UT Southwestern
Harold C. Simmons
Comprehensive Cancer Center
Department of Radiation Oncology

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Cancer Imaging and Therapy Behind the Barrier

Preclinical Imaging/Image-Guided Radiation Core Facility (PCIRCF)

DEPARTMENT OF RADIATION ONCOLOGY

Preclinical Imaging/Image-Guided Radiation Core Facility (PCIRCF)

Preclinical radiation research in cell or small animal models is a cornerstone for advancing our understanding of radiation therapy and its interactions with other treatment modalities. The PCIRCF, under the leadership of Debabrata Saha, Ph.D., and supported by the Cancer Prevention and Research Institute of Texas (CPRIT), addresses critical gaps in this domain. Key issues addressed by such facilities in preclinical radiation research include:

- **Radiation dosimetry and precision**: Ensuring reproducibility and reliability in dose delivery is vital for translating findings to clinical settings.
- **Biological response to radiation**: Understanding tissue-specific and cellular responses to radiation is essential.
- **Combination therapies**: Exploring how radiation interacts with chemotherapeutic agents, immunotherapy, or targeted molecular therapies.
- **Radiation-induced toxicity**: Studying potential toxic effects and off-target impacts, such as radiation-induced fibrosis or secondary cancer.
- **Translational challenges**: Bridging the gap between preclinical findings and human clinical trials.
- **Ethical and regulatory standards**: Upholding animal welfare standards and regulatory compliance while maximizing the scientific value of the research.

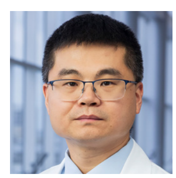
PCIRCF LEADERSHIP

Debabrata Saha, Ph.D.
Associate Professor and PCIRCF Core Director

- Radiation biology and cell signaling
- Combined modality with radiotherapy
- Preclinical study planning
- Animal modeling

Caroline Carter, M.S.
Research Associate

- Imaging and irradiator training
- Radiotherapy treatment planning
- Cell survival code
- Scheduling and machine maintenance



Kai Jiang, Ph.D.
Assistant Professor

- Dosimetry
- Treatment planning

Robert Timmerman, M.D.
Department Chair and Professor

Dr. Timmerman is renowned for pioneering stereotactic ablative radiotherapy (SAbR), which delivers precise, high-dose radiation to tumors, offering improved outcomes for patients with inoperable cancers.

Deepak Nijhawan, M.D., Ph.D.
Associate Professor; Chief, Section of Molecular Medicine; and Vice Chair of Research

Dr. Nijhawan's research focuses on uncovering the mechanisms of orphan compounds with anticancer activity, aiming to develop new cancer therapies. His work has led to patents, peer-reviewed publications, and novel drug development targets.

