INTERNATIONAL CANCER CONFERENCE

“LIVING WITH CANCER IN THE 21ST CENTURY”
17-18 September 2014

Trinity Biomedical Sciences Institute
Welcome

Dear Colleagues,

Welcome to our conference!

The International Cancer Conference has been established through a tripartite agreement developed in 1999 by the Departments of Health in Ireland and Northern Ireland and the US Administration. A collaboration originally linking the Belfast Cancer Centre with St James’s Hospital/ Trinity College Dublin (TCD) and the National Institutes of Health (NIH), Bethesda, Maryland, and a cancer conference hosted by St. James’s Hospital/TCD resulted from this association. The NIH initially supported the conference through the participation of academic staff and provided a broader association through fellowships and training workshops. Science Foundation Ireland helped make the conference a success and supported it all along.

The scientific conference is held as part of Cancer Week Ireland, which has been initiated this year by the Irish Cancer Society and Trinity College Dublin and will run from September 15th to 21st. The focus of the week is “Living with Cancer”. The aim of the week is to highlight the increasing rates of cancer survivorship and how more people are living well with, and beyond, cancer. “Living Well With Cancer” – the Irish Cancer Society’s National Conference for Cancer Survivorship 2014 – will follow our conference and will be held in Aviva Stadium on 19-20 September, with Cancer Survivorship Research Day on 18 September.

This year’s conference is the 9th. The theme of the conference is “Living with cancer in the 21st Century”, and cutting-edge fields will be presented by world-class international speakers deemed to be leaders in their areas.

We are especially delighted that Burkitt Lecture will be delivered by Dr John L. Ziegler, Founding Director of Global Health Sciences Graduate Program at University of California San Francisco, USA, who will be awarded a Burkitt Medal at the conference dinner. Denis Burkitt, known for discovery of Burkitt’s lymphoma, was a Trinity graduate and we celebrate his legacy by honouring the achievements of people who have made a substantial mark in the area of cancer.

The second named lecture is dedicated to Donal P. Hollywood, a colleague, who took part in previous conferences and whom we sadly lost to cancer last year in the prime of his life. Marie Curie Professor of Clinical Oncology in Trinity and St James’s Hospital consultant, Donal was a household name in the world of radiotherapy both within and outside Ireland and dedicated his working life to improving the radiotherapy service offered to patients in this country and internationally. Let us celebrate Donal’s life with the quality of care and research achievements that he aspired to.

Organising Committee

International Cancer Conference 2014
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## 9th International Cancer Conference 2014
### Living with Cancer in the 21st Century

**WWW.CANCERCONFERENCE.IE/**  
**STANLEY QUEK LECTURE THEATRE**  
**TRINITY BIOMEDICAL SCIENCE INSTITUTE**  
**17th-18th SEPTEMBER 2014**

### 17th September 2014

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Barling Chair of Surgery and Head of Department, University of Birmingham, College of Medical and Dental Sciences, School of Cancer Sciences, Birmingham, UK |
| 12.30 | Neuroendocrine Tumours: An Irish Perspective | Dr Dermot O’Toole  
Associate Professor, Trinity College Dublin, National Clinical Lead for Neuroendocrine Tumours, St James’s and St Vincent’s Hospitals, Dublin, Ireland |
| 12.45 | Modern Therapies for Digestive Neuroendocrine Tumours: State of the Art | Dr Marianne Pavlo  
Senior Physician and Leader of the Section for Neuroendocrine Tumours, Department of Hepatology and Gastroenterology, Charité University Hospital, Campus Virchow-Klinikum in Berlin, Germany |
| 13.15 | Lunch and Poster Viewing | |
| 14.00 | Restoring Sensitivity to Endocrine Therapy | Professor Nadia Harbeck  
Head of the Breast Center, Chair for Conservative Oncology at the University of Munich (LMU), Germany |
| 16.00 | Microbiota and Cancer | Professor Fergus Shanahan  
Head of Medicine, University College Cork, Alimentary Pharmacological Centre (APC), Bioscience Building, University College Cork, Ireland |
| 16.30 | Coffee Break and Poster Viewing | |

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**DENIS PARSONS BURKITT**  
DENIS PARSONS  
1935 from Trinity. In Africa he developed exceptional observational and analytical skills, which led him to develop a successful treatment for the commonest childhood cancer in Sub-Saharan Africa – Burkitt lymphoma. His contributions to cancer remain salient today, and his discoveries continue to generate new research.

Trinity has a strong tradition in translational cancer research. One of the people who is the embodiment of the best of Trinity is Denis Burkitt, a surgeon and research scientist, a household name in the medical profession. He received his BA, 1933 and graduated as a physician in 1935 from Trinity. In Africa he developed exceptional observational and analytical skills, which led him to develop a successful treatment for the commonest childhood cancer in Sub-Saharan Africa – Burkitt lymphoma. His contributions to cancer remain salient today, and his discoveries continue to generate new research.
SESSION 5
Emerging Challenges for Childhood Cancer Survivors

Chairs: 
Professor Maureen O’Sullivan, Clinical Professor, Trinity College Dublin; Dr Anne-Marie Tobin, Consultant Dermatologist, Tallaght Hospital, Dublin; Professor Richard O’Kennedy, Professor of Biological Sciences, Principal Researcher, Applied Biochemistry Group, Coombe Women and Infants University Hospital, Dublin.

12.00 Life after Childhood Cancer: When the Eradication of Disease is not Enough
Professor Cindy Schwartz
Professor of Pediatrics, University of Texas MS Anderson Cancer Center, USA

12.30 Adult Survivors of Childhood Cancer: Transition and Ongoing Care Needs
Karen Kinahan, MS, PCNS-BC
Clinical Nurse Specialist, Robert H. Lurie Comprehensive Cancer Center, USA

13.00 Improving Survival Rates in Adolescent and Young Adult Cancers through Research and Innovation
Professor Owen Smith
Regius Professor of Medicine, Professor of Haematology Trinity College Dublin, Department of Paediatric Haematology and Oncology, Our Lady’s Children’s Hospital Crumlin, Dublin; Dr Michael Capra, Our Lady’s Children’s Hospital Crumlin, Dublin

13.30 Lunch and Poster Viewing

SESSION 6
Cancer and the Environment

Chairs: 
Professor Kevin Conlon, Consultant Surgeon, Tallaght Hospital, Dublin; Dr Anne-Marie Tobin, Consultant Dermatologist, Tallaght Hospital, Dublin

14.30 Cancer Following Radiation Exposure – Putting the Risks into Context
Professor Geraldine Thomas
Professor of Molecular Pathology, Imperial College London, UK

15.00 Factors Moderating Survival from Melanoma
Professor Julia Newton Bishop
Professor of Dermatology, Leader of Melanoma Research Group within the Section of Epidemiology and Biostatistics, Institute of Cancer Studies and Pathology, St James’s Hospital, Leeds, UK

15.30 The Scourge of Tobacco and the Burden of Lung Cancer
Dr Finbarr O’Connell
Consultant Respiratory Physician and Clinical Director of Medicine, St James’s Hospital, Dublin, Ireland

16.00 Coffee Break

SESSION 7
Circulating Tumour Cells

Chairs: 
Professor Orla Sheils, Professor of Histopathology, Trinity College Dublin; Professor Richard O’Kennedy, Professor of Biological Sciences, Principal Researcher, Applied Biochemistry Group, Dublin City University

16.30 Conical Microhole Array Integrated into a Microcapillarity Device for Fast and Efficient Capture of Circulating Tumour Cells
Professor Yvon Cayre
Professor, Pierre and Marie Curie University, Department of Clinical Haematology, Hospital Robert Debre, Paris, France

17.00 Pharmacology and Nanopharmacology of Blood-Borne Mechanisms of Carcinogenesis
Professor Marek Radomski
Chair of Pharmacology, Trinity College Dublin, Ireland

17.30 Donal P. Hollywood Lecture - Lessons from the Metastatic Cascade
Professor John O’Leary
Professor of Pathology, Trinity College Dublin; Consultant Histopathologist, St James’s Hospital, Director of Pathology, the Coombe Woman and Infants University Hospital, Dublin, Ireland

18.00 Awards for Best Proffered Paper and Posters
Close of Conference: Professor John Reynolds

18.30 Wine reception
**Professor Derek Alderson**

Barling Chair of Surgery and Head of Department, University of Birmingham, College of Medical and Dental Sciences, School of Cancer Sciences, Birmingham, UK

The honorary president of SurgSoc, Professor Derek Alderson, is the Barling professor and head of the department of surgery at the University of Birmingham. He took up this post in 2005, having previously been professor of gastrointestinal surgery at Bristol. His main area of clinical interest is oesophagogastric surgery. He is a current editor of the British Journal of Surgery. Professor Alderson is committed to improving surgical standards at all levels through education, research and clinical performance. Outside work his hobbies include diving, walking and wine, depending upon temperature, location and time of day.

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**Professor Yvon Cayre**

Professor, Pierre and Marie Curie University, Department of Clinical Haematology, Hospital Robert Debre, Paris, France

Yvon E. Cayre is a professor of haematology at the University Pierre and Marie Curie, in Paris, France. He was director of research at the National Institute of Health and Medical Research (INSERM) from 1995 to 2007. He gained extensive clinical and biological experience and developed many researches, in the field of onco-haematology. Besides his activities in France, Yvon Cayre was a Head of several laboratories in the United States (successively at Memorial Sloan-Kettering Cancer Center, Cornell Medical, Columbia University in New York and the Kimmel Cancer Institute at Thomas Jefferson University in Philadelphia). He was also appointed as a professor (“Ordinari”) at the University “La Sapienza” in Rome (Italy) where he was teaching onco-haematology to pediatricians. Yvon Cayre has always been involved in teaching activities. As a professor, he is very concerned with issues of bioethics and is a member of the “Commission de Bioethique Medecale” (Medical Bioethical Committee) at the Central Consistory of Jewish institutions in France.

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**Professor Nadia Harbeck**

Head of the Breast Center, Chair for Conservative Oncology, University of Munich, Germany

Nadia Harbeck, MD, PhD, is head of the Breast Center and holds the chair for Conservative Oncology at the University of Munich (LMU), Germany. From 2009 to 2011, she was head of the Breast Center at the University of Cologne, Germany. Until 2009, she was an associate professor and head of Conservative Senology at the Technical University of Munich, where she obtained her specialist degree in obstetrics and gynecology in 1998. In 1989, she received her medical degree from the University of Munich.

Professor Harbeck is a member of the expert panel issuing the yearly updated evidence-based German Working Group for Gynecologic Oncology (AGO) Guidelines for breast cancer therapy (www.ago-online.de). She is an executive board member of the European Organization for Research and Treatment of Cancer (EORTC) and scientific director of the West German Study Group (WSG) (www.wsg-online.com). She is principal investigator or steering committee member of numerous national and international clinical breast cancer trials, focusing recently on trials using novel targeted compounds. She co-chairs the Trans-ALTTO committee. Her translational research focuses on prognostic and predictive factors in breast cancer and other solid tumors. She has authored > 300 papers in peer-reviewed journals (cumulative impact factor ~ 1300) and is coordinating editor-in-chief of Breast Care. For her clinical translational research, she has received numerous awards, including the 2012 Claudia von Schilling Award, the 2002 AGO Schmidt-Matthesian Award, a 2001 American Association for Cancer Research (AACR) Award, and the 2001 American Society of Clinical Oncology (ASCO) Fellowship Merit Award for the highest ranking abstract submitted. She is a faculty and panel member of the International Consensus Conferences on Breast Cancer in Young Women (BCY 2012, 2014), Advanced Breast Cancer (ABC 2011, 2013), and of the 2015 St. Gallen Meeting.

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**Professor Stephan Herzig**

Division Head, Joint Research Division, Molecular Metabolic Control German Cancer Research Center (DKFZ) Heidelberg, Center for Molecular Biology (ZMH) Heidelberg, Heidelberg University Hospital, Germany

Stephan Hering completed his PhD in 1999 at the University of Göttingen, Germany. After postdoctoral studies at the Salk Institute, La Jolla, CA, he established an independent Emmy Noether and Marie Curie Junior Research Group at the German Cancer Research Center (DKFZ) in Heidelberg, Germany, in 2004. In 2010, he became Head of the Department “Molecular Metabolic Control” at the DKFZ, and since 2011 he is heading a joint research division between the DKFZ, Heidelberg University and Heidelberg University Hospital. In 2012, he became a full professor at the Medical Faculty of Heidelberg University. His publications include papers in Nature (2001, 2003), Science (2003, 2010), Nat. Biotechnology (2012) and Cell Metabolism (2008, 2011, 2013). Stephan Hering is currently serving as the coordinator of the EU FP7 project DIABAT, the Helmholtz Cross Program Activity Metabolic Dysfunction, and as a co-speaker for the Collaborative Research Center Diabetic Complications funded by the German Research Foundation.

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**Dr Michaela Higgins**

Assistant Professor of Medicine, Harvard Medical School & Attending Medical Oncologist, Massachusetts General Cancer Centre, Boston, MA, USA

Dr Michaela Higgins has been an Assistant Professor of Medicine at Harvard Medical School and an Attending Physician with the Breast Cancer Program at Massachusetts General Hospital, Boston since 2015. She is a graduate of University College Dublin and trained both in Ireland and throughout in Johns Hopkins Hospital, Baltimore, Maryland where she served as Chief Fellow in Medical Oncology. During her time at Massachusetts General Hospital, Dr Higgins has led numerous national and international clinical trials for patients with breast cancer. Her research has been awarded multiple competitive grants and she has over 40 manuscripts in peer-reviewed journals. In January 2015, Dr Higgins will begin her appointment as Consultant Medical Oncologist at the Mater Misericordiae Hospital in Dublin.

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**Karen Kinahan**

Clinical Nurse Specialist, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, USA

Karen Kinahan is a Clinical Nurse Specialist at Robert H. Lurie Comprehensive Cancer Center of Northwestern University in Chicago, Illinois. She has spent her entire 26 year nursing career in pediatric oncology, and has spent the last 19 years working with survivors of childhood cancer exclusively. In 2001, with the support of Northwestern’s Lurie Cancer Center she started a comprehensive follow-up program for adult survivors of childhood cancer called the STAR Program (Survivors Taking Action & Responsibility). She has helped facilitate long term follow-up care for hundreds of childhood cancer survivors and her role includes direct patient care, patient and community education, and research. Karen is recognized as a nursing pioneer in the field of childhood cancer survivorship, adult transition and has made numerous presentations at both national and international nursing and medical meetings.
Professor Julia Newton Bishop
Professor of Dermatology, Leader of Melanoma Research Group within the Section of Epidemiology and Biostatistics, Institute of Cancer Studies and Pathology, St. James’s Hospital, Leeds, UK

Julia is Professor of Dermatology at the University of Leeds. She works within the Specialist Melanoma Multidisciplinary Team at St James’s Hospital. She leads a melanoma research group within the Section of Epidemiology and Biostatistics. The group uses genetic epidemiology to understand the aetiology or melanoma, susceptibility to melanoma and the determinants of survival.

Dr Finbarr O’Connell
Consultant Respiratory Physician and Clinical Director of Medicine, St James’s Hospital, Dublin, Ireland

Finbarr O’Connell graduated from UCD in 1984. Having completed his general medical training in Dublin, he worked with Prof Neil B Pride at the Hammersmith in London, where he completed his MD thesis on airway epithelial nerves. He was appointed Consultant Respiratory Physician at St James’s Hospital Dublin in 1996 and was appointed Clinical Director of Internal Medicine in 2014. He was the Medical Director of the William Stokes Postgraduate Centre from 1999-2010, and is currently the Intern Network Coordinator for the TCD/DSE Intern Network. He is a member of the Medical Committee and Lung Cancer sub-committee of the Irish Cancer Society. He is a co-founder of the All-Ireland Lung Cancer Forum and principal author of the 1st All-Ireland Guidelines for Clinical management of Lung Cancer. He has a particular interest in rapid diagnosis and staging of lung cancer though novel bronchoscopy techniques including EBUS, and is an advocate for lung cancer screening and prevention and for tobacco control.

Dr Dearbhailé O’Donnell
Consultant Medical Oncologist, St James’s Hospital, Dublin, Ireland

Dearbhailé O’Donnell graduated in medicine from University College Dublin. After initial training in medicine and oncology in Dublin, and a research MD, also in UCD, she moved to the UK. There she received a Clinician Scientist award to pursue research in cancer Immunology while completing specialist training in medical oncology. She was a Senior Lecturer in Medical Oncology and Consultant Medical Oncologist in Leeds before returning to a consultant post in St. James’s Hospital Dublin. There, she treats patients with gynaecological and urological cancers and is director of the cancer clinical trials unit. Her other roles include chairing the Gynaecological subgroup of ICORG and as an ex officio member of the Board of Directors of the Gynecological Cancer Intergroup.
Dr Lorraine O’Driscoll  
Associate Professor, School of Pharmacy & Pharmaceutical Sciences, Trinity College Dublin, Ireland

Lorraine O’Driscoll is Director of Research and Associate Professor of Pharmacology, School of Pharmacy & Pharmaceutical Sciences, TCD. Lorraine holds BSc(Hons.) Pharm; MSc(Res), Clinical Pharm; PhD, Biotech. Following her PhD, Lorraine worked on biotechnology/biomedical research studies for US and EU industry (incl. Berlex, Archport Ltd/Axonobel; MediSyn Ltd) before returning to academic research & teaching. At Post-Doctoral level, she gained experience at the Dana-Farber Harvard Cancer Institute and University of Miami. Prior to joining TCD in 2008, Lorraine most recently held the position of Senior Research Programme Leader, NCI Fox Chase Cancer Center and lectured in School of Biotechnology, DCU. Lorraine’s research group focuses on diagnostic, prognostic and predictive biomarkers; discovering new therapeutic targets; cancer cells communication via exosomes, microvesicles and CTCs; and elucidating resistance to targets and classical chemotherapy. She is PI on 5 ICORG translational clinical trials and has published over 80 research papers; 12 reviews; 2 books; 5 Editorials; 9 book chapters; 128 conference proceedings. Lorraine has graduated 16 PhDs, 7 MSc, 3 MD and mentored 14 PDs and 44 UGs. She is TCD’s P.I., SFI-supported Molecular Therapeutics for Cancer Ireland; Strand Leader, Irish Cancer Society-supported National Cancer Research Institute, Breast-PREDICT; and Lead PI/Chair, EU FP7 Network Cooperation on Exosomes & Microvesicles.

Professor John O’Leary  
Professor of Pathology, Trinity College Dublin, Ireland

John O’Leary is Chair of Pathology at TCD and a clinician scientist who has over 400 publications (170+ peer reviewed papers, 250 published abstracts, 28 book chapters and 3 books) with publications in Nature, Nature Medicine, Nature Immunology, The Lancet, PLoS One etc. He leads a multi-investigator unit at Trinity College Dublin, composed of 41 scientists. His research group works in the following cancer areas: prostate, ovary, cervix, head and neck, cancer stem cell biology, the cancer inflammasome, metastasis and circulating tumour cells and pregnancy transcriptomics and proteomics.

Dr Susan O’Reilly  
Director, National Cancer Control Programme, Ireland

Dr Susan O’Reilly was appointed as the Director of the National Cancer Control Programme, Ireland, in September 2010. She leads the planning and implementation of the National Strategy for Cancer Control in Ireland, across the spectrum of prevention, screening programmes, surgical oncology, radiation oncology and medical oncology.

Dr O’Reilly qualified in medicine at Trinity College, Dublin, and completed postgraduate training in internal medicine at Trinity College and University College Dublin. She subspecialised in medical oncology in Vancouver, British Columbia.

In 1995, following several years of clinical practice and research in lymphomas, breast cancer and gynaecological cancers, she was appointed as Clinical Professor and Head of the Division of Medical Oncology in the Faculty of Medicine at the University of British Columbia and Provincial Systemic Therapy Programme Leader at the British Columbia Cancer Agency, Vancouver. She developed and led programmes in medical oncology care and research, provincially.

From 2005 to 2010, she was the Vice President Cancer Care at the British Columbia Cancer Agency and was responsible for the leadership, planning and delivery of cancer care across all oncology disciplines (surgery, radiation oncology, medical oncology, pathology and allied health professionals). The British Columbia Cancer Agency is recognised for its excellent cancer survival rates and its organisation and delivery of provincial cancer control programmes.
Dr Dermot O'Toole
Associate Professor, Trinity College Dublin, National Clinical Lead for Neuroendocrine Tumours, St James’s and St Vincent’s Hospitals, Dublin, Ireland

Dermot O’Toole is a Consultant Gastroenterologist in St James’s Hospital and St Vincent’s University Hospital and is Associate Professor at Trinity College Dublin. His undergraduate and Doctoral studies were in Trinity College Dublin and subsequently obtained degrees from the University of Paris (DIU and HDR). Dermot is the Clinical Lead for both the National group devoted to neuroendocrine tumours (NET) and National Centre for Early Mucosal Neoplasia. He serves on the executive committee of the European Neuroendocrine Tumours Society (ENETS) and has helped develop guidelines papers and standards of care initiatives in the field of NET as well as chairing the ENETS-driven European Centre of Excellence program. His major interest is in the biology of the gastrointestinal cancers both neuroendocrine tumours (with numerous publications in field of angiogenesis and therapies for NET-related diseases) and Barrett’s oesophagus and Barrett’s-related neoplasia.

