Meeting Report on ICRR2019, the 16th International Congress on Radiation Research

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The 16th International Congress of Radiation Research (ICRR2019) was held in the Manchester Congress Centre, UK from August 25th to 29th. This Congress is held every four years and covers a broad spectrum of topics relevant for radiation biologists, chemists, physicists and oncologists. The host organisers were the Association for Radiation Research (ARR) with support from the International Association for Radiation Research (IARR). This is a pivotal meeting to foster international collaborations, learn state-of-art technologies and thinking and, importantly, establish friendships and working relationships. ICRR2019 also encompassed in-depth workshops on defined topics. The Congress was organised into four parallel themes; Basic Mechanisms, Translational Research, Radiotherapy and Health Effects/Ecology. Health Effects/Ecology will be covered elsewhere[1]. Each theme was divided into eleven sessions with a plenary speaker and, usually, two keynote and two shorter talks.

Rob Bristow opened the meeting with a plenary talk describing his elegant studies on the genomic hallmarks of prostate cancers. Two spirited debates followed. Christian Tomasetti spoke for the motion that there were potential risks with using a linear no-threshold (LNT) model for radiological protection that at low dose/dose rates risks may be underestimated. Richard Wakeford argued that a perfect model was unrealistic and LNT represented a reasonable, working model. The second debate discussed whether a reliable predictor of radiotherapy (RT) response is a holy grail and unattainable. Ted Lawrence supported the motion, arguing that biology is complex and encompasses a field littered with fake news due to a failure to validate. Søren Bentzen argued that a predictor could be identified if studies were carried out correctly, and encompassed all information including fractionation, comorbidities and treatments.

Theme 1: Basic Mechanisms.

Charlie Limoli presented the plenary talk for this theme, discussing the response of the brain to clinical and deep space radiation. Radiation-induced cognitive dysfunction is evident but complex, implicating multiple targets and interplay. The impact of ionising radiation (IR) on the brain, however, must be understood to allow travel to Mars and optimal treatment of neuronal tumours.

In Session 1 (DNA Repair), Lee Zou described the role of ATR in response to aberrant R-loop accumulation during replication, reporting that ATR senses R-loops during replication, especially at centromeres. Gaelle Legube described how double strand breaks (DSB) within PolII transcribed genes are repaired by homologous recombination (HR), require R-loop formation and subsequent removal by Senataxin. PolI-transcribed genes, in contrast, require cohesin and the HUSH complex for break-induced transcriptional repression of rDNA, followed by mobilisation of the breaks at the nucleolar periphery. Sophie Polo, (Session 2, DNA Damage Signalling and Chromatin) discussed the processing of ultraviolet light-induced lesions within heterochromatin and, using an interesting system for visualising new and parental histone dynamics at damage sites, revealed how histone variant patterns can be reshaped during repair. Jessica Downs talked about the role of the remodelling complex, PBAF, in establishing sister chromatin cohesion during transcriptional silencing and how genome rearrangements ensued when transcriptional silencing failed. Session 3 covered Bystander and Signalling Responses with Tom Hei arguing that non-target bystander effects driven by mitochondrial responses challenged the LNT model. Mitochondrial dysfunction caused by targeted cytoplasmic IR drives multiple responses including activation of autophagy. Mary-