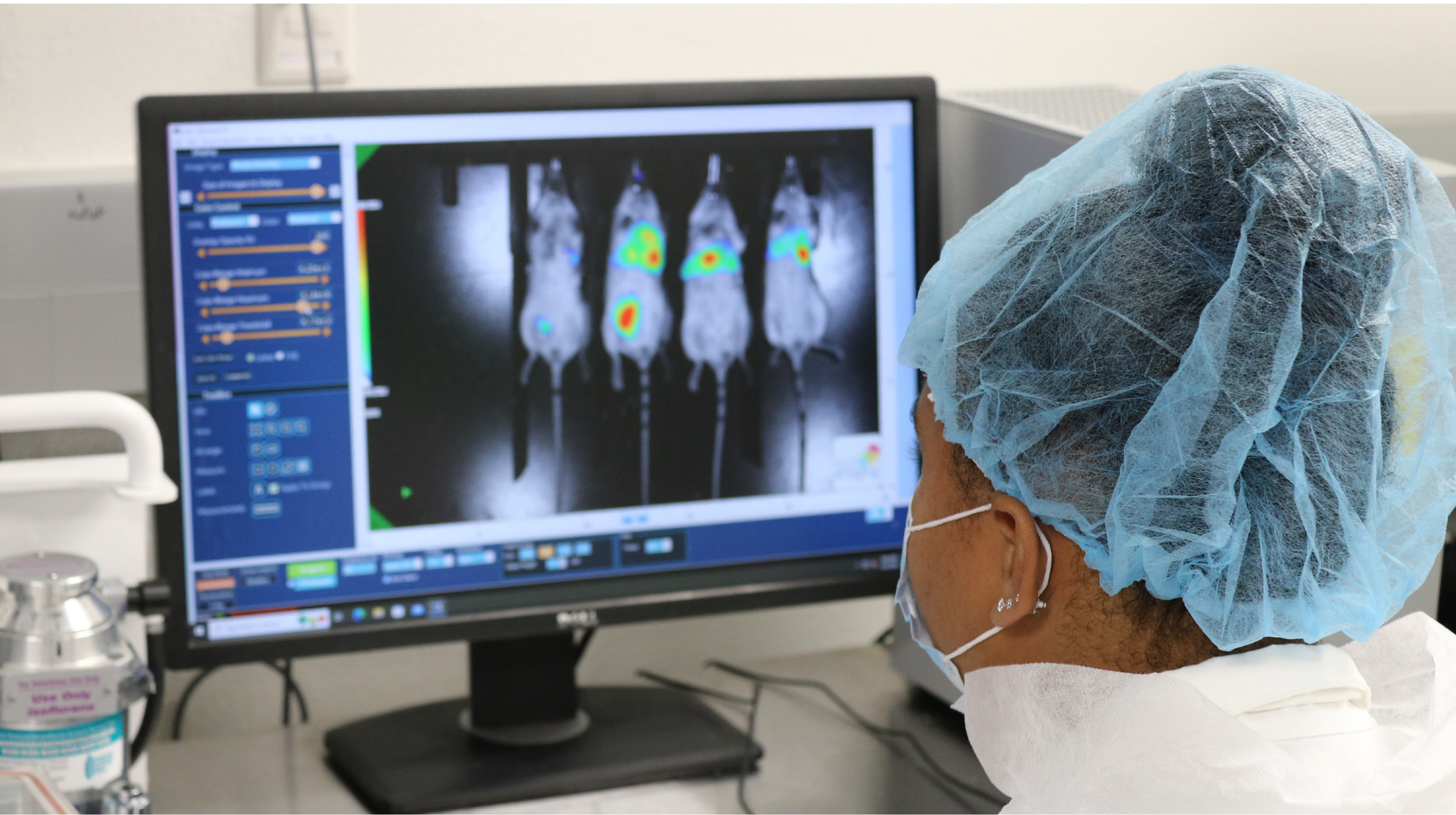
Advancing UT Southwestern as a Center of Excellence for Animal Irradiation Laboratory Practices

The mission of the PCIRCF is to ensure the precision and quality of preclinical radiation experiments, enabling the accurate communication of results. By promoting rigorous research practices and offering essential resources, the PCIRCF strives to elevate the quality and impact of preclinical radiation studies in advancing cancer therapies. To support this mission, the PCIRCF provides a comprehensive suite of resources, including:

- **Advanced equipment**: Access to cutting-edge irradiators and imaging technologies
- **Model systems**: Cell and animal models specifically developed for radiation research
- **Training and support**: Proper training on PCIRCF devices for investigators

Additionally, the following key responsibilities are essential for supporting safe and effective research and treatment practices in medical physics:

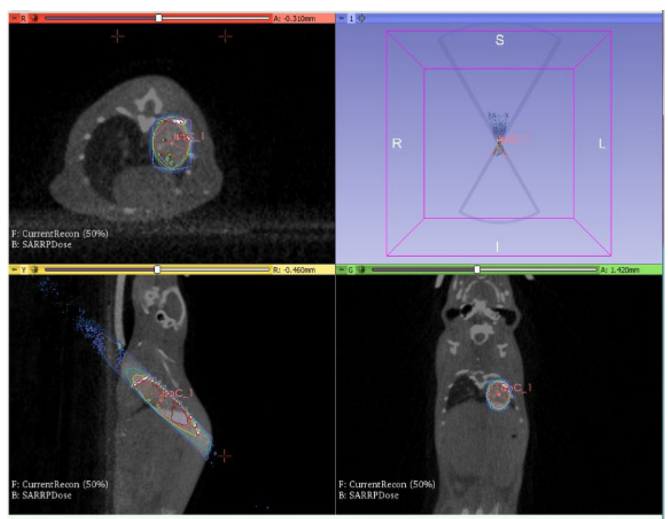
- **Medical physicists**: Ensure machines are calibrated accurately and that radiation doses are calculated correctly
- **Dosimetry plans**: Provide a complete description of dosimetry plans for experiments
- **Publication guidance**: Assist investigators in using appropriate terminology for research publications