Dr Marianne Pavel
Senior Physician and Leader of the Section for Neuroendocrine Tumours, Department of Hepatology and Gastroenterology, Charité University Hospital, Campus Virchow-Klinikum in Berlin, Germany

Marianne Pavel is a senior physician and leader of the section for neuroendocrine tumours in the Department of Hepatology and Gastroenterology at the Charité University Hospital, Campus Virchow-Klinikum in Berlin, Germany. She was an alumni of Prof Werner Creutzfeldt, and received her medical degree in 1992 from the Georg-August University in Göttingen, Germany. In 1994 she completed her residency at the Friedrich-Alexander University of Erlangen-Nürnberg in Erlangen, Germany. Between 1994 and 1997 she was resident physician at the Friedrich-Alexander University’s medical clinic. Board certified as a specialist in internal medicine in 2000, and endocrinology, and diabetes in 2001, she was appointed as Vice Head of the Department of Endocrinology and Metabolism at the Friedrich-Alexander University in 2001. In 2007 she took her current position as an assistant Director at the Charité University Hospital, Campus Virchow-Klinikum.

Dr Pavel has conducted numerous clinical trials since 1993 in Endocrinology and Gastroenterology with a strong focus on neuroendocrine tumours. Since 2005 she participates in ENETS activities. Under her guidance the NET Center at the Charité, CVK, was certified as ENETS Center of Excellence in November 2009. She was conferred a Professorship for Neuroendocrine Tumour Disease at the Charité University, Campus Virchow-Klinikum, Berlin in January 2010.
Professor Waldemar Priebe  
Professor of Medicinal Chemistry, Department of Experimental Therapeutics, Division of Cancer Medicine, University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA

Waldemar Priebe, PhD, professor of medicinal chemistry in the Department of Experimental Therapeutics at The University of Texas M. D. Anderson Cancer Center.  

Priebe’s research merges biology with chemistry and focuses on the design and development of drugs that selectively target DNA and inhibitors of signaling/transcription and metabolic pathways important to tumor progression and survival. He has a long term interest in the field of carbohydrates ranging from organic chemistry of carbohydrates to the exploitation of carbohydrate metabolism in normal cells and cancer cells.

Priebe is noted for his successful development of new therapeutic entities for the treatment of cancer. During his career, he has generated an extensive library of distinct, novel cancer-fighting compounds covering many structural scaffolds and diverse therapeutic areas. The invention of these agents has led to many patents and numerous licenses. Four of his drugs entered clinical trials and several others are in different stages of preclinical development.

In addition to his position at M. D. Anderson, Priebe holds the title of Professor of Chemistry in the Republic of Poland. He is the founder/founding scientist of five biotechnological companies and serves on the scientific advisory board of several pharmaceutical companies. Dr Priebe has published more than 195 peer-reviewed journal articles and his work has led to over 50 patents.

Professor Marek Radomski  
Professor Marek Radomski, Chair of Pharmacology, Trinity College Dublin, Ireland

Professor Radomski is a highly-cited pharmacologist (listed in www.isihighlycited.com, >18,000 citations to date by Google Scholar) who worked both in academia and pharmaceutical industry in Poland (Jagiellonian University in Krakow, Polish Academy of Sciences in Warsaw and Silesian Centre for Heart Diseases), UK (Wellcome Research Laboratories in Beckenham), Spain (Lacer SA in Barcelona), Canada (University of Alberta in Edmonton) and USA (University of Texas in Houston). He joined School of Pharmacy and Pharmaceutical Sciences Trinity College Dublin in 2006 as Professor and Chair of Pharmacology. He served as Director of Research and Head of the School of Pharmacy. He contributed to undergraduate teaching of medical,dentistry, nursing and pharmacy students in Europe, Canada and USA. He mentored many MSc, PhD students, as well as post-doctoral researchers. He has received a number of awards including doctor honoris causa award from the Complutense University in Madrid, Spain.

Over the past years he has been studying the role of blood platelets in carcinogenesis including angiogenesis, invasion, metastasis and survival of cancer cells.

Professor Radomski’s current research interest is focused on nanomedicine and the relevance of nanomedical tools for nanotherapeutics and nanotoxicology of cardiovascular diseases and cancer.
Professor John Reynolds
Consultant Surgeon, St. James’s Hospital, Head of Department, Trinity College Dublin, Ireland

Professor John V. Reynolds is Professor of Surgery and Head of Department at Trinity College Dublin. He took up this position in July 2001. He is a specialist oesophageal and gastric surgeon and is based at St James’s Hospital. His clinical and research training involved periods at the University of Pennsylvania, Philadelphia, the Memorial Sloan-Kettering Cancer Centre in New York, and St Mary’s Hospital, London. He was consultant oesophageal surgeon and senior lecturer in St James’s University Hospital in Leeds before returning to Dublin in 1997. He is the Director of Cancer Audit at St James’s Hospital. His research interests are in the molecular understanding of Barrett’s oesophagus and oesophageal cancer, the molecular prediction of response or resistance to chemotherapy and radiation therapy, obesity and cancer, and modulating the immune response following complex major surgery. Professor Reynolds has edited a book on oesophageal and gastric cancer and has published approximately 200 articles on these research themes.

Professor Cindy Schwartz
Professor of Pediatrics, University of Texas MD Anderson Cancer Center, USA

Dr Schwartz is Professor and Deputy Division Head of Pediatrics, Director for Clinical and Translational Research, and Director of Pediatric Phase I at MD Anderson Cancer Center with clinical and research interests in childhood cancer survivorship, Hodgkin lymphoma and osteosarcoma. Dr Schwartz developed and led the Survivorship programs for childhood cancer survivors at Johns Hopkins, Brown University, and the University of Rochester and is an editor of “Survivors of Childhood and Adolescent Cancer – A Multidisciplinary Approach” which outlines the consequences of childhood cancer therapy and methods for screening. She was Chair of the Hodgkin lymphoma Committee for the Children’s Oncology Group (1999-2011) developing ABVE-PC, the dose dense regimen used for Hodgkin lymphoma that tailors therapy based on early response to maximize efficacy while limiting long term toxicity. She has led the legacy CCG trials in Hodgkin lymphoma and osteosarcoma that evaluated dexrazoxane as a cardioprotectant, and is now involved in a study designed to evaluate the long term outcomes for these children. Her overall goals are to improve duration and quality of survival by tailoring therapy to disease risk, developing new therapies, and enhancing knowledge of the long term consequences of treatment.

Professor Fergus Shanahan
Head of Medicine, University College Cork, Alimentary Pharmabiotic Centre (APC), Biosciences Building, University College Cork, Ireland

Fergus Shanahan, MD, DSc is Professor and Chair of the Department of Medicine, University College Cork, National University of Ireland, and Director of the Alimentary Pharmabiotic Centre, a research centre funded by Science Foundation Ireland which investigates host-microbe interactions in the gut and the therapeutic potential of mining the microbiota. His interests include most things that affect the human experience. He has published over 450 scientific articles and several books in the areas of mucosal immunity, inflammatory bowel disease and the microbiota and including several articles relating to the medical humanities.
Professor Owen Patrick Smith  
Regius Professor of Medicine, Professor of Haematology Trinity College Dublin and Department of Paediatric Haematology & Oncology, Our Lady’s Children’s Hospital Crumlin, Dublin, Ireland

Professor Smith is a Consultant Paediatric Haematologist at Our Lady’s Children’s Hospital Dublin, and is Professor of Childhood Blood Disorders and Regius Professor of Medicine, Trinity College Dublin. Since returning from postgraduate training at Great Ormond Street Children’s Hospital, London in the early 1990’s he has devoted the last twenty five years of his career to caring for neonates, children and adolescents with cancer and blood disorders. One of his main areas of research has been in evidence-based randomised peer-reviewed paediatric haemat-oncology clinical trials, focusing on clinical questions within all domains of paediatric blood and cancer. He is a member of numerous associations and societies, including, the Medical Research Council Childhood Leukaemia Working Party, the International Berlin-Frankfurt-Munster Study Group for Childhood Leukaemia, and the United Kingdom Children’s Cancer Group. Professor Smith was awarded the St Luke’s Medal by the Royal Academy of Medicine and St Luke’s Hospital for his work on improving outcomes in adolescent cancers with specific reference to the haematological malignancies.

Professor Geraldine Thomas  
Professor of Molecular Pathology, Imperial College London, UK

Gerry Thomas is Professor of Molecular Pathology at Imperial College London and specialises in the molecular pathology of cancer. She is committed to developing infrastructures for molecular pathology research, both for use by her own research group but also by others. She strongly believes that public involvement and information is a key part of academic research, and is actively involved in the public communication of research, particularly with respect to radiation protection and biobanking.

Her initial work focused on animal models of cancer, in particular thyroid cancer. She has carried out research into the health effects of the Chernobyl accident since 1990, and established the Chernobyl Tissue Bank (CTB: www.chernobyltissuebank.com) in 1998. The CTB has provided infrastructural support (both physical and ethical) in Belarus, Ukraine and Russia for thyroid cancer outcomes in adolescent cancers with specific reference to the haematological malignancies.

Professor Jack Tuszyński  
Allard Experimental Chair, Professor of Experimental Oncology, Department of Oncology, University of Alberta, Cross Cancer Institute, Edmonton, Alberta, Canada

Dr Tuszyński is a Fellow of the National Institute for Nanotechnology of Canada. He is an Allard Chair and Professor in Experimental Oncology in the Department of Oncology at the University of Alberta’s Cross Cancer Institute and a Professor in the Department of Physics. Professor Jack Tuszyński received his M.Sc. with distinction in Physics from the University of Poznan (Poland) in 1980. He received his PhD in Condensed Matter Physics from the University of Calgary in 1983. He was a Post-Doctoral Fellow at the University of Calgary’s Chemistry Department in 1983. He was an Assistant Professor at the Department of Physics of the Memorial University of Newfoundland from 1983 to 1988, and at the University of Alberta’s Physics Department from 1988 to 1990. He became an Associate Professor from 1990 to 1993 and a Full Professor in 1993. He joined the Division of Experimental Oncology at the Cross Cancer Institute as the Allard Chair in 2005. He is on the editorial board of a number of international journals including the Journal of Biological Physics, Journal of Biophysics and Structural Biology (JBSB), Quantum Biosystems, Research Letters in Physics, Water: a Multidisciplinary Research Journal and Interdisciplinary Sciences-Computational Life Sciences. He is an Associate Editor of The Frontiers Collection, Springer-Verlag, Heidelberg. He had visiting professorships in Germany, Denmark, France, Belgium, Israel and China.

He has published over 360 peer-reviewed papers, over 50 conference proceedings, 10 book chapters and 10 books; delivered over 400 scientific talks (including 150+ invited talks) on five continents. His research has been supported by numerous research grants from Canadian, US and European funding agencies. In 2005 he was appointed to the prestigious Allard Research Chair in Oncology at the University of Alberta. The $3 million Chair is supported by the Alberta Cancer Foundation and the Allard Foundation.

Dr Jack Tuszyński heads a multi-disciplinary team creating “designer drugs” for cancer chemotherapy using computational biophysics methods. To make advances in this new promising field of biophysical modeling, Jack Tuszyński drew on his physics background to create computer software programs that screen proteins against chemical compounds to find the perfect match based on the lock and key principle. The goal of Tuszyński’s computational biophysics work is to create optimized drugs that would target cancerous cells with minimal side-effects to the healthy cells. Dr Tuszyński’s research interests are strongly linked to the protein tubulin and the microtubules assembled from it. His group is also developing physiologically-based models and simulations for pharmacokinetic and pharmacodynamic applications.

Dr Christopher P. Wild  
Director, International Agency for Research on Cancer (IARC), Lyon, France

Christopher Paul Wild obtained his PhD in 1984 from the Manchester University, UK. He conducted post-doctoral research at IARC, Lyon and the Netherlands Cancer Institute in Amsterdam. In 1987 Dr Wild re-joined IARC as a staff scientist and later became Chief of the Unit of Environmental Carcinogenesis. He was appointed to the Chair of Molecular Epidemiology at the University of Leeds in 1996, was Head of the Centre for Epidemiology and Biostatistics and subsequently became Director of the Leeds Institute of Genetics, Health and Therapeutics.

Dr Wild was elected Director of IARC from 1st January 2009.

Dr Wild’s main research interest is to understand the interplay between environmental and genetic risk factors in the causation of human cancer. He has particularly sought to apply biomarkers in population-based studies to this end. His specific areas of research have been focused on liver and oesophageal cancers.
Dr John L. Ziegler
Founding Director, Global Health Sciences Graduate Program
University of California San Francisco, USA

John Ziegler received his undergraduate degree (BA, English Literature) from Amherst College, Amherst Massachusetts, and his MD from Cornell University Medical School in New York City. Following medical house staff training at Bellevue Hospital in New York, he joined the National Cancer Institute (NCI) in 1966, beginning a life-long career in cancer research and care.

In 1967 he was assigned to begin a long collaboration with Makerere University in Kampala, Uganda, studying Burkitt’s lymphoma and other indigenous cancers. Together with Ugandan counterparts, he developed curative therapies for lymphoma and established a cancer institute that today has expanded to a major center of excellence in sub Saharan Africa.

After 5 years Ziegler returned to NCI to head clinical oncology, and in 1981 moved to UCSF. The AIDS pandemic made its first appearance in San Francisco, heralded by opportunistic infections and two malignancies – Kaposi’s sarcoma and non Hodgkin’s lymphoma. Ziegler and colleagues made important contributions to this field both in California and back in Uganda.

In his later career, earning an MSc in epidemiology from the London School of Hygiene and Tropical Medicine, Ziegler headed a cancer genetics clinic at UCSF, and most recently was founding director of a global health Master’s degree.
OP2: TEICOPLANIN DOSAGE IN ADULT PATIENTS WITH HAEMATOLOGICAL MALIGNANCY: IMPACT ON TROUGH LEVELS AND CLINICAL OUTCOMES

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A retrospective, single-centre, cohort study of 103 teicoplanin-treated patients with haematological malignancy was conducted from 1 March 2010 to 31 May 2012 to investigate whether the current dosage regimen used at Tallaght Hospital is adequate for this patient group in terms of reaching therapeutic plasma levels in a timely manner and whether there was any associated nephrotoxicity. Results suggest a positive relationship between serum trough concentrations and clinical outcome. A trough concentration of greater than 20 mg/L was associated with a favourable outcome but this was not often achieved especially early in the treatment course despite higher than conventional doses being used. Considerable variability in trough levels attained, despite similar doses, suggests pharmacokinetic variability in these patients. Mixed effects regression analysis was performed on the data collected to determine which variables influence the trough level attained. Significant predictors of trough level were dose per kg body weight, day of therapy, estimated glomerular filtration rate and a diagnosis of acute myeloid leukaemia (p<0.05). The final model explained 50% of the variability in teicoplanin trough levels. The a priori performance of this model was evaluated in another 23 patients and 61% of a priori predictions were within ±20% of the actual measured blood level. Findings suggest a risk of underexposure if conventional doses of teicoplanin are used for patients with haematological malignancy. More aggressive loading doses may be needed to achieve therapeutic levels early in the treatment course. At current hospital doses, findings suggest that teicoplanin is well tolerated renally which may provide scope to use higher doses. Given the variability in serum concentrations observed, and the link to clinical outcome, therapeutic drug monitoring appears crucial in patients with haematological malignancy, not primarily for concerns about toxicity, but to avoid inadequate blood levels. Individualised dosing of teicoplanin may be the most appropriate approach for these patients.

OP3: PHYSICAL FUNCTIONING POST OESOPHAGECTOMY

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Background: Physical functioning has become an important outcome in oesophageal cancer survivors. Side effects of the disease and its treatment may lead to unintentional weight loss or gain, loss of muscle mass and decreased physical fitness. Decreased strength and fitness levels may restrict survivor’s ability to carry out activities of daily living and increase the risk of second primary cancers and other chronic diseases. The aim of this study was to compare body composition, muscle strength and fitness levels between oesophageal cancer survivors and healthy controls.

Methods: Participants were examined at least six months post oesophagectomy with curative intent and were compared to age and gender matched control participants who had no history of cancer. Height, weight and waist circumference measurements were taken. Fitness levels were assessed by means of an incremental shuttle walking test (ISWT). Hand grip strength (HGS) was measured using a Jamar dynamometer.

Results: Thirty three oesophageal cancer survivors (28 male) with a mean age of 64 years and 7 healthy controls (6 male) with a mean age of 54 years completed the assessments. The mean (SD) BMI for survivors was 24.58 (4.2) compared to 26.67 (3.58) in controls (p=0.23). In men, the mean waist circumference was 89.87cm in survivors versus 95.5cm in controls (p=0.26). In women, the mean waist circumference was 82.2cm in survivors versus 68cm in controls. In terms of fitness, the average (SD) distance achieved in the ISWT by survivors was 528.75 (145.94) metres compared to 820 (135.65) metres completed by controls (p<0.001). In men, mean composite HGS was 75.47 kg for survivors and 86.75 for controls (p=0.21). In women, mean composite HGS was 48.59kg for survivors and 70.8kg for controls.

Conclusion: This cohort of oesophageal cancer survivors demonstrate significantly lower fitness levels than age and gender matched controls. These low levels of fitness highlight the fact that these cancer survivors may be at risk for other chronic diseases and suggest that this cohort may benefit from a specific multidisciplinary rehabilitation programme focused on maintaining a healthy weight and adequate nutrition while retaining optimal strength and fitness levels.
OP4: COMBINATION THERAPY WITH BAMLET AND THE TLR7 AGONIST R848 PROTECTS AGAINST MELANOMA IN A MURINE MODEL

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BAMLET, a bovine alpha-lactalbumin–oleic acid complex, is a novel and promising candidate for the treatment of cancer because of its capacity to specifically kill cancer cells while leaving normal cells and tissues relatively unharmed. While recent studies focused on direct tumoricidal effects of BAMLET, we investigated the potential of BAMLET to modulate immune responses against tumour cells, in combination with a TLR agonist, which also has anti-tumour activity by virtue of its ability to non-specifically stimulate innate and adaptive immune responses. We examined the protective efficacy of BAMLET and the TLR7 agonist R848 in the B16 melanoma murine tumour model and investigated the underlying mechanism of action. Consistent with previous studies, BAMLET induced killing of B16 melanoma cells but not normal cells in vitro. Moreover, BAMLET and R848 strongly activated dendritic cells (DCs) which are crucial for the induction of adaptive immune responses against tumours. Treatment of tumour bearing mice with either BAMLET or R848 alone increased the frequency of IFN-gamma-secreting CD4 T cells in vitro. Moreover, BAMLET and R848 strongly activated dendritic cells (DCs) which are crucial for the induction of adaptive immune responses against tumours. Treatment of tumour bearing mice with either BAMLET or R848 alone induced some protection against tumour growth. However, the combination of BAMLET and R848 conferred a high level of protection, with 57% of mice completely rejecting the tumour. We found a higher frequency of IFN-gamma-secreting CD4 T cells and an increased frequency of DCs in the tumour draining lymph nodes (LN) and splenome of mice treated with the combination of BAMLET and R848, compared with untreated mice or mice treated with either BAMLET or R848 alone. Our data are consistent with a role for BAMLET in directly killing tumour cells which release antigens that are taken up by DCs, but also suggest that BAMLET can promote DC maturation, especially when co-activated through a TLR. These activated DCs promote induction of IFN-gamma-secreting CD4 T cells that have anti-tumour activity. In conclusion, we demonstrated that BAMLET and R848 are a promising combination therapy against cancer as they target tumour cells directly and activate anti-tumour immune responses.

Basic Cell & Molecular Biology

PP1: DETECTION OF MUTATIONS IN SF3B1 IN CHRONIC LYMPHOCYTIC LEUKAEMIA PATIENTS BY Reverse TRANSCRIPTION POLYMERASE CHAIN REACTION, AN ALTERNATIVE APPROACH TO NEXT GENERATION SEQUENCING FOR ROUTINE MOLECULAR DIAGNOSTIC LABORATORIES?

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Genetic markers such as TP53, ATM mutations and somatic hypermutation status have been used to predict clinical behaviour and response to therapy in Chronic Lymphocytic Leukaemia (CLL) for the last decade. Recently identified markers including splicing factor 3 B1 (SF3B1), NOTCH and Bcl23 are also significant but their role cannot be fully evaluated until a robust assay is available for a routine molecular diagnostic laboratory. Patient samples with SF3B1 mutations display enhanced ibrutinib retention in transcripts involved in cancer related regulation. CLL patients with mutations in SF3B1 have been associated with shorter treatment free and overall survival. The screening methodology for SF3B1 mutations through deep sequencing is not available in routine diagnostic laboratories at present. As approximately 80% of CLL-associated SF3B1 mutations occur is 336bp region of the cDNA exome amenable to PCR amplification, we designed a PCR (sequencing based assay to detect mutations. The patient cohort consisted of 52 patients enrolled on a Phase II, multi centre study of fludarabine, cyclophosphamide and rituximab and included patients < 65 yrs, WHO status of 0, 1 or 2 without a deletion 17p. All samples were tested prior to treatment, end of treatment (4 or 6 cycles when minimal residual disease (MRD) negative), 6 monthly post-treatment for 5 years and then annually by 6 colour immunophenotyping. Patients (51/52) were screened prior to treatment for the presence of SF3B1 mutations. Five of 51 (9.6%) patients had SF3B1 mutations. All had favourable cytogenetics (normal or del 13q) and the majority (45%) had unmutated IGHV genes. Two patients had a mutation at c.2146A>G, p.K700E and one at c.2267G>A, p.G740E which have been described previously and two had novel mutations at c.2179G>C, p.A711P and c.2032C>T, p.H662Y. One patient has never achieved MRD negativity, two patients who became MRD negative at 3 months reved to MRD positivity 9 and 13 months later respectively. One patients MRD levels could not be tracked due lack of CD5 expression and one patient was withdrawn from the study. In summary, we have developed a simple PCR based technique to detect SF3B1 mutations in CLL patient samples with high disease burden which can be applied in routine molecular diagnostic laboratories.

