BIOGRAPHICAL SKETCH

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NAME: Roger W Howell

eRA COMMONS USER NAME (credential, e.g., agency login): RHOWELL

POSITION TITLE: Distinguished Professor of Radiology & Radiation Oncology; Chief, Division of Radiation Research

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Massachusetts, Amherst, MA	B.S.	02/82	Physics
University of Massachusetts, Amherst, MA	Ph.D.	10/87	Physics
Harvard Medical School, Boston, MA (SJ Adelstein and AI Kassis)	Pre-doctoral training	1984-1987	Radiobiology

A. Personal Statement

I bring 35 years of experience in dosimetry and biological effects of ionizing radiations with particular emphasis on the study of *radiopharmaceuticals used in the diagnosis and treatment of cancer*. My efforts have led to publication of >100 peer reviewed journal articles and numerous reports for national and international scientific bodies. Among the studies conducted in my laboratory are radiochemistry and radiobiology involving ^{3}H, ^{32}P, ^{33}P, ^{90}Y, ^{99m}Tc, ^{117m}Sn, ^{111}In, ^{114m}In, ^{117m}Sn, ^{123}I, ^{125}I, ^{131}I, ^{148}Gd, ^{195m}Pt, ^{193m}Pt, ^{210}Po, ^{212}Pb, ^{223}Ra, and ^{225}Ac. These studies were conducted in in vitro and in vivo models. The breadth and extent of my studies on the radiobiology of radiopharmaceuticals, and integration of radiobiological findings into theoretical dosimetry models have enabled me to lead several R01 and RC1 teams. I am also the PI on our recently awarded S10 grant for an MILabs VECTor6/CT which provides ultra-high resolution PET, SPECT, and CT for mice, rats, and medium-sized animals such as ferrets and rabbits. My leadership in the field of the radiation dosimetry and radiobiology of radiopharmaceuticals has been acknowledged by scientific peers in the form of the 2004 Loevinger-Berman Award and being named as a Fellow of the Society of Nuclear Medicine and Molecular Imaging (SNMMI). I am also co-author and sponsor of the recent ICRU report entitled Dosimetry-Guided Radiopharmaceutical Therapy.

B. Positions, Scientific Appointments, and Honors

Positions:

2021-present	Distinguished Professor, Rutgers New Jersey Medical School and Rutgers Robert Wood Johnson Medical School
2015-present	Professor, Rutgers Robert Wood Johnson Medical School
2013-present	Chairman, Radiation Safety Committee, Rutgers Biomedical and Health Sciences
2013-present	Professor, Rutgers New Jersey Medical School
2001-present	Chief, Division of Radiation Research, Department of Radiology, NJ Medical School
2001-2013	Professor, UMDNJ, New Jersey Medical School
2000-2013	Chairman, Radiation Safety Committee, UMDNJ Newark Campus
1995-2001	Associate Professor, UMDNJ, New Jersey Medical School
1989-1995	Assistant Professor, UMDNJ, New Jersey Medical School

1987-1989 Instructor, UMDNJ, New Jersey Medical School

Scientific Appointments:

2022 United States representative for International Atomic Energy Agency (IAEA) Technical Meeting on Auger Electron Emitters for Radiopharmaceutical Developments.

2021 Fellow of the Society of Nuclear Medicine and Molecular Imaging (FSNMMI)

2014-present Commissioner, International Commission on Radiation Units and Measurements (ICRU).

2004-2021 National Council on Radiation Protection and Measurements (NCRP) - Council Member.

2006-present ,1992-2000. Society of Nuclear Medicine Medical Internal Radiation Dose Committee.

Recent Study Section Service:

Review Panel for NCI P01 Program Projects, February 15-16, 2023.

Review Panel for NCI P01 Program Projects, February 24-25, 2022.

Review Panel for NIH/NCI 2021 Special Emphasis Panel/Scientific Review Group “Radiation Therapeutics and Biology” [ZRG1 OTC-L (02)], Aril 7, 2021.

Review Panel for NIH/NCI 2020 Special Emphasis Panel/Scientific Review Group 2020/10 ZCA1 SRB-2 (O2) R. Radiobiology of High Linear Energy Transfer (High LET) Exposure in Cancer Treatment. June 25, 2020.

