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

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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 the 6th of September 2017. This special issue 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, looking at Sir Oliver'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) [BJR-D-18-00402]. 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 [BJR-D-18-00188].

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 Geoff Higgins and James Coates [BJR-D-17-00843], on the shift of focus from oxygen supply to demand in strategies for targeting tumour hypoxia. This is followed by an extensive review on Tumor Oxygenation and Cancer Therapy - Then and Now, from Dietmar Siemann [BJR-D-17-00955] 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 [BJR-D-17-00915]. 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. Catharine West reviews the published hypoxia gene signatures, summarising their development and validation. She shows that current evidence supports investment in gene signatures as a promising hypoxia biomarker approach for future clinical utility [BJR-D-18-00036].

A novel angle is discussed in a review by Monica Olicina del Molino [BJR-D-18-00069] linking hypoxia and the microenvironment. Specifically, she explores 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 Peter Hoskin and Anamaria Rojas [BJR-D-17-00966] 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 Gillian Tozer and Chryso Kanthou [BJR-D-18-00405]. The development of blood vessels by the process of angiogenesis underpins growth and metastasis of many tumour types. Although clinical approaches have been focussed on targeting the major angiogenesis inducer vascular endothelial growth factor A (VEGF-A) and its receptors, a lack of suitable biomarkers has limited progress. Nevertheless there is significant potential for combining radiotherapy with anti-angiogenic therapies.

Our final review from the perspective of Oliver Scott's work is on HPV, hypoxia and radiosensitivity in head and neck cancer from Ester Hammond [BJR-D-18-00047]. HPV-positive tumours are remarkably radiosensitive compared to HPV-negative tumours and consequently the HPV-positive patients have a better prognosis. It is also know 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 Jack Fowler, we start with an excellent overview of his life, work, impact and legacy by Jolyon Hendry [BJR-D-17-00967].

This is followed by a commentary from Tracy Underwood and Stephen McMahon discussing the multi-scale problem of the proton relative biological effectiveness (RBE) [BJR-D-18-00004]. Particle therapy was an area of early interest to Jack Fowler and he input into substantive studies testing the potential of neutrons. They propose that accurate and robust optimization of proton radiotherapy ultimately requires a multi-scale understanding of RBE, integrating sub-cellular, 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 commentary from Jacki Williams and Wayne Newhauser [BJR-D-18-00048], 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 Jack Fowlers' work was at the boundaries of mathematical modelling, experimental radiobiology and clinical translation, so we start with an overview from Pedro Victoria and Francesca Buffa [BJR-D-18-00856R1] 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 [BJR-D-18-00097]. This covers the fundamental principles of the LQ model and BED models their applicability to not only photon but particle radiotherapies as well as low and high dose-ranges, dose-rates, hypoxia and repopulation.

A complimentary review from Roger Dale [BJR-D-18-00070] focuses on Radiation Repair models for clinical application. It highlights the impact of Jack Fowlers 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 Yarnold [BJR-D-17-00849] 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 [BJR-D-18-00008] on expanding the therapeutic index of radiation therapy by normal tissue protection. She discusses translatable pharmacological approaches that have been developed to prevent, mitigate, or reverse radiation injury based upon the targeting of cellular and signalling pathways. She also briefly highlights innovative approaches based upon novel radiotherapy delivery procedures.

Our final paper, in this special issue, is from Bleddyn Jones and John Hopewell [BJR-D-18-00111] 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 CNS radio-surgical treatment times.

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