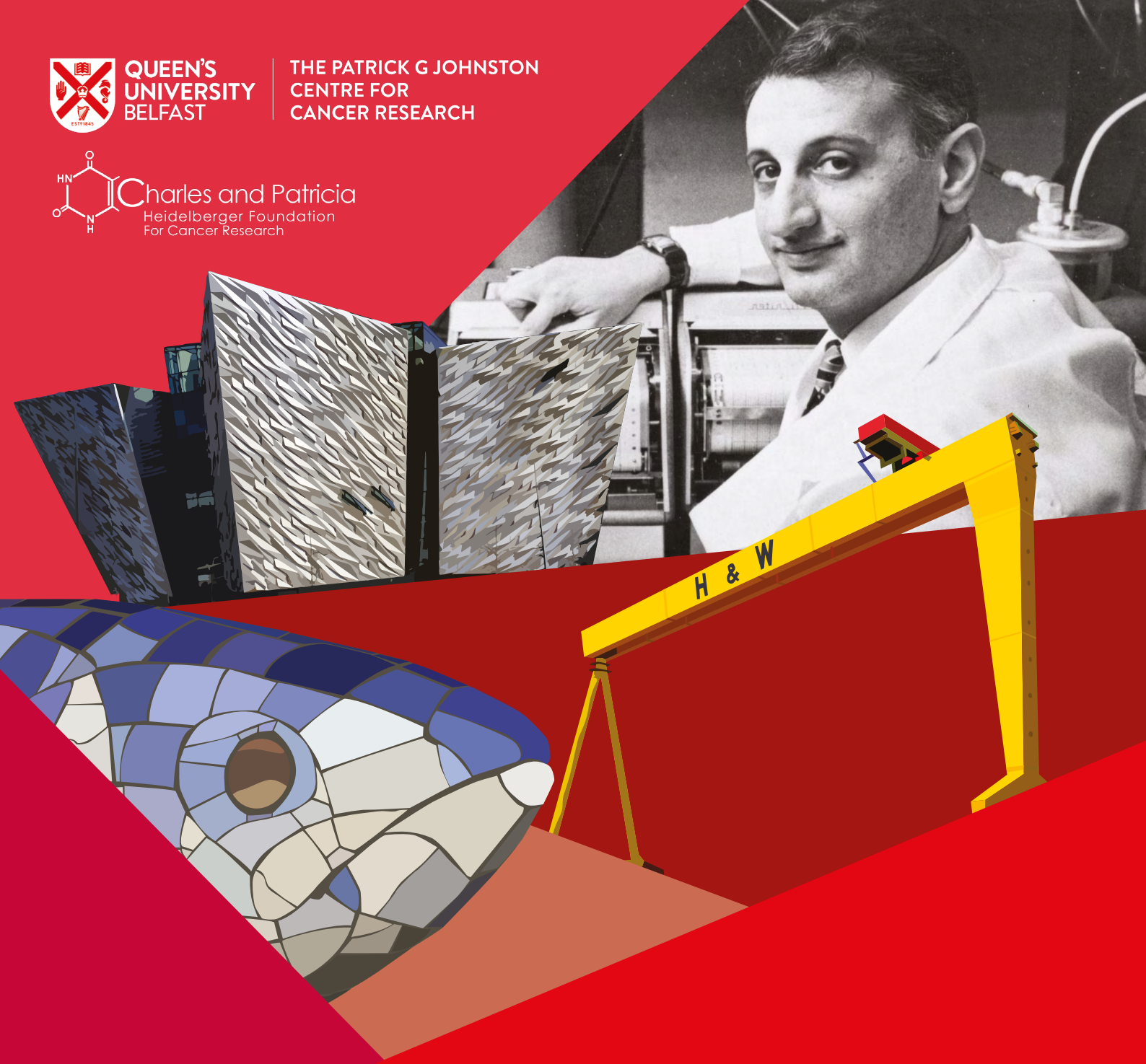
QUEEN'S UNIVERSITY BELFAST

THE PATRICK G JOHNSTON CENTRE FOR CANCER RESEARCH

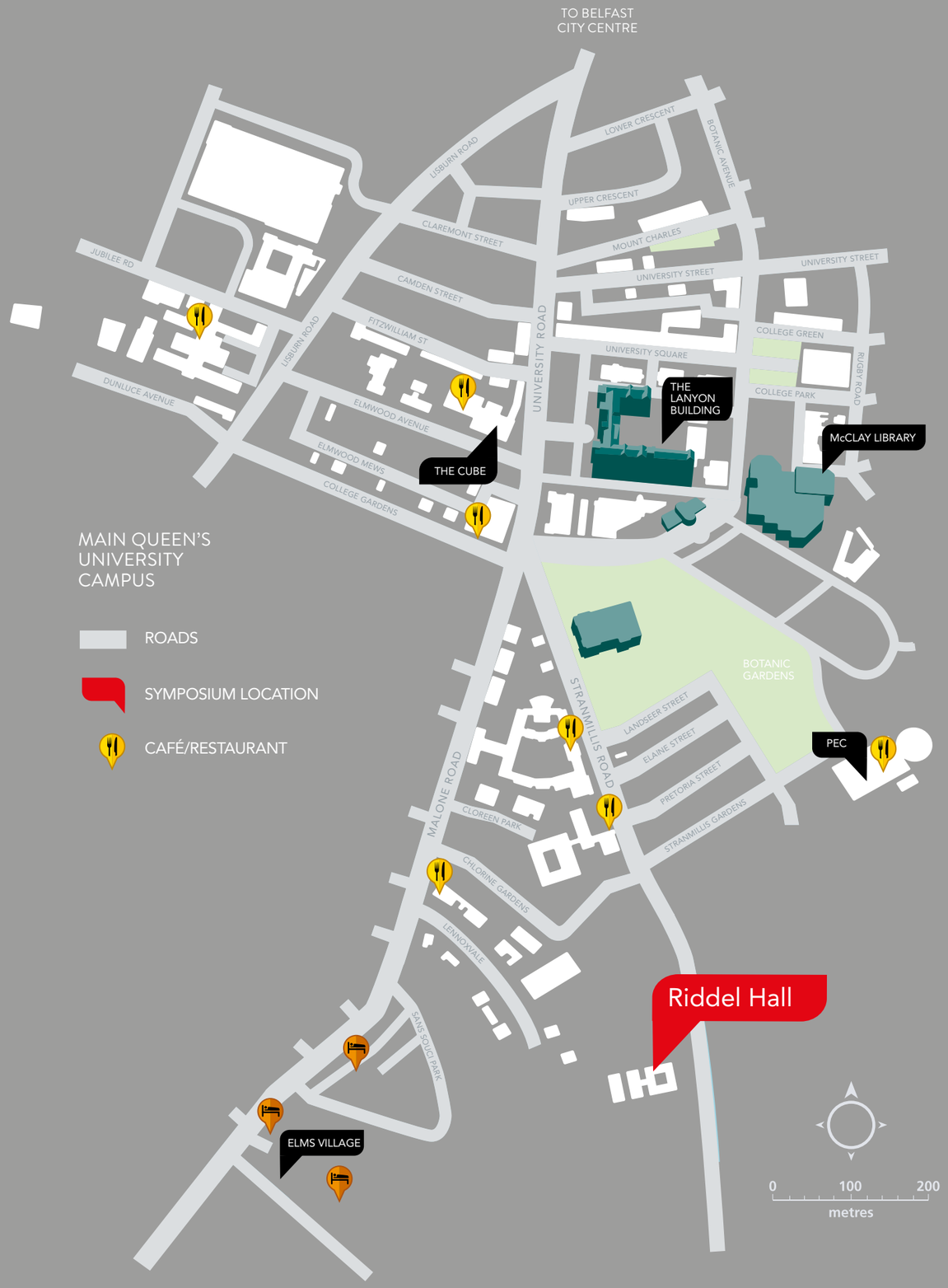
Charles and Patricia
Heidelberger Foundation
For Cancer Research



26th

International Charles Heidelberger Symposium on Cancer Research

October 2-4, 2024
Queen's University Belfast
Riddel Hall
Northern Ireland, UK



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Welcome

It is with great pleasure that I welcome you to the 26th International Charles Heidelberger Symposium on Cancer Research, held for the first time in the United Kingdom, and specifically, on the island of Ireland. We are honoured to host this prestigious event at Queen's University Belfast, an institution renowned for its commitment to advancing the frontiers of cancer research. This year's symposium represents a significant milestone, being the first time, the symposium has taken place in this region, offering an unparalleled opportunity to highlight the outstanding contributions of cancer researchers from both the UK and Ireland to the global scientific community.

This year's symposium is particularly special as it is supported by the Patrick G. Johnston Centre for Cancer Research, named in honour of the late Professor Patrick G. Johnston, an inspiring leader and a visionary in cancer research and translational medicine. Professor Johnston, affectionately known as Paddy, was a towering figure in oncology, renowned for his pioneering work in drug resistance and cancer therapeutics. As a driving force behind the modernization of cancer services across Northern Ireland, he led the development of the state-of-the-art Clinical Cancer Centre and the Centre for Cancer Research and Cell Biology (CCRCB), which later became the Patrick G. Johnston Centre for Cancer Research. Paddy's legacy continues to inspire and guide our efforts to translate scientific discovery into clinical practice for the benefit of patients worldwide. His remarkable achievements, including his leadership of the Northern Ireland Comprehensive Cancer Services programme and his role in establishing the NCI-All Ireland Cancer Consortium, have had a profound and lasting impact on cancer care and research.

I look forward to the meaningful discussions and collaborations that will emerge as we work together toward our common goal of transforming cancer treatment for patients everywhere.

This year's symposium, with its theme "Translational Cancer Therapeutics: Bridging Basic Research and Clinical Applications," builds upon the foundation laid by both Dr Charles Heidelberger and Professor Johnston. The symposium will bring together leading experts in carcinogenesis, tumour biology, precision oncology, and novel therapeutics, with the shared goal of turning laboratory breakthroughs into real-world cancer treatments. This focus on translational research reflects Professor Johnston's passion for ensuring that scientific advancements directly improve patient care and outcomes.

The International Charles Heidelberger Symposium on Cancer Research continues its tradition of celebrating the life and legacy of Dr Charles Heidelberger, whose pioneering work, particularly the development of 5-fluorouracil, laid the foundation for modern chemotherapy. The symposium has grown to become a vital platform for sharing cutting-edge research and fostering international collaborations that are essential for accelerating advancements in cancer treatment and prevention.

As we gather to share knowledge and explore the latest developments in cancer research, we honour both Charles Heidelberger and Paddy Johnston's vision of a collaborative, interdisciplinary approach to tackling cancer. Their dedication to fostering partnerships across borders and disciplines mirrors the spirit of this symposium, which has, for over two decades, connected cancer researchers from around the globe in pursuit of innovative solutions to one of the world's most pressing health challenges.

Over the course of the next few days, we will explore how scientific insights can be translated into innovative cancer therapies, with the goal of overcoming therapeutic resistance and improving the lives of cancer patients worldwide.

Our program is filled with an exciting array of lectures, discussions, and poster presentations that promise to stimulate thought and encourage collaboration across disciplines. In particular, we are eager to highlight the contributions of early-career scientists, whose fresh perspectives and innovative approaches are vital to the future of cancer research.

I extend my heartfelt thanks to the Charles and Patricia Heidelberger Foundation for Cancer Research for their continued support, and to all the participants who have contributed to the success of this event. Your presence here is a testament to the enduring legacy of Charles Heidelberger and Patrick Johnston, whose contributions have shaped the field of oncology and continue to drive progress toward eradicating cancer.

Sincerely,

Dr Robert Ladner
Chair, Organizing Committee
26th International Charles Heidelberger Symposium on Cancer Research
Queen's University Belfast

Introductory Remarks

The Charles Heidelberger Symposia are annual cancer research meetings organized to honour the remarkable contributions of Dr Charles Heidelberger, a distinguished former President of the American Association for Cancer Research and a member of the National Academy of Sciences of the USA.

Dr Heidelberger was a pioneering figure in the fields of carcinogenesis and cancer chemotherapy. Among his most notable achievements was the synthesis of 5-fluorouracil, one of the first rationally designed chemotherapeutic agents, which continues to play a critical role in cancer treatment today. His laboratory was also instrumental in demonstrating how polycyclic aromatic hydrocarbons (PAHs) are metabolized by cytochrome P450 enzymes, leading to their covalent binding to DNA, RNA, and proteins. These interactions were shown to induce mutations and trigger both morphological and malignant transformation in cells, using the C3H/10T1/2 mouse embryo cell model developed by his team.

The 26th International Charles Heidelberger Symposium on Cancer Research continues the tradition of inviting the most esteemed cancer researchers from laboratories and hospitals around the world. With participation from leading scientists and clinicians across North America, South America, Europe, and Asia, including several of Professor Heidelberger's former postdoctoral fellows, we aim to foster an advanced platform for the exchange of cutting-edge ideas and collaborative efforts in cancer research.

We are confident that the symposium will provide a unique opportunity to drive forward discussions and collaborations on the latest developments in our field, reflecting the legacy of both Dr Heidelberger and the many researchers who have been inspired by his groundbreaking work.

Joseph R Landolph Jr
Co-Chair, International Organizing Committee
26th International Charles Heidelberger Symposium on Cancer Research
Queen's University Belfast

In 1985, Dr. Eliezer Huberman of Argonne National Laboratory organized the first International Charles Heidelberger Symposium on Cancer Research at Argonne National Laboratory, in Argonne, Illinois, USA.

To date, the symposium has been held in the following locations:

1985 1st International Heidelberger Symposium, Argonne, Illinois, USA
1987 2nd International Heidelberger Symposium, Honolulu, Hawaii, USA
1989 3rd International Heidelberger Symposium, Kyoto, Japan
1991 4th International Heidelberger Symposium, Marina Del Rey, CA, USA
1994 5th International Heidelberger Symposium, Essen, Germany
1996 6th International Heidelberger Symposium, Honolulu, Hawaii, USA
1997 7th International Heidelberger Symposium, Gunzburg, Germany
2000 8th International Heidelberger Symposium, Marina Del Rey, CA, USA
2002 9th International Heidelberger Symposium, Bergen, Norway
2004 10th International Heidelberger Symposium, Yokohama, Japan
2006 11th International Heidelberger Symposium, Phitsanulok, Thailand
2007 12th International Heidelberger Symposium, Jerusalem, Israel
2007 13th International Heidelberger Symposium, New York City, NY, USA
2008 14th International Heidelberger Symposium, Urumqi, China
2010 15th International Heidelberger Symposium, Phitsanulok, Thailand
2010 16th International Heidelberger Symposium, Coimbra, Portugal
2011 17th International Heidelberger Symposium, Xi'an, China
2012 18th International Heidelberger Symposium, Ulm, Germany
2013 19th International Heidelberger Symposium, Kagoshima, Japan
2014 20th International Heidelberger Symposium, Arica, Chile
2016 21st International Heidelberger Symposium, Moscow, Russia
2017 22nd International Heidelberger Symposium, Urumqi, China
2019 23rd International Heidelberger Symposium, Sardinia, Italy
2022 24th International Heidelberger Symposium, Arica, Chile
2023 25th International Heidelberger Symposium, Hiroshima, Japan
2024 26th International Heidelberger Symposium, Belfast, Northern Ireland, UK

26th International Charles Heidelberger Symposium on Cancer Research

General Information

Date: October 2-4, 2024

Venue: **Riddel Hall**
Queen's University Belfast
185 Stranmillis Road
Belfast, BT9 5EE
Northern Ireland, UK

MEMBERS OF THE INTERNATIONAL ORGANIZING COMMITTEE

Robert D Ladner, **PhD**
Chair, (Founder and CEO of CV6 Therapeutics and Reader (Associate Professor), Patrick G Johnston Centre for Cancer Research, Queen's University Belfast)

Joseph R Landolph, **Jr**, **PhD**
Co-Chair and Secretary, *Treasurer*, and Member of the Board of Directors of the Charles and Patricia Heidelberger Foundation for Cancer Research (Associate Professor of Molecular Micro-biology and Immunology and Associate Professor of Pathology, Member, USC/Norris Comprehensive Cancer Center Keck School of Medicine, Associate Professor of Molecular Pharmacology and Toxicology, School of Pharmacy - University of Southern California)

Eliezer Huberman, **PhD**
Co-Chair (President and Member of the Board of Directors of The Charles and Patricia Heidelberger Foundation for Cancer Research and founder, scientific director, and CEO of Novadrug LLC)

Additional Member:
Wei Li, **PhD**
(Professor and Director of Genetics, Molecular & Cell Biology Graduate Program, Department of Dermatology and USC-Norris Comprehensive Cancer Center - The University of Southern California, Keck Medical Center)

