ADVANCES AND FUTURE DIRECTIONS IN PERSONALISED MEDICINE

Trinity St. James’s Cancer Institute:
11th International Cancer Conference
2019
Welcome

Dear Colleagues,

It is a pleasure to welcome you to our 11th International Cancer Conference, hosted by Trinity College Dublin and St. James’s Hospital, now formally partnering within the framework of the Trinity St. James’s Cancer Institute. We are delighted that this important event is being supported by a number of key sponsors as outlined throughout the programme. This series of conferences builds on the original international cooperative cancer initiative established through a tripartite agreement developed in 1999 by the Departments of Health in Ireland and Northern Ireland and the United States administration.

We are living in a very exciting era for cancer care delivery, research and education. Recognising the major advances in areas such as cancer genetics, genomics and immunotherapy, the theme of this year’s conference is “Advances and Future Directions in Personalised Medicine”. This conference provides a unique forum for the exchange of ideas and knowledge, relating research and clinical therapeutic innovation to excellent patient care. We look forward to exciting presentations from local and world-class international speakers which we anticipate will stimulate discussion and action aimed at improving outcomes for our cancer patients.

We are especially delighted that the Burkitt Lecture will be delivered by Professor Mina Bissell, who will be awarded a Burkitt Medal at the conference dinner. Denis Burkitt, internationally renowned for his pioneering cancer work including the 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.

We hope that you will both enjoy and learn from this conference, and indeed contribute to the essential discussions and developments which will bring forward cancer care innovation and discovery in Ireland over the next decade, for the benefit of all our patients.

Organising Committee,
Trinity St. James’s Cancer Institute
International Cancer Conference 2019
Supporters
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Foundation Medicine is a world-leading molecular insights company that is making precision medicine a reality for thousands. Our comprehensive genomic profiling approach broadly analyses the tumour genome to identify all clinically-relevant alterations and potentially expand patients’ treatment options.

To date, we have profiled more than three hundred thousand patients. Our CDx test is based on our analytically and clinically validated, FDA approved comprehensive platform. Foundation Medicine works with more than 50 bio pharma partners and has extensive published validation for all of its tests. FMI has more than 200 published articles.

We use hybrid capture technology which detects the four main classes of alterations in a single test. We leverage next-generation sequencing (NGS) technology to examine regions of the tumor genome that other tests miss. In the same test we also report microsatellite instability (MSI) and tumour mutational burden (TMB) alongside a comprehensive set of genes. A clear, in-depth report supports clinical decision-making by providing insights on the patient’s genomic profile as well as associated targeted therapies, immunotherapies and relevant clinical trials.

The FoundationOne Liquid test is a blood biopsy looking at circulating tumour DNA and is usually used when a tissue biopsy is not feasible, when there is insufficient tissue for analysis and/or when disease progression is suspected.

The FoundationOne Haem test is used for haematologic malignancies and sarcomas and sequences both DNA and RNA.
DAY 1 – 24th September

8.30 – 9.00am
REGISTRATION plus Tea/Coffee

Welcome address and official opening

SESSION 1:
Molecular classification of tumours: its importance in the cancer care pathway of patients
Chairs: Maeve Lowery, Stephen Finn

9.20 ————
Dr. Janessa Laskin Medical Oncologist, BC Cancer Agency. ‘Personalized Oncogenomics: Integrating State of the Art Genomic Technology into Cancer Care’

9.45 ————
Dr. Daniel Renouf Medical Oncologist, BC Cancer Agency. ‘Precision Medicine in Pancreatic Cancer: The New Standard of Care?’

10.10 ————
Prof. David Gallagher Medical Oncologist, TSJCI. ‘Clinical Cancer Genetics and colorectal cancer’

10.35 ————
Proffered paper: Dr. Gerard Brien, Research Fellow Smurfit Institute of Genetics, Trinity College Dublin. ‘Developing personalised approaches to cancer treatment in the genomics era’

10.50 ————
Proffered paper: Dr. Simon Furney, Royal College of Surgeons, Ireland. ‘Personalised tracking of response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer patients’

11.05 – 11.35
Coffee Break and Poster Viewing

SESSION 2:
Cancer Risk Factors and Prevention
Chairs: John O’Leary, Barry O’Connell

11.35 ————
Dr. Brid Ryan, Stadtman Investigator, Laboratory of Human Carcinogenesis, Centre for Cancer Research, NCI, USA.
Dopamine Signaling in Lung Cancer: Implications for Cancer Prevention and Therapy

12.05 ————
Prof. Richard Sullivan, Kings Health Partners Institute of Cancer Policy and Global Health

12.35 ————
Prof. Amanda Cross, Professor in Cancer Epidemiology and Prevention, School of Public Health and the Department of Surgery and Cancer, Imperial College London. Colorectal cancer: prevention requires shared responsibility

13.05 ————
Proffered paper: Dr. Maeve Mullooly, Royal College of Surgeons, Ireland. ‘Opportunities and challenges for understanding the molecular pathology of breast cancer risk factors in patients with benign breast disease’

13.20 ————
Proffered paper: Dr. Marie McIlroy, Royal College of Surgeons, Ireland. ‘Association of serum androgens with recurrence in an endocrine treated breast cancer patient cohort’

13.35 – 14.20
Lunch and Poster Viewing

SESSION 3:
Tumour Microenvironment
Chairs: Jacintha O’Sullivan, Paul Browne

14.20 ————
Prof. Adrian Harris, CRUK Prof of Medical Oncology, University Department of Oncology, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital. Breast cancer and new aspects of glutamine metabolism: metformin, exosomes, hormone resistance

14.50 ————
Prof. Johanna Joyce, Ludwig Institute for Cancer Research, Lausanne. Exploring and Exploiting the Tumor Microenvironment

15.20 ————
Dr. Ingo Ringhausen, Consultant Haematologist and Principal Investigator, Cambridge. Stem Cell Institute. Targeting tumour-stroma cells to improve therapies in B cell malignancies

15.50 ————
Proffered paper: Dr. Rachel Bleach, Royal College of Surgeons Ireland. ‘Androstenedione mediated metabolic alterations in aromatase inhibitor resistant breast cancer’

16.05 ————
Proffered paper: Dr. Mark Ward, Trinity College Dublin. ‘Influence of platelets and neutrophils on Circulating Tumour Cells (CTCs)’

16.20 – 16.40
Coffee break and poster viewing

16.40 ————
Introduction to Burkitt awardee

16.50 ————
Burkitt Lecture: Prof. Mina J. Bissell, Distinguished Scientist, Biological Systems and Engineering Division, Lawrence Berkeley National Laboratory, California. Why Don’t We Get More Cancer: The critical role of extracellular matrix and microenvironment in malignancy and dormancy

19.00
Conference dinner/presentation of 2019 Burkitt Medal: Dining Hall, Trinity College Dublin Front Square [additional to registration fee]
DAY 2 – 25th September

SESSION 4: Advances in Immunotherapy
Chairs: Michael McCarthy, Cliona O’Farrelly

9.00 ———— Dr. Seth Coffelt, Senior Research Fellow, Cancer Research UK Beatson Institute, Glasgow. Uncovering targets on gd T cells to mitigate metastasis

9.30 ———— Prof. Lorenzo Galluzzi, Assistant Professor of Cell Biology in Radiation Oncology, Weill Cornell Medical College, NY. Autophagy modulation as an example of precision cancer (immuno)therapy

10.00 ———— Prof. Guillem Argilés, Clinical Investigator, Vall d’Hebron University Hospital, Barcelona, Spain. New Immunotherapy strategies in mCRC

10.30 ———— Proffered paper: Dr. Roisin Loftus, Trinity College Dublin. ‘Dietary choices influence natural killer cell responses in obesity’

10.40 ———— Proffered paper: Maria Davern, Trinity College Dublin. ‘A potential role for immune checkpoint inhibitors in combination with chemotherapy for treating oesophageal adenocarcinoma patients’

10.50 – 11:20 Coffee break and Poster viewing

SESSION 5: Molecular agents in Radiation Oncology; Future Directions
Chairs: Lorraine O’Driscoll, Frances Duane

11.20 ———— Dr. Jonathan Coulter, Senior Lecturer in Nanotherapeutics, School of Pharmacy, Queen’s University Belfast. Development and pre-clinical validation of dual-function radiation modulating nanoparticles – successes and challenges

11.50 ———— Dr. Conchita Vens, Clinical Radiobiologist, Netherlands Cancer Institute. Towards radiotherapy and DNA repair inhibitor combinations: challenges and opportunities

12.20 ———— Prof Gerry Hanna, Associate Professor and Director of Radiation Oncology, Peter MacCallum Cancer Centre/University of Melbourne. Novel and Drug and Radiotherapy Combinations – Back to the Future?

12.40 ———— Proffered paper: Dr. Dania Movia, Senior Research Fellow, Trinity College Dublin. ‘Development for physically triggered nanotechnology-based medicines as radiosensitisers: the golden era!’

12.55 ———— Proffered paper: Aisling Heeran, Trinity College Dublin. ‘Radiation induced bystander effect (RIBE) induction using human ex vivo explants induces significant changes in the tissue secretome, immune cell function and bystander cellular metabolism’

13.10 – 14.30 Lunch and Poster viewing/judging

SESSION 6: Academic Cancer Centres
Panel: John Kennedy, Lorcan Birthistle, Linda Doyle, Susan O’Reilly

14.30 ———— Prof. Rene Medema, Director of Research, Chairman Board of Directors, Netherlands Cancer Institute, Amsterdam. Challenges for a Comprehensive Cancer Center; bridging basic and clinical research

15.00 ———— Dr. Jerome Coffey, Director of National Cancer Control Programme. Academic Cancer Centres: The NCCP Perspective

15.30 ———— Prof. Paul Browne, Director of Trinity St. James’s Cancer Institute. Trinity St. James’s Cancer Institute: Update and Future Plans

16.00 Panel Discussion

16.30 Concluding session followed by awards ceremony

17.00 – 18.00 Reception
Speakers

Mina Bissell

MINA J. BISSELL is Distinguished Scientist, the highest rank bestowed at Lawrence Berkeley National Laboratory (LBNL) and serves as Senior Advisor to the Laboratory Director on Biology. She is also Faculty of four Graduate Groups in UC Berkeley: Comparative Biochemistry, Endocrinology, Molecular Toxicology, and Bioengineering (UCSF/UCB joint). Having challenged several established paradigms, Bissell is a pioneer in breast cancer research and her body of work has provided much impetus for the current recognition of the significant role that extracellular matrix (ECM) signalling and microenvironment play in gene expression regulation in both normal and malignant cells. Her laboratory developed novel 3D assays and techniques that demonstrate her signature phrase: after conception, “phenotype is dominant over genotype.” Bissell earned her doctorate from Harvard Medical, won an American Cancer Society fellowship, and soon after joined LBNL. She was founding Director of the Cell and Molecular Biology Division and later Associate Laboratory Director for all Life Sciences. Bissell has published more than 400 publications, received numerous honours and awards and is one of the most sought-after speakers in the field. She is not only an elected Fellow of most U.S. honorary scientific academies, but she also sits on many national and international scientific boards.
Professor Paul Browne

Paul Browne is currently Director of the Trinity St. James’s Cancer Institute. He is a Professor of Haematology at Trinity College Dublin, and Consultant Haematologist and Director of the National Adult Stem Cell Transplant Programme at St. James’s Hospital Dublin. A graduate of Trinity College Dublin in 1986, he trained first in Ireland, and then as a Fellow and Faculty member at the University of Minnesota, USA. Since returning to Ireland in 1997, he has led the development of therapeutic programmes for leukaemia and myeloma, with a special interest in stem cell transplant and novel therapeutics. He has collaborated on laboratory studies of myeloma biology, including a focus on genetic susceptibility in DNA repair pathways, in work funded by the HRB and the Irish Cancer Society. He was Chair of the Irish Cooperative Oncology Research Group (ICORG, now Cancer Trials Ireland) from 2008 to 2012, leading the successful international peer-reviewed HRB multi-million euro grant renewal to support clinical and translational research in cancer. More recently, he has led the TCD work packages of two major projects in conjunction with colleagues in Cork and Galway, one on Cellular Therapy and cord blood cells, funded by the National Blood Centre, and the other a joint Irish Cancer Society/Science Foundation Ireland five-year programme establishing the infrastructure and clinical research activities for the Blood Cancer Network Ireland (BCNI).
**Seth Coffelt**

Seth Coffelt is a Senior Research Fellow within the Institute of Cancer Sciences at the University of Glasgow. His lab is based at the Cancer Research UK Beatson Institute. Seth obtained his Ph.D. from Tulane University in New Orleans, Louisiana, USA, in 2006. He undertook his first postdoc position at the University of Sheffield in the UK where he studied the role of macrophages in tumor progression. Afterwards, Seth was awarded a Marie Curie Intra-European Career Development Fellowship to join Karin de Visser’s lab at the Netherlands Cancer Institute in Amsterdam. During this time, Seth discovered how certain immune cells cooperate with each other to promote metastasis through the suppression of other immune cells. Seth moved to Scotland in the summer of 2016 to focus on the molecular mechanisms that regulate gd T cell function during the evolution of metastasis and cancer progression. Recently, Seth was awarded the British Association for Cancer Research AstraZeneca Young Scientist Frank Rose Award for 2018.

**Jerome Coffey**

Dr Jerome Coffey is the Director of the National Cancer Control Programme (NCCP). A graduate of TCD he completed internal medicine and radiation oncology training in Ireland. Following higher training in major academic oncology centres in Canada and the UK he was appointed as a Consultant Radiation Oncologist to the staff of the St Luke’s Radiation Oncology Network and the Mater Misericordiae University Hospital in 2006. Before taking up his current role he was Clinical Director of the St Luke’s Radiation Oncology Network, Chairman of the Radiation Oncology Committee in the Faculty of Radiologists (RCSI) and Radiation Oncology Advisor to the NCCP. Dr Coffey was appointed Chairperson of the Board of the National Cancer Registry in May 2017.
Jonathan Coulter
Dr Coulter is a Senior Lecturer, working within the Nanomedicine and Biotherapeutics research group at the School of Pharmacy, Queen’s University Belfast. His research has always had a focus on developing strategies to overcome treatment resistance in cancer, with a specific focus on radiotherapy. His work has spanned approaches that include the use of suicide gene therapy and more recently exploiting the unique physical properties of high atomic number nanoparticles as radiosensitisers. Recent iterations have been developed as biologically active formulations, designed to overcome tumour microenvironment properties which are known to confer treatment resistance, in addition to the core particle acting as a radiation dose modifier. This presentation aims to outline some of the successes we have experienced in this space while looking to spark discussion around the key challenges that have limited clinical translation to date.

