AAPM 2022
JULY 10–14 | WASHINGTON, DC
64TH ANNUAL MEETING & EXHIBITION

CELEBRATING MEDICAL PHYSICS
TRANSFORMING HUMAN HEALTH

From Pre-clinical to Vet-clinical imaging and therapy: Pathways to clinical translation

SAM multi-disciplinary scientific symposium

July 13th 2022

Session outline

- 1st section: Pre-clinical technology
  - Ken Wang: Introduction of recent progress in small animal technology
  - John Wong: FLASH radiation therapy: the road to translation
  - Ken Wang: Bioluminescence tomography-guided system for pre-clinical radiation research
  - Q&A (2 mins)

- 2nd section: Veterinary science
  - Parminder Basran: AAPM working group on veterinary radiation oncology and medical physics
  - Del Leary: State of the art in veterinary radiation oncology and medical physics
  - Kim Selting: A veterinary radiation oncologist perspective on clinical translation
  - Q&A (2 mins)

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CELEBRATING MEDICAL PHYSICS TRANSFORMING HUMAN HEALTH

UT Southwestern Medical Center

Pre-clinical technology; Introduction of recent progress in small animal technology

Ken Wang

Biomedical Imaging and Radiation Technology Laboratory (BIRTLab)

Department of Radiation Oncology

High precision small animal irradiators – SARRP & X-RAD SmART

- The major technology developments for pre-clinical radiation research.
- Primary goal of these systems is to mimic human treatment, bridging the technological gaps of human medicine and pre-clinical research
- CBCT-guided focal irradiation
- Commercialized around 2011, > 150 units world-wide

Small animal radiation research platform (SARRP)

Small Animal RadioTherapy (X-RAD SmART)

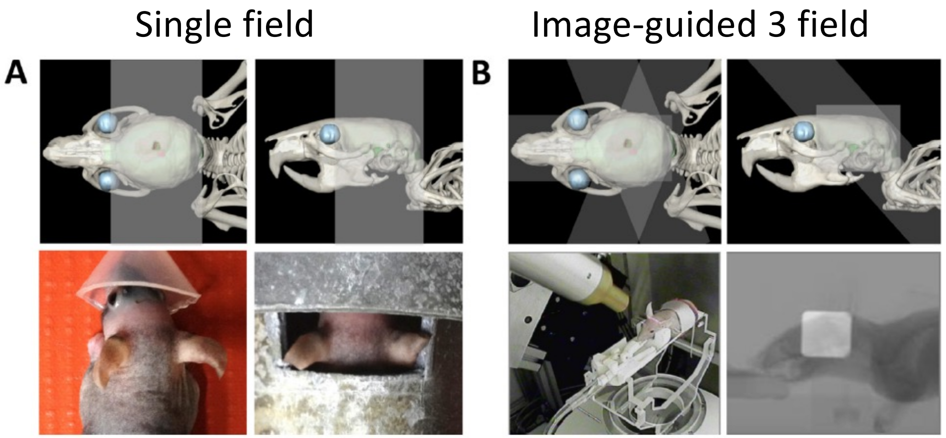
EDITORIAL

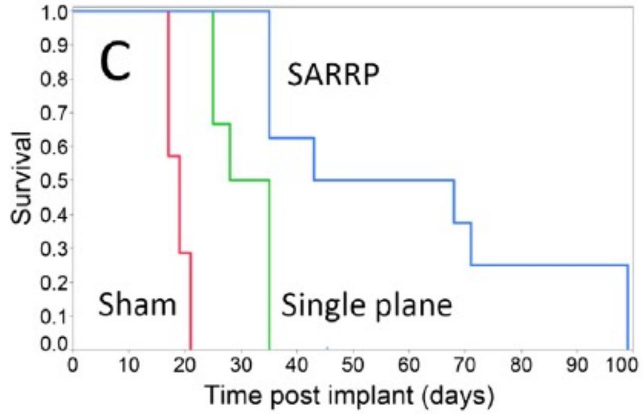
Preclinical Models for Translational Research Should Maintain Pace With Modern Clinical Practice

Joshua T. Dilworth, MD, PhD, Sarah A. Krueger, PhD, George D. Wilson, PhD, and Brian Marples, PhD

International Journal of Radiation Oncology biology • physics

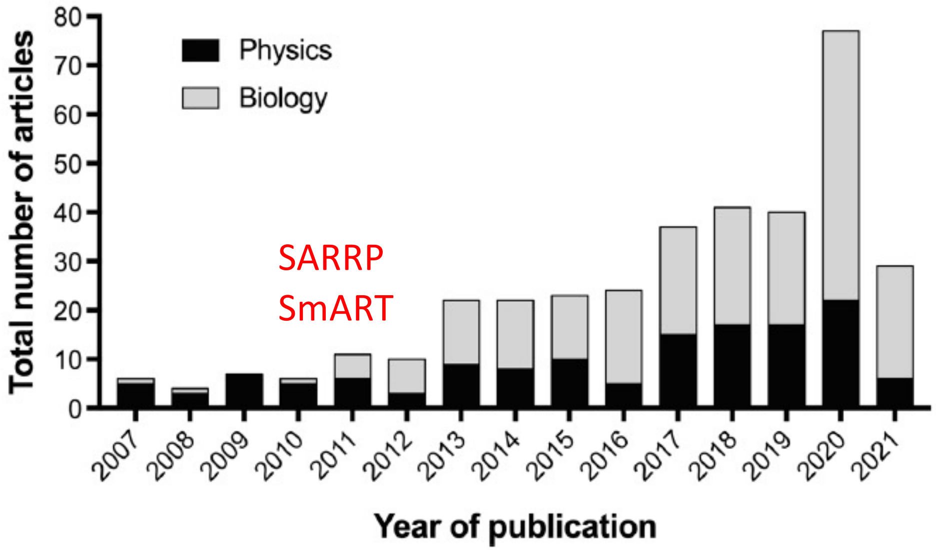
Vol. 88, No. 3, pp. 540–544, 2014



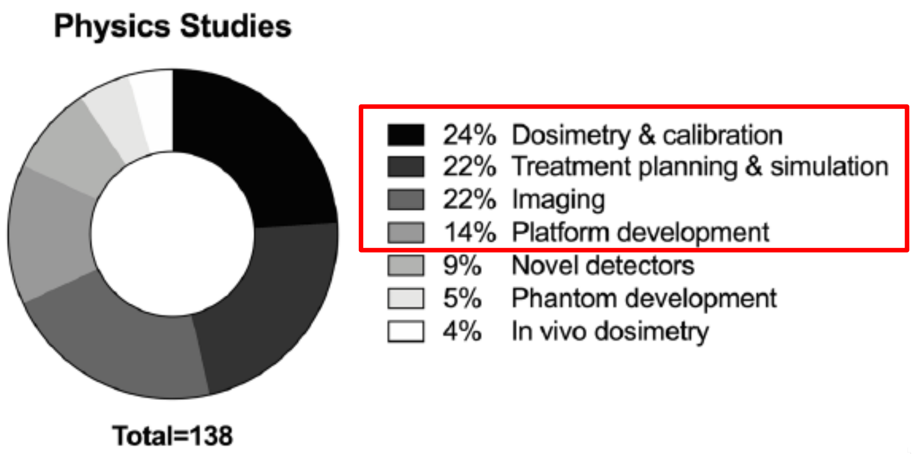


- (10Gy/week over 6 weeks); Mice with U87 tumor treated with single beam without imaging showed tumor growth and most met criteria for sacrifice before receiving 30 Gy.
- Image-guided irradiation shows significant tumor control over traditional single beam irradiation emphasizing the importance of technology development.

Technology enables high precision radiobiology studies



- Following commercialization of small animal irradiators in 2011, an increase in biology focused publications was observed.
- For physics research, dosimetry, planning, imaging and platform development are areas with major efforts.

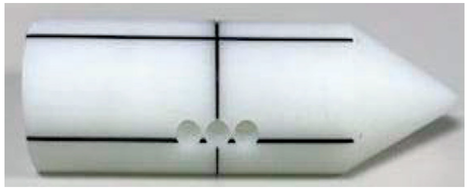


Brown et al, ctRO, (2022) 34, 112-119

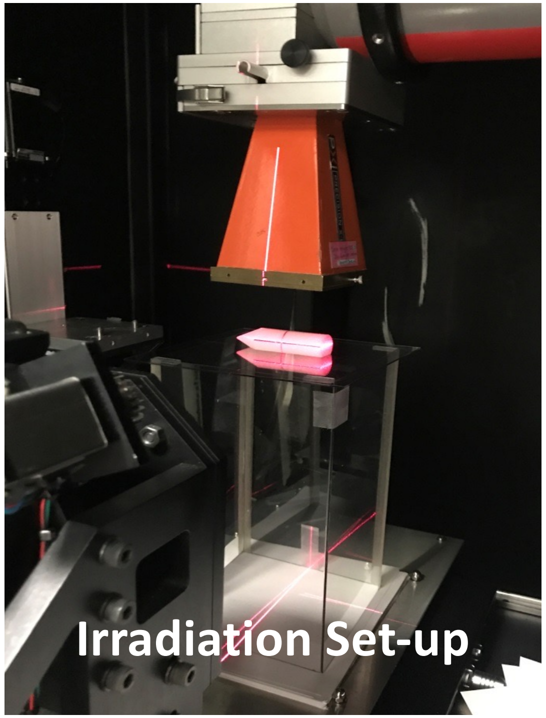
TLD mail audit system for small animal irradiators

- Dr. Rebecca Howell group from MD Anderson recently developed a mail-based, peer review system to verify dose delivery for X-RAD 225Cx irradiators (Precision X-Ray) to support study reproducibility - Gronberg *et al.* Radiat Res. 193, 4, 341, 2020.

- A robust, user-friendly mouse phantom was constructed from high-impact polystyrene



  - Dimensions similar a typical laboratory mouse
  - Accommodates 3 TLD to measure dose



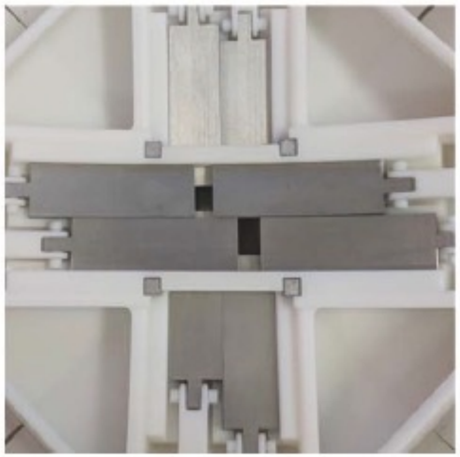
- Anticipated launch date spring 2023

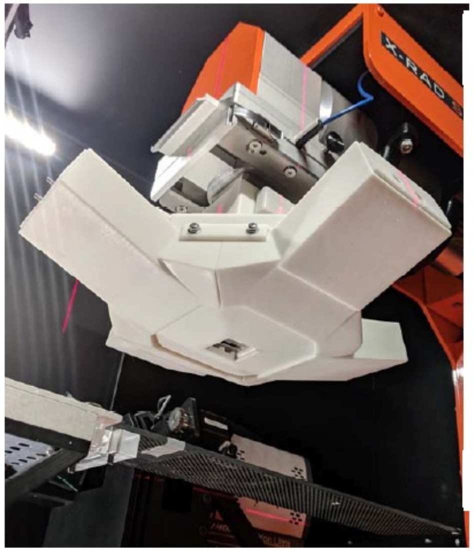
- TLD dose calculated using TG-191 formalism
  - Required K_Q characterization for each type of irradiator and beam quality

