PHYSICS NEEDS IN RADIATION SCIENCES

James Deye, Ph. D.
Contractor, NCI
Radiation Research Program
Reproducibility / Validation / Efficacy

Raise standards for preclinical cancer research

C. Glenn Begley and Lee M. Ellis propose how methods, publications and incentives must change if patients are to benefit.

Efforts over the past decade to characterize the genetic alterations in human cancers have led to a better understanding of molecular drivers of this complex set of diseases. Although we in the cancer field hoped that this would lead to more effective drugs, historically, our ability to translate cancer research to clinical success has been remarkably low. Sadly, clinical trials in oncology have the highest failure rate compared with other therapeutic areas. Given the high unmet need in oncology, it is understandable that barriers to clinical development may be lower than for other disease areas, and a larger number of drugs with suboptimal preclinical validation will enter oncology trials. However, this low success rate is not sustainable or acceptable, and investigators must reassess their approach to translating discovery research into greater clinical success and impact.

Many factors are responsible for the high failure rate, notwithstanding the inherently difficult nature of this disease. Certainly, the limitations of preclinical tools such as inadequate cancer-cell-line and mouse models make it difficult for even...
MEETING REPORT

Education and Training for Radiation Scientists: Radiation Research Program and American Society of Therapeutic Radiology and Oncology Workshop, Bethesda, Maryland, May 12–14, 2003

C. Norman Coleman,*1 Helen B. Stone,*1 George A. Alexander,* Mary Helen Barcellos-Hoff,† Joel S. Bedford,*
William H. McBride,* W. Gillies McKenna,* Simon N. Powell,* Michael E. C. Robbins,* Sara Rockwell,*
Peter B. Schiff,* Edward G. Shaw,* Dietmar W. Siemann,* Elizabeth L. Travis,* Paul E. Wallner,*
Rosemary S. L. Wong* and Elaine M. Zeman*1

BIOLOGY CONTRIBUTION

AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) SURVEY OF RADIATION BIOLOGY EDUCATORS IN U.S. AND CANADIAN RADIATION ONCOLOGY RESIDENCY PROGRAMS

Barry S. Rosenstein, Ph.D.,*† Kathryn D. Held, Ph.D.,‡ Sara Rockwell, Ph.D.,§
Jacqueline P. Williams, Ph.D.,‖ and Elaine M. Zeman, Ph.D.*"
(1) Establish a National Council of Radiation Sciences to develop a strategy for increasing the number of radiation scientists. The strategy includes NIH training grants, interagency cooperation, inter-institutional collaboration among universities, and active involvement of all stakeholders.

(2) Create new and expanded training programs with sustained funding. These may take the form of regional Centers of Excellence for Radiation Sciences.

(3) Continue and broaden educational efforts of the American Society for Therapeutic Radiology and Oncology (ASTRO), the American Association for Cancer Research (AACR), the Radiological Society of North America (RSNA), and the Radiation Research Society (RRS).

(4) Foster education and training in the radiation sciences for the range of career opportunities including radiation oncology, radiation biology, radiation epidemiology, radiation safety, health/government policy, and industrial research.

(5) Educate other scientists and the general public on the quantitative, basic, molecular, translational and applied aspects of radiation sciences.
The Importance of Dosimetry Standardization in Radiobiology

Marc Desrosiers¹, Larry DeWerd², James Deye³, Patricia Lindsay⁴, Mark K. Murphy⁵, Michael Mitch¹, Francesca Macchiarini⁶, Strahinja Stojadinovic⁷, and Helen Stone⁸

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http://www.nist.gov/pml/div682/grp02/dosimetry-standardization-for-radiobiology.cfm
1) Radiation equipment and methods are increasing in variety and complexity.

2) Radiation biologists rarely receive training in radiation dosimetry.

3) Radiation biologists usually use irradiation equipment dedicated to research that is not shared with and calibrated by their clinical colleagues.

4) Radiobiologists now rarely work with radiation physicists as part of their joint routine duties, and there are fewer radiation physicists who are trained in the unique characteristics of the equipment used and problems involved in performing dosimetry in support of radiation biology.
IT MATTERS!
## IT'S "COMPLICATED"

<table>
<thead>
<tr>
<th></th>
<th>cell culture</th>
<th>small animal</th>
<th>large animal</th>
</tr>
</thead>
<tbody>
<tr>
<td>buildup</td>
<td>XXX</td>
<td>X</td>
<td>XX</td>
</tr>
<tr>
<td>scatter (back/side)</td>
<td>XXX</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>depth dose (energy)</td>
<td>X</td>
<td>XX</td>
<td>XXX</td>
</tr>
<tr>
<td>dose uniformity</td>
<td>XX</td>
<td>X</td>
<td>XX</td>
</tr>
<tr>
<td>field size</td>
<td>X</td>
<td>XXX</td>
<td>XX</td>
</tr>
<tr>
<td>dose uniformity (1/r2)</td>
<td>XXX</td>
<td>XX</td>
<td>X</td>
</tr>
</tbody>
</table>

