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PHYSICS NEEDS IN RADIATION SCIENCES

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Radiation Research Program

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

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Reproducibility / Validation / Efficacy

BIOMEDICINE

NIH mulls rules for validating key results

US biomedical agency could enlist independent labs for verification.

BY MEREDITH WADMAN

In biomedical science, at least one thing is apparently reproducible: a steady stream of studies that show the irreproducibility of many important experiments.

In a 2011 internal survey, pharmaceutical firm Bayer HealthCare of Leverkusen, Germany, was unable to validate the relevant preclinical research for almost two-thirds of 67 in-house projects. Then, in 2012, scientists at Amgen, a drug company based in Thousand Oaks, California, reported their failure to replicate 89% of the findings from 53 landmark cancer papers. And in a study published in May, more than half of the respondents to a survey at the MD Anderson Cancer Center in Houston, Texas, reported failing at least once in attempts at reproducing published data (see 'Make believe').

The growing problem is threatening the reputation of the US National Institutes of Health (NIH) based in Bethesda, Maryland, which funds many of the studies in question. Senior NIH officials are now considering adding requirements to grant applications to make experimental validations routine for certain types of science, such as the foundational work that leads to costly clinical trials. As the NIH pursues such top-down changes, one company is taking a bottom-up approach, targeting scientists directly to see if they are willing to verify their experiments.

There is the looming

NATURE.COM
For more on the challenges of reproducibility:
go.nature.com/zqtrop

14 | NATURE | VOL 500 | 1 AUGUST 2013

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[1]. 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[2] make it difficult for even

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Previous Workshops:

RADIATION RESEARCH **160**, 729–737 (2003)
0033-7587/03 $15.00
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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,[a,1] Helen B. Stone,[a,1] George A. Alexander,[b] Mary Helen Barcellos-Hoff,[c] Joel S. Bedford,[d] Robert G. Bristow,[e] Joseph R. Dynlacht,[f] Zvi Fuks,[g] Lester S. Gorelic,[h] Richard P. Hill,[e] Michael C. Joiner,[i] Fei-Fei Liu,[e] William H. McBride,[j] W. Gillies McKenna,[k] Simon N. Powell,[l] Michael E. C. Robbins,[m] Sara Rockwell,[n] Peter B. Schiff,[o] Edward G. Shaw,[m] Dietmar W. Siemann,[p] Elizabeth L. Travis,[q] Paul E. Wallner,[a] Rosemary S. L. Wong[a] and Elaine M. Zeman[r]

ELSEVIER

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doi:10.1016/j.ijrobp.2009.05.009

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.¶

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2003 recommendations

(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.

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DOSE IS NOT JUST A NUMBER !

Volume 118 (2013) http://dx.doi.org/10.6028/jres.118.021
Journal of Research of the National Institute of Standards and Technology

The Importance of Dosimetry Standardization in Radiobiology

Marc Desrosiers[1], Larry DeWerd[2], James Deye[3], Patricia Lindsay[4], Mark K. Murphy[5], Michael Mitch[1], Francesca Macchiarini[6], Strahinja Stojadinovic[7], and Helen Stone[3]

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6 National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland
7 University of Texas Southwestern Medical Center Dallas, Texas

http://www.nist.gov/pml/div682/grp02/dosimetry-standardization-for-radiobiology.cfm

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CURRENT REALITIES

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.