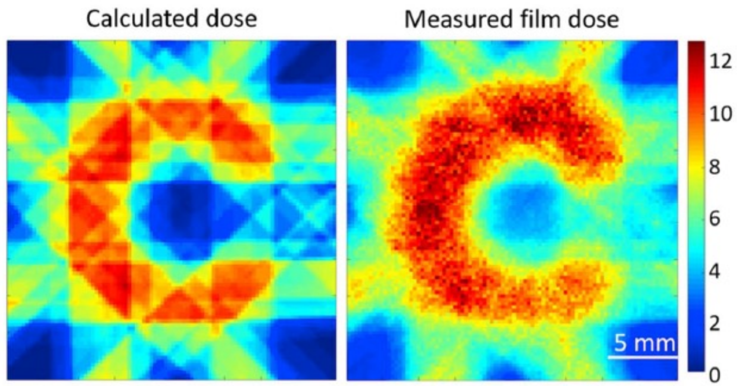
A sparse orthogonal collimator for small animal IMRT

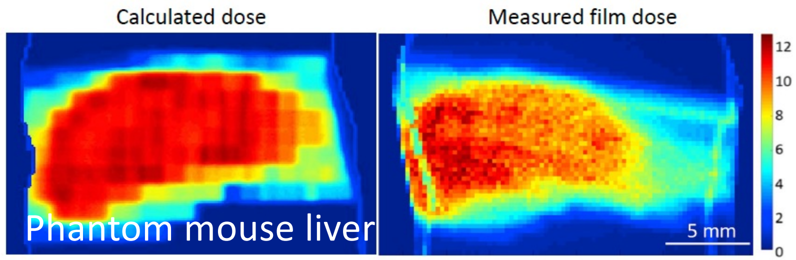
- Clinically used MLC is impractical for miniaturization, Dr. Ke Sheng’s group proposed a simpler sparse orthogonal collimator (SOC) for delivering small animal IMRT with a rectangular aperture optimization (RAO) TPS.
- To perform clinically similar treatment techniques and increase the translatability of preclinical research.

4 pairs of double focused orthogonal leaves, SOC

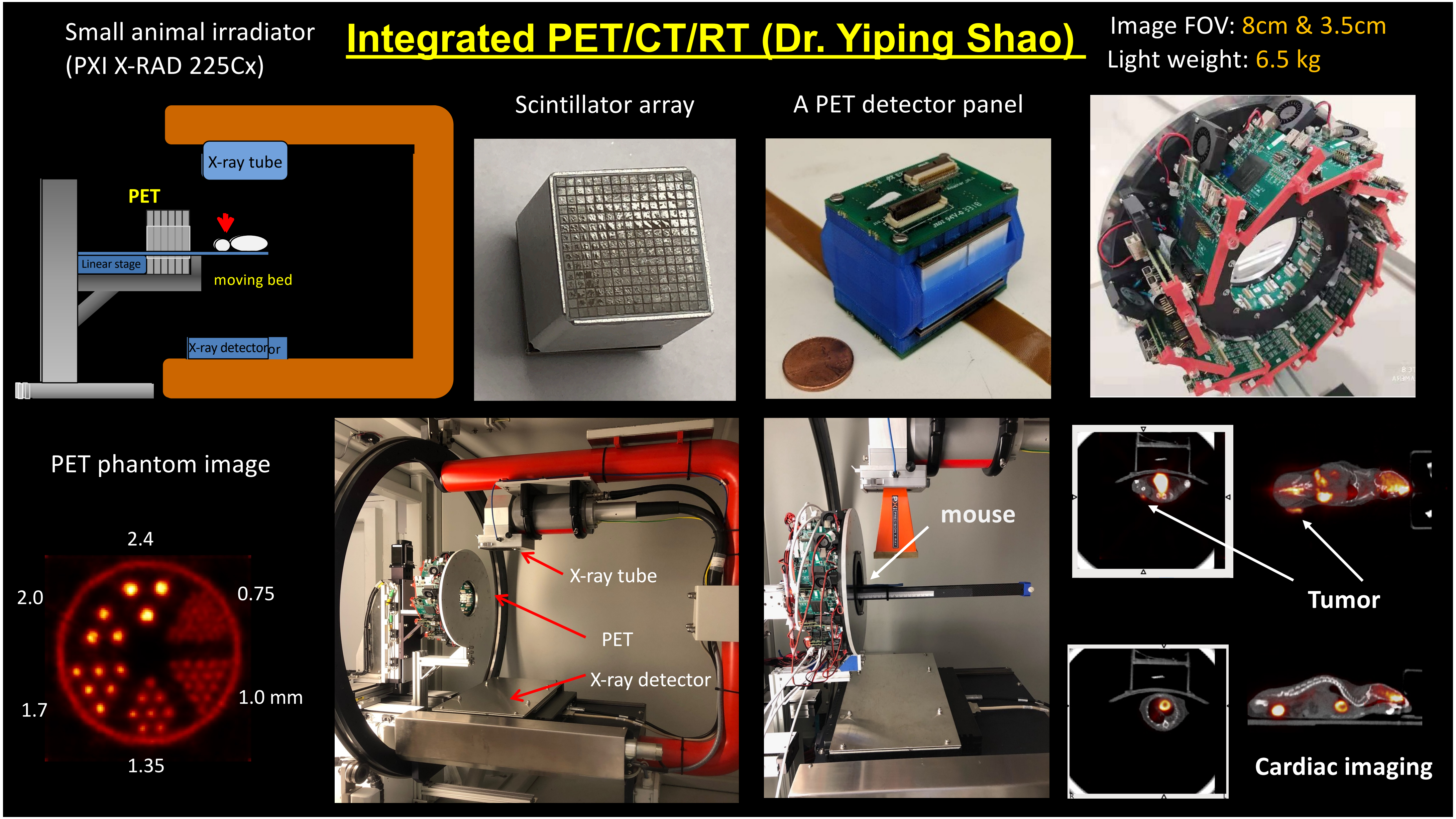








Med. Phys. 46, 12, 5733
Med. Phys. 46, 12, 5703

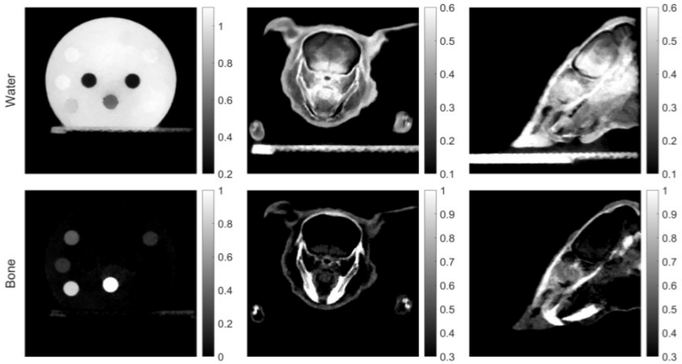


Integrated PET/CT/RT (Dr. Yiping Shao)
Small animal irradiator
(PXI X-RAD 225Cx)
Image FOV: 8cm & 3.5cm
Light weight: 6.5 kg
X-ray tube
PET
Linear stage
moving bed
X-ray detector
Scintillator array
A PET detector panel
PET phantom image
2.4
2.0
0.75
1.7
1.0 mm
1.35
X-ray tube
PET
X-ray detector
mouse
Tumor
Cardiac imaging

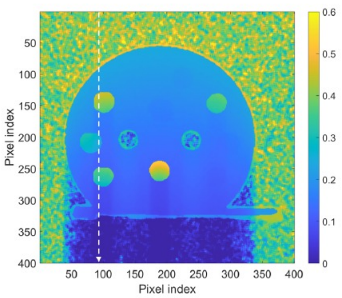
Multi-modality image-guided system

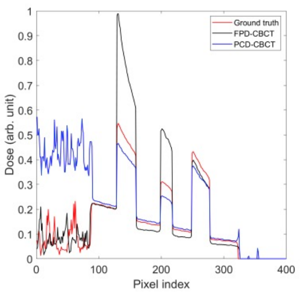
- Dr. Xun Jia's group incorporates
  - Photon-counting multi-energy CBCT to improve material differentiation and hence dose calculation.
  - PET-based functional image guidance
  - Rectangular jaw-based IMRT
  - GPU-based treatment planning with MC dose calculations

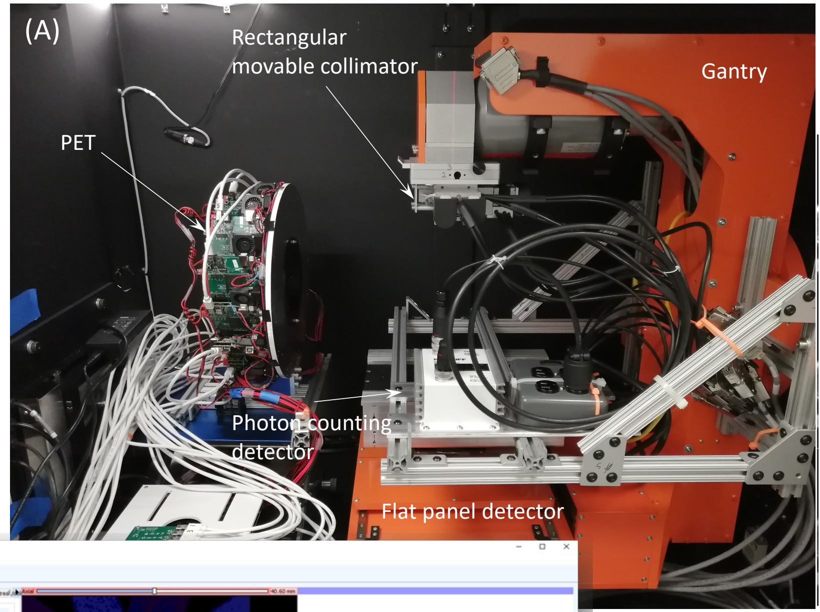
expected to achieve high precision and efficient functional image-guided irradiation