1 X ~ 10%

National Cancer Institute
MEASURED DOSE DEPENDS ON ENERGY
IN-VIVO DOSE DEPENDS ON ENERGY

The graph illustrates the dose per unit air kerma for different photon energies and sources, highlighting how in-vivo dose varies with energy. Key observations include:

- **Energy Influence:** The dose increases with increasing energy, with significant differences observed between energies below and above 6 MV.
- **Sources:** The graph shows contributions from various radionuclides and energies, including 50 kV, 250 kV, and different isotopes.
- **Tissue Types:** Dose curves are differentiated for different tissues, such as water, muscle, bone, and fat, each marked with distinct line styles.

The data underscores the complexity of dose calculations in vivo, influenced by both energy and tissue type, which are critical for accurate radiation therapy planning and dosimetry.
An early report from AFFRI (AFFRI TR89-1) observed that “the x-ray energy spectrum produced at a peak voltage of 50 kV and with added Al filters readily undergoes attenuation by the plastic tissue-culture Petri-dish covers or the culture media. For example, using a beam hardened with 0.18 mm of Al the attenuation due to the medium can be as high as 60% and the plastic cover will reduce the beam an additional 15%.”

Manufacturer-supplied calibrations for a number of commercially-available irradiators have been found to differ by +5% to -13% from their true values with variations in dose rate over irradiation volumes from 70% to 180% of the stated value. (Masterson and Febo Med Phys 19 (3), 1992 pp 649-657)
UW MRRC Mouse Phantom QA Testing Aggregate Results

| Institution | Cs137 | | Institution | Xray | | Institution | Co60 |
|------------|------| |           |      | |          |     |
| A          | 10.6 | | B          | 8.4  | | C          | 3.8  |
| B          | 8.4  | | D          | 12.6 | | E          | 1.6  |
| C          | 3.8  | | E          | 1.6  | | F          | 3.0  |
| D          | 12.6 | | F          | 3.0  | | G          | -17.0|
| E          | 1.6  | | H          | -53.6| | I          | -0.9 |
| F          | 3.0  | | J          | -17.1| | K          | -24.1|
| Avg        | 6.7  | | Avg        | -22.5| | Avg        | 1.8  |
| % Std Dev  | 67.3 | | % Std Dev  | -85.8| | % Std Dev  | 0.00 |

Each Institution is given a total of 6 Mouse Phantoms. 3 Phantoms are to be given an Absorbed Dose to Water of 1Gy and 3 Phantoms are to be given an ADW of 4Gy. The "% Error" reported above is an average of the percent difference between the target dose (1 & 4 Gy) and the measured dose for all 6 Phantoms from each individual Institution.
Table 1. The approximate rate of occurrence of specific information within 15 issues covering March, 2010 through March, 2011, articles in the journal Radiation Research

<table>
<thead>
<tr>
<th>Animal/Cell type</th>
<th>100 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal/Cell strain</td>
<td>100 %</td>
</tr>
<tr>
<td>Irradiator Manufacturer/Model</td>
<td>80 %</td>
</tr>
<tr>
<td>Source (nuclide, HVL, filtering)</td>
<td>100 %</td>
</tr>
<tr>
<td>Radiation Energy</td>
<td>78 %</td>
</tr>
<tr>
<td>Irradiation Geometry*</td>
<td>48 %</td>
</tr>
<tr>
<td>Dosimetry Method</td>
<td>37 %</td>
</tr>
<tr>
<td>Dose (relative to water, tissue?)</td>
<td>94 %</td>
</tr>
<tr>
<td>Dose Rate (fractionated?)</td>
<td>81 %</td>
</tr>
<tr>
<td>Location of Detector</td>
<td>20 %</td>
</tr>
<tr>
<td>Dose Reference Location</td>
<td>7 %</td>
</tr>
<tr>
<td>Published Standards/Guides Used</td>
<td>7 %</td>
</tr>
<tr>
<td>Uncertainty in Dose</td>
<td>4 %</td>
</tr>
</tbody>
</table>

*"TBI" or "PBI" were only given partial credit.

