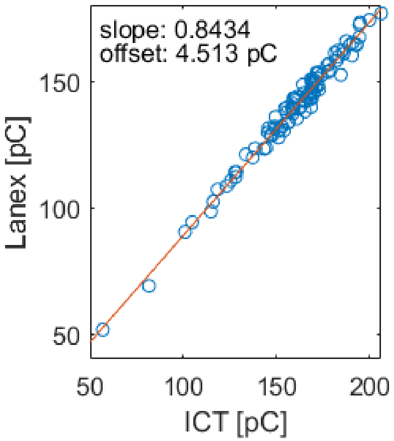
EBT3/4 calibrated with 300 kVp X-ray source
→ Cross calibration using 70 MeV electrons at varying dose rates scheduled at SLAC NLCTA in September through BeamNetUS (PI A. Lu)

Online dosimetry was established to support targeting prescribed doses

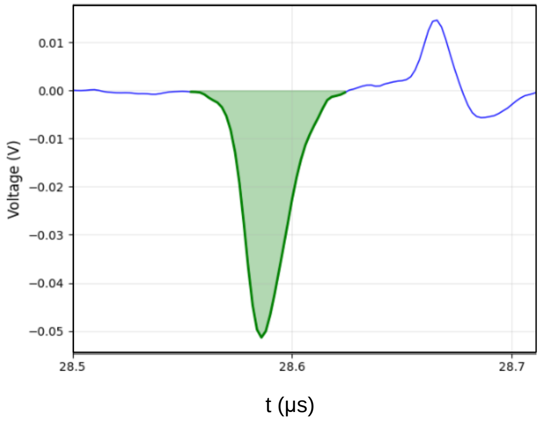


Beam profile on Lanex

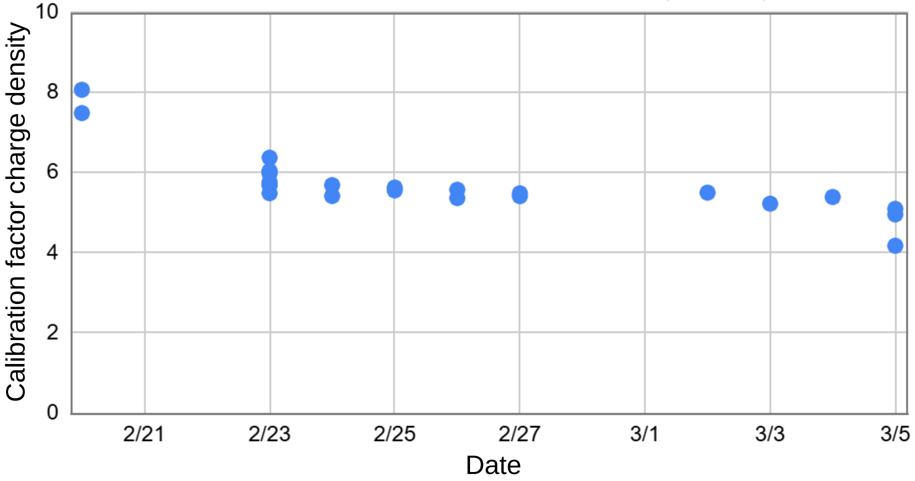




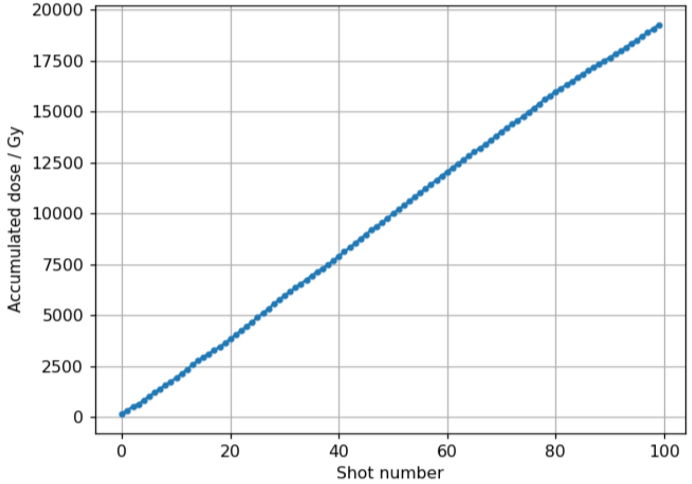
ICT charge measurement



Lanex calibration stable from day to day

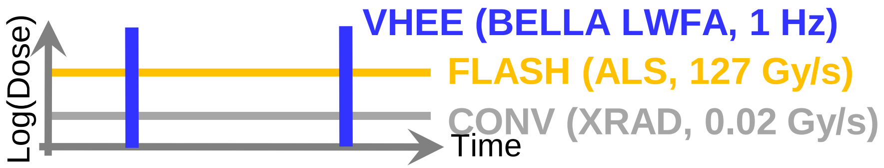


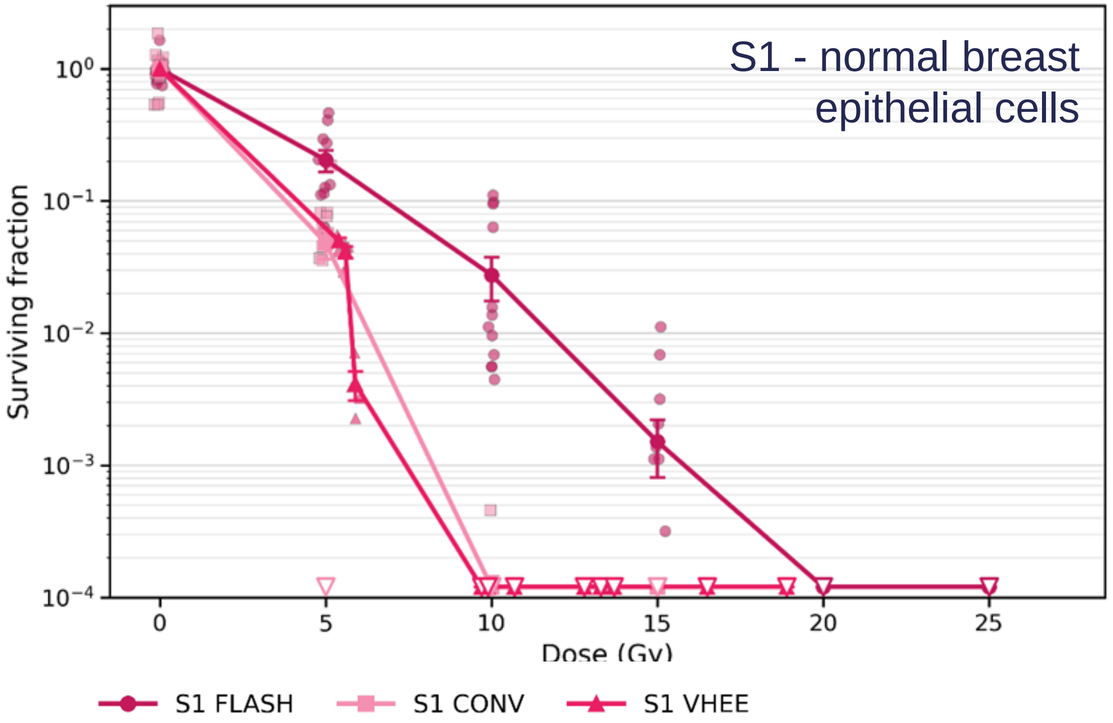
Dose accumulation at 1 Hz