Amanda Cross
Prof. Cross is a cancer epidemiologist with a joint appointment in the School of Public Health and in the Department of Surgery and Cancer within the Faculty of Medicine at Imperial College London. She is Head of the Cancer Screening and Prevention Research Group (http://csprg.org.uk). She completed her PhD at Cambridge University and then spent 11 years in the Division of Cancer Epidemiology and Genetics (DCEG) at the National Cancer Institute (NCI), National Institutes of Health (NIH), United States. As a tenure-track investigator at NCI, she was also a mentor for the Yale University–NCI Partnership Training Program and held the position of Assistant Professor Adjunct within the Division of Chronic Disease Epidemiology at Yale University. Her research interests are focused on aetiologic studies of diet and lifestyle factors in relation to cancer risk and survival, as well as colorectal cancer prevention and
early detection by screening and surveillance. Her projects include analyses of large international cohort studies as well as the conduct of randomised controlled trials.

Johanna Joyce

Prof. Johanna Joyce’s laboratory investigates the microenvironment in which a tumour arises and the critical influence that non-cancerous immune and stromal cells can have on tumour progression and metastasis. They have uncovered regulatory signals provided by the normal tissue stroma and immune cells to the cancer cells, and determined how normal cells can be modified by the cancer cells to produce a variety of factors that enhance tumour malignancy. Her group is also actively exploring the mechanisms underlying the contribution of the tumour microenvironment to therapeutic resistance. Their ultimate goal is to apply this collective knowledge to the clinic and develop targeted therapies that disrupt critical tumour-stromal interactions.

Johanna began her independent career at MSKCC in New York in 2004, rising through the academic ranks to Full Member and Full Professor at Cornell Medical School in 2014. Johanna moved to Switzerland in 2016, where she is a Full Professor at the University of Lausanne and Full Member of the Ludwig Institute of Cancer Research. In 2017, Johanna was elected as a Member of EMBO and a Fellow of the European Academy of Cancer Sciences. Johanna has been recognized for her contributions to cancer research through a series of awards including the Cloetta Prize, Swiss Bridge Award, American Cancer Society Scholar Award, Rita Allen Foundation Award, Sidney Kimmel Foundation Award, and the inaugural Pandolfi Women in Cancer Research Award from Harvard Medical School, among many others.
Janessa Laskin

Dr Laskin is a clinical Associate Professor in the Department of Medicine at the University of British Columbia and an active member of the medical oncology staff at BC Cancer Agency in Vancouver, Canada. Her clinical and research interests have primarily focused on lung and head and neck cancers. She is an active member of many national and international lung cancer trials and advisory groups. In the last 7 years her research has evolved towards cancer genomics and personalized medicine and she is the clinical program leader for the Personalized Oncogenomics (POG) Program which is a collaborative research project between medical oncologists and the Michael Smith Genome Sciences Centre in Vancouver. The POG program is truly translational research effort that uses in-depth genomic and transcriptomic sequencing to guide chemotherapy decision-making in a clinically relevant time-frame.

Lorenzo Galluzzi

Lorenzo Galluzzi (born 1980) is currently Assistant Professor of Cell Biology in Radiation Oncology with the Department of Radiation Oncology of the Weill Cornell Medical College (New York, NY, USA), Honorary Assistant Professor Adjunct with the Department of Dermatology of the Yale School of Medicine (New Haven, CT, USA), Honorary Associate Professor with the Faculty of Medicine of the Paris Descartes University (Paris, France), and Faculty Member with the Graduate School of Biomedical Sciences and Biotechnology of the University of Ferrara (Ferrara, Italy) and the Graduate School of Pharmacological Sciences of the University of Padova (Padova, Italy). Prior to joining Weill Cornell Medical College (2017), Lorenzo Galluzzi was a Junior Scientist of the Research Team “Apoptosis, Cancer and Immunity” at the Cordeliers Research Center (Paris, France; 2012-2016). Lorenzo Galluzzi did his post-doctoral training at the Gustave Roussy Cancer Center (Villejuif, France; 2009-2011),
after receiving his PhD from the Paris Sud University (Le Kremlin-Bicêtre, France; 2005-2008). He is also Associate Director of the European Academy for Tumor Immunology (EATI), Co-chair of the Society for Immunotherapy of Cancer (SITC) Immunogenic Cell Death Working Group, and Founding Member of the European Research Institute for Integrated Cellular Pathology (ERI-ICP). Lorenzo Galluzzi is best known for major experimental and conceptual contributions to the fields of cell death, autophagy, tumor metabolism and tumor immunology. In particular, he provided profound insights into the links between adaptive stress responses in cancer cells and the activation of a clinically relevant tumor-targeting immune response in the context of chemotherapy and radiation therapy. Lorenzo Galluzzi has published more than 400 scientific articles in international peer-reviewed journals. According to a survey published by Lab Times, he is currently the 6th and the youngest of the 30 most-cited European cell biologists (relative to the period 2007–2013), and he was nominated Highly Cited Researcher by Clarivate Analytics (formerly, Thomson Reuter) in 2016 and 2018. Lorenzo Galluzzi currently operates as Editor-in-Chief of three journals: OncoImmunology (which he co-founded in 2011), International Review of Cell and Molecular Biology, and Molecular and Cellular Oncology (which he co-founded in 2013). In addition, Lorenzo Galluzzi currently serves as Founding Editor for Microbial Cell and Cell Stress, and Associate Editor for Cell Death and Disease.

Gerry Hanna

Associate Professor Gerry Hanna is the Director of Radiation Oncology at the Peter MacCallum Cancer Centre, Melbourne and holds an honorary appointment with the University of Melbourne. A/Prof Hanna’s research interests are the use of PET/CT in radiotherapy planning for lung cancer, mechanisms of radiotherapy resistance, technical radiotherapy, stereotactic ablative radiotherapy and systemic therapy and
immunotherapy combinations with radiotherapy. He is chief investigator of the International Atomic Energy Agency’s “PERTAIN” study and previous co-chief Investigator of the CONCORDE study, a UK study of novel agents in combination with radiotherapy in the treatment of lung cancer. He is the Thoracic Sub-Study lead for the SARON study and a TMG member for the UK’s HALT and CONFIRM studies.

Adrian Harris

Adrian L Harris is the Cancer Research UK Professor of Medical Oncology at the University of Oxford and directs the Cancer Research UK Molecular Oncology Laboratories at the Weatherall Institute of Molecular Medicine (WIMM). He is a Consultant Medical Oncologist and a Professorial Fellow of St Hugh’s College Oxford. He is Editor-in-Chief of the British Journal of Cancer and on the Editorial Board of Cancer Cell. He is a Senior Investigator in the National Institute of Health Research and a Fellow of the Academy of Medical Sciences. He is a ‘Highly Cited Researcher 2014’ ranking among the top 1% most cited for their subject field and year of publication—between 2002 and 2012 and included in Thompson Reuters ‘2014 World’s most Influential Scientific Minds.’ He is also listed in Boyack KW, et al. A list of highly influential biomedical researchers, 1996-2011. Eur J Clin Invest. 2013 43:1339-65. These are Top 400 world-wide cited investigators in all biomedical fields. He has published over 500 papers and there are over 145,000 citations to them, h-index 184. He has received a Platinum Merit Award from then National Health Service for the last 15 years, given to the 200 most outstanding consultants for all specialities. He trained in Medicine and Biochemistry at Liverpool University, did a DPhil at Oxford University then trained at the Royal Marsden Hospital in Medical Oncology. He was appointed Professor of Clinical Oncology at Newcastle-upon-Tyne in 1982.
Since 1988 he has been the Professor of Medical Oncology at Oxford University. He directs the Molecular Oncology Laboratories at the Weatherall Institute of Molecular Medicine. He has managed breast cancer patients for over 30 years. His major laboratory interests involve the role of hypoxia in breast tumour biology, and tumour angiogenesis, the metabolic response to hypoxia, microRNAs induced by hypoxia and hypoxia-induced cell death. He has conducted many predictive and prognostic studies and early exploratory phase trials in new drug development, molecular pathology and biomarkers, to translate laboratory findings to clinical relevance and development of new agents.

In the Department of Oncology over 20 Phase I and II trials are run and current trials include new drugs blocking angiogenesis, metabolism inhibitors, DNA repair, immunotherapy, inhibitors of signal transduction and their interactions with radiotherapy. Specific emphasis is on classification of tumours by functional imaging, molecular profiles, and pharmacodynamic endpoints to targeted therapies.

**Daniel Renouf**

Daniel Renouf is a medical oncologist at BC Cancer, Vancouver Centre, and an Assistant Professor at the University of British Columbia, Department of Medicine. He received his Doctor of Medicine from the University of Alberta and completed his internal medicine and medical oncology training at the University of British Columbia and BC Cancer. He undertook further training in early drug development and gastrointestinal oncology at Princess Margaret Hospital and the University of Toronto, and obtained a Masters of Public Health from Harvard University. Daniel’s research interests include developmental therapeutics, genomics, and biomarker development within gastrointestinal cancers, with a focus on pancreatic
cancer. He is the leader of the BC Cancer Phase I program, the BC Cancer GI Tumour Group chair, the Co-Director of Pancreas Centre BC and is the Co-chair of the Canadian Cancer Trials Group Pancreatic Cancer disease group.

**Ingo Ringhausen**

Ingo Ringshausen studied medicine at the Johannes Gutenberg University in Mainz/ Germany and London/ Canada. After his graduation in 1999 he started his medical training in Internal Medicine and Haematology/ Oncology at the Technical University in Munich. Between 2003 and 2006 he joined the group of Gerard Evan at UCSF on a postdoctoral fellowship. After his board certification in 2010 he became a Consultant in the Department of Haematology/ Oncology in Munich and subsequently an independent group leader. In 2014 he joined the Department of Haematology in Cambridge and is now appointed as Consultant Haematologist at Addenbrooke’s hospital and a Principal Investigator at the Cambridge Stem Cell Institute.

**Brid Ryan**

Dr Ryan is a Principal Investigator at the National Cancer Institute. She came to the US in 2007 under a US-Ireland jointly funded program as a Cancer Prevention Fellow. She received all of her formal training in Ireland: from University College Cork (BSc Biochemistry), and University College Dublin (PhD Biochemistry, followed by Masters of Public Health). Dr Ryan is head of the Integrative Molecular Epidemiology Unit (IMEU) of the Laboratory of Human Carcinogenesis, CCR, NCI, and uses an integrative and translational approach to studying population differences in lung cancer, combining epidemiological and laboratory methods to her research. In particular, her research program aims to develop diagnostic and prognostic biomarkers for lung cancer, and uses a precision medicine
approach to understand cancer health disparities. She is the author of over 50 research papers and book chapters and has received numerous awards for her work, including the European Association for Cancer Research Young Scientist Award and the AACR Future Leader in Cancer Prevention Award.

Conchita Vens
Conchita Vens is a clinical radiobiologist at the Netherlands Cancer Institute. Her research focuses on molecular mechanisms involved in the cellular radiation response and on DNA repair defects in cancer. Next to revealing repair defects in tumours and characterizing the associated molecular processes, her projects aim to develop radiation combination strategies that exploit such tumour repair defects. She further supports the clinical application opportunities of DNA repair inhibitors with biomarker and radiation induced normal tissue toxicity studies. Her team developed DNA repair associated biomarkers to reveal the impact of repair defects on patient outcome and is interested in prognostic and predictive biomarkers to tailor head and neck cancer patient treatment. Her engagement in international and national radiation oncology societies reflects her strong commitment to support radiation oncology.
Addressing the toughest challenges in oncology takes all of us

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Poster Abstracts
C-REACTIVE PROTEIN AND C-REACTIVE PROTEIN BASED PROGNOSTIC SCORES IN UPPER GASTROINTESTINAL CANCER: A SYSTEMATIC REVIEW

CM Lorton1,2,3, L Higgins4, C Donohoe6, J O’Connell1,3, D Mockler7, L Zgaga5, JV Reynolds3,6, D Walsh8, J Lysaght1

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3Department of Surgery, Trinity Translational Medicine Institute, Trinity College Dublin, Dublin, Ireland
4, Health Products Regulatory Authority, Dublin, Ireland
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8Department of Supportive Oncology, Levine Cancer Institute, Atrium Health, Charlotte, NC, USA

Introduction
Serum C-reactive protein (CRP) is a widely-used inflammatory marker. Elevated CRP is associated with poor prognosis in Upper Gastrointestinal (UGI) cancer.
There is no guidance for clinicians regarding which CRP cut-off value or CRP-based prognostic score to use when assessing prognosis.
This systematic review examined what CRP cut-off and which CRP-based score best predict survival in adults with UGI cancers.

Methods
EMBASE, Medline, Web of Science, Cochrane, Scopus and CINAHL databases were searched.
Included: Adults with UGI cancers (oesophageal, gastro-oesophageal junction and gastric), CRP or CRP-based score and Hazard Ratio for overall or cancer-specific survival.
Excluded: language other than English or French, duplicate reports, editorials or reviews, case series ≤5 cases. The protocol was registered in PROSPERO.
Two investigators independently screened all papers based on title and/or abstract and all potentially eligible full text articles.

Results
Of 2078 papers screened, 87 were included. 79 were single-centre. CRP measurement was pre-op (n=38) or pre-chemotherapy (n=21) for most but timing was unclear in 17.
35 of 50 studies which investigated CRP as a prognostic factor found a high CRP predicted poor survival. Cut-offs ranged from 1.5 to 10mg/L. 15 of 20 papers using a 10mg/L cut-off found it predicted survival.
19 different scores were reported, most commonly Glasgow Prognostic Score (GPS) and modified GPS. 23 of 31 studies found the GPS predictive of survival. 17 of 26 studies found the mGPS predictive.
Discussion
This review confirms a significant relationship between CRP, alone or as part of a prognostic score, and survival in Upper GI cancer. The strongest evidence is for a 10mg/L cut-off and for the GPS and mGPS. Diverse cut-offs and scores, measurement timepoints, treatments received and survival outcomes measured are barriers to clinical implementation. Future studies should be multi-centre, use standardised cut-offs or focus on the GPS or mGPS.