MEMBERS OF THE LOCAL ORGANIZING COMMITTEE

Robert D Ladner, **PhD**
Chair, (Founder and CEO of CV6 Therapeutics and Reader, Patrick G Johnston Centre for Cancer Research, Queen's University Belfast)

Melissa LaBonte Wilson, **PhD**
Co-Chair (Senior Lecturer (Associate Professor), Patrick G. Johnston Centre for Cancer Research – Queen's University Belfast)

Additional Members:
Daniel Longley, PhD
(Director, Patrick G Johnston Centre for Cancer Research School of Medicine, Dentistry and Biomedical Sciences - Queen's University Belfast)

Rachael McGuickin
(Director of Business Development, Sustainability and Transformation - Visit Northern Ireland)

Running Order

October 2nd, 2024

Tea/Coffee/Pastry on arrival @ QUB Riddel Hall

8:00 - 9:00 — **REGISTRATION OPEN**

9:00 - 9:45 — **WELCOME**

Chair
Robert D Ladner, PhD

Eliezer Huberman, PhD
(President and Member of the Board of Directors of The Charles and Patricia Heidelberger Foundation for Cancer Research and founder, scientific director, and CEO of Novadrug LLC)

Joseph R Landolph, Jr., PhD
(Associate Professor of Molecular Microbiology and Immunology and Associate Professor of Pathology, Member, USC/Norris Comprehensive Cancer Center Keck School of Medicine, Associate Professor of Molecular Pharmacology and Toxicology, School of Pharmacy – University of Southern California)

9:45 - 11:00 — **HEALTH AND LIFE SCIENCE CANCER RESEARCH ACROSS THE ISLAND OF IRELAND**

Chair
Robert D Ladner, PhD

Daniel Longley, PhD
'Johnston Centre/Transformation of Cancer Care in NI'
(Director, Patrick G Johnston Centre for Cancer Research School of Medicine, Dentistry and Biomedical Sciences - Queen's University Belfast)

Mark Lawler, PhD
'Cancer Knows No Borders: From the Tripartite Agreement to the All-Island Cancer Research Institute and Beyond'
(Associate Pro-Vice-Chancellor and Professor of Digital Health, Chair in Translational Cancer Genomics, Patrick G. Johnston Centre for Cancer Research – Queen's University Belfast; Scientific Director DATA-CAN The UK's Health Data Research hub for Cancer and Chair of the International Cancer Benchmarking Partnership)

William Gallagher, PhD
'Cancer Knows No Borders: From the Tripartite Agreement to the All-Island Cancer Research Institute and Beyond'
(Full Professor of Cancer Biology and Co-Lead of the All-Island Cancer Research Institute, University College Dublin)

Robert D Ladner, PhD
'USA-Northern Ireland Connections and Transforming Cancer Care'
(Founder and CEO of CV6 Therapeutics and Reader (Associate Professor), Patrick G Johnston Centre for Cancer Research, Queen's University Belfast)

11:00 - 11:30 — **TEA/COFFEE BREAK**

11:30 - 12:00	POSTER SESSION I

Leanne Bradley
'Identification of novel immune activating agents for rationalised combination therapy in breast cancer'
Patrick G Johnston Centre for Cancer Research; Queen's University Belfast

Alessandro Cazzolla
'Enhancing chemotherapeutic efficacy through liposomal nanoparticles and ultrasound'
Technological University Dublin

Sarah Chambers
'18-colour immunological profiling of a syngeneic tumour model of prostate cancer after delivery of a radio sensitising molecular targeted gold nanoparticle'
School of Pharmacy; Queen's University Belfast

Jie Feng
'Drug-Induced activation of the ISR/eIF2a signaling axis mitigates metabolic radio sensitisation'
School of Pharmacy; Queen's University Belfast

Oscar Pooley
'Countering the proteinase activated receptor 1 (PAR-1) pro-tumour phenotype using a novel nanotherapeutic approach
School of Pharmacy; Queen's University Belfast

Mary-Kate Riley
'Modelling longitudinal impact of standard-of-care treatment on gene expression in colorectal cancer PDX models to identify novel vulnerabilities'
Patrick G Johnston Centre for Cancer Research; Queen's University Belfast

Michael Ryan
'In vitro modelling of ovarian cancer cell lines for the development of novel liquid biopsy tests'
School of Pharmacy; Queen's University Belfast

Tianxin Liu
'Development of a Novel Targeting Antimicrobial Peptide Conjugate for Selective Membrane Disruption in Non-Receptor-Targetable Cancer Cells'
School of Pharmacy; Queen's University Belfast

Tongchuan Wang
'Mannose enhances radiosensitivity in HPV-Negative head and neck cancer via metabolic reprogramming and impaired DNA damage repair'
School of Pharmacy; Queen's University Belfast

Arporn Wangwiwatsin
'Extrachromosomal circular DNA in cholangiocarcinoma: Exploring potential functions in RAS/BRAF signalling'
Khon Kaen University, Thailand

Janith Wanigasekara
'Novel therapeutic approaches for brain cancer treatment using 3D tumor spheroid and co-cultured multicellular tumor models'
Technological University Dublin

12:00 - 13:00	LUNCH

13:00 - 15:00	Session 1 UNRAVELLING CARCINOGENESIS: FROM INITIATION TO METASTASIS

Chair(s)
Max Costa and Leanne Bradley

Yoshinori Murakami, MD, PhD
'Construction of a new disease prevention digital twin by integrating multi-layered bioinformation'
(Professor, Department of Molecular Pathology, Institute of Advanced Medical Science; Nippon Medical School, Tokyo, Japan)

Cristina Branco, PhD
'Chemotherapy-induced microvascular remodeling and impact on (pre) metastatic microenvironment'
(Senior Lecturer, Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, UK)

Wei Li, PhD
'Heat Shock Protein-90 in Cancer Clinical Trials: History, Presence and Future'
(Professor, Director of Genetics, Molecular & Cell Biology Graduate Program, USC-Norris Comprehensive Cancer Center, USA)

Gloria M Calaf, PhD
'Unravelling breast carcinogenesis: From Initiation to Metastasis: Role of estrogen, acetylcholine and prolactin in breast carcinogenesis'
(Professor, Instituto de Alta Investigación, Universidad de Tarapacá, Chile)

15:00 - 15:30	TEA/COFFEE BREAK

15:30 - 17:00	Session 2 CANCER GENOMICS AND PRECISION MEDICINE: PERSONALIZING CANCER MEDICINE

Chair(s)
Wei Li and Parisa Naeli

Manuel Salto-Tellez, MD
'Digital Pathology, Artificial Intelligence and Multimodal Analysis'
(Clinical Professor, Chair of Molecular Pathology, Patrick G Johnston Centre for Cancer Research; Clinical Consultant Pathologist; Lead of QUB Precision Medicine Centre of Excellence; Queen's University Belfast, UKProfessor on Integrative Pathology; Institute for Cancer Research (ICR), London)

Brent Harris, MD, PhD
'Update on Senescence and Neurodegeneration'
(Director of Neuropathology, Georgetown University Medical Centre, USA)

Richard Kennedy, MD, PhD
'20 Years of Diagnostic Development: What have we learnt? What's Next?'
(Global VP Biomarker Development and Medical Director, Almac Group; Professor, Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, UK)

Paul Mullan, PhD
'The development of novel liquid biopsy assays for the improved clinical management of poor outcome cancers'
(Professor, Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, UK; Co-founder GenoME Diagnostics)

October 3rd, 2024

Tea/Coffee/Pastry on arrival @ QUB Riddel Hall

8:00 - 9:00 — **REGISTRATION OPEN**

9:00 - 10:00 — **KEYNOTE LECTURE**

Ruth Plummer, MD, PhD

Chair
Vicky Coyle

'Translational Research: From Bench to Bedside in Cancer Treatment – experience of academic drug discovery'

(Clinical Professor of Experimental Cancer Medicine, Translational and Clinical Research Institute; Newcastle University, UK)

10:00 - 11:30 — **Session 3**
TRANSLATIONAL RESEARCH: FROM BENCH TO BEDSIDE IN CANCER TREATMENT

Chair(s)
Kienan Savage and Niall Byrne

Watcharin Loilome, PhD

'Combating Cholangiocarcinoma in Thailand: Opportunities and Challenges'

(Associate Professor, Molecular Oncology; Director of Cholangiocarcinoma Research, Khon Kaen University, Thailand)

Udai Banerji, MD

'Exploration of combinations and sequences of administration of anticancer drugs to improve outcomes'

(Deputy Director of Drug Development Unit, Professor of Molecular Cancer Pharmacology; Institute of Cancer Research and The Royal Marsden Hospital NHS Foundation Trust, UK)

Vicky Coyle, MD

'Overcoming chemotherapy resistance in metastatic colorectal cancer through restoration of apoptotic function'

(Clinical Professor, Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, UK)

Roisin Connolly, MD

'Translational Breast Cancer Research; Opportunities & Challenges'

(Director Cancer Research and Professor Gerald O'Sullivan Chair, Cancer Research, University of College Cork and Cork University Hospital, Ireland)

11:30 - 11:45 — **TEA/COFFEE BREAK**

11:45 - 13:15 — **Session 4**
5-FLUOROURACIL: HONOURING A PIONEER IN CANCER THERAPY AND EXPLORING FUTURE AVENUES

Chair(s)
Udai Banerji and Ally-Jo Emerson

Bruce Chabner, MD

'Charles Heidelberger and the Legacy of 5-FU: A Historical Journey and Its Lasting Impact on Cancer Treatment'

(Director of Clinical Research, Massachusetts General Hospital Cancer Center, USA)

Emma Kerr, PhD

'Mitochondrial metabolism: a chemotherapy-imposed vulnerability in colorectal cancer'

(Senior Lecturer Cancer Metabolism, Cancer Research UK Werth Trust, Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, UK)

Robert D Ladner, PhD

'Targeting Uracil-DNA Biology: Inhibition of dUTPase transforms standard of care therapeutics through DNA uracilation'

(Founder and CEO of CV6 Therapeutics, Reader (Associate Professor), Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, UK)

Richard Wilson, MD

'A Modular, First-in-Human Study of the dUTPase Inhibitor CV6-168 in Combination with 5-Fluorouracil.'

(Professor of Gastro-Intestinal Oncology, University of Glasgow, UK)

13:15 - 12:45 — **LUNCH**

October 4th, 2024

Tea/Coffee/Pastry on arrival @ QUB Riddel Hall

8:00 - 9:00 — **REGISTRATION OPEN**

9:00 - 10:15 — **Session 5**
GENOMIC INSTABILITY AND CANCER: EXPLORING THE IMPACT OF DNA DAMAGE

Chair(s)
Gloria Calaf and Connor Brown

Kienan Savage, MD, PhD
'Optimizing chemo-immunotherapeutic combinations in breast cancer'
(Professor of Molecular Oncology, Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, UK)

David K Ann, PhD
'Lessons Learned from PARPi'
(Professor, Diabetes Complications and Metabolism; Dean, Irell and Manella Graduate School of Biological Sciences, Beckman Research Institute; City of Hope, USA)

Sean Rudd, PhD
'Towards precision cancer medicine with nucleoside analogues'
(Principal Researcher and Group Leader; Department of Oncology- Pathology; Science For Life Laboratory (SciLifeLab); Karolinska Institutet, Sweden)

10:15 - 11:15 — **EARLY CAREER SHOWCASE I**

Chair
Emma Kerr

Tilly Downs
'Can metabolic reprogramming alter T cell ability to kill lung tumour cells?'
(Patrick G Johnston Centre for Cancer Research - 3rd Year PhD Student)

Cory Fines
'STEALTH: Silent technology to deliver dngineered antigens for a lethal TH1 response against mutant p53 in TNBC'
(School of Pharmacy - Post-doctoral Research Fellow)

Kathryn Brown
'Characterisation of quantitative imaging biomarkers for inflammatory and fibrotic radiation-induced lung injuries using preclinical radiomics'
(Patrick G Johnston Centre for Cancer Research - Post-doctoral Research Fellow)

Fatemeh Mirzadeh Azad
'Epigenetic reprogramming in drug-tolerant persistent colorectal cancer cells'
(Patrick G Johnston Centre for Cancer Research - Post-doctoral Research Fellow)

Tim O'Brien
'Enhancing the neoadjuvant treatment of rectal cancer by targeting Inhibitor of Apoptosis Proteins (IAPs)'
(Patrick G Johnston Centre for Cancer Research - 3rd Year PhD Student)

Victoria Cairnduff
'Understanding Barrett's oesophagus: Insights from a population-based Barrett's oesophagus register'
(Centre for Public Health - Post-doctoral Research Fellow)

11:15 - 11:45 — **TEA/COFFEE BREAK**

11:45 - 12:30 — **EARLY CAREER SHOWCASE II**

Chair
Emma Kerr

Francisco Liberal
'The majority of DNA repair deficiencies do not alter the correlation between relative biological effectiveness (RBE) and linear energy transfer (LET) in CRISPR-edited cells'
(Patrick G Johnston Centre for Cancer Research - Post-doctoral Research Fellow)

Syed Umbreen
'Using Organoids as a Patient Avatar to support the development of liquid biopsy-based assays'
(School of Pharmacy - Post-doctoral Research Fellow)

Lydia Roet
'The cancer-associated SF3B1^{K700E} spliceosome mutation confers enhanced susceptibility to SMAC mimetics'
(Patrick G Johnston Centre for Cancer Research - Post-doctoral Research Fellow)

Scott Monteith
'Exploiting 5FU-Induced vulnerabilities in colorectal cancer'
(Patrick G Johnston Centre for Cancer Research - 3rd Year PhD Student)

12:30 - 13:30 — **LUNCH**

13:30 - 14:00 POSTER SESSION II

Bayan Alkhaldi
'The influence of hedgehog (Hh) signaling in modulating the radiosensitivity of Glioblastoma tumour models'
School of Pharmacy; Queen's University Belfast

Connor Brown
'Investigating cholesterol metabolism as a chemotherapy-induced metabolic vulnerability in colorectal cancer models'
Patrick G Johnston Centre for Cancer Research; Queen's University Belfast

Jiamei Fu
'Nintedanib alleviates radiation-related severe lung injury by remodeling immune microenvironment and inhibiting fibrogenic EMT progression'
School of Medicine, Tongji University, Shanghai, China

Poramate Klanrit
'Development of in vitro 3D cholangiocarcinoma model for personalized drug evaluation'
Khon Kaen University, Thailand

Shauna McClelland
'Targeting CXCR2 and cytokine interactions in the prostate tumour microenvironment: Implications for novel cancer therapies'
Patrick G Johnston Centre for Cancer Research; Queen's University Belfast

Ethna McFerran
'Skin in The Game: The cost consequences of skin cancer diagnosis, treatment and care in Northern Ireland'
Patrick G Johnston Centre for Cancer Research; Queen's University Belfast

Lydia McQuoid
'Early insights into novel AuNPs and the radiation-induced bystander effect'
School of Pharmacy; Queen's University Belfast

Xiyuan Qi
'Discovery and investigation of the mechanisms of synergy between Pol I inhibitors and 5-florouracil in colorectal cancer cell models'
School of Biological Sciences; Queen's University Belfast

Zelin Tan
'Phosphomannose-isomerase gene expression as a novel radiosensitising target in pancreatic cancer'
School of Pharmacy; Queen's University Belfast

Yaqin Zhou
'Investigation and therapeutic exploration of the epigenetic mechanisms underpinning the emergence of Drug-Tolerant Persister (DTP) cells in colorectal cancer'
Patrick G Johnston Centre for Cancer Research; Queen's University Belfast

14:00 - 15:00 Session 6 ADVANCES IN CANCER BIOLOGY

Chair(s)
Brent Harris and Maggie Barros

Miwako Kato Homma, PhD
'Cell cycle-dependent activation and genomic recruitment of protein kinase CK2: a prognostic factor for cancer recurrence.'
(Associate Professor, Department of Biomolecular Science, Fukushima Medical University, Japan)

Tim Harrison, PhD
'Exploiting Engineered Binding Domains in Next Generation Antibody-Drug Conjugate Design'
(McClay Professor of Medicinal Chemistry, Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, UK; Vice President Drug Discovery, Almac Discovery)

Christopher Scott, PhD
'Novel approaches to developing antibody targeted chemotherapies'
(Dean of Research, School of Medicine Dentistry and Biomedical Sciences; Professor, Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, UK)