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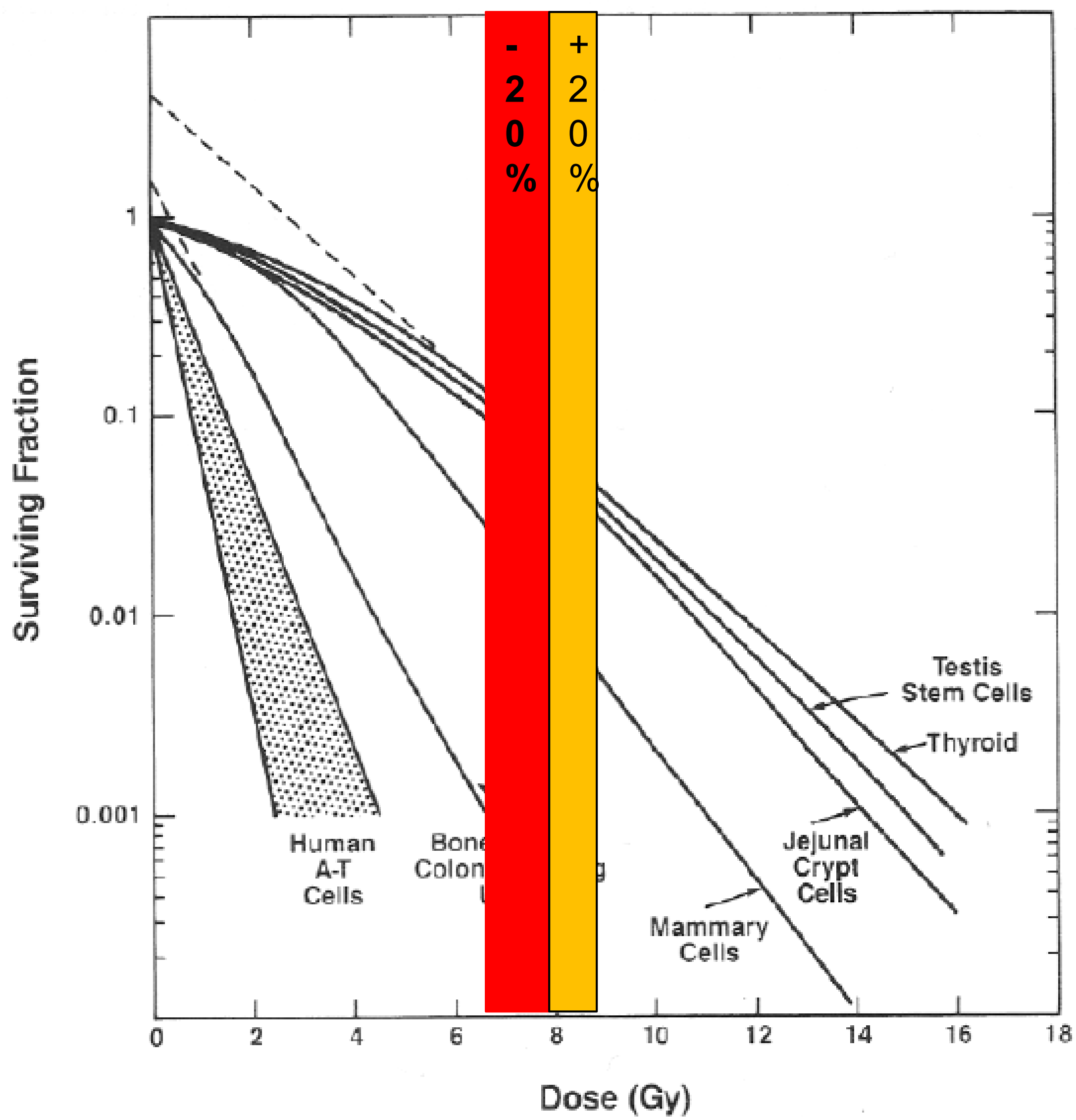
IT MATTERS !



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IT'S "COMPLICATED"

	cell culture	small animal	large animal
buildup	XXX	X	XX
scatter (back/side)	XXX	X	X
depth dose (energy)	X	XX	XXX
dose uniformity	XX	X	XX
field size	X	XXX	XX
dose uniformity (1/r2)	XXX	XX	X