Reviewer for Swiss National Science Foundation (SNSF). Sinergia funding instrument. Bern, Switzerland. April 28, 2020.

Review Panel for NIH/NCI 2019 Council ZRG1 OTC-K (04): Radiation Therapeutics and Biology Study Section (RTB). October 30, 2019.

Review Panel for NIH/NCI 2019/10 Council ZRG1 OTC-E 02 Radiation Therapeutics and Biology Study Section (RTB). May 29, 2019.

Honors:

2021 Highlighted Article in Oct 2021 issue of Molecular Cancer Research. Molec Canc Res. 19, 1739-1750. 10.1158/1541-7786.MCR-21-0005.

2020 Featured Basic Science Article. Journal of Nuclear Medicine, J Nucl Med 61, 89-95, 2020.

2020 Plenary Lecture. Radiation Research Society Winter Workshop: Challenges and Solutions in the Era of Targeted Radionuclide-based Therapy. Big Sky, MT. March 4-6 2020.

2019 Conference Keynote Lecture. 9th International Symposium Physical, Molecular, Cellular, and Medical Aspects of Auger Processes. Oxford, UK, Aug 22-24, 2019.

2013 Conference Lecture. 2013 Swedish Cancer Society Meeting, Gothenberg University, Gothenberg, Sweden. November 14-15, 2013.

2009 Basic Science Faculty of the Year Award, New Jersey Medical School

2007 Conference Keynote Lecture. 6th International Symposium Physical, Molecular, Cellular, and Medical Aspects of Auger Processes. Boston, MA, July 5-7, 2007.

2004 Loevinger-Berman Award, Society of Nuclear Medicine.

1995 Outstanding Dosimetry Manuscript Award by the Journal of Nuclear Medicine. S. Murty Goddu, R.W. Howell, D.V. Rao. "A generalized approach to absorbed dose calculations for dynamic tumor and organ masses". J. Nucl. Med. 36: 1923-1927 (1995).

C. Contributions to Science

Howell Bibliography: >100 peer reviewed articles (https://pubmed.ncbi.nlm.nih.gov/?term=howell+rw&sort=pubdate), Web of Science H-index = 41, Google Scholar h-index = 49, i-index = 121.

Radionuclide production, radiochemical synthesis, and radiopharmaceutical design

Development of radiopharmaceuticals plays an important role in the advancement of nuclear medicine. My laboratory has undertaken synthesis and purification of radiochemicals labeled with a variety of radionuclides such as ^{212}Pb, ^{193m}Pt, ^{195m}Pt, ^{125}I, ^{123}I, ^{131}I, etc. The radioplatinum studies showed the potential of combining the therapeutic potency of Auger electrons with platinum chemotherapy in a single agent. We are the first to show that the efficacy of radiopharmaceutical therapies can be improved by formulation of cocktails of agents and that specific activity of the ingredients is a key factor in determining efficacy. These studies translated to US Patents US 8,874,380 B2 and 9,623,262 B2.

1. Howell, R.W., Kassis, A.I., Adelstein, S.J., Rao, D.V., Wright, H.A., Hamm, R.N., Turner, J.E., & Sastry, K.S.R. (1994). Radiotoxicity of ^{195m}Pt labeled trans-platinum(II) in mammalian cells. Radiat Res, 140, 55-62. PMID: 7938455. https://pubmed.ncbi.nlm.nih.gov/7938455/
2. Akudugu, J.M., & Howell, R.W. (2012). A method to predict response of cell populations to cocktails of chemotherapeutics and radiopharmaceuticals: Validation with daunomycin, doxorubicin, and the alpha particle emitter ^{210}Po. Nucl Med Biol, 39(7), 954-61. PMID: 22503536, PMCID: 3399932. http://www.ncbi.nlm.nih.gov/pubmed/22503536.
3. Pasternack, J.B., Domogauer, J.D., Khullar, A., Akudugu, J.M., & Howell, R.W. (2014). The advantage of antibody cocktails for targeted alpha therapy depends on specific activity. J Nucl Med, 55(12), 2012-9. PMID: 25349219. http://www.ncbi.nlm.nih.gov/pubmed/25349219.
4. Ali, N.S., Akudugu, J.M., & Howell, R.W. (2019). A preliminary study on treatment of human breast cancer xenografts with a cocktail of paclitaxel, doxorubicin, and ^{131}I-anti-EpCAM (9C4). World J Nucl Med 18(1), 18-24 PMID: 30774541. https://www.ncbi.nlm.nih.gov/pubmed/30774541.