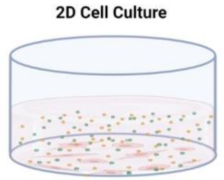


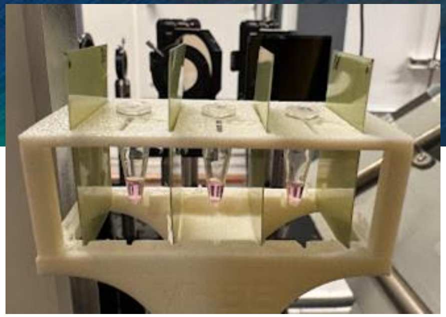
Geulig et al., Rev. Sci. Instrum., 93 (2022); Nakamura et al., PPCF 58 (2016)

BELLA VHEE preliminary cell survival results show cell killing consistent with conventional dose rate x-rays









Cell Samples

Low survival of normal cells following LPA VHEE indicate that mean dose rate (0.06 Gy/s) is too low to trigger a FLASH effect (even though instantaneous dose rate is ~10^{12} Gy/s), consistent with previous radbio literature using 1 Hz LPAs.

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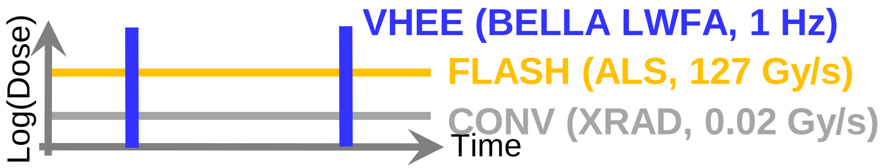