PP2: A THERAPEUTIC ROADMARK FOR OVARIAN CANCER USING MYD88 AND MAD2 AS PROGNOSTIC INDICATORS

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Introduction: MyD88 and MAD2 are two potential prognostic biomarkers that have been extensively investigated in ovarian cancer. High MyD88 IHC scoring is associated with poor patient prognosis including a reduced PFS and OS while low MAD IHC scoring is associated with reduced PFS. Additionally both MAD2 and MyD88 have been associated with the development of chemotherapy resistance to the front-line anticancer drug paclitaxel. The aim of this study was to assess the relationship between MAD2 and MyD88 through alteration of MyD88 expression in two ovarian cancer cell lines, a MyD88
negative cell line A2780 and a MyD88 positive cell line SKOV-3. Additionally two MyD88 regulatory microRNAs Mi-146a and Mi-21, which have been shown to be upregulated in MyD88 negative HCC samples, were also assessed in this study. Methods: Alteration of MyD88 expression in these two cell lines was achieved through the use of a MyD88 overexpression plasmid vector and through siRNA knockdown experiments respectively. Following overexpression/siRNA knockdown procedures, MyD88 and MAD2 expression was assessed through qPCR and Western blot analysis. Mi-21 and Mi-146a gene expression was also assessed by qPCR. Furthermore the effect of TLR4/MyD88 knockdown on chemoresponsa was assessed in SKOV-3 cells using the CCK-8 assay. Results/Discussion It was found that knockdown or overexpression of MyD88 in SKOV-3 or A2780 cells respectively had no effect on MAD2 expression or the expression of Mi-21 and Mi-146a. Additionally knockdown of TLR4 but not MyD88 in SKOV-3 cells restored chemosensitivity, consistent with previous reports in the literature. The results suggest that MAD2 and MyD88 may work separately and act as two independent prognostic biomarkers. Additionally if targeted therapeutically both mechanisms may need to be targeted separately. By using these markers it may be possible to triage women into chemoresistant/chemosensitive groups prior to the onset of chemotherapy.

**PP3: PLATELET CLOAKING OF CANCER CELLS IS A UNIVERSAL PHENOMENON**

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Disseminated malignancy is responsible for the majority of cancer-related deaths and circulating tumour cells (CTCs) play a central role in metastasis. We and others have described the phenomenon of platelet cloaking of CTCs and how it induces an epithelial mesenchymal transformation (EMT) signal in these cloaked cancer cells. A limitation of the current studies is the select number of cancer types that have been examined. In this study we sought to further our understanding by determining if it is a universal phenomenon.

The interaction between platelets and 14 in vitro human cancer cell lines of different origin and metastatic potential was assessed by flow cytometry. This work demonstrated that platelet cloaking of cancer cells is a universal phenomenon occurring across all tumour types examined (breast, cervix, lung, melanoma, ovary, prostate & thyroid). However, the process is heterogeneous with the extent of platelet adhesion varying both across and within tumour types, ranging from 34% (C33a, primary cervical carcinoma) to 83% (SK-MES-1, metastatic lung squamous cell carcinoma). We next examined whether EMT changes previously attributed to the interaction were a constant result across all cancer types. This was achieved through proteomic and RT-PCR analysis of an EMT marker panel. The effect of platelets on the epithelial phenotype of the cancer cells again showed the universal but heterogeneous nature of the interaction, with morphology changes akin to EMT observed at varying degrees across all cancer types. Analysis of the EMT markers supported these results, with all cell lines having EMT-like changes but with no consistent pattern to the alterations. One exception was plasmogen activator inhibitor 1 (PAI-1) where a significant and consistent increase was observed.

This is the first time the universal nature of the platelet cloaking phenomenon of cancer cells has been described. While the results of this study illustrate both the degree of physical interaction and subsequent downstream effects are heterogeneous, it does demonstrate similar dynamic processes are occurring. Understanding these processes could ultimately allow the establishment of therapies tailored to inhibiting metastasis, thus significantly reducing cancer mortality and morbidity rates.

**PP4: PLATELETS ENHANCE THE INVASIVE CAPABILITIES OF OVARIAN CANCER IN VITRO**

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Ovarian cancer is the 5th leading cause of cancer related deaths in women. Poor survival rates are due to late stage diagnosis, with most patients asymptomatic until the disease has metastasised. Previously we described that there is a potent dynamic interaction between ovarian cancer cells and platelets in vitro, which involves platelet adhesion, activation and the induction of pro-survival, pro-angiogenic and epithelial mesenchymal transition (EMT) signals in the cancer cells. This study looked to further investigate this phenomenon by assessing whether the interaction was leading to an enhanced metastatic state in the cancer cells and if so whether it was possible to inhibit this process.

Cell lines 59M and SKOV3 were used as in vitro models of metastatic ovarian cancer. Cancer cells alone were compared to those incubated with platelets or platelets pre-treated with anti-platelet agents, aspirin and 2AM/AMP. Platelet cloaking of cells was quantified by flow cytometry, gene expression changes were determined by RT-PCR and the capacity of cells to invade was assessed using matrigel assays.

Significantly more platelets adhered to SKOV3 cells than 59M cells (p<0.05). While there were different rates of adhesion the platelets induced similar gene expression changes in both. There was a significant loss in expression of epithelial markers and an increase in mesenchymal markers, indicating the cells were undergoing EMT. In the SKOV3 cells these EMT-like changes were associated with a significant increase (p<0.0001) in the invasive capacity of the cells. However, platelets did not enhance the invasive capacity of the already highly invasive 59M cells. 59M cells are inherently more mesenchymal-like than SKOV3, demonstrated by lower expression of the epithelial markers and higher expression of mesenchymal markers, which explains these contrasting results. Critically pre-treatment of platelets with anti-platelet agents significantly reduced the platelet-mediated invasive capacity of SKOV3 cells (p<0.05).

This study demonstrates that the interaction between platelets and ovarian cancer cells is highly important, with platelets enhancing the metastatic potential of the cancer cells. Significantly it also demonstrates that this process can be attenuated with the use of anti-platelet agents, such as aspirin.

**PP5: HIGHLY TUMOUR-SELECTIVE PROTEIN-FATTY ACID NANOPARTICLES**

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HAMLET (Human alpha-lactalbumin Made Lethal to Tumour cells) and its related partially unfolded protein fatty acid complexes are novel biomolecular nanoparticles that possess relatively selective cytotoxic activities towards tumour cells while leaving healthy differentiated cells intact [1,2]. Spearheaded by C. Svanborg and her associates, in vivo and pilot clinical studies have shown the efficacy of HAMLET against human skin papillomas, glioblastoma brain xenografts, bladder cancer, and colon cancer [3-6]. While molecular and cellular studies have helped in understanding the underlying tumoricidal mechanisms brought about by these complexes [7], from a reductors /structural biologists point of view, we have chosen to ask what would be the minimal cytotoxic unit to give rise to this remarkable property [8]. Interestingly, there is no requirement for the protein to recover to its native state, showing that it is possible to endow native proteins with additional, independent functions through alternatively folded states. Experimentally, charge-specific chemical modifications suggest that electrostatic interactions - and not just hydrophobic interactions - play an essential role in the molecular recognition between the two components [2]. Additionally, biomolecular NMR spectroscopy of 13C- and 15N-labeled recombinant human alpha-lactalbumin has provided atomic level insights into the binding surfaces and the conformational dynamics of the complex, providing deeper insight into its structure-function-dynamics relationship. A possible mechanism of the protein-oleic acid interaction and its cellular uptake is proposed.
Results: While in the in vitro growth of H460 and MDR PT cells in CSC selective media showed reduced cell viability, CD44+ cells from H460 PT cells had the ability to differentiate and give rise to a population of mixed expression. In vivo studies using ALDH1+/CD44+ cells from H460 PT cells are currently under investigation.

Conclusion: CSC cells formed colonies and expressed significantly higher levels of stem-like markers, identifying them as a CSC-enriched population. Selection of an ALDH1+/CD44+ population showed enhanced resistance to cisplatin and the ability to differentiate. We identified a miRNA profile of cisplatin resistance using the NSCLC cell line A549. Altered expression of miRNAs implicated in cisplatin resistance were significantly altered in CSC colonies derived from PT sublines.

PP9: HUMAN HEPATIC MYELOID REGULATORY CELLS: POTENTIAL REGULATORS OF TUMOUR IMMUNITY

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The liver is considered an immunologically tolerogenic organ. Liver transplant patients require loss immunosuppression and have less rejection than recipients of other transplanted organs. In addition, the liver maintains homeostasis despite constant exposure to dietary and commensal antigens from the gut. Despite this tolerogenic capacity, the liver has one of the lowest rates of primary cancer of any organ (IRC, 2012). Myeloid populations in the liver are thought to be critical to hepatic tolerance and may also play a role in tumour immunity in the liver. Here we characterised hepatic myeloid cell populations from donor liver perfusates obtained during liver transplants and determined their effect on autologous hepatic lymphocytes. Perifusates from donor livers (n=76) were found to be enriched with cells (16 ± 10). The myeloid cell population was identified as CD15+CD33+ cells, and made up 25% of total CD45+ cells (n=8). Hepatic myeloid cells suppressed cytotoxicity mediated by hepatic natural killer (NK) cells. We propose that the hepatic myeloid cells eliciting this effect are myeloid derived suppressor cells (MDSCs). These cells are heavily implicated in pathogenesis, in particular malignancy. Elevated levels of MDSCs were detected in the blood of colorectal patients presenting with liver metastasis (N=19). These cells were rarely detected in healthy individuals and therefore detection of increased peripheral MDSCs
PP10: SOLUBLE CD1D: A NOVEL REGULATOR OF INVARIANT NATURAL KILLER T CELLS IN HUMAN HEPATIC METASTASES?
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Human invariant natural killer T (NK) lymphocytes are important anti-tumour cells characterised by the expression of an invariant T-cell receptor and found in relatively large proportions in healthy human liver. We have previously shown that NK-T cell numbers and their activity are decreased in livers from patients with hepatic malignancy (Kenna, Golden-Mason et al. 2003, Norris, Doherty et al. 2003). NK-T cell function is restricted by the non-classical MHC-like molecule CD1D but little is known about CD1D in human liver. We aimed to examine CD1D in liver tissue from brain-dead organ donors and patients undergoing resection for liver metastases. RT-PCR was used to detect CD1D in human liver, we found evidence of several splice variants in metastatic liver leading us to hypothesise that a soluble form could inhibit NK-T cell activity. Bioinformatics analysis identified and mapped putative splicing events in the CD1D genomic region. A soluble splice variant of CD1D was predicted and primer sets were designed to detect it, which we designated soluble CD1D (sCD1D). qRT-PCR revealed high levels of the novel soluble splice variant of CD1D in human tumour bearing liver in comparison to relatively low levels in donor liver tissue (Geometric mean relative expression in donor = 0.0003 and tumour bearing liver = 0.002313, p<0.0001). High levels of sCD1D was detected in serum from patients with colorectal cancer (n=5) compared to healthy controls (n=5) (p<0.0001). These data suggest that sCD1D in tumour-bearing liver and serum may represent a poor prognostic indicator for colorectal cancer. Donor liver perfusates are an abundant source of viable mesenchymal cells. These are capable of suppressing the cytotoxicity of autologous hepatic NK cells. The detection of MDSCs in donor liver perfusates represent a novel finding. We propose they are a tissue resident population that are fundamental to regulating inflammation and maintaining homeostasis in the liver. IRC, 2012, Cancer Mortality Rates from the Central Statistics Office, http://www.cancer.ie/about-us/media-centre/cancer-statistics.

PP11: INFLAMMATION, CANCER AND CHEMORESISTANCE: THE ROLE OF THE TLR-NFkB SIGNALLING PATHWAY IN NSCLC
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Introduction: The NFkB pathway plays a central role in the initiation and maintenance of inflammatory responses and has previously been shown to be constitutively activated in several cancer types, including non-small cell lung cancer (NSCLC). While the importance of NFkB activation in NSCLC is known, the mechanisms of activation are poorly defined. We aim to elucidate the role of Toll-like receptor mediated NFkB activation in NSCLC, which may represent an important link between inflammation and cancer development as well as chemotherapeutic resistance. We have previously demonstrated that levels of NF-kB are increased in cisplatin resistant cells compared with sensitive Parent cells. We are currently assessing a number of NF-kB regulated targets in cisplatin resistant cell line models, using DHMEQ, a specific NF-kB inhibitor. DHMEQ treatment results in greater cell death in the cisplatin resistant cells compared with Parent. This study will elucidate the efficacy of DHMEQ to overcome cisplatin resistance and identify novel targets within the TLR-NFkB pathway that may improve therapeutic strategies for NSCLC patients.

PP12: INVESTIGATION OF CELL SIGNALLING EVENTS INDUCED BY EXPRESSION OF YWHAE-NUTM2, A FUSION PROTEIN RESULTING FROM T(10;17) IN CLEAR CELL SARCOMA OF KIDNEY
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Clear cell sarcoma of kidney (CCSK), the second commonest childhood renal cancer is diagnostically challenging, aggressive, therapy-resistant and has poor outcomes. Virtually nothing is known about CCSK biology. Three individual cases of single CCSK with balanced translocation t(10;17)(q22;p13) prompted our investigation and characterization of t(10;17). The translocation results in rearrangement of YWHAE (encoding the protein 14-3-3 epsilon) on chromosome 17 and NUTM2 on chromosome 10, producing an in-frame fusion transcript of ~3 kilobases, incorporating exons 1-5 of YWHAE and exons 2-17 of NUTM2. To investigate the cellular effect of the fusion protein, we developed cell lines allowing stable inducible expression of the YWHAE-NUTM2 protein in HEK293 and NIH3T3 cells. By subcellular fractionation, we show that HA-Ywae-Nutm2 is present in both nuclear and cytoplasmic fractions, compared to 14-3-3epsilon, which is localised primarily in the cytoplasm. Since 14-3-3epsilon binds a battery of phosphoproteins, and thus mediates signal transduction, we investigated whether expression of Ywae-Nutm2, with its ability to enter the nucleus, alters cell signalling events. A large scale protein and phosphorylated protein screen was carried out on unfractinated, nuclear and cytoplasmic HEK293 cell lysates, induced and not induced to express HA-Ywae-Nutm2, using an antibody microarray encompassing 850 total and phospho-specific antibodies. A number of proteins and phosphorylation events were identified by this screen as being increased or decreased in response to HA-Ywae-Nutm2 expression. Of these, the levels of the anti-apoptotic proteins Mcl-1, Bcl-2 and Bcl-xl, were shown to be increased in cytoplasmic fractions (Mcl-1), or decreased in nuclear fractions (Bcl-2 and Bcl-xl). Validation by individual western blot is being carried out for a subset of the proteins identified in the large-scale screen. Hsp60 has been identified by western blot as being increased following induction of HA-Ywae-Nutm2 in unfractinated and both the nuclear and cytoplasmic fractions. Further validation of, and investigation into, the altered cell signalling events in response to Ywae-Nutm2 expression will assist in identifying therapeutic targets within the cell.

PP13: PS5 GENETIC STATUS AND MODULATION OF RESPONSE TO CISPLATIN CHEMOTHERAPY IN NON-SMALL CELL LUNG CANCER CELLS
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Introduction: The tumour suppressor gene, p53, is one of the key genes that mediate cellular responses to many anti-cancer agents such as cisplatin.
PP14: CHROMOSOMAL & MUTATIONAL ANALYSIS OF THE CISPLATIN RESISTANT PHENOTYPE IN NSCLC

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Introduction: Primary and acquired resistance to platinum agents has become a major obstacle in the management of lung cancer patients, in particular non-small cell lung cancer.

Methods: In this study, high resolution array-based comparative genome hybridization (aCGH) was performed on a panel of five cisplatin resistant NSCLC cell lines to examine DNA copy number deletions and gains/amplifications. Chromosomal aberrations were identified using the CGH-segMNT algorithm (NimbleScan 2.4). For mutational analysis, Sequenom, a mass-spectrometry-based SNP genotyping technology, was used to identify mutations in our panel of resistant cell lines. Using a literature search and the Catalogue of Somatic Mutations in Cancer (COSMIC) database, a mutation panel was identified for the detection of 547 frequently occurring and potentially clinically relevant mutations in 49 cancer-related genes.

Results: Differential expression of p53 mRNA was observed in NSCLC cell lines of different histological subtype. A549 and H460 cell lines expressed high levels of p53 mRNA (wild-type), in contrast to SKMES-1 (mutant) cells. Approximately 50% of adenocarcinoma and squamous cell tumours showed increased levels of p53 relative to their matched normal lung tissue. There was a modest increase in the accumulation of p53 in H460 cells only in response to cisplatin. A549 cisplatin resistant cells showed increased levels of p53 mRNA compared to parental cells. Erk inhibition using PD908959 enhanced the sensitivity of A549 cisplatin resistant cells to cisplatin. A number of genes implicated in the regulation of apoptosis and cell cycle control were significantly altered between H460 wild-type and SKMES-1 mutant cells in response to cisplatin.

Conclusion: Identification of the molecular components of the p53 pathway involved in the regulation of the cellular response to cisplatin may provide potential targets for the development of novel therapeutics in enhancing cisplatin cytotoxicity in NSCLC.

PP15: INVESTIGATION OF THE PROLIFERATIVE AND INVASIVE POTENTIAL OF CELLS EXPRESSING YWHAE-NUTM2, THE FUSION PROTEIN RESULTING FROM T(10;17)(P22;p13) IN CLEAR CELL SARCOMA OF KIDNEY

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Clear Cell Sarcoma of Kidney (CCSK), the second commonest pediatric renal cancer, is aggressive, therapy-resistant, and has poor outcomes. The oncogenic mechanisms underpinning CCSK are currently poorly understood, and specific diagnostic prognostic markers or indeed effective therapies are lacking. Prompted by three independent case reports of a chromosomal translocation t(10;17)(p22;p13) occurring in CCSK, we were keen to characterise this chromosomal translocation.

We demonstrated that the translocation results in rearrangement of YWHAE on chromosome 17 and NUTM2 on chromosome 10, leading to a fusion transcript composed of exons 1-5 of YWHAE fused in-frame to exons 2-7 of NUTM2. To investigate the cellular effects of YWHAE-Nutm2, we generated stable cell lines allowing inducible expression of HA-tagged Ywahae-Nutm2 protein in HEK293 and NIH3T3 cells. The cells were shown by western blot and by qPCR to express HA-Ywahae-Nutm2 in a tetracycline or doxycycline dose-dependent manner. To ascertain whether expression of Ywahae-Nutm2 confers a growth advantage, or biological characteristics suggestive of oncogenic potential on our cell lines, proliferation, migration and invasion assays were carried out using the xCELLigence system (ACEA Biosciences). This system utilises the electrical impedance generated by cells growing on a microelectrode array in a culture vessel to monitor cell status in real-time, allowing analysis of cell proliferation, migration or invasion at multiple time points over a user-defined time frame. Using the xCELLigence system, cell migration in HEK293 cells induced to express HA-Ywahae-Nutm2 was higher than in cells not expressing the fusion protein. We are currently investigating the ability of cells expressing, and not expressing, Ywahae-Nutm2 to invade and migrate through a matrigel layer. To additionally investigate the molecular changes within the cell resulting from expression of Ywahae-Nutm2, gene expression profiling will be carried out on cells induced and not induced to express the protein. This will contribute to our understanding of the molecular events underlying CCSK, and, in conjunction with ongoing signalling studies in the laboratory, help to elucidate novel therapeutic targets.


PP16: COMPARATIVE BIOENERGETICS IN PARENTAL SENSITIVE AND CISPLATIN RESISTANT CANCER CELL SUBLINES

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An almost collective characteristic of invasive cancers is the increase in aerobic glycolysis, known as the Warburg effect. An increasing evidence points towards the necessity for modifications in mitochondrial bioenergetics and cellular metabolism in driving malignant progression. In this study we aimed to determine the metabolic changes behind acquired cisplatin resistance in the non small cell lung cancer cell line, H1399 and a mesothelioma cancer cell line, P31. Analysis of the bioenergetic differences between the parental sensitive cell line and resistant sub-line was determined by the Seahorse extracellular flux analyser, determination of mitochondrial abundance was assessed by the citrate synthase assay and growth rate was measured by the alamar blue assay. It was found that the parental sensitive cell lines demonstrate greater oxygen consumption rates, greater mitochondrial abundance and growth rates than their resistant sub-lines. Currently work is being carried out to determine the mechanism behind these mitochondrial/ bioenergetic differences.
Results: H1975 cells (PKH3CA mutant) were most sensitive to GDC-0980, however they were the first to develop resistance to the drug. A 33 miRNA signature was identified contrasting H1975 parent and resistant cells. Preliminary results have identified JAK/STAT pathway signalling as one potential mechanism of resistance to GDC-0980 in H1975 cells, along with a number of other genes and proteins which will be presented.

Discussion & Conclusion: While the panel of four NSCLC cell lines all responded well to GDC-0980 treatment initially, resistance to the drug developed rapidly, within 4-6 months. Initial data highlights pSTAT3 regulated proteins and others as potential mediators of resistance to the drug. Further elucidation of these bypass strategies is crucial to the design of optimal treatment protocols for patients.

