Council on Ionizing Radiation Measurements & Standards

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Orthovoltage X-Ray Irradiator for Preclinical FLASH Radiotherapy: Design, dosimetry, and in-vivo validation

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Disclosure

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    - AIP --- Hopkins, University of Pennsylvania, Xstrahl Inc.
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- Technology Transfer (Hopkins IP) agreement with Xstrahl, in progress

FLASH Radiotherapy

- FLASH radiotherapy is the delivery of high radiation dose (10-30 Gy) at ultrahigh dose rate (> 40 Gy/s), about 1000 times faster than conventional radiotherapy (ms. vs min)
- Reportedly, FLASH irradiation can increase the tolerance of normal tissues to radiation toxicity, while maintaining similar tumor response to conventional dose-rate irradiation. This is referred as FLASH Effect.
- Great excitement for the potential breakthrough in cancer treatment: Significant investment of technology industry, international research consortia, and workshops

<u>Why is FLASH RT important?</u>

If broadly validated, it can revolutionize radiotherapy:

- Higher doses can be safely delivered to tumor; or, established doses can be given with reduced toxicity to normal organs and tissues,
- Remove or simplify image guidance, motion management, and other technologies,
- Can reduce treatment time and No of fractions; more cost-effective

FLASH Irradiators: Proton & Electron Beams

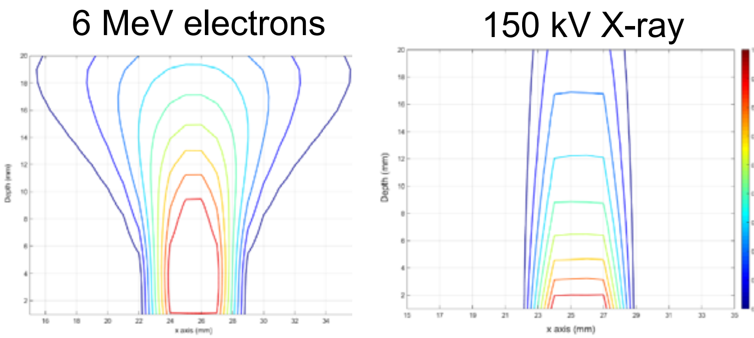
Cyclotron, 230 MeV, 40-100 Gy/s

Oriatron Linac, 5.6MeV, <300Gy/s

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

Clinical Linacs, 9 MeV, 74 Gy/s

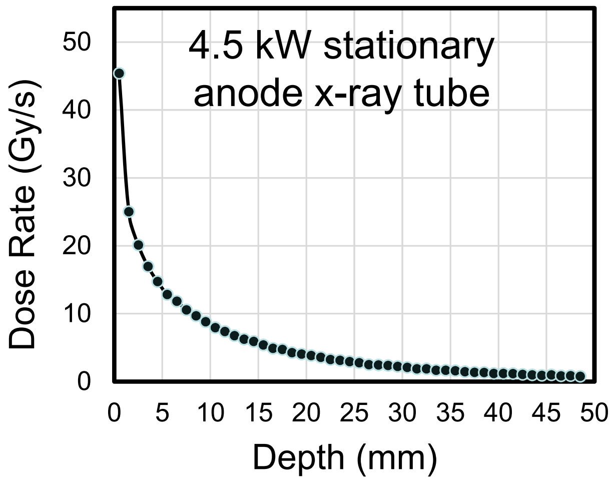
- Most irradiators used for FLASH studies are complex machines,
- The irradiators have limited accessibility for preclinical laboratory research

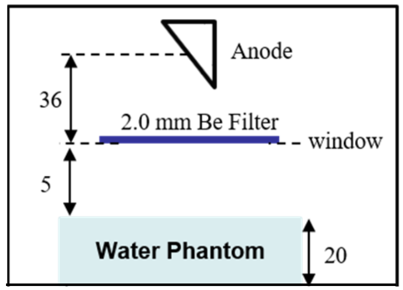


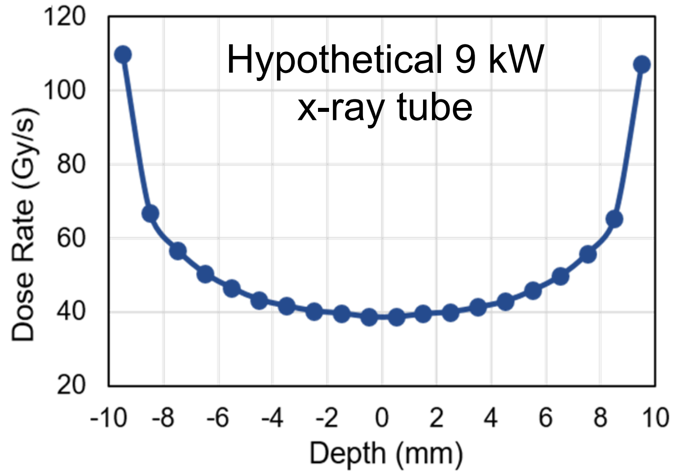
Lateral dose spread

Stationary Anode X-ray Sources

Extending capabilities of preclinical x-ray irradiators to support FLASH irradiation







kVp x-rays beam from a single x-ray tube have high depth dose gradient due to the inverse square effect.

Uniform depth dose rates is achievable by parallel-opposed x-ray sources.

Under best conditions and with minimum external filter, the achievable dose rates only meet the lower end of the dose rates suggested for FLASH irradiation.