Optimized Imaging and Treatment Planning with Close-Proximity MRI and Irradiator Integration

The **SARRP XStrahl irradiator** is an advanced tool used in molecular radiation biology to deliver controlled X-ray radiation to biological specimens. It offers several innovative features that enhance research capabilities, including:

- **4D gating**: Allows researchers to synchronize radiation delivery with the motion of the specimen, such as breathing in small animals. This precision minimizes damage to healthy tissues and improves the accuracy of radiation treatment, making it ideal for studying dynamic biological processes.
- **Cone-beam computed tomography (CBCT) imaging**: Provides high-resolution 3D images of the specimen before, during, and after irradiation. This capability enables researchers to visualize anatomical structures and assess radiation effects on tissues, facilitating more informed experimental planning and analysis.
- **MicroCT imaging**: Allows the irradiator to produce detailed, high-resolution images of small biological samples. It is particularly useful for examining the internal structures of small organisms and tissues at a microscopic level, allowing for in-depth analysis of radiation-induced changes.



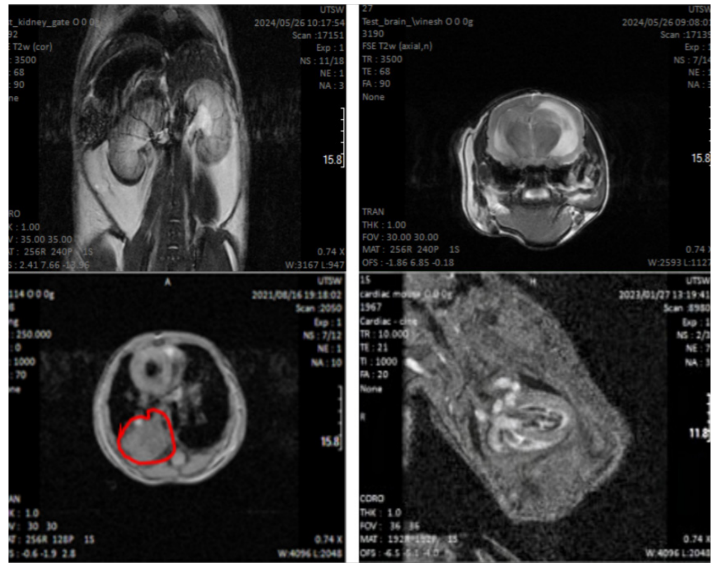
(left) The SARRP irradiator allows for 4D gating and high-resolution imaging for precise radiation studies on small specimens. Using a variable collimator offering a beam size of 2mm x 2mm minimum to 40mm x 80mm maximum, the system can target whole organs, xenografts, total body, or specific orthotropic tumors.

(above) SARRP treatment planning using a live mouse.

The **MRS 3017 3T MRI System** enables high-resolution imaging of target areas and fiducials, which are small markers used for precise localization. This imaging can be directly applied to create detailed phantom images for pre-treatment validation. Overall, close proximity between an MRI and an irradiator offers significant advantages, including:

- Streamlined workflows
- Facilitated accurate tumor localization
- More effective and personalized treatments

With an integrated setup, the treatment planning system can seamlessly load CBCT data, overlay it with MRI data, and conduct image registration to align fiducials accurately. This improves target identification and planning, as the MRI's soft tissue contrast enhances the precision of the treatment area.



