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Current Instrumentation and Technologies in Modern Radiobiology Research—Opportunities and Challenges

Eric Ford, PhD, FAAPM,* and Jim Deye, PhD†

There is a growing awareness of the gaps in the technical methods employed in radiation biology experiments. These quality gaps can have a substantial effect on the reliability and reproducibility of results as outlined in several recent meta-studies. This is especially true in the context of the newer laboratory irradiation technologies. These technologies allow for delivery of highly localized dose distributions and increased spatial accuracy but also present increased challenges of their own. In this article, we highlight some of the features of the new technologies and the experiments they support; this includes image-guided localized radiation systems, microirradiator systems using carbon nanotubes and physical radiation modifiers like gold nanoparticles. We discuss the key technical issues related to the consistency and quality of modern radiation biology experiments including dosimetry protocols that are essential to all experiments, quality assurance approaches, methods to validate physical radiation targeting including immunohistochemical assays and other biovalidation approaches. We highlight the future needs in terms of education and training and the creation of tools for cross-institutional benchmarking quality in preclinical studies. The demands for increased experimental rigor are challenging but can be met with an awareness and a systematic approach which ensures quality.

Semin Radiat Oncol 26:349-355 © 2016 Published by Elsevier Inc.

Introduction: Challenges in Modern Radiobiology Research

Though the technology that is available for radiobiology offers increasingly sophisticated avenues of research (Section New Technology and New Biology), it also presents new challenges. A recent review of the literature by Stone et al[1] found significant concerns with preclinical data concerning the efficacy of 10 drug-radiation combinations presented in 125 publications before 2015. Although the preponderance of concerns were related to the biological aspects of these studies, it was also noted that necessary radiation parameters were either "not reported (or were unclear)" to an extent that compromised the reproducibility of the experiment. This was true for both the in vitro and in vivo studies. Although the spatial and temporal precision of new technologies exacerbates the importance of any uncertainties in the radiation delivery and calibration, an National Cancer Institute cosponsored workshop[2] pointed out that there is an increasing separation of the radiation physics and biology disciplines. Even for traditional radiobiology that does not push the boundaries of experimental techniques, this disconnect has often resulted in the use of equipment that is not properly used or calibrated and publications of radiobiology results often lacking important dosimetry details.

Additionally, beyond the obvious need for proper use and calibration of irradiators, there is a growing awareness of more subtle effects including radiation interactions (physical, atomic, and nuclear) with the materials around the sample(s) as well as mechanical and environmental stresses on the cells being exposed in vitro and in vivo. Examples of such complexities that can modify molecular responses to irradiation are strong magnetic or other nonionizing fields as employed in magnetic resonance or ultrasound guided radiotherapy,[3] environmental

*Department of Radiation Oncology, University of Washington Medical Center, Seattle, WA.
†Radiation Research Program, National Cancer Institute, Bethesda, MD.
Conflict of interest: none.
Address reprint requests to Eric Ford, PhD, FAAPM, Department of Radiation Oncology, Gox 356043, 1959 NE Pacific St, Seattle, WA 98195. E-mail: eford@uw.edu

http://dx.doi.org/10.1016/j.semradonc.2016.06.002
1053-4296/© 2016 Published by Elsevier Inc.

stresses on cells being tested in high throughput irradiators[4] or physiological effects in animals that can alter radiation response. To assess such possible perturbations, Fowler et al[4] and others[5] have pursued the concept of "biovalidation" that entails the use of known biological endpoints and dose-response relationships to ascertain the completeness of the dosimetry characterization of the system.

Clearly, the increased sophistication of modern radiobiology demands an increased focus on the quality and reliability of experimental techniques. There are many dimensions to this, and this article attempts to present an overview of the key issues. In navigating this discussion Table 1 may be helpful. It presents a brief annotated summary, with references, of 6 key aspects in the utilization of modern technologies in radiobiology.

New Technology and New Biology

The gap in techniques and standards discussed above can be fully appreciated in the context of the new technologies for biology research that have emerged in the last 10 years. New technologies are being applied on both the physical and biological fronts. Preclinical radiobiology is increasingly using tools such as genetically engineered mouse models, Crispr-mediated genetic constructs, patient-derived xenografts, and orthotopic models to bridge the gaps across systems (cells to humans) and scale (nano to macro), whereas new technologies for irradiation have adapted radiation research to this new biological frontier. As described in this issue of Seminars in Radiation Oncology, 21st Century preclinical research addresses combined modalities involving radiotherapy and therefore it must try to understand drug-radiation interactions on the cellular and subcellular levels as they evolve overtime, which leads to the need for time resolved, spatially-precise delivery of the radiation component.

Particularly important in this context are the techniques that have been developed to deliver precision radiation in the laboratory setting. These come in many flavors. Perhaps the simplest approach is to modify existing laboratory devices, using for example lead shields and the like, an approach that many studies have employed. A somewhat more sophisticated approach is to use clinical systems to provide localized

Table 1 Key Topics in Precision Radiator Technology and Related References

Topic	Summary	Reference
Protocols for basic dosimetry	Protocol for x-ray dosimetry specific to laboratory systems (EURADOS collective).	58
	Basic protocol for dose calibration of low-energy x-ray beams.	68
	Establishment of dosimetry centers.	59,69
Integration of imaging	Image quality and image-guidance capabilities of a cone-beam CT based small-animal image-guided irradiation unit.	29
	Tumor visualization and accurate target localization for small field, high dose irradiation.	23
Validation of radiation targeting	This may be accomplished with histopathology, immunohistochemical assays for DNA damage (eg, γH2Ax), and other endpoints.	6,32,70,71
QA of new precision irradiator technologies	High throughput device for QA for precision irradiators.	65
	Comprehensive quality assurance phantom for the small animal radiation research platform.	63,72
	Monthly quality management program assessing the consistency of robotic image – guided small animal radiation systems.	64
	System for measuring and ensuring the accuracy of isocenter targeting.	66
Biovalidation	Behavior with absorbed dose escalation for the production of intracellular reactive oxygen species, physical DNA double strand breaks, and modulation of the cellular double strand break pathway.	4
	Biovalidation has value when considering new or more complex radiation technologies. For example the reference here on histologic biovalidation of synchrotron beams[5] and also carbon nanotube-based microbeams[71]. The latter includes a longitudinal study of tumor and normal tissue response with apoptosis and proliferation assays.	5,73
	Consideration of bioeffects because of imaging dose. More study is needed, but may be important effects above 10 cGy (see discussion in reference).	33
	Modality comparison for small animal radiotherapy: a simulation study .	74
Educational and training need	Current state of basic (preclinical) research in radiation oncology from the perspective of relevance to the modern clinical practice of radiation oncology, as well as the education of our trainees and attending physicians in the biological sciences.	75
	State of radiobiology as well as future research opportunities in radiation oncology from both a physician and radiobiologist perspective.	76
	Core physics curriculum for radiation oncology residents.	77
	Specific issues in small animal dosimetry and irradiator calibration.	69
	Training courses funded by governmental agencies. An example is the NIH-funded "Integrated Course in Biology and Physics of Radiation Oncology"[25]	62

Abbreviation: NIH, National Institute of Health.