Innovation in Preclinical Irradiators

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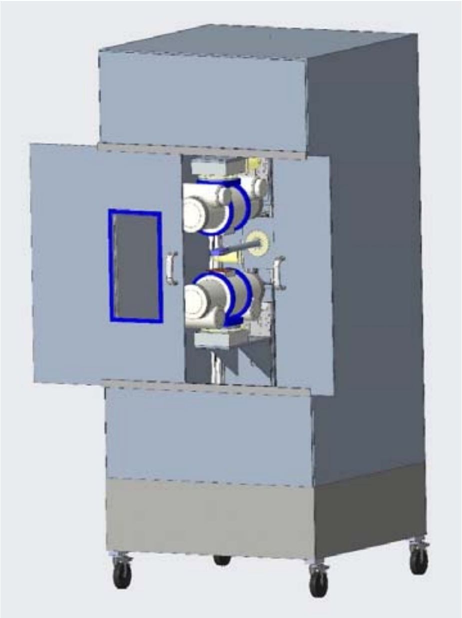
- High capacity rotating anode x-ray tube can be powered up to 100 kW. Maximum tube potential is presently limited to 150 kVp.
- Based on the technology, we have developed a self-shielded kVp x-ray cabinet system capable of delivering both **FLASH** (< 200 Gy/s) **and conventional** (< 0.1 Gy/s) dose rates irradiation for laboratory radiation research.
- We present results from feasibility studies using Monte-Carlo simulation (Geant4), dosimetric measurement, and *in vivo* model demonstration.

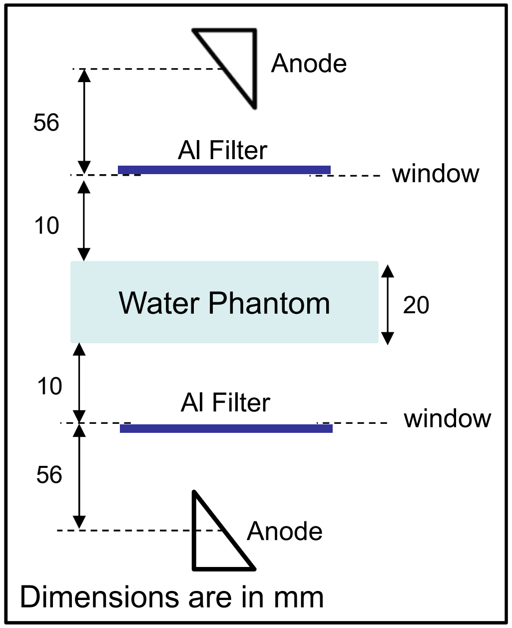
Novel Preclinical FLASH Irradiation System

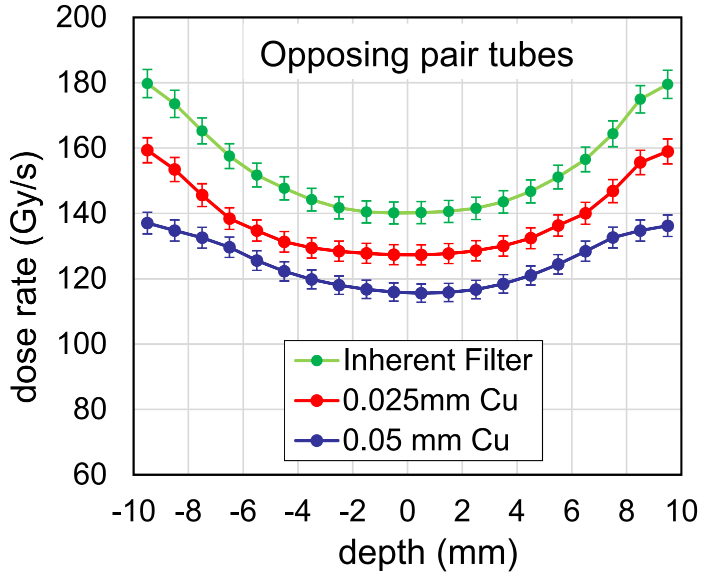
- Single pulse exposure
- Voltage: 150 kV
- Exposure time: 75-500 ms
- Phantom: 20 mm water
- Field size: 38 mm x 19 mm

Parallel-opposed x-ray sources can deliver:

- **200 Gy/s** and **60 Gy** to a 2-cm thick water equivalent media,
- in a single or multiple pulses of kV x-ray beam.