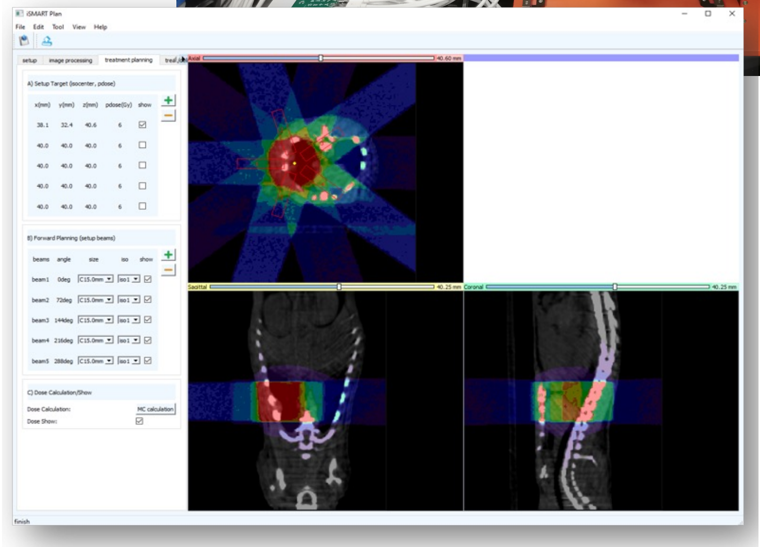


Bone insert





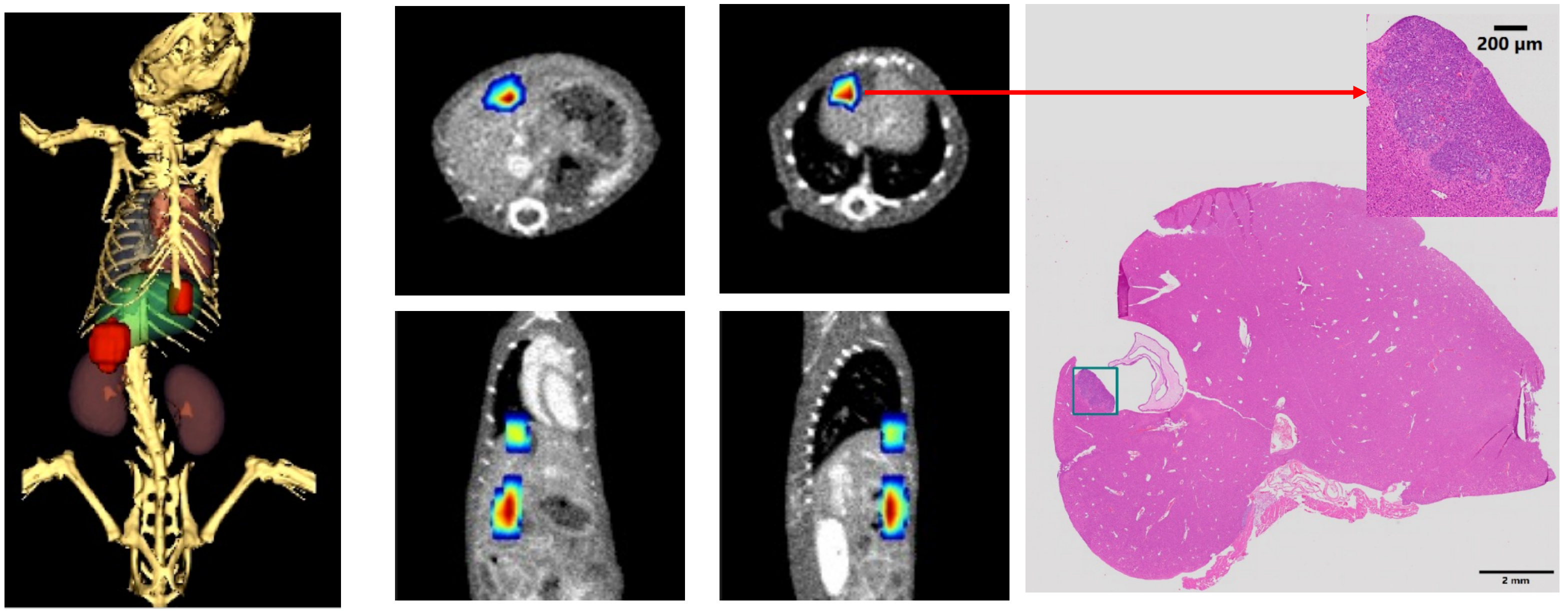




R37CA214639

Beyond irradiation guidance – metastasis detection

- Accurate detection of liver metastasis (~ 1 mm size) through integrated BLT/CT



Unpublished data (Dr. Yidong Yang group)

X-ray FLASH SARRP

- Xstrahl and Hopkins established a cabinet FLASH X-ray irradiator for pre-clinical studies.

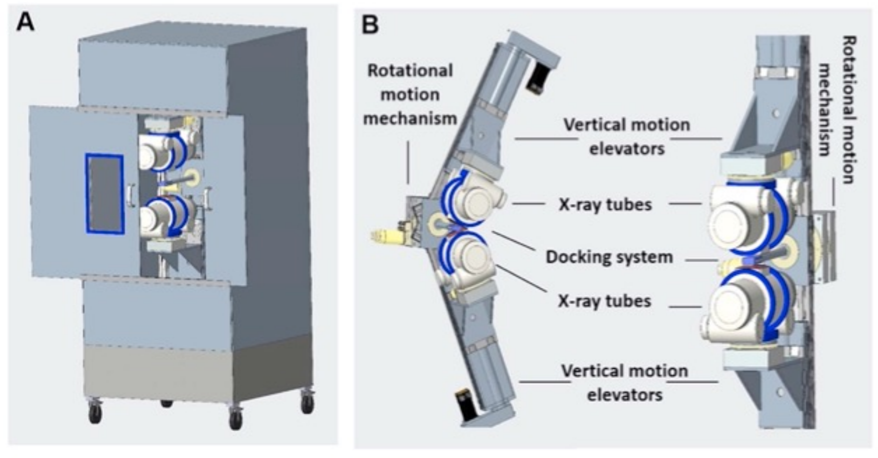


Figure 9. (A) Schematic of the FLASH cabinet system with parallel-opposed x-ray tubes. (B) Two system designs for FLASH irradiation including parallel-opposed (right) and rotated (left) x-ray sources, docking system, and computer-controlled vertical and rotational motion system.

R01CA262097 – Academic industrial partnership

Rezaee et al. Ultrahigh dose-rate (FLASH) x-ray irradiator for pre-clinical laboratory research. *Phys Med Biol* **66** 095006 (2021).

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MEDICINE
RADIATION ONCOLOGY &
MOLECULAR RADIATION SCIENCES

FLASH radiation therapy: the road to translation

John Wong

Acknowledgment

JHU School of Medicine

Mohammad Rezaee
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Akila Viswanathan

JHU Mechanical Engineering

Iulian Iordachita

NIH/NCI AIP R01 CA262097
(PI: Mohammad Rezaee)

University of Pennsylvania

Costas Koumenis
Anastasia Velalopoulou

Xstrahl Inc.

Merle Reinhart
Robert Lukasic

- JW: No financial disclosure on FLASH Irradiator; Provisional Patent filed

Fast forward to the new excitement of FLASH

- Transformative FLASH RT at 100x – 1000x conventional dose rate
  - lowers normal tissue toxicity and maintains tumor control
  - Uncertain required thresholds of minimal dose rate <u>and dose</u>
- Mechanisms complex and unresolved
  - Concentrated of ionization events in ultra-short time frame
  - Radiation chemistry implicated; “avoided” in ionization dosimetry
- Physics focuses (as usual) on the technology and measurement of FLASH
- How do we translate and prescribe FLASH?
  - --- Call for pre-clinical FLASH research

Pre-clinical FLASH Irradiation Technologies: Particle Accelerators

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IBA Cyclotron,
230 MeV, 40-100 Gy/s

Oriatron Accelerator,
5.6 MeV e- beam, → 300 Gy/s

Clinical Linear Accelerator,
9 MeV beam, 74 Gy/s

- Most irradiators (linacs, laser plasma, synchrotron, etc) are complex machines
- Not readily accessible for preclinical laboratory research.

X-Ray versus Electron Beams

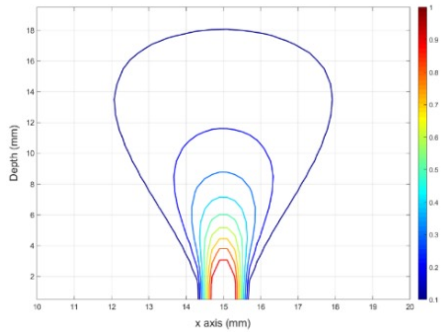
Geant 4 dose distributions in water phantom under ideal conditions:

- Planar square field
- infinite SSD

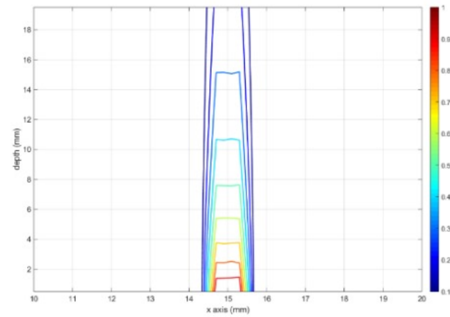
Lateral (e-) and depth (x-ray) dose gradients confound outcome assessment

