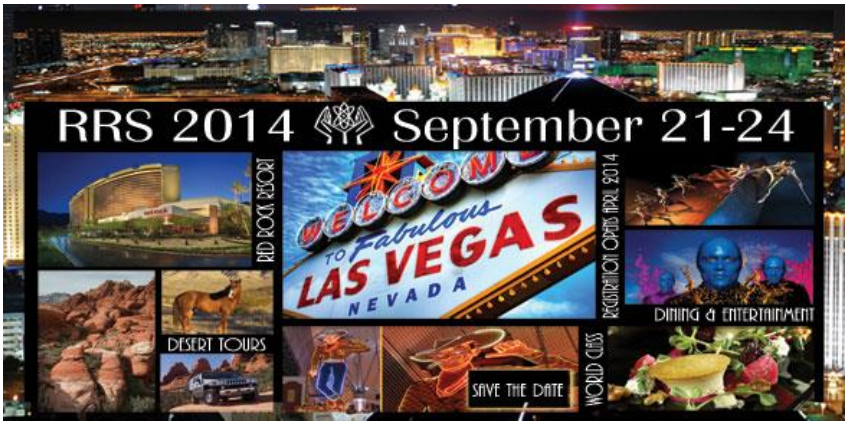
Radiation Research Society

Scholars in Training (SIT)

Newsletter October 2013

Welcome to the latest edition of the SIT newsletter. We hope you enjoyed the SIT workshop and mentors lunch at the annual meeting in the fantastic city New Orleans and are already starting to plan for RRS 2014 in Las Vegas!



SIT Programme 2013

We would like to thank all our speakers, mentors and SIT members for making the workshop and lunch such a success in New Orleans.

In order to improve the SIT workshop for next year and to increase our profile within RRS we need all SIT members to complete the post meeting survey. Please take a short time to complete this survey which is important for our continued development.

The survey can be found at;

http://www.radres.org/surveys/default.asp?id=2013_SIT_Workshop_Survey

The survey will remain open until October 11th, should you have any further ideas or suggestions please feel free to contact any of the committee members directly using the details at the back of the newsletter.

Mentors Lunch

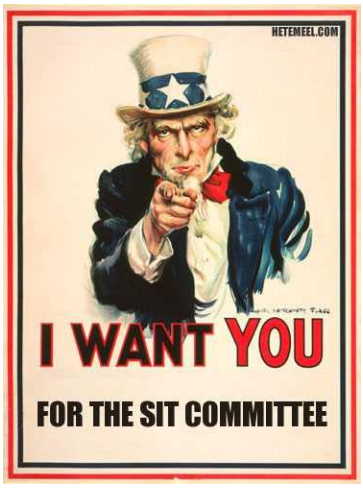
Thank you to all our mentors for making the lunch a huge success!








SIT Committee Recruitment



The SIT committee needs you! We are currently looking for ambitious SIT members to join the SIT committee. This is a great opportunity for personal and professional development by working as part of an international cross disciplinary team. All interested members should speak to any of the committee members to find out what is involved and send a CV and statement of interest to k.butterworth@qub.ac.uk. Applications should be received before Friday October 11th.

SIT Programme 2014

The SIT committee have already started putting together the programme for workshop next year. Please send your ideas and suggestions to k.butterworth@qub.ac.uk.

SIT Publications

Are you a SIT member who just had a publication accepted? **Please let us know** so we can highlight you accomplishments here in the SIT Newsletter! Just email your citation and abstract to k.butterworth@qub.ac.uk.

Hypoxia-Independent Downregulation of Hypoxia-Inducible Factor 1 Targets by Androgen Deprivation Therapy in Prostate Cancer

Harald Bull Ragnum, **Kathrine Røe,** Ruth Holm, Ljiljana Vlatkovic, Jahn Marthin Nesland, Eva-Katrine Aarnes, Anne Hansen Ree, Kjersti Flatmark, Therese Seierstad, Wolfgang Lilleby, Heidi Lyng.
Int J Radiat Oncol Biol Phys. 2013 Sep 10.

Purpose
We explored changes in hypoxia-inducible factor 1 (HIF1) signaling during androgen deprivation therapy (ADT) of androgen-sensitive prostate cancer xenografts under conditions in which no significant change in immunostaining of the hypoxia marker pimonidazole had occurred.
Methods and Materials
Gene expression profiles of volume-matched androgen-exposed and androgen-deprived CWR22 xenografts, with similar pimonidazole-positive fractions, were compared. Direct targets of androgen

receptor (AR) and HIF1 transcription factors were identified among the differentially expressed genes by using published lists. Biological processes affected by ADT were determined by gene ontology analysis. HIF1α protein expression in xenografts and biopsy samples from 35 patients receiving neoadjuvant ADT was assessed by immunohistochemistry.