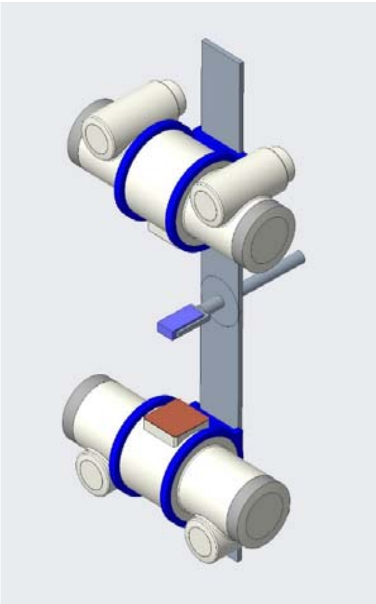


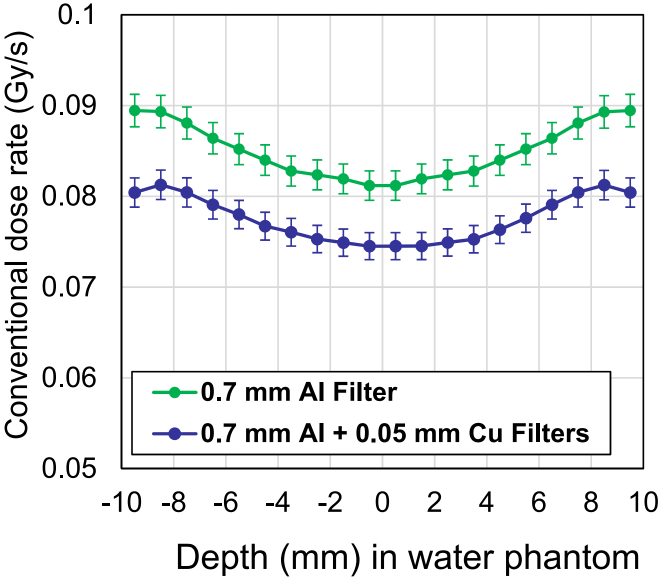


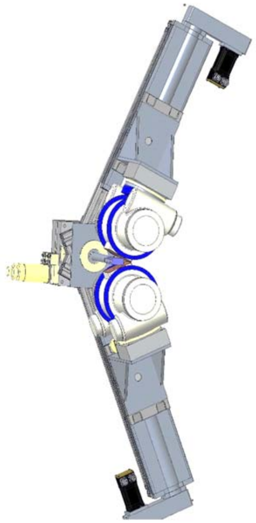
Conventional Dose Rate Irradiation

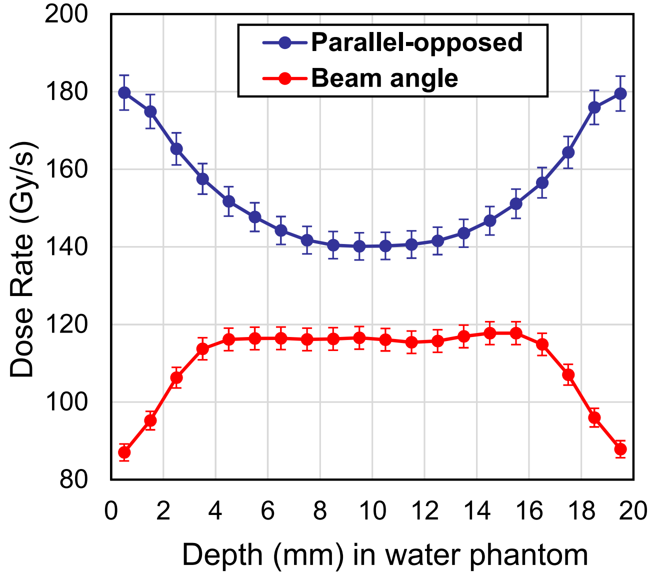
Dose rate is adjustable within <0.1 Gy/s to 200 Gy/s by controlling tubes separation distance and beam current

Rotation gantry reduces high entrance and exit doses, and enables conformal irradiation



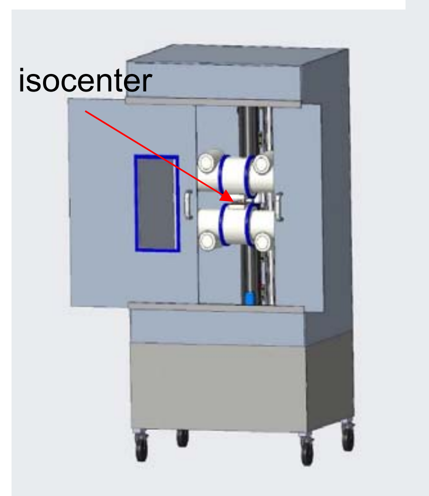






Properties of the Novel Irradiation System

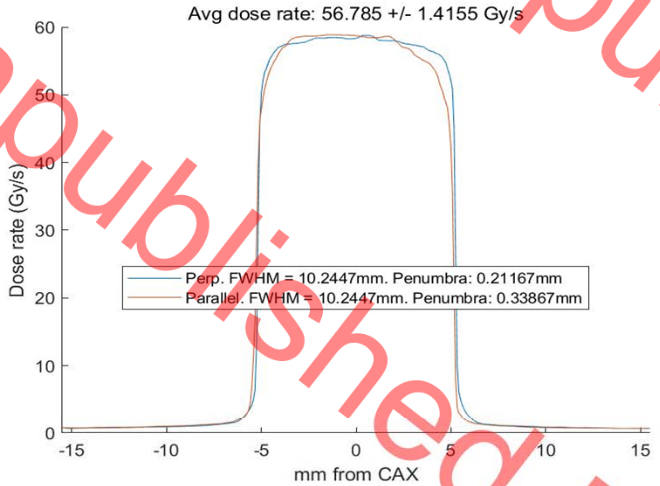
- The x-ray beam can be turned on/off within 5 ms, avoiding the need for mechanical shutter.
- FLASH beam can be delivered in a single pulse or multiple pulses, appropriate for mechanistic studies of FLASH effects.
- A wide range of dose rates (0.05 – 200 Gy/s) can be selected and controlled with < 5% uncertainty.
- The system can be installed in a self-shielded cabinet.
- Collimation can be achieved with 1-2 mm thick tungsten.
- Image guidance can be implemented.



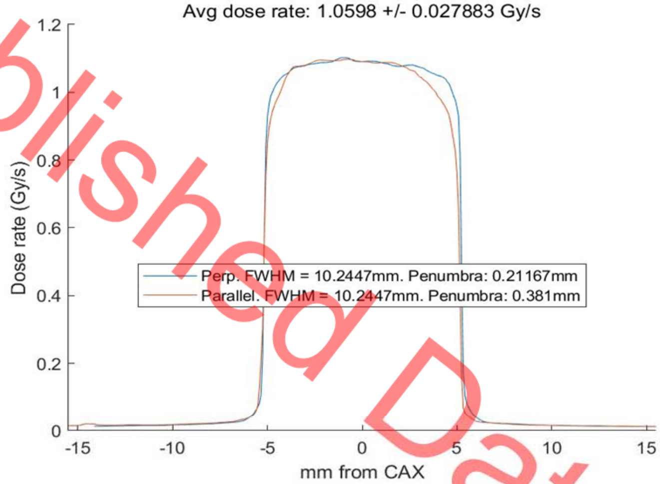
Dosimetry of a Single FLASH X-Ray Tube

150 kVp X-rays
75 kW generator
Single pulse of 5 – 6300 ms
Gafchromic film measurement