A Mullee¹, V McSharry², L McCann¹, D Brennan³ ⁴

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⁴School of Medicine, UCD, Dublin, Ireland

Introduction
Sarcopenia is a progressive and generalised loss of skeletal muscle mass, muscle strength and low physical performance¹. Myosteatosis is an increased proportion of intra and intermuscular fat and can be measured by muscle attenuation (MA), a radiologic characteristic of muscle. Both body composition phenotypes are associated with mortality, complications of cancer surgery and chemotherapy toxicity in a variety of tumour types ²-⁴. The aim was to review the prognostic impact of skeletal muscle index (SMI) and MA in relation to overall survival in ovarian cancer patients.

Methods
A systematic search for relevant articles published until May 2019 was performed using PRISMA guidelines, and included a search of the databases Ovid Medline, Scopus and Embase. Studies included were limited to those with measurements of muscle mass using computed tomography (CT) in ovarian cancer patients investigating overall survival.

Results
A total of 1695 articles were screened on the basis of title and abstract, resulting in the selection of 47 articles for full text assessment. Five studies (n=1037) were included. All five investigated the association of SMI and overall survival, none of which observed a significant association. One study observed a significant association with the loss of skeletal muscle, during neo-adjuvant chemotherapy, and reduced overall survival. Three of the studies investigated MA, all of which observed that low muscle attenuation was associated with decreased overall survival.
**Discussion**

Muscle attenuation was consistently associated with decreased overall survival after treatment. Lack of methodological consensus on the cut-off for MA and SMI used in these studies hampers the interpretation and clinical utilization of these findings.


**POSTER 3**

**Cancer Immunology**

**ELUCIDATING THE PATHOLOGICAL ROLE OF OBESITY, INFLAMMATION AND IMMUNITY IN CANCER RELATED SARCOPENIA IN UPPER GASTRONTESTINAL CANCERS.**

**MJ Conroy**, NE Donlon¹, M Durand², MR Conroy³, C Murphy³, A Bhardwaj⁴, P Beddy², JV Reynolds¹⁵, J Lysaght¹

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²Department of Radiology, St. James’s Hospital, Dublin, Ireland
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⁴Department of Surgery, Trinity College Dublin, Dublin, Ireland
⁵Gastro-intestinal Medicine and Surgery, St. James’s Hospital, Dublin, Ireland

**Introduction**

Cachexia is the ongoing involuntary loss of muscle mass (sarcopenia), leading to reduced treatment efficacy and increased mortality. This study aims to elucidate the soluble and cellular mediators underpinning the development of oesophageal cancer (OC) cachexia.

**Methods:**

Sarcopenic and non-sarcopenic patients within a cohort of 373 OC patients were identified by body composition measurements. Inflammatory mediators and muscle growth/breakdown markers were quantified by ELISA in serum (n=27) and muscle conditioned media (n=3) within an initial sub-cohort at time points pre- and post-chemoradiotherapy (CRT). Muscle biopsies were collagenase-digested and stained with antibodies against CD3, CD4, CD8, CD62L, CD45RA, CD27 and CD69 to ascertain the intramuscular T cell phenotype in OC patients.
**Results**

Preliminary analysis revealed that the number of sarcopenic OC patients doubled following CRT. Muscle growth factor follistatin was significantly higher in oesophageal cancer patient serum following CRT, with lowest levels identified within sarcopenic patients. Interestingly, circulating levels of the muscle breakdown protein Activin A, which is a target of follistatin-mediated inhibition, is also increased following CRT. As expected, well-published markers of muscle damage myoglobin and creatine kinase were increased following CRT indicating that treatment exacerbates muscle loss. Immunophenotyping data indicate substantial infiltrations of activated CD4+ and CD8+ T cells within the muscle of OC patients.

**Conclusions**

Our preliminary data indicate a role for the follistatin:activin axis in OC sarcopenia and suggest that CRT enhances their secretion. Further work will elucidate the inflammatory profile of intramuscular T cells and identify key immune players in the progression of OC cachexia.

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**POSTER 4**

**Cancer Immunology**

**IMMUNE CHECKPOINT BLOCKADE REVERSES OBESITY-ASSOCIATED DEFECTS IN ANTI-TUMOUR IMMUNITY**

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The development of immunotherapy has revolutionised the approach to cancer therapy. A significant limitation, however, is that it is only effective in a subset of patients. Thus, there is increasing urgency to identify predictors of response. Obesity is a global health problem and is strongly associated with an increased cancer risk. In this study, we aimed to decipher the mechanisms of tumour-promotion in obesity and examine the effects of obesity on the efficacy of immunotherapy.

Mice were fed with a high-fat diet to induce obesity which significantly increased the tumour burden and led to a “cold” tumour phenotype. In obesity, CD8 T cells were largely diminished from tumours, produced less IFN-γ and were metabolically impaired. Staining of the tumour vasculature revealed a failure of T cells to extravasate from blood vessels and infiltrate the tumour bed in obese mice. These findings suggest that tumour growth is enhanced in obesity, at least in part, by immune cell exclusion and metabolic suppression. To examine whether obesity-driven immunosuppression affects immunotherapy, lean and obese MC38 tumour-bearing mice were treated with anti-PD-1. Surprisingly, anti-PD-1 led to complete tumour eradication and immune memory in lean and obese mice. Anti-PD-1 restored CD8 T cell infiltration, pro-inflammatory cytokine production and metabolic activity and mice that previously cleared tumours were protected from re-challenge with MC38. Overall, these novel findings highlight an ‘obesity paradox’ in cancer. While obesity caused immune dysfunction and promoted tumour growth, immunotherapy was able to reverse these defects, resulting in tumour rejection.
TGFB DRIVES MITOCHONDRIAL DYSFUNCTION IN NK CELLS DURING METASTATIC BREAST CANCER

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Introduction
Natural Killer (NK) cells play a key role in immune defense against cancer. However, their functions become progressively impaired during cancer, which impacts the efficacy of NK cell based immunotherapies e.g. Trastuzumab in breast cancer. NK cell dysfunction may also leave a cancer patient susceptible to infection and metastasis. Hence, there is urgent demand to better understand NK cell dysfunction in cancer.

Methods and Results
We have shown that freshly isolated peripheral blood NK cells from metastatic breast cancer patients have altered cellular metabolism. Nutrient receptors fail to upregulate in response to cytokine and the same is observed for the activity of mTORC1, a master regulator of NK cell metabolism. Seahorse analysis indicates profound defects in both glycolytic and oxidative metabolism in IL2 stimulated patient NK cells. Confocal imaging and flow cytometry analysis on direct ex vivo NK cells from patients reveals clear structural and functional differences in NK cell mitochondria. This is characterised by increases in the number of fissed mitochondria, the mitochondrial mass, the mitochondrial membrane potential, and mitochondrial ROS.

Importantly, blocking elevated levels of TGFB improved mitochondrial mass and levels of both basal oxphos and maximal respiration. This was accompanied by increased mTORC1 activity, nutrient receptor expression, and essentially, IFNγ production.

Discussion
Overall we have described for the first time the metabolic dysfunction of NK cells in human cancer the ability to target and improve this metabolism in order to increase NK cell anti-tumour function. These findings have important implications for the design of future NK cell based immunotherapies.
Oesophageal adenocarcinoma (OAC) incidence is predicted to double in Ireland over the next few decades. Multi-modal neo-adjuvant chemoradiotherapy (neo-CT) treatments have improved survival outcomes, but only for a minority of patients, and there are currently no methods available to predict treatment response. There is an urgent need to determine reliable predictive methods, to prevent patients undergoing treatment and suffering associated side-effects with no benefit. Previous work by our group and others has shown that immune markers possess prognostic ability in OAC.

This study investigates whether immune markers in serum or tumours can be used to predict patient response to neo-CT. Levels of circulating 54 markers, encompassing key cytokines, chemokines, angiogenic factors and markers of vascular injury, were quantified using multiplex ELISA on serum from n=80 treatment-naive OAC patients, and were compared with tumour regression scores. Pre-treatment OAC biopsies (n=120) were stained using multiplex immunofluorescence for immune markers (CD3, CD8, Foxp3, HLA-DR, CD68). Percentage expression was scored manually, and digital pathology analysis is underway.

CCL4, a chemoattractant for natural killer cells and monocytes, was significantly less abundant in the serum of patients with a poor response to treatment (p<0.001). Levels of angiogenic factor Tie-2 were significantly higher in poor responders (p<0.05), compared to patients who experienced complete or partial responses. Only VEGF-C showed a significant prognostic ability when survival time was considered however, with higher than median expression linking with significantly shorter survival times (p=0.042, HR=2.32, 95% CI=1.03-5.19). In tumours, the majority of OAC biopsies showed evidence of innate and adaptive immune cell infiltration. Circulating marker profiles are currently being linked with levels of immune cell infiltration into tumour biopsies, to investigate the role of local and systemic immunity in predicting OAC patient clinical outcomes.

These preliminary results reveal an important role for angiogenic markers as prognostic and predictive tools in OAC.
Barrett’s oesophagus is an inflammatory condition and a neoplastic precursor to oesophageal adenocarcinoma (OAC) (1). Inflammasome signalling pathways contribute to acute and chronic inflammation. All inflammasome signalling results in caspase-1 activation, leading to the secretion of IL-1β and IL-18, and inflammatory cell death (pyroptosis) (2). A full understanding of inflammasome involvement during Barrett’s and OAC has yet to be achieved. Elevated cytokine levels of IL-6, IL-10 and in particular IL-1β are reported in Barrett’s (3, 4). Indeed, overexpression of IL-1β in the oesophagus of mice is responsible for the transgenic Barrett’s model, pL2-IL-1β. The resulting inflammation alone is enough to drive the development of Barrett’s metaplasia (5). Further evidence to suggest inflammasome involvement is provided by Nadatani et al. who showed that an LPS stimulated Barrett’s cell line was sufficient for priming and activation of the NLRP3 inflammasome (6).

We therefore hypothesized that caspase-1-mediated inflammation is an important driver of disease progression to Barrett’s and OAC. The aim of this study was to characterise the expression of inflammatory caspase-1 during oesophageal disease pathogenesis in three distinct disease model systems: a cell line model representing disease progression; a murine model of Barrett’s; and regions of adjacent normal, metaplasia, and OAC tissue from Barrett’s-associated OAC patients. Our findings show, for the first time, that caspase-1 is highly expressed during Barrett’s metaplasia in our human and mouse models. Inhibition of caspase-1 in ex-vivo biopsies from Barrett’s patients suggests that targeting inflammasome activity may represent an effective anti-inflammatory therapy to limit Barrett’s progression, particularly in obese patients.


POSTER 8
Cancer Immunology

IMMUNE CELL INFILTRATION IN PRE-TREATMENT BIOPSIES FROM OESOPHAGEAL ADENOCARCINOMA PATIENTS CORRELATES WITH IMPROVED SURVIVAL

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Introduction
Across many human tumours the presence or absence of specific immune cell subpopulations provides important patient prognostic information. CD3+ and CD8+ T cell infiltration generally correlates with favourable outcome, while Foxp3+ regulatory T cells and M2 macrophages typically correlate with poor survival in patients. In this study we carried out 5-plex immunofluorescent staining on biopsies from oesophageal adenocarcinoma (OAC) patients and correlated immune cell infiltration with patient outcome.

Methods
Sequential 3µM sections of pre-treatment biopsies from OAC patients (n=97) were stained using antibodies directed against CD3, CD8, Foxp3, HLA-DR, CD68 and CD163. Visualisation of each antibody was achieved using secondary antibodies and tyramide signal amplification probes supplied as part of Thermofisher tyramide SuperBoost kits. Slides were counterstained with Hoechst for the detection of nuclei and with an anti-pan-cytokeratin antibody for the detection of epithelial tissue. Following whole slide digitisation using a Zeiss Axioskop Z1 slide scanner, the percentage positivity of each marker was manually evaluated by two observers. The median positivity for each marker was then used to categorise patients as low or high expressers.

Results/Discussion
OAC patients with high levels of CD3+, CD8+, Foxp3+, CD68+ and CD163+ cell infiltration exhibited significant improvements in overall survival on univariate analysis (p<0.05). This study highlights the importance of immune cell infiltration in OAC patient survival. Furthermore it demonstrates the value of multiplex immunofluorescence as a tool for cancer research as it allows multiple biomarkers and immune cell subpopulations of interest to be visualised simultaneously within human tumours.
ASSESSMENT OF THE THERAPEUTIC POTENTIAL OF TWO LEAD ANTI-INFLAMMATORY MOLECULES WITH A NOVEL CARBON SCAFFOLD IN HUMAN EX-VIVO COLONIC EXPLANT TISSUE FROM ULCERATIVE COLITIS PATIENTS

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Introduction
Inflammatory Bowel Disease (IBD) is a range of diseases characterised by chronic inflammation of the large and/or small intestine consisting of two main types:

- Crohn’s Disease, which can affect any part of the intestine and can lead to the development of ulcers, malnutrition or fistula.

- Ulcerative Colitis (UC) is the long-lasting inflammation and development of ulcers in the innermost lining of your large intestine (colon) and rectum.

The chronic intestinal inflammation associated with IBD diseases has been identified as a primary risk factor in these patients for the development of malignancies including colorectal cancer, small bowel adenocarcinoma, intestinal lymphoma, anal cancer, and cholangiocarcinoma.

Studies previously conducted in Professor Sheridan’s group led to the design of 24 easily synthesised, low molecular weight analogues. Two lead molecules from these have been identified which demonstrate anti-inflammatory and anti-angiogenic effects in-vitro.

Methods
Human Ex-vivo colonic explant tissues were cultured for 24 hours (optimal) and 48 hours with either control/lead molecules, to generate tissue conditioned media (TCM) and analysed via 54plex ELISA.

Dendritic Cells (DCs) were then generated from monocytes from PBMCs from healthy donor buffy coats, immature DCs were then treated with TCM from lead molecules/control. Flow cytometry was used to detect DC activation.

Results
54plex ELISA data indicated an alteration in PIGF, bFGF, GM-CSF, IL-16, MIP-3, Eotaxin-3, IL-8, IL-10, IL-4, ICAM-1 and VCam-1 to investigate how these lead drugs affected the secretion of inflammatory mediators.

Control UC TCM showed activation for 6 markers: CD40, CD80, CD86, CD83, CD54 and HLA-DR. Lead molecules treated TCM showed activation of 5 markers: CD40, CD80, CD86, CD83, CD54 and HLA-DR.
Lead molecules cultured with UC explants demonstrated alterations in the secretions of anti-inflammatory and anti-angiogenic secretions TCM and boosted DC maturation markers. 