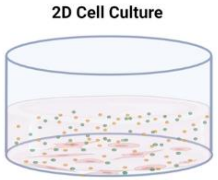

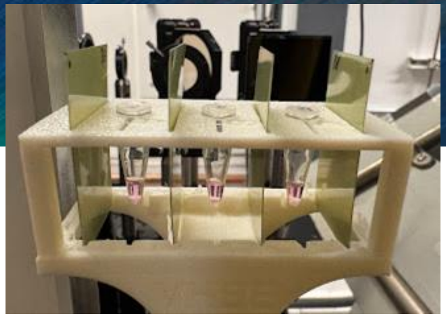

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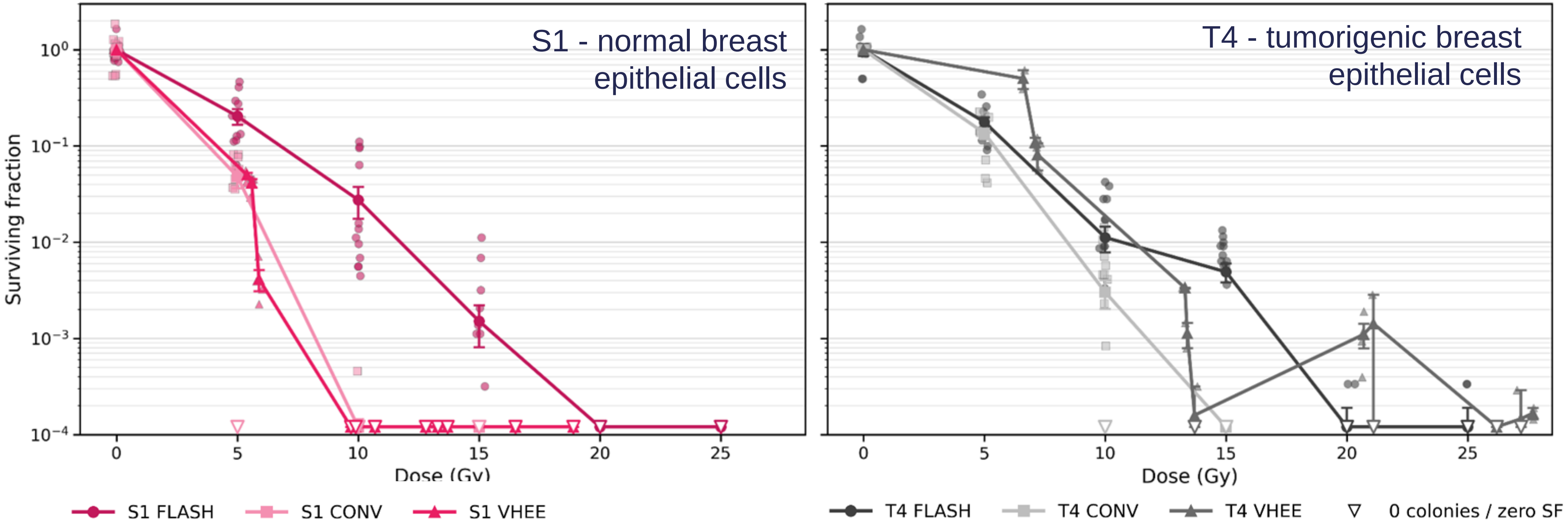

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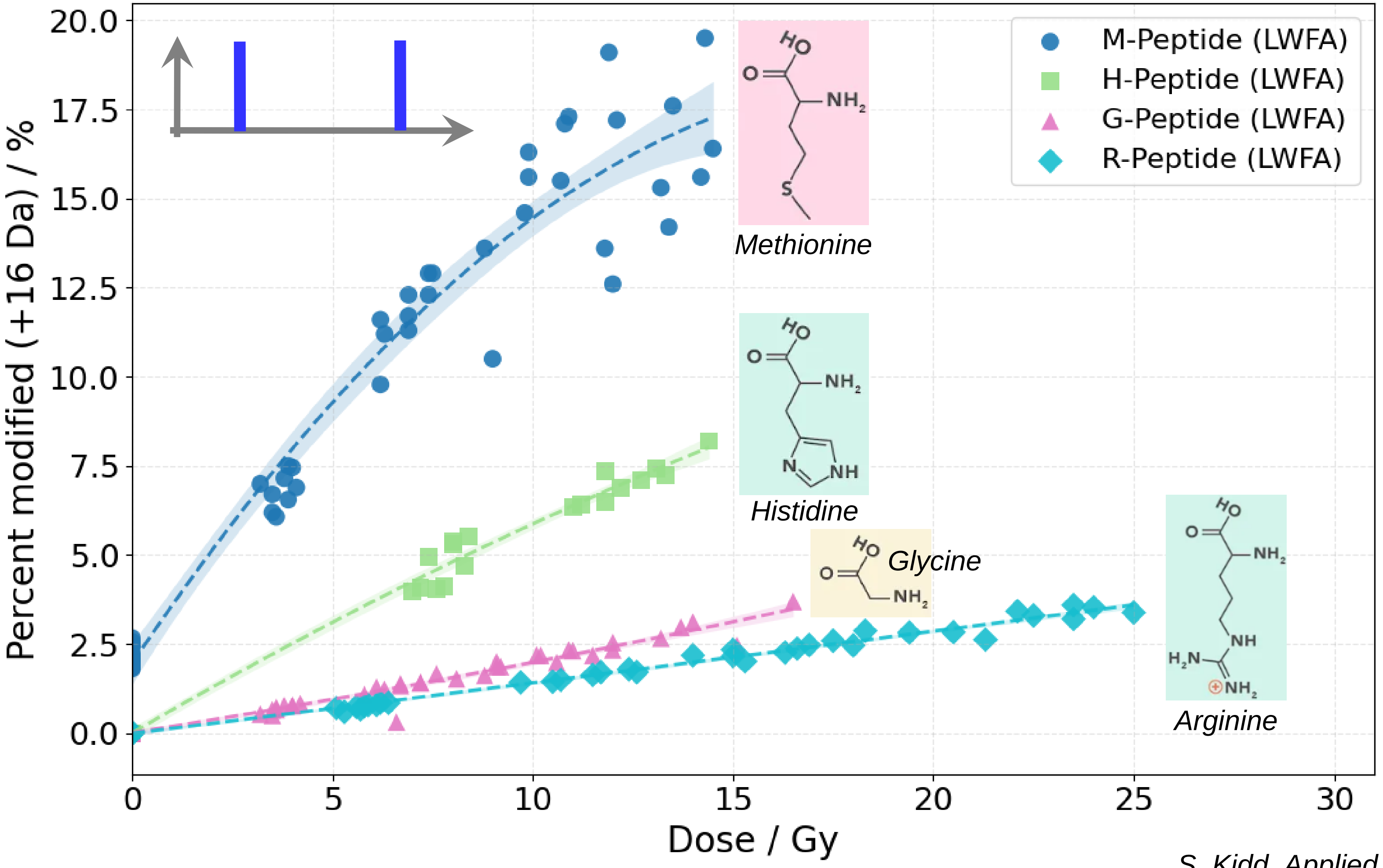
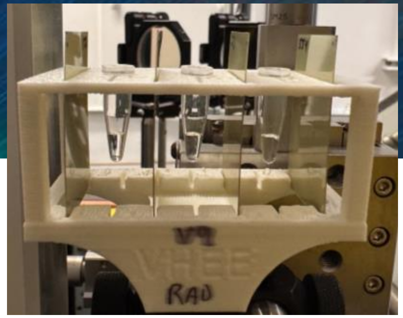
Peptides with Methionine (M) and Histidine (H) are more sensitive to hydroxylation (+16 Da) than those with Glycine (G) and Arginine (R)