1x1 mm field

6 MeV electrons

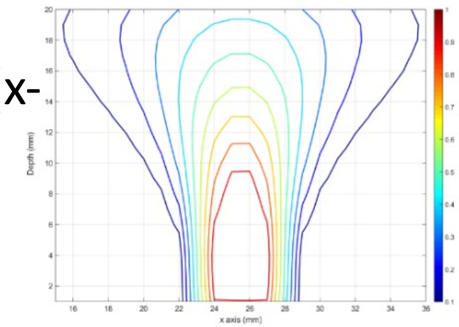


150 kV X-ray

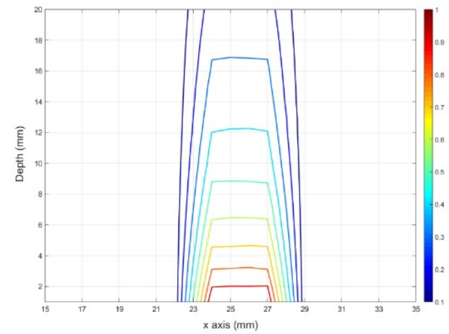


Beam direction

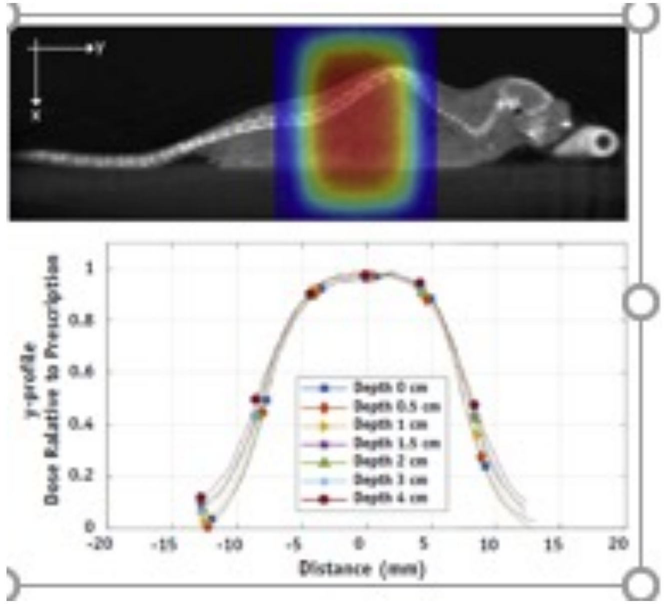
6 MeV electrons



150 kV X-ray



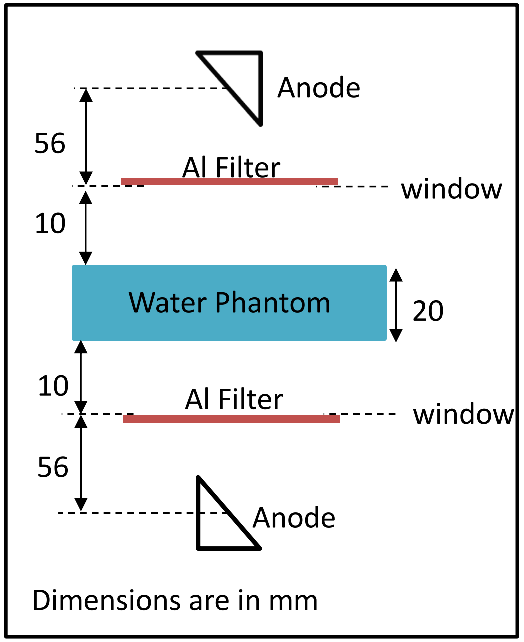
5x5 mm field

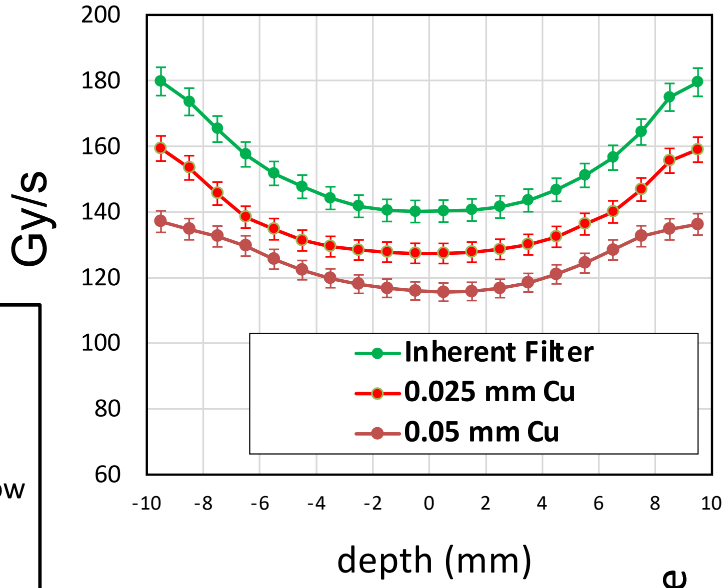


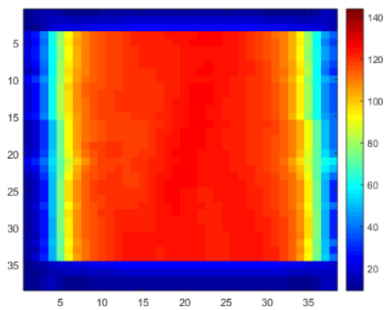
Same concerns for protons

Parallel Opposing fluoro-tubes:
Depth Dose Rate for Single Pulse FLASH Irradiation

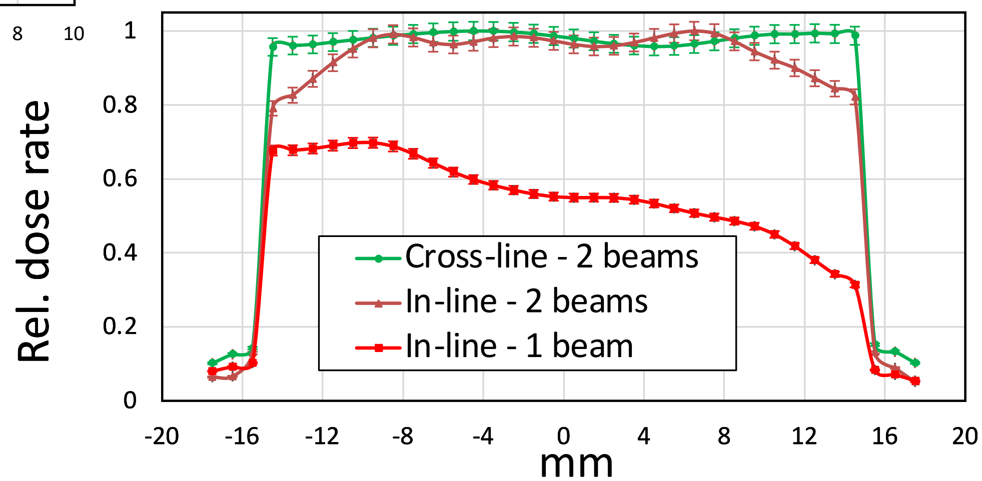
- Voltage: 150 kV
- 100 kW, 300 ms
- 20 mm water
- 38 mm x 19 mm



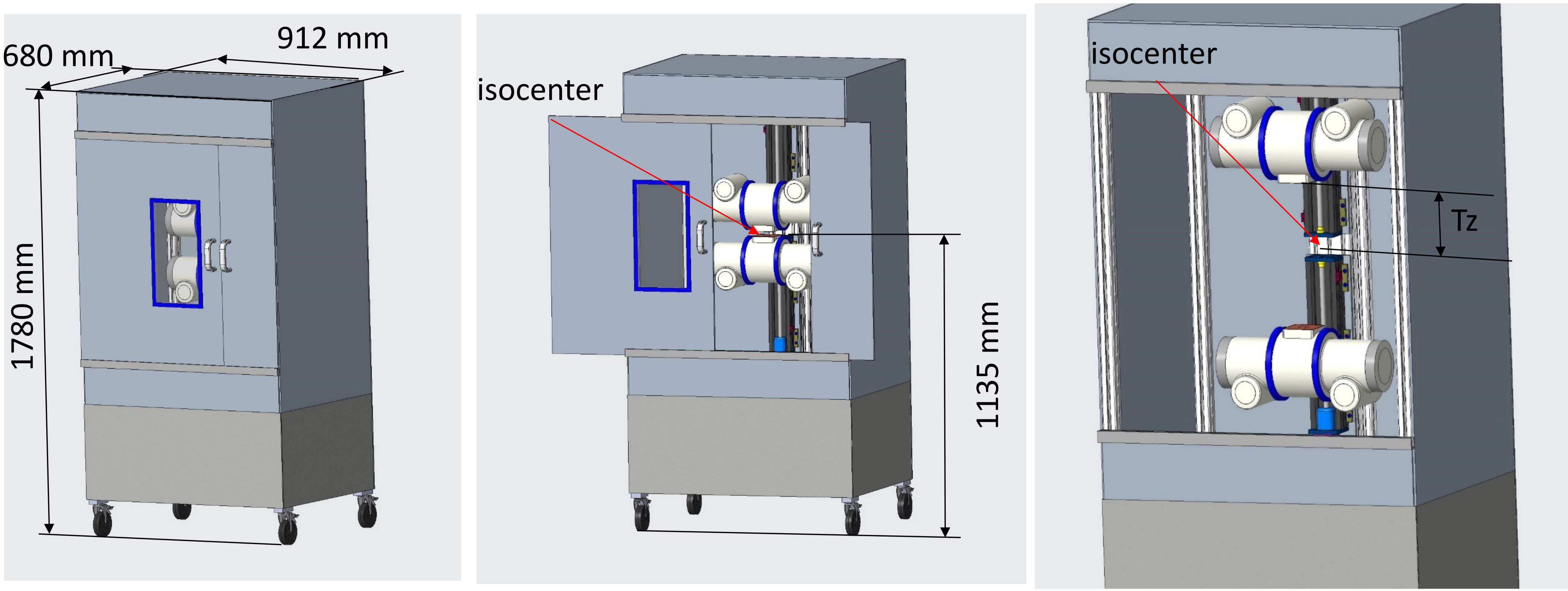




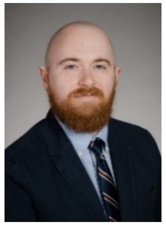
- Achieves FLASH dose rates
- <±5% for flatness and symmetry for a 30x20 mm^2 field, and for depth dose over central 10 mm.
- No need for shutter



FLASH Cabinet System

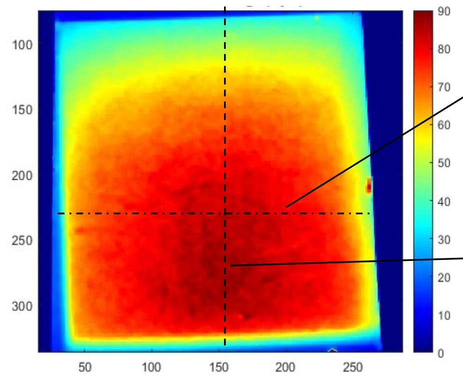


Dosimetry of a Prototype *Single* FLASH X-Ray Tube



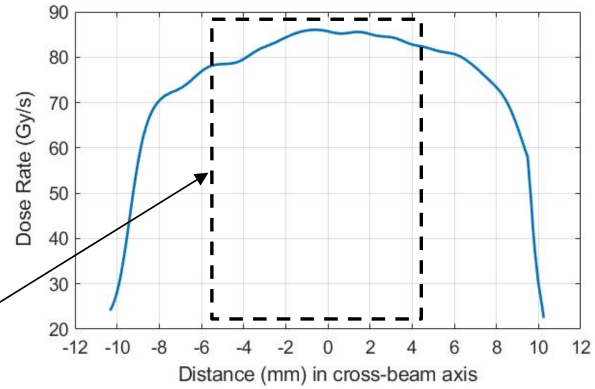
Devin Miles, PhD

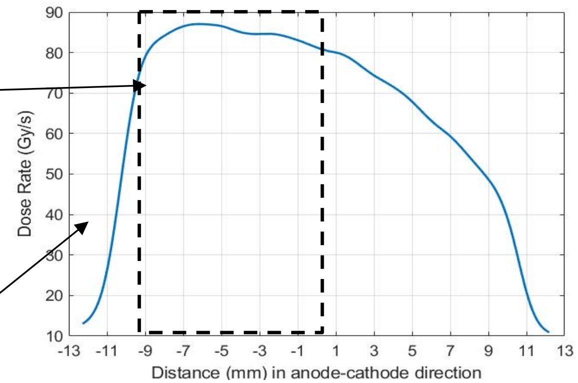
Film Measurements in Water Phantom:



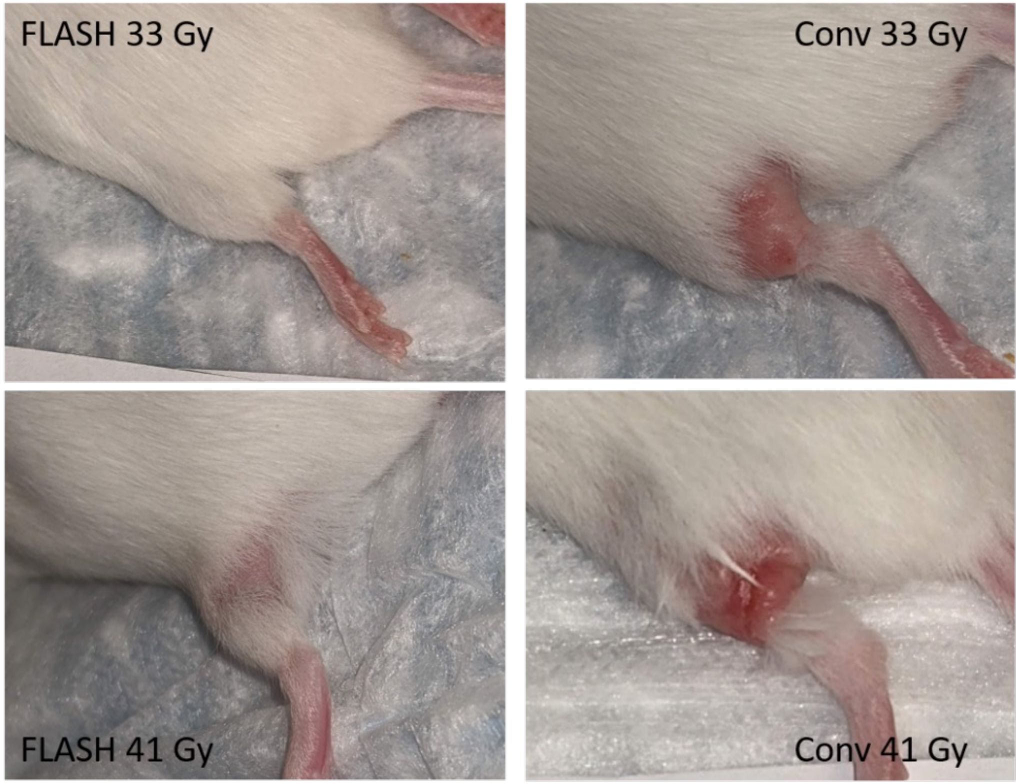
The area of field used for animal irradiation