Cellular and multicellular dosimetry and bioeffect modeling for radiopharmaceuticals

It has long been recognized that the microscopic distribution of radiopharmaceuticals in tissues has a major impact on their radiotoxicity. However, there was a dearth of tools available to assist the radiation research community to take this into account when interpreting their data. My laboratory has been steadily working toward conducting radiobiological research and integrating these findings into theoretical models in the form of tools that are made available to the scientific community. These publications have made a marked change in the field of radiation dosimetry. These efforts began when I joined the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine in 1992 and I have steered this process in the capacity of corresponding author and PI ever since. My contributions to this field were recognized by peers in the form of the Loevinger-Berman Award. Development of cellular and multicellular dosimetry approaches have progressed with the most recent effort being the Katugampola et al. article and on-line tool MIRDcell V3.12 (https://mirdcell.njms.rutgers.edu/). Most recently, I was awarded 1R01CA245139 to support the development of this radiopharmaceutical therapy treatment planning tool.

1. Goddu, S.M., Rao, D.V., & Howell, R.W. (1994). Multicellular dosimetry for micrometastases: dependence of self-dose versus cross-dose to cell nuclei on type and energy of radiation and subcellular distribution of radionuclides. J Nucl Med, 35, 521-30. PMID: 8113908. http://jnm.snmjournals.org/content/35/3/521.long
2. Vaziri, B., Wu, H., Dhawan, A.P., Du, P., Howell, R.W., Committee, S.M., & Committee, S.M. (2014). MIRD Pamphlet No. 25: MIRDcell V2.0 Software Tool for Dosimetric Analysis of Biologic Response of Multicellular Populations. J Nucl Med, 55(9), 1557-64. PMID: 25012457. http://www.ncbi.nlm.nih.gov/pubmed/25012457
3. S. Katugampola, J. Wang, A. Rosen, R.W. Howell. MIRD Pamphlet No. 27: MIRDcell V3, a revised software tool for multicellular dosimetry and bioeffect modeling. J Nucl Med. 2022 63 (9) 1441-1449; DOI: https://doi.org/10.2967/jnumed.121.263253. PMID: 35145016
4. Katugampola S, Wang J, Prasad A, Sofou S, Howell RW. Predicting response of micrometastases with MIRDcell V3: proof of principle with ^{225}Ac-DOTA encapsulating liposomes that produce different activity distributions in tumor spheroids. *Eur J Nucl Med Mol Imaging.* 2022; DOI: 10.1007/s00259-022-05878-7. PMID: 35802160.

Alpha particle radiobiology

Among the studies conducted in my laboratory that are of particular importance to targeted radionuclide therapy is attaching an alpha emitter to DNA in the cell nucleus which demonstrated that this does not increase the RBE. Also shown is a linear relationship between the RBE (for *in vivo* cell killing) of an alpha particle and its initial energy. This is one of the earliest radiobiological studies of Ra-223. My experimental studies with alpha emitters have quantified how their distribution among cell populations affects response of the whole population.