Discussion
This study has generated significant pre-clinical data on novel small molecule inhibitors in inflamed ulcerative colitis tissues and their interactions with Dendritic Cells.

POSTER 10
Cancer risk factors and prevention

PREVALENCE OF RISK FACTORS FOR ANAL SQUAMOUS CELL CARCINOMA AND IMPACT ON DISEASE OUTCOMES – NINETEEN-YEAR REVIEW AT A TERTIARY REFERRAL HOSPITAL

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Introduction
High-risk sexual activity is associated with Anal Intraepithelial Neoplasia (AIN) and Anal Squamous Cell Carcinoma (AC) 1. There is a notable overlap between those at risk of anal pathology, such as patients with Human Immunodeficiency Virus (HIV) or Human Papillomavirus (HPV), and males-who-have-sex-with-males (MSM), and those attending Genitourinary Medicine and Infectious Diseases (GUID) services. It is suggested that patients attending GUID clinics can access urgent colorectal assessment earlier than those in the community.

Methods
We performed a retrospective review of all anal pathology treated at a tertiary-referral hospital with a dedicated GUID clinic between 2000-2019.

Results
109 patients had anal pathology, 85 with AC (78%) and 24 with AIN (22%). 21% had concurrent AIN and AC at diagnosis, and 3.7% progressed from AIN to AC. 64% (n=70) were male. 28% (n=31) had HIV, 45% (n=49) had HPV, 26% (n=29) were MSM, and 35.7% (n=39) attended GUID clinics. Median (range) age at diagnosis was 51 (25–88) years. GUID patients were diagnosed significantly younger, with a median (range) of 41 (26–75) years (p=0.000).

GUID patients were more likely to have premalignant AIN (OR 9.143, 95% CI 3.208 – 26.054) than invasive carcinoma (OR 0.109, 95% CI 0.038–0.312). 75% of all AIN patients attended GUID (p=0.000). There were no significant associations between GUID and progression from AIN to AC (p=0.230), diagnosis at Stage I (p=0.778), metastatic disease (p=0.835), surgical management (p=2.86), poor response to chemoradiation (p=0.146), recurrent AC (p=0.781) or overall mortality (p=0.466). In the AC cohort, GUID patients had a survival advantage at 3 and 5 years on a Kaplan-Meier Curve, though it was not significant (p=0.103 and p=0.332, respectively).


Discussion
GUID involvement did not significantly impact disease outcome. However, the predominance of AIN without concurrent AC in the GUID cohort may reflect the early identification and referred to coloproctologists at a premalignant stage. GUID now offers vaccination against HPV to all MSM patients between 18–46 years.


POSTER 11
Cancer risk factors and prevention

NINETEEN-YEAR REVIEW OF ANAL SQUAMOUS CELL CARCINOMA MANAGEMENT IN A TERITARY REFERRAL HOSPITAL

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Introduction
Anal Squamous Cell Carcinoma (AC) accounts for 1.5% of all gastrointestinal malignancies¹. National and international trends suggest AC incidence is increasing²,³. Risk factors include smoking, immunosuppression and high-risk sexual activity⁴.

Methods
We performed a retrospective review of all AC cases managed a tertiary referral hospital over a nineteen-year period (2000-2019). We examined patient demographics, management strategies and patient outcomes. We also assessed time-related changes in AC incidence.

Results
85 patients were treated for SCC during the study period. Four patients (5%) progressed from previously detected AIN to invasive carcinoma, and 21 (25%) had concurrent AIN and SCC on initial histology. 59% (n=50) were male. 72% (n=61) of the cohort were smokers, 21% (n=18) had Human Immunodeficiency Virus (HIV) and 35% (n=30) had HPV. 41% (n=29) of the male cohort were male-who-have-sex-with-males (MSM), while 43% of the female cohort had co-existing gynaecological premalignancy (n=15). Median(range) age at diagnosis was 53(25–88) years. Patients with HPV (p=0.002), HIV (p=0.001), gynaecological premalignancies (p=0.020) and MSM (p=0.017) were all significantly younger at diagnosis.

The majority were treated with curative intent (n=80, 97.5%). 80% (n=67) had primary chemoradiation therapy. 72.5% were Stage II or less at diagnosis. 17 patients (21.5%) required surgical management, including eight Abdominoperineal Resections (APR). Seven APRs were salvage procedures for progressive disease, with R0 resection achieved in 71.5%.

One-fifth of patients (n=16, 21%) developed recurrent disease, 75% of which occurred locally (n=12). At recurrence, 43.75% were palliated. 3- and 5-year survival rates for all stages are 79% and 65%, respectively. 48% (n=12) of deaths to date were directly related to AC.
Discussion

The incidence of anal SCC is increasing. Chemoradiotherapy remains the mainstay of initial management. A small proportion of patients ultimately require salvage surgery. We have demonstrated salvage APR is associated with acceptable outcomes and satisfactory survival rates.


TESTING THE EFFECTIVENESS OF A PERSONALISED SELF-MANAGEMENT INTERVENTION FOR CANCER SURVIVORS

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Introduction

Cancer survivors experience persistent symptoms post-treatment such as pain, fatigue, anxiety and depression which affect daily activities and quality of life. Self-management interventions are recommended to enable individuals to manage the impact of these symptoms. The effectiveness of a group-based self-management intervention OptiMal, was tested on daily activities and health outcomes of cancer survivors.

Methods

A pragmatic, exploratory randomised controlled trial compared adult cancer survivors, who participated in a six-week, self-management intervention, OptiMal, with a control group receiving usual care. Outcome measures examined anxiety and depression levels, cognition, fatigue activity participation, self-efficacy and health-related quality of life. Data were collected at baseline and three months post- OptiMal.

Results

Sixty participants with mixed cancer types participated in the study. Statistically significant differences were observed in quality of life (p=0.035) and anxiety (p=0.04) from baseline to three month follow-up in favour of the intervention group. Although the intervention group showed greater improvements than the control group in all other measures at three months follow-up these differences were not significant.

Discussion

Up to 25% of cancer survivors have one or more physical or psychological consequences of their cancer treatment that affects their quality of life to a greater or lesser degree in the long-term and impacts on
return to pre-treatment routines and activities. This six-week self-management intervention, OptiMal, significantly reduced anxiety levels and improved quality of life in cancer survivors three months following completion of OptiMal. This self-management intervention is a promising intervention to address psychosocial difficulties identified by individuals following completion of cancer treatment.

POSTER 13
Genomics and Therapeutics

IDENTIFICATION OF MUTATIONS IN MEMBERS OF THE ‘PROTEIN TYROSINE PHOSPHATASE’ GENE FAMILY AS NOVEL THERAPEUTIC OPTIONS FOR THE TREATMENT OF SOLID TUMOURS.

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Introduction
The Protein Tyrosine Phosphatases (PTP) gene family regulates cellular processes central to oncogenesis. This bioinformatics study aimed to identify novel inhibitors for PTPN6 (protein tyrosine phosphatase non-receptor type 6) across 15 solid tumour types and determine cellular pathways affected.

Methods
The cBioPortal Database was used to identify PTP genes mutated in 15 solid tumours. The ‘MUTATED GENES’ refinement setting was chosen from the ‘STUDY SUMMARY’ page, and the PTPs in this dataset were noted, along with their frequency. This was repeated for 14 other datasets.

To establish if these PTPs could be potential oncogenes or tumour suppressor genes, the “copy number variation” filter was enabled and the amplified PTP genes in the tumour sample were noted.

Kyoto Encyclopaedia of Genes and Genomes (KEGG) Pathway Analysis was used to determine the signalling pathways affected by the chosen PTP. The location of the selected PTP gene in the pathways was noted.

The PubChem BioAssay tool from National Center for Biotechnology Information (NCBI) was used to search for inhibitors of the chosen PTP and to check for cross reactivity. A list of the total bioassays was available and active proteins that were inhibited were noted. This method was used for each of the chemical inhibitors of the selected PTP gene.

Results
PTPN6 was the most upregulated and mutated PTP (in 11 out of 15 tumours). PTPN6 mutations disrupted the JAK-STAT, VEGF, MAP-Kinase and PI3K pathways. CHEMBL509443 and CHEMBL449613 inhibitors were active against PTPN6 with limited cross-reactivity.
Discussion

The upregulation of PTPN6 in tumour samples indicates its potential as an oncogene. The pathways affected by PTPN6 mutations have been linked to cancer growth and metastasis. The inhibitors identified, if developed into clinical drugs, could potentially be used to treat solid tumours with PTPN6 mutations, which accounts for 38% of solid tumours on cBioportal.

1. CBioportal Database for Cancer Genomics, Memorial Sloan Kettering Cancer Centre. [Available at: http://www.cbioportal.org/]
10. National Cancer Registry, Ireland. [Available at: https://www.ncri.ie/]
Introduction
Due to a high incidence of aggregation in aqueous environments, protoporphyrin IX (PpIX) is frequently administered as a photosensitizer (PS) for photodynamic therapy (PDT) in the form of its biosynthetic precursor, 5-aminolevulinic acid (5-ALA). However, 5-ALA demonstrates limited diffusion due to its hydrophilic nature, and requires high doses over long periods of time in order to ensure acceptable levels of PpIX. Thus, an improvement in the biocompatibility of PpIX is attractive, as this would by-pass the need to use 5-ALA as a precursor. The work presented herein illustrates our approach to incorporate PpIX into a hydrogel network using poly(N-isopropylacrylamide).

Methods
Poly(N-isopropylacrylamide) (PNIPAM) hydrogels were synthesized with varying percentages of PSs as copolymers via an in situ dispersion polymerization method, which involves the mixing of organic (to handle the water-insoluble PS monomers) and aqueous solvents. Cell viability analysis was carried out on HT-29 cells via calorimetric assays.

Results
The absorption spectra for the PpIX-PNIPAM in H2O confirmed that PpIX exists in the monomeric state, as seen also by the increasing fluorescence emission intensity upon increasing PpIX concentration. The PpIX-PNIPAM hydrogels showed excellent biocompatibility, with cell viability remaining at >99% even at high concentrations of PpIX. Upon light irradiation, photocytotoxicity occurred and cell viability dramatically decreased. The drug dose required to kill 90% of the HT-29 cells was found to be 75 nM. This, in addition to the favourable on/off efficiency, suggests that the PpIX-PNIPAM hydrogel has the potential for in vivo testing.

Discussion
Our hydrogel preparations have demonstrated full solubility of PpIX in aqueous media, monomeric incorporation into the hydrogel network (i.e., photoactive and capable of 1O2 production), limited dark toxicity and a favourable on/off efficiency.

Introduction
Photodynamic therapy (PDT) is a modified anti-cancer treatment method, which uses the combined effect of a photosensitizing drug, light, and oxygen to cause selective damage to target tissue.[1] The BODIPY-based dyads discussed herein offer spectroscopic properties which make them potential photosensitizing and diagnostic agents. A new approach of charge-separated transfer states (CSS) generated by photoinduced electron transfer (PeT) recombine to form a locally induced triplet excited state, which can undergo charge transfer with molecular oxygen to generate highly reactive singlet oxygen (SO) and induce cell death. Moreover, the heavy-atom free BODIPY-based dyads can react with SO itself, leading to cycloaddition across the anthracene moiety and the formation of fluorescent photoproducts.[2,3]

Results
In the present work, a series of heavy atom-free water-soluble BODIPY-based dyads were synthesized using condensation, substitution and quaternization reactions. A lead compound has been identified from a library of water-soluble anthracene-, pyrene- and phenyl-BODIPYs based on its photophysical properties and in vitro cytotoxicity against human breast cancer cells (MDA-MB-468).

Discussion
Synthesized BODIPY-based dyads are promising compounds for PDT due to significant photocytotoxicity and minimal effect on cell viability in dark conditions. Moreover, tracking of the oxidative stress in the biological media sets a new pathway for BODIPY-based dyads as promising materials not only for PDT, but also for bioimaging and material sciences.[4]
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Background
Breast cancer is a complex and heterogeneous disease. Clinically, it has been characterized into intrinsic subtypes that predict disease outcome. Despite advances, heterogeneity at a cellular level remains poorly understood. A more comprehensive understanding of heterogeneity within breast cancer both at the time of diagnosis and with disease progression, will influence treatment decisions. In this study, we examine whether our understanding of the subtypes can help decipher clinically-relevant heterogeneity in endocrine resistant breast cancer.

Methods
A panel of cell surface markers was used to define heterogeneity across a panel of breast cancer cell lines representing the intrinsic subtypes. Fluorescence activated cell sorting was used to characterize populations in an in vitro model of endocrine resistance. RNA was isolated from freshly sorted populations and gene expression was performed using the PAM50 Nanostring gene expression assay. Single cell RNA sequencing was carried out using the 10x Genomics Chromium 3’ gene expression platform.

Results
EpCAM, CD49f and CD24 identified different populations in the intrinsic subtypes of breast cancer. PAM50 gene expression of freshly sorted populations confirmed these findings and identified the Luminal A, HER2-Enriched and Basal-like subtypes within the in vivo model of endocrine resistant breast cancer. Single cell RNA sequencing was successfully carried out for 6080 Luminal A cells, 3262 HER2-Enriched, 2686 Basal-like cells and 3410 cells isolated from the unsorted tumour bulk, offering valuable information on the transcriptional profile of each population.
Discussion
In this study, we have identified subtype heterogeneity in Luminal B endocrine resistant breast cancer. Further characterization of these populations at the single cell level will help us to better understand how these subtypes contribute to, and evolve with, treatment-resistant disease progression. Ultimately, this multi-faceted approach will help better stratify patients and redefine current treatment options.

POSTER 17
Other

A RANDOMIZED TRIAL OF EXERCISE ON QUALITY OF LIFE IN MEN WITH METASTATIC PROSTATE CANCER – THE EXPECT TRIAL

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Introduction
All patients living with cancer, including those with metastatic cancer, are encouraged to be physically active. This paper examines the feasibility of an aerobic exercise intervention for men with metastatic prostate cancer.

Methods
ExPeCT (Exercise, Prostate Cancer and Circulating Tumour Cells), was a multi-centre randomised control trial for men living with metastatic prostate cancer. Participants were randomized to either control or exercise arms. Participants in the exercise arm completed six- months of prescribed aerobic exercise. Quality of life assessments were completed at baseline, at 3 months and at 6 months. Physical activity was measured using a self-administered physical activity questionnaire. Exercise adherence
data was collected via Polar heart rate monitors, worn by the patient for every exercise session undertaken.