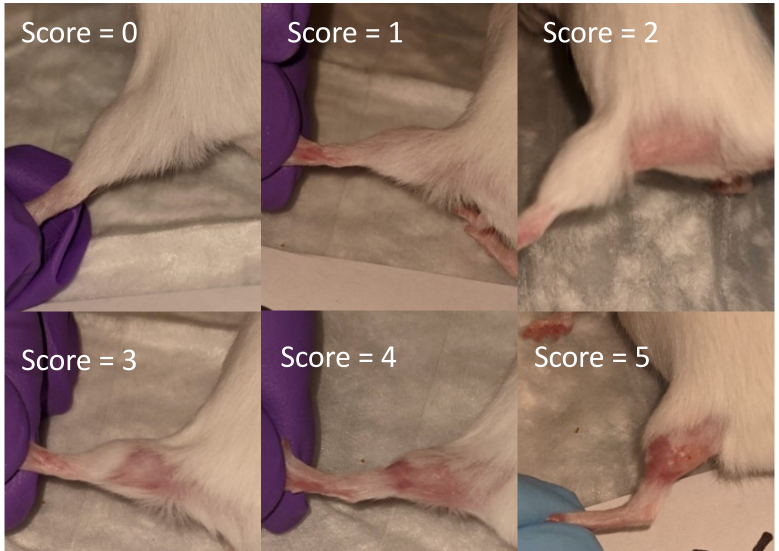
Dose rate at 46 mm from focal spot: <u>81.10 ± 4.97 Gy/s</u>

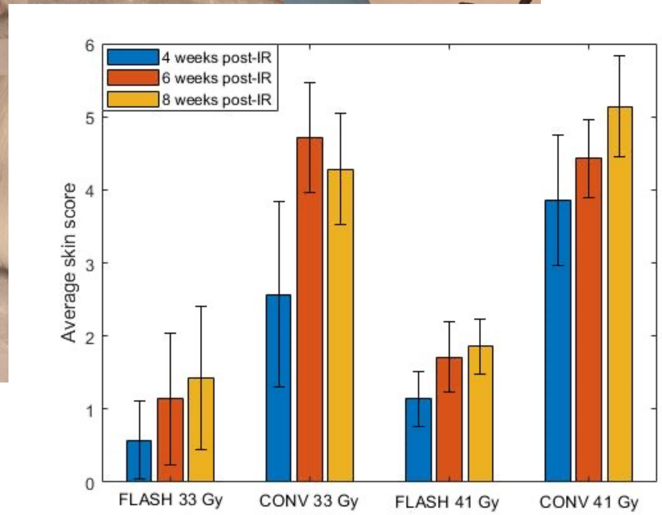




Skin Toxicity Study: X-ray FLASH Effects



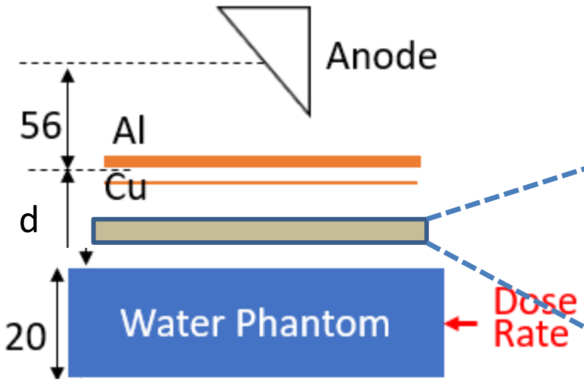


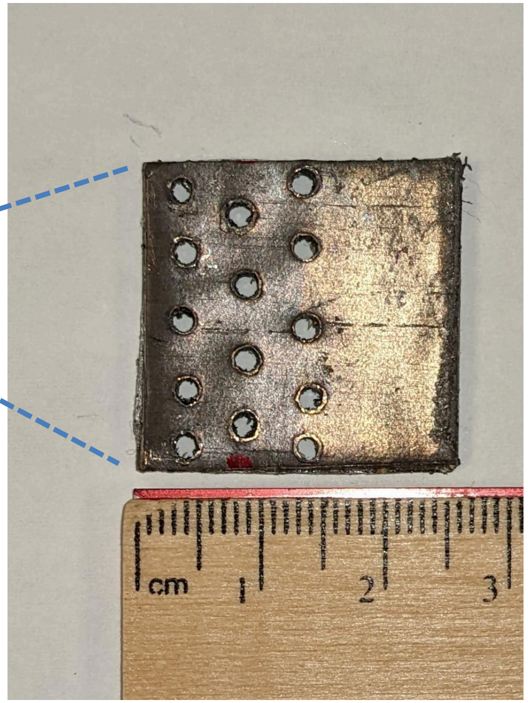


FLASH --- Translation Challenges

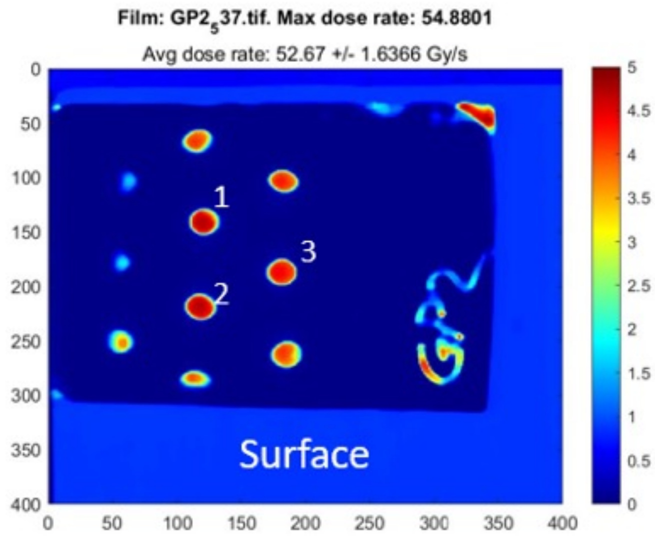
- Non-trivial criteria of absolute dose and dose rate for FLASH
  - Organ and end-point dependence
- Challenges of FLASH for 3D conformal irradiation
  – What are FLASH effects for partial organ vs total organ irradiation?
  – Are FLASH effects from individual beams independent?
- What are the temporal and spatial factors in FLASH RT (PBS)?
  – *Are FLASH and GRID complementary?*
  – *Explore FLASH and GRID irradiation using x-rays*

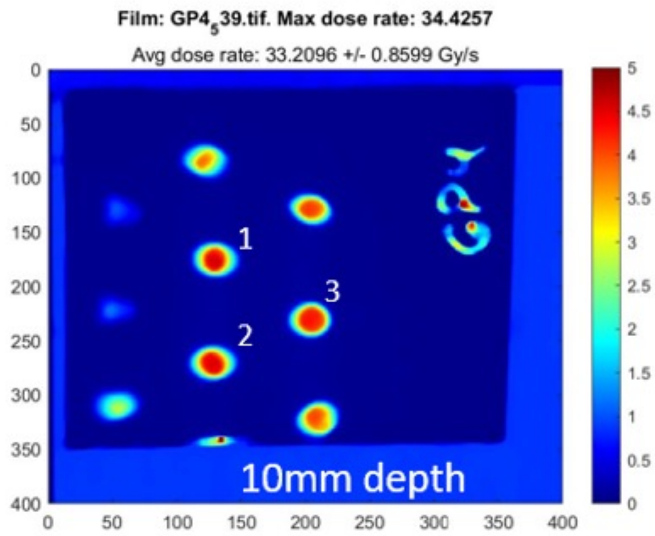
Pre-clinical x-ray pencil beam ---
Collimated FLASH x-ray beams





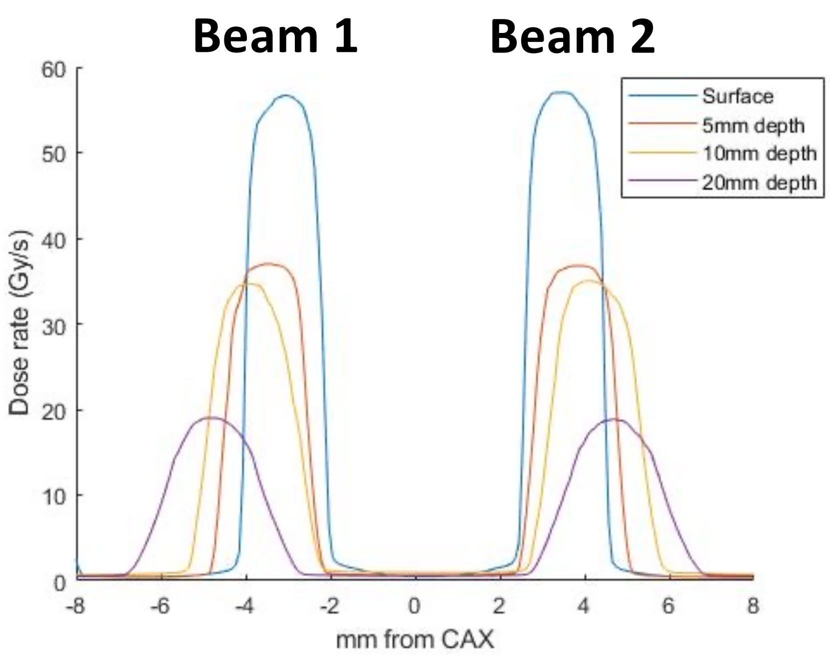
- Array of drilled 2mm dia. Apertures in a 25 mm-squared, 2.5 mm thick lead plate
- 8 mm (d) from x-ray window
- 2 mm above phantom surface with spacer