Peptide Samples

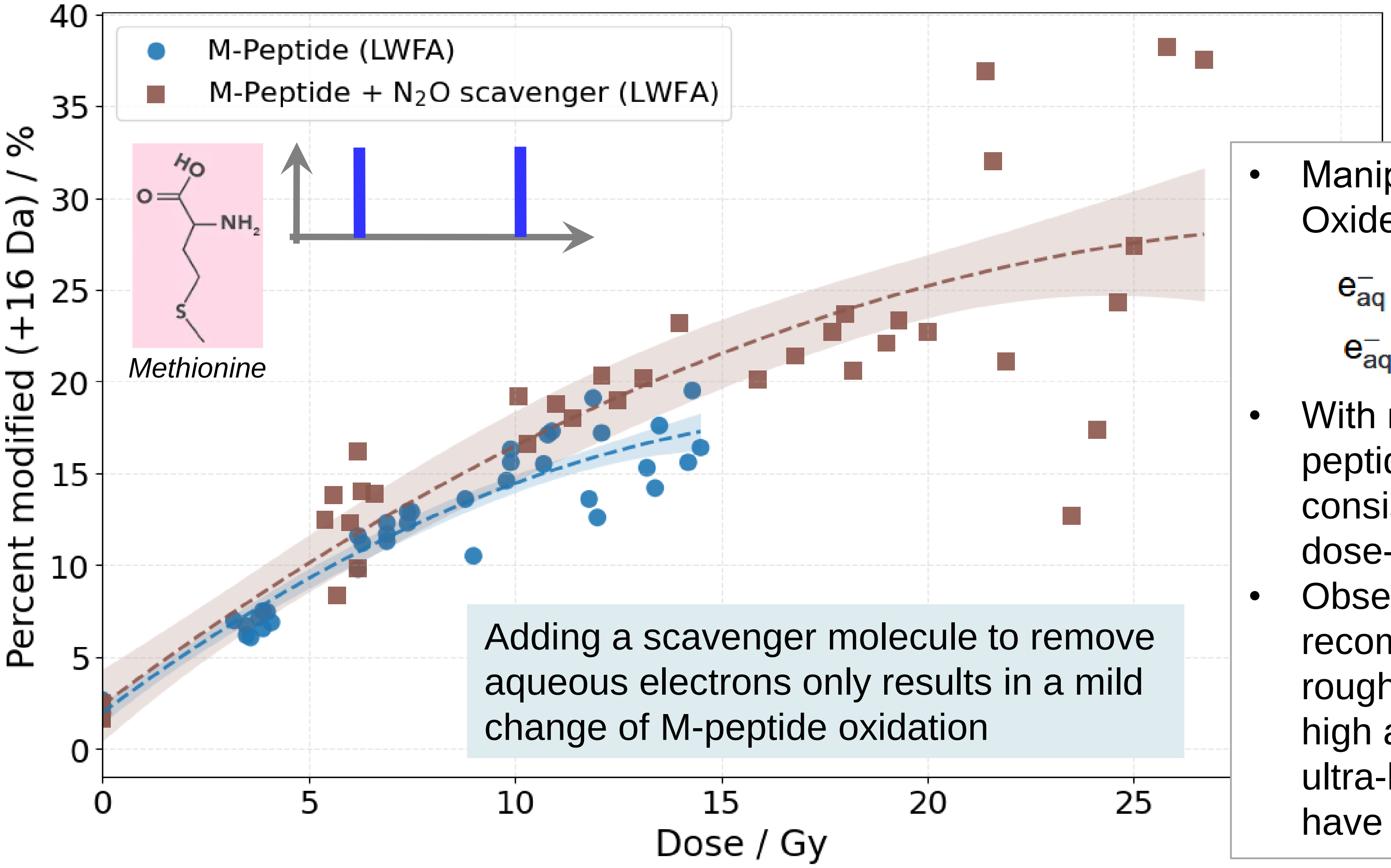
- Met side chain is thioether (S in non-oxidized state), oxidation of thioether to sulfoxide is kinetically favorable