1 X ~ 10%

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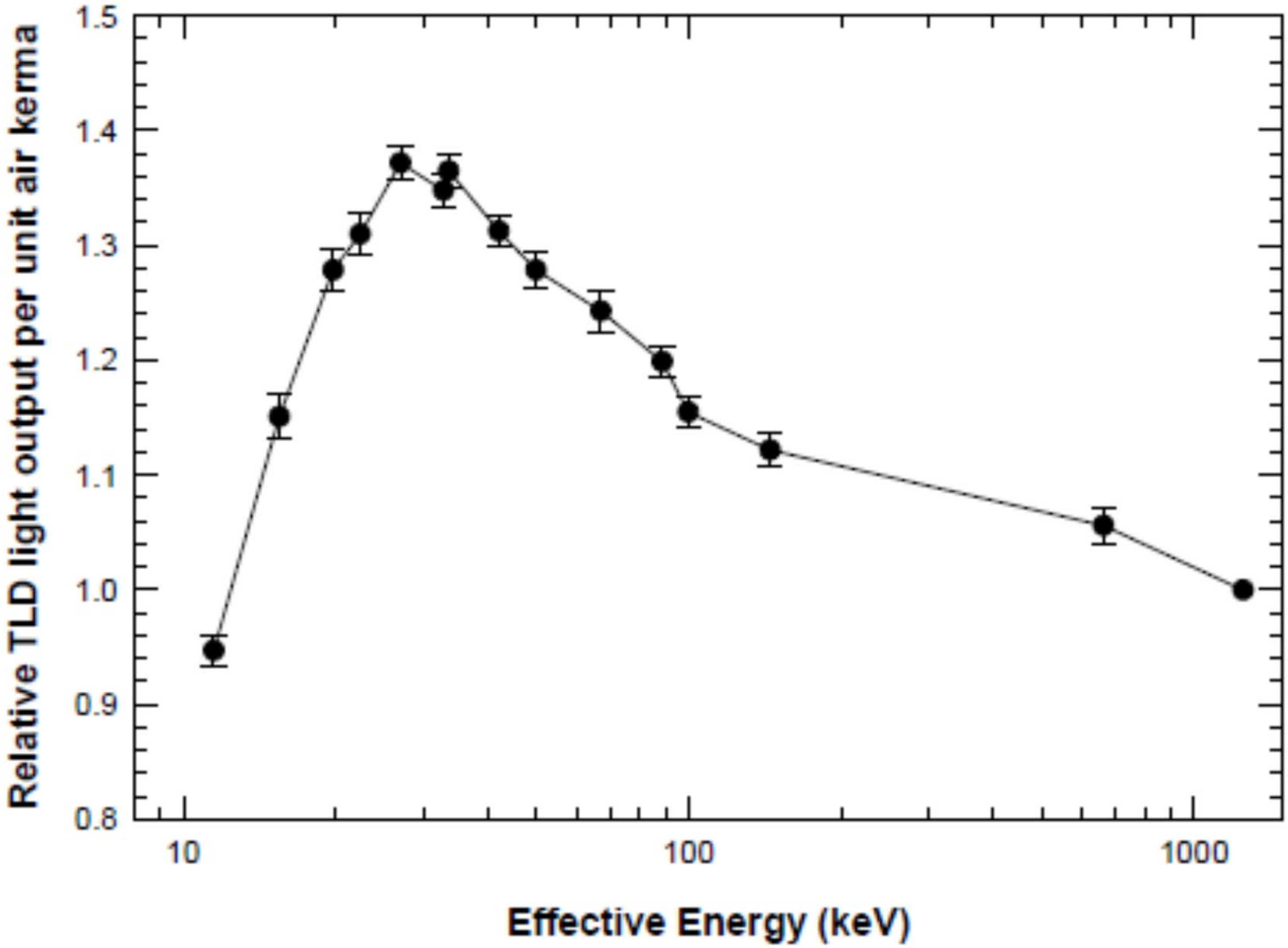