Helen Barcellos-Hoff focused on the contribution of the microenvironment to carcinogenesis, with cancer progression being driven by non-targeted alterations affecting intercellular signalling and homeostasis. Xueqing Zou in Session 4 (Radiation Exposure Signatures) discussed the mutational signatures obtained following exposure to known carcinogens using whole genome sequencing, and their relationship to cellular mechanism. Sally Amundson described how the pattern of gene expression changes provided a readout for IR exposure, acting as a biodosimeter, with some changes persisting long-term post exposure. A signature of expression changes reflecting IR exposure was observed using a genetically engineered mouse model, and was not influenced by pre-existing inflammatory status. Session 5 covered Basic Research into High Linear Energy Transfer (LET) and Proton Exposures. Kevin Prise overviewed studies defining the relative biological effectiveness of proton therapy, including the position of the spread out Bragg peak and DSB repair status. He also highlighted potentially important observations using FLASH, where dose rates of > 40 Gy/s provide significant protection to normal relative to tumour tissue. Claere Von Neubeck described a unique mouse experimental model to study RBE effects *in vivo.* A Neuroscience and Space Research session (Session 6) extended the subject of Charlie Limoli's lecture with Richard Britten and Kerry O'Banion describing mouse or rat models to assess neuronal pathology and function following high LET radiation, as well as following sleep deprivation, another facet of space travel. Session 7, also the subject of the morning's teaching session by Don Jones, was an excellent, longer session focusing on Radiation Chemistry and Oxidative Damage. The concept that radiochemistry pre-stages radiobiology was at the forefront, with Marc Greenberg focusing on understanding the chemistry of radical damage to DNA and the influence of histones. Cynthia Burrows considered how radical damage influences DNA structure and can hence be mutagenic. Doug Spitz described how differences in oxidative

metabolism in cancer cells can be targeted by exploiting redox biology. Session 8 covered the DNA Damage Response in Stem Cells, with Phil Jones describing how low dose radiation can drive p53 mutant cell expansion. Daohong Zhou discussed how IR can induce senescence and haematopoietic stem cell aging, and thus how senolytic drugs that selectively kill senescent cells can be used as radiation mitigators conferring anti-aging properties. Non-coding (nc)RNA and epigenetic changes were the subject of Session 9. Olga Kovalchuk overviewed the range of non-coding RNAs that can influence the radiation response, focusing on recently identified novel ncRNAs. Wei-Guo Zhu described some novel histone modifications that arise following genotoxic stresses, and how they confer genome instability. Session 10 focused on Hypoxia. Ester Hammond described hypoxia-induced replication stress and how it is affected when oxygen levels fluctuate i.e. cyclic hypoxia. Hiroshi Harada focused on HIF-1 in mediating radioresistance of hypoxic cancer cells and rationales for targeting. The final Session concerned Modelling Approaches. Michael Scholz described how different classes of DSBs could be quantitatively modelled and validated. David Brenner focused on mechanistic modelling of radiation carcinogenesis, introducing a new model encompassing multiple parameters.

Theme 2: Translational Research.

Amato Giaccia presented the Plenary Lecture covering Translational Research, discussing how hypoxia can promote the expansion of apoptotic and immune resistant clones, as well as clones resistant to chemotherapy and radiotherapy whilst tumour hypoxia also had the ability to confer inhibited repair, which could be exploited therapeutically.

Session 1 (Normal Tissue Radiobiology) commenced Marjan Boerma discussing how a reduction in levels of Activated Protein C (APC), an anticoagulant, enhanced long-term IR injury to the heart. Marie-Catherine Vozenin focused on FLASH-RT, an ultra-fast radiation delivery procedure, which uses an experimental electron beam delivering IR at dramatically higher dose rates than currently used and confers a striking protection of normal tissue. The potential efficacy of FLASH-RT was a meeting highlight, featuring in several presentations. Session 2 covered Radiation Response Modifiers with Michael Hay describing the development of hypoxia-activated DNA-PK inhibitors as potential radiosensitisers of hypoxic cells. Claire Rodriguez-Lafrasse reviewed the potential radiosensitisation capacity of nanoparticles containing metal atoms targeted to tumours by enhanced permeability and retention. Meredith Morgan in Targeting the DNA Damage Response (Session 3) overviewed the potential efficacy of combining DNA damage response inhibition with chemoradiation, including the combined use of PARP with ATR inhibitors, and ATM with immune checkpoint inhibition. Randi Syljuasen discussed the rationale and potential of combining CHK1 and WEE1 inhibitors to achieve synergy and enhanced radiosensitivity. Session 4 covered the exciting and topical area of Immune Response to Radiation, focusing on preclinical studies. Phuc Tran considered how abscopal responses in prostate cancer could be enhanced by combining immune checkpoint inhibitors with RT and ongoing clinical trials. Constantinos Koumenis discussed how PERK inhibitors in combination with RT can induce immunogenic cell death in hypoxic areas via infiltration of $CD8^+$ T cells. Session 5 covered Genomic Determinations: Radiation Response and Toxicity. Muhammad Abazeed described a cell-based, holistic approach of cancer genomics to identify alleles causing radiosensitivity by exploiting a neural network machine-learning algorithm using patient scans. Nic Denko presented his study on the use of papaverine to reduce oxygen consumption and therefore improve radiosensitivity