max dose rate: 56.79 Gy/s
Max dose: 28.5 Gy
Field size: 1 cm x 1 cm

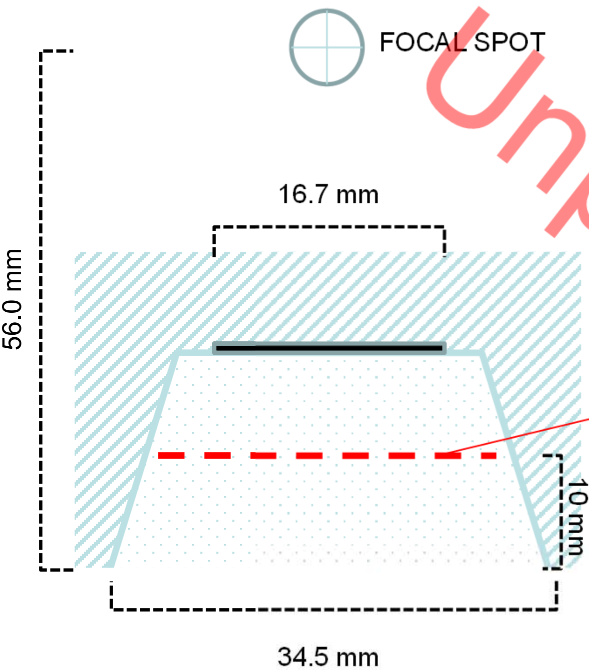


min dose rate: 1.06 Gy/s
Max dose/6.3s pulse: 6.7 Gy
Field size: 1 cm x 1 cm

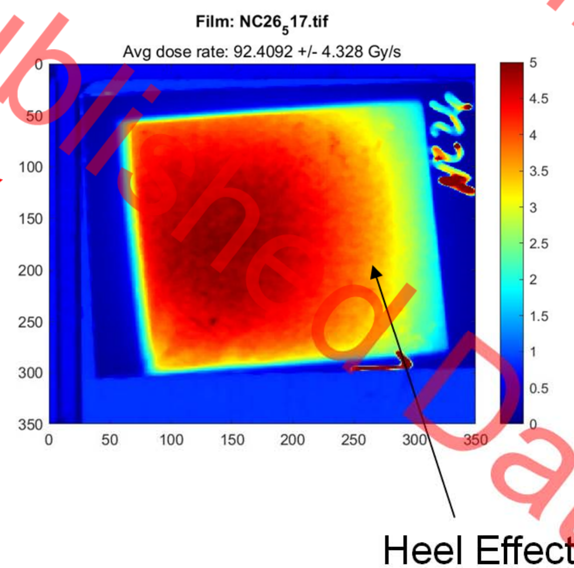


	Dose Rate (Gy/s)	Penumbra: 80%-20%	Umbra: 20%-2%	Flatness	Symmetry
FLASH	56.8 ± 1.4	0.28 mm	2.16 mm	±1.5 %	±2.9 %
CONV	1.06 ± 0.03	0.30 mm	2.05 mm	±1.1 %	±2.4 %

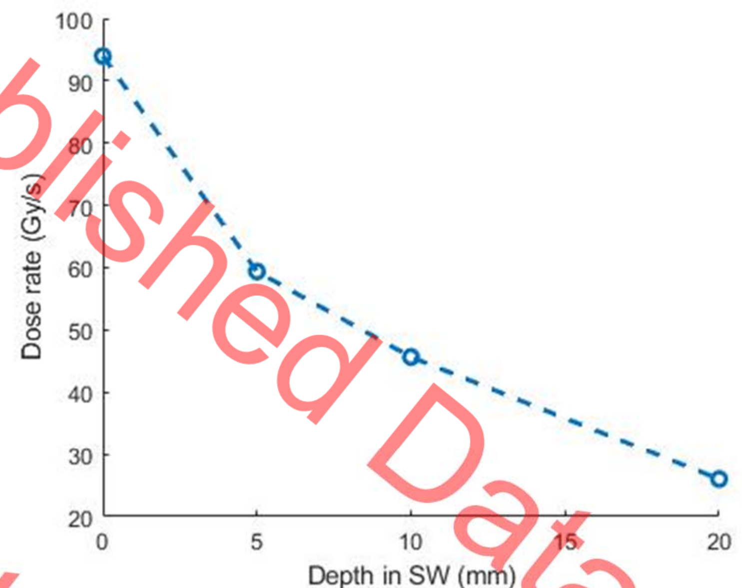
Dosimetry of a Single FLASH X-Ray Tube



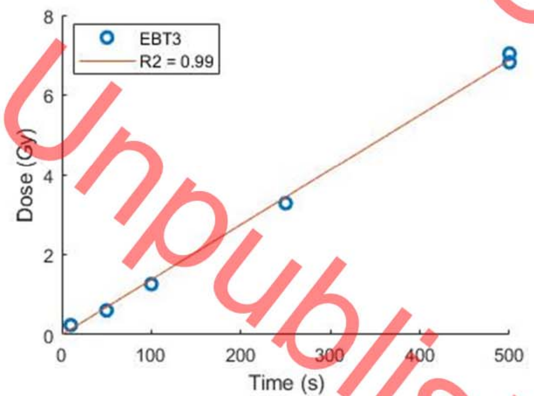
Dose rate: 92.4 ± 4.3 Gy/s
at 46 mm SSD
within solid water

