Dosimetry challenges in the clinical translation of FLASH radiation

John Wong, PhD
Radiation Oncology and Molecular Radiation Sciences
Johns Hopkins University

JOHNS HOPKINS MEDICINE
RADIATION ONCOLOGY & MOLECULAR RADIATION SCIENCES

Acknowledgment

- Physics: Mohammad Rezaee, Devin Miles, Daniel Sforza; Lingshu Yin
- Biology: Fred Bunz

Disclosure

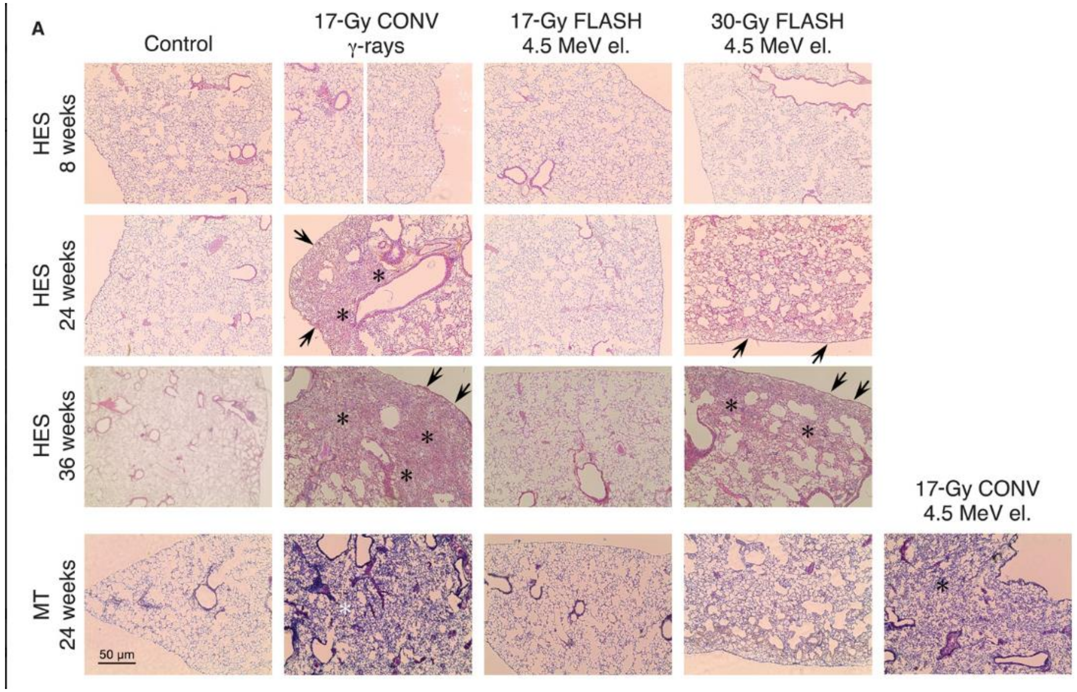
- FLASH kV x-ray system is funded by NIH/NCI Academic-Industrial Partnership (AIP) Grants, R01 CA262097
- The technology (x-ray FLASH irradiator) is patented and licensed to Xstrahl Inc.

Published Studies with Electron FLASH Radiation

Professor Marie-Catherine Vozenin
University Hospital of Lausanne

Professor Vincent Favaudon
Institut Curie, INSERM

Normal mouse lung



Favaudon *et al.*, *Science Transl. Med.*. 2014

Feline nasal SCC tumor

Vozenin *et al.*,
Clin. Cancer Res. 2018

Human Lymphoma Patient

Bourhis et al.,
Radioth & Oncol. 2019

FLASH Irradiators: Proton & Electron Beams

JOHNS HOPKINS MEDICINE
RADIATION ONCOLOGY & MOLECULAR RADIATION SCIENCES

Cyclotron, 230 MeV, 40-100 Gy/s

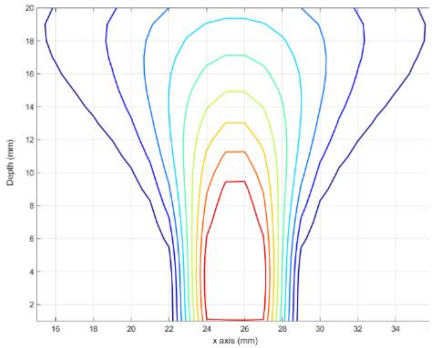
Oriatron Linac, 5.6MeV, <300Gy/s

Laser plasma accelerator,
<25 MeV, 10^9 Gy/s in pulse

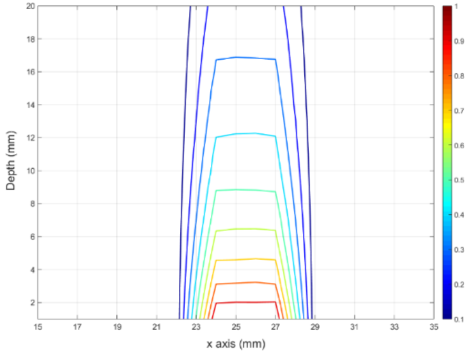
Clinical Linacs, 9 MeV, 74 Gy/s

- Most irradiators used for FLASH studies are complex machines,
- The irradiators have limited accessibility for preclinical laboratory research