PP19: NOVEL LUMINESCENT COMPLEXES AND CANCER CELLS

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Our group has recently developed a series of novel luminescent compounds that we have employed to image cancer cells. These compounds contain naphthalimide and Ruthenium chromophores, allowing for their uptake and localisation within cells to be monitored by microscopy. We have manipulated these chromophores with a variety of functional groups to regulate entry into cells and cytotoxicity. These compounds have been shown to offer several advantages over existing luminescent markers due to their characteristic photostability, water solubility, effective DNA binding as well as useful photophysics all combining to make them excellent candidates as spectroscopic probes. Some of these compounds were also found to be effective photodynamic therapy (PDT) agents. PDT involves use of a nontoxic light-sensitive compound that becomes toxic to malignant cells when exposed to light under certain conditions. These novel PDT agents potently induce apoptosis in cervical cancer cells following the production of reactive oxygen species (ROS). Efforts are currently underway to evaluate these novel imaging probes and potential PDT agents in vivo.

POSTER ABSTRACTS

CLINICAL STUDIES
PP21: PHASE II TRIAL OF TEMOZOLOMIDE AND REIRRADIATION USING CONFORMAL 3D-RADIOThERAPY IN RECURRENT BRAIN GLIOMAS

MA Osman

Purpose: This phase II trial was designed to assess the response rate, survival benefits and toxicity profile of temozolomide, and brain reirradiation using conformal radiotherapy for treatment of recurrent high grade gliomas.

Design: Open-label phase II trial.

Patients: Thirty patients had been enrolled in the study between February 2006 and June 2009. Patients had to show unequivocal evidence of tumour recurrence on gadolinium-enhanced magnetic resonance imaging after failing conventional radiotherapy with or without temozolomide and surgery for initial disease. Histology included recurrent anaplastic astrocytoma, glioblastoma multiforme, and anaplastic oligodendrogloma.

Interventions: Patients were treated by temozolomide at a dose of 200 mg/m²/day for chemonaïve patients, and at a dose of 150 mg/m²/day to previously treated patients, for 4-5 cycles. Then, patients underwent reirradiation by conformal radiotherapy at a dose of 30-40 Gy by conventional fractionation.

Main Outcome Measures: The primary end point of the study was response. The secondary endpoints included survival benefit.

Results: All the 30 patients were treated with temozolomide and reirradiation. Two patients achieved complete remission (CR), 9 achieved partial remission (PR), with an overall objective response rate of 33.3%, and further 10 patients had stable disease (SD), with a SD rate of 33.3%. The mean progression free survival (PFS) was 10.1 months, and the mean overall survival (OS) was 11.4 months. Additionally, treatment significantly improved quality of life (QOL). Treatment was tolerated well with mild grade 1-2 nausea/vomiting in 40% of cycles, and mild grade 1-2 hematological toxicities (neutropenia/thrombocytopenia) in 9.6% of cycles.

Conclusion: Temozolomide and conformal radiotherapy had an anti-tumor activity in recurrent high grade gliomas, and represented a good treatment hope for patients with recurrent brain gliomas.

PP22: UTILITY OF HPV DNA, MRNA AND P16INK4A/KI-67 OVEREXPRESSION IN WOMEN WITH MILD CERVICAL ABNORMALITIES

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Background: The management of minor cytological abnormalities remains problematic, due to the high prevalence of transient HPV infections in low-grade disease HPV DNA triage is limited. The use of HPV E6/E7 mRNA detection and biomarkers such as p16INK4A and Ki-67 has potential to identify clinically significant infections improving diagnostic specificity. The study is performed under CERVIVA funded by the Health Research Board Ireland and the Irish Cancer Society.

Methods: Cervical smears for HPV testing and immunocytochemical analysis were collected from 1079 women presenting with LSIL/AIS/CIS at their first visit to colposcopy at the National Maternity Hospital, Dublin. HPV DNA was detected by Hybrid Capture II (Qiagen, UK). HPV E6/E7 mRNA expression by the PreTect™ HPV Proofer (NorChip AS, Norway). In those with adequate sample remaining (n=471) p16INK4A/Ki-67 expression was assessed using CINtec PLUS (Roche). The sensitivity and specificity for detection of CIN 2+ was calculated for each test.

Results: Findings indicated that HPV E6/E7 and p16INK4A/Ki-67 expression offered a high specificity for detection of CIN 2+ (96.2% and 83.3%) compared to HPV DNA testing (46.7%), while HPV DNA testing yielded a higher sensitivity (81.5%). By combining the strengths of each test it was established that merging HPV DNA testing with p16INK4A/Ki-67 offered the most efficient approach for stratifying women presenting with minor cytological abnormalities at true risk of high grade pre-cancer.

Conclusion: An approach of combined HPV DNA and p16 INK4A/Ki-67 testing has potential to reduce colposcopy referrals.

PP23: CIGARETTE SMOKING AS A RISK FACTOR FOR HPV INFECTION AND DIAGNOSIS OF HIGH GRADE CERVICAL NEOPLASIA

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Introduction: Persistent HPV infection is considered the strongest epidemiology risk factor for cervical cancer. While it is necessary it is not a sufficient cause given the high prevalence of transient HPV infections in younger women. We examined the relationship between cigarette smoking and HPV infection status and subsequent risk of CIN 2+. In order to overcome issues such as under reporting of smoking habits and individual differences in smoking behaviour, urinary cotinine concentrations were used as an objective maker of exposure to tobacco smoke. The study is performed under CERVIVA funded by the Health Research Board Ireland and the Irish Cancer Society.

Methods: Subjects comprise of women presenting to the colposcopy clinic with minor abnormal cytology (LSIL and ASCUS) at the National Maternity Hospital, Dublin for their first time. Prior to colposcopic procedure women were requested to give a urine sample and a cervical smear for HPV testing and immunohistochemistry. HPV DNA was detected by Hybrid Capture II (Qiagen, UK). HPV E6/E7 mRNA expression by the PreTect™ HPV Proofer (NorChip AS, Norway) and p16INK4A/Ki-67 expression was assessed using CINtec PLUS (Roche). Urine cotinine analysis was performed using Immulite 2000 Nicotine Metabolite assay (Siemens, UK). A cut off value of 50ng/ml was used (1) to distinguish non-smokers from those exposed to tobacco smoke.

Results: 1079 women were enrolled from the colposcopy clinic at the National Maternity Hospital, Dublin. Urinary cotinine identified 38% of the population as active smokers. Findings indicated that women with urinary cotinine concentrations above 50ng/ml were at an increased risk of HPV DNA infection (OR 2.78 95% CI 1.83-4.23) and, to a lesser extent, at risk of a HPV mRNA (OR 1.53 95% CI 1.03-2.26) and p16/Ki-67 (OR 1.62 95% CI 1.07-2.43) positive tests results. There was no significant increase in risk of HPV DNA positivity with increasing concentration of urinary cotinine. Only women with urinary cotinine concentrations above 260ng/ml had an overall increased risk of CIN 2+.

Conclusion: Cigarette smoking may contribute to risk of the acquisition of HPV and persistent HPV infection. High concentrations of urinary cotinine, suggestive of a heavy smoker, have a significantly higher risk of developing high grade disease, CIN 2+.


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Background: Acute lymphoblastic leukaemia (ALL) is the commonest cancer in children. Treatment of the central nervous system (CNS) is an essential component of childhood ALL protocols. Before the introduction of CNS-directed therapy in the 1960s, more than 50% suffered from CNS relapse. Today, CNS relapse rates are less than 5%.

Method: Our Lady’s Childrens Hospital (OLCH) entered 257 patients into the Medical Research Council UK ALL 2003 randomised controlled trial. The purpose of this retrospective was to review the incidence of CNS relapse in our patients with reference to: (i) gender, (ii) incidence at presentation, (iii) incidence of relapse, (iv) total white cell count (WCC) at presentation, (v) leukaemic blast phenotype and genotype, (vi) molecular response and (vii) overall survival. Our results were then compared to the results to the main trial findings.

Results: A total of 824 children who relapsed had CNS involvement. - 6 males and 2 females. 5/8 (62.5%) had isolated CNS relapse. Of the 8 patients, the phenotype was T-Cell (2) and precursor B-Cell (6). WCC at presentation ranged from 5,000/µL to 250,000. 1 patient who relapsed had CNS disease at diagnosis. There was no obvious association between genotypes, molecular response and CNS relapse. 5/8 (62.5%) were alive and well following treatment and haemopoietic stem cell transplant (HSCT). 3/8 had refractory disease with 1/8 relapsing following HSCT.

Conclusion: Our results are in keeping with the results reported from the main trial, namely: bone marrow relapse is seen more frequently than CNS relapse, either isolated or combined with bone marrow relapse. With contemporary frontline therapy, CNS relapse has become a rare event; however the management of CNS relapse remains one of the major challenges because of the treatment-related long-term sequela. Our CNS-relapse survival rate of 62.5% rate would be considered a high disease-free survival rate by best international standards.

PP25: PROFILE OF HEAD AND NECK CANCER PATIENTS REFERRED FOR A PRE-RADIOTHERAPY DENTAL ASSESSMENT BETWEEN 1997-2013

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Objective: To assess the profile of H&N Cancer patients referred for a pre-radiotherapy dental assessment seen in the Dublin Dental University Hospital (DDUH) from 1997-2013. Method: The dental records of 746 patients who attended the H&N Cancer Oral Care Centre in the DDUH between 1997-2013 were reviewed.

Result: The patient numbers increased from 20 in 1997-98 to 441 in 2012-13. The age range was 17 to 89 years with a mean age of 57.4, SD=13.0 years and 76% were male. The diagnosis was squamous cell carcinoma in 85% of cases. 97% of patients were dentate and 82% had 11 teeth or more. 62% had coronal caries in 1-10 teeth while 4% had coronal caries in 11-20 teeth. The lowest CPITN score was 1 in 32% of cases. The highest CPITN score was 4 in 32% of cases. Oral hygiene included, dry mouth and dietary advice were planned in 193% of cases. 86% of patients needed scaling and fluoride therapy. Restorative, endodontic or prosthetic treatment was needed by 93% of patients. Between 1-16 dental extractions were required in 69% of cases and 90% of patients had their extractions completed within one week of dental assessment.

Conclusion: This review demonstrates increasing numbers of referrals for dental management pre-radiation. The group is dentate with a significant number of teeth. Substantial treatment could be provided by a dental hygienist on the team. Appropriate and comprehensive treatment should be provided in a timely, integrated manner for all H&N radiation patients to facilitate the urgent delivery of radiation therapy and the prevention of dental/oral problems in the future.

PP26: EVALUATING THE ROLE OF HPV DETECTION ASSAYS IN THE MANAGEMENT OF WOMEN REFERRED FOR COLPOSCOPY

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Background: Cytology based colposcopy referrals include a substantial number of women with low-grade abnormalities, only a small proportion of which are at risk of developing high-grade disease. It is therefore important that better management strategies are investigated. The role of HPV in development of cervical pre-cancer and cancer is now well recognised and various molecular detection methods are being employed to detect HPV DNA and mRNA in cytology smears. In this study, the role of HPV DNA testing and mRNA testing in the management of women presenting in colposcopy with abnormal smears is evaluated.

Method: The study comprises of 545 women who presented for their first visit to colposcopy following a series of abnormal smears. A smear sample was taken for HPV and mRNA analysis and in the majority of cases a biopsy was also taken. HPV DNA testing was carried out on the Cobas 4800 (Roche Diagnostics). HPV mRNA testing was performed using the Aptima mRNA assay.

Results: The age range of women recruited in the study was 18-65 years. Median age was 32 years. There were 188 active smokers in the study cohort. 135 women were referred with ASCUS cytology, 188 with LSIL and 205 with high grade cytology. There were 12 women with NAD cytology referral. For detection of high grade disease (CIN2+), the sensitivity was 83.9% and 93.3%, and specificity was 44.6% and 50.0% for Cobas HPV test and Aptima mRNA assays respectively. To date, the Aptima assay has performed slightly better in this cohort.

PP27: PHYSICAL FITNESS AND PHYSICAL ACTIVITY LEVELS FOLLOWING HAEMATOPOIETIC STEM CELL TRANSPLANT: A CASE CONTROLLED STUDY

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Background: A bone marrow transplant or haematopoietic stem cell transplant (HSCT) is a potentially curative treatment for haematological malignancy. The intense nature of conditioning treatment pre-HSCT and prolonged isolation post-HSCT leads to high levels of physical inactivity and reduced cardiorespiratory fitness. This study compared the physical activity and cardiorespiratory fitness of those following HSCT with age and gender matched healthy controls.

Methods: Participants (n=12) who were 6 months or more following HSCT were matched with age and gender controls (n=12). Cardiorespiratory fitness was determined by indirect calorimetry, measuring oxygen uptake during a sub-maximal exercise test, using the modified Bruce protocol. Physical activity levels were measured using the Actigraph accelerometer, which was worn for seven days. Data was examined for percentage of time spent sedentary and in moderate to vigorous physical activity (MVPA).

Results: HSCT participants (n=12), aged 20-48 yrs (mean 32.9 yrs), were compared to age and gender matched controls (n=12). Maximal oxygen uptake (VO2max) was significantly higher (p=0.04) in the control group, mean 54.32ml/kg/min compared to 30.77ml/kg/min in HSCT participants. There was no statistically significant difference (p=0.13) in percentage of time spent sedentary between HSCT group (6.9%) and control group (6.9%). Time spent in moderate to vigorous physical activity for HSCT group was 6.9% compared to 5.9% of control participants and was not statistically significant (p=0.97).

Conclusion: Physical activity levels are similar among HSCT patients and healthy matched controls. However, cardiorespiratory fitness is significantly lower in a HSCT population, despite six months since transplant. It is not clear if reduced cardiorespiratory fitness is due to pre-HSCT conditioning treatments, prolonged hospital stay or post-HSCT complications. Further research pre-HSCT would be valuable to obtain further information in an effort to identify rehabilitation needs for this cohort.
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Malignant rhabdoid tumor (MRT) is an extremely aggressive tumor of unknown cell origin that mainly occurs in infancy and has been reported in nearly every anatomical site. Genetically, MRTs are characterized by biallelic inactivation of the tumor suppressor gene SMARCB1, most commonly through deletion of the chromosome 22q region containing the SMARCB1 locus. This gene encodes BAF47, a core subunit of the chromatin remodeling BAF or SWI/SNF complex.

Nomenclature for the three recognized forms of rhabdoid tumor reflect their anatomic localization and include malignant rhabdoid tumor of the kidney (MRTK), extrarenal extracranial rhabdoid tumor (EERT), and atypical teratoid rhabdoid tumor (ATRT) involving the central nervous system. Between 1986 and 2013, 25 pediatric [aged under 16 years] patients were diagnosed with rhabdoid tumor in the Republic of Ireland. 13 of these patients presented with ATRT. It had MRTK and 4 patients had EERT. The mean age at diagnosis was 38.8 months with an equal sex incidence overall. Due to the lack of a standardized treatment strategy for rhabdoid tumors, these patients were treated largely according to anatomic site, based on sarcoma, renal or brain tumor protocols contemporary to their diagnoses. 84% of the patients received chemotherapy, 80% underwent surgery and 44% had radiation therapy. The outcome overall was poor, as per international reports and independent of anatomic location. The overall survival rate was 24%, and mean time to death was just under 9 months. Contrary to expectation, the cohort included several long-term survivors, a real rarity in this situation. Full data on these long-term survivor patients especially is presented.

Given the rarity of this tumor, international consensus on best treatment has only recently been achieved, in conjunction with the establishment of the European Rhabdoid Tumor Registry.

PP29: PRIMARY BILATERAL ADENAL LYMPHOMA WITH INTRAEMDULLARY AND OCULAR INVOLVEMENT
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This is a case of a 67y old male who presented with a 4 week history of lower limb weakness, urinary urgency and constipation. He had no relevant background history. A MRI whole spine showed intramedullary increased signal from T2 to T5. Spinal angiography showed no evidence of a dural fistula or vascular malformation. CT TAP showed bilateral enlarged adrenal glands, with no other abnormalities or lymphadenopathy. MRI brain showed no paracranial abnormalities. Biopsy of the adrenal gland confirmed high grade B cell lymphoma. As primary CNS lymphoma was a consideration at this point, he was sent for ophthalmology review. This confirmed bilateral retinal involvement, although he had no systemic abnormalities. Biopsy of the lymph nodes confirmed primary adrenal lymphoma with intramedullary spread.

During these years, 224 patients had colonic polyps, of whom 149 (66.5%) were men and 75 (33.5%) were women. The most common types of polyps were adenomatous (166), followed by hyperplastic polyps (24), juvenile (18), inflammatory (13), lipomatous (2) and one patient with Peutz-Jegher polyps. Tubulovillous adenoma was the commonest in men, while hyperplastic polyps included the majority of women. The most common sites for polyps were distal colon (40.6%), followed by rectum (38.3%) and ascending colon (22%). The degree of dysplasia were analyzed by software SPSS 17 and compared with other published studies from different geographic regions of the world.

The incidence of anal cancer in HIV positive MSM now exceeds that of cervical cancer prior to introduction of screening. Over 90% of anal cancers are associated with HPV -16. While optimal anal cancer screening and HPV vaccine strategies remain to be determined, documenting the molecular epidemiology of HPV infection will be important in guiding policy makers in formulating universal and/or targeted vaccination/screening guidelines. The aim of this study was to document the molecular epidemiology of HPV/HR-HPV infection in MSM.

Methods: A prospective cohort study enrolled HIV-positive and HIV-negative MSM >18 years. Provider performed anal swabs were collected and anal HPV infection was detected using consensus primer solution phase PCR followed by type specific PCR for HR-HPV types-16, 18 and 31. Between-group differences were analyzed by Chi-sq tests and wicoxon rank tests.

Results: 194 MSM (mean [SD] age 36[10] yrs, 99.5(1%) HIV+) were recruited. Median number of sexual contacts in the preceding 12 months was 4 [IQR 2-10]. HIV-positive subjects had a mean [SD] CD4 count 557[217] cells/mm3, 84% were on HAART. Thirty-one samples were B-globin negative and thus excluded from further analysis. 113 (68%) subjects had detectable HPV DNA. 68(42%) a had HR-HPV type detected. HR-HPV 16 was detected in 44 (27%), HR-HPV 18 in 26 (16%) and HR-HPV 31 in 14 (23%) of samples. 28 (17%) of subjects had greater than one type of HR-HPV detected. When HPV and HR-HPV were stratified by age those >30 years had a higher prevalence (p=0.001 and p=0.026 respectively).

Conclusion: Identified prevalence of anal HPV-infection was high. Additional work undertaken in a subgroup of 45 HIV- positive MSM included in this study has identified a high persistence of HPV DNA (49%) and HR HPV 16 (33%) and HPV 18 (36%). Emerging patterns of HPV related disease strength the call for universal vaccination of boys and girls with consideration for catch up and targeted vaccination of high risk groups such as MSM and those with HIV-infection. The concerning increase in anal cancer particularly in HIV-positive MSM suggests the need to consider introduction of targeted screening in this high risk patient group.

PP31: PROFILE OF COLORECTAL POLYPS: A RETROSPECTIVE STUDY FROM KING FAHAD HOSPITAL, MADINAH, SAUDI ARABIA
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Aim: To evaluate the predominant colorectal polyps in the Almadinah region of Saudi Arabia. Materials and Methods: In this retrospective study, we analyzed pathology reports of colonoscopies performed in King Fahad Hospital, Madinah, Saudi Arabia covering the period 2006 to 2013. Data based on patient age, gender, size, site and type of polyps and the degree of dysplasia were analyzed by software SPSS 17 and compared with other published studies from different geographic regions of the world.

Results: During those years, 224 patients had colonic polyps, of whom 149 (66.5%) were men and 75 (33.5%) were women. The most common types of polyps were adenomatous (166), followed by hyperplastic polyps (24), juvenile (18), inflammatory (13), lipomatous (2) and one patient with Peutz-Jegher polyps. Tubulovillous adenoma was the commonest adenomatous polyp (102), followed by tubular (41) and villous (23) types. The sigmoid colon was the most commonly involved region (26.6%). Dysplasia was significantly associated with female patients who had large size tubulovillous polyps located in the left colon.

Conclusions: The type and distribution of colorectal polyps in Saudi Arabia is very similar to Western countries. Patient gender, and size, histological type and location of polyps are closely related to dysplastic change in colonic polyps.

PP32: THE SPECTRUM OF BREAST DISEASES IN SAUDI PATIENTS: AN 8 YEAR PATHOLOGICAL SURVEY AT KING FAHAD HOSPITAL, MADINAH, SAUDI ARABIA
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Abstracts

PP33: A PROSPECTIVE INVESTIGATION OF NUTRITIONAL STATUS OF IRISH ONCOLOGY PATIENTS UNDERGOING CHEMOTHERAPY: PREVALENCE OF MALNUTRITION, CACHEXIA, SARCOPENIA AND IMPACT ON QUALITY OF LIFE.

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Rationale: Malnutrition is a significant factor in predicting cancer patients’ quality of life (QoL), tolerance to treatment, and overall survival. Our study describes prevalence of malnutrition, cachexia and sarcopenia and their impact on QoL for the first time in Irish cancer patients undergoing chemotherapy in a regional cancer centre.

Methods: A prospective cross-sectional study of adult cancer patients undergoing chemotherapy was conducted. Malnutrition Universal Screening Tool scores (MUST) and QoL (EORTC QLQ-C30) were measured. Cancer cachexia was defined as weight loss (WL) >5% over the past 6 months or WL >2% in combination with a Bodily Mass Index (BMI) <20kg/m2 or sarcopenia. Skeletal muscle was measured by CT scan in all patients. Sarcopenia was defined using published cut offs.