15:00 - 16:30 Session 7 METAL AND RADIATION BIOLOGY

Chair(s)
Watcharin Loilome and Fancisco Liberal

Joseph R. Landolph Jr., PhD
'Insoluble Nickel (II) Compounds Induce Mutations in Proto-Oncogenes/ Other Genes, Deletions of Genes, Amplifications of Proto-Oncogenes (Ect-2)/Other Genes, and Differential Expression of 150 Genes in C3H10T1/2 Mouse Mesenchymal Cell Lines, Leading to Morphological/ Neoplastic Transformation of 10T1/2 Cells'
(Associate Professor of Molecular Microbiology and Immunology, Pathology, and Pharmacology & Toxicology, University of Southern California, USA)

Max Costa, PhD
'Arsenic and Chromate cause methylation of MEG3 to induce carcinogenesis'
(Professor Environmental Medicine, Department of Medicine, New York University Grossman School of Medicine, USA)

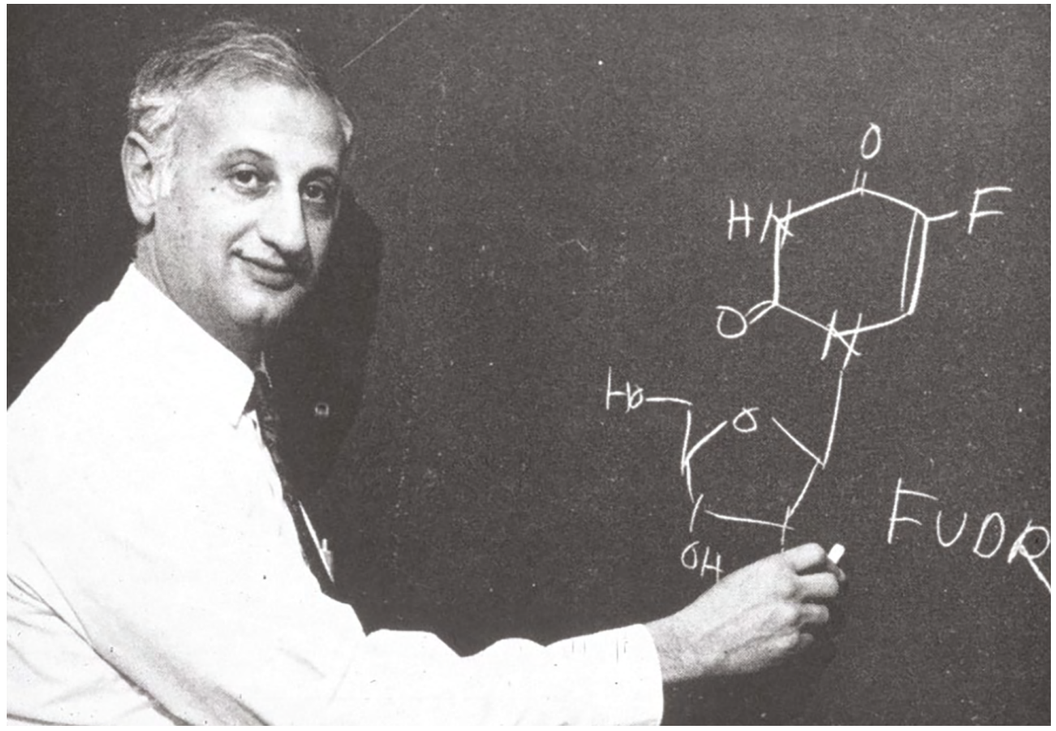
Joe O'Sullivan, MD, PhD
'Molecular Radiotherapy in Advanced Prostate Cancer- The current State-of-the-art and emerging opportunities'
(Clinical Professor of Radiation Oncology, Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, UK)

Arul Veerappan, PhD
'Polyadenylation of canonical histone H3.1 in bisphenol associated carcinogenesis'
(Assistant Professor, Division of Environment Medicine, New York University Grossman School of Medicine, USA)

16:30 - 17:00 MEETING CLOSING

Robert D Ladner, PhD
Joseph R Landolph, Jr, PhD

The Life and Achievements of Dr Charles Heidelberger in Cancer Science



Dr Charles David Heidelberger
December 20, 1920 - January 18, 1983

Early Life and Education

Dr Charles David Heidelberger was born on December 23, 1920, in New York City into a scientifically distinguished family. His father, Professor Michael Heidelberger, was a renowned immunochemist known as the “Father of Immunochemistry.” Growing up in this intellectually vibrant environment, Charles was exposed to science from an early age, developing a keen interest in the natural sciences. His early education took place at the Birch-Wathen School, where he excelled academically and participated in music, drama, and journalism.

Heidelberger was admitted to Harvard College in 1937, where he pursued a degree in chemistry, graduating with a Bachelor of Science in 1942. He continued his graduate studies at Harvard, earning a Master of Science (1944) and a Ph.D. in Organic Chemistry (1946) under the mentorship of Professors Louis and Mary Fieser, prominent chemists known for their work on carcinogenic compounds. His Ph.D. thesis, which focused on the synthesis of naphthoquinones, was influenced by war-related research efforts and laid the groundwork for his future studies in chemical carcinogenesis.

Postdoctoral Research and Early Career

After completing his PhD, Dr. Heidelberger joined the laboratory of Nobel laureate Melvin Calvin at the University of California, Berkeley, as a postdoctoral researcher. Here, he gained expertise in the use of radioactive isotopes to study metabolic processes, synthesizing the first radioactive carcinogen of the polycyclic aromatic hydrocarbon series, dibenz(a,h) anthracene, with carbon-14 labeling. His work at Berkeley sparked a lifelong interest in studying the mechanisms of chemical carcinogenesis, and he became well-versed in the use of carbon-14 as a tracer for studying metabolic reactions.

In 1948, Heidelberger moved to the University of Wisconsin-Madison to join the McArdle Laboratory for Cancer Research, where he established his research group. His early work at McArdle focused on studying the metabolism of polycyclic aromatic hydrocarbons and their covalent binding to cellular macromolecules such as DNA, RNA, and proteins. These studies were instrumental in understanding the carcinogenic potential of these compounds and how they contribute to cancer development.

Contributions to Chemical Carcinogenesis

Dr Heidelberger’s pioneering work in chemical carcinogenesis was foundational to the field. Using radiolabeled carcinogens, he and his research group were able to track how polycyclic aromatic hydrocarbons interacted with cells and how their binding to cellular macromolecules contributed to mutagenesis and cancer formation. One of his notable achievements was developing the permanent mouse embryo fibroblast cell line, C3H/10T1/2, which became a crucial model for studying chemical carcinogenesis and cellular transformation. This cell line allowed researchers to investigate how specific chemical compounds induce morphological and neoplastic transformations in cells.

Heidelberger’s research on the covalent binding of carcinogens to DNA provided critical insights into the mutagenic properties of these compounds and their role in the initiation of cancer. His studies contributed to a deeper understanding of how carcinogens are metabolized by the body and how they induce genetic mutations that lead to cancerous growths.

Development of 5-Fluorouracil and Contributions to Cancer Chemotherapy

Perhaps Dr Heidelberger’s most significant and enduring contribution to cancer science was his development of the chemotherapy drug 5-fluorouracil (5-FU). Based on his understanding of the metabolic pathways of pyrimidines, Heidelberger hypothesized that a fluorinated derivative of uracil could inhibit thymidylate synthetase, an enzyme critical for DNA synthesis. This inhibition would prevent cancer cells from proliferating, as they rely heavily on rapid DNA synthesis for growth.

In 1957, Dr Heidelberger successfully synthesized 5-FU, which was later shown to be effective in inhibiting the growth of various transplanted rodent tumorus. The success of 5-FU in preclinical trials led to its widespread use in human clinical trials, where it proved to be an effective treatment for several cancers, including colorectal, breast, and gastrointestinal cancers. 5-FU remains a cornerstone of cancer chemotherapy to this day.

In addition to 5-FU, Heidelberger’s lab synthesized other fluorinated pyrimidines, such as 5-fluorodeoxyuridine and 5-fluorocytosine, expanding the scope of chemotherapeutic agents. His research on these compounds not only revolutionized cancer treatment but also laid the groundwork for understanding the molecular mechanisms underlying chemotherapy’s effects, particularly the inhibition of DNA synthesis in rapidly dividing cancer cells.

Research on Mammalian Cell Transformation

Dr Heidelberger also made significant contributions to understanding how chemical carcinogens induce malignant transformation in mammalian cells. Early in his career, he recognized the limitations of studying carcinogenesis in whole animals and turned to cell culture systems. His work with C3H mouse prostate organ cultures and later with the C3H/10T1/2 cell line allowed him to study the effects of carcinogens on cells in a controlled environment, leading to discoveries about the genetic and molecular changes that accompany cancer transformation.

Heidelberger’s research provided a model system for studying tumour initiation and promotion in vitro, and his cell transformation assays became widely adopted in the field. His studies showed a quantitative relationship between the carcinogenic potency of polycyclic aromatic hydrocarbons and their ability to induce malignant transformation in cultured cells.

Leadership and Professional Contributions

Throughout his career, Dr Heidelberger was an influential leader in the field of cancer research. He was a prolific researcher, authoring numerous scientific papers and mentoring over 80 postdoctoral fellows and graduate students from around the world. He was also actively involved in several professional organizations, serving on committees of the National Cancer Institute and the American Association for Cancer Research, where he contributed to shaping cancer research policies and practices.

In 1976, Heidelberger moved to the University of Southern California (USC), where he was appointed Director for Basic Research at the USC Comprehensive Cancer Center. In this role, he played a key part in establishing the Cancer Center as a major research institution, continuing his research on cancer chemotherapy until his untimely death.

The Professional Activities and Awards of Dr Charles Heidelberger in Cancer Science

Awards and Honors

Dr Heidelberger's contributions to cancer research earned him numerous prestigious awards and honours. In 1978, he was elected to the U.S. National Academy of Sciences, a testament to his scientific achievements and his impact on cancer research. In 1982, he was awarded the inaugural Athayde International Cancer Prize, recognizing his contributions to cancer chemotherapy and his development of 5-fluorouracil. His peers recognized him as a leading figure in the field, and he was named the American Cancer Society's "1982 Man of the Year."

Other notable honours include the G.H.A. Clowes Award of the American Association for Cancer Research, the Walter Hubert Lecture of the British Association for Cancer Research, and the Lila Gruber Award of the American Academy of Dermatology.

Legacy and Final Years

Dr Heidelberger passed away on January 18, 1983, after battling nasal sinus cancer. Despite his illness, he continued his work in cancer research, driven by his desire to improve cancer treatment for future generations. His scientific legacy lives on through the many students and colleagues he mentored, the groundbreaking discoveries he made in chemical carcinogenesis and chemotherapy, and the enduring use of 5-fluorouracil as a critical tool in cancer treatment.

He is survived by his wife, Patricia, and their children, Nina, Philip, and Lisa, as well as his extended scientific family, who continue to build on the foundation he established in cancer research.

Conclusion

Dr Charles Heidelberger's life and work represent a significant chapter in the history of cancer science. His research on the metabolic effects of chemical carcinogens and his development of 5-FU have left an indelible mark on the field of cancer chemotherapy. A man of broad scientific talent, Dr Heidelberger's contributions continue to shape modern approaches to cancer treatment, ensuring that his legacy as a pioneering cancer researcher endures for generations to come.

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The Charles and Patricia Heidelberger Foundation for Cancer Research

In 2000, a generous gift from Mrs Patricia Heidelberger established the Charles and Patricia Heidelberger Foundation for Cancer Research, with the principal objective of ensuring that these Symposia would be held regularly in perpetuity. The Officers of the Heidelberger Foundation are: Mrs Patricia Heidelberger, President and Member of the Board of Directors, Dr Eliezer Huberman, Member of the Board of Directors, and Dr Joseph R. Landolph, Jr., Secretary, Chief Financial Officer, and Member of the Board of Directors.

The Charles and Patricia Heidelberger Foundation for Cancer Research honours the scientific contributions of Professor Charles Heidelberger, a pioneering figure in cancer research, whose development of fluorouracil (5-FU) remains a cornerstone in chemotherapy. His vision of collaborative research continues to drive the Foundation's efforts in fostering innovation and advancing the fight against cancer.

Since 2004, the more recent Heidelberger Symposia have been supported in part by the Foundation, continuing its vital role in bringing together leading cancer researchers. The purpose of these Heidelberger Symposia is to encourage information sharing, foster interdisciplinary collaboration, and accelerate advancements in cancer research—carrying forward the legacy of Professor Heidelberger. These symposia serve as a platform for exploring cutting-edge research, discussing novel therapeutic strategies, and expediting the translation of discoveries from bench to bedside in the pursuit of eradicating human cancer.

Through its support of scientific symposia, research grants, and collaborations, the Charles and Patricia Heidelberger Foundation remains steadfast in its mission to nurture the next generation of cancer researchers and contribute meaningfully to the global effort against cancer.

Through its support of scientific symposia, research grants, and collaborations, the Charles and Patricia Heidelberger Foundation remains steadfast in its mission to nurture the next generation of cancer researchers and contribute meaningfully to the global effort against cancer.

Conference Speakers

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Biosketch

Dr. David Ann currently serves as the Helen & Morgan Chu Dean's Chair of the Graduate School of Biological Sciences and is a Professor in the Department of Diabetes Complications and Metabolism. Over the past 36 years, he has trained numerous Ph.D. students and postdoctoral fellows in his laboratory. His research interests focus on signal transduction and cancer metabolism in health and disease.
David Ann earned his B.S. in 1978 from National Taiwan University and his Ph.D. in Biochemistry from Purdue University in 1985. After completing postdoctoral training at the University of California, Davis, he joined the University of Minnesota School of Medicine as an Assistant Professor of Pharmacology from 1988 to 1994. In 1994, Dr. Ann relocated to Los Angeles, where he served as an Associate Professor and later Professor at the University of Southern California, specializing in Molecular Pharmacology & Toxicology and Medicine, until 2006. In 2006, he joined the Beckman Research Institute at City of Hope Comprehensive Cancer Center in Duarte.

Conference Abstract

Lessons Learned from PARPi

David Ann

Poly(ADP-ribose) polymerase (PARP) is a key poly-ADP-ribosylation (PARylation) enzyme, and is critical for DNA damage repair (DDR). PARP inhibitors (PARPi) have shown great promise in ovarian cancer patients. However, most of the treated patients develop treatment resistance. Therefore, overcoming PARPi resistance (PARPi-R) is a major unmet medical need for ovarian cancer patients.

One of the most effective treatments for multiple solid tumors is to target the interactions between PD-L1 on the tumor cell surface and PD-1 on T cells. There is emerging evidence that intracellular PD-L1 in tumor cells also plays an important role in promoting tumor cell growth by facilitating DDR, and dampening antitumor immune responses in some cancer cells. BRCA proteins are known to mediate DDR. PARPi works more effectively in patients with BRCA deficiency. The term "BRCAness" refers to any tumor sharing phenotypic features with BRCA-deficient cancers, including increased sensitivity to PARPi. It has been shown recently that depleting PD-L1 can reduce DDR, induce BRCAness, and elicit synthetic lethality to PARPi in BRCA-proficient tumor cells.

For ovarian cancer, the responses to PD1/PD-L1 inhibition are low, as evidenced by multiple clinical trials, which could be due to low expression of PD-L1 by the tumor cells. However, our preliminary data showed elevated intracellular PD-L1 expression in both ovarian primary tumors and pelvic metastases, compared with the normal ovary tissues from the same patient. Strikingly, intracellular PD-L1 is significantly increased in the tumors of ovarian cancer patients after PARPi treatment, compared to their paired tumor samples prior to PARPi therapy. Similarly, intracellular PD-L1 was significantly increased in ovarian cancer cells after PARPi (Olaparib, the most frequently used PARPi on ovarian cancer) treatment in vitro. These results provide a new mechanistic explanation for the low response rates to PARPi and/or PD-L1/PD-1 inhibition in ovarian cancer patients.

Selected Publications

Wang YC, Kelso AA, Karamafrooz A, Chen YH, Chen WK, Cheng CT, Qi Y, Gu L, Malkas L, Taglialatela A, Kung HJ, Moldovan GL, Ciccia A, Stark JM, Ann DK. (2023) Arginine shortage induces replication stress and confers genotoxic resistance by inhibiting histone H4 translation and promoting PCNA ubiquitination. Cell Rep. 42(4):112296. PMID: 36961817.

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Udai Banerji, MD

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Biosketch

Professor Udai Banerji is the co-director of the Drug Development Unit at The Institute of Cancer Research and the Royal Marsden NHS Foundation Trust. The unit is internationally recognized for its expertise in running first in human clinical trails of anticancer drugs and associated translational research.

