

Cite this article as:

Martin S, Prise KM, Hill MA. Pushing the frontiers of radiobiology: A special feature in memory of Sir Oliver Scott and Professor Jack Fowler. *Br J Radiol* 2019; **92**: bjr.20189005.

PUSHING THE FRONTIERS OF RADIOBIOLOGY: A SPECIAL FEATURE IN MEMORY OF SIR OLIVER SCOTT AND PROFESSOR JACK FOWLER: EDITORIAL

Pushing the frontiers of radiobiology: A special feature in memory of Sir Oliver Scott and Professor Jack Fowler

¹STEWART MARTIN, ²KEVIN M PRISE and ³MARK A HILL

¹Department of Clinical Oncology, Translational & Radiation Biology Research Group, Division of Cancer and Stem Cells, University of Nottingham, Nottingham University Hospitals NHS Trust, Nottingham, UK

²Centre for Cancer Research and Cell Biology, Queen's University Belfast, Belfast, UK

³Department of Oncology, CRUK/MRC Oxford Institute for Radiation Oncology, Gray Laboratories, University of Oxford, Oxford, UK

Address correspondence to: Prof Stewart Martin

E-mail: stewart.martin@nottingham.ac.uk

The end of 2016 was a challenging period for the radiation research community as it lost two of its pioneering researchers who have made a major impact over many years, Sir Oliver Scott and Professor Jack Fowler. To mark the passing of these two highly influential scientists, a memorial symposium was held at the University of Oxford on 6 September 2017. This special feature brings together a collection of commentaries and reviews from some of the speakers at the symposium and from other contributors who were heavily influenced by Jack and Oliver during their scientific careers.

We start with a commentary, from Barry Michael,¹ looking at Sir Oliver Scott's seminal work and impact on the field of research, with discussion of some of the key events that shaped his career, with a view to its legacy and impact including the founding of the Gray Cancer Institute (formerly the British Empire Cancer Campaign Research Unit in Radiobiology). This is followed by further reflections in a commentary from Klaus Trott covering a less well-known aspect of Oliver's interest, namely the area of cancer immunology and radiobiology, currently very topical, and his struggle for the perfect tumour model in translational research.²

Oliver's key contribution was in defining the critical importance of oxygen in radiation response and we only have to look at the titles of the commissioned papers to see the extent of its impact. We start with a commentary from James Coates et al,³ on the shift of focus from oxygen supply to demand in strategies for targeting tumour hypoxia. This is followed by an extensive review, "Tumor Oxygenation and Cancer Therapy—Then and Now", from Dietmar Siemann and colleagues⁴ which reviews the landscape in this area, setting the scene for several of the following papers. The review discusses the physiological basis of

hypoxia, methods of detection and strategies to overcome the resulting therapy resistance.

The fundamentals of how Oliver's work has driven an understanding of the underlying chemistry of hypoxia and specifically the development of hypoxic radiosensitisers, based on misonidazole, are covered by Peter Wardman.⁵ He covers the challenges in the development of these agents whilst highlighting their utility as diagnostic probes for tumour hypoxia.

For clinical utility in the modern genomics era, there is a need for suitable biomarkers to enable progression to biologically personalised radiotherapy. Lingjian Yang and Catharine West review the published hypoxia gene signatures, summarising their development and validation. They show that current evidence supports investment in gene signatures as a promising hypoxia biomarker approach for future clinical utility.⁶

A novel angle is discussed in a review by Monica Olcina et al⁷ linking hypoxia and the microenvironment. Specifically, they explore how hypoxia alters regulation of complement proteins in different cellular components of the tumour microenvironment, as well as the downstream biological consequences of this regulation. The complement system is an innate immune pathway, part of the first line of defence against "non-self" species and is thought to have an active role in facilitating cancer-associated processes such as increased proliferation, angiogenesis and migration.

Many clinical trials have targeted hypoxia and despite disappointments, meta-analysis has shown a significant impact on tumour control and survival. These trials are reviewed by Hannah Tharmalingham and Peter Hoskin⁸

who highlight the lack of proper patient selection in the past which is now being addressed with the availability of histological necrosis, immunohistochemical intrinsic markers such as CAIX and Glut-1 and hypoxia gene signatures.