Results

A total of 1344 genes showed more than 2-fold change in expression by ADT, including 35 downregulated and 5 upregulated HIF1 targets. Six genes were shared HIF1 and AR targets, and their downregulation was confirmed with quantitative RT-PCR. Significant suppression of the biological processes proliferation, metabolism, and stress response in androgen-deprived xenografts was found, consistent with tumor regression. Nineteen downregulated HIF1 targets were involved in those significant biological processes, most of them in metabolism. Four of these were shared AR and HIF1 targets, including genes encoding the regulatory glycolytic proteins HK2, PFKFB3, and SLC2A1. Most of the downregulated HIF1 targets were induced by hypoxia in androgen-responsive prostate cancer cell lines, confirming their role as hypoxia-responsive HIF1 targets in prostate cancer. Downregulation of HIF1 targets was consistent with the absence of HIF1α protein in xenografts and downregulation in patients by ADT (P<.001).

Conclusions

AR repression by ADT may lead to downregulation of HIF1 signaling independently of hypoxic fraction, and this may contribute to tumor regression. HIF1α expression is probably not a useful hypoxia biomarker during ADT in prostate cancer.

Bystander signalling: exploring clinical relevance through new approaches and new models.
Butterworth KT, McMahon SJ, Hounsell AR, O'Sullivan JM, Prise KM.
Clin Oncol (R Coll Radiol) 25(10):586-92, 2013.

Classical radiation biology research has centred on nuclear DNA as the main target of radiation-induced damage. Over the past two decades, this has been challenged by a significant amount of scientific evidence clearly showing radiation-induced cell signalling effects to have important roles in mediating overall radiobiological response. These effects, generally termed radiation-induced bystander effects (RIBEs) have challenged the traditional DNA targeted theory in radiation biology and highlighted an important role for cells not directly traversed by radiation. The multiplicity of experimental systems and exposure conditions in which RIBEs have been observed has hindered precise definitions of these effects. However, RIBEs have recently been classified for different relevant human radiation exposure scenarios in an attempt to clarify their role in vivo. Despite significant research efforts in this area, there is little direct evidence for their role in clinically relevant exposure scenarios. In this review, we explore the clinical relevance of RIBEs from classical experimental approaches through to novel models that have been used to further determine their potential implications in the clinic.

Radiosensitization by gold nanoparticles: effective at megavoltage energies and potential role of oxidative stress
Butterworth KT, McMahon SJ, Taggart LE, Prise KM.
Transl Cancer Res 2(4)269-279, 2013.

The multidisciplinary field of nanotechnology has the potential to deliver many novel applications in the biomedical field including improved strategies for the detection, diagnosis and treatment of cancer. In the radiation research arena, gold nanoparticles (GNPs) have demonstrated strong potential as diagnostic imaging agents, drug delivery platforms and radiation sensitizers due to their attractive physico-chemical characteristics. In the pursuit of dose modifiers to improve the therapeutic index of radiotherapy, GNPs have attracted much research interest due to the high atomic number (Z) of gold which results in significantly improved contrast compared to soft tissue. In this review, we consider the physical properties of GNPs which make them widely utilizable in the field of radiation research as image contrast agents, drug delivery vehicles and radiation sensitizers. In particular, we focus on the growing amount of preclinical evidence which demonstrates GNPs as radiation sensitizers and highlight the disparity between observed experimental findings and predictions based on mass attenuation, GNP concentration and beam energy. Considering the large amount of studies performed using a wide range of GNPs, emerging evidence suggests oxidative stress as a central mechanism of radiobiological response.

Insights into the mechanism of X-ray-induced disulfide-bond cleavage in lysozyme crystals based on EPR, optical absorption, and X-ray diffraction studies
Sutton, K.A. (Co-first author), **Black, P.J.** (Co-first author), Mercer, K.R., Garman, E.F., Owen, R.L., Snell, E.H. & Bernhard, W.A.
(2013) *Acta Cryst. D* **69** doi:10.1107/S0907444913022117

Electron paramagnetic resonance (EPR) and online UV‑visible absorption microspectrophotometry with X-ray crystallography have been used in a complementary manner to follow X-ray-induced disulfide-bond cleavage. Online UVvisible spectroscopy showed that upon X-irradiation, disulfide radicalization appeared to saturate at an absorbed dose of approximately 0.5‑0.8 MGy, in contrast to the saturating dose of _0.2 MGy observed using EPR at much lower dose rates. The observations suggest that a multi-track model involving product formation owing to the interaction of two separate tracks is a valid model for radiation damage in protein crystals. The saturation levels are remarkably consistent given the widely different experimental parameters and the range of total absorbed doses studied. The results indicate that even at the lowest doses used for structural investigations disulfide bonds are already radicalized. Multi-track considerations offer the first step in a comprehensive model of radiation damage that could potentially lead to a combined computational and experimental approach to identifying when damage is likely to be present, to quantitate it and to provide the ability to recover the native unperturbed structure.