$$\text{Met} \xrightarrow{\text{oxidation}} \text{Met–S(O)} \quad (+16)$$

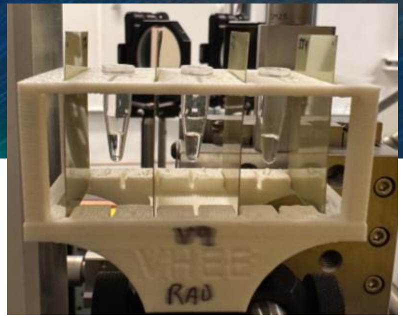
- Other peptides: less favorable reaction channels, might result in other oxidation products → lower abundance of +16 addition
- Limitation: peptide local environment influences individual amino acid reaction rates

S. Kidd, Applied Science 16 (2026); Xu and Chance, Chem. Rev. 107 (2007)

Ultrafast chemistry can be explored by manipulating the radical content in M-peptide exposures



Adding a scavenger molecule to remove aqueous electrons only results in a mild change of M-peptide oxidation



Peptide Samples

- Manipulating •OH population by adding Nitrous Oxide (N_2O) scavenger of e^-_{aq}:

  $$e^-_{aq} + N_2O \rightarrow N_2 + O\cdot^-$$

  $$e^-_{aq} + \cdot OH \rightarrow OH^-$$ *"Radical-radical recombination"*

- With more •OH available as a result, a higher peptide oxidation could be expected (and would be consistent with preliminary observations at high-dose-rate X-rays)
- Observed increase is low: e^-_{aq} scavenging, RR recombination, peptide oxidation all happen at roughly the same timescale, especially if there is a high abundance of e^-_{aq} and •OH (consistent with ultra-high instantaneous dose rate) → N_2O doesn't have big effect

Zhang et al., Medical Physics 51 (2024); Marciniak et al., Molecules 27 (2022)