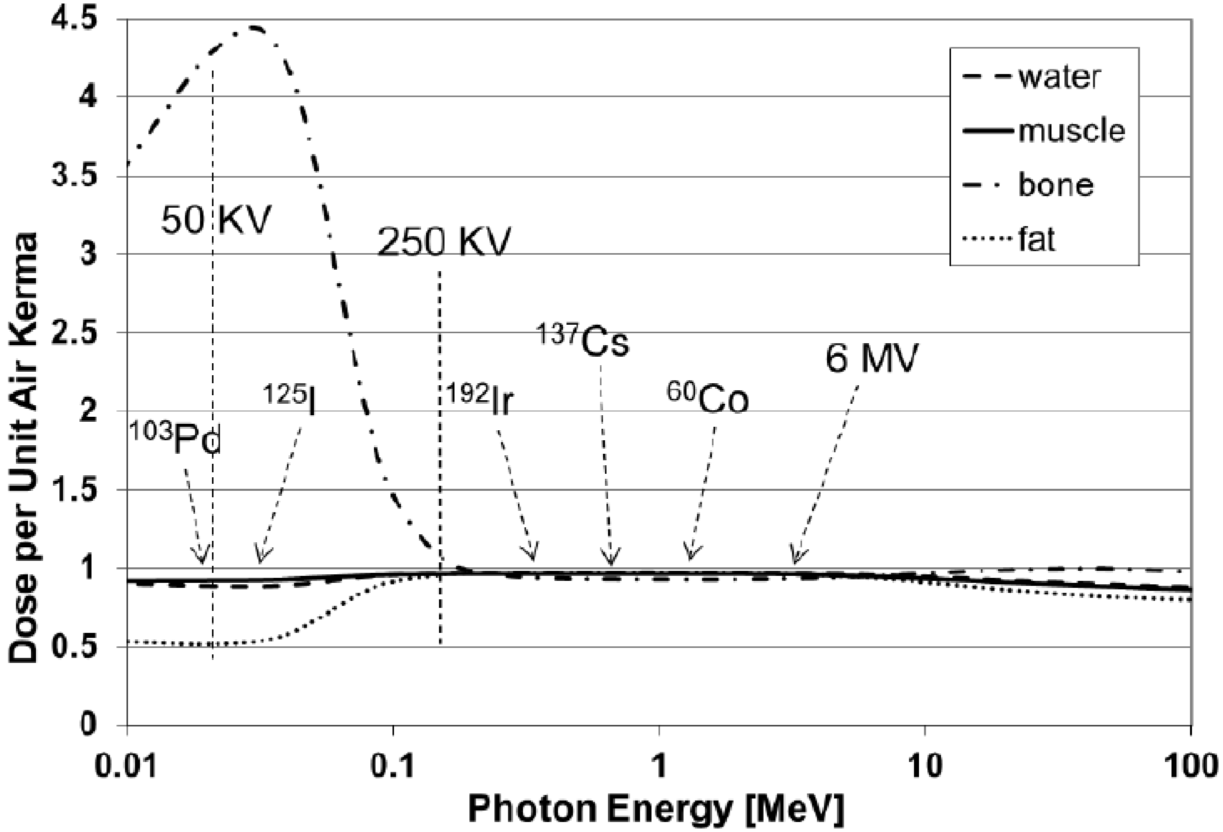
MEASURED DOSE DEPENDS ON ENERGY