Cetuximab Attenuates Its Cytotoxic and Radiosensitizing Potential by Inducing Fibronectin Biosynthesis
Eke I, Storch K, Krause M, Cordes N
Cancer Res. (2013) 73(19); 1-11, doi: 10.1158/0008-5472.CAN-13-0344

Inherent and acquired resistance to targeted therapeutics continues to emerge as a major clinical obstacle. For example, resistance to EGF receptor targeting occurs commonly, more so than was expected, on the basis of preclinical work. Given emerging evidence that cancer cell-substrate interactions are important determinants of therapeutic sensitivity, we examined the impact of cell-fibronectin interactions on the efficacy of the EGF receptor antibody cetuximab, which is used widely

for lung cancer treatment. Our results revealed the potential for cell-fibronectin interactions to induce radioresistance of human non-small cell lung cancer cells. Cell adhesion to fibronectin enhanced tumor cell radioresistance and attenuated the cytotoxic and radiosensitizing effects of cetuximab. Both in vitro and in vivo, we found that cetuximab treatment led to a remarkable induction of fibronectin biosynthesis. Mechanistic analyses revealed the induction was mediated by a p38-MAPK-ATF2 signaling pathway and that RNAi-mediated inhibition of fibronectin could elevate the cytotoxic and radiosensitizing potential of cetuximab. Taken together, our findings show how cell adhesion blunts cetuximab, which, by inducing fibronectin, generates a self-attenuating mechanism of drug resistance.

Articles of interest

CLINICAL ONCOLOGY
SPECIAL ISSUE
ADVANCES IN CLINICAL RADIOBIOLOGY (Part 1)
Vol 25 No. 10, October 2013, p.567-624

Guest Editors: R Paul Symonds and G Don Jones

Advances in clinical radiobiology
R. Paul Symonds and George D. D. Jones

The hallmarks of cancer and the radiation oncologist: updating the 5Rs of radiobiology.
James S. Good and Kevin J. Harrington.

Biological consequences of radiation-induced DNA damage: Relevance to radiotherapy.
Martine E. Lomax, Lisa K. Folkes and Peter O'Neill.

Bystander signalling: exploring clinical relevance through new approaches and new models.
Karl T. Butterworth, Stephen J. McMahon, Alan R. Hounsell Joe M. O'Sullivan, and Kevin M. Prise.

Radiosensitising nanoparticles as novel cancer therapeutics: pipe dream or realistic prospect.
Jonathan A. Coulter, Wendy B. Hyland, James Nicol, Fred J. Currell

Advances in Anticancer Radiopharmaceuticals.
Mark R. Jackson, Nadia Falzone and Katherine A. Vallis.

Biomarkers of radiation exposure: can they predict normal tissue radiosensitivity?
Melvin L. K. Chua and Kai Rothkamm.

Understanding radiation-induced cardiovascular damage and strategies for intervention.
Fiona Stewart, Ingar Seemann, Saske Hoving and Nicola S. Russell.

This Special Edition, which is the first of two Special Editions devoted to 'Advances in Clinical Radiobiology' (the second edition is scheduled be published in early 2014), contains a series of specialist reviews by well-known experts in the field. The topics covered in this first edition include: The hallmarks of cancer and the radiation oncologist; Biological consequences of radiation-induced DNA damage; Bystander signalling; Radiosensitising nanoparticles as novel cancer therapeutics; Advances in anticancer radiopharmaceuticals; Biomarkers of radiation exposure; and Understanding radiation-induced cardiovascular damage and strategies for intervention.

Dr. George DD Jones & Prof R Paul Symonds

Clinical Oncology Special Edition Editors

Upcoming professional meetings and courses

Do you know of any upcoming professional meeting. Please let us know, email details to k.butterworth@qub.ac.uk.