A closely related area is the underpinning role of the tumour vasculature and strategies to target this, which is reviewed by Chryso Kanthou and Gillian Tozer.⁹ The development of blood vessels by the process of angiogenesis underpins growth and metastasis of many tumour types. Although clinical approaches have been focused on targeting the major angiogenesis inducer vascular endothelial growth factor A and its receptors, a lack of suitable biomarkers has limited progress. Nevertheless there is significant potential for combining radiotherapy with antiangiogenic therapies.

Our final review from the perspective of Sir Oliver Scott's work is on human papillomavirus (HPV), hypoxia and radiosensitivity in head and neck cancer from Ester Hammond and colleagues.¹⁰ HPV-positive tumours are remarkably radiosensitive compared to HPV-negative tumours and consequently the HPV-positive patients have a better prognosis. It is also known that hypoxia is a negative prognostic factor and the challenge is to understand the implications for treating HPV-positive and -negative tumours.

For coverage of the impact of the career of Professor Jack Fowler, we start with an excellent overview of his life, work, impact and legacy by Jolyon Hendry.¹¹

This is followed by a commentary from Tracy Underwood and Stephen McMahon discussing the multiscale problem of the proton relative biological effectiveness.¹² Particle therapy was an area of early interest to Professor Jack Fowler and he input into substantive studies testing the potential of neutrons. They propose that accurate and robust optimisation of proton radiotherapy ultimately requires a multiscale understanding of relative biological effectiveness, integrating subcellular, cellular and patient-level processes, something that Jack would have agreed with.

Both Jack and Oliver appreciated the key role of suitable models of normal tissue damage. In a review from Jackie Williams and Wayne Newhauser,¹³ they discuss from a radiation biology and radiation physics perspective, normal tissue damage models and challenges for the future, especially against a background of less appreciation of their importance in clinical delivery.

Much of Professor Jack Fowler's work was at the boundaries of mathematical modelling, experimental radiobiology and clinical

translation, so we start with an overview from Pedro Victori and Francesca Buffa¹⁴ highlighting the general application of modelling in oncology and radiation therapy. This is followed by a more detailed review on the evolution of radiobiological modelling from Bleddyn Jones and Roger Dale.¹⁵ This covers the fundamental principles of the linear-quadratic and biologically effective dose models, their applicability to not only photon but also particle radiotherapies as well as low and high dose ranges, dose rates, hypoxia and repopulation.

A complimentary review from Roger Dale¹⁶ focuses on radiation repair models for clinical application. It highlights the impact of Jack's work in this area. Specifically it highlights a number of newly emerging clinical techniques that involve non-conventional patterns of radiation delivery which require an appreciation of the role played by radiation repair phenomena.

The essence of much of Jack's research was around optimising the use of fractionated radiotherapy. John Yarnold¹⁷ reviews the changes that have occurred in radiotherapy fractionation for breast cancer. He outlines that breast cancer responds more strongly to fraction size than many other common cancers. Specifically, hypofractionation can be exploited to modulate dose intensity across the breast according to relapse risk by varying fraction size across the treatment volume.

We come back to the theme of normal tissue damage in a review by Marie-Catherine Vozenin and colleagues¹⁸ on expanding the therapeutic index of radiation therapy by normal tissue protection. They discuss translatable pharmacological approaches that have been developed to prevent, mitigate or reverse radiation injury based upon the targeting of cellular and signalling pathways. They also briefly highlight innovative approaches based upon novel radiotherapy delivery procedures.

Our final paper, in this special feature, is from Bleddyn Jones and John Hopewell¹⁹ and covers modelling the influence of treatment time on radiosurgery single treatment biological effectiveness to produce protective dose modification factors. This would have been a paper of great interest to Jack, taking into account time variations to provide a simpler model for adjusting total dose to compensate for significant variations in central nervous system radiosurgical treatment times.

No special feature can, in any way, do justice to these two exceptional scientists or cover the full breadth of their impact but we hope that the selected articles presented here point readers to many of their substantive contributions.