1. Azure, M.T., Archer, R.D., Sastry, K.S.R., Rao, D.V., & Howell, R.W. (1994). Biologic effect of ^{212}Pb localized in the nucleus of mammalian cells: Role of recoil energy in the radiotoxicity of internal alpha emitters. Radiation Research, 140, 276-83. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3321059/

2. Howell, R.W., Goddu, S.M., Narra, V.R., Fisher, D.R., Schenter, R.E., & Rao, D.V. (1997). Radiotoxicity of gadolinium-148 and radium-223 in mouse testes: Relative biological effectiveness of alpha particle emitters *in vivo*. Radiat Res, 147(3), 342-8. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3321061/
3. Neti, P.V., & Howell, R.W. (2006). Log normal distribution of cellular uptake of radioactivity: implications for biologic responses to radiopharmaceuticals. J Nucl Med, 47(6), 1049-58. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2631404/
4. Neti, P.V.S.V., & Howell, R.W. (2007). Biological response to nonuniform distributions of ^{210}Po in multicellular clusters. Radiat Res, 168(3), 332-40. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2939868/

Radiation induced bystander effects

Research on radiation-induced bystander effects caused by incorporated radionuclides has been a major theme of my research. My laboratory has published about 12 articles on this important topic, the most recent being the phenotypic dependence of ^{125}I-induced bystander cell killing in human breast carcinoma cells.

1. Bishayee, A., Rao, D.V., & Howell, R.W. (1999). Evidence for pronounced bystander effects caused by nonuniform distributions of radioactivity using a novel three-dimensional tissue culture model. Radiat Res, 152(7), 88-97. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3547643/
2. Akudugu, J.M., Azzam, E.I., & Howell, R.W. (2012). Induction of lethal bystander effects in human breast cancer cell cultures by DNA-Incorporated Iodine-125 depends on phenotype. Int J Radiat Biol, 88(12), 1028–38. PMID: 22489958. http://www.ncbi.nlm.nih.gov/pubmed/22489958
3. Leung, C.N., Canter, B.S., Rajon, D., Back, T.A., Fritton, J.C., Azzam, E.I., and Howell, R.W. (2020). Dose-dependent growth delay of breast cancer xenografts in the bone marrow of mice treated with radium-223: the role of bystander effects and their potential for therapy. J Nucl Med 61, 89-95. https://pubmed.ncbi.nlm.nih.gov/31519805/
4. B.S. Canter, C.N. Leung, J.C. Fritton, T. Bäck, D. Rajon, E.I. Azzam, R.W. Howell. Radium-223-induced bystander effects cause DNA damage and apoptosis in disseminated tumor cells in bone marrow. *Molec Canc Res*. 19, 1739-1750. 10.1158/1541-7786.MCR-21-0005. **Highlighted Article in Oct 2021 issue of Molecular Cancer Research.** https://pubmed.ncbi.nlm.nih.gov/34039648/

Dose rate effects

Dose rate effects play an important role for both tumor control and normal tissue toxicity in radiopharmaceutical therapy. My lab was among the earliest to implement bioeffect modeling in this field. More importantly, I have developed instrumentation to study the effects of exponentially increasing and decreasing dose rates and conducted studies to show that uptake half-time plays a major role in the response.

1. Howell, R.W., Goddu, S.M., & Rao, D.V. (1994). Application of the linear-quadratic model to radioimmunotherapy: Further support for the advantage of longer-lived radionuclides. J Nucl Med, 35(11), 1861-9. https://pubmed.ncbi.nlm.nih.gov/7965170/
2. Howell R.W., Goddu S.M., Rao D.V. (1998). Proliferation and the advantage of longer-lived radionuclides in radioimmunotherapy. Med Phys. 25(1):37-42. doi: 10.1118/1.598171. PMID: 9472824; PMCID: PMC3046635. https://pubmed.ncbi.nlm.nih.gov/9472824/
3. Pasternack, J.B., & Howell, R.W. (2013). RadNuc: a graphical user interface to deliver dose rate patterns encountered in nuclear medicine with a ^{137}Cs irradiator. Nucl Med Biol, 40(2), 304-11. PMID: 23265668. http://www.ncbi.nlm.nih.gov/pubmed/23265668
4. Solanki, J.H., Tritt, T., Pasternack, J.B., Kim, J.J., Leung, C.N., Domogauer, J.D., Colangelo, N.W., Narra, V.R., & Howell, R.W. (2017). Cellular Response to Exponentially Increasing and Decreasing Dose Rates: Implications for Treatment Planning in Targeted Radionuclide Therapy. Radiat Res, 188(2), 221-34. PMID: 28541775. https://www.ncbi.nlm.nih.gov/pubmed/28541775