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An Integrated Robotic-Based Irradiation System for Small Animal Research

Eduardo G. Moros Ph.D.,Sunil Sharma Ph.D.,
Peter M. Corry Ph.D., Ming Chao Ph.D.,
Robert Griffin Ph.D., Ivaylo Mihaylov Ph.D.,
and Jose Penagaricano M.D.

Department of Radiation Oncology

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Learning Objectives

- Challenges of developing a high precision 3D conformal irradiator for small animals in the academic laboratory setting.
- Main hardware components of the system and their integration.
- Advantages of using a 6DOF robot for imaging (motion) and beam delivery (positioning).
- Potential research projects that such a system can make possible.

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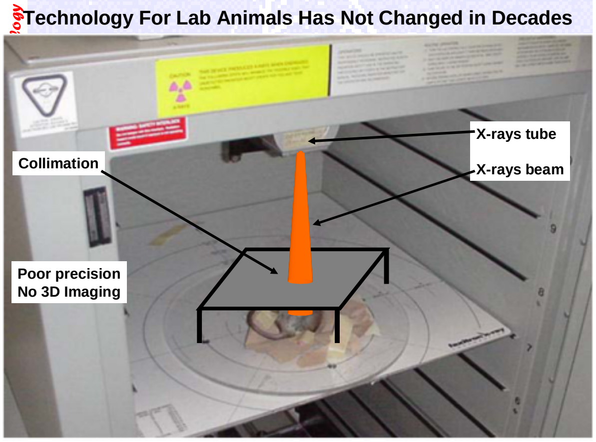
Technology For Lab Animals Has Not Changed in Decades



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A Few Reasons for Advanced Small Animal Irradiation Systems

- Clinical technology has advanced significantly while radiation delivery devices for laboratory animals have remained stagnant.
- Small animal imaging technologies have also made great strides in the last decade (microCT, microPET, microMRI, molecular imaging, etc.).
- New research frontiers will be possible if we are able to deliver doses to small animals with the same or better degree of precision we do in the clinic.
- Advanced small animal irradiation systems are key to the advancement of biological, functional, molecular, nanoparticle-based, etc., imaging / therapy techniques.

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THE X-RAYS SOURCE:

GEIT TITAN ISOVOLT 225 M2 (industrial grade)

- Up to 225 kV and 13 mA
- Cu and/or Al filtration
- Small focus: 0.4 mm, 640 W
- Large focus: 3.0 mm, 3000 W
- Inherent filtration: 1 mm Beryllium window.
- Emergent beam angle 40^0

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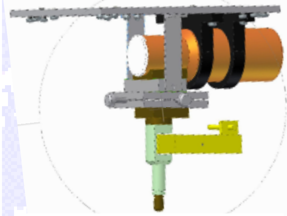
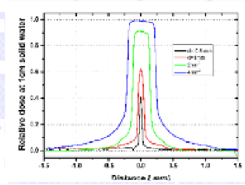
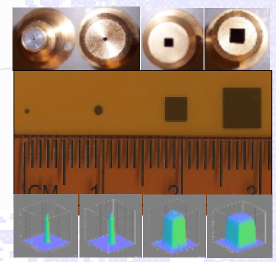
BEAM COLLIMATION







Cone tips and beam profiles for 0.5 mm,1 mm, 2x2 mm and 4X4 mm collimators at isocenter.

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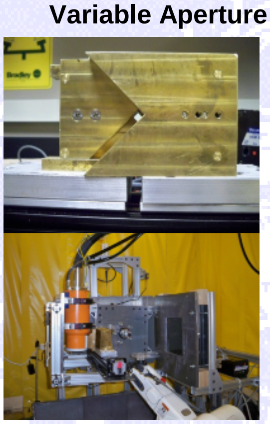
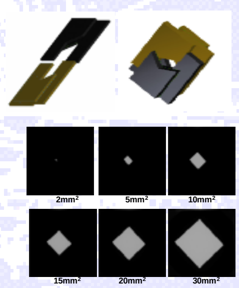
Variable Aperture Collimation System





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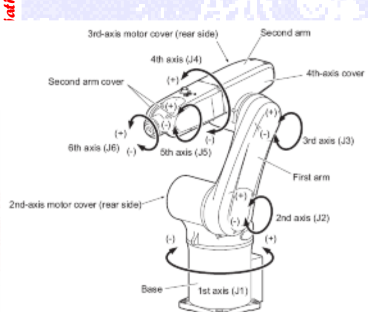
6DOF ROBOTIC ARM