Table 2. Recent review of radiation modifiers papers published since 2001 (n ~ 120) (H. Stone et al NCI/RRP private communication)

<table>
<thead>
<tr>
<th>PERCENT which supplied information about:</th>
<th>source</th>
<th>energy</th>
<th>dose rate</th>
<th>setup</th>
<th>dosimetry</th>
<th>NO INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell (n = 101)</td>
<td>85 %</td>
<td>52 %</td>
<td>60 %</td>
<td>20 %</td>
<td>7 %</td>
<td>15 %</td>
</tr>
<tr>
<td>Animal (n = 49)</td>
<td>85 %</td>
<td>50 %</td>
<td>50 %</td>
<td>75 %</td>
<td>10 %</td>
<td>10 %</td>
</tr>
</tbody>
</table>
RECOMMENDATIONS
(NCI, NIAID, NIST workshop report, 2013)

In summary, the workshop participants put forward the following recommendations:

1. Biologists and physicists should collaborate on study design and execution.
2. Study design should indicate the accuracy and precision required to meet the expected experimental result.
3. A qualified radiation physicist should help to establish the methods needed to achieve the required accuracy and precision.
4. The physicist should help to establish an ongoing dosimetry constancy program with traceability to National or International standards.
5. Authors should include in their publications sufficient detail concerning the setup and dosimetry used for the study, including references to written standards and/or protocols used. This will require journal editors and reviewers to ensure compliance.
6. The radiobiology community should publish a list of the minimum dosimetry information to be included within publications (see examples in the Appendix).
7. The radiobiology community should determine where gaps exist in written standards and protocols and publish standards to fill those needs. The workshop participants recommended formation of 3 working groups tasked to develop protocols for routine radiobiology experiments: one each for cells, small laboratory animals, and large laboratory animals.
8. The radiobiology community should decide whether a formal dosimetry intercomparison program needs to be implemented for the radiobiology researchers and, if so, how will it be established and sustained.
9. One suggested mechanism for implementation of many of these recommendations would be to establish continuing education venues in both the radiobiology and physics communities to foster communication and arrive at agreed upon standards.
RESOURCES
2. MINIMUM ESSENTIAL SYLLABUS FOR RADIOBIOLOGY

2.1. Introduction

2.2. Physics and chemistry of radiation interactions with matter
2.2.1. Sources of ionizing radiation
2.2.2. Types of ionizing radiation
2.2.3. Particulate radiations
2.2.4. Linear energy transfer
2.2.5. Radiation dose and units
2.2.6. Principles of radiation dosimetry
2.2.7. Direct and indirect effects

2.3. Molecular and cellular radiobiology
2.3.1. Radiation lesions in DNA
2.3.2. Major types of DNA repair
2.3.3. Damage recognition and signalling
2.3.4. Consequences of unrepaired DNA damage: chromosome damage
2.3.5. Radiobiological definition of cell death
2.3.6. Survival curves and models
2.3.7. Cell cycle effects
2.3.8. Relative biological effectiveness (RBE)
2.3.9. Cellular repair exemplified in survival curves
2.3.10. Cellular hyper-radiosensitivity (HRS) and induced repair (IRR)
2.3.11. Other molecular targets: bystander (epigenetic) effects
2.3.12. Radiation sensitisers
2.3.13. Radiation protectors
1) **ICRU 30 “Quantitative Concepts and Dosimetry in Radiobiology”** [13] is more comprehensive than most standards. Like TRS-398, it contains information on measuring accurate absorbed dose using ionization chambers but it also has a lot of information on survival curves, linear energy transfer (LET) and Lineal Energy, animal and cell culture exposure systems, scatter and charge particle equilibrium, along with recommended minimum dosimetric and irradiation geometry information required.

2) **AAPM TG 61 “40-300 kV X-ray Beam Dosimetry in Radiotherapy and Radiobiology”** [14] focuses on how to accurately measure absorbed dose of x-ray beams using ionization chambers in air or in water. Generally, the chambers are calibrated in terms of air kerma split into two major energy divisions (superficial and orthovoltage), centered around 100 keV.

3) **TG 51 and IAEA TRS-398 “Absorbed Dose Determination in External Beam Radiotherapy...”** [15-16] focuses on how to measure, traceably and accurately, absorbed dose in an external beam, in particular absorbed dose to water, whether for gamma ray, x-ray, Linac, electrons, or protons, whether using an ionization chamber in air or in water phantom. Generally, these two protocols are for megavoltage beams (i.e. energies greater or equal to that of Co-60) and use ionization chambers calibrated to absorbed dose to water. Various corrections that are needed
AAPM Working Group on Conformal Small Animal Irradiation

- Members from ~15 different institutions
- Intercomparison of dosimetry and image-guidance capabilities across member institutions
- Will look at small (1-5mm) and moderate (1-2cm) fields
- Using EBT-2 Film and solid water phantoms