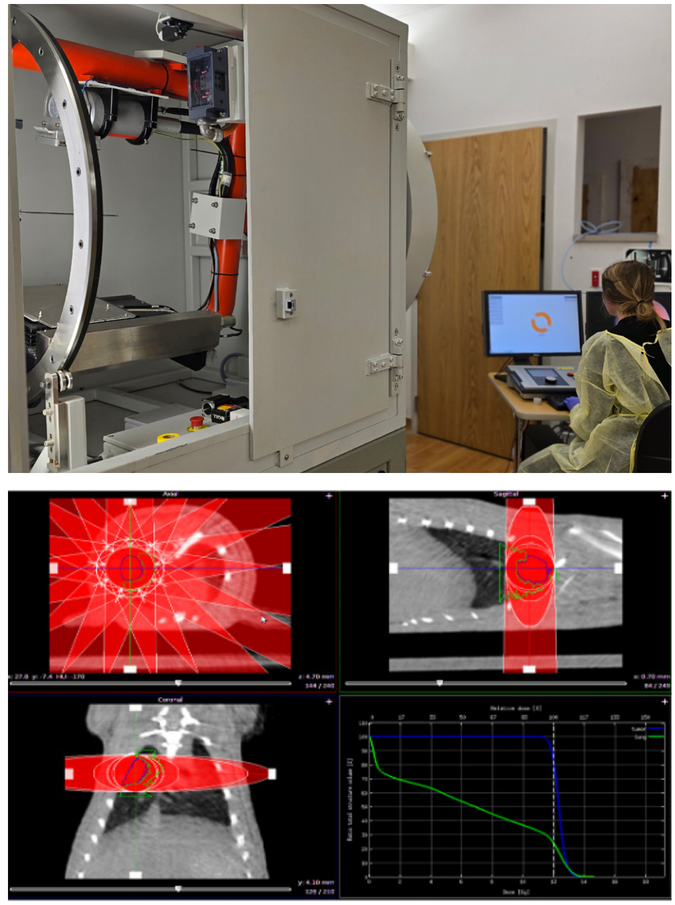
From left to right, top to bottom: T2w kidney, T2w brain, lung with tumor, and cardiac gating.

Both the SARRP XStrahl irradiator and the MRS 3T MRI System are within five feet of each other, enhancing precision of treatment.

Advancing Precision and Innovation in Preclinical Cancer Research

The **XRad 225Cx** is a high-precision preclinical radiation therapy system with advanced features that enhance its utility in molecular biology and cancer research. It offers high-resolution imaging through cone-beam CT, producing detailed 3D anatomical visualizations for accurate targeting. By simulating clinical radiotherapy workflows, including dose calculations and treatment delivery, it bridges the gap between preclinical studies and clinical applications.

The system ensures customizable dose delivery, allowing researchers to administer precise radiation doses, from single treatments to complex multi-fractionated regimens. Its exceptional targeting accuracy minimizes off-target effects by integrating imaging and planning, ensuring radiation is confined to intended sites. This system is instrumental in exploring key areas of cancer research, including:



The XRad 225Cx allows precise radiation delivery to small animals with the help of a cone-beam CT imaging system.

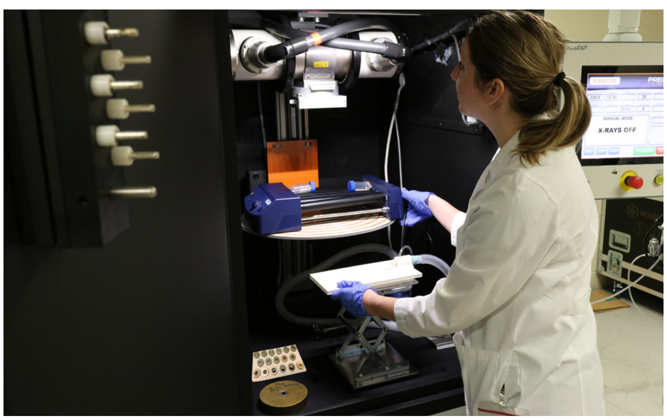
- **Organ-specific studies**: Particularly effective for studying radiation's effects on lung and prostate tissues, reflecting conditions like non-small cell lung cancer or prostate cancer.
- **Radiation sensitivity**: Facilitates experiments on how different tissues and cell types respond to varying radiation doses.
- **Therapeutic innovations**: Supports the testing and development of new radiosensitizers, radioprotectors, and adaptive radiotherapy techniques.