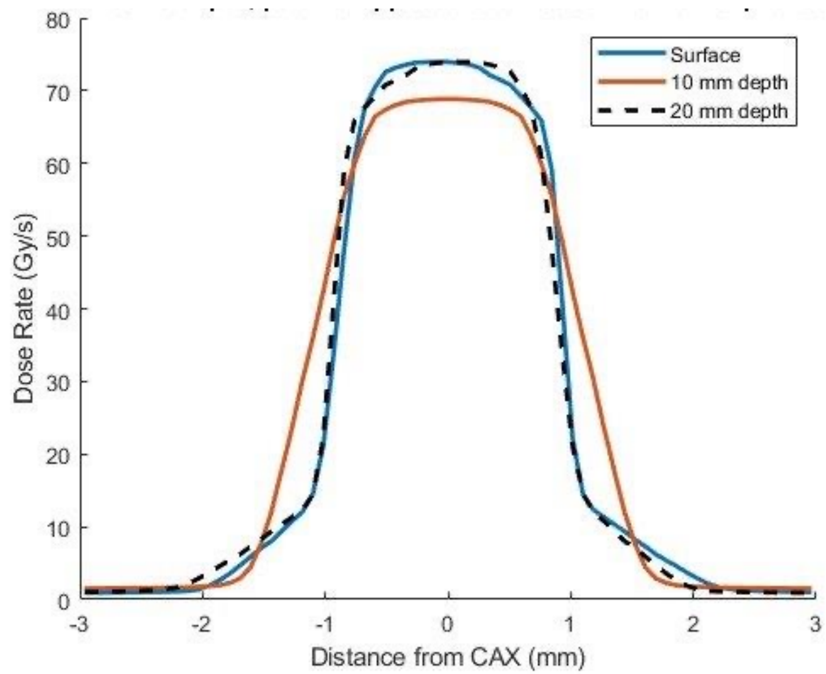


Flash-Grid beam – 150 kVp, ~ 50 Gy/s, “idealized” alignment

- Minimal dose floor (valley) for grid delivery



Parallel Opposed 2 mm FLASH beams

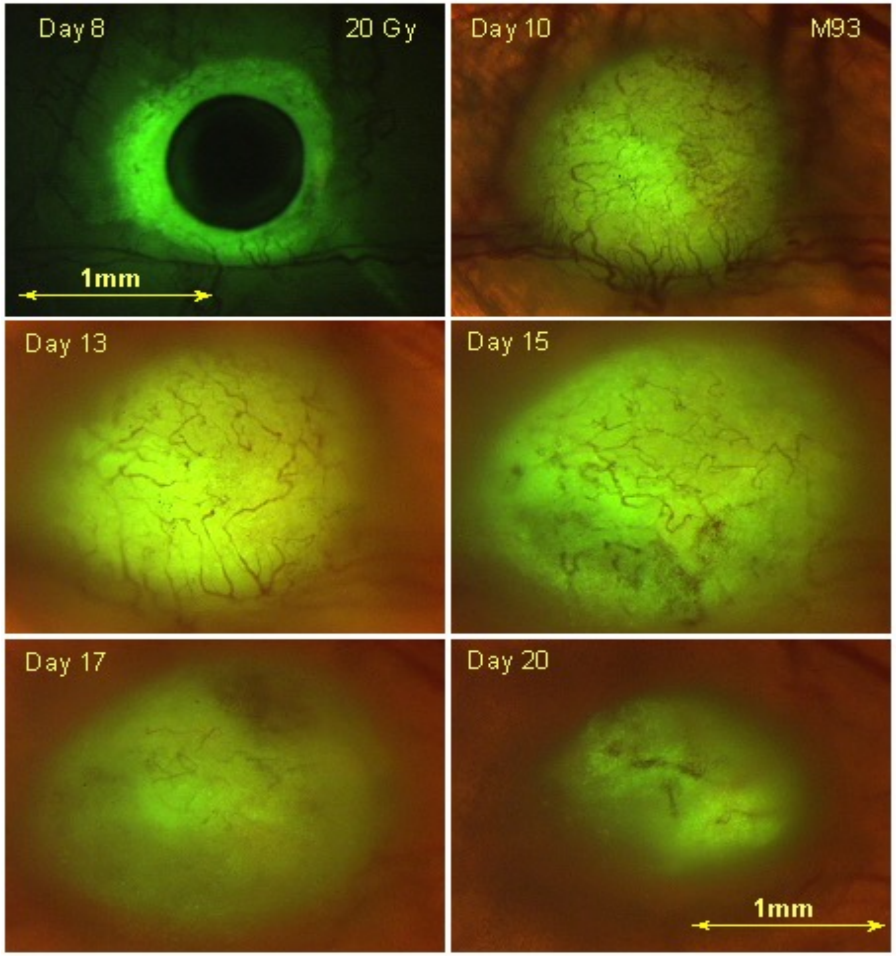


Conclusions and Discussions

- Platforms for Preclinical Radiation Research
  - FLASH effects in normal tissues are confirmed with x-rays
  - Mechanistic and Translational studies are needed
- Many questions remain with pre-clinical radiation research
  - Validation of TCP, NTCP; what is the “target volume” ?
  - Research with combination therapeutics
- Pressing issue
  - Is pre-clinical radiation research reproducible and generalizable
    -- challenges of target delineation, trials, data sharing

What is the target volume? --- The case of tumor microenvironment


Mouse Dorsal Window Chamber (Armour, 2002)

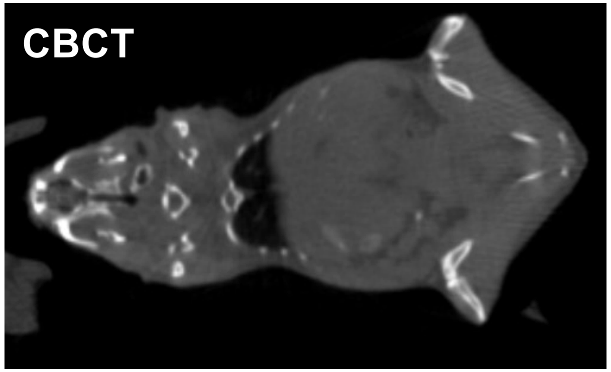


Irradiation with a central block (n=4):
Tumor regression --- 100% at 20 Gy; 50% at 10 Gy

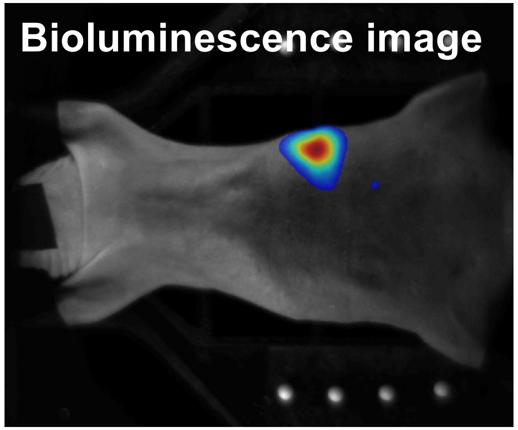
Pre-clinical technology;
Bioluminescence tomography-guided system for pre-clinical radiation research

Ken Wang
Biomedical Imaging and Radiation Technology Laboratory (BIRTLab)
Department of Radiation Oncology

Limitations of CBCT/CT-guided RT



- Limit in soft tissue target localization
- Unable provide functional information



- High contrast soft tissue imaging for localization
- Bioluminescence light related to cell viability → Quantitative imaging for treatment assessment

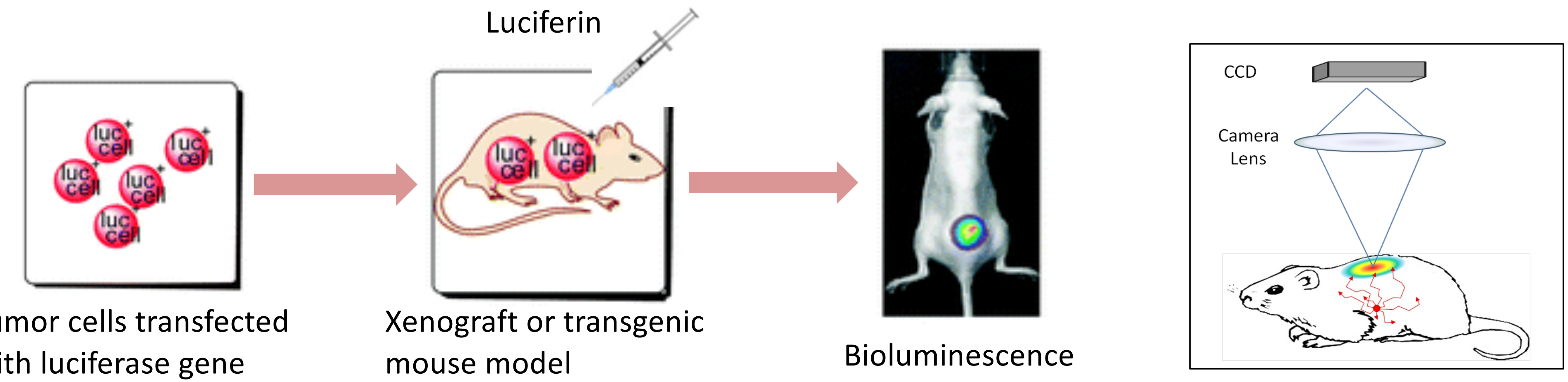
→ *Integrate bioluminescence (BL) imaging with small animal irradiator to improve in vivo localization*

Bioluminescence

- Cells(or bacteria/virus) are engineered with Luciferase (Luc) gene, and grow them in animals.
- After Luciferin is injected, bioluminescence from the cells is emitted.
- High sensitivity and specificity imaging.
- One popular BL reporter is firefly luciferase emitting at 450 – 700 nm.

Substrate | BL reporter

$$ATP + Luciferin + O_2 \xrightarrow{\text{Luciferase}} Oxyluciferin + AMP + CO_2 + \text{Light}$$

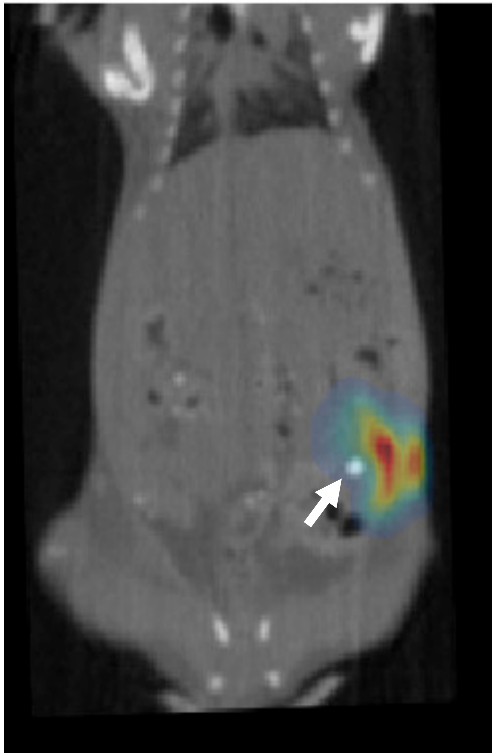


Tumor cells transfected with luciferase gene

Xenograft or transgenic mouse model

Bioluminescence

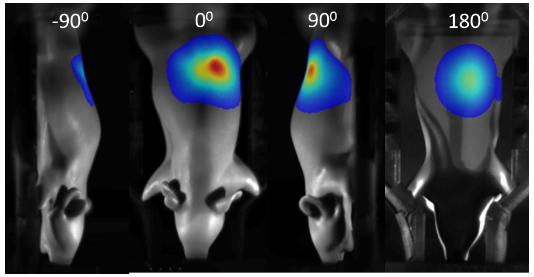
The need for 3D BL tomography (BLT) - localization



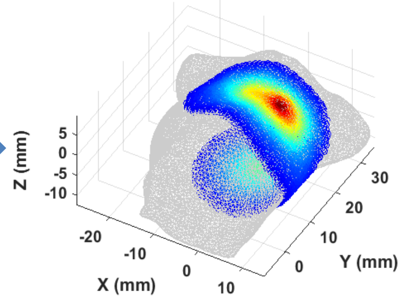
- 2D surface BL image (BLI) is a function of the optical path from the light source position and can be confounding for an irregularly shaped animal.
- 2D BLI is **inadequate** to support accurate radiation guidance
- 3D target shape is fundamental need for conformal irradiation.
  - Goal: Retrieve 3D target distribution using BLT

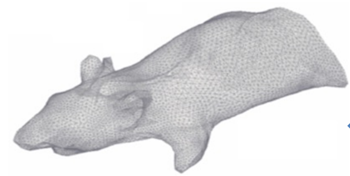
Workflow of Quantitative BLT(QBLT)-guided RT

