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Guest Editorial

Themed Issue: Radiation biology – can new concepts achieve better treatment outcomes?

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Due to an oversight by the publishing office the editorial for the special issue of JPP (Radiation biology – can new concepts achieve better treatment outcomes? JPP Volume 60, issue 8) was omitted from the journal. The publishers would like to apologize to the authors and readers for this mistake on our part.

The editorial that should have accompanied the special issue can be seen below.

The successful introduction of themed issues in the *Journal of Pharmacy and Pharmacology* was initiated in 2005. This, the fourth themed issue, is a summary of pertinent reviews based on the scientific presentations of several keynote speakers who attended the Association for Radiation Research Annual Meeting at The School of Pharmacy, Queen's University Belfast on 3rd–5th April 2007. This highly successful meeting brought together scientists from all over the world with a special interest in radiation biology and physics, with a view to understanding the effects of radiation at the cellular level and to discuss strategies for improving radiation-based therapies both on their own and in combination with other treatments. This special issue will focus on some of the key findings, bringing the readership up-to-date in this rapidly advancing area.

Radiation biology can be described as the study of the biological effects of radiation on living cells. Ionizing radiation is a well-known carcinogen and yet ionizing radiation is a highly effective modality for the treatment of solid tumours. Understanding how radiation induces DNA damage, leading to tumour cell kill or carcinogenesis in normal tissues was the focus of several reviews in this current issue. In particular, three reviews by Hei et al, Boyd et al and Chapman et al, focused on the intriguing concept of low dose radiation-induced bystander effects. This phenomenon, describing radiation-like damage in cells/tissue that have communicated with irradiated cells, but were not themselves irradiated, has important implications for the estimation of risks of exposure to ionizing radiation and for the efficacy of radiotherapy. These three articles provide the evidence for radiation-induced bystander effects and review our current knowledge of the biochemical and molecular events involved. Evidence to suggest that bystander effects can be harnessed to enhance targeted radionuclide therapy was also presented. In addition, McMillan et al describe similar bystander phenomena following exposure of cells to UVA radiation, a previously under-researched region of the electromagnetic spectrum, which is now demonstrating carcinogenicity in animal models. This review highlights the detrimental effects of UVA sun bed use and suggests that low dose rate UVA, such as that delivered to skin after sunscreen use, may have important and detrimental implications. Together, this group of articles highlights the need to further explore the long term effects of low doses of radiation and its implications for cancer induction and how these effects could be exploited to improve radiotherapy outcomes.

Whilst ionizing radiation as a treatment modality has been highly successful clinically, one major drawback is the dose-limiting toxicity to normal tissues. Three exciting reviews describe how agents can be used to enhance, target and radiosensitize tumours to radiotherapy. Hainfield et al discuss a novel approach, which has the potential to revolutionize radiotherapy treatment. This is based on the premise that the

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radiation dose is increased when a high-Z material is in the targeted zone. Hainfield proposes that loading tumours with gold could lead to increased X-ray deposition within tumours, enhancing tumour cell kill. Whilst most of the studies in this area are theoretical there are a few studies to support this hypothesis both in-vitro and in-vivo. The data demonstrate that more focused research in this area, in particular development of low energy radiation sources, best for maximizing gold absorption, and the development of functionalized gold nano-particles that can target tumours specifically, would advance this field further. The review by Ivanov et al also highlights a novel way to increase the sensitivity of haematological malignancies to radiation by using radionuclides conjugated to targeting antibodies. Single agent use of monoclonal antibodies (mAbs) has led to modest improvements in patient outcome for a range of human tumours; however, when combined with radiation there is a marked enhancement in response. Thus, mAb-derived constructs that are chemically conjugated to therapeutic radioisotopes lead to improved targeting and have shown real clinical benefit. Interestingly, antibody effector mechanisms appear to be as important in the tumour response as the ability of the antibody to carry the radioisotope to the target site. The authors highlight how radioimmunotherapy of this sort has resulted in FDA approval of two such agents, ^{90}Y-ibritumomab and ^{131}I-tositumomab, in addition to ^{90}Y-ibritumomab tiuxetan within the EU, which have shown impressive response rates and durable remissions in patients with lymphomas. Finally, McCarthy et al, using an entirely different approach, have demonstrated that increasing the levels of nitric oxide synthase in tumours using a gene therapy approach, resulting in high levels of the free radical nitric oxide, is an effective means of sensitizing hypoxic tumour cells to radiation. Several strategies are discussed to target the gene therapy to tumours including various radiation inducible promoters to drive gene expression only in irradiated tumour tissues, thereby restricting normal tissue toxicity. Furthermore, the authors reveal that nitric oxide synthase gene therapy has wide ranging applications in a host of other diseases, partly because the product of this procedure, nitric oxide, is not only cytotoxic, which is important for tumour cell kill and prevention of restenosis of arterial grafts, but has a host of other important cellular functions such as relaxation of the endothelium, useful for the treatment of atherosclerosis.