**Results**
A total of 61 patients were included (69.4±7.3 yr, Body Mass Index 29.2±5.8 kg/m²). The median time since diagnosis was 34 months (IQR 7-54). A total of 35 (55%) of participants had >1 region affected by metastatic disease. A total of 54 (81%) of participants completed the 3 month assessment and 52 (78%) of the participants completed the 6 month assessment. Adherence to the supervised sessions was 83% (329 out of 396 sessions attended). No adverse events were reported by participants enrolled in this study. There was no significant difference in physical activity levels, sedentary time or quality of life between either group at baseline, 3 months or 6 months. Systolic blood pressure was significantly lower in the exercise group when compared to the control group at 3 months (p=.008) and 6 months (p=.011).

**Conclusion**
The exercise intervention was tolerated well by a group of patients with a high burden of metastatic prostate cancer however did not lead to change in physical activity levels or quality of life. This trial provides proof of principle evidence for future exercise studies involving this patient group.

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**POSTER 18**

**Genomics and Therapeutics**

**PREOPERATIVE EXERCISE TO IMPROVE FITNESS IN PATIENTS UNDERGOING COMPLEX SURGERY FOR CANCER OF THE LUNG OR OESOPHAGUS (PRE-HIIT): STUDY PROTOCOL**

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**Background**
Patients with cancer of the lung or oesophagus, undergoing curative treatment, usually require a thoracotomy and a complex oncological resection. These surgeries carry a risk of major morbidity and mortality. Pre operative optimisation and enhanced recovery after surgery (ERAS) pathways are modern approaches to optimise outcomes. Pre-operative fitness is an established predictor of postoperative outcome, accordingly targeting pre-operative fitness through exercise prehabilitation has logical appeal. Exercise prehabilitation is challenging to implement however due to the short opportunity
for intervention between diagnosis and surgery. Therefore, individually prescribed, intensive exercise training protocols which convey clinically meaningful improvements in cardiopulmonary fitness over a short period need to be investigated. This project will examine the influence of exercise prehabilitation on physiological outcomes and postoperative recovery and, through evaluation of health economics, the impact of the programme on hospital costs.

**Methods**
The PRE-HIIT Randomised Controlled Trial will compare a 2 week high intensity interval training (HIIT) programme to standard preoperative care in a cohort of thoracic and oesophageal patients who are >2-weeks pre-surgery. A total of 78 participants will be recruited (39 per study arm). The primary outcome is cardiorespiratory fitness. Secondary outcomes include, measures of pulmonary and physical and quality of life. Outcomes will be measured at baseline (T0), and post-intervention (T1). Post-operative morbidity will also be captured. The impact of PRE-HIIT on well-being will be examined qualitatively with focus groups/interviews post-intervention (T1). Participant’s experience of preparation for surgery on the PRE-HIIT trial will also be explored. The healthcare costs associated with the PRE-HIIT programme, in particular acute hospital costs, will also be examined.

**Discussion**
The overall aim of this RCT is to examine the effect of tailored, individually prescribed high intensity interval training aerobic exercise on pre-operative fitness and postoperative recovery for patients undergoing complex surgical resections, and the impact on use of health services.
cells, improve treatment efficacy, and decrease toxicity to normal cells or tissues. Docetaxel (DTX) “a chemotherapeutic agent” has very low neurotoxic effect to the cancer patients. Therefore, we hypothesized that treating ovarian cancer (OC) ex-vivo explants by loading NDs with DTX would improve drug targeting and delivery of OC patients. Thus, we aimed to investigate the efficacy of ND-conjugated DTX on OC ex-vivo explants.

**Methods**
Bare, uncoated nanodiamonds were PEGylated and functionalised with DTX (NDs/DTX) and conjugated with anti-Her-3 antibody. Dynamic Light Scattering (DLS) was used to measure the hydrodynamic diameter of individual NDs dispersed in solution (NDs, ND/DTX/Her-3). Ex-vivo explants from OC patients were exposed to various concentrations of ND/DTX, ND/DTX/Her-3 and DTX for over 24 hour’s incubation. Cytotoxicity was examined by measuring cell viability changes, caspase 3 and 8 activation and the molecular cell stress variation was investigated by examining the activation of transcription factor-2 (ATF-2).

**Results**
Significant alterations of the examined biological markers were detected in OC ex-vivo explants. As expected no nuclear translocation of ATF-2 was observed in the nuclei of untreated explants. Interestingly, the ex-vivo explants showed greater responses to NDs/DTX/Her-3 versus ND/DTX and DTX alone.

**Conclusions**
Our study demonstrates that NDs loaded with DTX exert significant inhibitory activities on OC explants. Thus, the proposed drug delivery system of ND-conjugated chemotherapy represents a promising, biocompatible strategy for targeting and enhancing chemotherapy efficacy and safety.

**POSTER 20**

**Other**

**REHABILITATION STRATEGIES FOLLOWING OESOPHAGOGASTRIC AND HEPATOPANCREATICOBILIARY CANCER (RESTORE II); A PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL**

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Introduction
Curative treatment for upper gastrointestinal (UGI) and hepatopancreaticobiliary (HPB) cancers, involves complex surgical resection often in combination with neoadjuvant/adjuvant chemo/chemoradiotherapy. With advancing survival rates, there is an emergent cohort of UGI and HPB cancer survivors with physical and nutritional deficits, resultant from both the cancer and its treatments. Rehabilitation to counteract these impairments is required to maximise HRQOL in survivorship. The feasibility of a multidisciplinary rehabilitation programme for UGI survivors was established in the ReStOre feasibility study and pilot randomised controlled trial (RCT)\(^1\).\(^2\) ReStOre II will now further investigate the efficacy of that programme in a wider cohort of UGI and HPB cancer survivors, namely survivors of cancer of the oesophagus, stomach, pancreas, and liver.

Methods
ReStOre II will compare a 12-week multidisciplinary rehabilitation programme of supervised and homebased exercise, dietary counselling, and education to standard survivorship care in a cohort of UGI and HPB cancer survivors who are >3-months post-oesophagectomy/ gastrectomy/pancreaticoduodenectomy, or major liver resection. 120 participants (60 per arm) will be recruited to establish a mean increase in the primary outcome (cardiorespiratory fitness) of 3.5 ml/min/kg with 90% power, 5% significance allowing for 20% drop out. Study outcomes of physical function, body composition, nutritional status, HRQOL, and fatigue will be measured at baseline (T0), post-intervention (T1), and 3-months follow-up (T2). At 1-year follow-up (T3), HRQOL alone will be measured. Impact on well-being will be examined qualitatively with focus groups/interviews (T1, T2). Bio-samples will be collected from T0-T2 to establish a national UGI and HPB cancer survivorship biobank. Cost effectiveness will also be analysed.

Discussion
This RCT will investigate the efficacy of a 12-week multidisciplinary rehabilitation programme for survivors of UGI and HPB cancer compared to standard survivorship care. If effective, ReStOre II will provide an exemplar model of rehabilitation for UGI and HPB cancer survivors.

Multiple myeloma (MM) is a haematological malignancy characterised by the proliferation of malignant plasma cells in the bone marrow microenvironment. A better understanding of the pathophysiology of myeloma and advances in the treatment of MM has led to an increased median survival of patients from 3 to 6 years in the past decade. However, despite the effectiveness of the first-line treatments, patients invariably relapse and become drug refractory; therefore, novel therapeutics which target this incurable disease are still required.

Janus kinase (JAK)/Signal transducer and activator of transcription 3 (STAT3) pathway in MM can be both constitutively active or activated by the growth and survival factor interleukin-6 (IL-6) secreted by the bone marrow stromal cells and other cells within the tumour microenvironment. STAT3 upregulates expression of genes involved in apoptosis, proliferation and angiogenesis. Consequently, STAT3 has emerged as a therapeutic target in various cancers including MM.

In the present study, we identified a novel guanidinium based compound (VP79s) capable of inhibiting both constitutively active and IL-6 induced STAT3 signalling in MM cells. VP79s was found to decrease expression of STAT3 regulated anti-apoptotic gene products, Mcl-1 and survivin, and the cell cycle protein cyclin D1. VP79s induced caspase-3 activation and subsequent apoptosis in a dose and time-dependent manner. Our data have shown that VP79s potently reduced the viability of a panel of drug resistant and susceptible MM cell lines. VP79s was also found to be capable of overcoming bone marrow stromal cell induced drug resistance and synergise with standard (Bortezomib) and emerging (Venetoclax) treatments for MM.

In conclusion, the novel compound VP79s can target dysregulated STAT3 activation and induce apoptosis in myeloma cells, suggesting it’s potential as a novel anti-cancer therapeutic which can overcome tumour microenvironment induced resistance. Identification and development of novel drugs that can target STAT3 remains an important scientific and clinical challenge.
Background
Novel targeted strategies are needed to combat resistance and relapse in breast cancer (BC) particularly for the triple negative subtype (TNBC). Sigma receptors (SRs) are often upregulated in BC however their associated pathways are inadequately described and their functions in cancer unknown. Certain Sigma1-receptor (Sig1R) ligands have been shown to trigger apoptosis in BC cells while inducing minimal toxic effects in non-cancerous mammary cells (1). We aim to characterize SR expression, ligand response and interacting proteins in normal mammary cells vs BC to better understand their mechanisms of action.

Methods
SR expression was examined by Western blotting in BC cell lines and primary human mammary epithelial cells (HMECs). Cell viabilities following treatment with a putative Sig1R antagonist, IPAG were compared in HMECs and BC. RNAseq data (The Cancer Genome Atlas) and publicly available microarray datasets were used to compare SR transcript level expression in 141 matched breast tumour vs tumour-adjacent normal tissue samples and in 399 primary BC tumours with relapse (BCr) vs 352 without relapse (BCnr).

Results
Endocrine-sensitive MCF7s had the lowest expression of Sig1R compared to HMECs, triple negative MDA-MB-468 cells had the highest. Both BC models showed similar Sig2R expression (n=3). Treatment with IPAG at 4.5μM for 72 hours decreased viability of MCF7 and MDA-MB-468 cells by 65.7% and 54.2% respectively; HMECs showed 21.3% reduction (n=3). RNAseq analysis highlighted SR overexpression in BC particularly in hormone receptor (HR) negative subtypes. Microarray data showed oestrogen receptor (ER)+ and ER- BCr primaries had higher Sig1R compared to BCnr primaries of the same respective HR status.

Discussion
Tumour cells appear to be overly reliant on Sig1R mediated pathways. Sig1R expression could provide an indication of the proclivity of a primary breast tumour to relapse. Thus, Sig1R merits exploration as a potential target in BC, particularly for therapeutically refractory TNBC.

INTRODUCTION
Extracellular vesicles (EVs) released from cancer cells transmit undesirable traits such as drug-resistance to recipient cells. As EVs are heterogeneous, this study investigated if all EV sub-populations within the heterogeneous population of EVs released from the aggressive triple negative breast cancer (TNBC) cell line variant, HS578Ts(i)8, work together to result in transfer of aggressive traits or if a particular sub-population of EVs is responsible for the effects.

METHODS
The total heterogeneous EV population and four sub-populations of EV were separated from medium conditioned by the HS578Ts(i)8 cell line variant, using differential ultracentrifugation techniques. EVs were characterised by nanoparticle tracking analysis (NTA), Bradford colorimetric assay (BCA) and immunoblotting. The comparative ability of the four EV sub-populations, compared to the heterogeneous EV population, to increase the aggressiveness of the more docile parent HS578T cell line variant in terms of proliferation migration, invasion, apoptosis/anoikis was investigated.

RESULTS
HS578Ts(i)8 cells release sub-populations of EVs, termed 2K, 10K, 100K and 200K. They were characterised based on diameter (nm), concentration (vesicles/10^6 cells) protein content (µg/10^6 cells) and EV markers they contain. For example, the 200K had the smallest diameter (88±14 nm). The 100K had the highest concentration (3.43±9.69x10^10 vesicles/10^6 cells). The 2K and 10K sub-populations contained microvesicles markers whereas the 100K and 200K contained exosomal markers. All EV sub-populations increased the aggressiveness of the recipient HS578T cells. However, when compared to the effects of the heterogeneous EV population, evidently no sub-population(s) was solely responsible for the effects seen on HS578T cells.

DISCUSSION
The HS578Ts(i)8 EV sub-populations apparently work together to increase aggressiveness of HS578T cells. Efforts to collectively inhibit EVs release, rather than blocking some specific sub-populations(s), may be the optimal route to blocking the undesirable effects transmitted by EVs.

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Introduction
Poor pathological response to neoadjuvant chemoradiation therapy (neo-CRT) is a significant clinical problem in rectal cancer patients. There is a global unmet need to determine the molecular factors influencing response to neo-CRT. Evidence supports a role for the innate inflammatory complement cascade in tumourigenesis and therapeutic response in several human cancers. The role of complement in the response to neo-CRT in rectal cancer is unknown. This study aimed to characterise the complement cascade in a panel of colorectal cancer cell lines and determine if this correlates with inherent radiosensitivity.

Methods
Radiosensitivity of the HCT116 (human colon adenocarcinoma) and SW837 (human rectal adenocarcinoma) cell lines was assessed by clonogenic assay. Expression of complement genes (C3, C5 and CFB) was assessed by qPCR. C3 protein expression was assessed by ELISA. Expression of the complement regulatory proteins CD46, CD55 and CD59 and complement receptors C3aR and C5aR, was determined by flow cytometry.

Results
The HCT116 cell line is more radiosensitive compared to the SW837 cell line. C3 and C5 mRNA was expressed by both cell lines concomitant with CFB expression, suggesting for the first time that the alternative complement activation pathway is active in these cell lines. The radioresistant SW837 cell line had significantly increased protein secretion of C3 and mRNA expression of C3 and C5, when compared to the radiosensitive HCT116 cell line, suggesting that increased complement activation is associated with radiosensitivity in rectal cancer. Both cell lines express CD46, CD55, CD59 and the complement receptor C5aR, suggesting that colorectal cancer cells can respond to complement signalling.

Discussion
This study demonstrates for the first time that complement is activated in colorectal cancer cells. Importantly, we demonstrate that complement expression is increased in radioresistant rectal cancer cells. This highlights a potential role for the complement cascade in the radioresistance of rectal cancer.
Introduction
The resistance of rectal cancer to radiation treatment is a significant clinical problem. Emerging evidence supports an association between altered tumour metabolism and radioresistance in various cancer types, including gastrointestinal cancers. However, the role of metabolism in the radioresistance of rectal cancer is largely unknown. This project aims to investigate altered tumour metabolism in radioresistant rectal cancer and the potential anti-metabolic and radiosensitising effects of a novel compound, P3, in rectal cancer.