6 MeV electrons



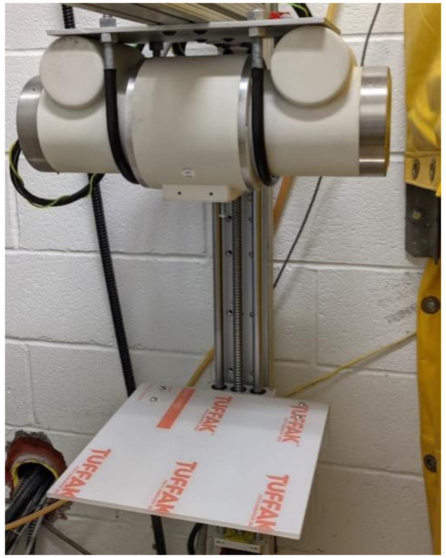
150 kV X-ray

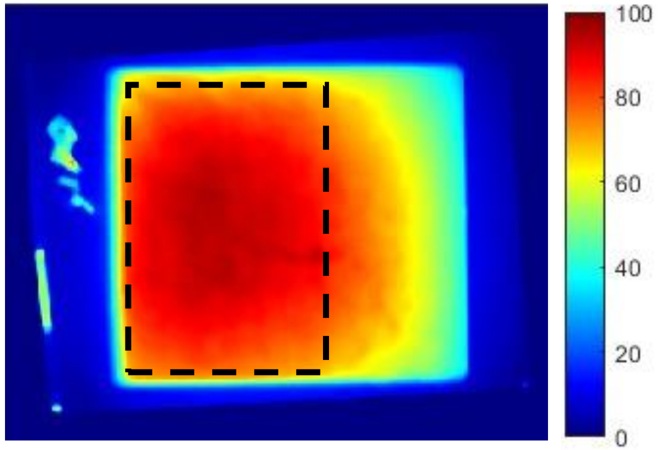


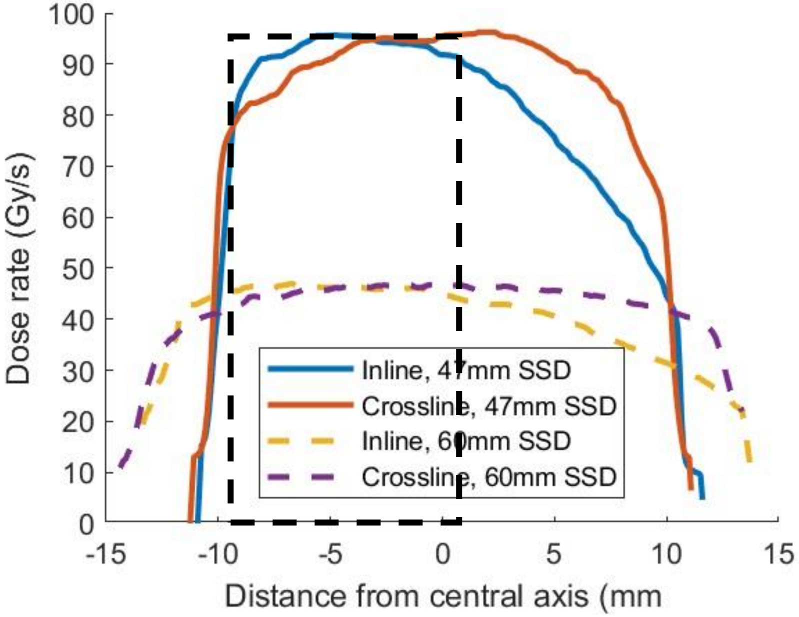
Lateral dose spread

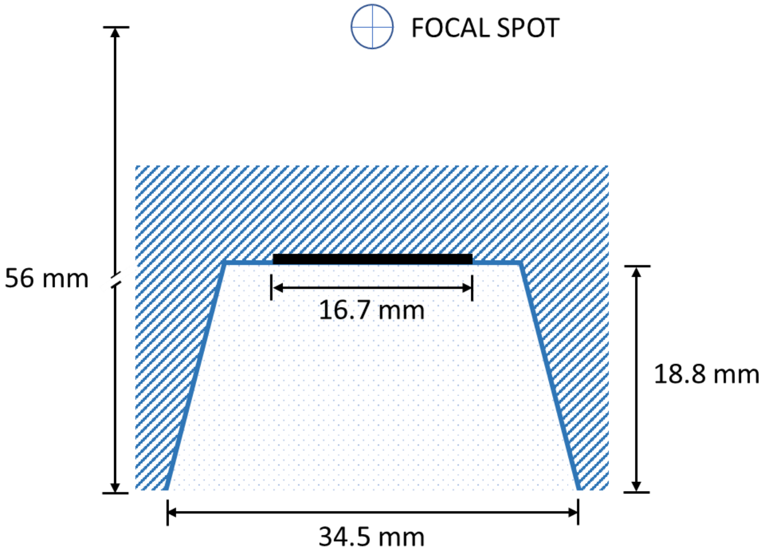
Single FLASH X-Ray Tube

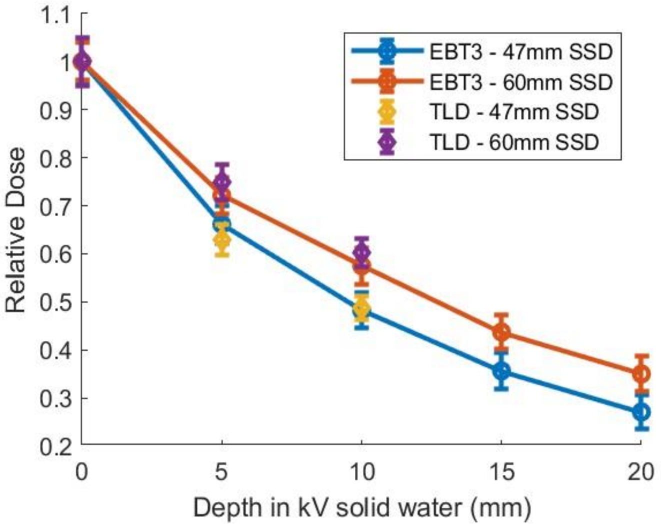
150 kVp X-rays, 75 kW











TLD from UW RCL

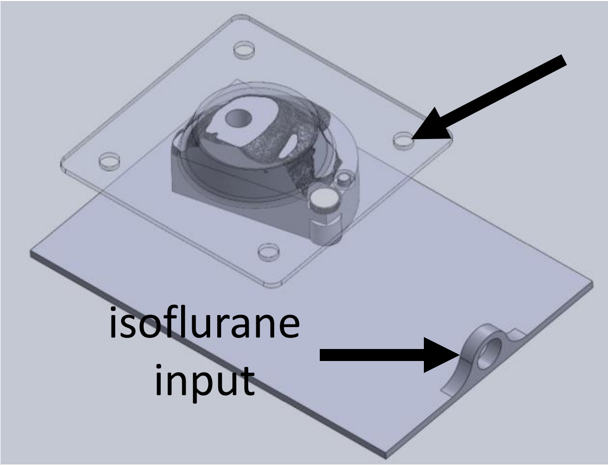
- Max dose rate: 96.5 Gy/s at 47mm SSD from a single pulse of x-rays,
- Dose gradient: 6.8% and 2.9% per mm at 47 and 60 mm SSDs,
- Useful field size: 10mm x 20mm.

X-ray FLASH Effects: I-Skin Murine Model

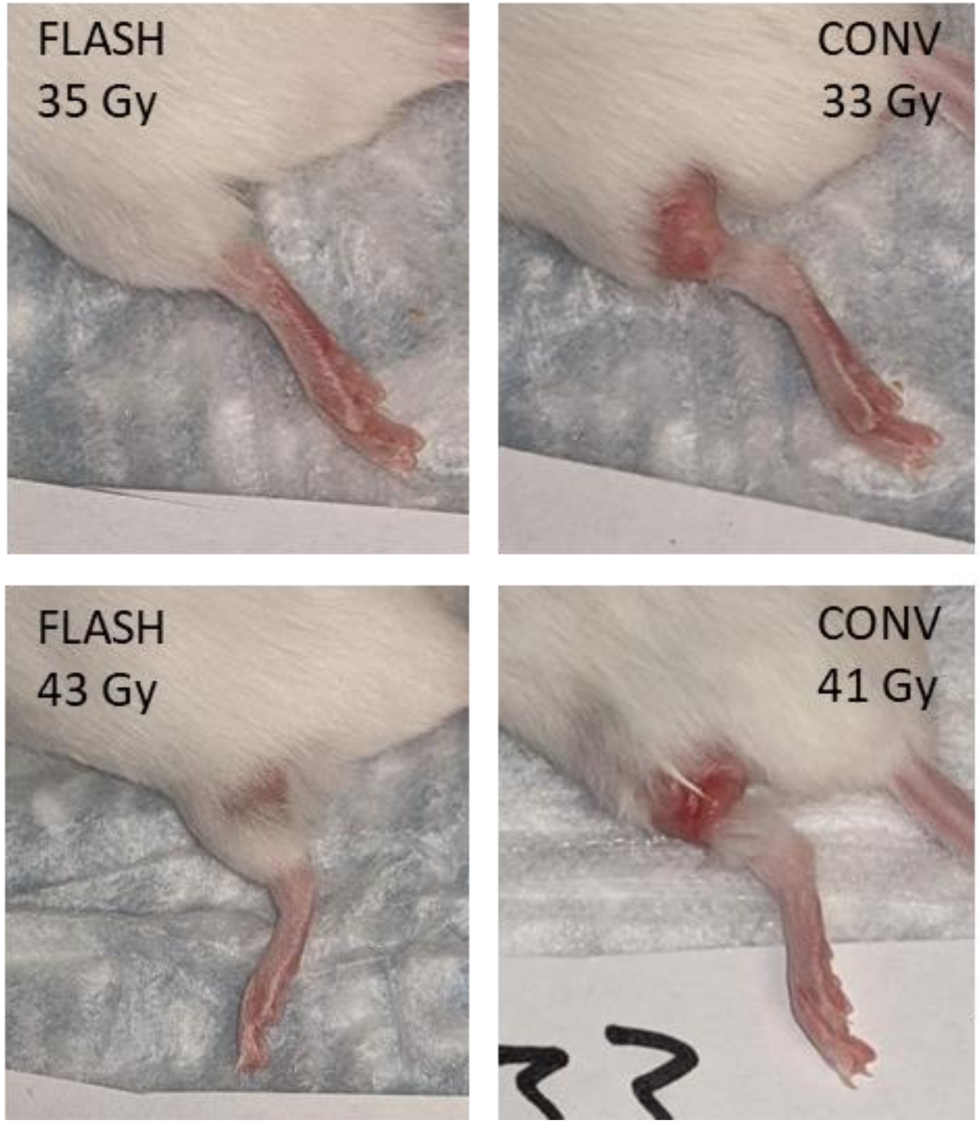
JOHNS HOPKINS MEDICINE
RADIATION ONCOLOGY & MOLECULAR RADIATION SCIENCES

Sparing effects on normal skin:

- Wild type mice - C57BL6J, FVBN;
- Dose rates: 87 Gy/s vs < 0.5 Gy/s
- Dose levels: 33 - 43 Gy
- N=7 animals per experiment arm

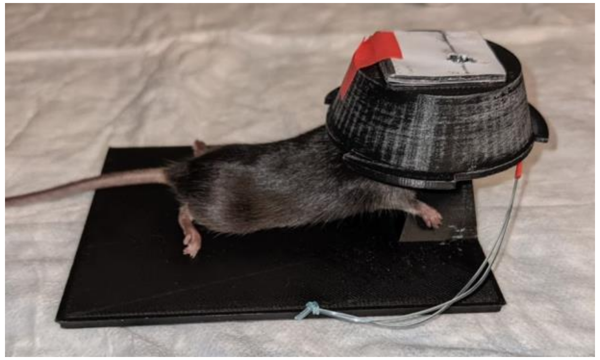


Docking immobilization to tube

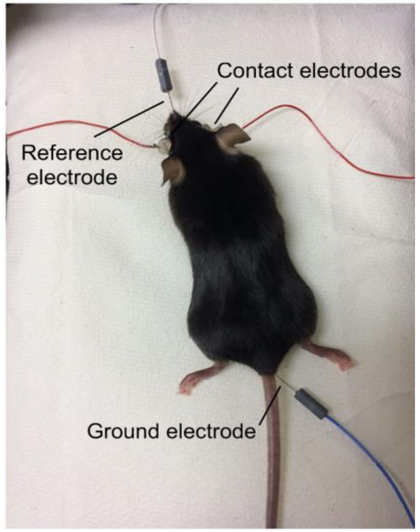


Investigation of Ocular FLASH-RT

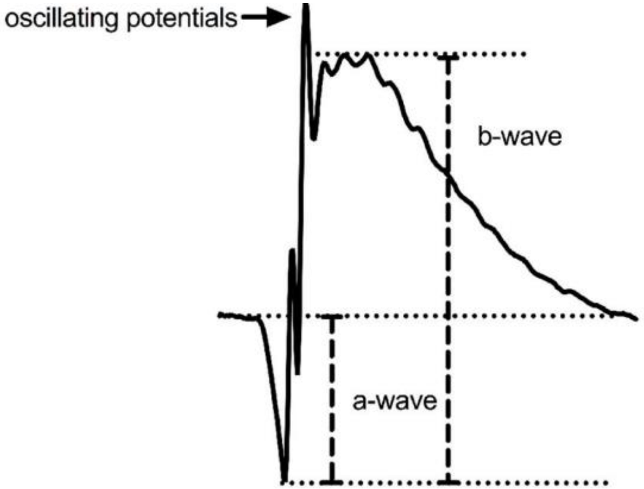
- 8-week C57BL6J mice,
- Dose rates:
  - 53.0±4.5 Gy/s vs. 0.5±0.1 Gy/s
- Dose levels:
  - 21 and 26 Gy to eye center



TLD-100 microcubes



- Assessment vision function before and 2 months after IR using electroretinography (ERG)