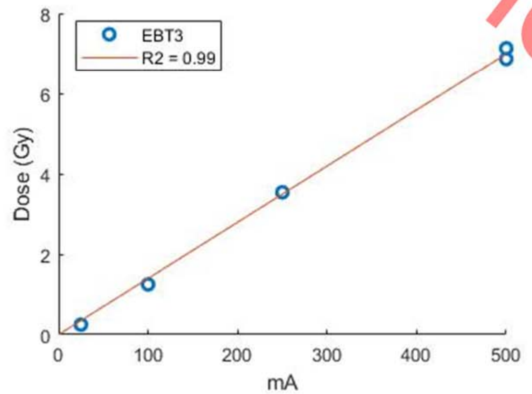


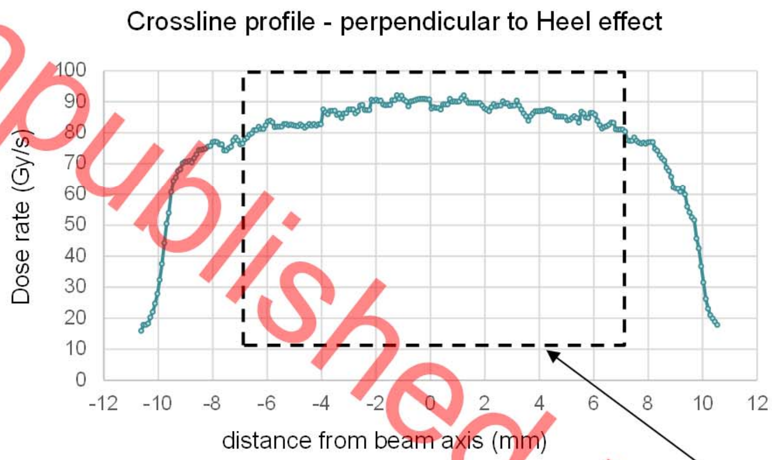
Depth dose-rate curve at 46 mm SSD

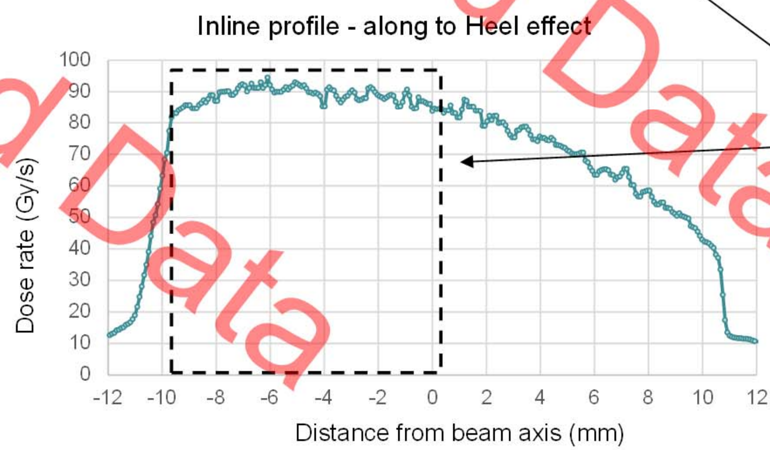


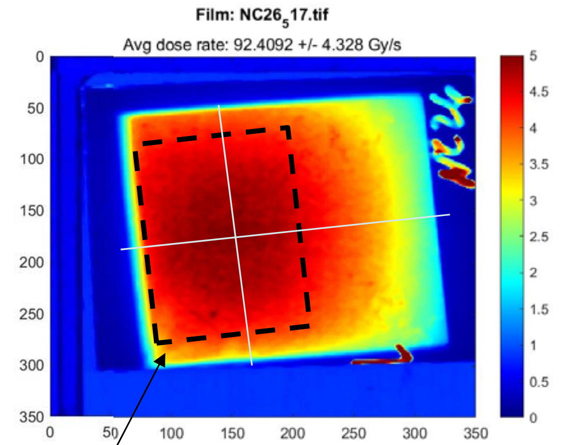
Dosimetric Characteristics: Gafchromic film