Methods
Irradiations were performed using an X-Strahl RS225 X-ray cabinet irradiator at a dose-rate of 1.74 Gy/min. Radiosensitivity was assessed by the gold-standard clonogenic assay. Metabolic profiles were analysed using the Seahorse live-cell metabolic assay. Mitochondrial function was assessed using fluorescent probes. Data were normalised to cell number using the crystal violet assay.

Results
The inherent radiosensitivities of colon (HCT116) and rectal (SW837) cancer cell lines were characterised. SW837 rectal adenocarcinoma cells were significantly more radioresistant, when compared to radiosensitive HCT116 cells at 2 Gy, 4 Gy and 6 Gy X-ray irradiation. The basal metabolic profiles of colorectal cancer cell lines were profiled, with SW837 rectal cancer cells demonstrating significantly higher reliance on oxidative phosphorylation than glycolysis, when compared to HCT116 (colon) and HRA-19 (rectal) cancer cells. Treatment with the novel compound, P3, significantly reduced both oxidative phosphorylation and glycolysis in radioresistant SW837 cells. P3 treatment also resulted in a dose-dependent increase in reactive oxygen species (ROS) production and mitochondrial membrane potential (MMP) in vitro.

Discussion
We have identified an in vitro model of inherent radioresistant colorectal cancer and demonstrated that alterations in metabolism, specifically oxidative phosphorylation, is associated with a radioresistant phenotype. Importantly, we also demonstrate that P3 is anti-metabolic and impacts mitochondrial function in a dose-dependent manner in radioresistant rectal cancer cells. We are currently investigating the potential radiosensitising effects of P3 in colorectal cancer.
Introduction
Radiotherapy is a mainstay in the treatment of oesophageal cancer (OC); however, novel therapeutic agents and effective delivery strategies are needed to enhance tumour sensitivity to radiation. We previously demonstrated that re-expression of lost miR-31 in radioresistant OC cells (OE33R) increased sensitivity to clinically-relevant irradiation, suggesting miR-31 as a radiosensitiser. We characterised and optimised miR-31 release from a thermostable collagen I-based hydrogel loaded with lipoplexed miR-31, resulting in the in vitro transfection of several OC cell lines. The final goal is to create an injectable delivery platform that can sustain regulated release of miR-31 over an extended period in an established murine xenograft model of OC.

Methods
Collagen I-based hydrogels containing the lipoplexed miR-31 were prepared using the 4S-StarPEG cross-linker and incubated at 37°C for 5 min to induce gelation. Opti-MEM medium was overlaid onto each scaffold and incubated at 37°C overnight. Hydrogel physicochemical characterisation in vitro involved assessment of storage modulus and miRNA degradation behavior. Supernatants were collected and applied to the radioresistant OE33R, radiosensitive OE33P and SKGT4 cell lines, previously seeded in a 6-well plate. After 24h the cells were harvested for fluorescent Ribogreen assay, miRNA extraction, retrotranscription and qPCR analysis.

Results
The miR-31 release profile from the hydrogels showed regulatable release of miRNA with differential per cent crosslinking with 4S-StarPEG over 168 hours, suggesting a good control of the miRNA release over time. Degradation profile data demonstrated that miR-31 remained intact for up to 48h post-release. Preliminary data demonstrate that released lipoplexed miR-31 is successfully transfected into OC cell lines in vitro. The in vitro transfection efficiency and functional radiosensitising experiments are currently in progress.

Discussion
This study proposes the use of a 4S-StarPEG cross-linked collagen-based hydrogel for the delivery of exogenous miR-31 to target OC cells. Once validated in vitro, this system will be tested in a pre-clinical mouse xenograft model as a radiosensitising strategy for OC tumour treatment.
Introduction
The role of stereotactic radiosurgery (SRS) in the treatment of breast cancer brain metastases (BCBM) in selected patients is well established.

Aim
To report outcomes following SRS for BCBM treated at a single institution and to identify any significant prognostic factors including tumour receptor subtype.

Methods
Patients treated with SRS for BCBM between 2013 and 2018 were identified from a prospective institutional database. Survival rates were determined using the Kaplan Meier method. The long rank test was used to compare differences in survival.

Results
154 lesions in 72 patients were treated between 2011 and 2018. SRS was delivered in 1–5 fractions respecting normal brain tissue constraints. Median follow-up time from SRS was 13 months (range 0.4–67.9). Molecular breast cancer subtype was grouped as follows: ERposHer2neg (n=16), HER2pos (n=41) and triple negative (TN) disease (n=15). Treatment intent was as follows: SRS alone (n=24), boost after surgery (n=25), after WBRT (n=23). Median overall survival (OS) after CNS diagnosis was 22.8 months (95%CI 16.6–29.0), and was statistically significantly worse for patients with triple negative disease, 14.9 months (95%CI 13.4–16.4), compared to other patients, 29.4 months (95%CI 18.2–40.5) (p=0.002). Median local failure free survival (L-FFS), distant brain failure free survival (DB-FFS), and leptomeningeal disease free survival (LMD-FS) from SRS completion was 8.6 months (95% CI 5.6–11.5), 7.7 months (95%CI 4.7–10.8), and 8.6 months (95%CI 4.8–12.5), respectively. Univariate analysis identified only TN disease (HR=2.1, p=0.031) as a predictor of L-FFS and LMD-FS. Univariate analysis identified TN disease (HR=2.1, p=0.031) and lesion diameter ≤vs>2cm (HR=1.7, p=0.045) as predictors of DB-FFS. These remained statistically significant on Cox multivariate analysis. Extra-cranial disease status, and prior treatment with whole brain radiotherapy or surgical resection had no impact on any outcome.

Conclusion
In this cohort of patients with BCBM treated with SRS, and in the era of targeted therapies, survival outcomes for patients with TN disease is worse compared to other subtypes.
INHIBITION OF PHOSPHOPROTEIN PHOSPHATASE 2A (PP2A) SENSITIZES PANCREATIC CANCER (PC) TO PARP INHIBITORS BY MODULATION OF HOMOLOGOUS RECOMBINATION REPAIR (HRR).

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Background
Pancreatic cancer remains one of the most lethal cancers with a 5-years survival of less than 6%. The PP2A inhibitor (LB-100) sensitizes PC cells to chemotherapy and radiation in preclinical studies through modulation of DNA damage repair pathways (1). PARP inhibitors including Talazoparib have shown modest efficacy in vivo in patients with PCs deficient in HRR (2). We assessed the activity of LB-100 against PC cells as monotherapy and in combination with PARP inhibition (Talazoparib) and investigated the mechanism by which LB-100 and Talazoparib synergize through modulation of cell cycle regulatory proteins and control of HRR.

Material and methods
Human PC cell lines Panc-1, MIA-Pa-Ca-2 and BxPC-3 were studied. PP2A activity was measured by PP2A Immunoprecipitation phosphatase assay Kit (Millipore), cell cytotoxicity were measured by MTT assay, cell cycle determined by flow cytometry. Western blot assessed levels of proteins associated with regulation of cell cycle (Cdc2, p-Cdc2, and Cdc25c), apoptosis (caspase3) and DNA damage (γ-H2AX). Data are expressed as the mean ± (SEM) and analysed by an analysis of variance (ANOVA).

Results
LB-100 decreased PP2A activity in all PC cells in dose dependent manner. LB-100 significantly decreased cell viability of Panc-1, MIA-Pa-Ca-2 and BxPC-3 with IC50 (3.94 μM, 6.86 μM, and 10.87 μM) respectively. Addition of 25 nm of Talazoparib further significantly decreased IC50 in all cells compared to monotherapy (1.88 μM, 5.24 μM and 5.83 μM). Combined treatment attenuated cell growth through caspase activation and G2/M cell-cycle arrest. Significantly increased induction of γ-H2AX with combination treatment compared to monotherapy was observed.

Discussion
The combination of PP2A inhibitor LB100 with PARP inhibitor Talazoparib demonstrated a synergistic effect in vitro, likely through modulation of the DNA damage response pathway and cell cycle checkpoint abrogation. Further in vivo studies will explore this combination as an effective option in the treatment of PC.

Introduction
Ovarian cancer (OC) is the fifth most common cancer among Irish women. OC patients have a good response rate to first line chemotherapy treatment. However, the prognosis for OC is very poor in the majority of OC patients. Peptidyl arginine deiminase type 4 (PADI4) performs post-translational modification and catalyzes the arginine residue to a citrulline in numerous protein substrates. Citrullination of histones, cytokeratin, antithrombin and fibronectin have been confirmed to be involved in abnormal apoptosis, altered coagulation, and disordered cell proliferation, all of which are main features of primary tumors and metastasis. PADI4 can interact with tumor suppressor p53 and regulate its transcriptional activity. Histone deacetylases (HDACs) were also determined as a PADI4-interacting protein and they both were shown to bind to p53 and simultaneously associate with the p21 promoter in response to DNA damage. Thus, we hypothesized that targeting PADI-4 with small molecule inhibitors GSK484 and GSK199 in OC cell line (SKOV3) and ex-vivo patient explants could lead to a novel therapeutic strategy.

Methods
SKOV3 cell line and OC ex-vivo explants were exposed to various concentrations of PADI4 inhibitors over 24h. PADI4 expression, cell cycle, cell viability, caspase 3, 8 and 9 expression, P53, P21 and HDACs were measured using immunoblotting, immunohistochemistry, high content screening tool and FACS analysis.

Results
We observed that the inhibition of PADI4 led to cell cycle arrest at G2/M phase, reduction in cell viability, increased expression of caspase 3 and 9, and P53, P21 and HDACs.

Conclusion
These results suggest an important role for PADI4 in the p53 pathway and the regulation of the proliferation, apoptosis and migration of OC explants and cell lines. GSK484 and GSK199 presents a promising direction in the search for novel OC treatment strategies.
CHARACTERISING THE IMMUNE-METABOLIC SIGNATURE IN VISCERAL AND SUBCUTANEOUS ADIPOSE TISSUE IN OESOPHAGEAL ADENOCARCINOMA PATIENTS

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Introduction
Oesophageal cancer is the 7th most common cancer and the 6th most common cause of cancer deaths. Oesophageal adenocarcinoma is the predominant subtype in Western societies owing to lifestyle risk factors such as obesity. The standard of care for OAC is neoadjuvant chemoradiation (neo-CRT) however only 20-30% of patients achieve a complete pathological response. Previous work in our group has shown that overweight and obese OAC patients were more likely to have a better response to neo-CRT compared to normal weight patients and the underlying mechanisms are unknown. Unravelling the immune-metabolic signatures of adipose tissue may reveal a mechanistic basis for this observation. We hypothesised that different metabolic pathways will predominate visceral adipose tissue (VAT) compared to subcutaneous adipose tissue (SAT) and the inflammatory secretions will differ between the fat depots.

Methods
Following informed written consent, VAT and SAT were taken from twelve OAC patients undergoing elective oesophagectomy. The metabolic profile of both VAT and SAT were investigated using Seahorse technology. The adipose conditioned media of VAT and SAT were screened for the expression of 54 inflammatory mediators using MSD technology.

Results
Oxidative phosphorylation was significantly higher in VAT compared to SAT while glycolysis was higher in SAT. Fourteen mediators; VEGF, PIGF, Flt-1, bFGF, IL-15, IL-16, IL-17A, CRP, SAA, ICAM-1, VCAM-1, IL-2, IL-13, IFN-γ (p<0.05) were secreted at significantly higher level from VAT compared to SAT. VEGF-D secretion was higher from SAT compared to VAT (p<0.05).

Discussion
Metabolic pathways differ between VAT and SAT with VAT depending more on oxidative phosphorylation and SAT being more dependent on glycolysis. Angiogenic, vascular injury and pro-inflammatory cytokines were secreted at higher levels from VAT than SAT, indicating that VAT may have a greater role in promoting angiogenesis and inflammation.
NO CORRELATION BETWEEN ENUMERATION OF CIRCULATING TUMOUR CELLS AND MILLER-PAYNE GRADE IN A COHORT OF BREAST CANCER PATIENTS UNDERGOING NEOADJUVANT CHEMOTHERAPY

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Background
Detection and enumeration of Circulating Tumour Cells (CTCs) has been evaluated in many cancers such as breast cancer. The association between pathological complete response (pCR) in patients receiving neoadjuvant chemotherapy (NAC) for breast cancer and CTCs is still unclearly known. The aim of this study was to assess if CTCs could be used to predict pathological response to NAC in breast cancer patients.

Methods
26 patients were recruited, and blood samples taken pre- and post-neoadjuvant chemotherapy. CTCs were captured using the ScreenCell device and stained using a modified Giemsa stain. CTCs were enumerated by 2 pathologists and classified as single CTCs, doublets clusters/microemboli. Counts were then correlated to the pathological response as measured by the Miller Payne grading system. The associations between CTCs and pathological variables were evaluated with χ² test performed in the SPSS 24.0 statistics software.

Results
89% of the patients had invasive ductal carcinoma (IDC) and 11% invasive lobular carcinoma (ILC). At baseline 85% of patients had CTCs present and only 4 patients were negative. Median baseline CTC count was 7 (0-161) per 3mls of whole blood. Post-chemotherapy, 58% of patients had an increase in CTCs. This change in CTC count did not correlate with the Miller Payne grade of response to chemotherapy. No significant association was identified between the number of CTCs and clinical characteristics. However, we did observe a correlation between pre-treatment CTC counts and body mass index, p<0.05.