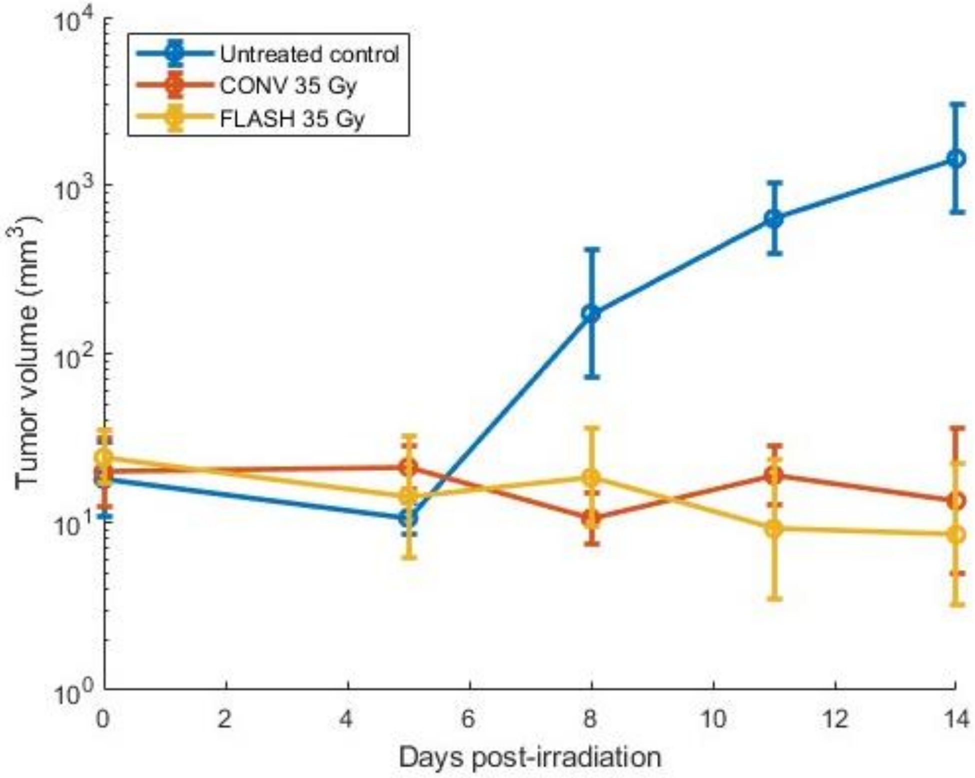


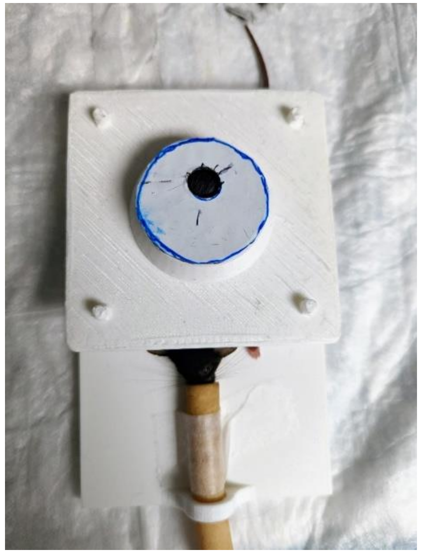
a-wave: measure of the initial response of photoreceptors to a flash of light

b-wave: measure of response from downstream retinal neurons - from bipolar cells to photoreceptor stimulation

X-ray FLASH Effect - Tumor Control

- B16F10 cells - C57BL6J flanks
- Tumors irradiated 1wk after seeding
- Tumor size: 7mm diameter, 5 mice per arm
- Radiation Dose: 35 Gy
- Dose rates: 87 Gy/s vs < 0.5 Gy/s

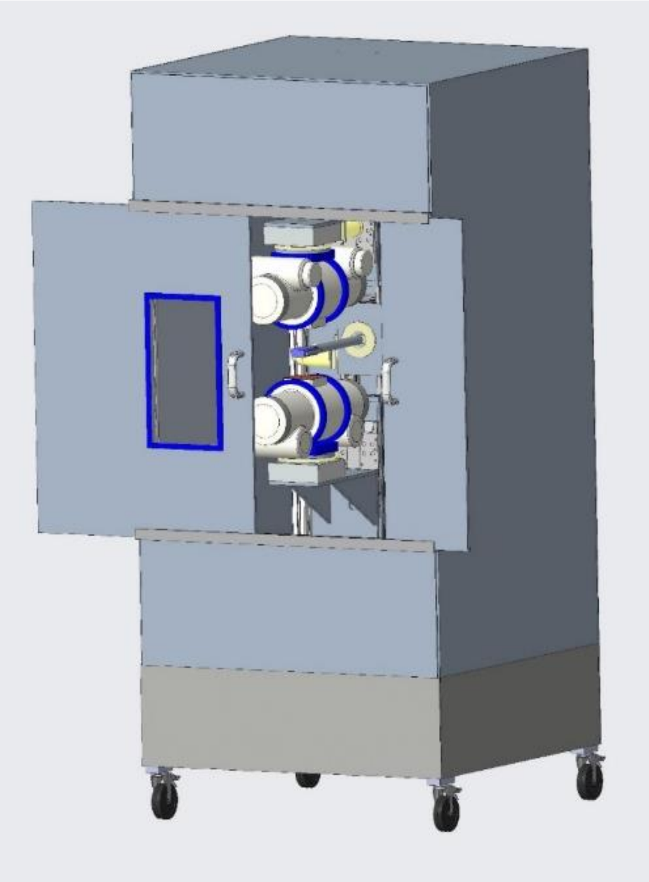




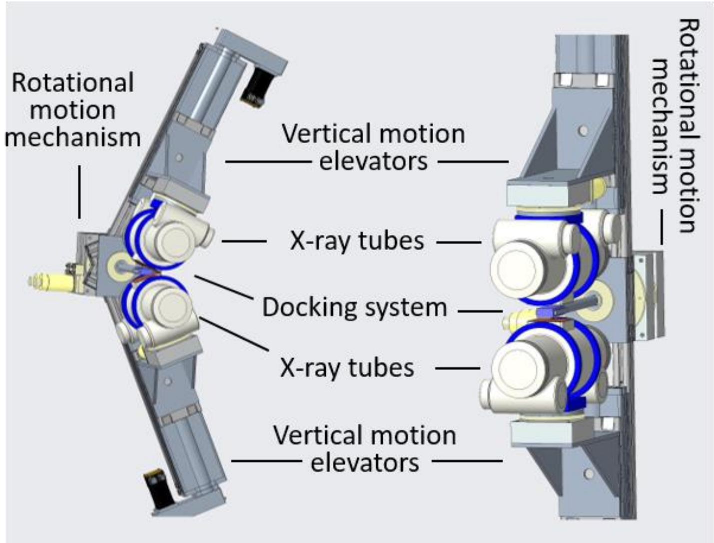
X-Ray FLASH System for Pre-clinical Studies

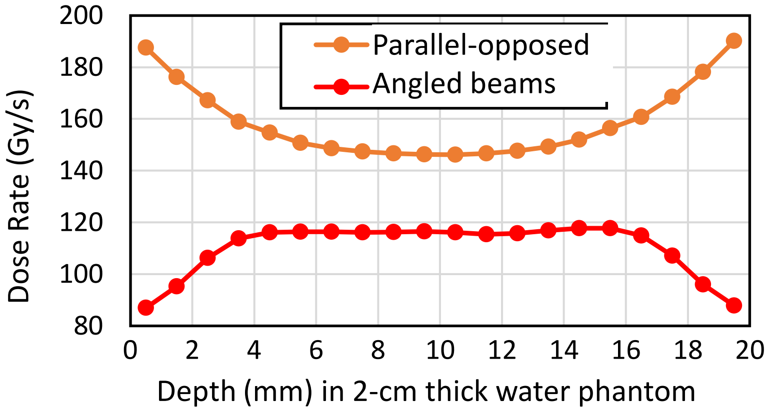
JOHNS HOPKINS MEDICINE
RADIATION ONCOLOGY & MOLECULAR RADIATION SCIENCES

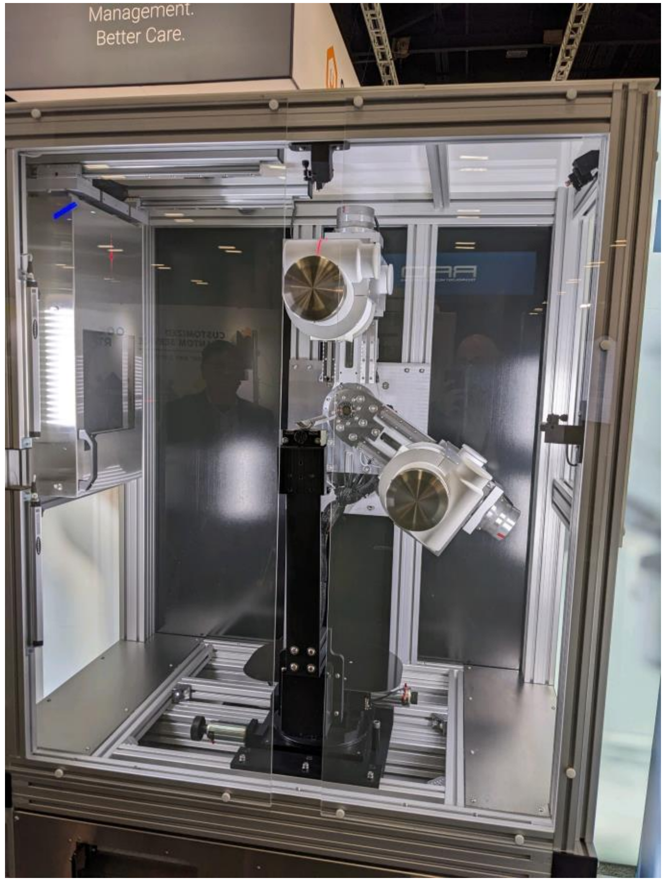
- Opposing-pair rotating anode x-ray tubes provide > 120 Gy/s over 2 cm thick medium.
- Enabling *in vitro* and *in vivo* investigations of fundamental questions in FLASH research