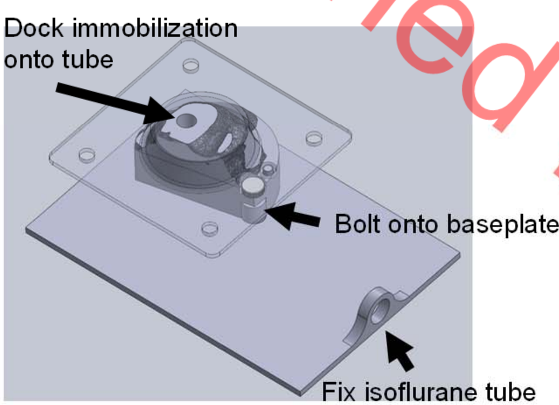


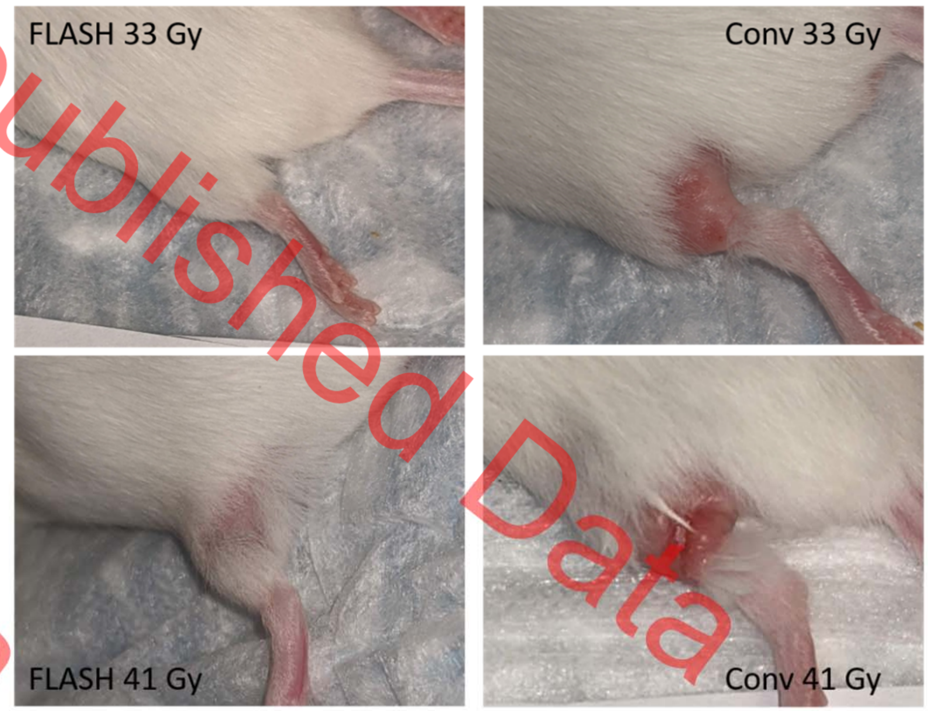


Field area used for animal irradiation

Flatness: ± 5%

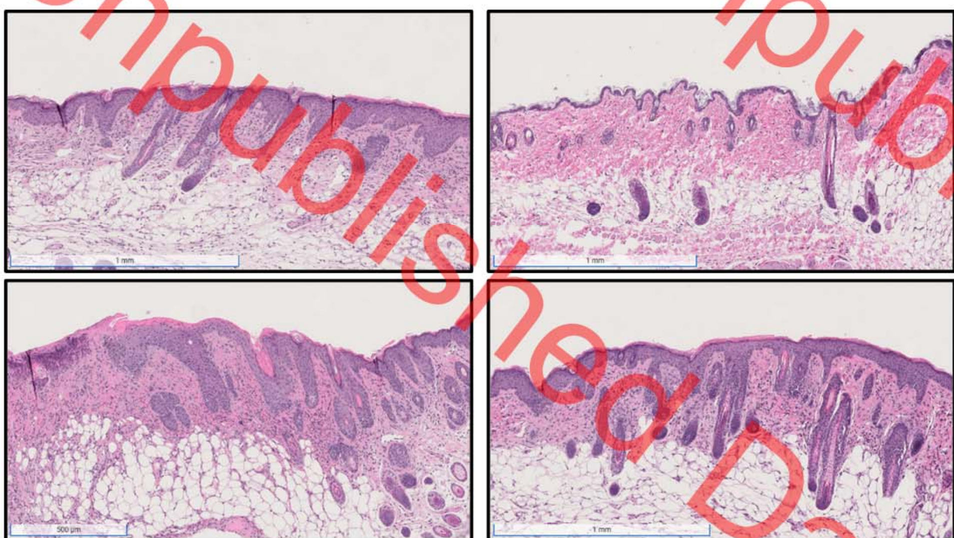
Skin Toxicity Study: X-ray FLASH Effects



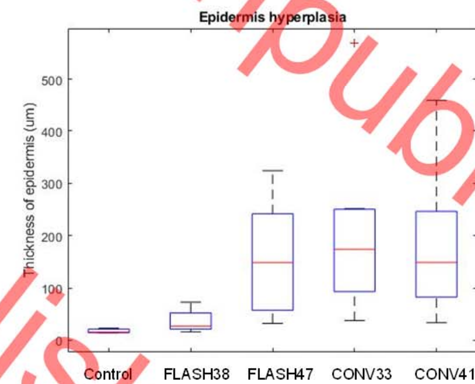


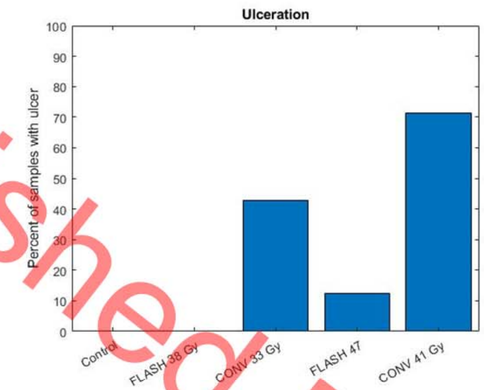
Skin Toxicity Study: X-ray FLASH Effects