It is now widely recognized that treating tumours with agents that target multiple pathways is more likely to achieve a response than single-agent therapy. There are several articles within this issue highlighting combined modality approaches. These include the use of small molecule targeted drugs or monoclonal antibodies in combination with radiation. Zips et al review two agents that block the epidermal growth factor receptor (EGFR), which controls tumour growth and progression upon ligand binding; EGFR overexpression is correlated with radioresistance. In these preclinical studies, cetuximab (Erbitux), an IgG1 monoclonal antibody against the extracellular ligand-binding domain of EGFR, was superior in terms of improved local tumour control when given concurrently with radiation, compared to the small molecule intracellular tyrosine kinase inhibitor, BIBX1382BS. Early indications suggest that cetuximab alters both repopulation and reoxygenation, key processes affecting radiation induced cell kill. Further work will be required to fully characterize the mechanisms involved before these agents can be fully exploited clinically. Shannon and Williams discuss the potential of combining radiotherapy with the highly topical anti-angiogenic inhibitors. This class of agents target endothelial cells and can paradoxically 'normalize' the vasculature, decreasing the radioresistant hypoxic fraction within tumours. Several of these agents are discussed, which have been successfully combined with radiotherapy and the importance is emphasized of accurate scheduling if they are to play an important role in advancing positive clinical outcomes.

Whilst the majority of the reviews in this issue have focused on understanding radiation-induced effects in tumours and harnessing these by treatment with radiation/radiation-based combinations, Rezvani has focused on adverse side effects of radiation on normal tissues. In particular, this review evaluates the usefulness of several groups of agents that protect against normal tissue damage. The most widely studied mediators of radiation damage appear to be substances that interfere with prostaglandin synthesis and eicosanoid metabolism and, although there have been some successes, there are many contradictory reports suggesting that further research in this important area is highly justified. Finally, the review by Hyodo et al highlights the importance of cancer imaging, with the development of novel metabolic responsive contrast agents to assess tissue redox status. This innovative strategy can be used to determine the response of tumours to certain chemotherapy agents, which are dependent on the redox status of a tumour. This unique approach has allowed a therapeutic radioprotective agent, Tempol, to be visualized by MRI in preclinical models, thus allowing optimal timing of Tempol administration with respect to radiation treatment in order to provide selective radioprotection to normal tissues. More research in this area will facilitate improved imaging and progression of this exciting technology to the clinic.

In summary, this issue encompasses diverse fields in radiation research from basic radiation science, such as bystander effects, and more clinically translational reviews covering 1) tumour radiosensitization, 2) combined modality therapy, 3) normal tissue radioprotection, and 4) tumour imaging. The diversity in this field suggests a continued and sustained interest in this important area of cancer research, which is perhaps not surprising since radiotherapy remains a highly effective modality in 50% of cancer patients. This supports the view that new biological concepts as applied to radiotherapy can indeed achieve better treatment outcomes for cancer patients.

The production of this themed issue has benefited from the input of many people and we would like to thank them for their tireless efforts on behalf of the journal. Firstly, we would like to acknowledge the authors for agreeing to write these excellent reviews, which will act as an important

reminder of the Association for Radiation Research's Belfast Meeting. Secondly, we would like to thank Professor David Jones, for proposing the concept of this themed issue and we must thank Mrs Grainne Caffrey at the JPP editorial office in Belfast and the staff, particulary Dr Shahnaz Khan, at Pharmaceutical Press for ensuring that the papers were carefully processed, reviewed and published to their deserved high standard.

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