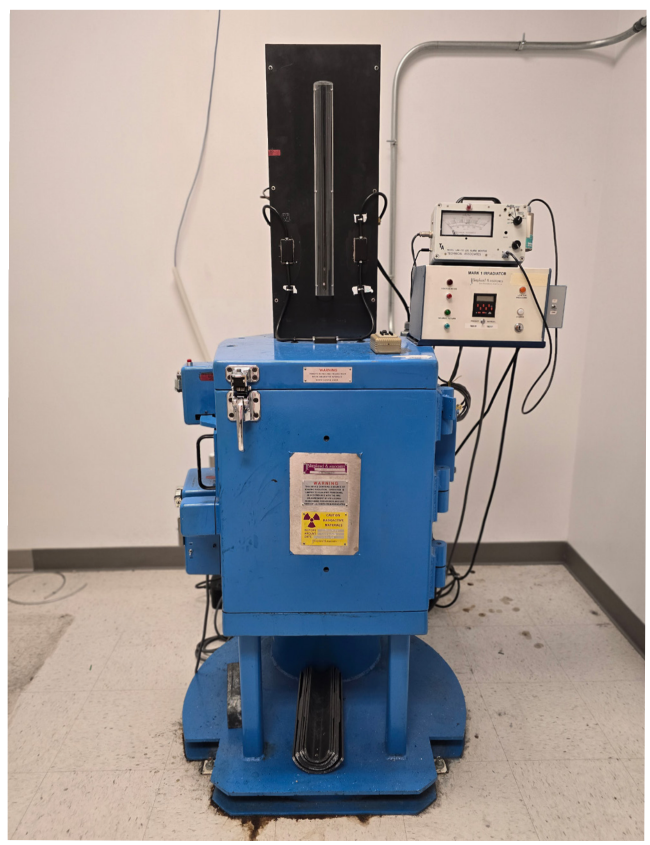
By enabling groundbreaking research on radiation-induced DNA damage, repair mechanisms, and tumor control in preclinical models, the XRad 225Cx significantly advances ultrapersonalized medicine, optimizes combination therapies, and enhances our understanding of radiation toxicity, contributing to more effective and tailored cancer treatments.

Precision for Cancer, Genetics, and Cellular Studies

The **XRad320 X-ray irradiator** delivers controlled doses of radiation to biological specimens, with the PCIRCF providing training, dosimetry services, and maintenance. Its adjustable dose rates and precision targeting are ideal for animal and cell studies. Under the Cesium Irradiator Replacement Project, the Department of Energy's Office of Radiological Security offers financial incentives for users transitioning from cesium-137 irradiators to non-radioisotopic options. The XRad320 is particularly suited for:

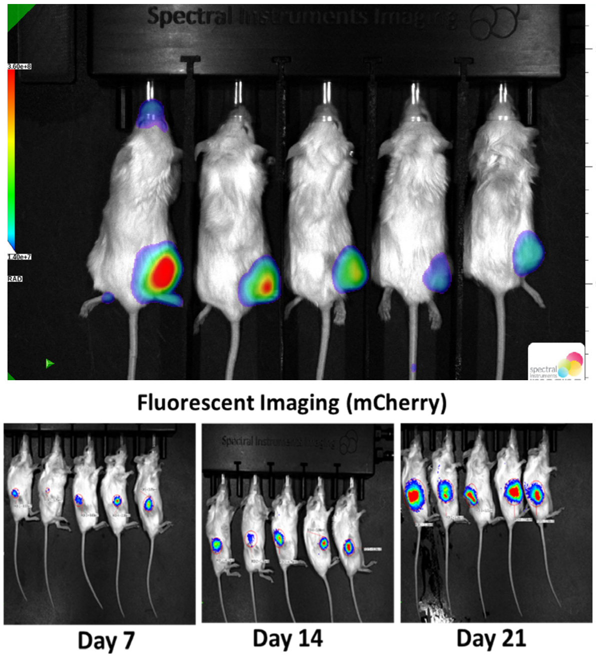
- **Mouse and rat total body and focal radiation**: Can perform whole-body irradiation of mice, making it valuable for studying radiation's effects on the entire organism, modeling radiation exposure scenarios, and researching cancer therapies.
- **Fly radiation**: Used to expose flies to X-rays, allowing researchers to study genetic mutations, developmental changes, and survival rates in response to radiation, often for genetic and aging studies.
- **Cell radiation**: Widely used to irradiate cell cultures, facilitating studies on DNA damage, repair mechanisms, cell death, and cellular responses to ionizing radiation.





(left) The XRad320 X-ray irradiator delivers precise dose to specimens and allows for quick changes between total body radiation and focal radiation treatment. (right) Additionally, cesium-137 is available for low-dose application for cell imaging.