**Multi-spectral and –
projection imaging**

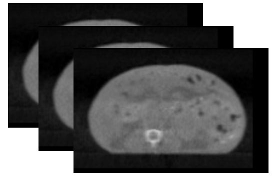


Data mapping





**3D mesh
generation**



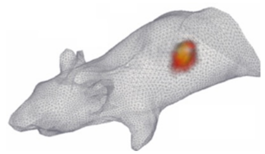
**SARRP
CBCT**

BLT algorithm

1. Diffusion equation
2. Optimization algorithm

**BLT
reconstruction**

1. Optical properties
   (Absorption & Scattering)
2. Cell Spectrum
3. In vivo signal dynamic



Quantitative volumetric-guided RT

**irradiation
(Margin, TPS)**

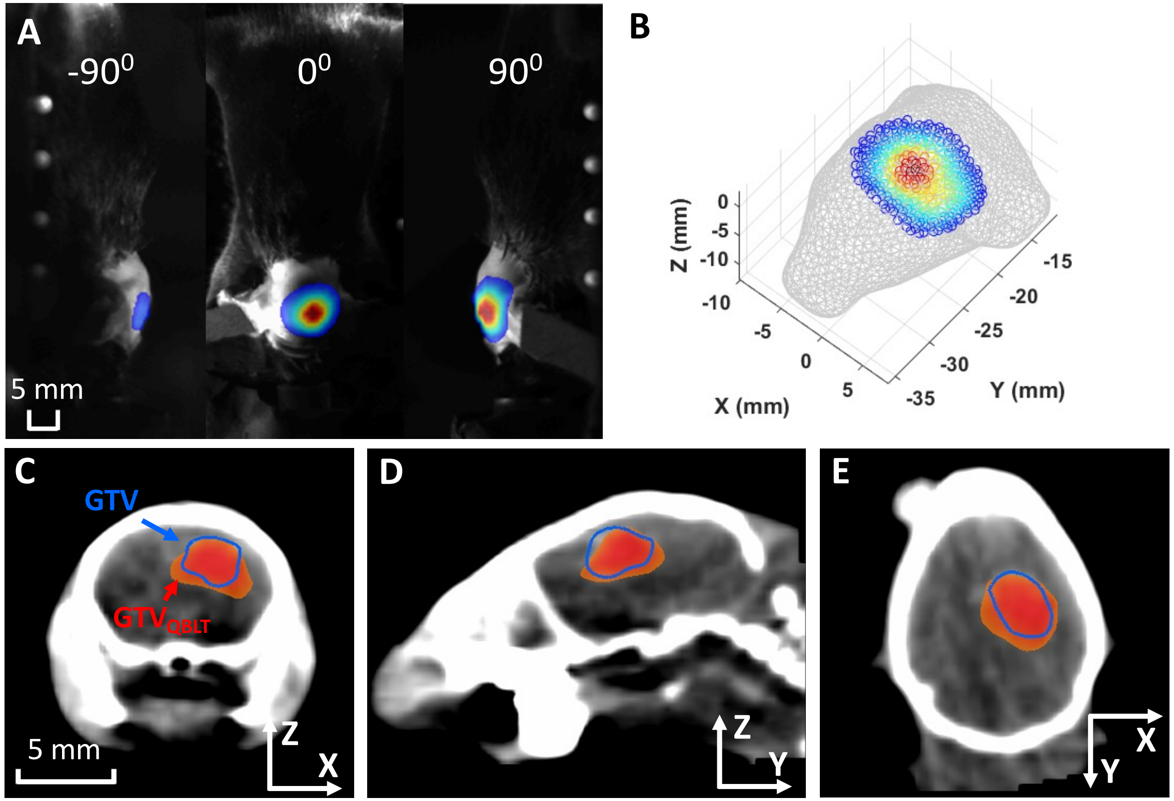
In vivo QBLT validation with GBM model

- GL261-*Luc2*, 2nd week after cell implantation

GTV: gross target volume

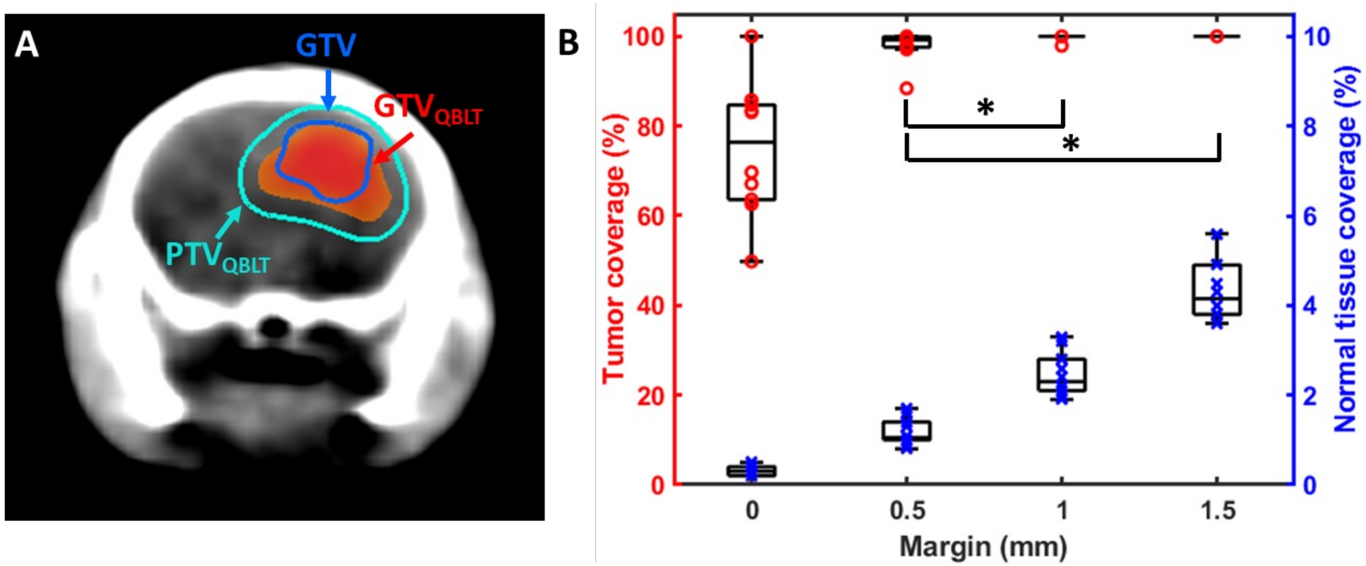
GTV: contrast labelled GBM

GTV_{QBLT}: BLT reconstructed GBM volume



○ BLT qualitatively retrieved the in vivo GBM shape.

Margin to account for uncertainties

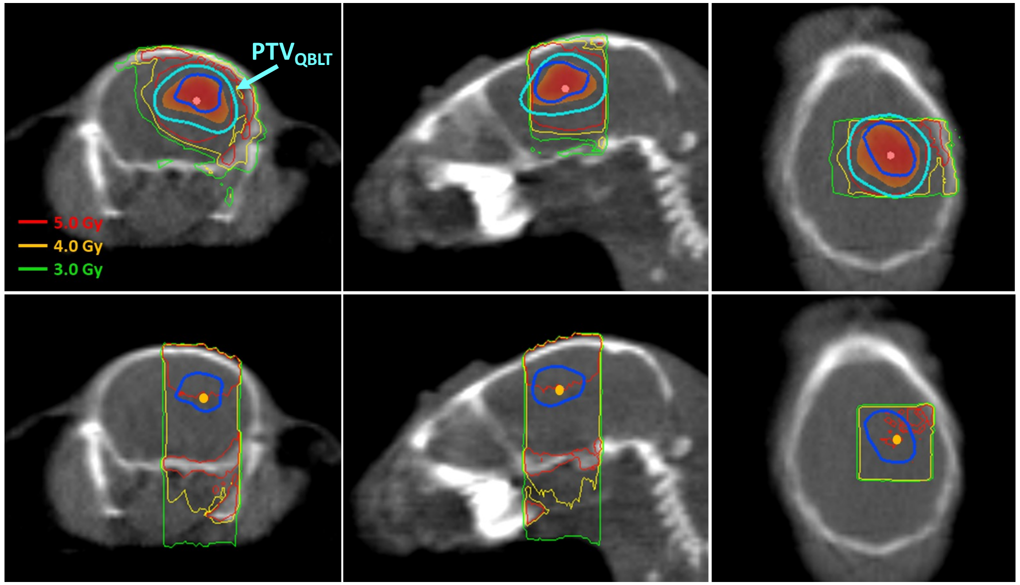


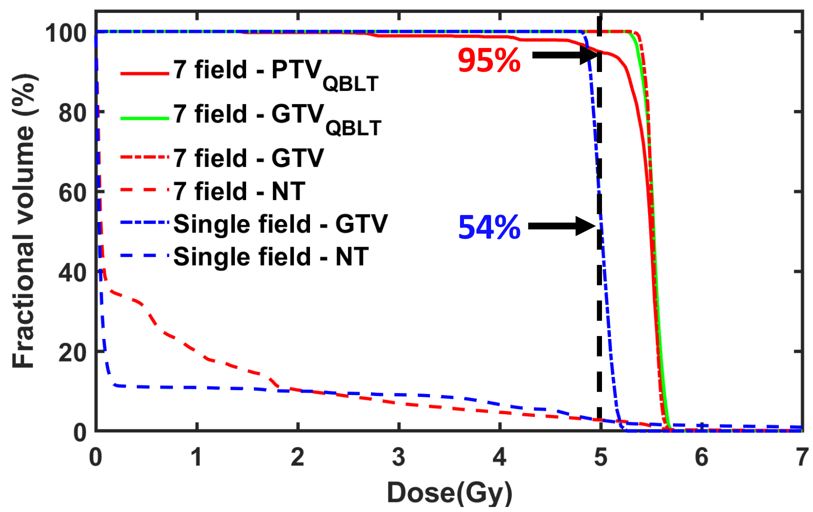
- Ave. CoM deviation (n = 10) between GTV and GTV$_{QBLT}$ is 0.62 ± 0.16 mm.
- Considering the uncertainty of GTV$_{QBLT}$ in target positioning and volume delineation, we add a margin for radiation guidance.
- The margin size was determined by tumor and normal tissue coverage. For our data cohort, 0.5-mm margin allows PTV$_{QBLT}$ covering 97.9 ± 3.5% GTV and 1.2 ± 0.3% normal tissue.