His clinical interests include finding optimal dose and schedules of novel anticancer drugs using preclinical and clinical pharmacokinetic and pharmacodynamic data along with toxicity. Another area of interest is designing and running clinical trials of combination therapy that is a clinical translation of his preclinical laboratory programs.

Professor Banerji's runs two laboratories. The first is the Clinical Pharmacodynamics Biomarker Labs which sets and runs bespoke pharmacodynamic assays to be used in tumour biopsies and surrogate normal tissue in samples taken during phase I trials. The second laboratory, the Clinical Pharmacology Adaptive Therapy group studies drug resistance and methods to overcoming this using combination therapy. He profiles dynamic phosphoproteimic changes and in collaborations with bioinformaticians creates executable models to predict combinations to overcome drug resistance. Other areas of interest include finding new drug targets and designing novel anticancer agents, study of tumour stroma in drug development including cancer associated fibroblasts and herding of cancer evolution.

Conference Abstract

Exploration of combinations and sequences of administration of anticancer drugs to improve outcomes

Treatment with targeted anticancer drugs used as single agents for metastatic cancers have resulted in prolonged survival, but not cure. Understanding and overcoming drug resistance to targeted therapy is critical to improving outcomes or these patients. Much of the focus on finding biomarkers of sensitivity and resistance to targeted agents have focused on genomic biomarkers. Mechanisms of resistance to targeted therapy often includes redundancies in signal transduction pathways and this could be overcome by combination therapy.

Conversely, treatment with chemotherapeutic agents are often used in combination regimens. Here the main aim is to cause maximal damage to cancer cells using drugs that do not have overlapping side effects. These lead to effective but toxic schedules. The selection pressure of chemotherapeutic drugs cause evolution of cancer cells into drug resistant and sensitive populations leading to tumour heterogeneity. Understanding the dynamics of growth of these clonal populations in the laboratory can open opportunities to use chemotherapy as single agents in specific sequences rather than in combinations with an aim to achieve similar efficacy but less side effects. Preclinical experiments and methods of clinical translation will be presented.

Cristina M Branco, PhD

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Biosketch

Dr Branco is a cancer physiologist working on host-mediated mechanisms that facilitate metastasis. She gained her expertise in hypoxia responses and vascular remodeling during her postdoctoral tenure at UC San Diego and at the University of Cambridge, having demonstrated the determining role of endothelial cells in the development of lung metastasis. She was awarded a Scientific Fellowship by Breast Cancer Now to establish her own research group while in Cambridge, and is currently a Senior Lecturer at Queen's University Belfast. Using molecular, cellular and pre-clinical in vivo models the Branco Group investigates how tumour- and therapy-derived stimuli impact the organ-specific microvascular and perivascular microenvironment, and how organ-specific remodeling affect organotropism and metastatic success.

Conference Abstract

Chemotherapy-induced microvascular remodeling and impact on (pre)metastatic microenvironment

Cristina M Branco

Chemotherapy is an all but inevitable component of treatment for many aggressive malignancies, particularly those with no targetable receptors. For cancers showing clear primary tumour regression, such as Triple Negative Breast Cancer (TNBC), chemotherapy is often delivered in the neoadjuvant setting. Despite the dose-dense approach and encouraging initial primary tumour responses, this patient group has an alarmingly high frequency of distant relapse (46%), associated with the shortest life expectancy following a diagnosis of disseminated disease (6-13 months), more commonly found in visceral organs, primarily brain and lung. Chemotherapy thus neither prevents nor treats metastatic breast cancer, and several studies indicate that relapse-free survival is not improved by treatment with chemotherapy. Furthermore, recent reports warn that chemotherapy may enable metastasis.

Chemotherapy is delivered intravenously, and thus cells in the vessel lumen (endothelial cells, EC) are the first exposed to these compounds. Blood vessels are also the most common route used by disseminated tumour cells to reach distant organs, and the barrier to their extravasation from the blood stream into a host organ. We investigated how EC responses to cytotoxic stress affect the microenvironment of tumour-free organs (pre-metastatic niche). Our data shows that anthracycline-stress compromises barrier integrity, angiogenic and regenerative function, and the secretory profile of microvascular EC; importantly, it is clear that the impact of treatment on microvascular networks is organ-specific. Using a combination of human and murine primary cells, complemented by in vivo studies, we are currently exploring the impact of chemotherapy-induced vascular remodeling on the frequency and location of distant metastasis.

Selected Publications

McErlain, T et al. Pericytes require physiological oxygen tension to maintain phenotypic fidelity. (under review); *preprint at bioRxiv 2024.08.28.606682; doi:10.1101/2024.08.28.606682*

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Biosketch

Dr. M. Calaf is a full professor at the Instituto de Alta Investigación, Universidad de Tarapacá, Chile. She earned her MS and Ph.D. in Biological Sciences from Michigan State University. Following her Ph.D., she worked at institutions including the University of Chile, Henri Mondor Hospital (France), Michigan Cancer Foundation, Fox Chase Cancer Center, and Columbia University.

Her research focuses on breast carcinogenesis induced by environmental factors, such as radiation and pesticides, and the influence of hormones. She has authored over 200 publications and organized the 20th and 24th International Charles Heidelberger Symposium on Cancer Research in 2014 and 2022.

Dr. Calaf has contributed as an expert to the IARC monographs on carcinogenic hazards in several volumes and has been an Emeritus member of the American Association for Cancer Research since 2017. She appeared on the cover of the International Journal of Oncology in 2023 and was named among the World's Top 2% Scientists by Stanford University in 2022.

Conference Abstract

Unravelling breast carcinogenesis: From Initiation to Metastasis: Role of estrogen, acetylcholine and prolactin in breast carcinogenesis

Gloria M Calaf

Breast cancer is the most prevalent cancer type, with about 2.3 million new cases worldwide. The most frequent subtype of this disease is the estrogen receptor (ER) positive tumors that represent almost 80% of cases, suggesting a high level of dependence for cell growth on the 17ß-estradiol (E2) having a major role in the initiation and progression of breast cancer. For such reason, hormonal therapies that suppress endogenous estrogen production are the most common treatments. This work aims to analyze the key role of ER signaling in metastasis through complex crosstalk with Acetylcholine (ACh), a neurotransmitter, and other hormones like prolactin. There are important links between environmental pollutants, among them Organophosphorus Pesticides (OPs), as malathion and parathion, and breast cancer. We demonstrated through an established experimental rat mammary gland cancer model that parathion and malathion in the presence of E2 underwent a stepwise transformation into malignant cells with the formation of rat mammary carcinoma. Such results indicated a decrease in the acetylcholinesterase activity, with an increase of ACh in the serum and an increase in muscarinic receptors (MR), suggesting a connection between ACh and mammary carcinoma formation. Results also indicated that ACh which functions in the peripheral organs, activated the MR, and such signaling led to the release of Ca+2 into the cytosol affecting signaling pathways as MAPK/ERK1/2. ACh induced ERα activation through increased phosphorylation with consequent nuclear translocation influencing EMT that results in changes in gene expression in response to signals such as hormones like prolactin, a polypeptide hormone synthesized and secreted from cells of the anterior pituitary gland that promote lactation but also control cancer. ACh increased the production of paracrine prolactin in positive and negative ERa cells. The prolactin Receptor (PRLR) activated signaling pathways, such as Stat5a among others. Thus, an emerging role of ACh, ERα, and prolactin has been proposed for breast carcinogenesis. GRANT: FONDECYT #1231537.

Selected Publications

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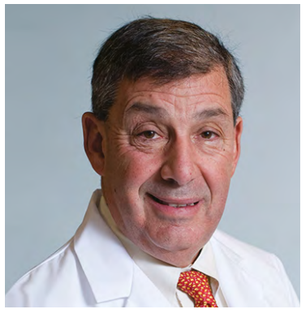

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Biosketch

Dr. Chabner serves as the Clinical Director, Emeritus, at the MGH Cancer Center, where he previously served as Chief of Hematology/Oncology and Clinical Director from 1995 to 2007. He also held the position of Associate Director for Clinical Sciences at the Dana Farber/Harvard Cancer Center from 1995 to 2010.

Prior to his appointment at Harvard and MGH, he served as a senior investigator at the National Cancer Institute (NCI) from 1972 to 1995 and was the Director of the Division of Cancer Treatment and Scientific Director of NCI from 1982 to 1995. His laboratory focused on the pharmacology of anticancer drugs, their metabolism, pharmacokinetics, mechanism of action and resistance, and clinical application.

Conference Abstract

Charles Heidelberger and the Legacy of 5-FU: A Historical Journey and Its Lasting Impact on Cancer Treatment

Bruce A. Chabner, M. D.

In this talk, Dr. Chabner will trace the legacy of the Heidelberg family, noting the landmark contributions of Charles Heidelberger and his father Michael. In a career spanning the early decades of the 20th century, Michael Heidelberger was considered the father of immunochemistry as he made unique contributions to defining the structure of antibodies and their interaction with specific epitopes. Michael spent the majority of his career at Columbia University. His son, Charles, followed his father into science and focused his research on carcinogenesis, but ats a young faculty member of the McCardle Institute at the University of Wisconsin, he noted the rapid incorporation of labeled uracil into DNA by tumor cells and reasoned that analogs of uracil might be mis-incorporated into DNA and disrupt tumor growth. Subsequent research has clarified the biochemical and molecular basis for the antitumor activity of 5-FU. The discover of 5-fluorouracil antitumor activity has had a profound influence on the field of cancer treatment. His work laid the basis for solid tumor chemotherapy, identifying a drug that remains the cornerstone of therapy for gastro-intestinal malignancies.

Further research by others (Santi, Johnston, Leichman) revealed the details of 5-fluourouracil action against thymidylate synthase and directed attention to the antitumor potential of tight-binding enzyme inhibitors, now the basis of targeted therapies for cancer. Quite interestingly, with the development of immunotherapy as an alternative to small molecules for cancer treatment, these two fields (chemotherapy and immunology) has come together in the development of antibody-drug conjugates, marrying the fundamental work of the Heidelbergers.

Selected Publications

Chabner, BA, and Longo, DL. Cancer Chemotherapy, Immunotherapy and Biotherapy: *Principles and Practice*. Seventh Edition, 2024. Wolters Kluwer, Philadelphia.

Roisin Connolly, MD

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Biosketch

Professor Roisin Connolly was appointed the Professor Gerald O'Sullivan Chair in Cancer Research at University College Cork (UCC) and Cork University Hospital in September 2019, and is the Director of Cancer Research @UCC. Prior to same, Roisin was Associate Professor of Oncology (Breast and Ovarian Cancer Program) and Co-Director of Developmental Therapeutics Program at the Sidney Kimmel Comprehensive Cancer Center (SKCCC) at Johns Hopkins.

Professor Connolly is a medical oncologist and clinical investigator with expertise in the design and conduct of clinical trials that test predictive biomarkers of response to therapy, and investigational new drugs in the treatment of patients with early- and late-stage cancers.

She has led numerous multicenter clinical trials in collaboration with the Cancer Therapy Evaluation Program (CTEP) at the National Cancer Institute (NCI), the Translational Breast Cancer Research Consortium (TBCRC), and the Eastern Co-operative Oncology Group (ECOG)-ACRIN in the US. Professor Connolly is the Co-Chair for the EA1211/DIRECT trial activated in summer 2023 investigating the role of imaging as a predictor of response toHER2-directed therapies, and is a Breast Cancer Research Foundation (BCRF)-funded investigator.

Roisin leads the HRB-funded UCC Cancer Trials Group, which brings together the three Oncology Clinical Trials Units in Cork and Waterford. Roisin is Principal Investigator with Cancer Trials Cork at CUH. She held the role of Co-Chair of the Cancer Trials Ireland Breast Disease Specific Group from 2020-2023 and is a member of the AICRI S teering Committee.

Her goal is to improve outcomes for patients with cancer through innovative clinical and translational research, in collaboration with UCC, national and international researchers.

Conference Abstract

Translational Breast Cancer Research: Opportunities & Challenges

Selected Publications

Connolly RM, *et al*. Updated Results of TBCR026: Phase II Trial Correlating Standardized Uptake Value with Pathological Complete Response to Pertuzumab and Trastuzumab in Breast Cancer. *J Clin Oncol*. 2021 Jul 10. doi 10.1200/JCO.21.00280. [Epub 2021 May 17] (PMID 33999652).

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Jenkins S, *et al*. 'Phase 1 Study and Cell-Free DNA Analysis of T-DM1 and Metronomic Temozolomide for Secondary Prevention of HER2-Positive Breast Cancer Brain Metastases'. 2023 Apr 14; doi; 10.1158/1078-0432.CCR-33-0855 (PMID:36705597)

LaRose M, *et al*. 'A Phase 1 Study of a Combinations of Liposomal Irinotecan and Veliparib in Solid Tumors' 2023 May 8; doi: 10.1093/oncolo/oyad023. (PMID: 37010988)

Hennessy MA, *et al*. 'Correlation of SUV on Early Interim PET with Recurrence-Free Survival and Overall Survival in Primary Operable HER"-Positive Breast Cancer (the TBCRC026 Trial). J *Nucl Med*. 2023 Nov;64(11):1690-1696. doi: 10.2967/jnumed.123.265853. (PMID: 37652539)

Roussos Torres ET, *et al*. 'Entinostat, nivolumab and ipilimumab for women with advanced HER2-negative breast cancer: a phase Ib trial.' *Nat Cancer*. 2024 Feb 14. doi: 10.1038/s43018-024-00729-w. (PMID: 38355777)

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Biosketch

Dr. Costa is Professor and Division Director of Environmental Medicine at NYU Grossman School of Medicine. Dr Costa received a Bachelor of Science degree from Georgetown University and a Ph.D degree from University of Arizona in Pharmacology. He does research and teaches medical and graduate students at NYU School of Medicine and NYU graduate school of arts and sciences. He has published over 500 papers in scientific journals and has been continuously funded by NIH grants. Dr. Costa studies the epigenetic mechanisms of how Nickel, Arsenic, and Chromium compounds cause cancer in humans.

Conference Abstract

Arsenic and Chromate cause methylation of MEG3 to induce carcinogenesis

Max Costa, Huailu Tu, Zhuo Zhang

Maternally expressed gene 3 (MEG3) encodes a long noncoding RNA that is expressed in normal tissues but significantly downregulated or lost in tis¬sues from various human cancers. Loss of MEG3 expression is involved in a variety of tumors. In recent years there has been much research on the mechanisms of how high expression of MEG3 inhibits tumor growth. As a member of the tumor suppressor long non-coding RNAs, MEG3 will become a new target for tumor diagnosis and treatment. MEG3 negatively regulates cell migration and invasion through NQO1 and FSCN1. MEG3 is down regulated in As-transformed (As-T) BEAS2B cells, in As-treated cells, and in the tissues from human lung squamous cell carcinomas and adenocarcinomas. Upregulation of DNMT3a in As-T cells and As-treated cells would lower MEG3 levels by methylation of its promoter. There is increased methylation of the MEG3 promoter in As-T cells and As-treated cells. DNMT3a negatively regulates MEG3 in BEAS-2B cells. Overexpression of MEG3 in As-T cells reduces cell transformation. Knockdown of MEG3 promots anchorage-independent growth in BEAS-2B cells. NQO1 and FSCN1 are upregulated in As-T cells and As-treated cells. MEG3 negatively regulates HIF-1*a* and NQO1 and is an upstream regulator of HIF-1 alpha. NQO1 regulates HIF-1*a* through direct binding. Overexpression of MEG3 inhibits malignant cell transformation of Cr(VI) and As transformed cells. There is good correlation of MEG3 expression to the overall survival of lung cancer patients.

Selected Publications

Li P, Yang L, Park SY, Liu F, Li AH, Zhu Y, Sui H, Gao F, Li L, Ye L, Zou Y, Tian Z, Zhao Y, Costa M, Sun H, Zhao X. Stabilization of MOF (KAT8) by USP10 promotes esophageal squamous cell carcinoma proliferation and metastasis through epigenetic activation of ANXA2/Wnt signaling. Oncogene. 2024 Mar;43(12):899

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Li A, Park S, Li P, Zhou C, Kluz T, Li J, Costa M, Sun H. Transcriptome Analysis Reveals Anti-Cancer Effects of Isorhapontigenin (ISO) on Highly Invasive Human T24 Bladder Cancer Cells. Int. J. Mol. Sci. 2024, 25(3):1783

Liu S, Costa M, Ortiz A. Chronic nickel exposure alters extracellular vesicles to mediate cancer progression via sustained NUPR1 expression. J Inorg Biochem 2024; 252:112477.

