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

SAM multi-disciplinary scientific symposium
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)
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.
• (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
A robust, user-friendly mouse phantom was constructed from high-impact polystyrene.

- Dimensions similar to 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

Calculated dose  
Measured film dose

Med. Phys. 46, 12, 5733
Med. Phys. 46, 12, 5703
Small animal irradiator (PXI X-RAD 225Cx)

Integrated PET/CT/RT (Dr. Yiping Shao)

Image FOV: 8cm & 3.5cm
Light weight: 6.5 kg

PET phantom image

1.35
1.7
2.0
2.4

PET
X-ray tube
X-ray detector

Scintillator array

Linear stage
moving bed

A PET detector panel

Cardiac imaging

Tumor
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
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.

R01CA262097 – Academic industrial partnership

FLASH radiation therapy: the road to translation

John Wong
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▪ 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 and dose
• 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

- 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

Same concerns for protons
• 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 mm² field, and for depth dose over central 10 mm.
- No need for shutter
FLASH Cabinet System

Dimensions:
- Width: 680 mm
- Depth: 912 mm
- Height: 1780 mm

Isocenter:
- Isocenter is located within the cabinet system.
Dosimetry of a Prototype Single FLASH X-Ray Tube

Devin Miles, PhD

Film Measurements in Water Phantom:

Dose rate at 46 mm from focal spot: $81.10 \pm 4.97$ Gy/s

The area of field used for animal irradiation
Skin Toxicity Study: X-ray FLASH Effects

FLASH 33 Gy  Conv 33 Gy

Score = 0  Score = 1  Score = 2
Score = 3  Score = 4  Score = 5
Score = 6

Skin scoring:
- Normal
- Hair loss in < 50% of treated area
- Hair loss in > 50% of treated area
- Erythema in < 50% of treated area
- Erythema in > 50% of treated area
- Ulceration in < 50% of treated area
- Ulceration in > 50% of treated area

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 to 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.

![Bioluminescence Diagram](image)

- **Substrate**: ATP + Luciferin + O₂
- **BL reporter**: Luciferase
- **Oxyluciferin + AMP + CO₂ + Light**
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

BLT algorithm
1. Diffusion equation
2. Optimization algorithm

Data mapping

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

3D mesh generation

Quantitative volumetric-guided RT

irradiation (Margin, TPS)
In vivo QBLT validation with GBM model

- GL261-Luc2, 2\textsuperscript{nd} week after cell implantation

GTV: gross target volume

GTV\textsubscript{contrast labelled GBM}

GTV\textsubscript{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\textsubscript{QBLT} is 0.62 ± 0.16 mm.
- Considering the uncertainty of GTV\textsubscript{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\textsubscript{QBLT} covering 97.9 ± 3.5% GTV and 1.2 ± 0.3% normal tissue.
QBLT-guided irradiation vs. conventional single field

- 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.

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

- **Mouse 1**
  - No irradiation - Day 14 after GBM cell implanted
  - 3 fields conformal 3D-BLT
  - 3 days after 10 Gy irradiation – Day 17 after GBM cell implanted

- **Mouse 2**
  - Single field guided by 2D-BLI

- **Control**
  - Day 14
  - Day 17
The challenge to localize movable tumor - pancreas

- 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

- BLT-guided conformal irradiation.
- 1.5 mm margin applied to GTVBLT.
- Non-coplanar 6-arc conformal plan. 5 Gy was prescribed to cover 95% of PTVBLT.

- 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 PTVBLT, 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° projection
- The bed is transportable and compatible with SARRP and SmART irradiators to integrate the BLT-guided system.
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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