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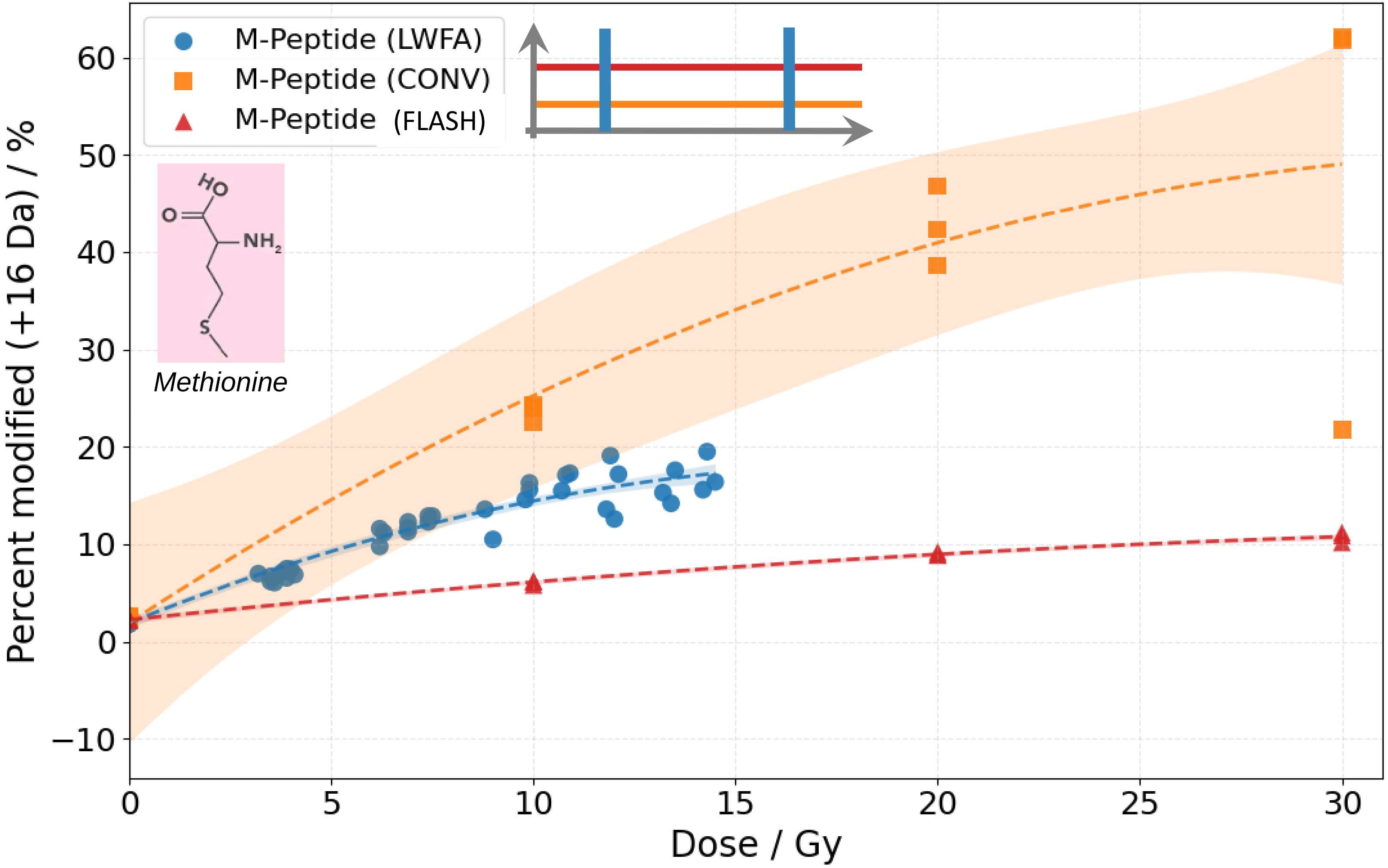
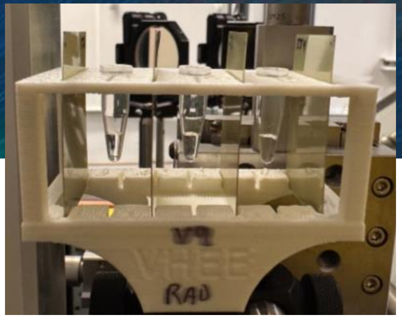
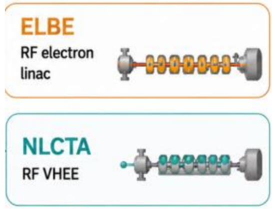
M-peptide oxidation is sensitive to different dose rates





Peptide Samples

- Dose rate dependence observed: oxidation from ultra-short LWFA bunches different from both conventional and high dose rate (quasi-continuous) X-ray exposures
- Experiments performed at ELBE (HZDR) and NLCTA (SLAC) to explore the interplay between instantaneous and mean dose rate for VHEE