FLASH Cabinet System



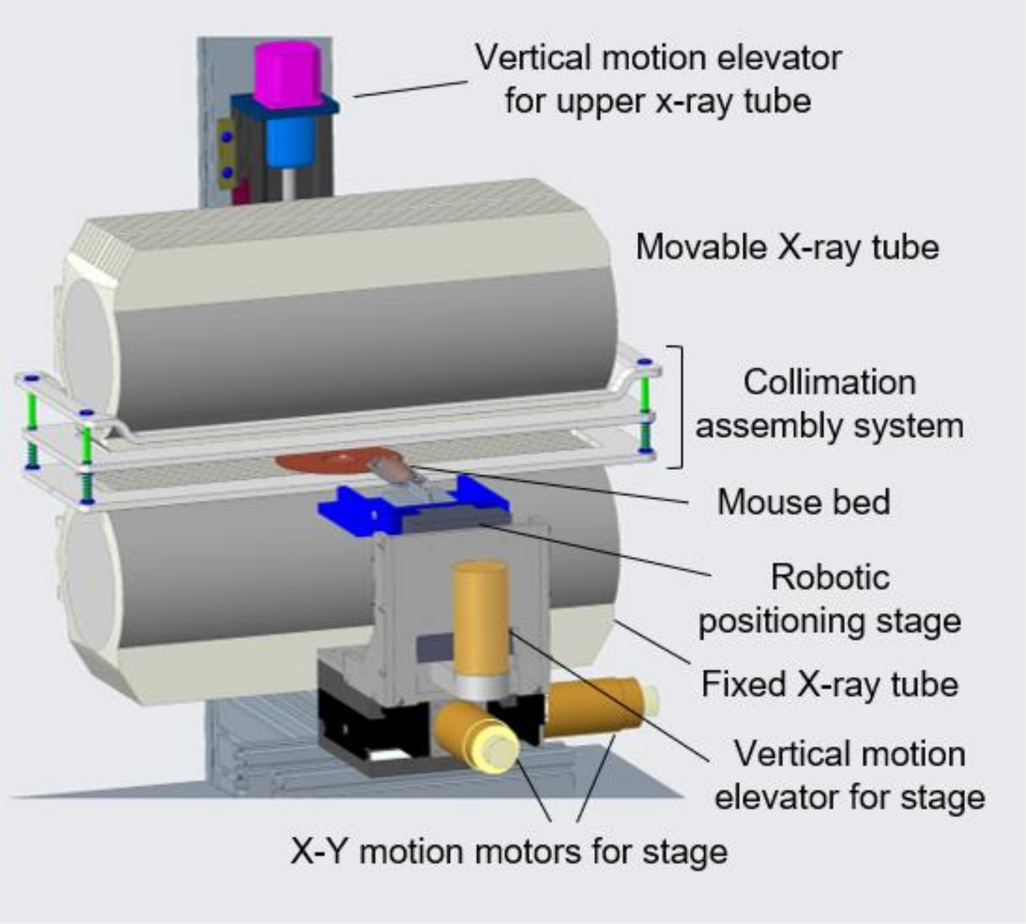




FLASH-SARRP – Rotating Gantry

FLASH Delivery Challenges

- Thresholds/Windows/Uniformity for dose and dose rate to achieve FLASH effects
- Temporal and spatial dependence of FLASH effects --- study with pencil beam scanning

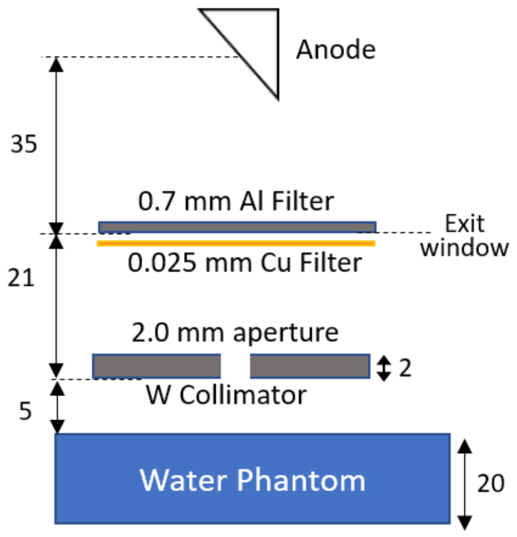


X-ray Pencil Beam: Simulation and Measurement

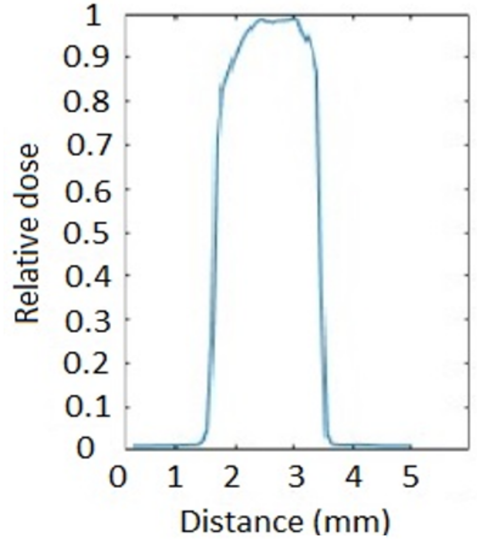
JOHNS HOPKINS MEDICINE
RADIATION ONCOLOGY & MOLECULAR RADIATION SCIENCES

Single x-ray source (75 kW) for pencil beam measurement and simulation at 61 mm SSD.

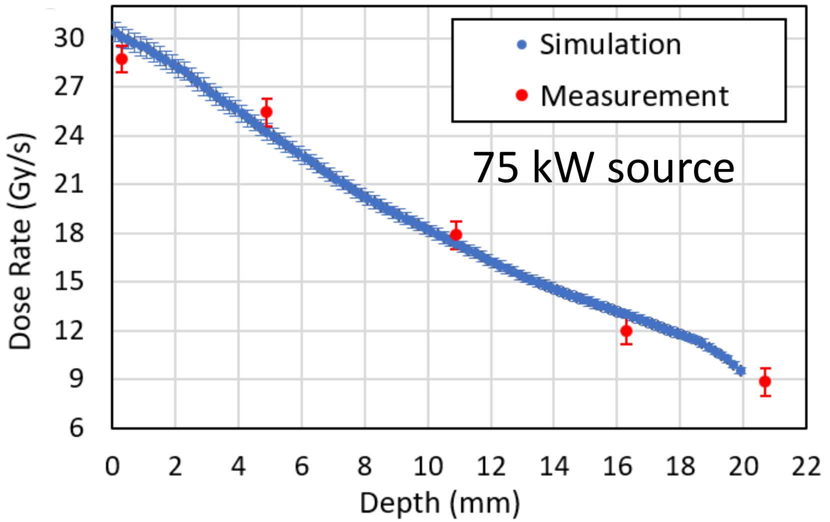
2mm aperture diam.



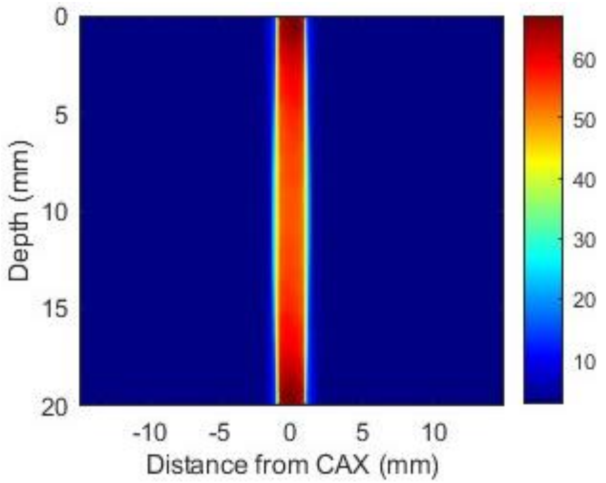
phantom surface profile

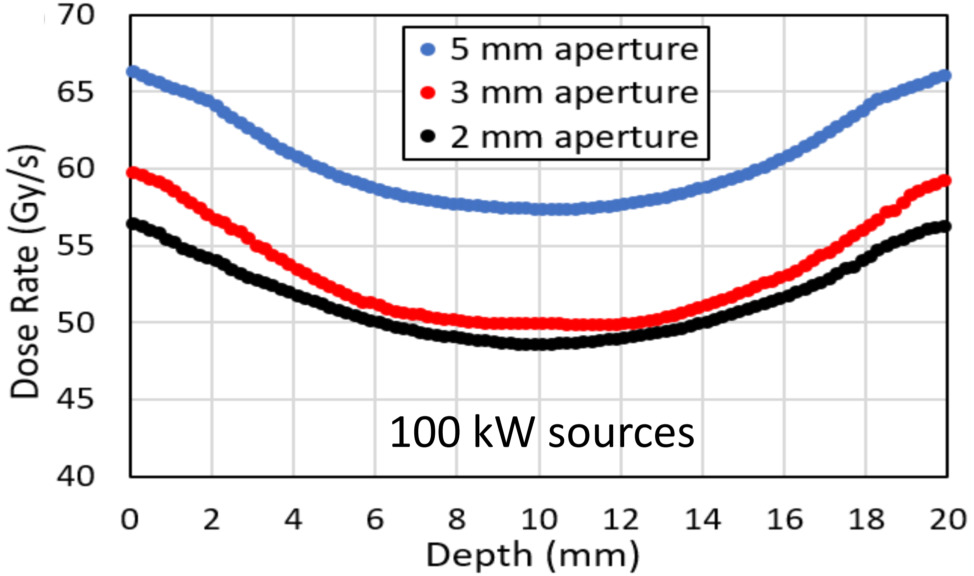


Depth dose-rate curve



- X-ray pencil beam from parallel opposed beams with ideal alignment.
- Higher power sources and generators support higher achievable dose rates