Discussion
There was no correlation between the pre- and post-chemotherapy total number of CTCs/clusters and the Miller Payne grade. It is not enough to evaluate pathological response for NAC for breast cancer patients utilising CTCs identified by Giemsa staining alone. Additional characterisation is needed to further characterise CTCs isolated pre- and post-chemotherapy. Long-term follow-up will determine the significance of CTCs in NAC breast cancer patients.
Pancreatic adenocarcinoma (PAC) is a lethal malignancy with a 5-year survival rate of less than 6%. Due to a lack of diagnostic, predictive and prognostic biomarkers, ~75% of PAC patients will die within one year of diagnosis, making it the 4th leading cause of cancer-related death globally. One main challenge concerning PAC is resistance to chemoradiotherapy, which is the standard of care. As such, there is a substantial unmet need to characterise the mechanisms underpinning resistance to chemoradiotherapy in PAC. Emerging evidence has revealed that epigenetic alterations, such as microRNA (miR) dysfunction, play important roles in cancer progression and resistance to cytotoxic therapy. However, the role of miRs in resistance to chemoradiotherapy in PAC remains unstudied. MiR-31 is encoded on a genomic fragile site, 9p21.3, which is reportedly disrupted in many PAC tumours. Here, we aimed to determine the influence of miR-31 on PAC sensitivity to chemoradiotherapy. A synthetic miR-31 mimic was expressed both transiently and stably via liposomal transfection into miR-31-low BxPC-3 PAC cells. Additionally, using anti-miR technology, endogenous miR-31 expression in miR-31-high Panc-1 cells was stably suppressed. Our data demonstrate that miR-31 overexpression in miR-31-low BxPC-3 cells enhances radiosensitivity compared with controls, but paradoxically promotes a chemoresistant phenotype. Reciprocally, suppression of miR-31 in miR-31-high Panc-1 cells significantly enhanced clonogenic radioresistance, but promotes sensitivity to chemotherapeutic agents. Preliminary data indicates the radiosensitising effect of miR-31 may involve alterations in DNA damage repair efficiency, as we previously demonstrated that miR-31 regulates several DNA repair genes, while the promotion of miR-31-mediated chemoresistance involves altered drug trafficking between the plasma membrane and nucleus, resulting in attenuated DNA damage induction. Our results suggest miR-31 as a therapeutic target for enhancing PAC chemoradiosensitivity, possibly via synthetic miR replacement therapy, which is being tested in clinical trials for a variety of different maladies, including cancer.
A NOVEL ROLE FOR THE COMPLEMENT CASCADE IN CHEMORADIATION THERAPY RESISTANT OESOPHAGEAL ADENOCARCINOMA

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Background
Resistance to chemoradiation therapy (CRT) in oesophageal adenocarcinoma (OAC) is a significant clinical challenge. Elucidating underlying mechanisms of treatment resistance is crucial to improving survival rates.

Aim
Determine if complement may act as a predictor of treatment response in OAC.

Methods
Tumour conditioned media was generated by culturing pre-treatment OAC biopsies for 24h. Natural killer cells were isolated from whole blood by density centrifugation. C3, CFB and MCP-1 mRNA expression was assessed by qPCR. Secreted C3, C3a and MCP-1 were measured by ELISA. An isogenic model of radioresistant OAC was established by chronically irradiating OE33 cells. C5aR, CD107a and IFN-γ expression were determined by flow cytometry. C3 was knocked-down using siRNA.

Results
The central factor of the complement cascade, C3, is expressed in OAC tumours and is increased in pre-treatment OAC biopsies from patients (n=13) who have a subsequent poor response to neoadjuvant CRT (p<0.05). C3 is secreted from OAC tumours and correlates with monocyte chemoattractant MCP-1 (p<0.008) and complement factor B (CFB), a component of the alternative complement activation pathway (p<0.0001). In vitro, radioresistant OE33R cells had increased mRNA expression of C3, CFB and MCP-1 (all, p<0.05) compared to radiosensitive OE33P cells. OE33R cells secreted more C3 and C3a, than OE33P cells (both p<0.001). Furthermore, the anaphylatoxin receptor C5aR is expressed by OAC cells, suggesting they are capable of responding to complement. In co-culture experiments, OE33R cells have a reduced capacity to activate anti-tumour natural killer cells compared to OE33P cells (CD107a p<0.01; IFN-γ p<0.05). Knockdown of C3 in OE33R cells resulted in increased CD107a expression on NK cells (p<0.05).

Conclusion
This study highlights, for the first time, a novel role for the complement cascade in the resistance of OAC to CRT and highlights complement as a novel predictive marker of treatment response in OAC.
Introduction
Prostate cancer (PrCa) is the second most common cancer in Irish men [1]. While, five-year survival rates for primary localised PrCa are high at over 90%, metastatic disease infers a worse prognosis, with rates reducing to approximately 30% [2]. Although, enzalutamide, an androgen receptor (AR) signalling inhibitor, has been shown to significantly increase survival in advanced disease, intrinsic and acquired resistance are major clinical issues [3, 4]. Though, a number of resistance mechanisms have been identified, including EMT plasticity, enzalutamide resistance has yet to be fully understood [5]. The aim of this study was to examine EMT features of enzalutamide resistant PrCa cells.

Methods
This study utilised an isogenic model of enzalutamide resistance, which consisted of (i) parental control cells (drug sensitive), (ii) Clone 1 (highly drug resistant) and (iii) Clone 9 (moderately drug resistant). An expanded panel of EMT makers (ECAD, FN1, SLUG, SNAIL, NCAD, TWIST, ZEB1, ZEB2, VIM, TGFB1, TGFB2 and EPCAM) were examined at the mRNA level using qPCR.

Results
Gene expression analysis demonstrated a differential pattern of EMT marker expression within the isogenic model. Clone 1 (highly drug resistant) displayed changes associated with a more metastatic phenotype. ECAD, a key maker of EMT, was significantly down-regulated (p<0.05) in both Clone 1 and Clone 9 compared to parental cells. NCAD, TWIST and ZEB2 were up-regulated in Clone 1 compared to parental and Clone 9 cells (p<0.05). However, VIM and ZEB1 were up-regulated in Clone 9 versus Clone 1 and parental cells (p<0.05). Other EMT associated genes including FN1, SNAIL and SLUG were significantly down-regulated in Clone 1 compared with Clone 9 and parental cell (<0.05).

Discussion
This study identified differential EMT marker expression in enzalutamide resistant cells. Thus, suggesting that EMT may play a critical role in the development of drug resistance in PrCa.


Introduction
Evidence supports the advantages of inhalation over other drug-administration routes in the treatment of lung diseases, including cancer. Although data obtained from animal models and conventional in vitro cultures are informative, testing the efficacy of inhaled chemotherapeutic agents requires human-relevant preclinical tools. Such tools are currently unavailable.

Methods
We developed and characterized in vitro models for the efficacy testing of inhaled chemotherapeutic agents against non-small-cell lung cancer (NSCLC). These models recapitulated key elements of both the lung epithelium and the tumour tissue, namely the direct contact with the gas phase and the three-dimensional (3D) architecture. Our in vitro models were formed by growing, for the first time, human adenocarcinoma (A549) cells as multilayered mono-cultures at the Air-Liquid Interface (ALI).

Results
The in vitro models were tested for their response to four benchmarking chemotherapeutics, currently in use in clinics, demonstrating an increased resistance to these drugs as compared to sub-confluent monolayered 2D cell cultures. Chemoresistance was comparable to that detected in 3D hypoxic tumour spheroids. Being cultured in ALI conditions, the multilayered monocultures demonstrated to be compatible with testing drugs administered as a liquid aerosol by a clinical nebulizer, offering an advantage over 3D tumour spheroids.

Discussion
In conclusion, we demonstrated that our in vitro models provide new human-relevant tools allowing for the efficacy screening of inhaled anti-cancer drugs.

Introduction
Tumour infiltrating lymphocytes (TIL's) are capable of mounting an anti-tumour response. TIL's, however encounter a myriad of suppressive elements in the tumour microenvironment (TME), such as regulatory immune cells, soluble factors released by tumour cells and the presence of inhibitory molecules on the surface of tumour cells. Metabolic competition within the TME results in the modulation of immunometabolism, which may skew the T-cell response to a pro-tumour like phenotype resulting in exhaustion and failure to carry out effector functions. Understanding the impact of elements within the TME is vital to improving responses to new therapies such as immunotherapy.

Methods
Human PBMC’s were cultured for in conditioned media simulating aspects of the TME. Nutrient deprivation was simulated with glucose and glutamine free media. Cells were analysed by Flow Cytometry and effector subset differentiation was evaluated by levels of transcription factors (T-bet, EOMES, FOXP3, GATA3, RORyt).

Results
CD4+ and CD8+ T-cells cultured in conditions of nutrient deprivation had significantly lower expression of T-bet suggesting that nutrient deprivation within the TME can affect TIL subset generation at a translational level. P=0.026, 0.044 Paired T-test.

Discussion
This study demonstrates that metabolic competition within the TME polarises T-cell responses by directly acting on transcription factors guiding the differentiation of distinct effector subtypes. Therefore, targeting T cell metabolism represents a promising immunomodulatory therapy for use in combination with immunotherapy.
TLR2 REPRESENTS A POTENTIAL TARGET TO LIMIT INFLAMMATION AND DISEASE PROGRESSION IN BARRETT’S DYSPLASIA AND OESOPHAGEAL ADENOCARCINOMA PATIENTS.

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Introduction
The oesophageal adenocarcinoma (OAC) is aggressive cancer with high mortality and an overall 5-year survival rate of less than 20%. Patients with Barrett’s dysplasia (BE) are at increased risk of developing OAC, the incidence of which is dramatically increasing in the developed world. Chronic inflammation plays a very important role in BE and OAC. TLR2 is a conserved receptor involved in the innate immune response to microbial pathogens through recognition of their microbial products. Macrophages are a major component of the immune cells reaction and in the tumour site, they can differentiate into tumour-associated macrophages (TAM) which have a crucial role in tumorigenesis and metastatic potential. Recent studies suggest that TLR2 and TAM are associated with poor prognosis of OAC patients.

Methods
TLR2 expression and signalling capabilities were evaluated by western blot and real-time PCR in a panel of oesophageal cell lines, ranging from pre-malignant dysplasia to advanced grade OAC. Macrophages were stimulated with conditioned media (CM) from TLR2-pretreated OAC cells. Western blot, real-time PCR and QUANTI-Blue™ assay were used to characterise immune cells stimulated with OAC CM.

Results
Data suggests that TLR2 signalling is only relevant during dysplasia and early stages of OAC disease and that TLR2 expression may be downregulated during malignant progression. We showed that inhibition of TLR2 with anti-TLR2 neutralising antibody potently inhibits TLR2-mediated cytokine release and TLR2 upregulation in dysplastic and early-stage OAC cells. TLR2 stimulation of BE and OAC cell lines resulted in the secretion of TLR2-stimulatory factors into the conditioned media, which polarised macrophages into TAM-like phenotype.

Discussion
Overall, this study suggests a strong TLR2 involvement in the development and progression of OAC. Thus, inhibition of this receptor, may represent a valid therapy to limit inflammation and disease progression during Barrett’s metaplasia and early-stage OAC patients.

HEPG2 3D SPHEROIDS FOR THE PRECLINICAL ASSESSMENT OF NANOBIOMATERIALS FOR CANCER APPLICATIONS

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Introduction
Predictive in vitro models are of vital importance in both drug and nanomaterial screening alike. Current safety profiling methods fall short when assessing the risk of these materials, with only 60-70% of hepatotoxins being detected from conventional screening methods. The primary reason for this failure is thought to be variation between donors and the rapid decline in function of ex vivo hepatocytes. In addition to this, when cultured in two-dimensional (2D) environments, immortalized hepatocarcinoma cell lines such as HepG2, Huh7 and C3A illustrate an altered phenotype and low functionality in comparison to in vivo human hepatocytes. Because of this, the development of new in vitro pre-clinical assessment methods is of vital importance.

Methods
Non-adherent cell culture plates were used for scaffold-free HepG2 spheroid formation. Spheroids were assessed for a variety of parameters including morphology of 3D structure and spheroid size using Brightfield microscopy, viability using 3D CellTiterGlo assay and liver-specific spheroid functionality using confocal microscopy. Different methods of spheroid formation were also assessed to find the optimal culture conditions. Two-dimensional HepG2 cultures and spheroids were treated with various nanobiomaterials and imaged using Confocal microscopy to compare and contrast between 2D and 3D cell models.

Results
HepG2 spheroids can be easily cultured in scaffold-free environments and remain viable up to 30 days. Cells remain intact in spheroid formation throughout culture period and formation of secondary structures (bile canaliculi) begins at day 4 and structures interconnect around day 18. Compounds penetrate spheroids exogenously, as judged by Doxorubicin treatment. Nanomaterial uptake was assessed in 2D and 3D cell cultures via immunofluorescence staining and confocal microscopy.

Conclusion
Preliminary results indicate that there is potential for in vitro 3D models to bridge the gap between conventional 2D cell cultures and animal modes, and 3D spheroids are now recommended for both drug and nanomaterial screening, as a support for pre-existing 2D testing, and more indicative of response in animal models.
Proffered Papers
Recent technological advances have significantly impacted our ability to identify cancer specific therapeutic vulnerabilities. These advances are providing a foundation for the development of the next generation of targeted, mechanistically anchored cancer therapies. These rationally designed targeted therapies will likely provide major benefits to cancer patients; hopefully combining high clinical efficacy with reduced systemic toxicity. Our work aims to identify novel therapeutic targets in childhood cancers; and to exploit these findings toward the development of new treatments. To do this we are using CRISPR/Cas9-based functional genomic screening approaches to identify molecular vulnerabilities in cancer cells. Moreover, by combining these approaches with cutting-edge drug design we are developing novel small-molecules targeting these newly identified vulnerabilities.

**PERSONALISED TRACKING OF RESPONSE TO NEOADJUVANT CHEMORADIOThERAPY IN LOCALLY ADVANCED RECTAL CANCER PATIENTS**

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**Introduction**

One-third of all colorectal cancers (CRCs) are located in the rectum. The vast majority of rectal cancer patients present with locally advanced rectal cancer (LARC). The standard treatment for LARC is neoadjuvant chemoradiotherapy (NACRT), followed by surgical resection. However, >70% of patients do not achieve a complete pathological response and have high subsequent rates of relapse and death. Currently, there are no known prediction factors that determine response to NACRT based on variables such as gender, age, stage, and tumour location. Therefore, there is an urgent need to identify biomarkers to predict which patients are likely to respond to therapy.

**Methods**

We performed whole exome sequencing (WES), high-depth targeted sequencing, and RNA-sequencing of tumour samples collected from 33 patients prior to, during and after NACRT. Treatment response to NACRT for 26 patients was based on the Royal College of Pathologists tumour regression grading, and patients were classified as good (RCPath A; n=5), intermediate (RCPath B; n=11) or poor (RCPath C; n=10).
Results

WES of pre-treatment tumours revealed mutations in known CRC genes: APC (86% of samples), TP53 (68%), and KRAS (32%). Notably our LARC cohort showed an absence of NRAS driver mutations (TCGA Rectum Adenocarcinoma cohort: 6.6%), and a higher frequency of BRAF mutations (LARC: 10.7%; TCGA: 1.6%).