Robot Specifications	
Reach	653 mm
Payload	2.5 kg (rated)
Joint Range	
Joint 1	±170°
Joint 2	+45°, -190°
Joint 3	+256°, -29°
Joint 4	±190°
Joint 5	±120°
Joint 6	±360°
Inertia Moment (max)	
Joint 4	0.295 kgm²
Joint 5	0.295 kgm²
Joint 6	0.045 kgm²
Composite Speed (max)	8,200 mm/sec
Joint Speeds	
Joint 1	375°/sec
Joint 2	300°/sec
Joint 3	370°/sec
Joint 4	410°/sec
Joint 5	410°/sec
Joint 6	660°/sec
Repeatability (XYZ)	±0.020 mm

Adept Viper s850

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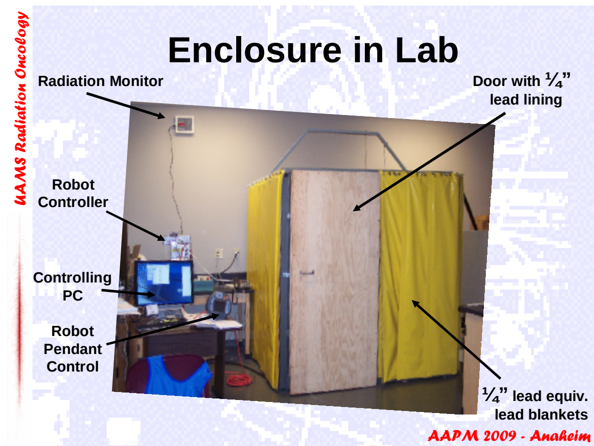
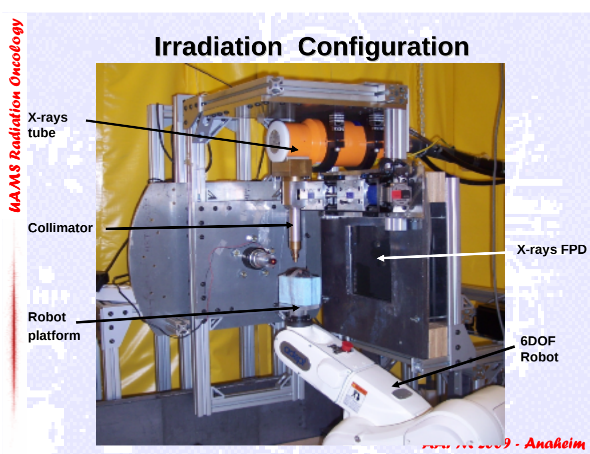
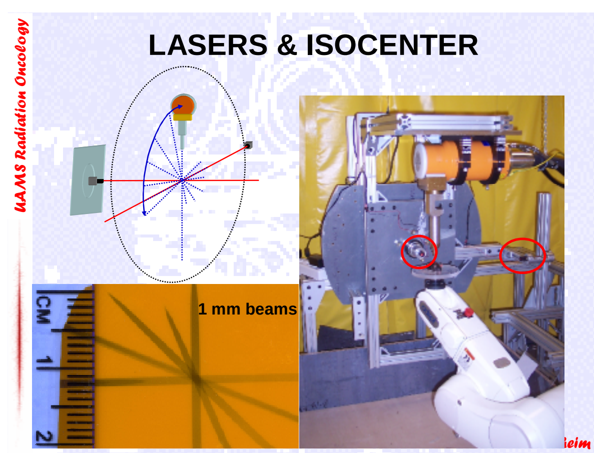
Sensor:	
Total pixel number	1024x1024
Active pixel number	1000x1000
Pitch	200 µm
Total area	204.8x204.8mm²
Diode capacity	2.1 pF
Dark current	<1 pA/Pixel
Detector:	
Protection Class	- protection class II
Dynamic range	> 80 dB
Response Non-Uniformity	< +/- 2% (10 % to 90 % of FSR)
Image lag	< 8 % (1st frame)
Maximum frame rate	7.5 fps @ 200µm 15 fps @ 400µm (2x2 Binning)
Scintillator	CsI (Tl), needles directly deposited on the aSi photodiodes
Radiation energy	25 keV – 225 keV







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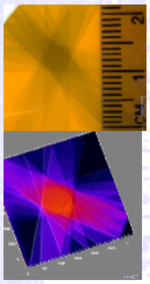
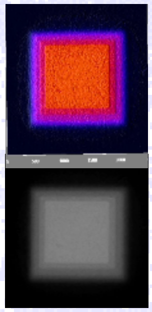
Alignment of 4 x 4 mm Beams & Robot Motion



Alignment of X-rays collimator (beam) with respect to isocenter for several gantry angles.