Prescription Challenges

JOHNS HOPKINS MEDICINE
RADIATION ONCOLOGY & MOLECULAR RADIATION SCIENCES

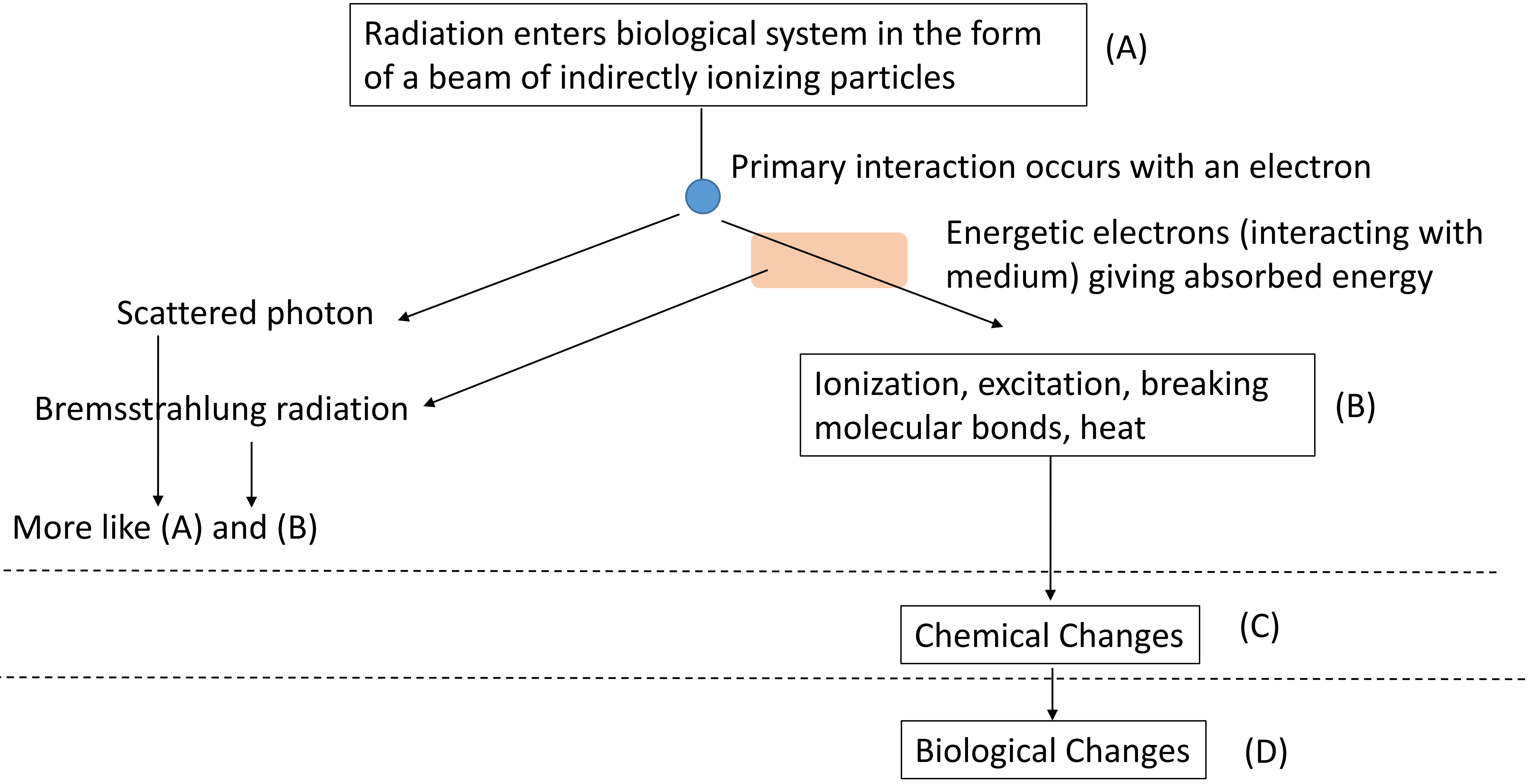
- How to prescribe FLASH irradiation?
- Do we need a Dose Modifying Factor (DMF ~ RBE) for FLASH-RT?

Can ionization energy be the descriptor of FLASH effects?

- Ionization measurement (e.g. using ionization chamber) is developed to measure the output of radiation machines.
- Absorbed dose (Gy) is a conversion of measured ionization energy from gas to water
- Ionization dosimetry is overly simplified to conveying radiation damage potential

Hypothesis: Quantification of molecular damage under well controlled environmental conditions can be a descriptor of FLASH effects

Absorption of Radiation Energy

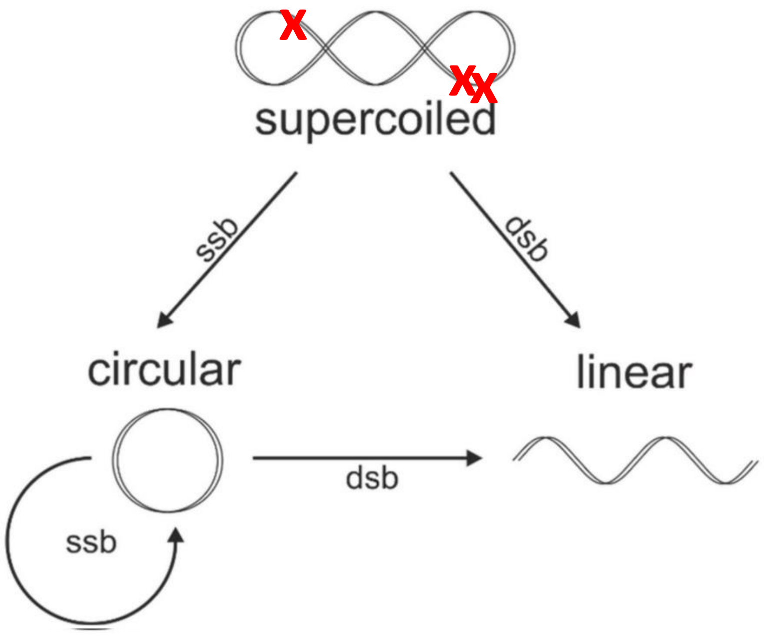


Molecular Damage Induced by FLASH-IR

Plasmid DNA model to quantify:

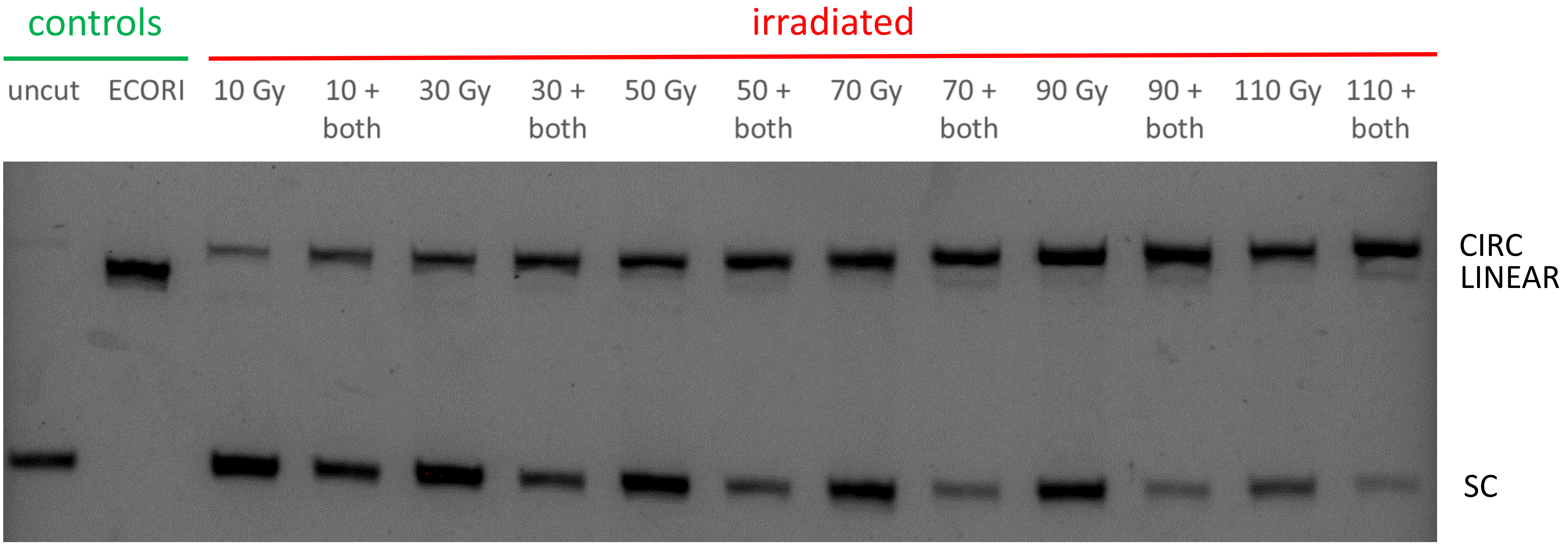
- Direct SSB and DSB

Non-DSB clustered lesions.