Analysis of summary genomic burdens showed no significant differences between the response groups in mutational or copy number burden. Transcriptome sequencing of 16 pre-treatment tumours enabled consensus molecular subtyping and microbiome analysis, highlighting a potential difference in Fusobacteria abundance between the response groups. Analysis of matched pre-treatment, on-treatment and post-NACRT tumours allowed personalised tracking of tumour evolution at the genomic level, revealing distinct patterns of evolution and selection in each patient.

Discussion

Our study highlights the in-depth personalised medicine approaches required to survey tumour evolution and response to therapy in LARC and reveals a potential microbial biomarker of response.

Introduction

The molecular pathology of many breast cancer risk factors remains ill-defined. Benign breast disease (BBD) is a heterogeneous group of high risk benign breast cancer precursor lesions. However, mechanisms driving the positive associations between increasing BBD severity and risk of breast cancer are unclear. Microscopic measures of breast epithelial lobules, which involute with aging, have been identified as independent risk markers among women with BBD. To date, they have been primarily quantified using visual assessment. Digital pathology provides an opportunity for automated tools to quantify epithelial lobules, which may also improve understanding of BBD. This study aimed to examine epithelial breast tissue histology using an automated approach among women diagnosed with BBD.

Methods

The epithelial breast tissue composition from whole slide images of image-guided clinical breast biopsies (n=262), among women diagnosed with BBD was assessed using two methods. Firstly using a visual quantification of terminal duct lobular units (TDLU counts/100mm², median acini count/TDLU), metrics inversely associated with epithelial lobular involution, and secondly using a digital pathology...
algorithm that quantified the nuclei count per unit epithelial area (epithelial nuclear density (END)). Ordinal logistic regression models were used to examine relationships between tertiles of TDLU with END measures adjusting for age and body mass index (BMI).

**Results**

TDLU measures were positively associated with increasing tertiles of END (TDLU count/100mm², OR₁: 3.42, 95%CI: 1.87, 6.28; acini count/TDLU, OR₂: 2.40, 95%CI: 1.39, 4.15). However, associations were attenuated when analyses was stratified by BBD severity.

**Conclusion**

These findings suggest that the investigated visual and automated measures of epithelial tissue reflect complementary but different histologic features and quantitative scales. Thus information gained and lost through such approaches must be considered. These findings merit continued evaluation in assessing the cellularity of breast tissue using novel approaches, to understand the etiology and molecular pathology of BBD.

ASSOCIATION OF SERUM ANDROGENS WITH RECURRENCE IN AN ENDOCRINE TREATED BREAST CANCER PATIENT COHORT.

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**Background**

There is strong epidemiological evidence which indicates that estrogens may not be the sole steroid drivers of breast cancer. Understanding individual steroid levels will be critical to evaluating this clinically as it is known that elevated levels of weak androgens are associated with breast cancer risk >2 years prior to cancer detection. We hypothesize that abundant adrenal androgenic steroid precursors, such as androstenedione (4AD), promote an endocrine resistant breast cancer phenotype.

**Methods**

Serum levels of 4AD were evaluated by ELISA in a cohort of breast cancer patients who had failed endocrine therapy (n=42). LC-MS/MS was performed on serum samples from an age, stage and grade matched cohort of patients that were non-recurrent or recurrent on aromatase inhibitor (AI) therapy (n=8). Levels of androgens, progesterone and estradiol were quantified in serum from this cohort pre and post-AI therapy (>12 months). RNA was extracted from AI non-recurrent and recurrent FFPE tumour sections and subjected to analysis by Philips Oncosignal to evaluate activation of AR and ER signalling pathways.

**Results**

In a screen of breast cancer patients with reported sensitivity and resistance to endocrine therapy, ~50% of resistant patients fell outside the normal reference range for 4AD (Signed rank p<0.001). More sensitive LC-MS/MS analysis of an AI sensitive and resistant cohort (n=8) showed a significant increase in levels of 4AD between serum post AI-therapy only in recurrences (p=0.0174). Oncosignal analysis showed an increased ratio of AR:ER gene signalling pathways in patients failing AI therapy (t-test p=0.023).
**Discussion**
Steroid levels are known to be altered by diet, exercise and other lifestyle choices; understanding their potential role in breast cancer development could therefore have wide-ranging implications. This research area has the potential to be extrapolated into a large-scale global study which may have a radical impact on our understanding of breast cancer development.

**ANDROSTENEDIONE MEDIATED METABOLIC ALTERATIONS IN AROMATASE INHIBITOR RESISTANT BREAST CANCER.**

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**Introduction**
There is a major unmet clinical need for effective therapeutic options for the 30% of postmenopausal breast cancer patients whose disease progresses while on aromatase inhibitor (AI) therapy. AI therapy works by diminishing the conversion of circulating androgens into estrogens by >99%, creating a predominantly androgenic steroid environment. Clinical and in vitro evidence from this study suggests that as a mechanism to promote resistance and survival under AI therapy, cancer cells adapt to utilise the adrenal prohormone, androstenedione (4AD).

**Methods**
Metabolic shifts in response to the androgen receptor (AR) ligand 4AD were assessed in isogenic AI sensitive and resistant cell models using a Seahorse XFe96 analyser. To elucidate the mechanism of 4AD induced metabolic alterations a mass spectrometry (LC–MS/MS) experiment targeted at identifying the differential AR interactome in AI resistance cell models was performed. Androgen-mediated, AR protein interactions were validated by co-immunoprecipitation, western blotting and imaging experiments.

**Results**
AI resistant cells display increased mitochondrial respiration coupled with increased number of mitochondria compared to AI sensitive cells. Furthermore, mitochondrial uncoupling enhanced the extracellular acidification rate (ECAR), an indicator of glycolysis, in the presence of 4AD in AI resistant cells. By modelling breast cancer steroid milieu in vitro, our research has elucidated alterations in 52 differential AR interacting proteins specific to AI therapy resistance. IGFBP5 and SLIRP were identified and validated as two specific 4AD mediated AR interactors in AI resistance which are both known to play a role in cellular metabolic processes.

**Discussion**
In this study we have shown metabolic adaptation in AI resistant cells in response to the androgenic steroid environment arising from AI treatment. The AR-interacting proteins identified could be used in the clinic to identify pro-tumorigenic AR as their expression patterns become dysregulated as a consequence of 4AD in AI resistance.
Background
Circulating tumour cells (CTCs) are silent precursors of metastatic disease that utilise various mechanisms to survive in circulation and metastasise to a distal site. Classical CTC detection relies on EpCam affinity-based technologies; however, CTCs are highly heterogeneous and often undergo EMT. Recent research highlights the ability of platelets and neutrophils to ‘cloak’ CTCs and crosstalk to aid in their proliferation and survival in the circulation.

Aims
Assess the role of platelets and neutrophils in the characterisation of CTCs.

Methods
Cell lines: MCF-7 and SKOV-3 cells were exposed to healthy donor isolated platelets (CD42b+/CD62p−) and neutrophils (CD66b+) for 24 h. EMT and immune evasion TaqMan gene assays were performed and flow cytometric analysis following co-culture. Cell proliferation was assayed by MTS assay.

Patient samples: Breast and ovarian patient CTCs and immune cells were isolated from peripheral blood using ClearCell FX microfluidic device. FX isolated cells were immunophenotyped by flow cytometry and single cell sorted using BD FACS Melody for subsequent scRNAseq.

Results
Platelet co-culture alters EpCam, PLEK2, CCL2 and TWIST1 mRNA expression in MCF-7 cells. Platelet and neutrophil co-culture alters EpCam and PD-L1 mRNA and protein expression in SKOV3 cells. Neutrophils co-cultured with cancer cells have increased cell viability, while induction of NETosis increases cancer cell proliferation. CTCs isolated from breast and ovarian patients were EpCam+/E-Cadherin+/CD45- as well as N-Cadherin+/CD45- indicating quasi-mesenchymal transition. CTCs were also identified as PD-L1+/EpCam+/E-Cadherin+/CD45- as well as on N-Cadherin+/CD45-. Isolated single-cell CTCs and CD45+/CD66b+ cells were sorted based on their immunophenotypes for downstream scRNAseq.

Conclusion
Platelets and neutrophils alter the expression of markers used in the identification of CTCs. Neutrophils were found to increase the proliferation of cancer cells as well as increase PD-L1 expression. We identified a heterogeneous population of CTCs across different patients. Molecular scRNAseq signatures will form the basis for identifying the most clinical relevant CTCs in circulation.

1. Jie, X.X., Zhang, X.Y. and Xu, C.J., 2017. Epithelial-to-mesenchymal transition, circulating tumor cells...

DIETARY CHOICES INFLUENCE NATURAL KILLER CELL RESPONSES IN OBESITY

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Introduction
Obesity is one of the leading preventable causes of cancer (1). Natural Killer (NK) cells are early responding effector immune cells with an important role in the anti-cancer immune response (2). Our lab recently showed that obesity causes a profound metabolic defect in NK cells, which may contribute to the increased cancer in obesity (3). However, little is currently known about how dietary choices shape the metabolic landscape of immune cells.

Methods
To investigate how diet shapes NK cell responses, mice were fed a High Fat Diet (HFD) (45%) from different fat sources including plant, dairy, animal and nut based fats. We then challenged the mice with cancer and found that certain HFD accelerated tumour growth, as expected, but surprisingly, some HFD did not compared to Standard Fat Diet (SFD), despite all HFD groups being equally as obese. We isolated NK cells from mice in the different groups and profiled their metabolic and functional states.

Results
Mice on a butter diet developed significantly larger tumours, which correlated with metabolic and functional paralysis of NK cells. Surprisingly, mice fed a palm oil diet displayed no obesity-associated acceleration of tumour growth, despite being equally as obese. In addition, NK cells isolated from palm oil fed mice were metabolically and functionally comparable to mice on a SFD. Feeding and diet absorption did not account for the differences observed.

Discussion
We are now using proteomics and metabolomics to investigate the differential effects of dietary fats on systemic and intracellular (immune cell and cancer) metabolism. This research will contribute to our understanding of how dietary nutrients shape anti-cancer immune surveillance.

A POTENTIAL ROLE FOR IMMUNE CHECKPOINT INHIBITORS IN COMBINATION WITH CHEMOTHERAPY FOR TREATING OESOPHAGEAL ADENOCARCINOMA PATIENTS

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Introduction
Immune checkpoint (IC) expression was profiled in oesophageal adenocarcinoma (OAC) patients to identify novel therapeutic targets, as more than two-thirds of patients fail to respond to chemoradiotherapy.

Methods
Expression of a range of IC ligands and receptors were investigated on tumour-infiltrating and peripheral blood T-cells in OAC patients ex vivo by flow cytometric analysis. The effect of clinically relevant combination chemotherapy regimens FLOT, CROSS and MAGIC on the expression of ICs and stemness in OAC cells was determined by flow cytometric analysis.

Results
PD-1, CTLA-4, LAG-3, TIGIT, TIM-3, CD160, PD-L1 and PD-L2 were expressed on tumour-infiltrating and peripheral blood T-cells, determined by flow cytometric analysis. PD-1, CTLA-4, LAG-3, TIGIT, TIM-3 and PD-L2 was expressed at significantly higher levels on tumour-infiltrating T-cells than peripheral blood T-cells ex vivo.

Clinically relevant chemotherapy regimens FLOT and CROSS upregulated HMGB1 and calreticulin damage-associated molecular patterns on the surface of OAC cells in vitro, identifying an immunostimulatory role for chemotherapy in OAC.

Conclusion
This data demonstrates the immunostimulatory and immunosuppressive effects of clinically relevant chemotherapy regimens in OAC and identifies a link between chemotherapy and immune-resistance. Our data highlights that careful consideration must be given when combining IC inhibitors with chemotherapy to optimise clinical outcomes.
In the past 5 years several nanotechnology-based solutions have been developed and pre-clinically verified as radiosensitisers and advanced drug delivery system for cancer treatment. More recently, clinical investigation has advanced in two combination treatments where Gold Nanoparticle (GNP) and Iron Oxide Nanoparticles (IONP) have been exploited as adjuvants. This talk will focus on presenting the latest achievements of the LBCAM lab at TTMI, as part of two large European Commission research projects, and will put them in an international perspective on where we stand on the clinical translation of this advanced cancer treatments.

**RADIATION INDUCED BYSTANDER EFFECT (RIBE) INDUCTION USING HUMAN EX VIVO EXPLANTS INDUCES SIGNIFICANT CHANGES IN THE TISSUE SECRETOME, IMMUNE CELL FUNCTION AND BYSTANDER CELLULAR METABOLISM.**

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**Introduction**
Neoadjuvant-chemoradiotherapy is standard of care for locally advanced rectal cancer, however only 15-27% of patients achieve a complete response to treatment. Mechanisms controlling this resistance are largely unknown. Radiation-induced bystander effect (RIBE) occurs where cells that have not been irradiated behave as if they have resulting from signal propagation from irradiated cells. We profiled the effect of ex vivo RIBE in rectal cancer on inflammatory mediators, immune cell function and bystander cell metabolism for the first time.

**Methods**
Human rectal cancer and normal rectal tissue were cultured as ex vivo explants and either mock-irradiated or received 1.8Gy radiation. Following 24hours, the tissue conditioned media was screened for 54 inflammatory mediators to determine if inflammatory secretions differ between rectal cancer and normal rectal tissue following RIBE induction. The effect of RIBE on bystander rectal cancer SW837 cell metabolism was investigated using Seahorse. The effect of RIBE on dendritic cell (DC) maturation was assessed by flow cytometry measuring CD86, CD80, CD83, PD-L1 and CD11c.
**Results**
Radiation increases the secretion of MDC, GM-CSF, IL-15 and IL-17A (p<0.05) in normal rectal tissue and may increase IL-15, TNF-β and MIP-1α in rectal cancer tissue (p=0.05). Ex vivo RIBE-induction caused significant metabolic alterations in bystander SW837 cells, specifically reductions in oxidative phosphorylation and glycolysis. RIBE-induction in our ex vivo rectal cancer model significantly enhanced DC maturation markers.

**Discussion**
RIBE-induction ex vivo causes significant alterations in the inflammatory secretome in both normal and malignant rectal tissue along with significant metabolic alterations in bystander cellular metabolism. Ex vivo RIBE-induction in rectal cancer tissue enhances DC maturation. This may offer greater understanding of the effects of RIBE on inflammation and metabolism and the connection with treatment response in rectal cancer patients.