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Tu H, Zhang Z, Li J, Shi S, Costa M. Loss of MEG3 contributes to the enhanced migration and invasion in arsenic-induced carcinogenesis through NQO1/FSCN1 pathway. Am J Cancer Res 2023;13(6):2307

Vicky Coyle, MD

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Biosketch

Vicky Coyle is a Clinical Professor in Queen's University Belfast and Consultant Medical Oncologist in the Belfast HSC Trust. Her clinical practice focuses on colorectal cancer and early phase cancer clinical trials. She has an interest in translational and clinical research in colorectal cancer focusing on mechanisms of treatment response and resistance to standard of care therapies.

Conference Abstract

Overcoming chemotherapy resistance in metastatic colorectal cancer through restoration of apoptotic function

V Coyle, N Crawford, T O'Brien, E Kerr, S McDade, M Salto Tellez, T Kerr, S Irvine, J Graham, R Wilson, H Walter, D Longley.

Cytotoxic chemotherapies remain the mainstay of treatment of metastatic colorectal cancer (CRC). Inhibitor of Apoptosis Proteins (IAPs) are frequently deregulated in cancer and are a major contributor to chemo-resistance through apoptotic inhibition and pro-survival NF-kappaB signalling. Restoration of apoptotic function through inhibition of IAPs is an attractive therapeutic strategy with additional potential for enhanced cell death through immunomodulation of the tumour microenvironment.

We have shown that elevated expression of cIAP1 and cIAP2 correlates with poor prognosis in patients with Stage 3 microsatellite stable CRC treated with adjuvant fluorouracil-based chemotherapy. Tolinapant, a novel IAP antagonist, is a dual antagonist of both XIAP and cIAP1 that causes rapid and sustained downregulation of cIAP1 in CRC models confirming on target effect. Our pre-clinical modelling has shown: (i) in the presence of TNF*a* (mimicking an inflammatory tumour microenvironment) tolinapant induces caspase-8 dependent apoptosis in CRC cell line models; (ii) tolinapant sensitises CRC cell lines to oxaliplatin/fluorouracil chemotherapy and (iii) tumour growth is inhibited *in vivo* following treatment with FOLFOX (oxaliplatin/fluorouracil) chemotherapy in combination with tolinapant.

Tolinapant has been evaluated as monotherapy in advanced solid cancers and lymphoma with a Recommended Phase 2 Dose (RP2D) and schedule identified. A clinical trial (ASTFOX) evaluating the combination of tolinapant with FOLFOX chemotherapy in patients with advanced CRC is underway. Pre- and on-treatment tumour biopsies and blood sampling will enable evaluation of the pharmacodynamic and immunomodulatory effects of treatment and explore potential biomarkers of response.

Selected Publications

Crawford N, Stott K, Sessler T, McCann C, McDaid W, Latimer C, Fox J, Munck JM, Smyth T, Shah A, Martins V, Lawler M, Dunne P, Kerr E, McDade S, Coyle V, Longley DB. Clinical positioning of the IAP antagonist tolinapant (ASTX660) in colorectal cancer. *Mol Cancer Ther.*, 2021 Sep 20 (9): 1627-1639. Doi: 10.1158/1535-7163.MCT-20-1050. Epub 2021 Aug 13.

William M Gallagher, PhD

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Biosketch

Professor William Gallagher is Full Professor of Cancer Biology at University College Dublin (UCD) and Deputy Director of Precision Oncology Ireland, a large-scale Science Foundation Ireland (SFI) Strategic Partnership Programme involving 5 academic institutions, 6 cancer charities and 7 companies (www.precisiononcology.ie). He is also Scientific Director of the St. Vincent's-UCD Cancer Centre (www.stvincentsucdcancercentre.ie/).

Prof. Gallagher is a primary driving force behind the All-Island Cancer Research Institute (AICRI), which is creating an overarching framework for cancer research across the entire island of Ireland (www.aicri.org). AICRI-linked programmes were recently awarded over 12 million euro under the HEA North-South Research Programme, including an all-island Doctoral and Post-Doctoral Training Programme in Precision Cancer Medicine (AICRIstart) which Prof. Gallagher co-leads, together with Prof. Mark Lawler (Queen's University Belfast).

Prof. Gallagher has received a number of awards for his research and innovation achievements in the oncology arena, including the inaugural Irish Association for Cancer Research Medal in 2017, the SFI Entrepreneurship Award in 2019 and the SFI Researcher of the Year Award in 2021. Prof. Gallagher has co-founded two molecular diagnostics companies, OncoMark Ltd. and OncoAssure Ltd., the former being acquired in March 2021 by the US company Danaher (Cepheid division).

Conference Abstract

Cancer Knows No Borders: From the Tripartite Agreement to the All-Island Cancer Research Institute and Beyond

William Gallagher, Ciaran Briscoe, Chantal Halley, Shashank Srinivas, Fiona Lanigan and Mark Lawler

The Good Friday Agreement has had a lasting positive impact on cancer research and cancer care across the island of Ireland (Lawler et al., 2023). In 1999, a Memorandum of Understanding (MOU) was signed between the respective Departments of Health in Ireland, Northern Ireland and the US National Cancer Institute (NCI), giving rise to the Ireland - Northern Ireland - National Cancer Institute Cancer Consortium, an unparalleled tripartite agreement designed to nurture and develop linkages between cancer researchers, physicians and allied healthcare professionals across Ireland, Northern Ireland and the US, delivering world class research and better care for cancer patients on the island of Ireland and driving research and innovation in the US. This year marked the 25th anniversary of this key tripartite agreement which has had a marked impact on elevating the cancer research and care landscape across the island of Ireland, recognized as an international exemplar of the health dividend of p eace (Ghebreyesus et al., 2024).

In 2020, the All-Island Cancer Research Institute (AICRI; www.aicri.org) was established as a virtual entity to bring together the combined strengths of cancer researchers and innovators across the island o f Ireland. Its mission is to help provide an overarching framework for cancer research across the island of Ireland, from discovery to implementation, for the benefit of cancer patients and wider society. AICRI has brought together ten academic institutions across the island of Ireland, along with multiple other stakeholders from the healthcare sector, cancer patients, cancer charities, industry partners and government agencies. It has a broad research agenda from cancer prevention to cancer diagnosis and treatment to survivorship and quality of life.

This joint presentation will cover the historical context of all-island collaboration in cancer research and innovation, focusing on the vision, progress and plans of AICRI and beyond.

Selected Publications

Lawler M, Sullivan R, Abou-Alfa GK, McCloskey K, Keatley D, Feighan J, Dahut W, Mulroe E, Ladner R, Genead M, Lowery M, Gulley JL, Scott CJ, Longley DB, Culhane A, Gallagher WM, Orr N, Chanock SJ, Gopal S.
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Ghebreyesus TA, Mired D, Sullivan R, Mueller A, Charalambous A, Kacharian A, Tsagkaris C, Soto-Perez-de-Celis E, Grigoryan H, Gralow J, Ilbawi A, Ghanem K, Mula-Hussain L, Mikkelsen B, Yimer M, Hammad N, Arakelyan S, Kutluk T, Salman Z, Lawler M, Tamamyan G, Babak MV, Arakelyan J.
A manifesto on improving cancer care in conflict-impacted populations.
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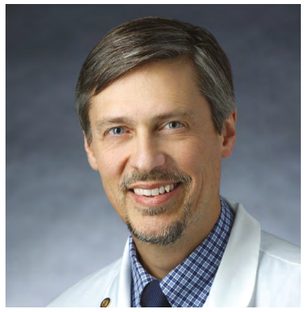

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Biosketch

Conference Abstract

Update on Senescence and Neurodegeneration

With the exception of a few small niches in the CNS, neurons are generally thought to be terminally differentiated and thus without the ability to divide and replace themselves. Not so for glial cells, the other equally numerous collections of cells in the CNS. Astrocytes, oligodendrocytes, and microglia can turnover and do so in normal physiology at a slow rate and at an increased rate in some pathological processes. Astrocytes have myriad of normal functions in the CNS from processing neurotransmitters at the synapse, to regulating ions in the extracellular space, to producing growth factors to help keep neurons alive. In collaboration with the NCI/NIH, we have been undertaking experiments to better understand the processes of controlled proliferation of astrocytes in the human brain, of uncontrolled proliferation in glial neoplasms, and for arrested proliferation in senescence in aging, cancer treatment, and neurodegeneration. Over the last 8 years our labs have used human postmortem tissue from individuals of different ages and with different neurological diseases to study TP53 isoforms and senescence pathways. We've found that p53beta which can drive cells into senescence is upregulated in advance aged brains, as well as brains from individuals with radiation treatment for brain cancer, and several neurodegenerative diseases such as Alzheimer disease, and ALS. We've also been recently studying senescence changes found in human epilepsy and Chronic Traumatic Encephalopathy (CTE). On the flipside delta133p53 is upregulated in younger brains and people with neurological disease, though it diminishes as one ages. A central hypothesis we have is that brain aging and neurodegenerative diseases occur in some part due to the glial cells that have used up their number of mitoses in advanced age and attained senescence associated secretory phenotype (SASP), one that is detrimental to the surrounding neighborhood of cells. We are continuing to investigat how we might alter the balance of p53beta/delta133p53 to slow cellular senescence.

Selected Publications

Turnquist, C; Horikawa, I; Foran, E; Major, EO; Vojtesek, B; Lane, DP; Lu, X; Harris, BT; Harris, CC. p53 isoforms regulate astrocyte-mediated neuroprotection and neurodegeneration. Cell Death Differentiation. 2016 Sep 1;23(9):1515-28. doi: 10.1038/cdd.2016.37. Epub 2016 Apr 22. PMID:27104929

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Ungerleider, K, Beck, J, Lissa, D, Turnquist, C, Horikawa, I, Harris, BT, Harris, CC. Astrocyte Senescence and SASP in Neurodegeneration: Tau joins the loop. Cell Cycle. 2021 Apr;20(8):752-764. doi: 10.1080/15384101.2021.1909260. Epub 2021 Apr 5. PMID: 33818291

Turnquist, C., Ryan, B.M., Horikawa, I., Harris, BT., Harris, CC., Cytokine Storms in Cancer and COVID-19, Cancer Cell Volume 38, Issue 5, 9 November 2020, Pages 598-601 doi:10.1016/j.ccell.2020.09.019. PMID: 33038939

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Biosketch

After obtaining a First Class degree in Chemistry and PhD in organic chemistry at Nottingham University, and completing postdoctoral studies at the University of California, Irvine, Tim joined Merck's UK based Neuroscience Research Centre where he rose to the position of Director, Medicinal Chemistry Department. Whilst at Merck Tim was part of the team which discovered the marketed Substance P antagonist Aprepitant (Emend) for which he received the Thomas Alva Edison Patent Award, was Global Chemistry Project Leader for Merck's *a*-secretase programme, and delivered multiple candidate drugs across different therapeutic areas. In 2007, he moved to Northern Ireland and set up Almac Discovery, a biotech company based in Belfast focused on targeted protein degradation and the development of next generation antibody-drug conjugates, where he is currently Vice President of Drug Discovery, and leads a team of 50 researchers across 3 sites.

Tim also holds a Chair position at the Patrick G Johnston Centre for Cancer Research at Queen's University, Belfast, where he is the McClay Professor of Medicinal Chemistry. His research focuses on apoptosis and he splits his time between his Almac role and this academic position. In 2022, a drug discovery project that Tim co-led with Prof. Dan Longley was licensed to Ipsen Pharma.

Tim has served as a member of the Medical Research Council's Developmental Pathway Funding Scheme panel and the British Heart Foundation Translational Awards Committee, sits on the Boards of the Odyssey Trust and W5 Science Centre, and is author/inventor on over 150 papers and patents.

Conference Abstract

Exploiting Engineered Binding Domains in Next Generation Antibody-Drug Conjugate Design

Almac Discovery is a biotech company based on the Life and Health Sciences campus at Queen's University, Belfast, and utilises its blend of protein engineering and small molecule capabilities to create and develop First in Class and Best in Class NCEs. Its core expertise is built on two areas: (i) a Next Generation Antibody Drug Conjugate (ADC) technology platform which utilises engineered antibodies incorporating small antigen-binding domains in bispecific and biparatopic formats for the enhanced delivery of payloads (including degrader-antibody conjugates (DACs)), and (ii) targeted protein degradation through the application of its proprietary UbiPlex technology platform which incorporates expertise in deubiquitinating enzymes and the development of small molecule molecular glue degraders.

This talk will showcase some of these capabilities through the disclosure of ALM-401, a First in Class Bispecific Antibody Drug Conjugate (ADC) for the treatment of refractory lung cancer. Over the past number of years, ADCs have emerged as some of the most exciting new entrants in pharma pipelines, and the development of next generation ADC formats including bispecific and biparatopic pairings, which overcome some of the long-standing limitations of current ADCs, represents an important stepping stone in the evolution of the field. The selection of target binding domains has been driven by detailed bioinformatic analysis of tumour antigen co-expression in solid tumours with high unmet medical need. ALM-401 has demonstrated an excellent preclinical efficacy profile in a range of models, and the bispecific nature of the molecule enhances both its activity and selectivity relative to monospecific drug conjugates. The architecture of ALM-401 has been designed to be significantly smaller than a conventional ADC to promote improved tumour penetration and ease of manufacture.

Miwako Kato Homma, PhD

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Biosketch

Dr Homma has been studying intracellular signaling pathways, especially phosphorylation, in order to understand pathogenesis of various diseases. She earned her M.Sc. and Ph.D. degrees from The University of Tokyo, where she conducted biochemical research on phosphatidyl inositol metabolism activated by v-erbB. She then obtained a faculty position at Tokyo Medical and Dental University, where she investigated molecular functions of a causative gene of familial adenomatous polyposis, APC, and found that APC interacts with protein kinase CK2. She is currently engaged in research and medical and graduate school education, as well as development of intellectual property.

Short CVE:
MSc in Medical Science, Faculty of Medicine, The University of Tokyo
PhD in Medical Science, Dept. Biochemistry, Faculty of Medicine, The Univ of Tokyo
JSPS Fellowship for Japanese Junior Scientists
Research Associate at the Molecular Oncology, Tokyo Medical and Dental University
Research Associate at the Department of Immunology, FMU
Associate Professor at the Department of Biomolecular Sciences, FMU
Visiting Scientist at University of Washington, Seattle (Professor Edwin G. Krebs)
Visiting Scientist at University of Colorado, Boulder (Professor Natalie G. Ahn)

Conference Abstract

Cell cycle-dependent activation and genomic recruitment of protein kinase CK2: a prognostic factor for cancer recurrence.

Miwako Kato Homma, So Yamamoto, Yoshimi Homma

CK2*a* is a serine threonine protein kinase that is involved in cell survival, proliferation, and various cellular processes. Protein and/or mRNA expression levels of CK2 are often elevated in human cancers. Our immune-histochemical analysis of primary invasive ductal carcinoma of the breast ($p < 0.0001$), and lung adenocarcinoma ($p = 0.0019$), demonstrate that nucleolar CK2*a*-positive staining is an independent prognostic factor for future recurrence-free survival. We hope that application of this analysis will contribute to early treatment strategy decisions and companion diagnostics for these malignancies.

Therefore, our research seeks to discover molecular mechanisms of CK2*a* by phosphor-proteomic analysis, ChIP-seq and bioinformatics, and to develop highly sensitive CK2*a* monoclonal antibodies. We found that when normal human fibroblasts synchronously progress through the cell cycle into the proliferative phase, a pool of CK2*a* is translocated from the cytoplasm into the nucleus. Using CK2*a*-ChIP-Seq analysis to investigate the function of CK2*a* in the nucleus, and with CK2*a*-knockout cells as a control, we demonstrated that CK2*a* binds to histone loci, and proliferation-related genes, consistent with global gene expression through recruitment togenomic loci. We propose that CK2*a* is involved in cell proliferation by activating gene expression through recruitment to genomic loci. Such epigenetic regulation of gene transcription appears to be tightly regulated in a cell cycle-dependent manner.

Selected Publications

Homma, MK *et al.* (2023) *Life Science Alliance* 7: e202302077 doi:10.26508/lsa.202302077
cf. https://x.com/LSAjournal/status/1719377953883058397?s=20

Homma, MK *et al.* (2022) *The Lancet Oncology* 23: S25(Abstact)
doi:10.1016/ s1470-2045(22)00424-7

Homma, MK *et al.* (2021) *Cancer Science* 112: 619-628
doi:10.1111/cas.14728

Homma, MK *et al.* (2015) *Advs in Biochemistry in Health and Disease* 12: Eds. by Ahmed K et al, doi. org/10.1007/978-3-319-14544-0_12

Homma, MK *et al.* (2005) *Proc Natl Acad Sci USA* 102:15688-15693.
doi: 10.1073/ nas.0506791102

Homma, MK *et al.* (2002) *Proc Natl Acad Sci USA* 99: 5959-5964.
doi:10.1073/ nas.092143199

Homma, MK *et al.* (1996) *Cell Growth & Differentiation* 7: 281-288

Homma, MK *et al.* (1987) *J Biol Chem* 262: 5696-5704

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Eliezer Huberman, PhD

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Biosketch

Dr. Huberman serves as CEO of Novadrug, LLC. and as a Partner of Biotherapy Investments, which are dedicated to the development of novel antiviral and anticancer therapies, respectively.