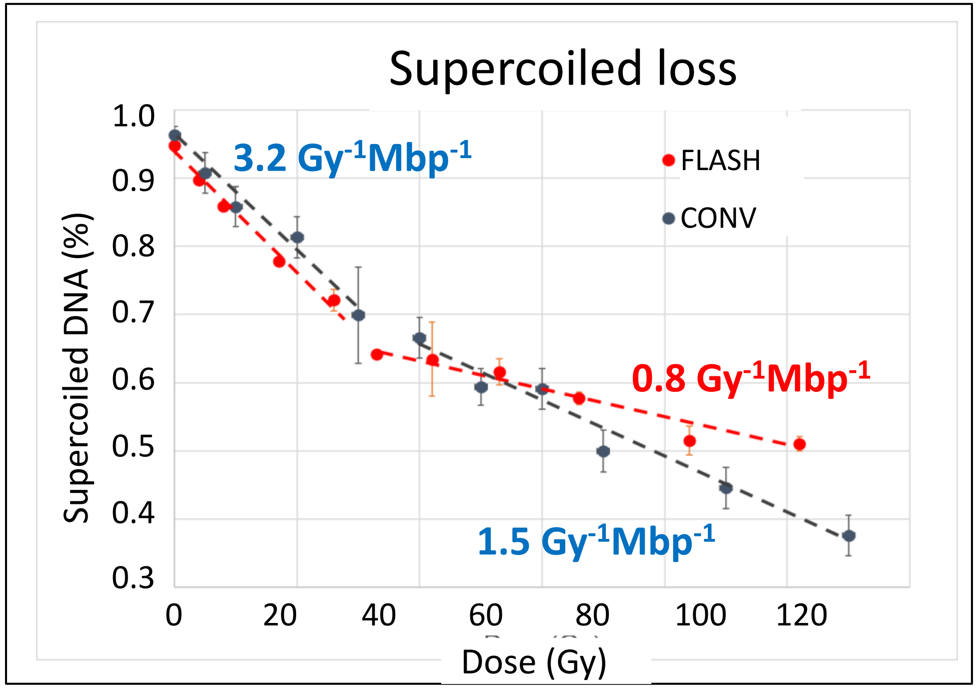
Gel electrophoresis

Example: Conventional, low scavenging, with Fpg and Nth

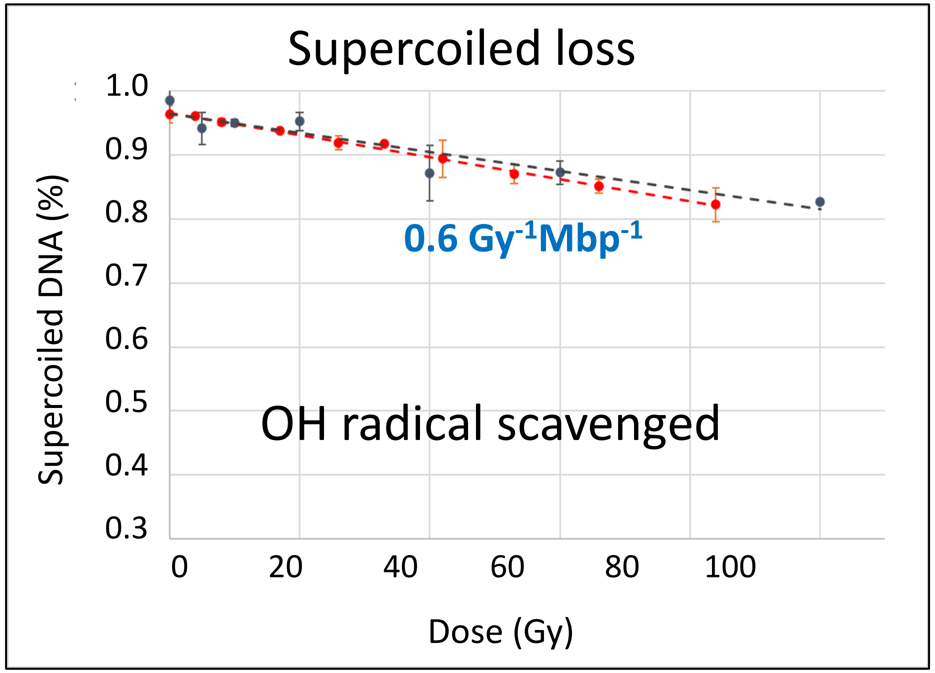


DNA Strand Breaks under FLASH-IR

ddH2O + <u>2.5 mM Tris</u> + 21% O2



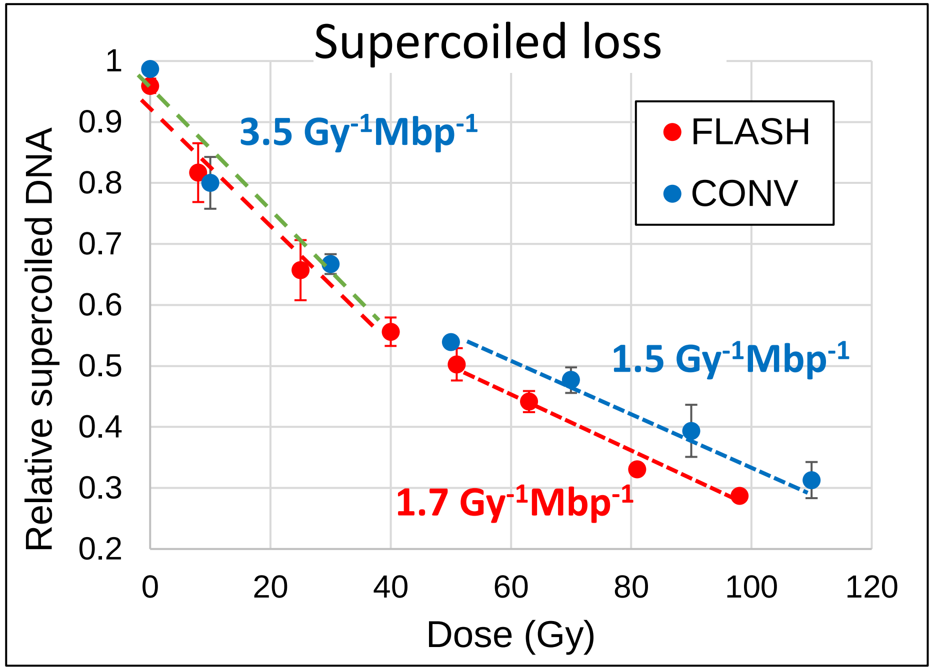
ddH2O + <u>250 mM Tris</u> + 21% O2



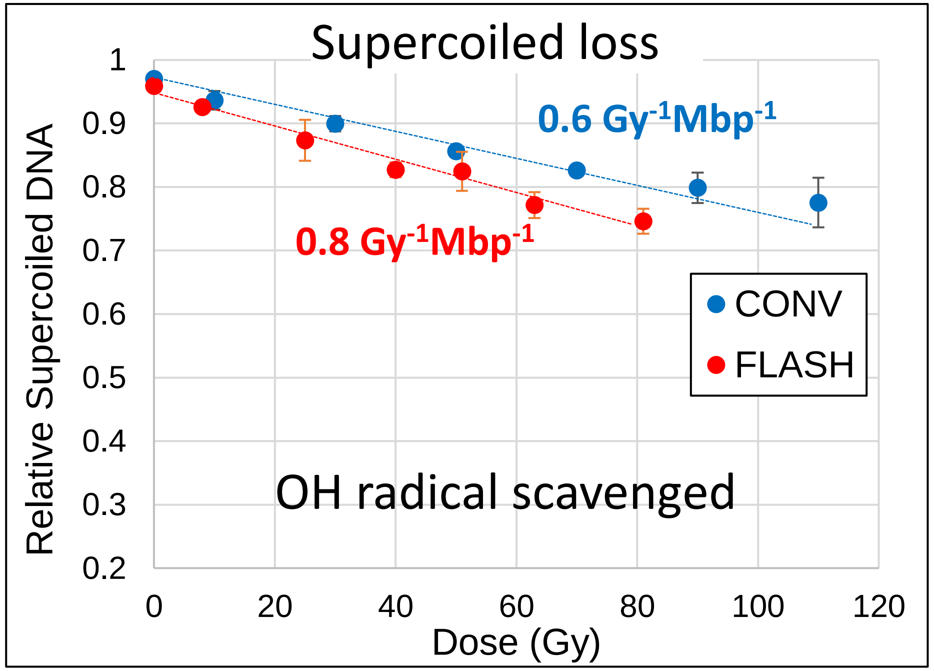
OH radical plays an important role in the supercoiled loss (less) at high doses under FLASH (55 Gy/s) vs conventional dose rate (0.1 Gy/s)

