First Symposium of the European Working Group on the Radiobiology of Molecular Radiotherapy

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First Symposium of the European Working Group on the Radiobiology of Molecular Radiotherapy

Bart Cornelissen, PhD[1,2], Samantha Terry, PhD[3], Julie Nonnekens, PhD[4,5], Jean-Pierre Pouget, PhD[6], on behalf of the European Working Group on the Radiobiology of Molecular Radiotherapy

[1]MRC Oxford Institute for Radiation Oncology, Department of Oncology, University of Oxford, UK; [2]Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, The Netherlands; [3]Department of Imaging Chemistry and Biology, School of Biomedical Engineering and Imaging Sciences, King's College London, UK; [4]Department of Molecular Genetics, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands; [5]Department of Radiology and Nuclear Medicine, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands; [6]Institut de Recherche en Cancérologie de Montpellier, Inserm U1194, Université de Montpellier, Institut Régional du Cancer de Montpellier, Montpellier, France

Cancer therapy using radionuclides is gaining much attention. Attached to tumor-specific vectors, isotopes emitting α, β, or Auger electron particles are being increasingly investigated for their ability to deliver radiation damage selectively to cancer tissues. In light of the recent approval of ^{177}Lu-DOTATATE and $^{223}RaCl_2$ therapy by regulators on both sides of the Atlantic and the highly promising results just reported for ^{177}Lu–prostate-specific membrane antigen, investment and research interests in these and other radionuclide therapies are rapidly expanding. The purpose of the European Working Group is to promote knowledge, investment, and networking in the area of (radio)biology of radionuclide therapy.

This report details recent research and inspiring insights presented at the inaugural International Workshop on Radiobiology of Molecular Radiotherapy, held as a hybrid meeting in Montpellier, France, on March 17 and 18, 2021. After a 2019 call to arms (1), the workshop was another pioneering step in bringing the community together. The aim of the workshop was to promote networking within the community, increase understanding of the biological effects of cancer therapy with radionuclides emitting ionizing particles, determine how this understanding can assist in improving therapeutic outcome, and explore the best ways to translate these findings into the clinic. On average, 150 attendees from 37 countries in 5 continents participated in talks, debates, and roundtable discussions. Proffered talks and posters were selected from more than 40 abstract submissions.

Emmanuel Deshayes, from the host institution, the Institut du Cancer de Montpellier, gave the first keynote address, highlighting the role of radiobiology in treatment of neuroendocrine cancers. As a nuclear medicine physician, he stressed the importance of 6 major areas in radiobiology of radionuclide therapy, including: (i) physical parameters of the radionuclide and normal tissue response, including accurate dosimetry; (ii) role of radiopharmaceuticals and targeted distribution at both the (sub)cellular and tissue levels; (iii) role of the tumor microenvironment and other systemic interplay; (iv) identification of biomarkers of response to potentially allow adaptive dose scheduling, including biomarkers for prediction of therapy outcome; (v) determining optimal combination therapies, based on improving perfusion, target receptor upregulation, coadministration of other DNA damaging agents, or the addition of targeted drugs that manipulate associated signaling pathways; and (vi) studying the effects of molecular radionuclide therapy (MRT) on healthy tissues.

A series of proffered talks highlighted the best work submitted as abstracts by junior colleagues. Danny Feijtel (Erasmus Medical Center; Rotterdam, The Netherlands) detailed his work on somatostatin receptor heterogeneity and its influence on ^{177}Lu-DOTATATE therapy efficacy. Ines Costa (King's College; London, UK) talked about the potential of ^{99m}Tc as a radionuclide for therapy, employing a classical approach using DNA plasmids to assess therapeutic potential, while highlighting that subcellular microdistribution is of utmost importance for these Auger electron emitters. Tiffany Chan (University of Oxford; UK) described their methodology to acquire and analyze high-throughput screens of several thousand drugs in combination with ^{177}Lu-DOTATATE therapies, compared with external-beam radiotherapy combinations. Uta Eberlein (University of Würzburg; Germany) talked about their ability to visualize tracks of DNA damage repair foci in peripheral blood monocytes after irradiation with α particles from ^{223}Ra therapy and the potential to use this as a biodosimeter to determine radiation absorbed dose in hematopoietic tissues.

In the second keynote address of the day, Elif Hindie (Centre Hospitalier Universitaire de Bordeaux; France) spoke on physical differences between several radionuclides for MRT and their potential for treatment of micrometastases, approached using Monte Carlo modeling. With this methodology, his team investigated the radiation absorbed dose from the medium-range β-emitter ^{177}Lu and compared this with ^{161}Tb, which emits β particles as well as substantial numbers of short-range, low-energy conversion and Auger electrons. They concluded that this type of isotope would allow not only for optimal treatment of large tumors but simultaneously enable more optimal targeting of smaller metastases. For even smaller tumor sections, such as circulating tumor cells, Auger electron emitters, with even shorter emission ranges, were proposed and identified as potentially therapeutic, even at low absorbed radiation doses.

The final session on the first day included a presentation from the members of the European Working Group on their research and profiles.