Dr. Huberman received a M.Sc. in Clinical Microbiology from Tel Aviv University (1964) and a Ph.D in Genetics from the Weizmann Institute of Science in Rehovot (1969), both in Israel. During 1969-1971, he was a Postdoctoral Fellow at the University of Wisconsin in Madison, Wisconsin with Prof. Charles Heidelberger.

After this period, Dr. Huberman returned to the Weizmann Institute as a scientist where he was promoted to a Senior scientist and thereafter to the rank of a tenured Associate Professor. In 1976, he went for five years to the US Oak Ridge National Laboratory and then to the US Argonne National Laboratory (ANL) near Chicago as the Division Director for Biological and Medical Research. Upon the end of his appontment as a Division Director in 1999, Dr. Huberman was promoted to the rank of a Distinguished ANL Fellow. He retired from ANL in 2006.

During his tenure at ANL, Dr. Huberman was also a professor at the University of Chicago in the departments of Microbiology, Molecular Genetics and Cell Biology as well as in Radiation a nd cellular Oncology.

Dr. Huberman has over 200 peer reviewed publications in respected scientific journals and a significant number of patents. He served on various national and international advisory and review committees as well as an associate Editor of a number of scientific journals.

Dr. Huberman was the recipient of an honorary Doctorate from the Russian Academy of Sciences Engelhart of Molecular Biology, a Prime Minister Nakasone and University of Tokyo Fellowship for Cancer Research and a visiting professorship at the Kobe University.

Dr Huberman's studies dealt with carcinogenesis, mutagenesis, cellular differentiation and stem cell research.

Conference Abstract

Heparanase-neutralizing monoclonal antibodies (mAb) attenuate tumor progression

Eliezer Huberman, Uri Barash and Israel Vlodavsky

Heparanase is the only human enzyme responsible for heparan sulfate (HS) breakdown, an activity that remodels the extracellular matrix (ECM) thereby promoting cancer metastasis dissemination and angiogenesis. A key process by which heparanase drives cancer progression is by promoting the bioavailability of HS-bound growth factors, chemokines, and cytokines, residing in the tumor microenvironment.

Usually, Heparanase is expressed at low levels in normal tissues. However, its marked increased expression in tumors appears to be associated with shorter survival of cancer patients. These observations support the notion that heparanase can be a suitable drug target in cancer control and encourage the development of specific heparanase inhibitors. Interestingly, heparanase knock-out animals exhibited no obvious defects, implying that inhibition of heparanase will most likely cause minimal side effects in patients. The current available heparanase inhibitors are mostly HS/heparin-like compounds that lack specificity and exert multiple off-target side effects.

Our program has generated mAbs that specifically and effectively neutralize heparanase enzymatic activity. These antibodies attenuate tumor growth in experimental mouse models as a monotherapy and to a higher extent in combination with conventional anticancer drugs.

Richard Kennedy, MD, PhD

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Biosketch

Almac Diagnostic Services was established in 2004 and over the past 20 years has been involved in the discovery, development and delivery of biomarkers for over 300 precision medicine clinical studies, in partnership with multiple pharmaceutical companies. The biomarker field has evolved rapidly in this time with the advent of new technologies, a move towards biological rather than anatomic classification of cancer, increased scrutiny from regulatory bodies and changing requirements for commercialisation and clinical adoption. Successful biomarker development therefore requires a multidisciplinary approach from early discovery through to clinical implementation. Important considerations and common pitfalls in the biomarker development process will be discussed in this presentation.

Conference Abstract

20 Years of Diagnostic Development: What have we learnt? What's Next?

Richard Kennedy

Richard Kennedy is the McClay Professor of Medical Oncology at Queen's University Belfast and serves as the Global Vice President and Medical Director for Almac. A 1995 medical graduate of the same university, he pursued post-graduate training in medical oncology and was awarded a PhD in Molecular Biology in 2004. Between 2004 and 2007, Prof Kennedy was an Oncology Instructor at Harvard Medical School in the USA, during which time he discovered new cancer biomarkers and therapeutic targets. His research led to high-impact publications and a patent that was acquired by a start-up in Boston in 2007.

In August 2007, Prof Kennedy took on the role of molecular lab director at Almac Diagnostic Services, accredited by the College of American Pathologists. He has played a pivotal role in the development and implementation of clinical biomarkers across more than 300 clinical trials for various major pharmaceutical companies. In 2011, he founded a research group at Queen's University Belfast dedicated to precision medicine, and he remains an active contributor to publications in the field.

Prof Kennedy is a current member of the MATRIX NI Government science advisory panel and the Oncology Advisory group of the Royal College of Physicians Faculty of Pharmaceutical Medicine. His past contributions include membership of the MRC Stratified Medicine Panel and the CR-UK new agents committee.

Selected Publications

Parkes EE *et al*. Activation of a cGAS-STING-mediated immune response predicts response to neoadjuvant chemotherapy in early breast cancer. Br J Cancer. 2022 Feb;126(2):247-258

Sharma P *et al*. Validation of the DNA Damage Immune Response Signature in Patients With Triple-Negative Breast Cancer From the SWOG 9313c Trial. J Clin Oncol. 2019 Dec 20;37(36):3484-3492

Jain S *et al*. Validation of a Metastatic Assay using biopsies to improve risk stratification in patients with prostate cancer treated with radical radiation therapy. Ann Oncol. 2018 Jan 1;29(1):215-222

Walker SM *et al*. Molecular Subgroup of Primary Prostate Cancer Presenting with Metastatic Biology. Eur Urol. 2017 Apr 10. pii: S0302-2838(17)30238-5. doi: 10.1016/j.eururo.2017.03.027

Parkes EE *et al*. Activation of STING-Dependent Innate Immune Signaling By S-Phase-Specific DNA Damage in Breast Cancer. J Natl Cancer Inst. 2016 Oct 5;109(1). pii: djw199

Niedzwiecki D *et al*. Association Between Results of a Gene Expression Signature Assay and Recurrence-Free Interval in Patients With Stage II Colon Cancer in Cancer and Leukemia Group B 9581 (Alliance). J Clin Oncol. 2016 Sep 1;34(25):3047-53

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Biosketch

Dr Emma Kerr is a Group Leader based at the PGJCCR, QUB. Her lab focuses on deciphering metabolic mechanisms of drug resistance in hard-to-treat, KRAS driven cancers. Using multiomic approaches and state-of-the-art in vivo cancer modelling they are mapping the role of altered metabolism in dictating or enabling drug resistance and identifying therapy-induced metabolic vulnerabilities.

Dr. Kerr completed her PhD in 2011 at Queen's University Belfast, working with Profs. Johnston and Longley on mechanisms of cell death regulation in colorectal cancer, before moving to MRC Cancer Unit at University of Cambridge as an MRC Postdoctoral Fellow in 2012. There, working with Dr Carla Martins, her research explored metabolic reprogramming and therapeutic vulnerabilities in KRAS mutant cancers. In 2018, Dr Kerr established her own research group at QUB supported by a prestigious Cancer Research UK Career Development Fellowship.

Conference Abstract

Mitochondrial metabolism: a chemotherapy-imposed vulnerability in CRC

Emma Kerr

Therapy resistance is attributed to over 80% of cancer deaths per year emphasizing the urgent need to overcome this challenge for improved patient outcomes. Despite its widespread use in colorectal cancer (CRC) treatment, resistance to 5-fluorouracil (5FU) chemotherapy is common and mechanisms promoting resistance remain poorly understood.

Reprogramming of cell energetics is fundamental to tumour progression and spread, but is also critically linked to therapeutic efficacy. Targeting such metabolic programs presents novel opportunities to enhance drug responses and improve patient outcomes. Therefore, a better understanding of the metabolic programs critical in supporting cancer cell survival following 5FU treatment has the potential to rationally design more effective combination chemotherapy regimens.

Our research, leveraging multi-omic approaches, multimodality imaging, and molecular analyses, reveals that 5FU profoundly alters mitochondria to promote vulnerabilities that we can therapeutically exploit to enhance its anti-cancer efficacy.

Selected Publications

Moss, DY *et al*. Mitochondrial metabolism is a key determinant of chemotherapy sensitivity in Colorectal Cancer (2024, preprint online on bioRxiv)

Moss, DY. *et al*. Rerouting the drug response: Overcoming metabolic adaptation in KRAS-mutant cancers. *Science Signaling* 15(756) (2022). https://doi.org:10.1126/scisignal.abj3490

McCann, C. & Kerr, E. M. Metabolic Reprogramming: A Friend or Foe to Cancer Therapy? *Cancers* 13 (2021). https://doi.org:10.3390/cancers13133351

Kerr, E. M. & Martins, C. P. Metabolic rewiring in mutant Kras lung cancer. *FEBS journal* 285, 28-41 (2018). https://doi.org:10.1111/febs.14125

Turrell, F. K. *et al*. Lung tumors with distinct p53 mutations respond similarly to p53 targeted therapy but exhibit genotype-specific statin sensitivity. *Genes and Development* 31, 1339-1353 (2017). https://doi.org:10.1101/gad.298463.117

Kerr, E. M., Gaude, E., Turrell, F. K., Frezza, C. & Martins, C. P. Mutant Kras copy number defines metabolic reprogramming and therapeutic susceptibilities. *Nature* 531, 110-113 (2016). https://doi.org:10.1038/nature16967

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Biosketch

Dr Robert D Ladner is the CEO and Founder of CV6 Therapeutics, a clinical-stage biotechnology company developing first-in-class treatments for oncology and inflammatory diseases. He is also an Associate Professor of Molecular Oncology (Reader) at Queen's University Belfast and member of the Patrick G. Johnston Centre for Cancer Research. His research focuses on uracil-DNA biology as a transformative treatment strategy for cancer and inflammatory conditionals.

Dr Ladner earned his MSc and PhD degrees from Rutgers University, where he studied uracil-DNA metabolism and repair. His work identified human dUTPase and its variants, providing critical insights into uracil-DNA misincorporation and resistance to thymidylate synthase (TS) inhibitors. He was the first to report the dUTPase overexpression's link to 5-fluorouracil resistance in colorectal cancer. In 2004, Dr Ladner joined the University of Southern California's Norris Comprehensive Cancer Center as Assistant Professor, focusing on uracil-DNA repair and synthetic lethal strategies to enhance TS inhibitor efficacy. In 2014, he founded CV6 Therapeutics, which recently a UK Phase 1a clinical trail for their oncology drug, CV6-168, in combination with 5-FU.

Conference Abstract

Targeting Uracil- DNA Biology: Inhibition of dUTPase transforms standard of care therapeutics through DNA uracilation

Thymidylate synthase (TS) inhibitors, such as 5-Fluorouracil (5-FU), capecitabine, and pemetrexed, are widely used in cancer treatment, but response rates remain limited, due to inherent or acquired resistance. This highlights the need for novel strategies to enhance therapeutic efficacy.

Deoxyuridine triphosphate nucleotidohydrolase (dUTPase) prevents uracil mis-incorporation into DNA by hydrolysing dUTP to dUMP, thereby maintaining DNA integrity. Inhibition of dUTPase in combination with TS inhibitors leads to thymidine triphosphate (TTP) depletion, dUTP accumulation, and uracil misincorporation into DNA (DNA uracilation), causing DNA damage and cancer cell death. Additionally, this process promotes immunogenic signalling, enhancing immune-mediated tumour destruction.

This study explores co-targeting dUTPase and TS in colorectal cancer cell models. Using molecular techniques, we assessed DNA damage, DNA uracilation, and base excision repair (BER) activity, and immune microenvironmental changes.

Our findings show that dUTPase inhibition significantly increases 5-FU efficacy by promoting DNA uracilation and BER-induced DNA damage. It also stimulates intrinsic immune signalling through increased cytoplasmic ds DNA and altered immune modulators, including calreticulin and PD-L1. Inhibition of uracil-DNA repair further amplifies these effects, highlighting potential for combining dUTPase and TS inhibitors with immune checkpoint therapies.

Selected Publications

Ladner RD, *et al*. Characterization of distinct nuclear and mitochondrial forms of human dUTPase. *J Biol Chem* 271(13): 7745–7751, 1996. doi: 10.1074/jbc.271.13.7745

Wilson PM, *et al*. Inhibition of dUTPase induces synthetic lethality with thymidylate synthase-targeted therapies in non-small cell lung cancer. *Mol Cancer Ther*. 2012 Mar;11(3):616-28. doi: 10.1158/1535-7163.MCT-11-0781 (COVER ARTICLE)

Wilson PM, *et al*. Standing the test of time: Targeting thymidylate biosynthesis in cancer therapeutics. *Nat Rev Clin Oncol*. 2014 May;11(5):282-98. doi: 10.1038/nrclinonc.2014.51

Davison C, *et al*. Targeting nucleotide metabolism enhances the efficacy of anthracyclines and anti-metabolites in triple-negative breast cancer. *NPJ Breast Cancer*. 2021 Apr 6;7(1):38. doi: 10.1038/s41523-021-00245-5.

Sulieman H, *et al*. Harnessing nucleotide metabolism and immunity in cancer: a tumour microenvironment perspective. *FEBS J*. 2024 doi: 10.1111/febs.17278.

Joseph R Landolph, Jr., PhD

Associate Professor of Molecular Microbiology and Immunology, Associate Professor of Pathology, and Member, USC/Norris Comprehensive Cancer Center With Tenure

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Biosketch

Joseph Landolph, Jr., Ph.D., is an Associate Professor of Microbiology, Immunology, and Pathology at the Keck School of Medicine, University of Southern California (USC), and a member of the USC/Norris Comprehensive Cancer Center. He serves as a scientific consultant, reviewing grants for the National Cancer Institute (NCI), the National Institute of Environmental Health Sciences (NIEHS), and the U.S. Environmental Protection Agency (EPA). He is also a member of California's Carcinogen Identification Committee and the Scientific Review Panel for Toxic Air Contaminants.

Dr. Landolph received his B.S. in Chemistry from Drexel Institute of Technology and his Ph.D. in Biophysical Chemistry from the University of California, Berkeley, where he studied under Nobel Laureate Melvin Calvin, Ph.D. He completed postdoctoral research on BaP-induced mutations and neoplastic transformation in mouse cells under Dr Charles Heidelberger at USC. Dr Landolph joined the USC faculty in 1980, earning tenure in 1987.

Conference Abstract

Insoluble Nickel (II) Compounds Induce Mutations in Proto-Oncogenes/ Other Genes, Deletions of Genes, Amplifications of Proto-Oncogenes (Ect-2)/Other Genes, and Differential Expression of 150 Genes in C3H10T1/2 Mouse Mesenchymal Cell Lines, Leading to Morphological/Neoplastic Transformation of 10T1/2 Cells

Joseph R Landolph, Jr, Jessica Grondin, Zarko Manojlovich, Maged Manswer, John J Shin, Sharon Chand, Eric Kwok, and John D Carpten .

Inhalation exposure of Nickel (Ni) refinery workers who smoked cigarettes to mixtures of soluble/insoluble Ni (II) compounds increased incidences of nasal/lung cancer in Clydach, Wales, U. K. (1920). Inhalation of insoluble Ni(II) compounds by rodents causes nasal/lung tumors. We (Miura et al, 1989) showed treatment of C3H/10T1/2 Cl 8 (10T1/2) mouse embryo cells with insoluble Ni(II) compounds caused phagocytosis of particles of insoluble Ni(II) compounds – nickel subsulfide, green NiO, black NiO, crystalline NiS – into 10T12 mouse embryo cells/induced foci of morphologically transformed (Tx) 10T1/2 cells. Injection of Tx cell lines derived from Ni(II) compound-induced foci of 10T1/2 cells into Balb/c nude mice, caused fibrosarcomas. We (2002) showed a sample of Ni refinery dust from a Ni refinery in Clydach, Wales, U. K., archived in 1920, induced morphological transformation (Tx) of 10T1/2 cells, but archived sample of Ni refinery dust from 1929 did not. In 1920, working at this Ni refinery caused excess induction of nasal/lung cancer in workers. After refinery process was changed in 1929, lowering arsenic-/orcelite (nickel arsenide) content in refinery dust by 90%, there were no excess respiratory cancers in workers. Therefore, content of the 1920 sample, including green NiO/orcelite, is responsible for excess nasal/respiratory cancers in Ni refinery 1920 sample and lack of lung/nasal cancers in workers after 1929. In Tx 10T1/2 cell lines induced by green/black NiO and crystalline NiS, there were 150 alterations in gene expression compared to non-Tx cell lines. Total genomic sequencing of Ni compound Tx and non-Tx 10T1/2 cell lines showed in Ni(II) Tx 10T1/2 cell lines, there were mutations in 8 proto-oncogenes/other genes, amplifications of Ect2 gene/other genes, deletions of genes. Hence, insoluble Ni(II) compounds are mutagenic. Inhalation of insoluble Ni(II) compounds and smoking cigarettes are likely responsible for a significant fraction of mutagenicity/cell transforming ability/carcinogenicity of green NiO /orcelite inhaled by workers at the Ni refinery in Clydach, U. K. (1920).