DNA Strand Breaks under FLASH-IR

0% O2 - ddH2O + 2.5 mM Tris



0% O2 + ddH2O + 250 mM Tris



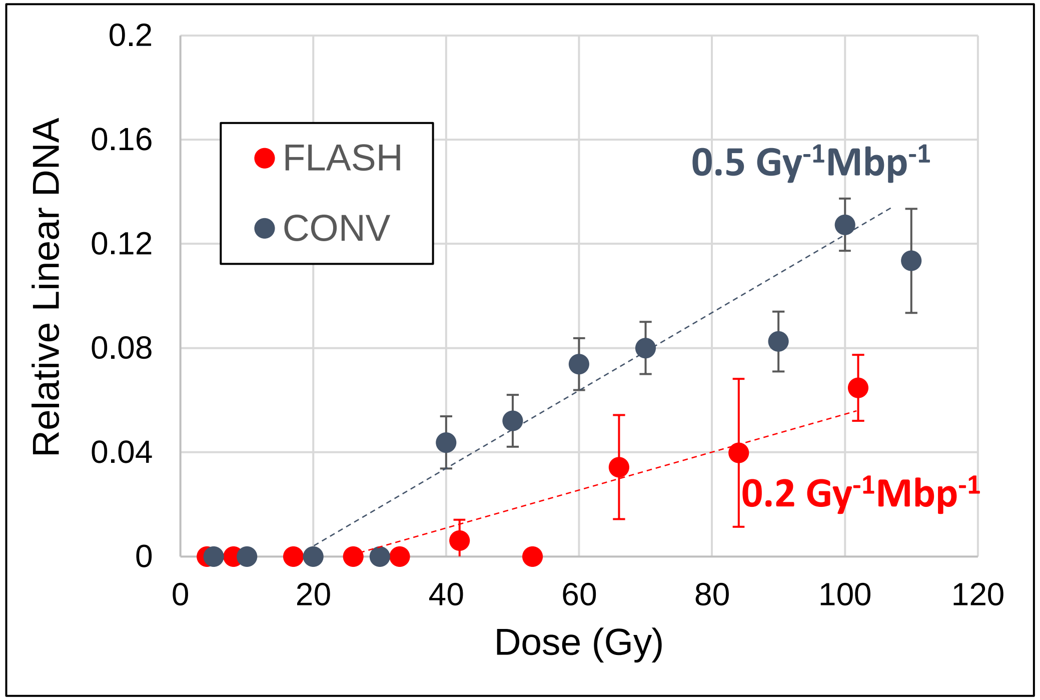
Role of OH radical at conventional and FLASH dose rate diminishes when oxygen is removed in the plasmid DNA damage model

Clustered DNA Damage under FLASH-IR

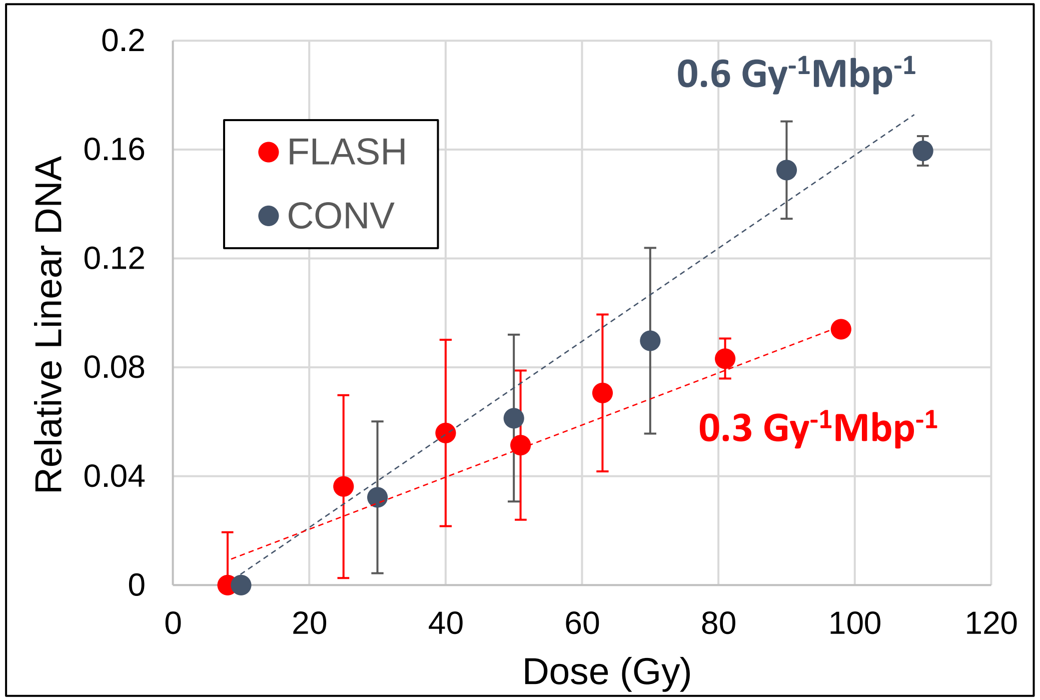
JOHNS HOPKINS
MEDICINE
RADIATION ONCOLOGY & MOLECULAR RADIATION SCIENCES

Non-DSB Clustered Damage: base lesions and SSB

Oxygenated Aqueous Medium

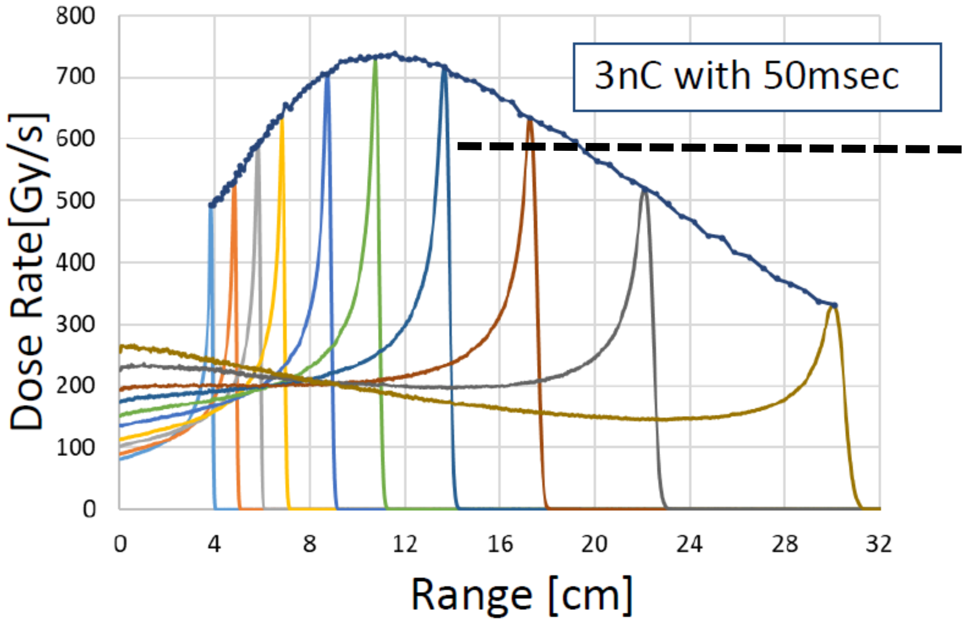


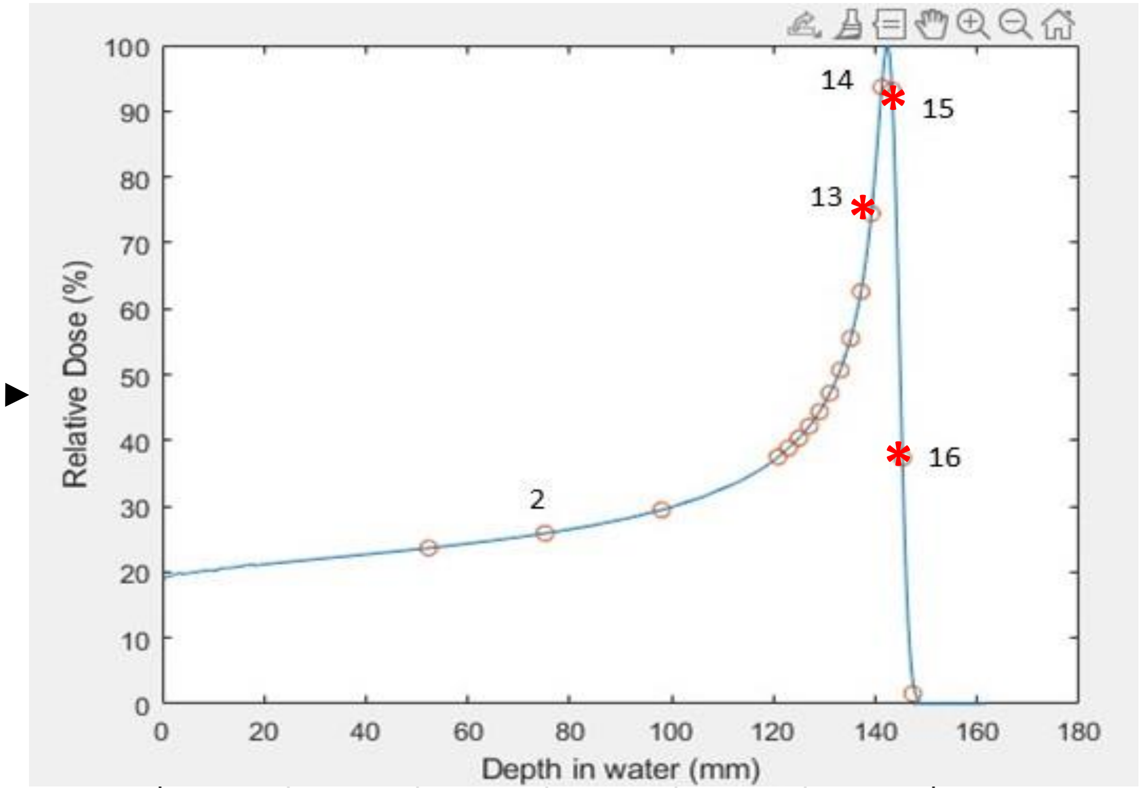
Deoxygenated Aqueous Medium

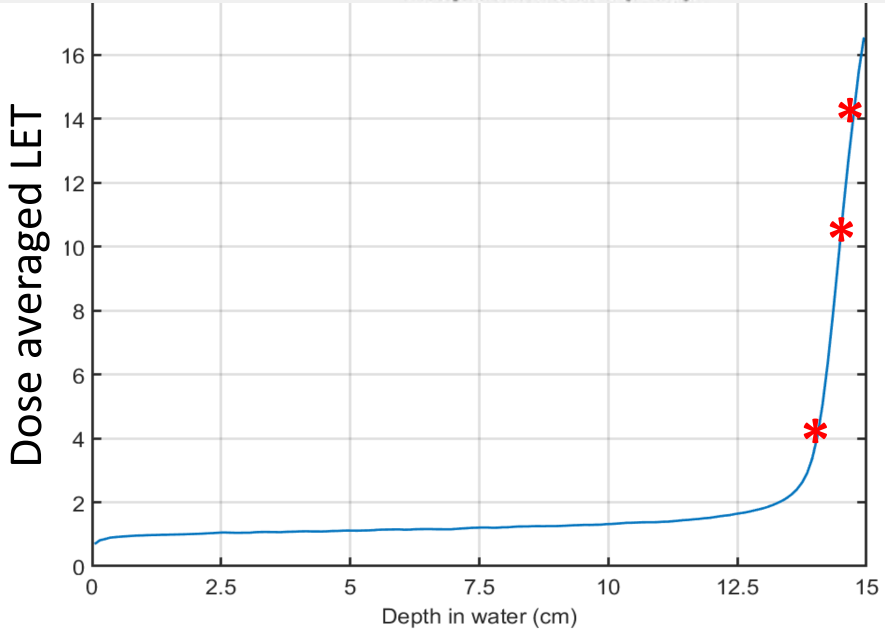


FLASH irradiation induces smaller amount of complex (clustered) damage in plasmid DNA, regardless of oxygen presence.