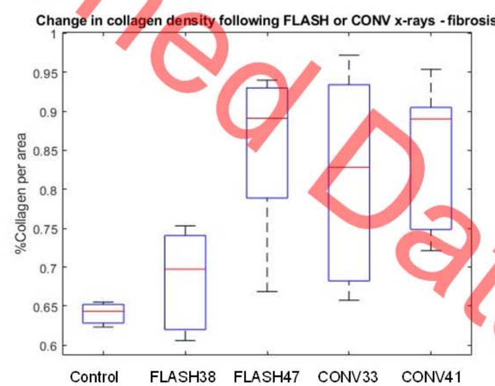
CONV 33 Gy FLASH 38 Gy

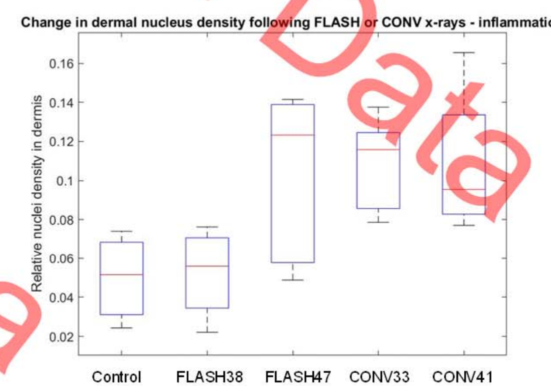


CONV 41 Gy FLASH 47 Gy

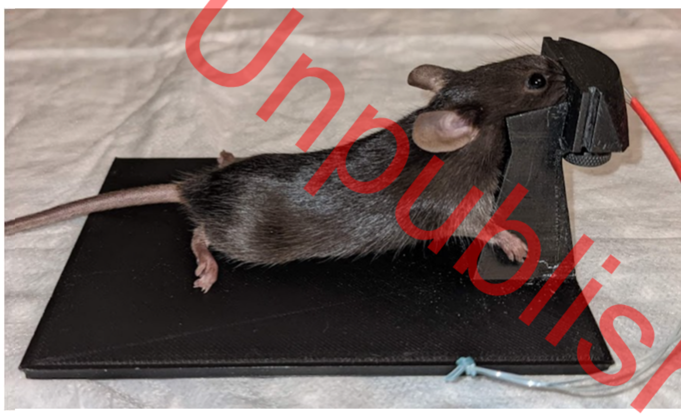


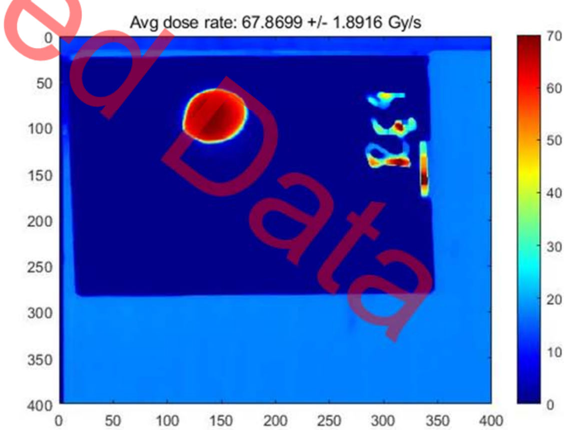


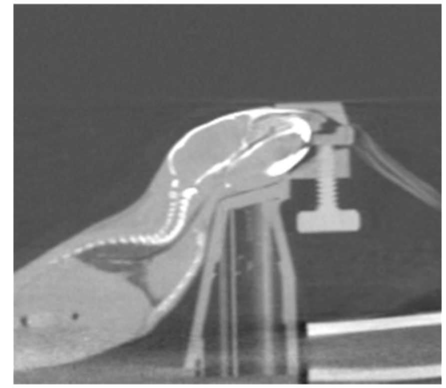


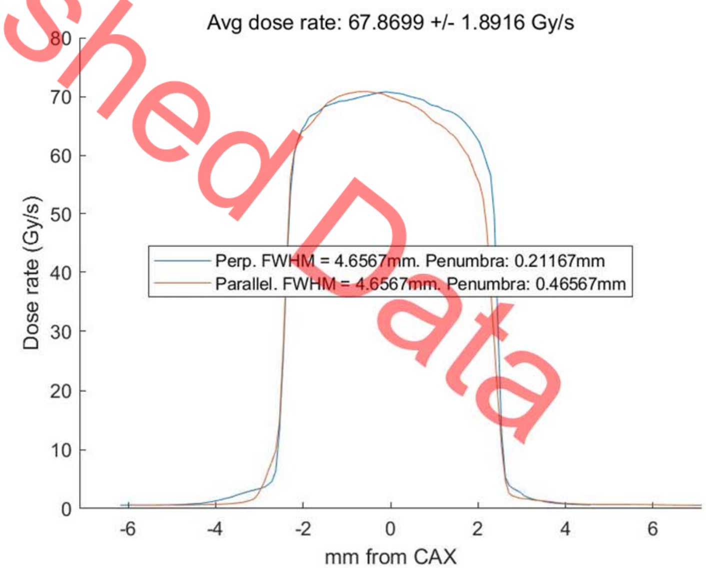


Ocular FLASH X-Ray Irradiation

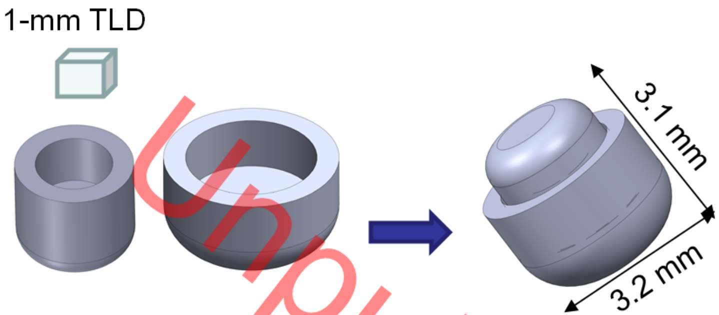


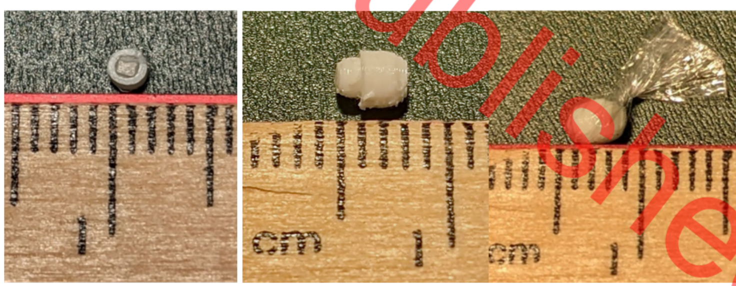


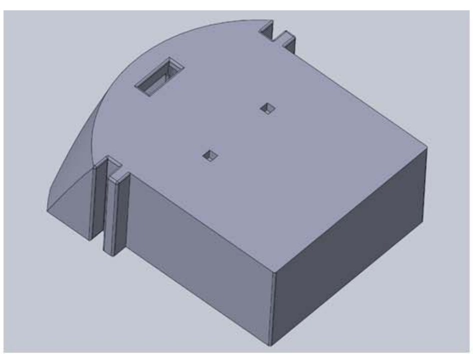




In Vivo Dose Measurement using TLD







- TLD vs Film measurement: within ~ 10%
- Average FLASH dose rate at the middle of eye: 64.1 ± 3.7 Gy/s
- Average Conv dose rate the middle of eye: 1.2 ± 0.1 Gy/s