Selected Publications

Landolph JR, *et al*. Molecular biology of deregulated gene expression in transformed C3H/10T1/2 mouse embryo cell lines induc ed by specific insoluble carcinogenic nickel compounds. *Environ Health Perspect*, 2002, doi:10.1289/ehp.02110s5845.

Clemens F, and Landolph JR. Genotoxicity of samples of nickel refinery dust. T*oxicol Sci*, 2002, doi:10.1093/toxsci/kfg080.

Verma R, *et al*. Molelcular biology of nickel carinogenesis: Identification of differentially expressed genes in morphologically transformed C3H10T1/2 Cl 8 mouse embryo fibroblast cell lines induced by specific insoluble nickel compounds. *Mol Cell Biochem*, 2004, doi: 10.1023/b:mcbi:0000007276.94488.3d

Clemens F, *et al*. Amplification of the Ect2 proto-oncogene and over-expression of Ect2 mRNA and protein in nickel compound and methylcholanthrene-transformed 10T1/2 mouse fibroblast cell lines. *Toxicol Appl Pharmacol*, 2005, doi:10.1016/j.taap.2005.02.009

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Biosketch

Mark is Professor of Digital Health and Chair in Translational Cancer Genomics at Queen's University Belfast. He is Scientific Director of DATA-CAN, the UK's Health Data Research Hub for Cancer. Mark is Chair of the International Cancer Benchmarking Partnership, which sets a benchmark for cancer outcomes globally. He is Chair of the Lancet Oncology European Groundshot Commission, the most comprehensive analysis of cancer research in Europe ever, which is informing cancer research and policy in Europe. He recently became co-chair of European Cancer Organisation's new Focussed Topic Network on Emergencies and Crises and co-authored a Manifesto on improving cancer care in conflict-impacted populations in the premier medical journal The Lancet

Mark is Co-Lead of the All Island Cancer Research Institute (AICRI) a coalition of 10 universities across the island of Ireland. He co-leads two AICRI HEA funded North South Research Programmes focusing on precision medicine and digital health. In 2021, Mark received the Irish Association for Cancer Research's Outstanding Contribution to cancer research award, for his pioneering work on cancer research and care on the island of Ireland.

Mark has a strong commitment to patient-centred research and addressing cancer inequalities. He was architect of the European Cancer Patient's Bill of Rights, launched in the European Parliament (World Cancer Day). He received the 2018 European Health Award, a prestigious award for partnerships that yield real health impact in Europe. Mark co-led the work that led to ECO's European Code of Cancer Practice, which delineates what patients should expect from their health system. His pioneering work on Covid-19 and cancer received the Royal College of Physicians Excellence in Patient Care Award and the prestigious European Communique Award, which recognised the use of data to enhance cancer services and effect policy change. In 2022, he and his team won the prestigious HDR-UK Impact of the Year Award for providing the crucial intelligence to inform a change in policy for treating colorectal cancer in England. In November 2023, Mark received a Special Merit Award from ECO, Europe's largest multi-professional cancer organisation, in recognition of his ground-breaking work in Covid and Cancer and his work on cancer inequalities.

Mark is Scientific lead of ECO's European Cancer Pulse which captures data intelligence to inform mitigation of cancer inequalities. He was one of the leadership involved in developing and launching a radical new data-informed UK plan for cancer research and cancer care in the House of Commons, Westminster. In January 2024 he provided the crucial evidence on the need to re-establish a National Cancer Plan to the Health and Social Care Select Committee Future Cancer Inquiry in the House of Commons.

Conference Abstract

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Wei Li, PhD

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Biosketch

Following college education at the Xinjiang University, China, Li came to the US through the CUSBEA (China-US Biochemistry Examination and Application) graduate program in 1985. He received M.S. and Ph.D. degree in molecular biology of signal transduction from the Albert Einstein College of Medicine (New York City) under E. Richard Stanley and completed an 18-month post-doctoral fellowship with Joseph Schlessinger at the NYU Medical Center, prior to becoming a NIH-supported independent investigator. He first joined the faculty of the University of Chicago (Chicago, IL) Cancer Center as an Assistant Professor on tenue track in 1993, was then recruited by University of Southern California (USC) as an Associate Professor with tenue in 1999 and has since served as a Professor and Director of GMCB graduate program at USC in Los Angeles, USA. Li has more than 140 peer-reviewed publications (research articles, reviews and book chapters). Li's laboratory discovered the secreted (or extracellular) form of heat shock protein-90 (eHsp90) in promoting wound healing and tumor cell invasion, which have entered clinical trials.

Conference Abstract

Heat Shock Protein-90 in Cancer Clinical Trials: History, Presence and Future

Wei Li

Targeting the Hsp90 chaperone machinery in cancers has so far been unsuccessful after close to 200 monotherapy and combined therapy cancer clinical trials. Blames for the failures were unanimously directed at Hsp90 inhibitors or tumors or both. However, analyses of recent cellular and genetic studies together with data from the Human Protein Atlas database suggest that the vast variations in Hsp90 expression among different organs in the host might have been the actual cause. It is evident that Hsp90b is the root of dose-limiting toxicity (DLT), whereas Hsp90*a* is buffer of penetrated inhibitors. The more Hsp90*a*, the safer Hsp90b and lower DLT are. Unfortunately, the variations of Hsp90, from total absence in eye, muscle, pancreas and heart to abundance in reproduction organs, lung, liver and gastrointestinal track, would cause selections of any fair toxicity biomarker and effective maximum tolerable dose (MTD) of inhibitors challenging. In theory, a safe MTD for organs with high Hsp90 could harm organs with low Hsp90. In reverse, a safe MTD for organs with low or undetectable Hsp90 may have little impact on the tumors, which exhibit 3-7% Hsp90 over 2-3% Hsp90 in normal cells. Moreover, not all tumor cell lines follow the "inhibitor binding-client protein degradation" paradigm for clinical trials. Interestingly, the orally administered Hsp90 inhibitor TAS-16 (Pimitespib), which bypasses the blood circulation and conveniently hits tumors along gastrointestinal track, showed some beneficiary efficacy in clinical trials for gastrointestinal tumors in Japan, like by inhbiting the tumor-secreted Hsp90*a* or extracellular Hsp90*a* (eHsp90*a*). Our new theory explains the failures of intracellular Hsp90 inhibitors in cancer clinical trials in the past and points out a promise of inhibiting tumor-secreted or extracellular Hsp90*a* in cancer patients.

Selected Publications

Cheng Chang, *et al.* (2024) Discovery of [Cell Number- Interstitial Fluid Volume] (CIF) Ratio Reveals Secretory Autophagy Pathway to Supply eHsp90*a* for Would Healing. *Cells* in press

Cheng Chang, *et al*. (2024) What Might Have Been the Underlying Cause of the Failure of Hsp90 Inhibitors in Cancer Clinical Trials in the Past? *Cells*, in press

Tang X, *et al.* (2022) Heterogeneous Responses and Isoform Compensation the Dim Therapeutic Window of Hsp90 ATP-Binding Inhibitors in Cancer. *Mol Cell Biol*. Feb 17;42(2): e0045921.

Zou, M, *et al*. (2017) Evolutionarily Conserved Dual Lysine Motif Determines the Non-Chaperone Function of Secreted Hsp90alpha in Tumor Progression. *Oncogene*, 36: 2160-2171

Jayaprakash, P, *et al*. (2015) Hsp90*a* and Hsp90*a* together operate a hypoxia and nutrient paucity stress-response mechanism during wound healing. J *Cell Sci* 128: 1475-1480.

Tsen F, *et al*. (2013) eHsp90 Signals Through Subdomain II and NPVY Motif of LRP-1 Receptor to Akt1 and Akt2: A Circuit Essential for Promoting Skin Cell Migration In Vitro and Wound Healing In Vivo. *Mol Cell Biol*., 33:4947-4953.

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Biosketch

Dr Loilome has worked at Khon Kaen University, northeast Thailand, for over 20 years, where the highest global incidence of cholangiocarcinoma (CCA) is observed. Her research focuses on uncovering the molecular mechanisms behind liver fluke-associated CCA, aiming to identify targets for chemoprevention, treatment, and biomarkers for improved diagnosis and prognosis.

Together with the late Professor Narong Khuntikeo, Dr Loilome co-developed the Cholangiocarcinoma Screening and Care Program (CASCAP; (https://cloud.cascap.in.th/, Isan Cohort), which systematically monitors, screens, diagnoses, and treats patients at risk of CCA. CASCAP's database tools track medical information from screening to treatment (ultrasound/CT/MRI, chemotherapy, or surgery) and follow-up, facilitating better patient care and research. This system is now also implemented in Lao PDR, addressing similar CCA challenges.

Conference Abstract

Combating Cholangiocarcinoma in Thailand: Opportunities and Challenges

Loilome, W, Titapun, A, Wangwiwatsin, A, Klanrit, P, Namwat, N, Thanasukarn, V, Jareanrat, A, Sitthithaworn, P, Chamadol, N

Cholangiocarcinoma (CCA), also known as bile duct cancer, is caused by liver fluke infection resulting from the habits of eating raw or undercooked cyprinoid fish dishes. This silent disease remains a major public health problem in Thailand which presents the high mortality rate of up to 20,000 per year. More than half of the infected population is people in northern and northeastern regions. CCA is most frequently diagnosed among people in the working-age population, at ages of 40-60 years, which are considered heads of the family. Costs of care and treatment both affect family budgets and patients' health. This serious illness has, therefore, large impacts not only on socioeconomic status but also on the quality of life of people in the society. Cholangiocarcinoma Screening and Care Program (CASCAP) is a project developed by Cholangiocarcinoma Research Institute, Khon Kaen University, Thailand that aims to reduce the incidence of liver fluke infection and mortality of CCA in Thailand. This project involves developing a public health system and innovation for health promotion, disease prevention, disease screening, diagnosis and care of patients with liver fluke infection and CCA using an integrated operating model by collaborating with relevant network partners, nationally and internationally, from both government and public sectors. This CASCAP is intended to raise awareness and provide an access of quality health services and resources for liver fluke and CCA to individuals as our equal, endowed with dignity and an equal opportunity to pursue a healthy life, which in turn will enable an effective and sustainable way to solve this major health problem in Thailand.

Selected Publications

Khuntikeo N, *et al.* A Comprehensive Public Health Conceptual Framework and Strategy to Effectively Combat Cholangiocarcinoma in Thailand. *PLoS Negl Trop Dis*. 2016 Jan 21;10(1):e0004293. doi: 10.1371/journal.pntd.0004293.

Khuntikeo N, *et al.* Cohort profile: cholangiocarcinoma screening and care program (CASCAP). *BMC Cancer*. 2015 Jun 9;15:459. doi: 10.1186/s12885-015-

Worasith C, *et al*. Application of urine antigen assay to evaluate outcomes of praziquantel treatment and reinfection in opisthorchiasis in northeast Thailand. *Trans R Soc Trop Med Hyg*. 2020 Oct 5;114(10):751-761. doi: 10.1093/trstmh/traa057.

Worasith C, *et al*. Accuracy of a new rapid diagnostic test for urinary antigen detection and assessment of drug treatment in opisthorchiasis. *Infect Dis Poverty*. 2023 Nov 21;12(1):102. doi: 10.1186/s40249-023-01162-4.

Daniel Longley, PhD

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Biosketch

Prof Longley's research is focussed on cancer therapy response and resistance. In particular, his work investigates the therapeutic relevance of the caspase 8 inhibitor FLIP and the inhibitor of apoptosis proteins (IAPs). We have shown that FLIP and IAPs are key regulators of death receptor-, chemotherapy- and radiation-induced apoptosis in a range of in vitro and in vivo cancer models. We have developed clinical trials exploring the use of IAP inhibitors in colorectal cancer and have developed first-in-class inhibitors of FLIP that are approaching candidate selection stage.

Another element of my research is to investigate fundamental aspects of death receptor biology. We recently characterized the critical protein-protein interactions between FLIP and its key binding partners FADD and procaspase 8 that occur at complexes formed by death receptors following death ligand binding. The mechanism that we propose is a unique, paradigm-changing model that is likely to have implications for other multimeric procaspase activating platforms such as the apoptosome (caspase 9). We have also uncovered two novel aspects of FLIP biology that we are currently investigating: (1) FLIP's regulation by the ubiquitination-proteasome system via cullin RING E3 ubiquitin ligases; and (2) the role of nuclear FLIP in regulating DNA damage responses. Prof Longley is the Director of the Patrick G Johnston Centre for Cancer Research at Queen's University Belfast. He is also a founder of the Cancer Vaccine company AilseVax (https://www.ailsevax.com/).

Conference Abstract

The Patrick G Johnston Centre for Cancer Research: Transforming Cancer Care in Northern Ireland

Daniel Longley

Since its establishment in 2006, the Patrick G Johnston Centre for Cancer Research (PGJCCR) has been a leading role in cancer research in the UK, Ireland and internationally. The brainchild of the late Professor Paddy Johnston, research in the Centre has significantly transformed the cancer outcomes in Northern Ireland, with a 13% increase in 5-year survival for all patients. A key strength of the Centre is the involvement of Clinical Academics, who make up a quarter of our Principal Investigators, enabling cutting-edge research with an established strong track record in understanding response and resistance to standard-of-care anti-cancer therapeutics, including chemotherapy and radiotherapy. Leveraging resources such as the Northern Ireland Biobank (https://www.nibiobank.org.uk) and our Precision Medicine Centre of Excellence (https://www.qub.ac.uk/research-centres/PMC/), the PGJCCR centre is able to drive the discovery of and implementation of novel patient-stratifying biomarkers. Our research also identifies new therapeutic approaches, including the development of first-in-class and best-in-class small molecules and biologics, along with innovations in radiotherapy that are shaping clinical practice changes. Through its patient-focused research programmes, the Centre is now at the heart of the Life and Health Sciences Sector in Northern Ireland, fostering commercial innovation, while improving patient outcomes.

Selected Publications

Jurisic, A. *et al*. USP7 inhibitors suppress tumour neoangiogenesis and promote synergy with immune checkpoint inhibitors by downregulating fibroblast VEGF. *Clin Transl Med* 14, e1648 (2024).

Davidovich, P., Higgins, C.A., Najda, Z., Longley, D.B. & Martin, S.J. cFLIP(L) acts as a suppressor of TRAIL- and Fas-initiated inflammation by inhibiting assembly of caspase-8/FADD/RIPK1 NF-kappaB-activating complexes. *Cell Rep* 42, 113476 (2023).

Stachtea, X. *et al*. Stratification of chemotherapy-treated stage III colorectal cancer patients using multiplexed imaging and single-cell analysis of T-cell populations. *Mod Pathol* 35, 564-576 (2022).

Salvucci, M. *et al*. Patients with mesenchymal tumours and high Fusobacteriales prevalence have worse prognosis in colorectal cancer (CRC). *Gut* 71, 1600-1612 (2022).

Roberts, J.Z., Crawford, N. & Longley, D.B. The role of Ubiquitination in Apoptosis and Necroptosis. *Cell Death Differ* 29, 272-284 (2022).

Lindner, A.U. *et al.* An atlas of inter- and intra-tumor heterogeneity of apoptosis competency in colorectal cancer tissue at single-cell resolution. *Cell Death Differ* 29, 806-817 (2022).

Paul B Mullan, PhD

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Biosketch

Professor Mullan serves as Director, Chief Scientific Officer and Founder of GenoME Diagnostics, a biotechnology company focused on the development of liquid biopsy assays for the improved disease monitoring, early detection and diagnosis of several poor outcome cancers.