Molecular Damage – Fluence Rate and LET

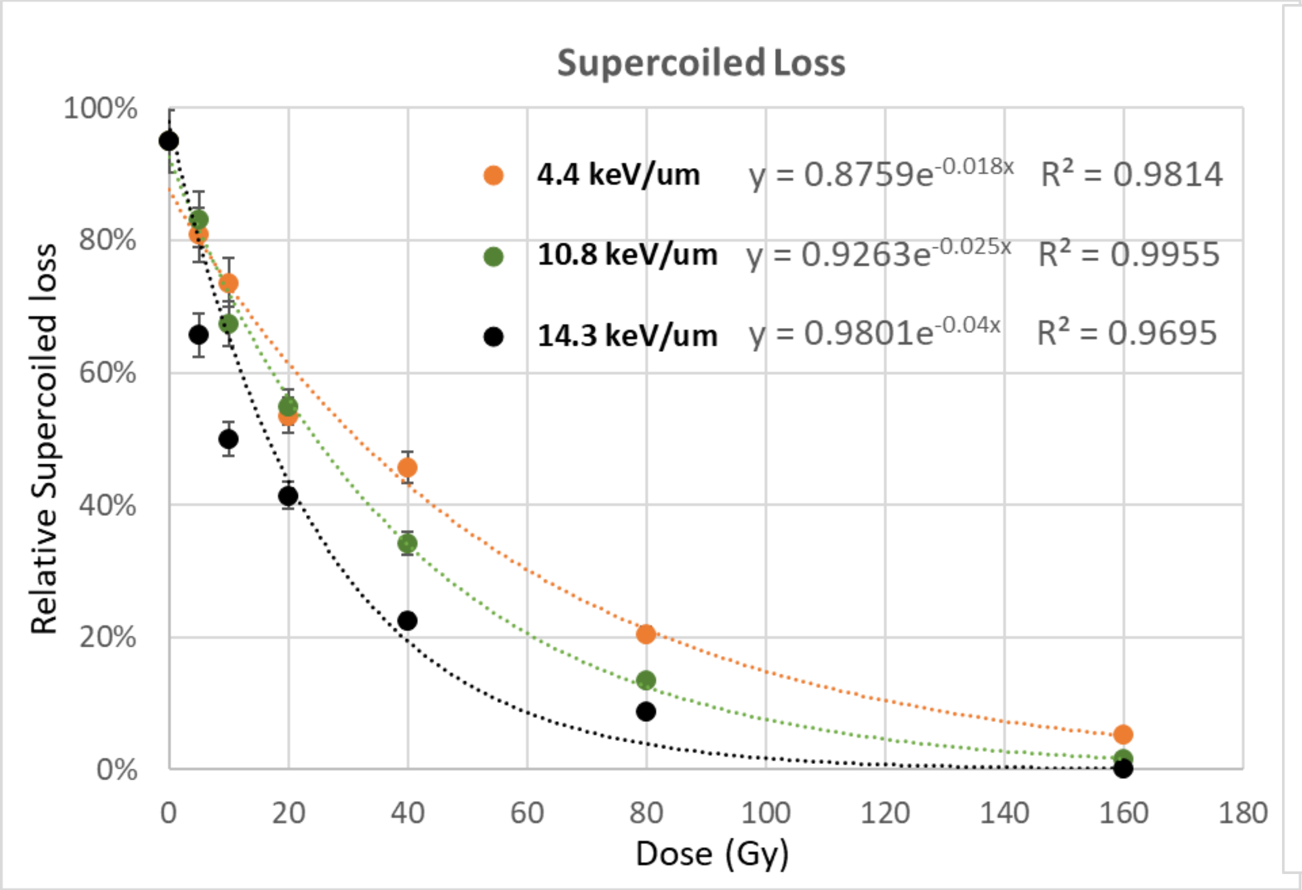


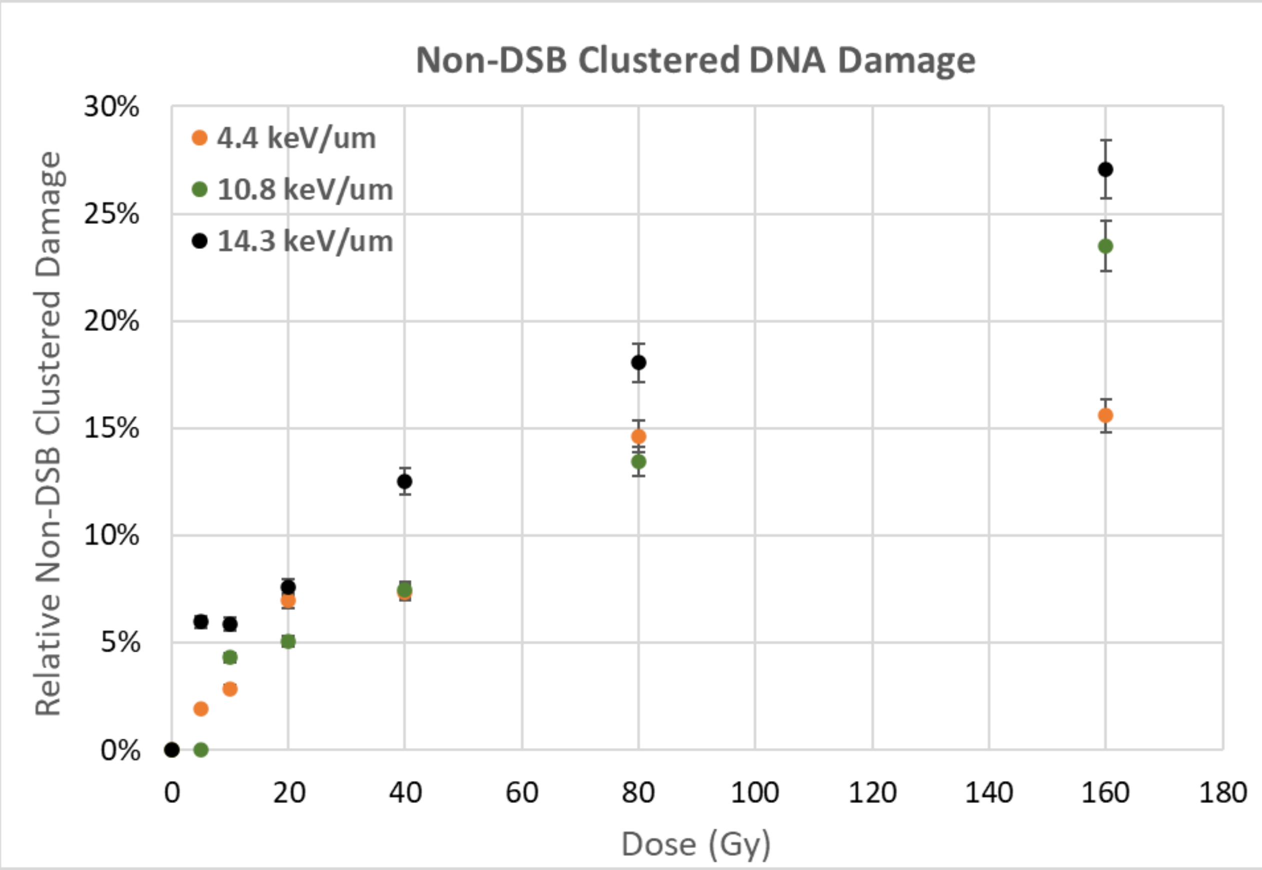




- Extend plasmid DNA damage studies with FLASH proton beam – Hopkins' Hitachi PROBIT Synchrotron.

Plasmid DNA damage vs LET





Supercoil loss and Clustered DNA damage increase with LET at conventional dose rate (~ 1 Gy/s)

- FLASH studies on-going

Conclusions and Discussions

- FLASH irradiation shows remarkable capacity for normal tissue sparing
    - Mechanisms remain to be understood
- Translation of FLASH RT requires monitoring of machine output --- need to know what is delivered
- Present ionization standard does not address the effects of fluence rate and LET on molecular and biological damage
- Consideration of fluence, fluence rate and LET compels study of molecular damage, in the inanimate state, and in vivo response
- Clinical translation of FLASH treatment necessitates the re-consideration of basic temporal and spatial factors in radiation treatment, such as uniformity of dose, dose rate and LET.