Second Symposium of the European Working Group on the Radiobiology of Molecular Radionuclide Therapy

Julie Nonnekens[1,2], Bart Cornelissen[3,4], and Samantha Y.A. Terry[5]; on behalf of the European Working Group on the Radiobiology of Molecular Radiotherapy

[1]Department of Molecular Genetics, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Department of Radiology and Nuclear Medicine, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands; [3]Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [4]Department of Oncology, University of Oxford, Oxford, United Kingdom; and [5]Department of Imaging Chemistry and Biology, School of Biomedical Engineering and Imaging Sciences, King's College London, London, United Kingdom

Molecular radionuclide therapy is a relatively novel anticancer treatment option using radiolabeled, tumor-specific vectors. On binding of these vectors to cancer cells, radioactive decay induces DNA damage and other effects, leading to cancer cell death. Treatments, such as with [^{177}Lu]Lu-octreotate for neuroendocrine tumors and [^{177}Lu]Lu-PSMA for prostate cancer, are now being implemented into routine clinical practice around the world. Nonetheless, research into the underlying radiobiologic effects of these treatments is essential to further improve them or formulate new ones. The purpose of the European Working Group on the Radiobiology of Molecular Radiotherapy is to promote knowledge, investment, and networking in this area. This report summarizes recent research and insights presented at the second International Workshop on Radiobiology of Molecular Radiotherapy, held in London, U.K., on March 13 and 14, 2023. The symposium was organized by members of the Cancer Research U.K. RadNet City of London and the European Working Group on the Radiobiology of Molecular Radiotherapy.

Key Words: cancer treatment; collaboration; external-beam radiotherapy; molecular radionuclide therapy; radiobiology

J Nucl Med 2023; 64:1788–1790
DOI: 10.2967/jnumed.123.265956

This second workshop (a hybrid meeting) on molecular radionuclide therapy was a follow-on from the call-to-arms editorial article published in 2019 (*1*) and the inaugural meeting in 2021 in Montpellier (*2*). The aim of this workshop was to update the community on the current state of the art and research on radiobiology in the field of molecular radionuclide therapy (MRT), to be inspired by research performed in the field of external-beam radiotherapy and cancer biology, and to network during dedicated times in the schedule. In total, 120 attendees (100 live and 20 online) from 11 countries participated in talks, debates, and poster sessions. Proffered talks, posters, and poster pitches were selected from more than 40 abstracts.

Received May 1, 2023; revision accepted Jun 20, 2023.
For correspondence or reprints, contact Samantha Terry (samantha.terry@kcl.ac.uk).
Published online Jul. 13, 2023.
COPYRIGHT © 2023 by the Society of Nuclear Medicine and Molecular Imaging.

Jonathan Wadsley from the University of Sheffield, U.K., gave the first keynote lecture, highlighting the state of the art of MRT, and indicated where efforts are best invested for impactful clinical success. He started with an overview of current clinical indications for MRT such as ^{131}I for thyroid cancer, ^{223}Ra for prostate cancer bone metastases, radioembolization, [^{177}Lu]Lu-octreotate for neuroendocrine tumors, and [^{177}Lu]Lu-PSMA for prostate cancer. Future work, he proposed, should focus on novel tumor indications, novel radionuclides, and combination treatments. He discussed 6 gaps in our current knowledge, indicating the challenges in standardized dosimetry and poorly understood radiobiology: how we can personalize therapy to ensure that each patient receives the most effective absorbed dose to treat the tumor while maintaining safety and not damaging organs at risk; what absorbed doses are being delivered, and what the radiobiologic significance is of dose-rate effects; what the radiobiologic consequences are of different types of emissions with different energies and pathlengths; how tumor heterogeneity is managed; what the role of radiosensitizers is; and what the effect of immune interactions on therapeutic efficacy can be. Wadsley also discussed some lessons learned from clinical trials (e.g., the SELIMETRY trial) and where we as a community might best lay our efforts to achieve impactful clinical success, such as by focusing on personalizing treatment to ensure that every patient gets the maximum possible benefit from the activity delivered and by performing rigorous, multidisciplinary clinical trials addressing meaningful clinical questions such as dosimetry, radiobiology, and molecular biomarkers.

A series of proffered talks highlighted the best-scored abstracts that had been submitted. Simone Kleinendorst (Radboudumc, Nijmegen, The Netherlands) discussed the potential of combining carbonic anhydrase IX–targeted ^{177}Lu treatment with immune checkpoints inhibitors. Hanna Berglund (Uppsala University, Sweden) talked about how p53 stabilization potentiates [^{177}Lu]Lu-octreotate therapy in neuroblastoma. Jordan Cheng (King's College London, U.K.) highlighted the option of using chemotherapeutics targeting replication to enhance [^{177}Lu]Lu-octreotate therapy in vitro.