Results: 432 patients receiving chemotherapy (276 male), with a mean age of 63 (SD 13.8) were included. The percentage of patients with colorectal cancer was highest (30.8%) followed by upper gastrointestinal cancer (19.7%), and hepatobiliary cancer (10.6%). 53.6% were overweight or obese (BMI >25kg/m2) and 35% were malnourished (MUST score <45). 31% of patients were sarcopenic. Sarcopenic patients had a lower BMI (26.6 vs. 30.9kg/m2, p<0.001) compared to non-sarcopenic pts. Grade 3-4 toxicity was experienced neutropenia in the first 3 cycles vs 0% receiving a dose <25% of prescribed dose. The prevalence of malnutrition, cachexia and sarcopenia was very high in Irish cancer patients but is disguised by a mantle of adipose tissue. Early screening by MUST and CT assessment of body composition would allow for prompt nutrition intervention in these patients.

Conclusion: The prevalence of malnutrition, cachexia and sarcopenia is very high in Irish cancer patients but is disguised by a mantle of adipose tissue. Early screening by MUST and CT assessment of body composition would allow for prompt nutrition intervention in these patients.

PP34: IMPACT OF BODY COMPOSITION ON TREATMENT OUTCOMES IN PATIENTS WITH METASTATIC PROSTATE CANCER TREATED WITH DOCETAXEL

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Introduction: Body composition is an important prognostic factor in cancer and evidence supporting a strong link between low skeletal muscle mass (sarcopenia) and chemotherapy toxicity is increasing. Docetaxel is standard first line treatment for castration resistant prostate cancer (CRPC). The aim of this study was to correlate body composition (by computed tomography (CT)) with toxicity to docetaxel in CRPC.

Methods: Patients with CRPC who received docetaxel between 2008-2013 were included. Correlations between patient characteristics, body composition and toxicity to chemotherapy were analyzed. Toxicity was assessed using Common Terminology Criteria for Adverse Effects v4.0.

Results: 62 pts, mean age 69y (SD 7), were included. In total 73% of pts were overweight or obese (BMI>25kg/m2). Sarcopenia was present in 68% (n=42) and of these 28(66.6%) were both sarcopenic and overweight or obese. Sarcopenic patients had a lower BMI (26.6 vs. 30.9kg/m2, p=0.001) compared to non-sarcopenic pts. Grade 3-4 toxicity was experienced neutropenia in the first 3 cycles of treatment, the most common being fatigue(48%), pain(23%) and anaemia(15%). There was no effect of sarcopenia on toxicity. However, patients with a skeletal muscle index (SMI)<25th centile (45cm2/m2) received less treatment compared to patients with SMI>75th centile (89 days vs 159 days, p=0.06). Analysing the drug dosage according to SMI(cm2/m2), 31% of patients receiving a dose >75th centile (1.98mg/SMI) experienced neutropenia in the first 3 cycles vs 0% receiving a dose <25th centile (1.347mg/SMI, p=0.048). High BMI was associated with better survival, BMI<25kg/m2 vs BMI>25kg/m2 had no survival benefit. BMI>25kg/m2 was also prognostically significant, with values >75th centile (150 vs. 661 days, p=0.01).

Conclusion: Sarcopenia is highly prevalent in pts with CRPC receiving docetaxel but is masked by excessive adiposity. Very low skeletal muscle mass is associated with less treatment days and poor tolerance to chemotherapy. High BMI is associated with longer survival.

PP35: BODY COMPOSITION BY COMPUTED TOMOGRAPHY SCAN AS A PREDICTOR OF CHEMOTHERAPY TOXICITY IN PATIENTS WITH RENAL CELL CARCINOMA TREATED WITH SUNITINIB

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Background: Sunitinib is standard first-line treatment for metastatic renal cell carcinoma (mRCC). Patients with severe depletion of skeletal muscle (sarcopenia) are prone to dose-limiting toxicity (DLT) during targeted drug therapy. We investigated if body composition by computed tomography (CT) scan predicted DLT from sunitinib in mRCC.

Methods and Materials: Patients with mRCC received sunitinib 50mg as first-line therapy between 2007-2012 were included. Skeletal muscle cross-sectional area at L3 was measured by CT. Sarcopenia was defined using published cut offs. Toxicity was assessed after 4 cycles of drug by CTCAE v4 criteria.

Results: 55 patients (43 male), mean age 64yrs were included. 67% were overweight/obese (BMI>25kg/m2). Sarcopenia was present in 33% (65% of normal BMI and 44% of overweight groups). Overall 40 patients (73%) experienced DLT. DLT occurred in <6 months in 53% and these patients who experienced DLT were older (mean 68 yrs vs. 60 yrs, P=0.01), had lower skeletal muscle mass (SMM) (51.8 cm2/m2 vs. 59.4 cm2/m2, P=0.012), and had lower systolic blood pressure (SBP) (131.4 vs 137.4, P=0.13), and received higher drug dose in mg/kg FFM (0.9 vs. 0.8, P=0.02). 92% of patients with SMM <25th centile experienced DLT compared to 57% patients with SMM >75th centile (P=0.03). Patients <25th centile had an average of 5
toxicities vs. 2 in those >75% centile (p=0.003). 77% (n=10) of patients receiving a drug dose >75% centile (1.105mg/KgM) experienced DLT in ≥6 months vs. 44% (n=17) receiving a dose ≥75% centile (<1.09mg/KgM, p=0.037).

Conclusion: Sarcopenia is prevalent in patients with mRCC, is an occult condition in patients with normal/high BMI, and is a significant predictor of DLT in patients receiving Sunitinib. Our results highlight the potential use of baseline body composition to predict toxicity.

PP36: POOR AWARENESS OF RISK FACTORS FOR CANCER IN IRISH ADULTS
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Background: Knowledge of cancer risk factors is unknown in Ireland. An understanding of this could help inform cancer prevention programmes.

Aims & Methods: To assess knowledge levels of the public on risk factors for cancer. A 48-question online survey was designed to gather data.

Results: 748 people (648 women, 100 man) participated. Mean age was 37.4 years (range: 18-74). The vast majority (81%) were concerned about developing cancer, however 20% believed cancer was unavoidable if a family history existed; furthermore 27% believed that greater than 65% of cancers are inherited; and 54% believed 10-20% of cancers are inherited. 30% were unaware risk increased with age. The top five risk factors listed by respondents were: smoking (85%), diet (74%), alcohol (44%), genetics (38%), and environment (31%). Only 32% were aware that obesity is a risk factor and 33% did not think the location of fat was important. 33% believed wearing a tight bra and 49% believed a blow to the breast could increase the risk of breast cancer. 85% believed ‘stress’ increased risk and 86% believed mobile phones ‘strongly’ increased risk. 12% believed ‘tattoo’ diet and 61% believed organic food reduced risk. The majority were aware that physical activity of 30 minutes/day can help to lower risk.

Conclusions: A sizable portion of the population is misinformed about cancer risk. Most are aware of classic risk factors (e.g. smoking, diet). Many overestimate risk attributable to genetics, environment, stress, and underestimate age, obesity and sunlight. One in five believes lifetime risk of cancer is non-modifiable.

PP37: CHILD AND ADOLESCENT DOWN SYNDROME ASSOCIATED LEUKAEMIA: THE IRISH EXPERIENCE
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Background: Down syndrome (DS), the most common syndromic chromosomal abnormality, is associated with a unique susceptibility to develop both acute myeloid (ML) and lymphoblastic leukaemia (ALL). These leukaemias differ from the non-DS related types of leukaemia and are thought to be distinct biological entities.

Aims: To perform a retrospective review of our experience of treating DS-related leukaemia at Our Lady’s Children’s Hospital.

Methods: Data was extracted from a database established in 2000 to prospectively gather data on DS associated leukaemias and their outcomes following polychemotherapy. Kaplan-Meier Survival Curves were constructed.

Results: Nineteen patients with DS-ML were treated and 19 with DS-ALL. Sixteen (84%) patients with DS-ML are alive and in complete remission with a median follow up of 7 years. All deaths in this cohort were due to treatment related mortality (TRM). Of the DS-ALL patients, 12 (63%) remain alive with a median follow-up of 3.6 years. TRM accounted for 5 of the 6 deaths. One death was due to leukemic relapse.

Conclusion: High cure rates are seen in DS-ML using contemporary polychemotherapy protocols, however, there is significant TRM in this cohort. DS-ALL does not have the same high cure rate as non-DS-ALL (>90%) and again this is mainly due to an excess of TRM.

ENHANCED PATIENT CARE POSTER ABSTRACTS

PP38: CHILDREN AND ADOLESCENTS INVOLVEMENT IN SHARED DECISION-MAKING: PARENTS, CHILDREN, AND PROFESSIONAL VIEWS AND EXPERIENCES
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Background: Cancer is a potentially life-threatening illness where important decisions are made at several points in the treatment process. Children with cancer generally prefer to be involved in decision making (Stogenga and Wasl-Smith 2008, Zwaanswijk et al. 2007) and want to have the opportunity to take part in decisions concerning their healthcare, even in end-of-life decisions (Hinds et al. 2001). International Society of Paediatric Oncology (SIOP) encourages healthcare professionals to share developmentally relevant information with children that will improve their ability to participate in the decision making process (Spinetta et al. 2003). Despite decision-making featuring throughout the trajectory of cancer care, children’s participation in decision-making remains an area much under-researched and complicated by conflicting opinions. Aim: To explore children and adolescents participation in shared decision-making (SDM) from multiple perspectives from one haematology/oncology unit in Ireland.

Methods: Qualitative research design was used to explore participants experiences of children’s decision-making. Interviews were conducted with children aged 7-16 years (n=20), their parents (n=22) and healthcare professionals (n=40). Data were managed with the aid of NVivo (version 8).

Results: Parents and children’s role in decision-making was significantly influenced by the seriousness of the illness. Cancer was a life-threatening illness and so the treatment ‘had to be done’. Children were not involved in major decisions (treatment decisions) as refusal was not an option. They were generally involved in minor decisions (choices about care delivery) with the purpose of gaining their cooperation, making treatment more palatable, giving back a sense of control and building trusting relationships. These choices were termed small decisions that would not compromise child’s welfare. Some adolescents were aware that choices were not real decisions since they were not allowed to refuse and expressed feelings of frustration.

Conclusions: Healthcare professionals and parents controlled the process of SDM and the children’s accounts revealed that they held a minimal role. Children appeared content that adults held responsibility for the major treatment decisions. However they desired and valued receiving information, voicing their preferences and choosing how treatments were administered to them.

PP39: A COCHRANE REVIEW OF INTERVENTIONS FOR PROMOTING PARTICIPATION IN SHARED DECISION-MAKING (SDM) FOR CHILDREN WITH CANCER
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Background: There is considerable support for involving children in healthcare decision-making at a level commensurate with their experience, age and abilities. Thus healthcare professionals and parents need to know how they should involve children in decision-making and what interventions are most effective in promoting SDM for children with cancer.

Aim: To examine the effects of interventions for promoting shared decision-making (SDM) for children with cancer who are aged 4-18 years.
PP41: GROUPING BREAST AND AXILLARY SURGERIES TOGETHER IN THE BREAST CANCER SETTING: IS A TWO SPEED APPROACH TO THE PHYSICAL REHABILITATION OF PATIENTS INDICATED?

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Breast and axillary nodal surgery are commonly performed during the same surgical episode in the breast cancer setting. Invasiveness of these surgical procedures as well as their combination; mastectomy (mast) or breast conserving surgery (BCS) combined with axillary lymph node dissection (ALND) or sentinel lymph node dissection (SLND) influences physical outcomes. Little is known about post-operative outcomes and optimal physiotherapy management in this post-operative setting. The aim of this study was to evaluate early post-operative quantitative and functional outcomes after breast and axillary surgeries. Patients were 279 breast cancer patients (Mast/ACi=n=74, Mast/SNBl=n=54, BCSiAC (n=48) and BCS/SNBl (n=63)). Assessment of function [upper extremity functional index (UEFI)], physical activity [International Physical Activity Questionnaire (IPAQ)], degrees of shoulder flexion and abduction (visual estimation) and pain (numerical ratings scale (NRS)) was conducted post-operatively and reassessed 1-month post-operatively. All patients underwent a standardised physiotherapy pathway which consisted of specific range of movement exercises and patient education. As all data were non-normally distributed, medians and interquartile ranges were reported. Fishers exact test was used to compare the percentages and medians were compared using the Mann-Whitney U test. Results showed that pain levels were low throughout (median 0) and there was no difference (p=0.06) in pain levels across the surgical groups. Flexion and abduction improved significantly (p<0.001), but by the 1-month time-point approximately two-thirds had a decrement in range of movement in the Mast/SNBl and Mast/ACi groups [flexion (median 49°) restriction] and abduction (median 50° restriction). There was a higher incidence of cording in the Mast/ACi group (42%) and BCS/ACi group (16%) versus the Mast/SNBl (18%) and BCS/SNBl groups (14.6%) (p=0.004). In conclusion pain and functional scores were similar between all surgery groupings, but movement restriction was noted in the Mastectomy/AC group. Overall this study showed better physical outcomes in less invasive surgical combinations. This research suggests that in the breast cancer setting, longer and more comprehensive physiotherapy follow-up is needed for more invasive surgical combinations with early discharge for newer less invasive surgeries.

PP40: SYMPTOMATIC AVASCULAR NECROSIS IN CHILDREN AND ADOLESCENTS WITH ACUTE LYMPHOBLASTIC LEUKAEMIA TREATED ON THE MRC - ALL PROTOCOL (2003 - 2011)

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Background: Avascular necrosis (AVN) is a well-recognised orthopaedic complication of therapy for Acute Lymphoblastic Leukaemia (ALL) in children and adolescents. Clinical features vary considerably, but symptoms may progress from intermittent pain during exercise to significant disability. Risk factors for AVN include; age at diagnosis, cumulative dose and dose density of corticosteroid therapy, corticosteroid type (dexamethasone or prednisolone), and host metabolic and genomic factors. The current MRC-ALL 2011 trial explores minimisation of this toxicity whilst maintaining anti-leukaemic efficacy.

Methods: A retrospective analysis of the healthcare records and radiology of patients enrolled on the MRC-ALL 2003 protocol at Our Lady’s Children’s Hospital (OLCH) and presenting with symptomatic AVN was undertaken.

Results: Between 2004 and 2011, 257 consecutive patients were enrolled on the MRC-ALL 2003 trial at OLCH. Sixteen patients (6.2%) developed symptomatic AVN at thirty-eight skeletal sites. Mean number of sites affected per patient was 3.9 (range 1-5). 87.5% had multiple joint involvement; 16 patients (100%) had at least one weight-bearing joint affected by AVN. Median age at diagnosis of ALL in patients with AVN was 13.5 years (range 3.3 - 16.8 years). 81.3% of patients with AVN were >10 years of age at time of ALL diagnosis. Onset of AVN symptoms occurred during Delayed Intensiﬁcation or Maintenance phases of ALL therapy in 15 patients, and following relapse therapy in one patient. Patients with symptomatic AVN were routinely referred to Orthopaedic and Physiotherapy services. 7 patients (43.8%) underwent surgery. 5 patients (31.3%) required adjustments to corticosteroid therapy due to progressive AVN.

Conclusions: In line with overall MRC-ALL 2003 trial results, we report a high incidence rate of AVN amongst patients aged 10 years and older, and high frequency of multiple joint involvement in our cohort of patients. We provide baseline data for comparison with future trials, including the current MRC-ALL 2011 trial.
PP43: FEASIBILITY OF A NEW SCREENING TOOL TO OPTIMISE THE MANAGEMENT OF PATIENTS WITH CHEMOTHERAPY INDUCED NEUROPATHY (CIPN)

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Background: The Chemotherapy Induced Neuropathy Dublin screening tool (CIN-D) was developed to enhance the quality of pre-chemotherapy examinations in patients receiving Vincristine, thereby improving detection rates of Chemotherapy Induced Peripheral Neuropathy (CIPN), and facilitating appropriate onward referral.

Method: A retrospective review, undertaken in 2010, highlighted limitations in the pre-chemotherapy assessment of patients receiving Vincristine at a tertiary children’s cancer centre. The CIN-D screening tool was consequently developed. It was piloted throughout 2013, as part of pre-chemotherapy assessment in patients receiving Vincristine. A prospective review evaluated the quality of pre-chemotherapy assessment, CIPN detection rates, and subsequent management of CIPN. Compliance with the screening tool and user satisfaction rates were also evaluated.

Results: Introduction of the CIN-D screening tool at a tertiary children’s cancer centre resulted in increased recognition of potential signs and symptoms of CIPN (66% versus 33.3%). It prompted more frequent modification of Vincristine doses (19.2% versus 8.3%). Close monitoring of CIPN changes allowed administration of higher cumulative doses of Vincristine before dose modification was necessary (10.33 mg/m² versus 7.26 mg/m²). Staff compliance with utilisation of CIN-D was 83%. Satisfaction rates were very high, although difficulties in examination of children less than 5 years of age were highlighted.

Conclusion: Introduction of the CIN-D screening tool resulted in increased detection rates of CIPN, more timely recognition of severe CIPN, and more frequent modification of Vincristine doses at a tertiary children’s cancer centre. We recommend that the CIN-D screening tool, with minor amendments, be adopted as routine standard of care at this centre.

PP44: PHYSICAL ACTIVITY LEVELS AFTER OESOPHAGEAL CANCER SURGERY: A CASE-CONTROL STUDY

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Background: It has been shown that cancer survivors are at an increased risk of becoming sedentary and seldom return to pre-diagnosis activity levels. This may increase the risk of developing cardiovascular and metabolic disease. Knowledge of physical activity (PA) levels in the increasing number of oesophageal cancer survivors is limited. Accurate measures of PA are needed to determine the extent of adherence to guidelines in this population. The American College of Sports Medicine (ACSM) recommends that adults engage in at least 150 minutes of moderate-intensity exercise each week. For health benefits it is recommended that time spent in moderate and vigorous intensity activity is accumulated in bouts of at least 10 minutes. The aim of this study was to investigate physical activity levels in oesophageal cancer survivors and compare with age and gender matched controls.

Methods: Participants were at least six months post oesophagectomy with curative intent and were compared to age and gender matched controls (who had no history of cancer). PA levels were recorded over seven days using an RT3 accelerometer.

Results: PA levels were recorded for 38 participants; 31 oesophageal cancer survivors (26 male) with a mean age of 64 years and 7 healthy controls (6 male) with a mean age of 54 years. The mean (SD) time spent engaging in moderate intensity activity per day was 30.38 (21.06) minutes in survivors and 69.77 (33.29) minutes in controls (p=0.002). When the data was analysed to determine adherence to the ACSM guidelines in terms of accumulating activity in 10 minute bouts 16% of survivors compared to 71% of controls were meeting the guidelines.

Conclusions: These results show that this cohort of oesophageal cancer survivors spend significantly less time engaged in moderate intensity activity than age and gender matched controls and the majority do not meet the ACSM guidelines recommended for health benefits. The implementation of rehabilitation programmes to encourage higher PA levels may be of benefit in this population.

PP45: A PROSPECTIVE SURVEILLANCE TOOL TO ENHANCE PATIENT COMMUNICATION AND IDENTIFY THOSE IN NEED OF REHABILITATION FOLLOWING TREATMENT FOR BREAST CANCER

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Background: Sixty percent of women treated for breast cancer have at least one treatment-related problem that does not resolve itself over a six year time span (1). Treatment sequelae can have wide ranging consequences for health, function and quality of life (2). There is therefore a need to address any physical or emotional problems that may arise. Prospective surveillance has been proposed as the way forward in the management of treatment related sequelae. However the symptoms that warrant monitoring have not until now been identified.

Methods: An exploratory mixed methodology study (focus groups followed by questionnaire) was used to identify the breadth of aspects of health affected by treatment for breast cancer or amelioration. Disability and Health (ICF) from the perspective of women with breast cancer. The ICF contains categories that cover physiological function, anatomical structure, activities and participation in life events and contextual or environmental aspects relevant to the individual. Having mapped the relevant issues, health professionals involved in treating women in the eight centres of excellence were asked if women report the identified symptoms and if so, which health professionals manage the particular aspect of health.

Results: The mixed methodology study (focus groups =34, questionnaire (n=298) revealed many altered aspects of health that were remendable such as pain reduced energy levels, reduced endurance difficulties with everyday activities, memory and return to work. It identified a gap between need for and referral to rehabilitation. Health professionals (n=96) responses indicated that women report functional difficulties (mean 24 of 42 categories) but less frequently problems with activities or participation (mean 7.5 of 30 categories) and or environmental or contextual issues (mean 6 of 26 categories). Lack of reporting of issues may play a role in symptom perseverance. The ICF list of categories could be used to facilitate reporting, enhance communication, and encourage self-management.

Conclusion: A list of health categories that warrant prospective surveillance has been identified and is proposed as a patient self-assessment tool which may enhance patient-professional communication and contribute to symptom amelioration.

PP46: THE COST-EFFECTIVENESS OF HUMAN PAPILLOMAVIRUS SCREENING FOR THE PREVENTION OF CERVICAL CANCER: REVIEWING THE CHOICE OF COMPARATOR STRATEGIES

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Background: It is estimated that 1/2 of all women in Ireland are at risk of cervical cancer and 1/3 of those with cervical cancer will die from it. It is therefore important to develop a screening programme that is cost-effective. In practice, cost-effectiveness analysis often uses microsimulation models to examine the cost-effectiveness of HPV screening. Because of the need to compare HPV screening to an ideal comparator, one challenge of microsimulation models is to define this ideal comparator. In this study, we compare HPV screening to three different comparator strategies: no screening; yearly screening using cytology; and yearly screening using a combination of cytology and HPV testing.

Results: In our Markov model, we found that using cytology as the comparator resulted in the lowest incremental cost-effectiveness ratio (ICER) and is therefore the most cost-effective comparator strategy of the three. However, this result is not robust to varying assumptions about costs and effectiveness of HPV screening and the comparator strategies. When even a small proportion of women who are HPV negative are referred for cytology, cytology becomes the most cost-effective comparator strategy.