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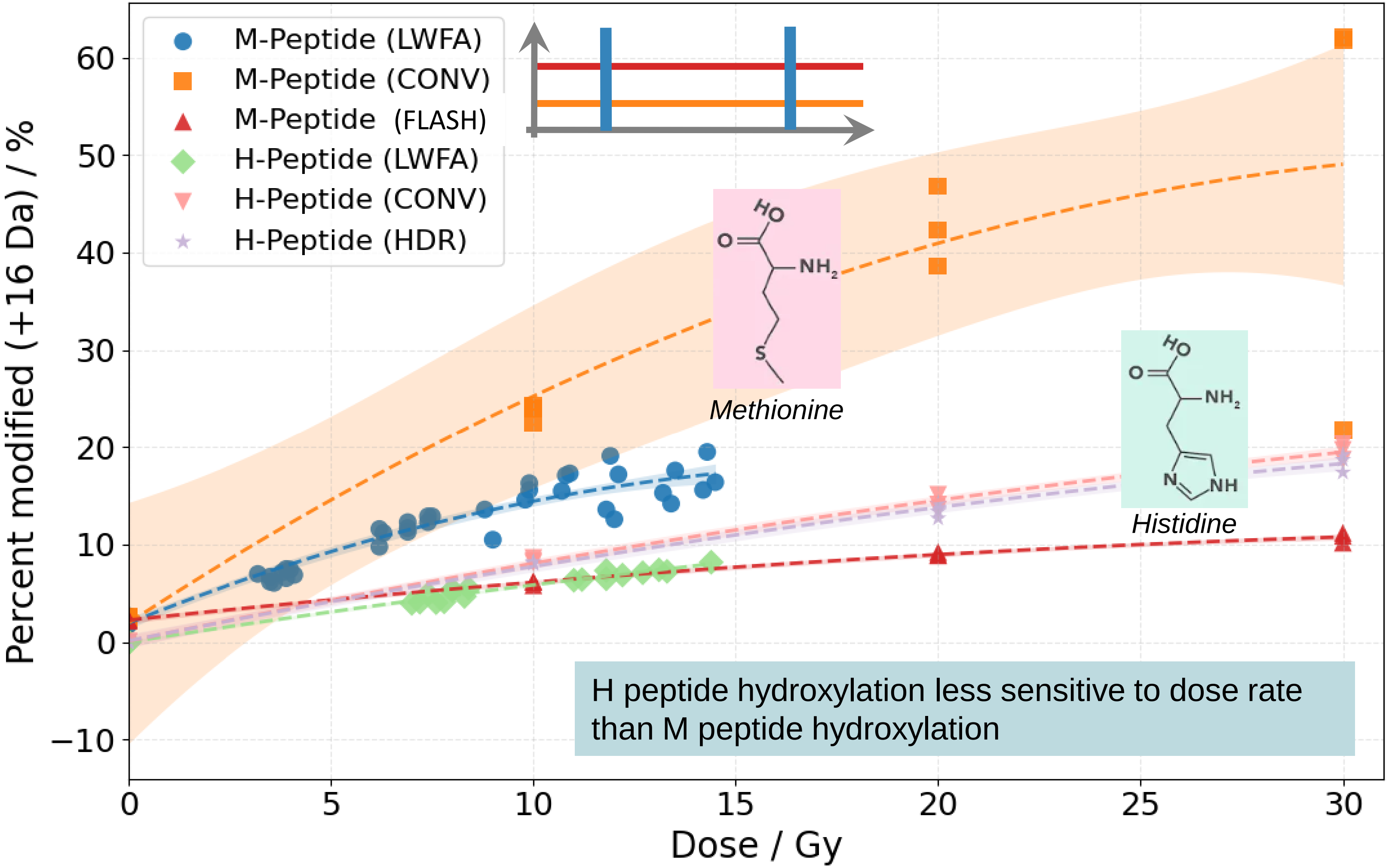
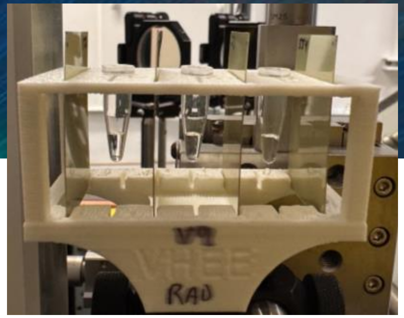
S. Gupta et al., Radiation Research 200(6), 523-530 (2023);S. Kidd et al., Applied Science 16 (2026);

M-peptide oxidation is sensitive to different dose rates





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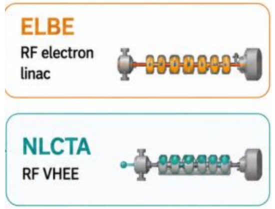

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S. Gupta et al., Radiation Research 200(6), 523-530 (2023);S. Kidd et al., Applied Science 16 (2026);

Summary and next steps

- LPA VHEE beamline for radiobiology experiments established at BELLA HTT
- Low clonogenic survival observed in cell samples consistent with low mean dose rate exposures
- Explore ultra-fast radiochemistry using peptide oxidation assays to probe specific aspects of radiation damage like radical-radical recombination

Next steps

- Explore role of instantaneous dose rate versus mean dose rate (ELBE, DRACO, NLCTA)
- Focus e-beam to increase average dose rate and improve dose precision
- Develop ultrafast optical probe for radical absorption spectroscopy