The second session focused on the role of the tumor microenvironment (TME) and immune response in MRT efficacy. The first talk was an invited lecture by Julie Constanzo from the Montpellier Cancer Research Institute, France, on the topic of MRT and vesicle signaling in the context of anticancer immunity. She showed how the TME plays a major role in the cellular response

to radiotherapy (including MRT). MRT acts via induction of targeted effects (such as direct DNA breaks) and nontargeted effects (such as via excretion of cytokines, extracellular vesicles, danger-associated molecular patterns, or chemokines). The latter will lead to direct killing of surrounding cells or activation of the immune system. Furthermore, her work showed that membrane targeting with radionuclides can activate the cGAS-STING pathway (cyclic guanosine monophosphate–adenosine monophosphate synthase and stimulator of interferon genes). She also showed that extracellular vesicles play a role in enhancing the therapeutic effect via the immune system, since extracellular vesicles isolated from MRT-treated cells can effectively be used to treat immune-competent xenografted mice but not immunodeficient mice. Future work will focus on the combination of MRT with immune checkpoint inhibitors and when to use this combination. What would, for example, be the best treatment schedule and which patients would be eligible?

The session was continued with proffered talks on submitted abstracts. Yasmine Bouden (University of Montpellier, France) gave a talk on the role of double-stranded DNA contained in extracellular vesicles released by irradiated cells. Gemma Dias (University of Oxford, U.K.) talked about her work on the antitumor immune response induced by [^{177}Lu]Lu-PSMA, and Sapna Lunj (University of Manchester, U.K.) showed her data on the systemic immune response induced by MRT in men with prostate cancer. The session was followed by poster pitches from the highest-ranked poster abstracts. Concluding the first day, participants were divided into groups and were asked to discuss 4 questions and upload their answers in Padlet, an online visual board for organizing and sharing content. Question 1 was, "My research in radionuclide therapy would progress if I could just …." Question 2 was, "The next big thing should be …." Question 3 was, "What other suggestions do you have on how to progress the field?" Question 4 was, "How will we fund this?" All answers were compiled and discussed during an audience-engaged discussion on day 2.

The second day started with an invited talk by Isabel Pires from the University of Manchester, U.K., who gave an extensive overview on how to target hypoxia biology as a radiosensitizing approach in breast cancer. Years of research by many groups has shown that hypoxia causes resistance to radiotherapy, as well as increased genomic instability, increased metastatic potential, metabolic and angiogenic switches, and stemness. Pires discussed her work on WSB-1, an E3 ligase associated with hypoxia signaling. WSB-1 is a HIF1 target and has a positive feedback loop with HIF1. High expression of WSB-1 is associated with poor prognosis (distant metastasis–free survival) for hormone receptor–negative breast cancer patients, and downregulation leads to decreased angiogenic and metastatic capacity in vitro and in vivo. More recent data indicate that WSB-1 could regulate the DNA damage response, which gives opportunities for combination treatment strategies. She concluded with the statement that WSB-1 could be a potential novel breast cancer gene biomarker for dysfunctional DNA damage response in hypoxic breast cancer. Similarly detailed radiobiologic studies should be on the horizon for MRT.

During the audience-engaged discussion, the outcomes of the group discussion of the first day were debated. The participants saw various promising developments both in the lab and in the clinic, including novel treatment options such as drug combinations and the use of Auger electron emitters. In addition, the participants indicated that more emphasis should be put on radiogenomics, dosimetry, and novel models such as 3-dimensional spheroids and animals. Furthermore, they concluded that it is essential to include radiobiology and dosimetry in clinical practice—for example, to enable biomarker research and to develop quick and easy functional tests for patient selection and prediction of therapy efficacy. The audience showed a clear consensus on standardization of terminology (e.g., what is this therapy called: molecular radionuclide therapy, radiopharmaceutical therapy, or targeted radiotherapy?). The audience also found that it is essential to better report on experimental procedures and use appropriate controls to allow for standardization and increase reproducibility. Additionally, the participants believed there to be a great need for better interaction and knowledge exchange within the community. The working group is currently following up on these points.