Conclusion: Our study highlights the importance of examining the impact of assumptions about the costs and effectiveness of comparator strategies on the results of cost-effectiveness analyses.
Background: Cost-effectiveness analysis (CEA) is the standard framework for the economic appraisal of healthcare interventions. The primary metric used in CEA is the incremental cost-effectiveness ratio (ICER). The ICER is estimated by comparing the costs and effects of a given intervention relative to its next best alternative. In the case of screening, the next best alternative is typically a screening strategy with a longer screening interval. For example, the ICER of screening every 4 years should be estimated relative to screening every 5 years rather than to no screening. If the next best comparator is not included in the analysis then the resulting ICER estimates will be biased downwards.

Methods: A systematic review of model-based CEAs of HPV testing in cervical screening in the PubMed, World of Knowledge and Scopus databases yielded 30 relevant CEAs. The cost and effects estimates from the studies were extracted and checked by two reviewers to assess the completeness of the comparisons made between screening strategies. Results: Nineteen studies did not include sufficient comparator strategies to reliably estimate ICERs. Notably, 23 studies did not include strategies with intervals of longer than 5 years. The omission of relevant comparator strategies is likely to lead to a large underestimation of the ICER in some cases. To estimate the ICER reliably, CEA analysts should include as many relevant comparator strategies as practicable. Meanwhile, policy makers should be aware of the influence of the choice of comparator strategies on ICERs when interpreting cost-effectiveness evidence.

PP47: MANAGING THE ELDERLY IN RADIOTHERAPY USING GERIATRIC ASSESSMENT (MERGE)

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Introduction: The benefits of geriatric assessment (GA) have been demonstrated in many geriatric medicine settings, and include greater diagnostic accuracy, improved functional and mental status, reduced hospitalisation and improved survival and quality of life. In order to address the current lack of consensus as to the optimal method of geriatric assessment in Oncology, a Delphi study was carried out by the lead investigator, which represents consensus of experts in the field of geriatric oncology. This important consultation process provides the basis for GA assessments and interventions in the current study. Objectives: The aim of this study is to evaluate the feasibility and effect of geriatric assessment (GA) on the outcomes of older cancer patients receiving radiotherapy +/- chemotherapy. To determine the feasibility of incorporating GA in the treatment decision making process in patients requiring radiotherapy. To evaluate the potential impact of GA on the outcomes of older cancer patients by evaluating rates of treatment tolerance and quality of life in both arms. To estimate the influence of GA on radiation oncologists in the clinical care of older patients with cancer by looking at factors influencing treatment decisions and decision regret. Methods: A two arm phase 2 randomised trial will be employed, as follows: Arm 1 = Usual care. This does not typically include geriatric assessment domains. Arm 2 = Usual care plus GA. Results: GA results and interventions. GA will be completed at baseline and at three months post treatment completion, as per the consensus guidelines presented previously at SIOD 1. Basic sociodemographic variables, tumour characteristics and study endpoint data will be captured from the patient’s medical record. Quality of life will be measured, using the EORTC QLQ-C30. Conclusion: This study is due to commence recruitment in July 2014. Preliminary results will be presented. Potential benefits include predicting complications of treatment, detection of problems not found using standard oncology performance measures, allowing for an individual evaluation of overall treatment benefit. Results: This study is due to commence recruitment in July 2014. Preliminary results will be presented. Potential benefits include predicting complications of treatment, detection of problems not found using standard oncology performance measures, allowing for an individual evaluation of overall treatment benefit. Conclusions: The incorporation of geriatric assessment methods in oncology is widely advocated, however there is little prospective data regarding such aspects as feasibility and efficacy.

PP49: TOBACCO SMOKING EFFECTS ON LUNG CANCER WITHIN SIBERIA

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The Siberian Federal District (SFD) occupies 35% of Russia territory. The low population density (9.6 people per square kilometers) and unevenness of its distribution complicate cancer care in the District. Among 8 Russian Federal Districts, the SFD has the highest cancer incidence rate (252.8 per 100,000 population). Out of the total cancer cases registered in the SFD, smoking-associated lung cancer is the most common (59.9%). In the SFD, the highest incidence rates in males were observed in the Altai Krai (71.0), Omsk Oblast (68.8), Irkutsk Oblast (68.8), Altai Republic (67.0) and Tomsk Oblast (65.1). For females, the highest incidence rates were registered in the Tyva Republic (15.5), Zabaykalsky Krai (12.6), Republic of Buryatia (12.0), Irkutsk Oblast (11.3) and Tomsk Oblast (10.5). The median age of male patients is less than the average for Russia, while females are around the same. The tendency for increasing incidence was observed among females. Public opinion surveys (2011) showed smoking escalation among adolescents of the SFD. Number of young smokers aged 15-17 is 30% and half of them smoke 4-10 cigarettes daily. Against the overall orientation of youth of the SFD on a stable family and health, in some federal subjects (the Republic of Buryatia and Khakassia, the Altai Krai) education and education are more relevant than taking care of their health. Anticancer education closely related to the promotion of healthy lifestyles should begin at school. The program “Basics of Oncology” for school has been devised at the Cancer Research Institute, Oncology Department of Siberian Medical Institute and at Tomsk Institute of Teacher Training. This program provides basic knowledge of cancer.
Abstracts

PP50: COMPUTATIONALLY GUIDED DISCOVERY AND DEVELOPMENT OF NON-LBP NOVEL ANDROGEN RECEPTOR SMALL MOLECULE ANTAGONISTS - IMPROVING TREATMENT OF PROSTATE CANCER

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Prolonged treatment of prostate cancer (PCa) leads to development of resistance so alternative therapies are urgently required. By developing compounds which interact with the androgen receptor (AR) distant from the endogenous dihydrotestosterone binding site and block co-activator recruitment it is possible to overcome this resistance regardless of the AR mutation status. Three recently published papers (PMID: 22280402, 22853713 and 23834240) detailing our compounds demonstrate non-ligand binding pocket (nLBP) AR affinity, selectivity over other nuclear receptors and low toxicity, point to the viability of an alternative approach to classical PCa therapy. My talk will detail the biological problem, computational screening and design approaches applied, discuss initial SAR around the lead series and give an overview to the viability of an alternative approach to classical PCa therapy. My talk will detail the biological problem, computational screening and design approaches applied, discuss initial SAR around the lead series and give an overview to the viability of an alternative approach to classical PCa therapy.

PP51: SYSTEMS BIOLOGY DERIVED BIOMARKERS FOR IMPROVES DIAGNOSIS OF CERVICAL PRE-CANCER

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Our objective was to ascertain the utility of a novel panel of pre-selected, systems biology derived proteomic biomarkers for improving cervical pre-cancer diagnosis. This project is conducted within the framework of a FP7 funded research programme called SYSTEMCERV. Through SYSTEMCERV and a previous FP7 project, AUTOCAST, a panel of novel biomarkers has been identified using a systems biology approach. Biomarker expression patterns, from six biomarkers, were examined by immunohistochemistry on a range of histological disease. In parallel, pre-frk4a IHC was performed on all tissue specimens and used a benchmark stain.

To date 31 patient specimens have undergone immunohistochemistry. The median age of the population is 39 years (range: 18-83years). Histology identified 13 with no CIN (Normal), 18 had a diagnosis of CIN 3. Systems biology derived biomarkers demonstrated over expression in up to 100% of CIN 3 lesions. Positive staining, indicating over expression, was identified in less than 20% of cases with no detectable CIN. Immunohistochemistry of CIN 1 and CIN 2 is currently underway to further investigate the clinical utility of these biomarkers.

Novel biomarkers have the potential to distinguish normal from high grade CIN based on the gene expression status in cervical tissue. It is conceivable that this will lead to more accurate grading and stratification of CIN disease, ultimately improving patient management.

PP52: CHEMOKINE-MEDIATED RECRUITMENT OF INFLAMMATORY T CELLS INTO THE LIVER AND VISCERAL ADIPOSE TISSUE OF OBESITY-ASSOCIATED CANCER PATIENTS

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Conclusions: Chemokine-mediated trafficking of such cells to VAT contributes to obesity-associated inflammation and disease, and may be at the expense of an effective anti-tumour response.

Methods: The effector memory phenotypes, cytokine profiles and chemokine receptor expression profiles of T cells were examined in the liver, blood and omentum of obese and non-obese OAC patients, along with the levels of a panel of secreted chemokines and cytokines using flow cytometry and MSD multiplex ELISAs.

Results: Significantly higher proportions of IFN-γ-, IL-17- and TNF-aa-producing effector/memory T cells were observed in the VAT and liver when compared to blood. In addition, we have demonstrated that T cells in the VAT and liver can effectively and specifically kill autologous OAC tumour cells. In addition, significantly higher IL-8, Fractalkine, MIP-1β, MIP-1α, IP-10 and MIP-1β levels were observed in the omentum and liver compared to blood serum, while levels of ITAC and RANTES were highest in the serum, with highest levels observed in obesity. The differential expression levels of the chemokines in blood serum, liver and omentum were reflected in the expression profiles of their known receptors on T cells at these sites indicating that these chemokines are actively recruiting T cells to omentum and liver in these OAC patients. Further evidence of this was found in the preferential migration of T cells isolated from the blood of OAC patients to adipose tissue in vitro.

Conclusion: Chemokine-mediated recruitment of inflammatory T cells into omentum and liver appears to contribute to obesity-associated inflammation in OAC and may be at the expense of effective anti-tumour immunity.

PP53: A COMPARATIVE ANALYSIS OF CIRCULATING TUMOUR CELL DETECTION PLATFORMS USING PROSTATE CANCER CELL LINES

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Conclusions: This project is conducted within the framework of a FP7 funded research programme called SYSTEMCERV. Through SYSTEMCERV and a previous FP7 project, AUTOCAST, a panel of novel biomarkers has been identified using a systems biology approach. Biomarker expression patterns, from six biomarkers, were examined by immunohistochemistry on a range of histological disease. In parallel, pre-frk4a IHC was performed on all tissue specimens and used a benchmark stain.

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Introduction: Circulating tumour cells (CTCs) shed off the primary tumour into the bloodstream and act as a precursor to metastasis (Maheswaran and Haber 2010). Thus, CTCs hold invaluable prognostic and diagnostic information. Currently, Cellsearch is the only FDA approved device for the extraction of CTCs, relying on the use of epithelial surface marker, EPCAM. However, a sub-population of tumour cells experience a loss of their epithelial cell properties having undergone EMT (Gorges and Pantel 2013). Size based detection platforms e.g. Screencell and Cell Sieve are predicated on the fundamental mechanism of separating the different detection platforms currently available and to determine the most efficacious method of CTC isolation. Methods Prostate cancer cell lines DU145 and PC-3 were transfected with lentiviral particles containing the GFP construct. Cells were selected with the antibiotic blasticidin. Upon positive selection, cells were FACS sorted for the highest level of fluorescence. 100, 50 and 10 cells from both cell lines were spiked into whole blood and prepared according to the specific details of detection platforms Fluxion, Screencell and Cell Sieve. Cells were mounted and enumerated under a fluorescent microscope (FITC and DAPI channels) Counterstaining was performed using May-Grunwald Glemsa. Results PC-3 cells spiked onto the Fluxion detection platform resulted in a capture efficiency rate of 74%. As a consequence of the heterogeneous expression of EPCAM exhibited by DU145 cells, cell numbers were too low to count presenting as quenched levels of fluorescence. The Screencell filters produced an increased capture efficiency rate of 78%. Secondary May-Grunwald Glemsa staining displayed the morphology of tumour cells in contrast to inflammatory cells present in the blood. Preliminary tests using the CellSieve technology resulted in a very low capture efficiency rate of 14%. Conclusion The markedly variable capture efficiency rates of the different detection platforms, highlights the need for specific CTC markers and highlights the weakness of relying solely on EPCAM/size based systems.


PP54: GENERATION AND CHARACTERISATION OF AN ISOCINETIC CELL LINE MODEL FOR RADIATION RESISTANT PROSTATE CANCER

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The understanding of the molecular mechanisms underlying the radioresistant phenotype of tumours forms the basis for the identification of prognostic markers of radiotherapy treatment failure. Resistant isocinetic cell lines have been successfully generated for a number of cancer lines to determine mechanisms associated with survival advantage to radiation of the generated sub lines. An isocinetic radiation resistant model was generated using the 22RV1 (primary) prostate cancer cell line. The radiation resistant cell line was selected for its ability to reproduce in vivo adaptation of CaP tumours to repeated radiation exposures. Cells were treated weekly with 2 Gy fractionated ionising radiation. Survival capacity to radiation was measured using clonogenic cell survival assays, after every 10 Gy cumulative dose. Survival curves were compared to wild type untreated cells and age matched controls. The isocinetic subtype IR22RV1 was found to have significant survival advantage over wild type cells treated with 100 Gy after 60 Gy cumulative dose (1.3 fold increase in survival after 20 Gy and 1.7 fold increase after 100 Gy). Preliminary results suggest estimated radiation sensitivity is associated with deregulated apoptosis ( Annexin V-PI), DNA damage repair (COMET assay, Y H2AX assay) and reactive oxygen species responses. This model has potential to facilitate the identification of key biomarkers of the response of prostate tumours to radiation therapy.

PP55: TOWARDS NEW AND SELECTIVE INHIBITORS OF THE RAS/RAF/MEK/ERK PATHWAY: GUANIDINIUM DIAMOMIC DERIVATIVES

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It is thought that 30% of all human tumours are caused by a mutated ras sarcoma (RAS) oncogene that causes uncontrolled cell division. Further downstream, other proteins can be found such as the rapidly accelerated fibrosarcoma (RAF), mitogen-activated protein kinase/extracellular signal-regulated kinases (MEK) and extracellular signal-regulated kinases (ERK). Therefore, inhibiting the RAS/RAF/MEK/ERK pathway is an attractive prospect for targeted chemotherapeutic agents. Considering the unknown target of previous cytotoxic and pro-apoptotic compounds prepared in our laboratory and taking into account similarities with known kinase inhibitors, it is expected that new families of compounds were synthesised during the last five years. These guanidine based compounds inhibit the RAF/ MEK pathway in 96-99%, probably acting as type III (allosteric) MEK inhibitors 2,3.5 Three different moieties were identified: (i) a polar moiety, responsible for forming ionic and hydrogen bond interactions with ATP; (ii) a hydrophobic moiety, that interacts with a hydrophobic pocket in the kinases; and (iii) an articulation X, responsible of the curvature of the ligand making the molecule fit very nicely in the allosteric site orientating the different moieties. We present the preparation of novel compounds with several structural modifications (relative orientation, polar moiety, hydrophobic moiety, length of the molecule or nature of the aromatic ring) to confirm their mechanism of action as type III PKIs non-ATP competitive that bind to allosteric sites of MEK.

References

PP56: LINKING KNOWLEDGE OF BREAST CANCER TO PREVENTIVE PRACTICE IN MALAYSIAN SCHOOL-TEACHERS

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The study investigated the association between knowledge of breast cancer and practice of breast self examination (BSE) and clinical breast examination (CBE) in a cross-sectional sample of 700 Malaysian secondary school teachers. A simple random sample of 10 out of 24 schools was selected and all teachers invited to participate. The following data were collected using a self-administered questionnaire: (i) socio-demographic data, (ii) five categories of breast cancer knowledge: general, signs and symptoms, risk factors, mammography, recommended frequency of BSE and CBE and (iii) BSE and CBE practice. Separate knowledge scores were computed for each category and an overall summative score. Backwards stepwise logistic regression models were developed (PPSS V20) with BSE and CBE practise as dependent variables. The co-variates were: socio-demographic, lifestyle factors, total score or knowledge score for each category. The response rate was 74% (518/700). Level of exercise was associated with BSE (p<0.02) and CBE (p=0.01), with exercise twice a week showing the strongest association compared to never exercising, OR=2.71 (95% CI=1.38-5.33, p=0.02) for BSE and OR=2.40 (95% CI=1.27-4.55, p=0.007) for CBE. Self-report of annual medical check up was associated with BSE, OR=2.13, (95% CI=1.29-3.52, p<001) and CBE, OR=2.41, (95% CI=1.57-3.70, p<001). Likelihood of practicing BSE and CBE practice. Separate knowledge scores were computed for each category and an overall summative score. Backwards stepwise logistic regression models were developed (PPSS V20) with BSE and CBE practise as dependent variables. The co-variates were: socio-demographic, lifestyle factors, total score or knowledge score for each category. The response rate was 74% (518/700). Level of exercise was associated with BSE (p<0.02) and CBE (p=0.01), with exercise twice a week showing the strongest association compared to never exercising, OR=2.71 (95% CI=1.38-5.33, p=0.02) for BSE and OR=2.40 (95% CI=1.27-4.55, p=0.007) for CBE. Self-report of annual medical check up was associated with BSE, OR=2.13, (95% CI=1.29-3.52, p<001) and CBE, OR=2.41, (95% CI=1.57-3.70, p<001). Likelihood of practising
PP57: A URINE DNA METHYLATION BIOMARKER PANEL FOR NON-INVASIVE DETECTION OF HIGH-RISK PROSTATE CANCER

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Introduction: Opportunistic PSA testing has increased prostate cancer (PCa) incidence, resulting in significant over-treatment of clinically indolent disease. The poor tumour-specificity of PSA causes unnecessary invasive biopsies, associated with substantial economic burden and trauma and anxiety to patients. Conversely, sampling bias means that needle-biopsies cannot conclusively rule-out the presence of PCa or the co-existence of more aggressive lesions. The aim of this study is to develop a ‘liquid-biopsy’ DNA methylation biomarker panel to alleviate the problems surrounding early detection of PCa and improve non-invasive early detection of aggressive PCa.

Methods: Post-DRE first catch urines from 156 men undergoing TRUS-biopsy were used for DNA isolation and methylation analysis by quantitative methylation specific PCR. Sensitivity and specificity of the methylation panel and serum PSA were determined using logistic regression. All analyses were done blinded from TRUS-biopsy findings.

Results: The patient cohort consisted of 48 biopsy-negative and 108 biopsy-positive (14 low-risk, 58 intermediate-risk and 36 high-risk) men. DNA methylation analysis revealed significantly higher frequencies and quantitatively higher levels in biopsy-positive men compared with serum PSA, AUC of 0.96. Focusing specifically on high-risk PCa, biopsy-positive men; most exemplified in the high-risk group. Urinary methylation discriminated between biopsy-positive and -negative men with an AUC of 0.86, compared with serum PSA, AUC of 0.56. Focusing specifically on high-risk PCa, the methylation panel gave an AUC of 0.87, compared with PSA, AUC of 0.56. Finally, combining methylation with PSA for non-invasive detection of high-risk PCa, produced an AUC of 0.96.

Conclusion: Early indications suggest that urinary profiling of DNA hypermethylation can selectively detect high-risk PCa and improve non-invasive early detection of aggressive PCa.

PP59: CIGARETTE SMOKE EXTRACT ALTERS THE INFLAMMATORY TISSUE MICROENVIRONMENT, INDEPENDENT OF NFkB AND HIF-1A ACTIVITY, IN HUMAN AND MURINE MODELS OF COLITIS

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Introduction: Ulcerative Colitis (UC) is an inflammatory bowel disease, characterised by chronic or relapsing inflammation. Colorectal cancer is one of the most serious complications of ulcerative colitis with approximately 25 to 30% of patients developing colorectal cancer after 40 years of colitis. The severity of UC is higher in non-smokers than smokers; however, the biological mechanisms controlling this effect are unknown. This study aims to examine the effect of Cigarette Smoke Extract (CSE) using mouse in vivo and human ex vivo models of UC to determine if inflammatory mediators and transcription factors are altered following CSE treatment.

Materials and Methods: Colonic biopsies were obtained from consenting UC and control patients. These ex vivo biopsies were cultured in the presence or absence of CSE. Multiplex ELISAs assessed the levels of inflammatory mediators. In mice, colitis was induced with 3% DSS. CSE was injected intraperitoneally. Disease activity index (DAI) scores and weight were recorded daily. Gene expression of DNA damage and repair markers (MRE11a, ATM, BRCA1, OGG1) and inflammatory mediators were measured in murine colonic tissue. NFkB and HIF-1a activity was measured by ELISA in human and mouse colonic tissue.

Results: Secreted levels of CXCL1, IL-6, CCL2, CCL20, MMP9 and MMP13 from treated UC biopsies were decreased (all, p < 0.05). Mice treated with CSE had lower DAI scores (p<0.001). Gene expression of MMP9, CCL2 and OGG1 were downregulated in CSE treated mice (p < 0.001, p < 0.05 and p < 0.05 respectively). This effect was specific to recto-sigmoid tissue. NFkB and HIF-1a activity were not significantly different between the treated and untreated groups in humans and mice.

Conclusion: CSE elicits a similar anti-inflammatory effect in mouse and human models of UC. These treatments observed are independent of NFkB and HIF-1a activity.
PP61: NOVEL SMALL MOLECULE INHIBITORS THAT ALTER ENERGY METABOLISM AND DNA REPAIR AND IMPROVE RADIORESPONSE IN AN ISOGONIC MODEL OF OESOPHAGEAL RADIATIONRESISTANCE

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Introduction: Tumours display high levels of angiogenesis (1) leading to leaky blood vessels and hypoxia, mechanisms of radioresistance (2,3). Tumours also have altered energy metabolism (4). We have shown that altered energy metabolism and DNA repair is associated with radioresistance in oesophageal cancer (5,6). Targeting tumour angiogenesis, metabolism and DNA repair may therefore increase radiosensitivity. Zebrafish intersegmental blood vessel screening identified a novel small molecule inhibitor, RUD1, with strong anti-angiogenic properties. Structural analogues of this compound (RUD2-4) were created. We examined the ability of these inhibitors to alter metabolism, DNA repair gene expression and radiosensitise in oesophageal cancer.