IN-VIVO DOSE DEPENDS ON ENERGY



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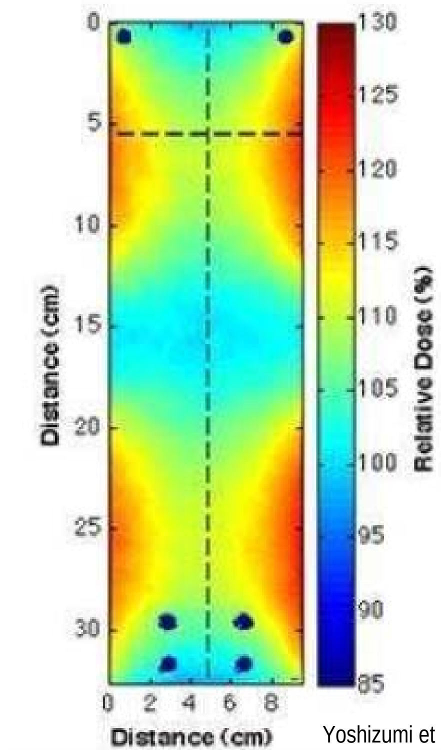
DOCUMENTED ERRORS In- VITRO

* 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



Yoshizumi et al , IJRB,

DOCUMENTED ERRORS In- VIVO

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UW MRRC Mouse Phantom QA Testing Aggregate Results

Cs137		Xray		Co60	
Institution	% Error	Institution	% Error	Institution	% Error
A	10.6	G	-17.0	L	1.8
B	8.4	H	-53.6		
C	3.8	I	-0.9		
D	12.6	J	-17.1		
E	1.6	K	-24.1		
F	3.0				
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.

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MUST REPORT IT

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

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

*"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)

PERCENT which supplied information about:

	source	energy	dose rate	setup	dosimetry	NO INFORMATION
Cell (n = 101)	85 %	52 %	60 %	20 %	7 %	15 %
Animal (n = 49)	85 %	50 %	50 %	75 %	10 %	10 %

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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.

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RESOURCES

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IAEA
International Atomic Energy Agency

Radiation Biology: A Handbook for Teachers and Students

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CALIBRATION PROTOCOLS

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

http://dx.doi.org/10.6028/jres.118.021

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FROM THE PHYSICS SIDE

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 liase 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.

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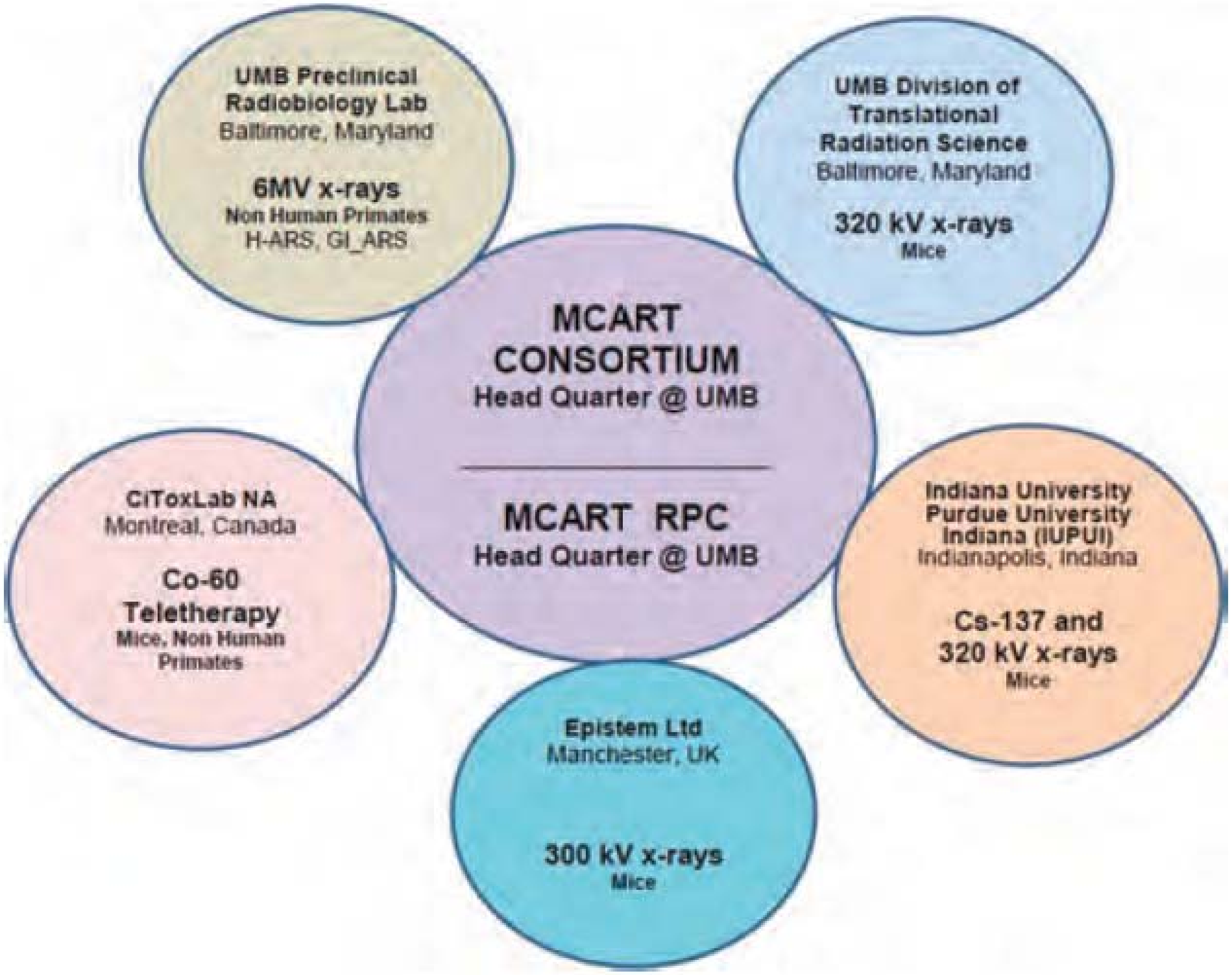
SERVICES