REFERENCES

1. Michael BD. An appreciation of the science and philanthropy of Sir Oliver Scott, founder of the Gray Cancer Institute. *Br J Radiol* 2019; **92** (1093): 20180402. doi: <https://doi.org/10.1259/bjr.20180402>
2. Trott K-R. Cancer immunology and radiobiology: Oliver Scott's struggle for the perfect tumour model in translational research. *Br J Radiol* 2019; **92** (1093): 20180188. doi: <https://doi.org/10.1259/bjr.20180188>

3. Coates JT, Skwarski M, Higgins GS. Targeting tumour hypoxia: shifting focus from oxygen supply to demand. *Br J Radiol* 2019; **92** (1093): 20170843. doi: <https://doi.org/10.1259/bjr.20170843>
4. Hughes VS, Wiggins JM, Siemann DW. Tumor oxygenation and cancer therapy—then and now. *Br J Radiol* 2019; **92** (1093): 20170955. doi: <https://doi.org/10.1259/bjr.20170955>
5. Wardman P. Nitroimidazoles as hypoxic cell radiosensitizers and hypoxia probes: misonidazole, myths and mistakes. *Br J Radiol* 2019; **92** (1093): 20170915. doi: <https://doi.org/10.1259/bjr.20170915>
6. Yang L, West CM. Hypoxia gene expression signatures as predictive biomarkers for personalising radiotherapy. *Br J Radiol* 2019; **92** (1093): 20180036. doi: <https://doi.org/10.1259/bjr.20180036>
7. Olcina MM, Kim RK, Melemenidis S, Graves EE, Giaccia AJ. The tumour microenvironment links complement system dysregulation and hypoxic signalling. *Br J Radiol* 2019; **92** (1093): 20180069. doi: <https://doi.org/10.1259/bjr.20180069>
8. Tharmalingham H, Hoskin P. Clinical trials targeting hypoxia. *Br J Radiol* 2019; **92** (1093): 20170966. doi: <https://doi.org/10.1259/bjr.20170966>
9. Kanthou C, Tozer G. Targeting the vasculature of tumours: combining VEGF pathway inhibitors with radiotherapy. *Br J Radiol* 2019; **92** (1093): 20180405. doi: <https://doi.org/10.1259/bjr.20180405>
10. Göttgens EL, Ostheimer C, Span PN, Bussink J, Hammond EM. HPV, hypoxia and radiation response in head and neck cancer. *Br J Radiol* 2019; **92** (1093): 20180047. doi: <https://doi.org/10.1259/bjr.20180047>
11. Hendry JH. Commemoration of Jack Fowler's life, work, impact and legacy. *Br J Radiol* 2019; **92** (1093): 20170967. doi: <https://doi.org/10.1259/bjr.20170967>
12. Underwood TS, McMahon SJ. Proton relative biological effectiveness (RBE): a multiscale problem. *Br J Radiol* 2019; **92** (1093): 20180004. doi: <https://doi.org/10.1259/bjr.20180004>
13. Williams JP, Newhauser W. Normal tissue damage: its importance, history and challenges for the future. *Br J Radiol* 2019; **92** (1093): 20180048. doi: <https://doi.org/10.1259/bjr.20180048>
14. Victori P, Buffa FM. The many faces of mathematical modelling in oncology. *Br J Radiol* 2019; **92** (1093): 20180856. doi: <https://doi.org/10.1259/bjr.20180856>
15. Jones B, Dale RG. The evolution of practical radiobiological modelling. *Br J Radiol* 2019; **92** (1093): 20180097. doi: <https://doi.org/10.1259/bjr.20180097>
16. Dale RG. Radiation repair models for clinical application. *Br J Radiol* 2019; **92** (1093): 20180070. doi: <https://doi.org/10.1259/bjr.20180070>
17. Yarnold J. Changes in radiotherapy fractionation-breast cancer. *Br J Radiol* 2019; **92** (1093): 20170849. doi: <https://doi.org/10.1259/bjr.20170849>
18. Montay-Gruel P, Meziani L, Yakkala C, Vozenin MC. Expanding the therapeutic index of radiation therapy by normal tissue protection. *Br J Radiol* 2019; **92** (1093): 20180008. doi: <https://doi.org/10.1259/bjr.20180008>
19. Jones B, Hopewell JW. Modelling the influence of treatment time on the biological effectiveness of single radiosurgery treatments: derivation of "protective" dose modification factors. *Br J Radiol* 2019; **92** (1093): 20180111. doi: <https://doi.org/10.1259/bjr.20180111>