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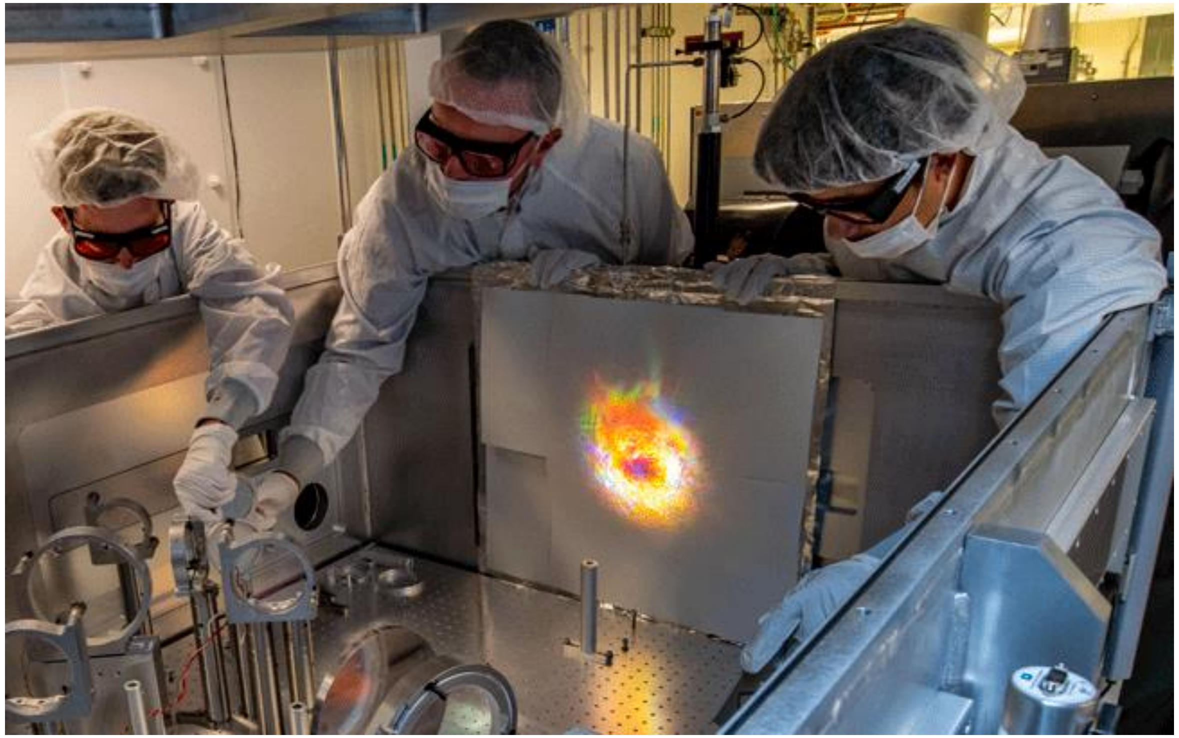
User access to BELLA VHEE beamline



BELLA HTT is accessible for user experiments through LaserNetUS (lasernetus.org) and BeamNetUS (beamnetus.org).

The BeamNetUS call for proposals is currently open until September 4th!

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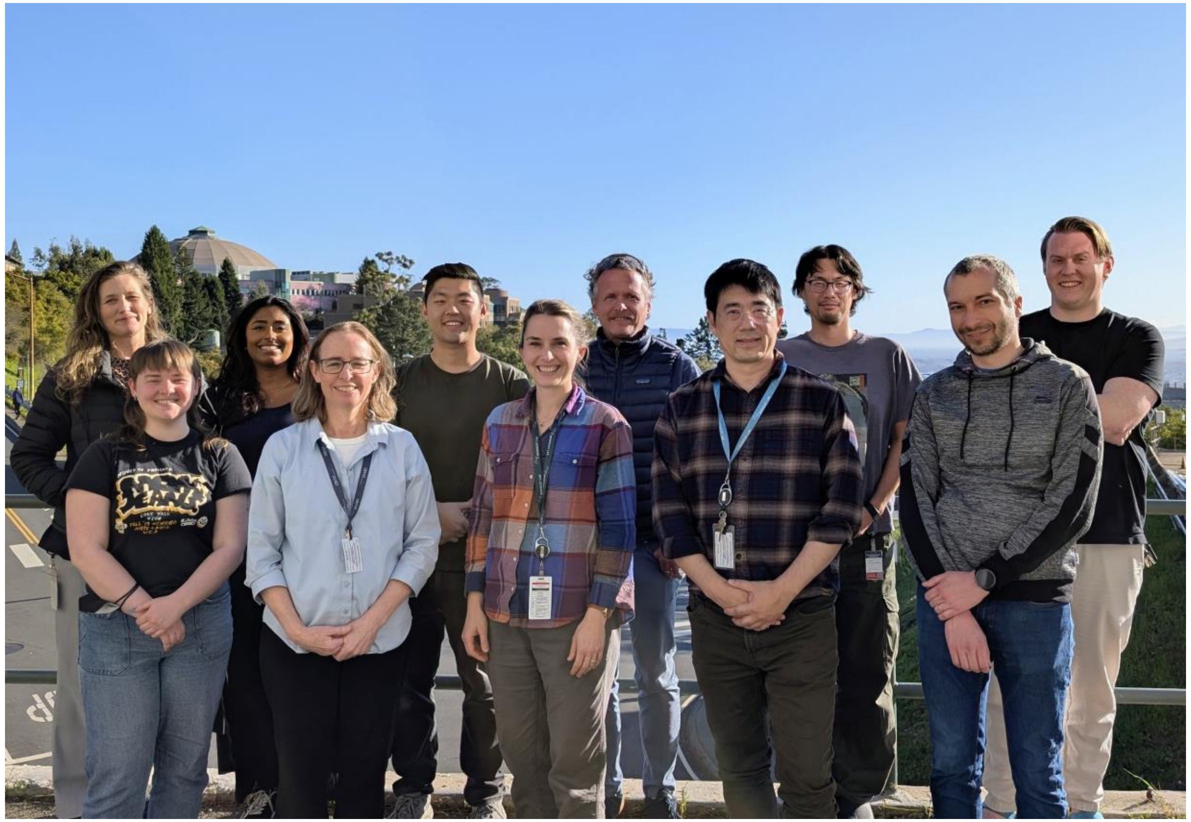
Thank You!



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