Film exposed at Isocenter, and at 5 and 10 cm beyond.

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Dosimetry and Film calibration

X-rays tube (0.5 mm inherent copper filter) operated at 225 kV 13 mA with larger focus (3 mm), field size of 20 x 20 cm²

In air dose, at isocenter (32.5 cm), and at 1 cm and 2 cm solid water beyond isocenter using TG-61 protocol using Gafchromic film

In air	
At isocenter	**3.94 Gy/min**
Solid water	
1 cm	**2.921 Gy/min**
2 cm	**2.626 Gy/min**

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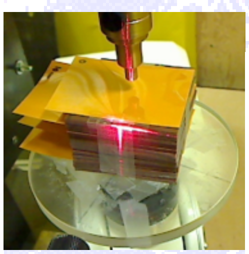
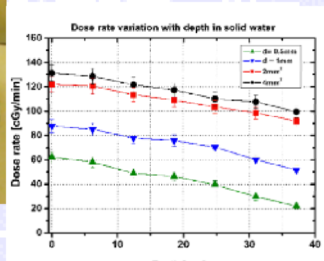
Dose rate at 1 cm solid water at SSD of 32.5 cm

4 mm²	125 cGy/min
2 mm²	116 cGy/min
d = 1 mm	81 cGy/min
d = 0.5 mm	51 cGy/min





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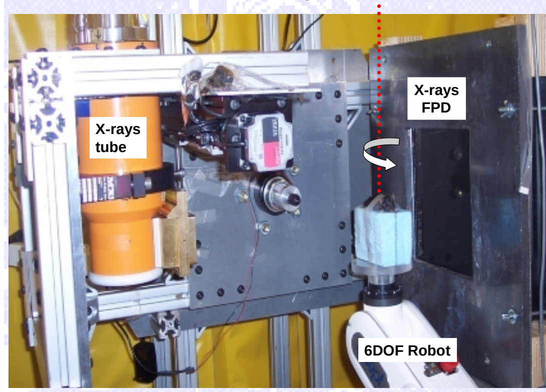
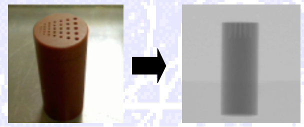
CBCT Configuration



Raw Radiograph Image Acquisition

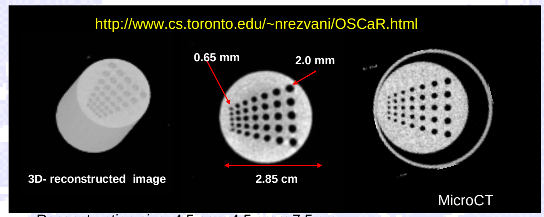
- Sequential images for CBCT reconstruction can be acquired in either continuous mode or stop-and-capture mode.
- 360 projection images are acquired in ~ 50 seconds.
- 1024 x 1024 pixels, 16 bit gray images are acquired at a rate of 7.5 fps.

CBCT Reconstruction of Phantom



-360 projections
-cropped and downsampled 301 × 301 pixels (400 μm)
-70 kV, 2 mA

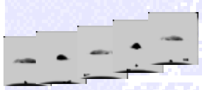
L = 7 cm; d = 2.86 cm



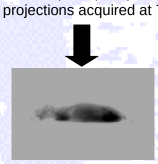
Reconstruction size: 4.5 cm× 4.5 cm × 7.5 cm
Resolution = 0.3 mm

CBCT Reconstruction of a Mouse

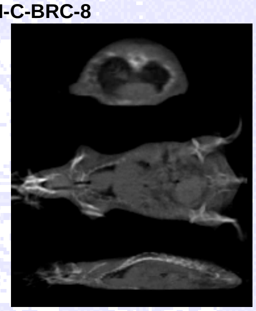
Session Number TH-C-BRC-8



1024 X1024 pixel (200 μm resolution)
360 projections acquired at 70 kV, 2 mA



Cropped and downsampled 401 X 251 pixel (400μm)



Reconstruction size: 9cm × 4.5cm × 3cm
Resolution = 0.3 mm

http://www.cs.toronto.edu/~nrezvani/OSCaR.html

APPLICATION:

Spatially Fractionated Radiation Therapy

(a.k.a. GRID Therapy, 100 y.o.)