of hypoxic tumours. Session 6 focused on Exploiting Microbeams, Radiation Quality and Dose Rate for RT. Yolanda Prezado reviewed the use of microbeam (MRT) and minibeam (MBRT) RT to enhance the spatial fractionation of the dose to improve the sparing of normal tissue. MBRT was a favoured delivery approach although the underlying biological mechanisms enhancing the improved normal tissue response remain unclear. Kristoffer Petersson reported described the conversion of a conventional clinical linac to allow FLASH delivery, enhancing the ability to examine the process *in vivo* and *in vitro*. In Session 7 (The Influence of Cancer Metabolism on RT). Marianne Koritzinsky focused on the high ROS levels in cancer cells and dependency on anti-oxidants, similar to the situation post-irradiation. Peroxiredoxin (PRDX4) was shown to be important for cancer cell proliferation and to confer radiosensitivity. Ioanna Papandreou presented her findings on the role of HILPDA in the generation of lipid droplets and how this impacts malignant progression and therapeutic response. David Kirsch exploited mouse models to explore the changes in metabolism in cancer cells and following RT. Glutamine metabolism was shown to mediate both tumour growth and the radiation response in sarcomas, raising possible targets conferring radiosensitisation. Session 8 provided a thought-provoking overview of Combined Treatment Modalities. Steve Lin discussed the harmful effects of radiation-induced lymphopenia and the importance of mitigating strategies. Alan Melcher focused on the translational opportunities presented by combining immune modulation and RT, including PD-L1. The interface of Immunotherapy with RT was a further meeting highlight occurring in multiple themes and the subject of a teaching session. The responses of cancer or normal stem cells was another recurrent theme in the meeting. In Session 9 (Targeting/Avoiding Cancer or Normal Stem Cells), Frank Pajonk discussed the ability of tumour cells to de-differentiate into cancer stem cells following genotoxic stress, mimicking regeneration in normal tissues. Importantly, he has identified

compounds that promote normal tissue regeneration but prevent dedifferentiation in tumours. Rob Coppes described his organoid system to bioengineer patient derived salivary and thyroid gland stem cells and how they can be exploited to treat glandular radiation damage. Olga Martin in Session 10 (Intercellular Signalling) highlighted the importance of unrepaired systemic DNA damage to RT-induced pathologies, and the ensuing production of plasma cytokines. Eric O'Neill focused on immunoradiotherapy combinations particularly in pancreatic ductal adenocarcinoma. The final Session (Tumour/Cancer Cell Detection) had talks by Sarah Bohndiek and James O'Conner describing new non-invasive methods for imaging hypoxia, namely photoacoustic imaging (PAI) and magnetic resonance imaging (MRI). PAI had strength in quantifying and predicting the tumour response to oxygen modifying surgery whilst MRI could distinguish well from poorly oxygenated tumour regions.

Theme 3: Radiotherapy

A plenary talk by Fei-Fei Liu highlighted the metabolic dysregulation associated with radiation-induced fibrosis, and its potential for pharmacological inhibition to re-balance homeostasis of the extracellular matrix. In Session 1 (Second Cancers and Survivorship), Lindsay Morton emphasised the importance of inherited genetic susceptibility alongside treatment exposure for risk of RT-related second cancers. Wayne Newhauser summarised findings showing radioactive iodine treatment confers a small, long-term increased risk of death from a solid cancer with the dose-response for breast cancer induction being compatible with findings from the Lifespan Study. In Predicting RT Outcomes (Session 2) Javier Torres-Roca argued that the current "one-size-fits-all" approach is not optimal and could be improved by tumour profiling. Catharine West presented the findings from a GWAS