Methods: An isogenic model of oesophageal radioresistance, OE33P (sensitive) and OE33R (resistant), was treated with the inhibitors. Metabolism profiles were generated using Seahorse technology. Expression of DNA repair genes was assessed using qPCR. Radiosensitivity was assessed by clonogenic assay.

Results: Oxidative phosphorylation was reduced in OE33P treated with RUD2 and RUD3 (p<0.0001) and OE33R treated with RUD1-4 (p<0.0001). Glycolysis was reduced in OE33P treated with RUD2 (p<0.05) but none of the inhibitors affected (glycolysis in OE33R. Expression of several DNA repair genes was reduced following treatment with the inhibitors. OE33P expression was reduced in OE33P and OE33R treated with RUD-2 (p<0.0001). PARP1 expression was reduced in OE33P and OE33R treated with RUD1 (p<0.01). RUD1 also reduced expression of MMS19 in OE33R (p<0.01). RUD4 increased radiosensitivity of OE33P and OE33R (p<0.0001) and RUD5 also increased radiosensitivity in OE33P (p<0.05).

Conclusion: We have identified a number of novel anti-angiogenic small molecules that alter energy metabolism and DNA repair gene expression, processes linked to radiation resistance, in an isogenic cell line model of oesophageal adenocarcinoma radioresistance. Two of these inhibitors also improve radiation response.


PP62: EVALUATING THE ANTIPROLIFERATIVE ACTIVITY OF 1,3-BIS(ARYL)-2-NITRO-1-PROPENES AND RELATED COMPOUNDS

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Cancers of the lymphatic cells (lymphomas) account for approximately 10% of all malignant diseases in children and 60% of these cases are subdivided into non-Hodgkin lymphomas (NHL). Burkitt’s lymphoma (BL) is a NHL, which manifests as tumours composed of small non cleaved B-cell lymphocytes[1]. Structural derivatives of 4-Methylxanthophanate have previously been shown to express significant antiproliferative effects in vitro[2,3]. More recently the potent, selective pro-apoptotic activity of 1,3-bis(aryl)-2-nitro-1-propenes was evaluated[4]. Based on these previous studies, libraries of structurally related compounds were designed. Many of these compounds contained a classic nitrovaseline core - which has also been previously shown to possess anticancer activity. These compounds were synthesised via a number of routes using variations of the Baylis-Hillman, Henry-Knoevenagel and Wittig reactions. Each compound was subsequently characterised by 1H and 13C NMR spectroscopy, IR and HRMS. The antiproliferative activity of each compound was evaluated using the Alamar blue assay and FACS analysis using two BL cell lines: EBV- B95-8 and the chemoresistant EBV- DGS75. Preliminary screening has also been carried out in CLL, HU60, MCF-7 and HeLa cell lines. The antiproliferative effects and the structure activity relationships for the series of products will be presented together with a discussion of the possible targets and biochemical mechanism of action.

Facilitated by an atypically low mutation frequency and poorly delineated pathobiology, prostate cancer (PCA) has continued to evade any molecular taxonomic sub-classification. Accordingly, efficient prognostication of the world's most prevalent non-cutaneous malignancy remains challenging, with over-treatment of the indolent sub-type, as well as missed early intervention for the aggressive form, emerging as significant clinical issues. Analogous to mutations, numerous epidemiological studies have been reported by us and others which drive prostate tumorigenesis. Herein, we apply a methylome-wide discovery approach to unravel novel prognostic DNA methylation signatures of clinical relevance. Three discrete patient cohorts were identified: benign (n=10), indolent (n=7) and aggressive PCA (n=8). Tissue specimens underwent laser capture micro-dissection and the corresponding DNA was then subjected to genome-wide methylation profiling using Infinium 450k BeadChip (Illumina). Methylation data were analysed with RnBeads software. Methylome-wide profiling of patient samples revealed incremental methylation variability with disease progression. Furthermore, a gross shift in methylation status of CpG islands from hypo- to hyper-steady was observed from benign through tumour types, corroborating the methylator phenotype as a signature of carcinogenesis. Comparison of the epigenetic lesions demarcating the transition from benign to either indolent or aggressive cancer revealed the majority of changes, 3,166 differentially methylated regions (DMRs), are shared regardless of tumour behaviour. 1,383 indolent-specific DMRs showed enrichment for dysregulation of cell adhesion-associated genes (BH p < 5.40E-06), while 1,240 aggressive-specific DMRs revealed more sinister epigenetic lesions of genes involved in development and differentiation (BH p < 4.30E-04). Amongst the top 1,000 differentially methylated probes between indolent and aggressive cases, 40 DMRs were unmapped, primarily targeting S-regulatory regions and CpG islands. Twenty DMRs (14 aggressive-specific, 6 indolent-specific) showing the greatest prognostic capacity on the basis of methylation difference and subtype-specificity were selected and are currently undergoing further validation in two large patient cohorts. Here, we report the first methylome-wide profiling of LCM-enriched prostate epithelia. From this discovery approach, a novel methyl signature has been unmapped which may be translated to the clinic to facilitate personalised treatment management for the patient post-biopsy.

PP65: ASSESSING THE IMPACT OF THE OESOPHAGEAL TISSUE MICROENVIRONMENT ON INNATE IMMUNE CELL FUNCTION DURING PROGRESSION FROM BARRETT’S OESOPHAGUS TO OESOPHAGEAL ADENOCARCINOMA

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It is widely reported that solid tumours can function in the inactivation of immune cells, enabling immune escape and tumour development. How early this occurs however remains unclear. Patients with Barrett’s Oesophagus (BO), a condition where oesophageal squamous cells are replaced by columnar epithelial cells in response to chronic reflux, have a 30–40 fold increased risk of developing oesophageal adenocarcinoma (OAC). We used BO as a model pre-malignant tissue microenvironment and analysed its effects on innate immune cell subsets, in particular dendritic cells (DC), gamma/delta T cells and mucosal associated invariant T (MAIT) cells. Innate cells play a role in immunosurveillance and initiating immune responses, and are integral to development of anti-tumour immune responses and activation of adaptive immunity. We aimed to compare the effects of the BO and OAC tissue microenvironments on innate cell function. Oesophageal biopsies from 18 patients with BO, and 7 patients with OAC, were cultured in vitro for 24 hours. Media was removed and added to wells containing monocyte-derived DC, gamma/delta T or MAIT cells, prior to stimulation. DC maturation was assessed by analysis of CD80, CD86, CD40L and CD86-DC expression by flow cytometry. Similar results were observed in samples taken from BO and OAC patients. CD69 expression. Levels of IL-6 significantly increased in BO compared to normal CM. A mixed inflammatory milieu was observed in OAC. The proportion of T-cells expressing TNF-α, IFN-γ, IL-12 and IL-10 was significantly reduced following treatment with BO, and OAC and O33 CLS. Treatment with O33 CLS caused a significant reduction in CD45RO and CD69 expression. Similar results were observed upon treatment of PBMCs with CM from oesophageal biopsies. BCM caused a significant reduction in IFN-γ and TNF-α producing cells. Treatment of PBMCs with Het-1A CLS caused a significant reduction, whereas O33 CLS significantly enhanced T-cell proliferation. Furthermore, cytotoxic activity significantly decreased following pre-treatment with BO, GD and O33 CLS. Conclusion: Results suggest a reduced proportion of activated T-cell within tumour tissue. This increased in IL-6 in BO may promote a predominantly Th2 T-cell profile within the tissue microenvironment, suggesting in an inefficient anti-tumour immune response which allows for disease progression. Furthermore secreted factors within the tissue microenvironment were shown to be capable of inhibiting T-cell activation, altering cytokine expression and T-cell profile, and impacting on T-cell function through alterations in cytotoxic ability and proliferation.


PP66: DRIVING THE BARRETT’S TO OESOPHAGEAL ADENOCARCINOMA SEQUENCE: IMPACT OF THE TISSUE MICROENVIRONMENT ON T-CELL PROFILE AND FUNCTION

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Background: The premalignant lesion, Barrett’s oesophagus (BO), is associated with an increased risk of developing oesophageal adenocarcinoma (OAC) [1]. BO is known to have a chronic inflammatory component and an important role for T-cells in oesophageal inflammation has recently been identified [2, 3]. It is therefore important to delineate the role of T cells at each stage of disease progression to identify potential immunotherapeutic targets that can modulate this progression. The aim of this study was to examine the T-cell profile in normal, BO and OAC tissue using ex-vivo patient samples and to examine factors released into the tissue microenvironment which may impact T-cell profile and function.

Methods: 1) Oesophageal biopsies were enzymatically digested for T-cell phenotyping by flow cytometry. 2) Biopsies were cultured to generate tissue-conditioned media (CM) and levels of cytokines were assessed by ELISA. 3)BiMCs were pre-treated with CM or cell line supernatant (CLS) from Het-1A, GH, GD and O33 cells (representing normal, BO, HGO and OAC). Expression of activation markers and intracellular cytokines were measured by flow cytometry. Cytotoxic activity was assessed by CD107a or granzyme-B expression, T-cell proliferation was measured by CFSE staining.

Results: Expression of CD45RO significantly decreased from normal to OAC tissue. A decrease was also observed CD69 expression. Levels of IL-6 significantly increased in BO compared to normal CM. A mixed inflammatory milieu was observed in OAC. The proportion of T-cells expressing TNF-α, IFN-γ, IL-12 and IL-10 was significantly reduced following treatment with BO, and OAC and O33 CLS. Treatment with O33 CLS caused a significant reduction in CD45RO and CD69 expression. Similar results were observed upon treatment of PBMCs with CM from oesophageal biopsies. BCM caused a significant reduction in IFN-γ and TNF-α producing cells. Treatment of PBMCs with Het-1A CLS caused a significant reduction, whereas O33 CLS significantly enhanced T-cell proliferation. Furthermore, cytotoxic activity significantly decreased following pre-treatment with BO, GD and O33 CLS.

Conclusion: Results suggest a reduced proportion of activated T-cell within tumour tissue. This increased in IL-6 in BO may promote a predominantly Th2 T-cell profile within the tissue microenvironment, suggesting an inefficient anti-tumour immune response which allows for disease progression. Furthermore secreted factors within the tissue microenvironment were shown to be capable of inhibiting T-cell activation, altering cytokine expression and T-cell profile, and impacting on T-cell function through alterations in cytotoxic ability and proliferation.
were assessed by immunoblotting. Apoptosis and cell cycle progression were determined using Annexin V and PI staining. Cell surface expression of adhesion markers were assessed by flow cytometry.

Results and Conclusion: Inhibition of the JAK2/STAT3 pathway inhibited cell cycle progression and induced apoptosis in LLC cells. JAK2/STAT3 pathway inhibition and siRNA knockdown of STAT3 enhanced the anti-angiogenic activity of flurbiprofen. LLC cell adhesion to fibronectin or HSS stromal cells rescued LLC cells from spontaneous and drug-induced apoptosis. Co-culture with HSS caused an increase in the expression of serine pSTAT3 which was down regulated by JAK2/STAT3 pathway inhibition. In addition the integrin L-selectin profile of LLC cells was altered by JAK2/STAT3 pathway inhibition. The CXCR4 ligand and pro-survival chemokine, CXCL12, induced a transient increase in serine pSTAT3 expression, while the CXCR4 receptor antagonist, AMD3100 (Flumixivat), decreased serine pSTAT3 expression in LLC cells. In summary, this study shows a role for STAT3 in LLC cell survival by mediating microenvironmental prosurvival signaling and suggests novel therapeutic strategies for the treatment of this disease.

PP68: PROFILING THE AUTOANTIBODY REPERTOIRE OF OVARIAN CANCER TO IDENTIFY NOVEL BIOMARKERS

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Currently there are no reliable biomarkers for the diagnosis of early ovarian cancer (OC). A lack of specific symptoms of the disease means only 20% of ovarian cancers are diagnosed at an early stage (Stage I). This highlights the urgent need for biomarkers to diagnose early stage ovarian cancer. Autoantibodies to cancer antigens can be detected up to 5 years before a tumour can be identified by other means1, meaning autoantibodies are an extremely attractive biomarker entity, as they are present in blood and easily adapted into current diagnostic platforms. Study approval was obtained from SJH/SL O’Kane 1

Methods: Serum was obtained from Discovary Bioresource (Trinity College, Dublin). Twenty serum samples were screened on 48 well prototype arrays using the hEx1 library, 22 early and 14 late OC serum samples, 5 benign ovarian disease samples and 26 healthy samples were profiled. Using prototype arrays, 7 early and 14 late OC serum samples, 5 benign ovarian disease samples and 5 healthy control samples were profiled. Approximately 250 proteins have been identified as being associated with initiating an autoantibody response in early OC (detected in early OC samples and not associated with late OC samples, healthy/control samples or with benign ovarian disease). Preliminary validation data of these antigens will be presented. Protein array platforms can be used to identify autoantibody profiles in OC serum. Analysis of these profiles enables the identification of candidate biomarkers for diagnosis of OC.


PP69: CAN PATHWAY ANALYSIS AID BIOMARKER SELECTION FOR OVARIAN CANCER?

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Currently there are no reliable biomarkers for the diagnosis of early ovarian cancer (OC), resulting in the majority of OC’s diagnosed at late stage. Autoantibodies are an extremely attractive biomarker entity as they are present in blood and easily adapted into current diagnostic platforms1. We have profiled the autoantibody repertoire of serum from 53 patients with OC on protein arrays and this study aimed to investigate the potential of pathway analysis in aiding biomarker discovery2 using a small cohort of these serum samples.

Serum was obtained from Discovery Bioresource (Trinity College, Dublin). Twenty serum samples were screened on Invitrogen Protascreenarrays ( > 10000 purified, full length human proteins spotted on a Nitrocellulose coated microarray).

PP70: NOVEL CELL LINES MIRROR THE COMPLEXITY OF RESISTANCE MECHANISMS IN OVARIAN CANCER

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Background: Ovarian cancer (OC) is the leading cause of death from a gynaecological malignancy. Standard carboplatin/taxol chemotherapy often fails and patients relapse with chemoresistant disease. A comparative selection strategy was devised to produce novel taxol and carboplatin resistant OC cell lines in order to better understand resistance mechanisms in ovarian cancer. R7-U-CALT models carboplatin resistance and R7-U-T (Taxol) models taxol resistance. R6-U-CALT and R6-U-TAXOL were exposed to both agents during development. All of these sublines have been derived from UPN251 ovarian cancer cells.

Method: Affymetrix mRNA arrays were used to characterize gene signatures linked with the development of chemoresistance in ovarian cancer cell lines R7-U-C (carboplatin) and R7-U-T (Taxol). Bioinformatic analysis of array data was carried using RANKPRIDC software analysis.

Results: All UPN251 sublines developed using taxol were significantly resistant to taxol, vinblastine and etoposide (P-gp substrates). Resistance was reversed when ecladir (P-gp inhibitor) was added. Significant up-regulation of the ABCB1 gene was seen in R7-U-T which was reflected at the protein level by western blotting. Cross-resistance in UPN251 carboplatin models was seen with cisplatin and CUS240. The top deregulated genes involved in carboplatin resistance include PLAC8, EphA7, EEF1A2, D2G15, CHST9, POF1B and LIN28B (Up-regulated) and SLC44A4, CDH6, SERPINB7, DPP4, EMR1B, MAL, MAMD2 and TMEM247 (Down-regulated). Of these genes PLAC8 was found to also be up-regulated in the top deregulated genes involved in taxol resistance.

Conclusion: Results indicate that P-gp over-expression is a dominant mechanism for taxol resistance in our cell lines. Mechanisms for carboplatin resistance are more complex. MRP2 may be involved due to cisplatin cross-resistance and this is currently being investigated. The top deregulated genes are involved in numerous pathways including apoptosis, tissue differentiation and maintenance, cellular transformation, signal transduction, embryo genesis, inflammation and cell migration. These targets will be interrogated in clinical samples from ovarian cancer patients. Ultimately this study could improve treatment and outcome in chemoresistant ovarian cancer patients.
PP71: THE ESTABLISHMENT OF AN ISO COMPLIANT CANCER BIOBANK FOR JORDAN AND ITS NEIGHBOURING COUNTRIES THROUGH KNOWLEDGE TRANSFER & TRAINING: A MIDDLE EASTERN-EUROPEAN INITIATIVE

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Introduction: The King Hussein Cancer Center (KHCC) is a specialized cancer centre in the Middle East where over 3,500 new cancer patients present annually from Jordan and its neighbouring countries. A cancer biobank (KHCCBIO) was established in November 2011 with the support of Seventh Framework Programme (FP7) funding from the European Union (INCOC 2011.6.2), making it the first cancer biobank of its kind in Jordan.

Methods: A state-of-the-art, standardised biospecimen repository of matched normal and tumour tissue, in addition to blood components, was established by KHCCBIO through the support and experience of its partners, Trinity College Dublin and two European SMEs, Biostór Ireland, a licensed tissue establishment, and accelopment AG (ACCEL), a Swiss company expert in EU project management. To date, KHCCBIO along with its partners, have worked closely in establishing an ISO Quality Management System (QMS) under which the biobank will operate.

Results: The development of standard operating procedures (SOPs) for consenting policies on ethical issues, data privacy, confidentiality and biobanking byelaws were drafted according to best international practices and in addition, were implemented for the donation, procurement, processing, testing, preservation storage & distribution of tissues and blood samples from lung cancer patients which will form the basis for the procurement of other cancer types. Qualification and validation of equipment and systems infrastructure, policy development and training, were designed and implemented as part of the development of a Quality Management System for KHCCBIO. Dissemination of KHCCBIO and capacity building to sustain KHCCBIO through international networking is envisaged over the duration of this 2-year programme.

Conclusion: KHCCBIO will be the first ISO accredited cancer biobank from a diverse ethnic Middle Eastern and North African population that will provide a unique and valuable resource in the study of cancer. Moreover, it will provide standardised human biospecimens and anonymised clinicopathological data to the cancer research communities and aid in the integration of Jordanian’s scientific and medical communities with its European neighbours in Horizon 2020.

PP72: THE ASSOCIATION BETWEEN METABOLISM, INFLAMMATION, PS3, HYPOXIA AND OBESITY IN BARRETT’S OESOPHAGUS IN-VIVO

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Introduction: Recent research in our lab has demonstrated that both oxidative phosphorylation and glycolysis are reprogrammed early in the Barrett’s disease sequence and act mutually to promote disease progression in Barrett’s oesophagus (BO). However, the link between energy metabolism and other central metabolic processes involved in disease progression in BO have not yet been ascertained. Therefore, the aim of this study was to investigate the association between metabolism, inflammation, ps3, hypoxia and obesity in BO in-vivo.

Methods: Tissue microarrays consisting of BO patient tissue (n=29) were screened for oxidative phosphorylation (ATPSB), glycolytic (GAPDH), inflammatory (IL1ß and SERPIN3A), ps3, and hypoxic (HIF1a) protein markers. The expression of both metabolic markers was subsequently correlated with IL1ß, SERPIN3A, ps3 and hypoxia (Spearmann rank). Moreover, levels of metabolism were correlated to waist circumference (n=15) and to the length of the Barrett’s segment (n=22). Furthermore, the link between ps3, inflammation and hypoxia in BO was additionally examined.

Results: Levels of ATPSB (r=0.53, P=0.0031) and stromal GAPDH (r=0.46, P=0.012) significantly positively correlated with ps3 expression in Barrett’s tissue. Levels of ATPSB (n=71, P=0.0001) strongly positively correlated with HIF1a expression in the epithelium. Glycolysis significantly positively correlated with levels of epithelial IL1ß (r=0.44, P=0.0167). Additionally, levels of oxidative phosphorylation in the epithelium strongly positively correlated with SERPIN3A (r=0.6644, P=0.0001) and IL1ß (r=0.8, P<0.0001). Moreover, levels of ps3 (r=0.455, P=0.015) positively correlated with HIF1a in the Barrett’s tissue. Interestingly, obesity showed a strong reciprocal relationship with metabolism whereby waist circumference was significantly negatively associated with oxidative phosphorylation (r=-0.6016, P=0.0177) but positively associated with glycolysis (r=0.743, P=0.0015). In addition, the length of the Barrett’s segment significantly positively correlated with glycolysis (r=0.5192, P=0.0333). In sequential follow up material, levels of ps3 (P=0.05) and ATPSB (P=0.05) were significantly higher in Barrett’s patients who went on to progress to high-grade dysplasia and adenocarcinoma compared to those Barrett’s patient who did not progress beyond intestinal metaplasia (Mann-Whitney).

Conclusion: We have shown that energy metabolism is significantly associated with inflammation, hypoxia, obesity, the length of the Barrett’s segment and ps3 status in BO. Identifying and exploring the underlying molecular mechanisms that link metabolism to these key cellular processes would significantly aid in understanding how these processes interact and may provide some insight into the development of novel multi-targeted therapies.

PP73: A NOVEL ANTI-ANGIOGENIC APPROACH OF PGE 2 EP RECEPTOR ANTAGONISM FOR THE PREVENTION/TREATMENT OF DESOPHAGEAL ADENOCARCINOMA

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Introduction: Esophageal adenocarcinoma (OAC) is the 7th leading cause of cancer deaths worldwide, with its incidence increasing in Ireland. COX-2 is overexpressed in the progressive stage from Barrett’s oesophagus to OAC. While COX-2 inhibitors hold promise for prevention/treatment, they have been associated with cardiovascular toxicity. Down-stream prostaglandin E2 (PGE2) and its corresponding EP receptors have been associated with angiogenesis and tumourigenesis in a number of cancers, including OAC. This study aimed to investigate PGE2 receptor (EP) antagonism as a novel anti-angiogenic approach for OAC prevention and/or treatment.