- Radiation field is "GRIDDED"
- A large dose is given in one fraction
  - (Dmax ~10 times a typical normal fraction size)
- Originally used to spare skin reactions in the pre-megavoltage era
- Used as palliative treatment to debulk large tumors since 1990's
- UAMS: Dr. Penagaricano applying it with curative intent to H&N cancers: one 20 Gy (D_{max}) fx to GTV followed by conventional chemoradiotherapy.
- **See paper in IJROBP**

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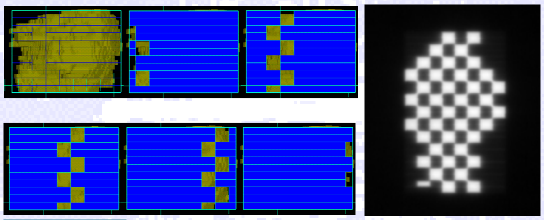
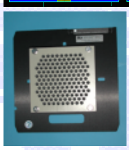
Typical MLC segments used for GRID treatment of GTV





GRID Block for large GTVs

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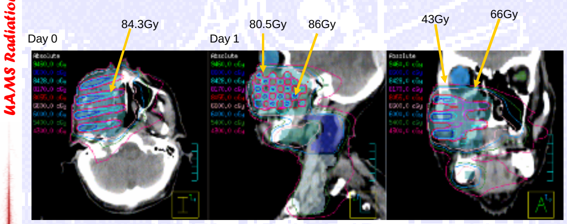
GRID + IMRT Isodose Distribution



SQCC maxillary sinus
T4N2bM0

IMRT:

- 9 coplanar equi-distant beams.
- SIB: 66, 60, 54Gy.
- Concomitant chemotherapy (on day 0).

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We know little about how GRID Therapy works

A pilot proposal for animal studies

Specific Aim 1: Determine optimal GRID pattern for radiation-induced tumor growth delay with acceptable normal tissue consequences.

Specific Aim 2: Assess the effects of GRID therapy on tumor vasculature and determine the level of treatment synergy afforded by anti-angiogenic therapy combined with GRID.

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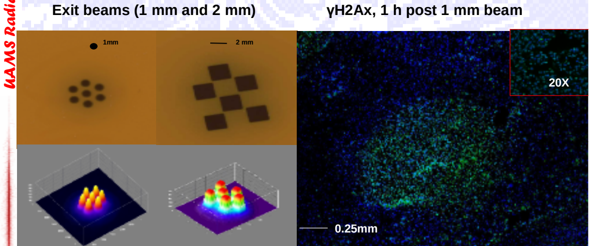
GRID of Implanted Tumor on Mouse using 1 mm X-ray beams

Exit beams (1 mm and 2 mm) **γH2Ax, 1 h post 1 mm beam**



Exit patterns recorded at isocenter (32.5 cm from source) 225 kV,13 mA, 10 Gy (4.2 min for at each location).

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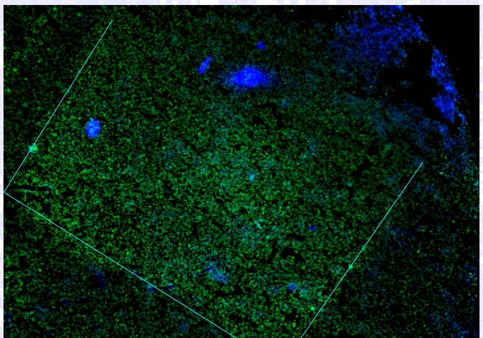
B16 melanoma
1 h post 2x2 mm 10 Gy GRID 10X



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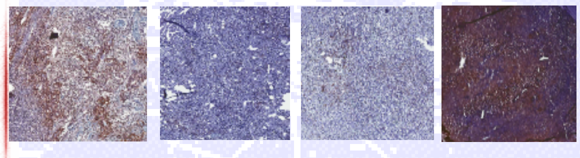
B16 melanoma hypoxia (brown) staining via pimonidazole injection after 10 Gy GRID

Control 1 h 3 h 24 h



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Summary of GRID Irradiation Study

Poster Display Number:SU-FF-J-160

- Tumors can be accurately irradiated with a variety of patterns
- Cellular kill by 10 Gy GRID significant; effect on subsequent fractionation to be determined
- γH2Ax foci localize to field, bystander foci variable and dynamic over time; oxygenation changes and role in subsequent fractionated RT to be determined
- Anti-angiogenic agents may exacerbate tumor effect of GRID suggesting importance of vascular response

Working hypothesis

GRID changes tumor physiology and cell viability to an extent significant enough to improve overall radiation response to subsequent standard fractionation

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RIHD

- Developing techniques for precise motion-gated partial irradiation of murine hearts

THANKS

UAMS — UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES: **Department of Radiation Oncology**

Arkansas Biosciences Institute: **Major Equipment**

CARTI: **Personnel & Supplies**

JOHNS HOPKINS MEDICINE: **Cone collimators**