The second keynote talk was by Fran Balkwill of Queen Mary University of London, U.K. She talked about how the TME might influence MRT success. Cancers are not just masses of malignant cells but complex organs, to which many other cells are recruited and are sometimes corrupted by the transformed cells. Interactions between those cells create the TME, which can vastly differ between different tumor types. Balkwill showed her team's work on high-grade serous ovarian cancer, which often metastasizes to the omentum. Mouse models can be used to study this tumor type and its response to treatment since there are many common elements between mouse and human samples, such as the type of infiltrated immune cells. Her work showed that chemotherapy can stimulate the immune response and modulate the TME and that, to study this change, it is essential to obtain pre- and posttreatment samples. Very recent work showed live imaging of human tissue slices and cocultures of different types of cells to follow tumor and immune cell movement using antibodies (data not published).

The last 2 sessions of the conference comprised the last proffered talks. Paula Raposinho and Ana Belchior (both from the Technical University of Lisbon, Portugal) talked about cellular studies using ^{67}Ga- and ^{177}Lu-labeled nanoparticles for theranostics of glioblastoma and dosimetric challenges from nanoscopic patterns to biologic effectiveness, respectively. Emmanuel Deshayes (Montpellier Cancer Research Institute, France) gave a lecture on the dose–effect relationship in tumors and healthy organs for patients treated with [^{177}Lu]Lu-DOTA-octreotate. The last 2 talks focused on drug screens to find novel combination treatments. Edward O'Neill (University of Oxford, U.K.) used a clonogenic assay–based drug screen to identify cyclin-dependent kinase 4/6 inhibitors as potential radiosensitizers for ^{177}Lu-based MRT, and Thom Reuvers (Erasmus University Medical Center Rotterdam, The Netherlands) performed a plate reader–based high-throughput screen and identified DNA–protein kinase catalytic subunit inhibitors as potent radiosensitizers of [^{177}Lu]Lu-DOTA-octreotate.

Simone Kleinendorst was awarded first place for the best oral presentation, and Thom Reuvers and Sapna Lunj were jointly awarded second place. Isabella Strobel was awarded first place for the best poster, and Anthony Waked and Katarina Gleisner were jointly awarded second place.

The radiobiology of MRT is gaining much attention, and various studies are showing an important role for clinical MRT implementation. Symposia such as this are highly effective opportunities for networking and establishing novel collaborations. Although growing, the field is not yet overcrowded; in fact, we would go so far as to state that researching the biologic mechanisms that influence radionuclide therapy effectiveness would make an excellent niche for many early-career researchers, as well as more established

academics, to move into. At the workshop, follow-up meetings were also planned to identify concrete ways forward for the working group. Equally, the scholar-in-training committee will now be reinstated to increase the visibility of scholar-in-training members within the radiobiology-of-MRT community and will work to offer networking and community opportunities. Several recommendations were made to help the community move the field of MRT forward at a faster pace, including standardizing the name of MRT to aid visibility among other research areas, sharing protocols, collaborating more, and standardizing reporting of results. Additional information is available online (www.mrtradiobiology.com).

DISCLOSURE

The symposium was generously sponsored by Artios, AstraZeneca, Mediso, MiLabs, RPS Service, and Viewpoint Molecular Targeting (now Perspective Therapeutics) and by the Radiation Research Unit at the Cancer Research U.K. City of London Centre (C7893/A28990). No other potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

The local organization organizing committee included Hafiza Bibi, Vittorio de Santis, Jordan Cheng, and Samantha Terry. The scientific committee included Jordan Cheng, Paul Gape, and Mark Gaze, Jane Sosabowski, Bart Cornelissen, Julie Nonnekens, and Samantha Terry. We thank all panel members, chairs, and others who helped make the symposium a success.

KEY POINTS

QUESTION: This symposium set out to enable a networking opportunity for biologic researchers working in MRT and ascertain how they as a group should best proceed.

PERTINENT FINDINGS: Several suggestions were made to help move the field of MRT forward at a faster pace, including creating a scientist-in-training committee, sharing protocols, collaborating more, and standardizing reporting of results.

IMPLICATIONS FOR PATIENT CARE: By moving the field of MRT forward through new connections and more in-depth biologic research, further highly effective therapeutic options will become available for patients.

REFERENCES

1. Terry SYA, Nonnekens J, Aerts A, et al. Call to arms: need for radiobiology in molecular radionuclide therapy. *Eur J Nucl Med Mol Imaging.* 2019;46:1588–1590.
2. Cornelissen B, Terry S, Nonnekens J, Pouget JP; European Working Group on the Radiobiology of Molecular Radiotherapy. First symposium of the European Working Group on the Radiobiology of Molecular Radiotherapy. *J Nucl Med.* 2021; 62(7):14N–15N.