Powering Precision: Advancing Radiation Treatment with Imaging Systems



The **Ami HTX Optical Imaging System** is designed for non-invasive in vivo imaging of small animals, primarily mice. This system supports various imaging modalities that enable the monitoring of biological processes and disease progression at the molecular level. It also aids in visualizing how cells respond to radiation at the molecular level, tracking DNA repair mechanisms, and assessing the effectiveness of radiation therapies by monitoring tumor response in real time. Key features of this imaging system include:

- Bioluminescent imaging
- Fluorescent imaging
- Near-infrared imaging
- X-ray imaging
- Five mice platform

Alongside a small animal PET/CT, this dual system enables the assessment of tumor growth, tracking radiolabeled biomarkers for DNA repair and hypoxia, understanding tissue responses to radiation, aiding in personalized therapy development, and exploring radiation resistance.

The Ami HTX Optical Imaging System offers real-time, non-invasive imaging of tumor response and molecular processes in small animals.

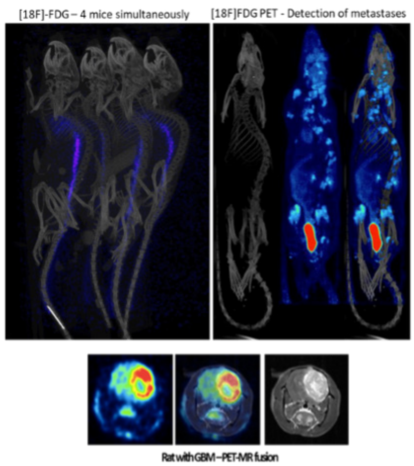
The CT/PET workstation and radioisotope area allow for precise imaging and tracer handling for monitoring disease and treatment.

The **small animal PET/CT system** integrates positron emission tomography (PET) and computed tomography (CT) for detailed functional and anatomical imaging, allowing precise localization and quantification of molecular processes in small animals. PET detects gamma rays from radiotracers, providing insights into metabolic activity, cell proliferation, and receptor density, while CT offers high-resolution anatomical context.

The following components provide this system with enhanced imaging and research:

- **CT/PET workstation:** Provides high-resolution imaging of small animals, enabling detailed molecular and anatomical analysis to track disease progression and treatment effects while integrating PET and CT data for enhanced accuracy.
- **Animal prep station**: Prepares small animals for imaging procedures, ensures proper handling and safety protocols for radioactive tracers, and allows controlled injection of radioisotopes for PET scans.
- **Radioisotope working area**: Provides a dedicated space for handling and preparing radioactive tracers, ensures the safe use of radioisotopes for imaging biological processes, and facilitates the precise application of tracers to monitor tumor activity and treatment response.

High-Resolution Imaging for Accurate Preclinical Research



(left) With the mouse hotel, images can be combined with MRI for treatment accuracy; image reconstruction is at 200µm. (right) Bone density scan reconstructed at 50µm.

Our **CT/PET systems** offer simplicity, speed, and high-resolution imagery. 3D reconstruction levels of 200, 100, 50, and 20µm ensure precise imaging. The mouse hotel is able to image up to four mice simultaneously using both CT and PET. Common modalities include:

- Lung, kidney, and neuro metastasis
- Cardiac gating
- Osteo fracture and remodeling
- Pharmacokinetic and therapeutic efficiency

Mapping Metabolic Shifts: Uncovering Cellular Vulnerabilities in Radiation Therapy

The **XFe24 Seahorse Extracellular Flux Analyzer** measures oxygen consumption and extracellular acidification rates, providing insights into cellular metabolism like mitochondrial respiration and glycolysis. Radiation exposure induces metabolic changes that affect cell survival and therapy response. Using the XFe24, researchers can track shifts in metabolic pathways, identify biomarkers, and target metabolic vulnerabilities to enhance radiotherapy effectiveness while reducing damage to healthy tissue.

The **Seahorse Prep Station** standardizes cell preparation for the XFe24, automating steps like cell plating and media changes. This ensures consistent and accurate measurements of metabolic parameters which is essential for studies on cellular responses to treatments like radiation.

The XFe24 allows for measuring cellular metabolism changes for optimized radiation therapy.