ICTR-PHE 2014

February 10-14, 2014

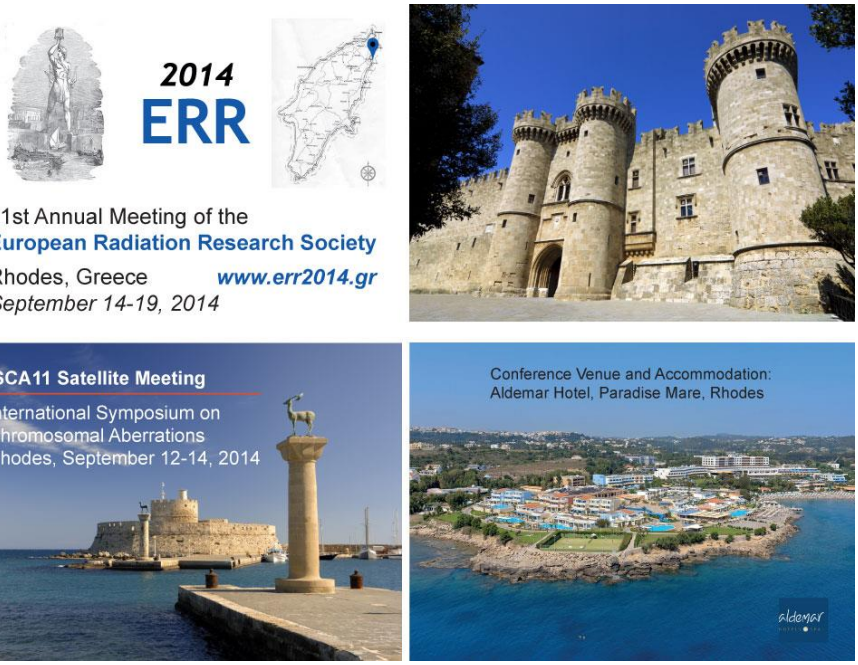
A conference that brings together the International Conference on Translational Research in Radio-Oncology and Physics for Health in Europe.

http://ictr-phe14.web.cern.ch/ictr-phe14/

April 04-08, 2014

ESTRO 33 is the premier European event in Radiation Oncology and will focus on new and emerging developments in the field.

http://www.estro.org/congresses-meetings/items/estro-33



http://www.err2014.gr/

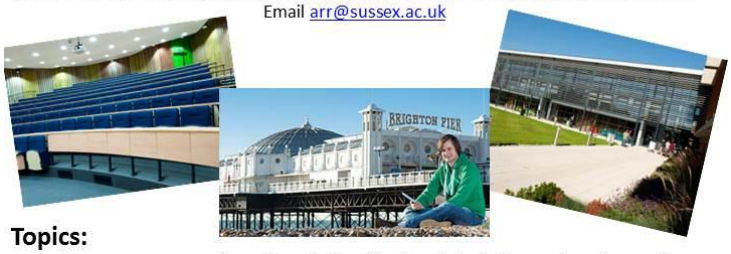
ARR Association University of Sussex

for Radiation Research Annual Conference

29th June – 2nd July 2014

At University of Sussex, Brighton

Organisers:, Penny Jeggo, Rhona Anderson, Ester Hammond, Eric O'Neill, Marie Boyd..
Email arr@sussex.ac.uk



Topics:

DNA damage response (repair and signalling) and its influence by chromatin, LET and cell cycle phase.
Predictive markers for the response to radiation: imaging biomarkers, predictive biomarkers for sensitivity to RT
Radiation Protection: is low dose radiation exposure a concern; monitoring low dose radiation exposure.
Enhancing radiotherapy: hypoxia, 3D imaging and combinational therapy.
Tumour microenvironment.
Nuclear Medicine and its exploitation for tumour control
Stem Cells and their response to radiation

Confirmed speakers
Steve Jackson, Marco Durante, Mats Harms-Ringdahl, Martin Brown, Markus Lobrich, Mark Pearce, Ester Hammond, Mike Atkinson, Marie Boyd, John Waterton, Kai Rothkamm, Kate Vallis.

Weiss Award Lecture | **Travel Awards/poster prizes** | **SIT session**

http://www.le.ac.uk/cm/arr/home.html

Career opportunities

Assistant Professor, Physics, Cleveland State University
http://www.higheredjobs.com/search/details.cfm?JobCode=175692624&Title=Assistant%20Professor%20-%20Physics

Associate Professor / Assistant Professor, Biology, University of Wisconsin-Madison
http://www.higheredjobs.com/faculty/details.cfm?JobCode=175805954&Title=Assistant%20or%20Associate%20Professor

Assistant Professor, Biological Sciences, Rowan University
http://www.higheredjobs.com/faculty/details.cfm?JobCode=175805647&Title=Assistant%20Professor%2C%20Biological%20Sciences%20-%20Full%20Time%20Tenure%20Track

Research Associate, Neurochemistry, University of Virginia
http://www.higheredjobs.com/faculty/details.cfm?JobCode=175803912&Title=Research%20Associate%20-%20Neurochemistry

Research Associate, Radiation Oncology, University of Virginia
http://www.higheredjobs.com/search/details.cfm?JobCode=175795386&Title=Research%20Associate%20-%20Radiation%20Oncology

SIT Committee contact details

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