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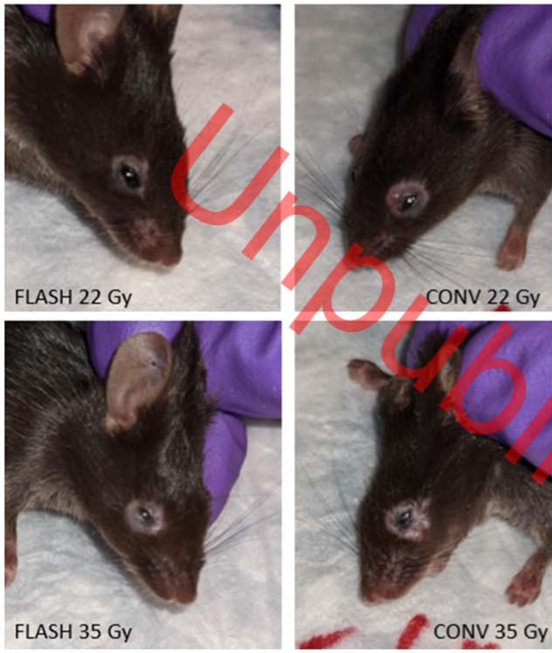
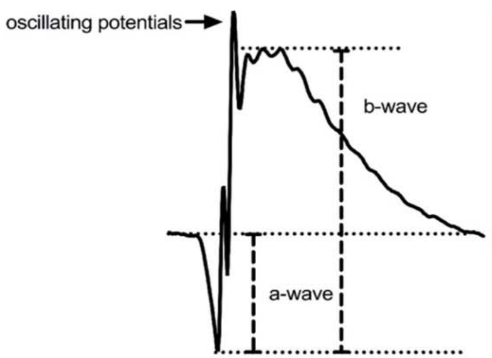
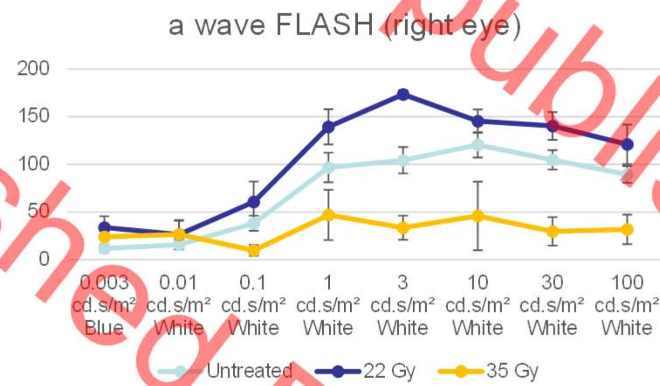
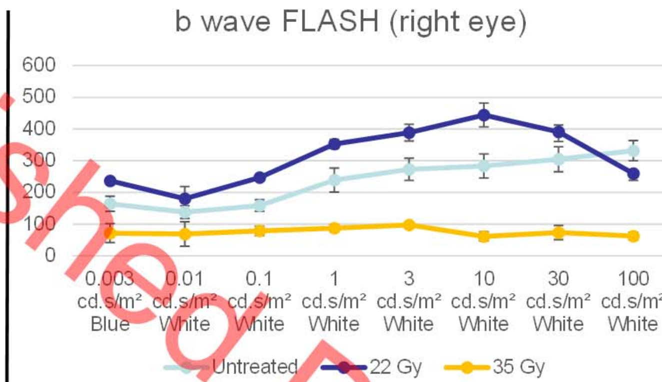
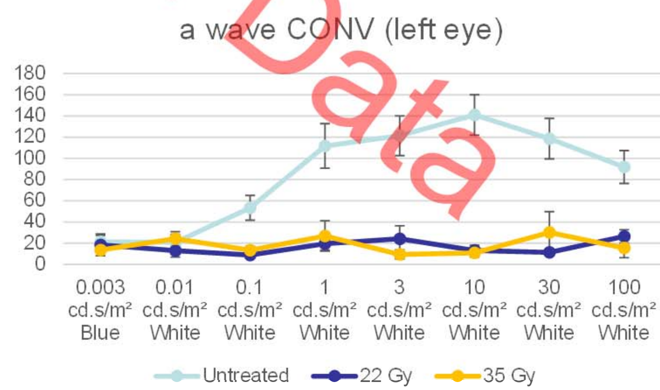
Dark-adapted (scotopic) Electroretinography (ERG) Response

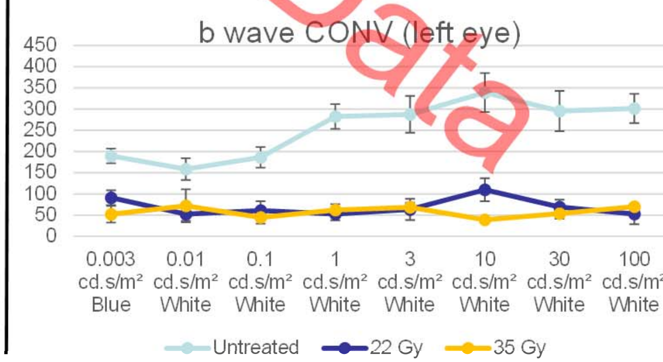












X-ray FLASH - Recap and Translation Challenges

FLASH effects can be achieved with **single pulse** kV x-rays

- Confirmed in normal tissues; Need to determine tumor response
- Need mechanistic studies -- Several competing or parallel models

Translation Challenges

- Non-trivial criteria of absolute dose and dose rate to attain FLASH
  - Organ and end-point dependence
- “Inevitable” --- the question on FLASH effects with volumetric irradiation
  - Conformal (partial organ) vs Large (total organ) irradiation
  - Are FLASH effects from individual beams independent?
  - What are the temporal and spatial factors in FLASH RT?
    - Implications on the use of (FLASH) proton pencil beam scanning

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