**Charge** To generally promote research ideas and opportunities related to small animal conformal irradiation. This could be done, but is not limited to, the following opportunities: 1. Promoting awareness of the existence and the current development of small animal conformal irradiation systems. Specifically:

a) To define terminology and specifications in collaboration with end users.
b) To establish interdisciplinary communications (review paper in a biological-oriented journal).
c) To identify (aside from Radiation Research) potential audiences for symposium on this area.
d) To liaise with Radiation Research Society.
e) To involve cancer/radiation biologists in this working group.
f) To develop a funding strategy for foundational issues 1. Software, imaging, and process development, 2. phantom, QA 3. data sharing, databasing of outcomes.
PS3: Monday 1:45 to 2:30 PM, on commissioning of XRAD320 irradiator for radiobiological study of small animals
Radiation Dosimetry Services

Mailed Dosimeters for Quality Assurance

Radiation Dosimetry Services offers several quality assurance dosimetry services. Our current services and prices include:

- Check of therapy machine output for:
  - Photon beams  $70.00 each beam
  - Electron beams  $90.00 each beam
  - One time set up fee for Platform ($50.00) and Phantom ($100.00)

- Check of total body dosimetry (12 pack)  $300.00

- Check of total skin dosimetry (15 pack)  $300.00

- Check of absorbed dose in blood irradiators
  - 12 pack  $350.00
  - 15 pack  $400.00
  - 20 pack  $500.00
## Small animal radiotherapy research

### PLATFORMS — F. Verhaegen et al, PMB 56 (2011) pp. 55-83

<table>
<thead>
<tr>
<th>System</th>
<th>Photon energy range (keV)</th>
<th>Field range at treatment site</th>
<th>Fixed fields/arcsec</th>
<th>Max dose rate (Gy min⁻¹)</th>
<th>Image resolution at treatment site (μm)</th>
<th>Targeting accuracy (μm)</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARRP (Johns Hopkins University)</td>
<td>5–225</td>
<td>0.5 mm²–10 x 10 cm²</td>
<td>F/A</td>
<td>4</td>
<td>130</td>
<td>200</td>
<td>Wong <em>et al</em> 2008, Tryggestad <em>et al</em> 2009, Matinifar <em>et al</em> 2009</td>
</tr>
<tr>
<td>X-RAD (Princess Margaret Hospital)</td>
<td>5–225</td>
<td>1 mm²–10 x 10 cm²</td>
<td>F/A</td>
<td>4</td>
<td>200</td>
<td>200</td>
<td>Clarkson <em>et al</em> 2010</td>
</tr>
<tr>
<td>Washington University (¹⁰⁹Ir)</td>
<td>380</td>
<td>5–15 mm²</td>
<td>F</td>
<td>2.9</td>
<td>N/A</td>
<td>100–180</td>
<td>Stojadinovic <em>et al</em> 2006, 2007, Kiehl <em>et al</em> 2008</td>
</tr>
<tr>
<td>Stanford University</td>
<td>70–120</td>
<td>0.1–6 cm²</td>
<td>F/A</td>
<td>2</td>
<td>49</td>
<td>100</td>
<td>Graves <em>et al</em> 2007, Rodriguez <em>et al</em> 2009, Zhou <em>et al</em> 2010</td>
</tr>
<tr>
<td>University of Texas Southwestern</td>
<td>5–320</td>
<td>1–20 mm²</td>
<td>F/A</td>
<td>&gt;10</td>
<td>113</td>
<td>65</td>
<td>Song <em>et al</em> 2010, Pidikiti <em>et al</em> 2011</td>
</tr>
</tbody>
</table>

* Mean photon energy of gamma rays.
RADIATION SCIENCE AND MEDICINE
RELATED SESSIONS

TUESDAY, APRIL 21, 2015

MEET THE EXPERT SESSION
Radiation and Immunotherapy: From Preclinical Models to Cancer Patients
Tuesday, April 21, 2015, 7:00 a.m. - 8:00 a.m.
Room 108, Pennsylvania Convention Center
CME-Designated
Silvia C. Formenti. New York University, New York, NY

POSTER SESSIONS
Special Populations, Supportive Care, and Survivorship Research / Radiation Oncology
Tuesday, April 21, 2015, 8:00 a.m. - 12:00 noon
Section 23

Targeting Cell Death and DNA Repair
Tuesday, April 21, 2015, 8:00 a.m. - 12:00 noon
Section 32

Radiation Biology 1: DNA Damage and Repair, Molecular Modulators of Radiation Response, and Resistance
Tuesday, April 21, 2015, 8:00 a.m. - 12:00 noon
Section 18

Radiation Biology 2: Modifiers and Signal Transduction, Sensitivity, Resistance, and Therapy