Radiation Dosimetry: Routine Quality Assurance Measurements

Figure 1: The configurations used for dose measurements include: **a**) in-air calibration setup, **b**) solid water phantom, **c**) small water box phantom, **d**) silicon rubber mouse phantom, **e**) silicon rubber rat phantom, and **f**) mouse pie cage. The fully opened collimator, with a max irradiation field of 26.4 x 26.4 cm², is projected on to the steel plate at a focal spot distance of 65 cm. ***Figure 2***: The collimation system includes: **a**) collimator inserts, **b**) an insert holder, **c**) a bracket in which the holder is installed, and **d**) an illustration of collimation mechanism. The nominal diameter of the inserts: 1, 2, 3.5, 5, 7.5, and 10 mm. The holder alone can also be used as a 20 mm collimator.

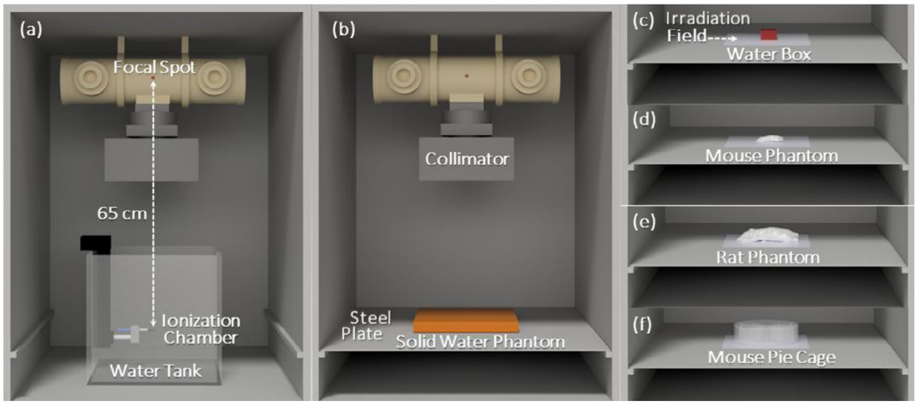


Figure 1

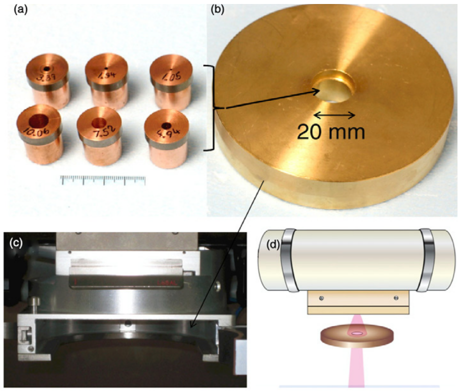


Figure 2

Consulting with Collaboration

The consulting service offers a collaborative approach to research and experimentation across various institutions, including academic partners like UT Arlington, UT Dallas, and the University of North Texas (UNT), as well as commercial entities. Each institution brings a unique specialization to the table: UT Arlington focuses on drug delivery and radiation research, UT Dallas is known for its work in photodynamic therapy, and UNT specializes in lung biochip technology. On the commercial side, Vaxdome, based in Denton, Texas, specializes in virus radiation, and Colossal Laboratories and Biosciences offers cutting-edge research capabilities.

The Core facility provides comprehensive support to collaborators, including the ability to conduct animal experiments for those outside of UT Southwestern. In addition, the Core assists in the development of animal protocols for external collaborators, ensuring that all necessary guidelines and procedures are met. Researchers from other UT system schools, such as UT Arlington, UT Dallas, and UNT, are granted access to the UTSW animal facility once they have received proper training.

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UT Southwestern is an Equal Opportunity Employer.

Resources

The PCIRCF provides the following resources to all UTSW PIs (specifically new assistant professors) and other UT system investigators:

- Help write animal protocols that include PCIRCF protocols
- Help write the radiation design in their animal protocol
- Help write a section in their grant proposal regarding animal studies using radiation and imaging devices
- Provide methodologies and dosimetric information on radiation-related studies for their manuscript
- Provide a letter of support for their grant proposal

Acknowledgement

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- *National Institutes of Health (NIH): 1S10OD032303-01*

Location:

2201 Inwood Road
Dallas, Texas 75390

For more information, visit our website:

utsouthwestern.edu/departments/radiation-oncology/facilities-equipment/preclinical/

Contact Us:

Phone: 214-648-7750

Email: debabrata.saha@utsouthwestern.edu

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