Materials and Methods: The effect of selective EP blockade (with a panel of commercially available and novel EP1-4 antagonists) on blood vessel formation was investigated in-vivo using a transgenic zebrafish model (TgEGFP fli-1). Dose responses were carried out with the most effective 1st to following preliminary screening. The most effective antagonists were brought forward for in-vitro functional studies. EP receptor expression profiles were assessed in a panel of cell lines representing endothelial (EAhy926, HUVEC), Barrett’s (QH) and OAC (OE-33, SKGT4) cells by qRT-PCR and western analysis. Cell survival analysis was carried out in all cell lines following EP antagonism using MTT (24 h, 48 h, 72 h).

Results: Selective EP antagonism significantly reduced intersegmental vessel formation in-vivo. Significant anti-vascular effects were observed following EP1 antagonism (SC19200, SSD1322), EP2 antagonism (PF-44165948) and EP4 antagonism (L161-982) (all, p < 0.05). The EP3 antagonist (L798-106) had the greatest effect on vessel growth (p < 0.001). Significant anti-vascular effects (p < 0.05 p < 0.001) were also observed following dose response analysis. EP2 and EP4 were expressed in all cell lines, with EP4 expression the most abundant. EP1 and EP3 were expressed in selected cell lines only. With the exception of L798-106 (EP3 antagonist), no effect on cell viability was observed following treatment with commercial or novel selective EP antagonists.

Conclusion: Selective EP antagonism has anti-angiogenic efficacy in-vivo, with EP2, EP3 and EP4 blockade demonstrating the greatest anti-vascular effect. While selective targeting did not affect cell viability in-vitro, its anti-angiogenic efficacy may be validated with further functional studies.
PP74: ISOLATION, ENUMERATION AND CHARACTERISATION OF CIRCULATING TUMOUR CELLS FROM CANCER PATIENTS

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Cancer related mortality is predominantly linked to metastasis. Tumours can invade local tissues and disseminate to distant sites via lymphatic and haematogenous routes. Circulating tumour cells (CTCs) are the class of tumour cells that have mobilised into the circulatory system. This study aims to isolate, enumerate and characterise the morphological forms of CTCs across three malignancies (melanoma, lung and ovarian cancer). As the study progresses these numeric and morphological characteristics will be linked to therapeutic responsiveness, progression free and overall survival. The isolation and verification of CTCs from whole blood is technically challenging. Protocols have been established to isolate, Giemsa stain, wash and immunofluorescently stain CTCs. Protocols have also been established to digitise isolated cells on slides, allowing for accurate verification and enumeration of CTCs by a panel of pathologists. Initial findings demonstrate that CTCs exist in multiple physical forms, from single CTCs to doublets, clusters (malignant and benign) in histological appearance) and CTCs embedded in organic material (suspected lipid or platelet aggregations). Early data indicate that CTC counts and morphologies are influenced by therapy. One ovarian cancer patient, pre-therapy had 9 histologically malignant single CTCs and 5 clusters of CTCs (all are per 3 ml of whole blood), whilst at a mid-therapy (3 of 6 cycles) time point the same patient had 0 malignant single CTCs and 9 clusters (128 cells total) of histologically benign CTCs. CTCs have the potential to inform diagnosis. A borderline ovarian cancer case exhibited 3 histologically malignant CTCs. This patient had no sign of local tissue invasion, but did have ascitic cells in her pleural effusions. Each CTC morphology identified may have different roles as diagnostic and prognostic indicators. CTC analysis may inform therapeutic responsiveness at early time points, expediting the use of alternative therapies in the case of resistant tumours. Furthermore, data indicates the that CTC analysis of whole blood may be of value in cases where malignancy is unsure via traditional histopathological assessment. As this study progresses all such roles will be elucidated.

PP75: MICRONRNA-187 MODULATES RADIOSENSITIVITY IN OESOPHAGEAL ADENOCARCINOMA

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Background: Radiation therapy is fundamental to the treatment of oesophageal cancer. However, radioresistance is a significant clinical problem, with only ~30% of patients achieving a complete pathological response to neoadjuvant chemoradiotherapy (CRT), which is a surrogate marker of improved outcome. The elucidation of biomarkers and molecular mechanisms underlying this radioresistance would be of substantial clinical benefit.

Materials and Methods: An isogenic model of radioresistant oesophageal adenocarcinoma (OAC) was established by chronically irradiating OE33 cells with clinically-relevant doses of 2 Gy X-ray radiation. Radiosensitivity was assessed by colony growth assay. Global microRNA (miRNA) expression in 20 pre-treatment OAC diagnostic biopsies and OAC cell lines was assessed using Exon miRNA arrays. miR-187 expression in pre-treatment OAC patient sera was assessed by qPCR. Overexpression of miR-187 was performed using plasmid vectors. miR-187-regulated gene targets were investigated using digital gene expression sequencing. Chromosomal alterations were investigated using array CGH.

Results: miRNA profiling in pre-treatment OAC tumour biopsies, demonstrated that decreased miR-187 expression was significantly associated with a poor response to neoadjuvant CRT (p < 0.0015), suggesting a role for miR-187 in the tumour response to treatment. This was supported in vitro, where miR-187 was silenced in radioresistant OAC cells. This altered expression was not associated with chromosomal alterations. Importantly, overexpression of miR-187 re-sensitised the radioresistant OAC cells to radiation (p < 0.01) and significantly altered inflammation and interferon (IFN)-associated molecular hubs.

Conclusion: We demonstrate for the first time a functional role for miR-187 in modulating the cellular response to radiation in OAC. Reduced expression of miR-187 in tumours from poor responders suggests a mechanism for resistance to neoadjuvant CRT, possibly via increased inflammation and altered IFN-signalling. Our data imply a role for miR-187 as a biomarker of response to neoadjuvant CRT in oesophageal adenocarcinoma.

PP76: THROMBOXANE PATHWAY TARGETING AS A NOVEL ANTI-ANGIOGENIC APPROACH FOR THE TREATMENT OF COLORECTAL CANCER

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Introduction: Colorectal cancer (CRC) is the third most common cancer worldwide. The VEGF inhibitor avastin is commonly used to treat metastatic CRC. However, just 40% of patients respond, suggesting further anti-angiogenic strategies are warranted. COX-2 inhibitors are promising, although chronic use is associated with cardiovascular risk. The downstream thromboxane (TX) signaling pathway may promote cancer growth via increased tumour-associated angiogenesis. This study aimed to examine the TX signalling pathway as a novel approach for CRC treatment.

Methods: 200 patient colorectal tissue microarrays (TMAs) were stained for CDX-2, TXS, TP, and VEGF expression by IHC. Circulating levels of TXB2, TP, and VEGF were measured in CRC serum by ELISA (n=165) and correlated with cancer 3D-control average (n=50). The effect of TX-pathway inhibition (using thromboxane synthase (TXS) inhibitors, thromboxane receptor (TP) antagonists and dual inhibitors; n=15) on blood vessel formation in vitro was examined using a transgenic zebrafish model (TgEPPF5:fl). The most effective TX-pathway inhibitors (n=3) were brought forward into an in vivo human 3D-control explant culture model. 7 angiogenic and 4 inflammatory protein secretions from CRC tumour explants were assessed using multi-exclus (MULS), and compared with avastin.

Results: Preliminary data suggests that CDX-2, TXS, TP and VEGF are increased in tumour tissue, relative to matched normal mucosa, with further analysis ongoing. TXB2 and VEGF levels were significantly higher in serum from cancer patients, compared to controls (p<0.01, TXB2, p<0.001, VEGF), while TXB2 levels were correlated with VEGF in the same samples (p<0.05; r=0.32). TX-pathway inhibition significantly decreased intersegmental vessel (ISV) formation in zebrafish. The 3 inhibitors with the greatest anti-angiogenic effect were coagulase (TXS inhibitor, p<0.001), sarotradot (TP antagonist, p<0.0001) and AH-23848 (TXS/EP4 inhibitor; p<0.0001). Human explant culturing demonstrated that the secretion of a number of angiogenic metabolites from CRC tumour explants was significantly reduced following thromboxane pathway targeting, including VEGF, BFGF, Ang-2, IL-6 and IL-9 (all p<0.05).

Conclusion: TX pathway targeting has anti-angiogenic effects in vitro. These effects are partly mediated through a reduction in angiogenic protein secretions. Targeting this pathway may be a novel anti-angiogenic approach for the treatment of CRC alone, or combined with standard chemotherapeutics.

PP77: P3K TARGETED INHIBITION AS A FIRST LINE THERAPY IN NSCLC; AN IN VITRO EVOLUTION AND MUTATION PREVALENCE IN AN IRISH PATIENT COHORT

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Background: The success of P3K targeted inhibition has been hampered by a high rate of drug resistance, which may be facilitated by MEK pathway signaling. As such, investigation of P3K-MEK co-targeted inhibition is warranted. GDC-0941 is a pan-PI3K inhibitor which has been investigated in combination with GDC-0973, a MEK inhibitor, in early clinical studies. No data has been published to date on the combination of GDC-0980 (a dual PI3K/mTOR inhibitor) and GDC-0973, which
we believe may induce greater responses. We aim to elucidate the role of mutation status in response to this co-targeted inhibition approach in vitro, as well as investigating the frequency of PI3K/AKT pathway mutations in a well-characterized Irish NSCLC patient cohort.

Methods: The effects of GDC-0941, GDC-0980 and GDC-0973 on proliferation, apoptosis and protein expression were examined in a panel of 4 NSCLC cell lines by BrdU-Asay, HCA, PathScan protein array and Western blot. DNA was extracted from 120 NSCLC patient tissue samples, and screened for nearly 500 mutations in 59 genes using the Sequenom platform.

Results: GDC-0941 and GDC-0980 treatment induced dose-dependent anti-proliferative and pro-apoptotic responses across all 4 NSCLC cell lines, while GDC-0973 treatment induced only anti-proliferative responses. GDC-0980 & GDC-0973 combination treatment induced significantly greater phosphoprotein inhibition than treatment with either inhibitor alone, most notably in cell lines harbouring PIK3CA mutations. This combined treatment approach also led to significant increases in apoptosis and synergistic reductions in proliferation across the panel of cell lines as calculated using the Chou-Talalay method. NSCLC patient mutational profiling identified a PIK3CA mutation frequency of >11%. Further mutational profiling results will be presented.

Conclusion: This research underpins the importance of mutation status in sensitivity to targeted therapies. Combined inhibition of the PI3K and MEK pathways is a promising strategy for first-line treatment of NSCLC, although efficacy is dependent on molecular subtype. In the era of personalised medicine, patient genotyping is crucial to improve patient survival and reduce toxicities.

PP78: EVALUATION OF NOVEL BIOMARKERS TO IDENTIFY SUBCLINICAL ANTHRACYCLINE-MEDIATED EFFECTS ON ORGANS

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Introduction: Anthracycline chemotherapeutics are successfully utilised in the treatment of oncological and haematological malignancies. However, treatment with anthracyclines can result in myocyte damage leading to ventricular dysfunction and renal injury (Cottin et al., 1995, Pristos and Ma, 2000). Novel biomarkers of cardiac and renal impairment have been shown to detect earlier subclinical alterations in comparison to conventional detection techniques (Sawaya et al., 2011, Stabuc et al., 2000).

Aims: To assess the clinical utility of novel cardiac biomarkers high sensitive troponin-I (hs-Tn-I), galectin-3 (GA-3) and renal biomarkers cystatin C and neutrophil gelatinase associated lipocalin (NGAL) in identifying subclinical anthracycline-mediated organ damage.

Methods: Eighty five patients were recruited (40 anthracycline and 45 controls on non-anthracycline regimens). Serum and urine samples were obtained prior to each cycle of treatment. Biomarkers were analysed using Abbott immunoassays. Wilcoxon tests were used for statistical analysis with interim results reported here.

Results: There was a statistically significant increase in Hs-Tn-I among the anthracycline cohort following the third (p = 0.0256) and fourth (p=0.0078) cycles of chemotherapy with median increases in Hs-Tn-I from 1.9 pg/ml to 12.55pg/ml after 4 cycles. There was a statistically significant decrease in GA-3 (p=0.0108) among the anthracycline cohort following 3 cycles of chemotherapy with median decreases from 14 ng/ml to 11.5 ng/ml. Median cystatin C remained constant for the anthracycline cohort following the first 3 cycles with higher concentrations observed for the non-anthracycline cohort (P = 0.0117). NGAL analysis revealed no difference between cohorts when stratified for age and gender. Conclusions: This study highlights the diagnostic benefits of the novel Hs-Tn-I, with levels as low as 5.0 pg/ml (CV < 10%) analytically dependent on molecular subtype. In the era of personalised medicine, patient genotyping is crucial to improve patient survival and reduce toxicities.

PP79: PHYSICAL ACTIVITY MODIFIES OXIDATIVE STRESS PROFILES IN BRCA-MUTATION CARRIERS

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Background: In recent years, there has been increased penance of BRCA-mutations which may be due to lifestyle-influences. There is a need to identify approaches to reduce penetrance of BRCA-mutations. Understanding how modifiable lifestyle-factors affect cancer-risk in BRCA-mutation carriers may have implications for risk-reduction in this group. At the molecular level, oxidative-stress and genomic-instability are early events in cancer development and these processes may be considered surrogate-markers of cancer-risk. BRCA-mutation carriers are more susceptible to these pro-carcinogenic processes than non-carriers. There is some evidence that obesity and physical-inactivity promote oxidative-stress, though this has not been investigated in BRCA-mutation carriers.

Objective: The aim of this pilot-study was to prospectively examine the effect of physical-activity and lifestyle-factors on oxidative-stress profiles in a cohort of unaffected BRCA-mutation carriers.

Methods: Participants (n=68) were recruited from breast-cancer family-risk clinics and cancer-genetics clinics. Body-composition (BMI), waist-circumference, adiposity), metabolic-profiles and physical-activity (Minnesota Leisure-Time Physical-Activity Questionnaire) were measured for each participant. Serum levels of the oxidative-stress markers 8-hydroxy-2-deoxyguanosine (8-oxo-DG) and 4-hydroxynonenal (4-HNE) were measured in a subset of participants (n=16) by ELISA. Results: Participants demonstrated poor adherence to physical-activity guidelines with 93% of our cohort not reaching recommended physical-activity levels. Analysis of body-composition in this cohort revealed that the majority were overweight (37%) or obese (34%) with 72% exhibiting abdominal-obesity. Correlation of serum levels of oxidative-stress markers with physical-activity and lifestyle-factors revealed a novel inverse association between physical-activity levels and serum markers of oxidative DNA-damage (8-oxo-DG) and lipid-peroxidation (4-HNE). These associations trended towards statistical significance p = 0.08 and 0.07 respectively.

Conclusion: This pilot-work has provided compelling evidence that in this cohort of BRCA-mutation carriers, unhealthy lifestyle-patterns are prevalent. In addition, these results suggest that the potential may exist to modify pro-carcinogenic processes in this cohort through physical-activity modifications and this is currently under further investigation in our laboratory.
The Aim: To delineate how excess adiposity affects tumour metabolism, one of the newly identified hallmarks of cancer, and investigate inhibitors of the glycolytic pathway as anti-cancer agents in obesity driven oesophageal cancer.

Methods: OE33, oesophageal adenocarcinoma cells were co-cultured with Adipose Conditioned Media (ACM) from obese (WFA+HE.8cm2 in males, WFA+80.1 cm2 in females) (n=10) or non-obese (WFA+HE.8cm2 in males, WFA+80.1 cm2 in females) (n=10) patients and RNA isolated. A panel of genes and glucose transporters, which were previously shown to be upregulated in glycolytic pathway using an Affymetric array platform (PKM2, HK2, ALDOc, Glut1, Glut4), were assessed with quantitative polymerase chain reaction (qPCR). The Protein expression of the glycolytic enzymes was confirmed by Immunohistochemistry (IHC) (n=10) in tumours from both obese and non-obese oesophageal cancer patients.

Results: qPCR analysis demonstrated a significant upregulation of all genes in OE33 cells co-cultured with ACM from obese patients and fat explants, compared to untreated controls. Conversely, there was no significant difference in gene expression in OE33 treated cells with ACM from non-obese patients, when compared to control. Significant difference in PKM2 (p<0.01), HK2 (p<0.01), Glut1 (p<0.05), Glut4 (p<0.05), and ALDOc (p<0.05) expression was observed in OE33 cells cocultured with ACM from obese patients compared to the cells treated with ACM from non obese patients. Treatment of the cells with the glycolytic pathway inhibitors, bromopyruvic acid (HK2 inhibitor) and sodium oxamate (PKM2 inhibitor), decreased ACM-induced cell proliferation, and this effect was more pronounced under hypoxic conditions (0.5% O2).

Conclusion: Secreted factors from adipose tissue from obese individuals activate glycolytic pathways in esophageal cancer cells. This effect is more pronounced in hypoxic conditions and targeting these enzymes in tumour cells co-cultured with adipose tissue decreases cell growth. Glycoltic pathway inhibitors may have strong therapeutic potential in obesity associated malignancy.

PPR1: THERE IS A POSITIVE ASSOCIATION BETWEEN LIPOXYGENASE EXPRESSION AND EXPRESSION OF KEY ANGIogenic FACTORS IN OESOPHAGEAL CANCER

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Background: Lipoxygenases (LOs) are a class of enzymes that metabolise arachidonic acid into a number of bioactive lipid signalling molecules involved in inflammation. There is evidence in the literature suggesting the potential of LO enzymes as therapeutic targets in a number of different solid malignancies, including prostate and breast cancer. Angiogenesis (i.e. the formation of new blood capillaries from pre-existing vessels) is one of the hallmarks of cancer and is essential for the progression and aggressiveness of any solid tumour. Mounting evidence supports the significance of angiogenesis in the development of oesophageal cancer. Experimental studies in other cancers have shown that LO expression is associated with upregulated levels of potent angiogenic mediators such as VEGF and the matrix metalloproteinases (MMPs). We are interested in exploring the association of LO activity with VEGF and other markers of angiogenesis in a retrospective oesophageal cancer patient tissue microarray.

Methods: Tissue micro-arrays (TMAs) were constructed from 200 patients (80% oesophageal adenocarcinoma OAC and 20% oesophageal squamous cell carcinoma OSCC). Expression patterns of 5LO and 12LO were investigated in both core and leading edge samples. Levels of these two enzymes were correlated with available clinicopathological parameters. Additionally, we investigated whether LO expression is associated with upregulated levels of key angiogenic markers such as VEGF, the VEGF receptor KDR, MMP-9 and also vessel density in these samples as indicated by CD31 staining.

Results: Similar expression level of LO were observed in both the tumour core and the invasive leading-edge. Over 85% of the patients showed 12LO staining in the tumour epithelium and surrounding stromal tissue. Interestingly, 5LO staining was predominantly in the stromal tissue, with only a small fraction of patients showing modest tumour epithelial expression (<10%). A strong correlation between 12LO tumour and stromal levels and KDR expression was noted in OSCC (P<0.01). Similarly, a correlation between 12LO tumour expression, VEGF and KDR in OAC was noted (P<0.001 and P<0.05 respectively).

This suggests that LOs and their metabolites may play a role in enhancing tumour-associated angiogenesis in oesophageal cancer.
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Conference Information

Conference Venue
The conference will take place in Trinity College Biomedical Sciences Institute on Pearse Street (corner of Pearse Street & Cumberland Street).

Registration Desk
Enquiries for the following should be made at the registration desk:
- To register for the conference and collect your participant pack
- Any payment queries relating to your registration
- General information regarding the conference
- Get CPD credits certificates
- To collect complimentary tickets to the Library/Book of Kells and make a private visit with no tour.

Opening Hours
Wednesday, 17 September 08.00 – 18.00
Thursday, 18 September 08.00 – 18.00

CPD Credits
The conference is accredited by Royal College of Physicians in Ireland for 12 CPD points, 6 points for each of the two days. Please collect the certificates at the registration desk.

Papers
Papers are only available directly from the presenters at their discretion.

Photocopying
Please contact the registration desk.

Internet Access
To get WiFi access code please contact registration desk.

Dress Code
The dress code for the conference including the reception and dinner is business attire.

Refreshments & Lunch
Refreshments will be served during the breaks. Lunch will be served both days in Gandon Suite O’Callaghan Davenport Hotel at Merrion Square. (Please see the map.)

Social Events and Tours
Wednesday 17th September
Tour of the Old Library and Book of Kells – depart from conference venue.
Departure time: 14.30
Conference Dinner
Venue: Dining Hall, Trinity College (Please see the map.)
Time: 19.30
With prior booking only, cost €50

Thursday 18th September
Tour of the Old Library and Book of Kells – depart from the conference venue.
Departure time: 14.30
Reception
Venue: Foyer of the Stanley Quek Lecture Theatre
Time: 18.30
Complimentary

PP82: ALTERED EXPRESSION OF INFLAMMATORY CASPASES-4 AND -5 DURING INFLAMMATORY BOWEL DISEASE AND COLORECTAL CANCER HIGHLIGHTS A NOVEL DIAGNOSTIC TOOL WITH THERAPEUTIC POTENTIAL
Brian Flood, Katarzyna Oficjalska, Debby Laukens, Joanna Fay, Kingston H.G. Mills, Kieran Sheahan, Elizabeth J. Ryan, Glen A. Doherty, Elaine Kay and Emma M. Creagh
MOUTH CANCER AWARENESS DAY
Wednesday, September 17, 2014

www.mouthcancerawareness.ie
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