QBLT-guided irradiation vs. conventional single field

QBLT-guided
7-field RT

Single field



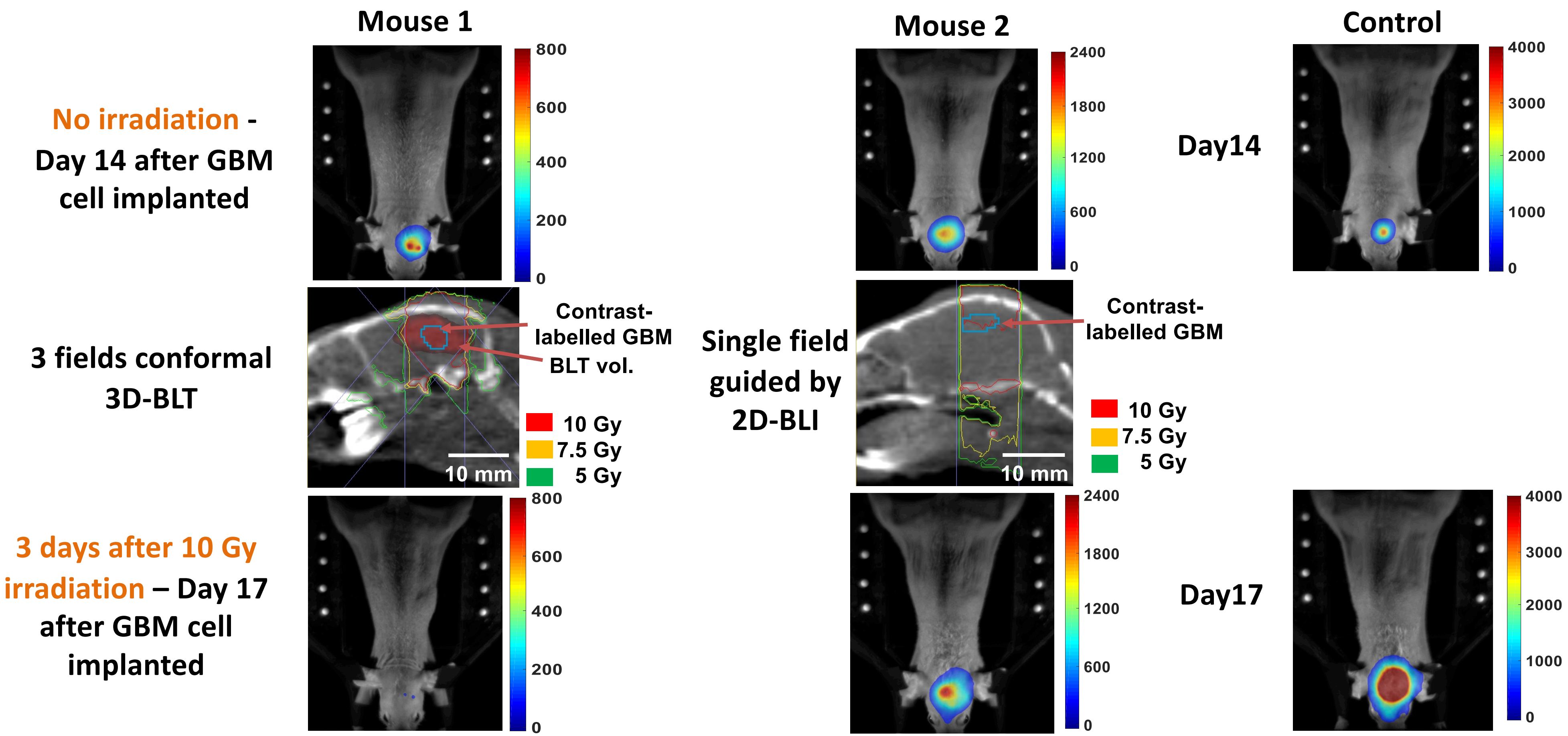


Single field: Dose prescribed at 3 mm depth (yellow dot) from surgical opening where cells were implanted.

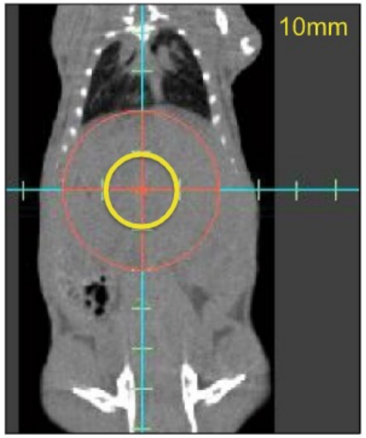
- Significant underdose is shown in the single-field irradiation at prescribed dose (5Gy).
- QBLT-guided irradiation allows clinic similar delivery and largely improves GTV coverage.

NIH R01 CA240811

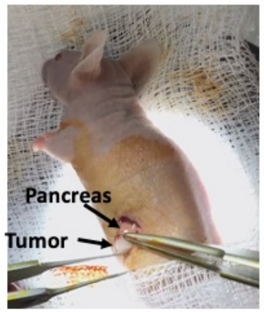
Treatment response by 2D vs. 3D-guided RT



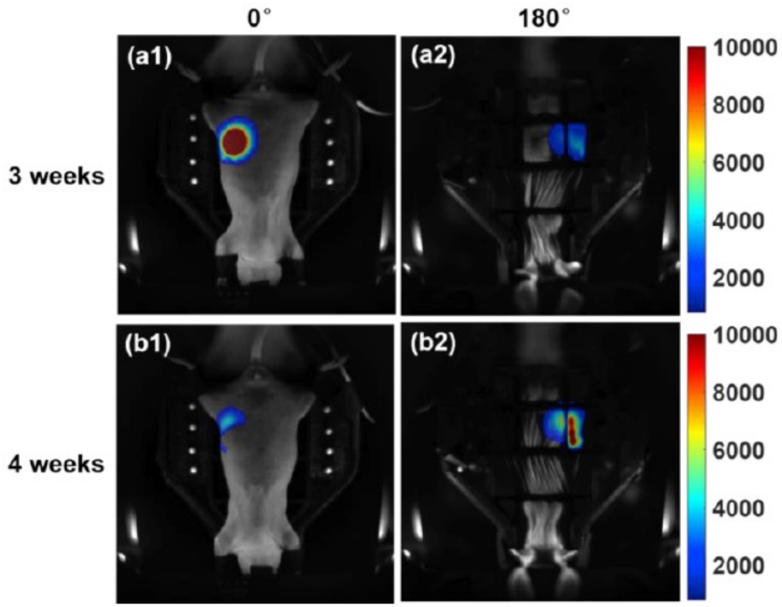
The challenge to localize movable tumor - pancreas



10 mm collimator
Spontaneous pancreatic tumor



Orthotopic
pancreatic tumor



- Abdominal tumor, i.e. pancreatic tumor, not only suffers low CBCT contrast but also motion.
- Challenging for fractionation study
- Large collimator is unavoidable to irradiate tumor but sacrifice organ at risk.
- Commercial single projection BLI system can confound longitudinal studies.

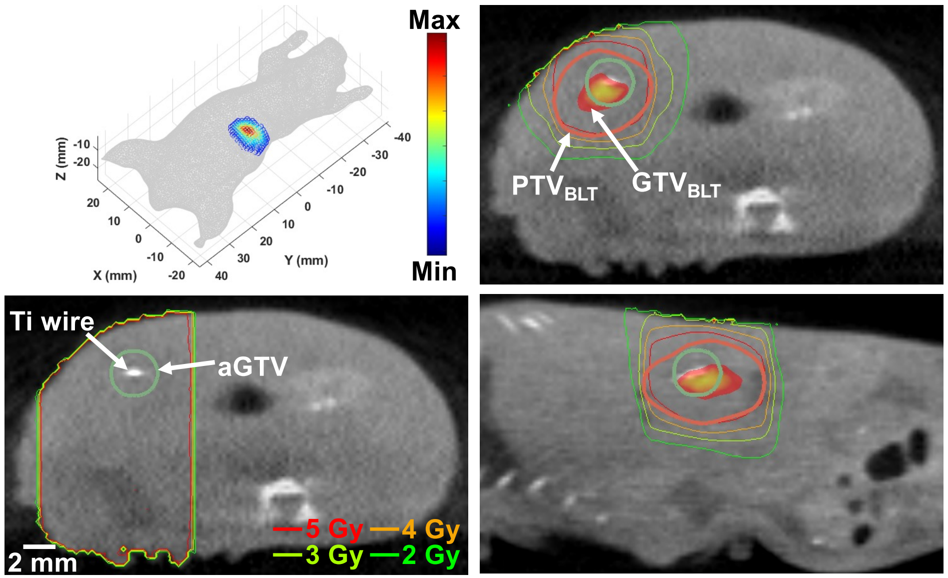
Molkentine et al. Sci. Rep. 9, 1949, 2019

Deng et al. Proc. of SPIE 1122409, 2020

Multi-projection BLT for orthotopic pancreatic tumor model

2D BLI mapped to mouse mesh

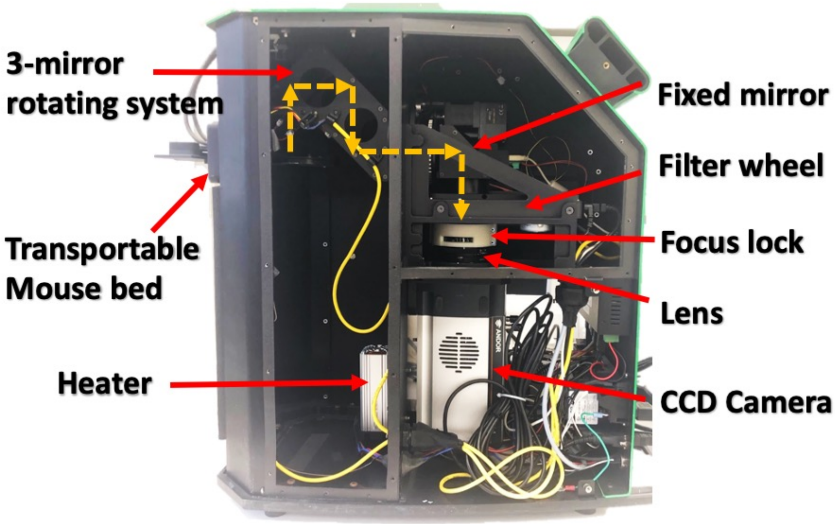
AP – PA 10 mm collimation with max BLI point for beam positioning

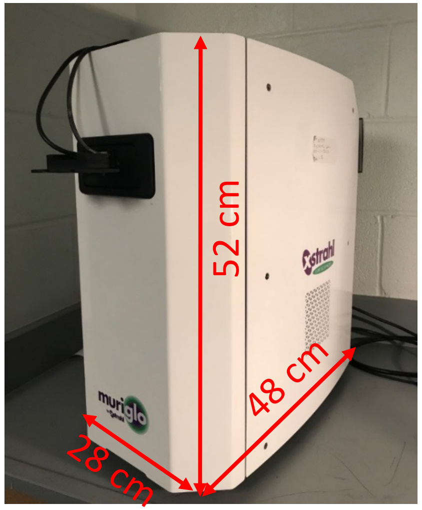


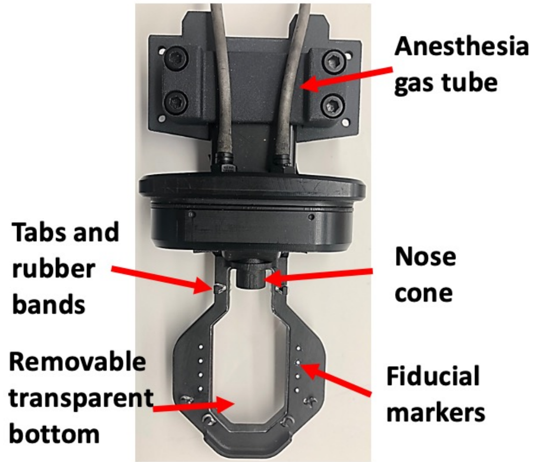
- BLT-guided conformal irradiation.
- 1.5 mm margin applied to GTV$_{BLT.}$
- Non-coplanar 6-arc conformal plan. 5 Gy was prescribed to cover 95% of PTV$_{BLT.}$

- Tumor is in size of 3 mm in diameter for the implantation, and Ti wire is placed inside the tumor/approximated GTV (aGTV).
- The center of mass (CoM) between the BLT volume and the wire is 1.0 mm.
- The high-dose isodose curves are conformally constrained around the PTV$_{BLT}$, largely reducing dose to normal tissue compared to conventional APPA irradiation.

Academic-industrial partnership- BLT MuriGlo







- AIP translates our know-how to industrial partner to disseminate our development to society.
- Mirror system + transparent bed design allows 360^0 projection
- The bed is transportable and compatible with SARRP and SmART irradiators to integrate the BLT-guided system.

Summary

- Quantitative bioluminescence tomography (QBLT) provides a new imaging capability to define targets for high precision conformal irradiation and support study reproducibility.

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