(Medical Counter Measures Against Radiological Threats- MCART)

Health Physics January 2014, Volume 106, Number 1



PS3: Monday 1:45 to 2:30 PM, on commissioning of XRAD320 irradiator for radiobiological study of small animals

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SERVICES

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

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

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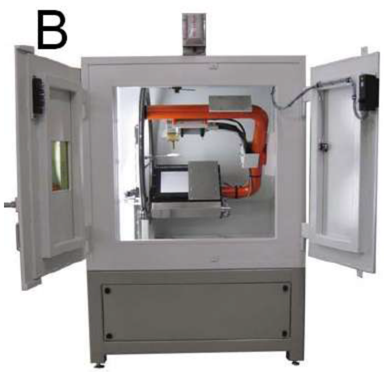
Small animal radiotherapy research PLATFORMS – F. Verhaegen et al, PMB 56 (2011) pp. 55-83

Table 2. Characteristics of small animal radiation research systems for rodents. All devices are based on x-ray tubes except the Washington University system which is based on an ^{192}Ir brachytherapy source.

System	Photon energy range (keV)	Field range at treatment site	Fixed fields/ arcs	Max dose rate (Gy min^{-1})	Image resolution at treatment site (μm)	Targeting accuracy (μm)	Refs
SARRP (Johns Hopkins University)	5–225	0.5 mm∅–10 × 10 cm^2	F/A	4	130	200	Wong *et al* 2008, Tryggestad *et al* 2009, Matinfar *et al* 2009
X-RAD (Princess Margaret Hospital)	5–225	1 mm∅–10 × 10 cm^2	F/A	4	200	200	Clarkson *et al* 2010
Washington University (^{192}Ir)	380[a]	5–15 mm∅	F	2.9	N/A	100–180[b]	Stojadinovic *et al* 2006 , 2007, Kiehl *et al* 2008
Stanford University	70–120	0.1–6 cm∅[c]	F/A	2	49	100	Graves *et al* 2007, Rodriguez *et al* 2009, Zhou *et al* 2010
University of Texas Southwestern	5–320	1–20 mm∅	F/A	>10	113	65	Song *et al* 2010, Pidikiti *et al* 2011

[a] Mean photon energy of gamma rays.

SARRP (XStrahl/JohnsHopkins)



XRad225Cx (PrecisionX-Ray/ PrincessMargaret Hospital)

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RADIATION SCIENCE AND MEDICINE

RELATED SESSIONS

AACR.org

AACR American Association for Cancer Research

ANNUAL MEETING 2015 | PHILADELPHIA

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