The second day began with Mark Konijnenberg (Erasmus Medical Centre), who emphasized the continued importance of radionuclide dosimetry, given its necessity in facilitating comparison of different studies. However, he continued by highlighting the difficulties in obtaining reliable dosimetry, especially in smaller tumors. He went further by questioning the general applicability of the linear-quadratic model and the term "biological equivalent dose" for radionuclide therapy, despite the fact that the concept is tried and tested for

external-beam radiotherapy. Reliable dosimetry becomes further constrained by limitations at the cellular or even suborgan structural scales. It is difficult to calculate true radiation dose in grays, and a gray may not be a gray in terms of biological consequences, such as tumor growth inhibition or healthy tissue toxicity.

An entertaining debate on the necessity of radiobiology followed, with Erik Verburg (a clinician at Erasmus Medical Centre investigating MRT) arguing for and Christophe Badie (a senior radiobiologist at Public Health England's Centre for Radiation, Chemical, and Environmental Hazards [Chilton, UK]) arguing against the proposition: "This house believes that radiobiology is useful for improving MRT." A selection of the more notable arguments (some hyperbolic or facetious and some irritably germane) included: (i) We are a storytelling species (quoting Jonathan Gottschall). Thus, we either ignore evidence that does not fit our story or blend and mold it until it does. Therefore, we use radiobiology when it fits with our desire to promote MRT or to disguise our knowledge deficiencies. (ii) MRT works and has a great future, so that we are likely to see an increase in the number of patients treated with MRT. (iii) The gray is not a useful unit for MRT. If we cannot even get dosimetry right, we have no chance of coming to grips with the intricacies of (radio)biology; the multidimensionality of the problem is too complex. (iv) There is a lack of data to investigate MRT with the same vigor and intensity as we do chemotherapy drugs, especially in the clinic. (v) We do not need to understand the biology of MRT for it to be effective. (vi) Administered activities or radiation absorbed dose do not predict outcome, biology does. After an entertaining debate, the motion was accepted, reinforcing the need for the entire symposium.

A discussion on bridging the gap between laboratory and clinic for MRT followed, with panel members answering questions on immediate clinical questions in MRT. Panelists included Deshayes, Hindie, Katherine Vallis (University of Oxford), and Mark Gaze (University College London Hospitals; UK). The panelists recognized that the field still faces major hurdles in translating basic research into clinical and practical applications. Kevin Prise (Queen's University Belfast; Ireland) gave his expert view on the need to understand the biology of molecular radiotherapy by considering high-linear-energy transfer radiation effects, target expression, crossfire, bystander, and abscopal contributions. This was followed by Simon Bouffler (Public Health England's Centre for Radiation, Chemical, and Environmental Hazards), with expert perspectives on European Union funding. In a roundtable discussion, the following issues were identified as important: optimized dosimetry; determining the optimal therapeutic window of dose, including normal tissue toxicity studies; accelerated clinical trials; standardization (including whether to use the name MRT or targeted radionuclide therapy); and biobanking to make tissues available.

Eva Forssell-Aronsson (University of Gothenburg; Germany) spoke on low-dose and low-dose-rate radiobiology of MRT. She highlighted the great differences in dose rate between MRT and external-beam radiotherapy and the resulting lack of understanding of how much radiation absorbed dose is needed for tumor control or to avoid normal tissue toxicity (a recurring theme). She advocated a new radiobiological framework, in which various 'omics' and large datasets are compounded to better understand the radiobiology of MRT. She further highlighted research on the influence of circadian rhythm on thyroid toxicity following ^{211}At, a unique perspective.

The second series of proffered talks included those by Treewut Rassamegevanon (Oncoray; Dresden, Germany) and Sara Lundsten et al. (Uppsala University; Sweden) on combining radionuclide therapy with external-beam radiotherapy or a p53-activating peptide, respectively. Justine Perrin (Centre de Recherche en Cancérologie et Immunologie Nantes Angers; France) talked about the tumor microenvironment and targeted α particle therapy, and Julie Constanzo (Institut de Recherche en Cancérologie de Montpellier) offered insights on the role of extracellular vesicles in immunologic reactions to external-beam and molecular radiotherapy.

The final lecture of the symposium, by Claire Vanpouille-Box (Weill Cornell Medicine; New York, NY), centered on the interplay between radiation oncology and immunology and lessons that may be learned for MRT. Her group investigates key factors affecting the immunogenicity of radiotherapy in glioblastomas to achieve better understanding of metabolic changes, molecular pathways, and cellular responses from the host and/or the tumor that result from radiation therapy. With this lecture, she showed new actionable targets for modulation of antitumor immune responses against glioblastomas.

Many congratulations were forwarded to Justine Perrin and Tiffany Chan, who were awarded prizes for best oral presentations, and Elise Verger and Jihad Karam, who won in the best poster category.

Radiobiology remains as important as ever and has an important role to play in interpreting and improving radionuclide therapy. New contacts were established, with follow-up meetings planned to identify concrete ways forward and to expand the working group. A Scholar-in-Training Committee, inspired by the Radiation Research Society, was also created. It aims to increase the visibility of scholar-in-training members within the radiobiology of molecular radiotherapy community and works to offer networking and community opportunities. Additional information is available at: www.mrtradiobiology.com.

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