on prostate cancer highlighting how international collaborative efforts continue to identify new genetic variants that increase risk of RT toxicity. Session 3 (RT Modifiers) commenced with Michael Horsman describing the impact of targeting hypoxia, and a need for better standardisation in pre-clinical studies including assessment of dose response relationships and normal tissue effects. Anthony Chalmers highlighted the challenges of early phase trials combining DNA damage response inhibitors with RT, and the need for more data on side-effects and innovative platform trials. Clinical Application of Particle Therapy (session 4) had Marco Durante stressing the potential for combining particle therapy with immunotherapy. He showed evidence that protons elicit better immune responses than photons due to physical (fewer circulating immune cells irradiated) and biological reasons. Tatsuya Ohno summarised the status of carbon ion RT in Japan, highlighting its effectiveness against intractable, photon-resistance cancers. In Fractionation Revisited (Session 5), Mike Joiner stressed that the linear quadratic model over estimates cell kill/tumour control at high doses per fraction (the linear-quadratic-cubic model is better). He highlighted that the biological effective dose is increased for low α/ß tumours with shorter overall treatment times that reduce proliferation. Giuseppe Sanguineti reported reducing dose per fraction and increasing total dose (versus current tolerance of 35-36.5 in five fractions) is safe with stereotactic RT of the prostate when using a rectal spacer. In RT and Immunotherapy (Session 6), Tim Illidge highlighted the benefits of combining RT with immunotherapy, particularly using novel immuno-oncology agents. Quynh-Thu Le focused on immunotherapy for treating head and neck cancer, and biomarkers for patient stratification. Marianne Aznar in Precision RT (Session 7) described how multi-modality imaging can increase variability in contouring because the different approaches can give different volumes. She highlighted the value of workshops to increase the consistency in contouring.

David Jaffray described how MR-guided RT progressed from the fringe to mainstream (use in planning). He highlighted its potential use in the adaptive setting (e.g., daily imaging would allow for reduced margins in some patients) and a need to ensure the community develops a full understanding of the capabilities and risks of the new MR-linac platforms. Session 8 on Molecular Imaging in Patients highlighted the potential of the emerging field of radiomics, where medical images can be translated into quantitative data for profiling to aid diagnosis and outcome prediction (Ludwig Dubois). Daniela Thorwarth summarised the potential of hypoxia dose-painting RT in head-and-neck cancer by showing its feasibility to implement clinically, but stressed a need for large multi-centre trials. In Targeting Normal Tissue (Session 9), Peter Van Luijk discussed strategies to reduce normal tissue toxicity, focusing on cardio-pulmonary effects and how to counterbalance heart sparing without increasing the mean lung dose. Marcel Van Herk in Modelling and Theranostics (Session 10) reminded us about the revolution in hardware and software that has given RT unprecedented physical precision. He highlighted the new methodology available to learn from treating every patient but since uncertainties remain and patient outcomes are multifactorial, new planning tools are required. Petra Seibold described findings from the REQUITE study showing validation of some factors that predict for a risk of RT toxicity (e.g. abdominal surgery and several single nucleotide polymorphisms for rectal bleeding) but others did not (e.g. diabetes for urinary symptoms). In the final Session on Hypoxia-Clinical Studies, Brita Singers Sorensen reported on a hypoxia-specific gene expression signature for head and neck cancer being used in the DAHANCA30 trial to personalise RT. Heidi Lyng reported on a positive correlation between hypoxia (pimonidazole) and proliferation. She highlighted how gene signatures and imaging biomarkers could be combined to predict RT outcomes.

Summary.

ICRR2019 covered a broad range of areas and disciplines. A major goal of ARR and IARR is to promote the careers of future radiation biologists. We had a great representation of scholars/scientists in training (one quarter of those attending) with many superb shorter oral presentations and posters and contribution to session chairing. Unfortunately, we are unable to cover these and other presentations here. Abstracts remain available on the meeting website (http://icrr2019manchester.com/) and the meeting proceedings will be available on the ARR (https://www.le.ac.uk/cm/arr/home.html) and IARR https://www.radres.org/page/IARR) websites. A special issue of BJR will include articles covering award lectures. The organisers of ICRR2019 and the programme committee would like to thank all presenters for their enthusiasm and high quality presentations.

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