Professor Mullan's academic and research career includes appointments as Research Fellow, Lecturer, Senior Lecturer, Reader and Professor in the School of Medicine, Dentistry, and Biomedical Sciences at Queen's University Belfast. He earned his DPhil degree from the University of Ulster, where he conducted research on the induced differentiation of Promyelocytic Leukamias. During his tenure at QUB, Professor Mullan has a long-standing track record in oncogenic signalling in breast and ovarian cancers. His research team has identified several biomarkers of response for Triple Negative Breast Cancers (TNBCs), in addition to novel treatment strategies for the poorest outcome TNBCs. He has also identified novel treatment strategies for subgroups of breast cancers typified by genomic amplifications such as 17p23, and overexpression of driver oncogenes (such as T-Box2). Most recently, his group have an interest in uncovering epigenetic drivers of cancer pathology, to advance the development of novel treatment and diagnostic approaches.

Conference Abstract

The development of novel liquid biopsy assays for the improved clinical management of poor outcome cancers

Paul B Mullan, Shannon Beattie, Charlotte McBrien, Charity Hall, Alex McIntyre, Micheal Ryan

Epigenetics is defined as 'the study of how cells control gene activity without changing the DNA sequence' and represents an exciting new area of cancer biology. The best characterised epigenetic alteration is DNA methylation (DNAme), whereby methyl groups are added to DNA to alter gene expression. Our group are interested in investigating how epigenetic alterations like DNAme can help drive cancer growth and how we can take advantage of this knowledge to develop new diagnostic tests and treatments.

One such type of novel test is the development of "Liquid Biopsies" (LBs). LBs (blood sampling for cancers) offer many advantages over tissue biopsies including being faster, cheaper, and more routinely available. To develop a LB test, we have profiled DNAme events in blood samples taken from patients with aggressive cancers, cancers which are currently often diagnosed in late stages, including Ovarian Cancer (OC), Triple Negative Breast Cancer (TNBC), and Pancreatic Cancer (PC). The poor collective outcomes for these cancer types reflects their late-stage diagnoses, with high rates of metastases, chemoresistance and heterogeneity. Focusing on OC, we will outline how we have taken DNAme profiles and using a range of resources, used this information to develop a LB test, based on OC-specific DNAme markers. We will also provide updates on progress in the other cancer types.

Whilst some cancers have shown remarkable improvements in patient survival over the past few decades, this has not been the case for the cancers mentioned above. Clearly there is a dire clinical need, and much work to do, to improve survival outcomes for these patients. Better disease monitoring, earlier/improved diagnosis, and longer-term screening (for example, in high-risk subpopulations) are all potential applications where successful LB tests could improve survival rates for aggressive cancers.

Selected Publications

Angel CZ, *et al*. A SRC-Slug-TGFß2 Signaling Axis drives Poor Outcomes in Triple-Negative Breast Cancers. *Cell Communication & Signaling*, in press.

McIntyre AJ, *et al*. TBX2 acts as a potent transcriptional silencer of tumour suppressor genes through interaction with the CoREST complex to sustain the proliferation of breast cancers. *Nucleic Acids Res* 2022 Jun 24;50(11):6154-6173.

Beirne JP, *et al*. A bespoke target selection tool to guide biomarker discovery in tubo-ovarian cancer. *Comput Struct Biotechnol J* 2022 Jun 17;20:3359-3371.

Beirne MP, *et al*. Defining the molecular evolution of extrauterine high grade serous carcinoma. *Gynecol Oncol* 2019 Nov;155(2):305-317.

Mullan PB, *et al*. NUP98 - a novel predictor of response to anthracycline-based chemotherapy in triple negative breast cancer. *BMC Cancer* 2019 Apr 2;19(1):236.

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Biosketch

Dr. Yoshinori Murakami is currently serving as Senior Professor at the Institute of Advanced Medical Sciences, Nippon Medical School, after retiring from the University of Tokyo in March 2024 as Professor Emeritus. Dr. Murakami graduated from the University of Tokyo with his MD in 1983. After clinical training at the University of Tokyo Hospital, he began his research in molecular oncology at the National Cancer Center Research Institute (NCCRI), Japan. He participated in the establishment of the SSCP technique and identified various gene mutations in cancers. From 1992 to 1994, he worked with Dr. Raymond White at the University of Utah, USA, where he mastered various approaches to analyze cancer genomes. After returning to NCCRI, he identified a new tumor suppressor, TSLC1/CADM1, involved in cell adhesion. In 2007, he moved to the Institute of Medical Science, the University of Tokyo, as a professor, and studied the role of cell adhesion in cancer invasion and metastasis. He has also been involved in cancer genome analysis from the perspective of recessive and disease-associated genes as a member and principal investigator (2014-2019) of Biobank Japan project, one of the world's largest disease cohorts (approximately 270,000 cases of various diseases), and has led several human genome projects in Japan. He is currently involved in a research project on genomic medicine and disease prevention based on health check-up cohorts in Japan. He was the local organising chair for ICHSCR2023 in Hiroshima last November and is delighted to be reunited with many of the scientists at ICHSCR in Belfast.

Conference Abstract

Construction of a new disease prevention digital twin by integrating multi-layered bioinformation

Yoshinori Murakami

The most effective solution to reduce the incidence of common adult diseases, including cancer, is to prevent them before they develop. Recent advances in genomics and omics sciences have made it possible to obtain multi-layered biological data for each individual (1). In addition, Japan is the only country in the world that requires companies to conduct health check-ups for their employees, and each company has accumulated a large amount of health check-up data over the years. Therefore, by integrating this large-scale, longitudinal data while protecting personal information and analyzing it with the latest information science, we can build a platform that can predict disease risks for each individual, create digital twins from each individual's data, and simulate future health conditions by virtually changing lifestyle habits, etc.

Since 2019, we have been collaborating with Nippon Telegraph and Telephone Corporation (NTT) to conduct a research project to collect genome-wide SNP typing data with the consent of NTT employees, integrate it with long-term health check-up data, and explore the significance of personalized disease prediction and prevention programs based on integrated biomedical information. To date, we have successfully constructed a cohort of more than 100,000 people, of which 35,000 health chec-kup data (average 17 years) and SNP typing data have been analyzed. Polygenic risk scores for representative common diseases in Japanese people, such as obesity, hyperlipidemia, and peptic ulcer, have been constructed by analyzing a large number of cases in Biobank Japan (2), and their medical significance is being investigated in the NTT cohort. The overall design and recent progress of this precision prevention project will be presented (3).

Selected Publications

Yue G, Kasai Y, Yuto T, Ohashi-Kumagai Y, Sakamoto T, Ito T, Murakami Y. IGSF3 is a homophilic cell adhesion molecule that drives lung metastasis of melanoma by promoting adhesion to vascular endothelium. *Cancer Sci* 115:1936-1947, 2024.

He Y, Koido M, Sutoh Y, Shi M, Ohtsuka-Yamasaki Y, Munter HM, BioBank Japan, Morisaki T, Nagai A, Murakami Y, Tanikawa C, Hachiya T, Matsuda K, Shimizu A, Kamatani Y. East Asian-specific and cross-ancestry genome-wide meta-analyses provide mechanistic insights into peptic ulcer disease, *Nat Genet*, 55(12):2129-2138, 2023.

Usui Y, Taniyama Y, Endo M, Koyanagi Y, Kasugai Y, Oze I, Ito H, Imoto I, Iwasaki Y, Aoi T, Hakozaki N, Takata S, Hirata M, Sugano K, Yoshida T, Kamatani Y, Nakagawa H, Matsuda K, Murakami Y, Spurdle AB, Matsuo K, Momozawa Y. Helicobacter pylori infection modifies gastric cancer risk associated with germline pathogenic variants in homologous recombination pathway genes, *New Engl J of Med*, 388(13):1181-1190, 2023.

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Biosketch

Joe O'Sullivan is Professor of Radiation Oncology at the Patrick G Johnston Centre for Cancer Research, Queen's University Belfast and a Consultant Prostate Cancer Oncologist at the Northern Ireland Cancer Centre, Belfast. Joe is a world expert on advanced prostate cancer and in particular the use of ionising radiation and has worked at Queens University for over 20 years.

Conference Abstract

Molecular Radiotherapy in Advanced Prostate Cancer- The current State-of-the-art and emerging opportunities

Joe M O'Sullivan

Advanced prostate cancer has been the most fruitful disease space for the development of Radionuclide therapy (Molecular Radiotherapy) with 2 life-extending therapies approved (Radium-223 and Lu-177-PSMA-617) and many varied alternatives in the pipeline.

In this talk, I will explore the history and clinical trial data and consider potential future directions for Molecular Radiotherapy.

Selected Publications

Synergistic Activity of DNA Damage Response Inhibitors in Combination with Radium-223 in Prostate Cancer. Dunne VL, Wright TC, Liberal FDCG, O'Sullivan JM, Prise KM. Cancers (Basel). 2024 Apr 15;16(8):1510. doi: 10.3390/cancers16081510. PMID: 38672592; PMCID: PMC11048209.

An objective measure of response on whole-body MRI in metastatic hormone sensitive prostate cancer treated with androgen deprivation therapy, external beam radiotherapy, and radium-223. Giacometti V, Grey AC, McCann AJ, Prise KM, Hounsell AR, McGarry CK, Turner PG, O'Sullivan JM. Br J Radiol. 2024 Mar 28;97(1156):794-802. doi: 10.1093/bjr/tqae005. PMID: 38268482; PMCID: PMC11027342.

Integrating radium-223 therapy into the management of metastatic prostate cancer care: a plain language summary. O'Sullivan JM, Abramowitz E, Sierra-Scacalossi L Future Oncol. 2023 May;19(15):1021-1028. doi: 10.2217/fon-2022-1296. Epub 2023 Mar 21. PMID: 36942803.

Toxicity and Efficacy of Concurrent Androgen Deprivation Therapy, Pelvic Radiotherapy, and Radium-223 in Patients with De Novo Metastatic Hormone-Sensitive Prostate Cancer. Turner PG, Jain S, Cole A, Grey A, Mitchell D, Prise KM, Hounsell AR, McGarry CK, Biggart S, O'Sullivan JM. Clin Cancer Res. 2021 Aug 15;27(16):4549-4556. doi: 10.1158/1078-0432.CCR-21-0685. Epub 2021 Jun 29. PMID: 34187853.

Real-world effectiveness, long-term safety and treatment pathway integration of radium-223 therapy in patients with metastatic castration-resistant prostate cancer. O'Sullivan JM, McKay RR, Rahbar K, Fizazi K, George DJ, Tombal B, Schmall A, Sandström P, Verholen F, Shore N. Front Med (Lausanne). 2022 Dec 22;9:fmed-09-1070392. doi: 10.3389/fmed.2022.1070392. PMID: 36619649; PMCID: PMC9812947.

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Biosketch

Ruth Plummer is Professor of Experimental Cancer Medicine, Newcastle University and an honorary consultant medical oncologist in Newcastle Hospitals NHS Foundation Trust. She directs the Sir Bobby Robson Cancer Trials Research Centre and leads the Newcastle Experimental Cancer Medicine Centre and CRUK Newcastle Cancer Centre. She leads one of the most active adult early phase cancer trials units in the UK and has taken multiple agents into the clinic, including the first-in-human PARP and ATR inhibitors. In addition, she has an active clinical practice treating skin cancer, both in the advanced and adjuvant settings, and with an associated clinical trials portfolio.

Nationally she sits on grant funding committees for CRUK, MRC and NIHR, chairing the Experimental Medicine Panel. She was elected a Fellow of the Academy of Medical Sciences in 2018 for her work developing PARP inhibitors as novel cancer treatments for patients. In 2021 she was awarded the ESMO-TAT Lifetime Achievement award for her work in early phase trials and in 2022 an MBE for Services to Medicine.

Conference Abstract

Translational Research: From Bench to Bedside in Cancer Treatment – experience of academic drug discovery

Ruth Plummer

In the last two decades we have seen remarkable advances in our ability to treat cancers with targeted agents, monoclonal antibodies immune checkpoint inhibitors, ADCs and cellular therapies being added to classical chemotherapy in the armamentarium offered to cancer patients. Worldwide, there are more cancer clinical trials than in any other disease area, with between 35-40% of all trials listed recruiting cancer patients.

In this active area with very significant industry investment this presentation will discuss the role of academic drug discovery and that of clinical academics in the cancer drug development pathway and translational research.

In particular, the development of rucaparib from preclinical science to entry into the clinic will be used to illustrate the challenges and opportunities of this route. Additionally the presentation will discuss changing trial designs over the last decade and the way these are facilitating translational research.

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Biosketch

Dr. Sean Rudd is a Group Leader at SciLifeLab and Karolinska Institutet, affiliated with the Department of Oncology-Pathology.

Dr. Rudd obtained his BSc in Biochemistry at the University of Manchester (UK) and subsequently his PhD in Biochemistry at the Genome Damage and Stability Centre at the University of Sussex (UK). Here, Dr Rudd's thesis work centred upon understanding how eukaryotic cells tolerate DNA damage during genome duplication. For his postdoctoral research, conducted at Karolinska Institutet (Sweden), he investigated how damaged DNA precursors influence genome stability in cancer cells and whether this can be exploited therapeutically. In 2019, he established his independent research at SciLifeLab and Karolinska Institutet which seeks to better understand the metabolism and molecular mode-of-action of commonly used chemotherapies and use this knowledge to design strategies to refine their use.

Selected Publications

Yagüe-Capilla M & Rudd SG. Understanding the interplay between dNTP metabolism and genome stability in cancer. 2024. *Disease Models and Mechanisms*. 17(8):dmm050775.

Rudd SG. Targeting pan-essential pathways with cytotoxic chemotherapy: challenges and opportunities. 2023. *Cancer Chemotherapy & Pharmacology*, 92;4 241-251

Zhang SM *et al*. Identification and evaluation of small-molecule inhibitors against the dNTPase SAMHD1 via a comprehensive screening funnel. 2024. *iScience*, 27;2 108907.

Rudd SG *et al*. Ribonucleotide Reductase Inhibitors Suppress SAMHD1 ara-CTPase Activity Enhancing Cytarabine Efficacy. 2020. *EMBO Molecular Medicine*; 12(3):e10419.

Conference Abstract

Towards precision cancer medicine with nucleoside analogues

Sean Rudd

Nucleobase and nucleoside analogues are a central pillar of cancer treatment. These agents are synthetic mimics of endogenous metabolites, such as DNA precursors, and are typically understood to exploit nucleotide metabolic pathways in cancer cells to induce cytotoxic DNA damage. However, despite consistent use for many decades, treatment responses remain subject to large interpatient variability that we often cannot predict or explain. Thus, there is a need to identify additional factors involved in the action of these drugs and utilise these for the development of new strategies to refine their clinical use, which is a major focus of our research group. In my presentation, I will exemplify these efforts with our work identifying a hydrolase that can inactivate several of these therapies and discuss how we used small molecule screens to identify pharmacological approaches to overcome this barrier to therapeutic efficacy. In addition, I will detail new work in the group in which we employ chemical genomics and proteomic approaches to identify new pathways associated with these therapies.

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Biosketch

Professor Manuel Salto-Tellez (MD-LMS, FRCPath, FRCPI) is Chair of Molecular Pathology at Queen's University Belfast (QUB), a clinical consultant pathologist and the lead of QUB's Precision Medicine Centre of Excellence. He is also the the Professor on Integrative Pathology at the Institute for Cancer Research in London (ICR), and the lead of the Royal Marsden Hospital / ICR Integrated Pathology Unit.

Manuel studied Medicine in Spain (Oviedo), Germany (Aachen) and The Netherlands (Leiden). He specialized in Histopathology in the UK (Edinburgh and London) and in Molecular Pathology in USA (Philadelphia). For more than 10 years he worked at the National University of Singapore and its National University Hospital, where he was associate professor, senior consultant, director of the Diagnostic Molecular Oncology Centre, Vice-dean for Research and senior scientist at the Cancer Research Institute.

Prof Salto-Tellez is author or co-author of more than 330 internationally peer-reviewed articles in translational science, molecular pathology and diagnostics, has published a similar number of abstracts in international conferences, and is editor or contributor to some of the key textbooks of pathology and oncology, including the WHO Blue book on Digestive Tract (5th edition, co-editor); Ian Talbot, Ashley Price, Manuel Salto-Tellez. Biopsy Pathology in Colorectal Disease, 2Ed; and the Oxford Textbook of Oncology. Third Edition. Manuel has served in key committees in cancer and academia, at national and international levels, and holds more than £21M in competitive grant funding, including major programmes with UKRI and NIHR. He is scientific advisor to 2 companies in the digital pathology and artificial intelligence space.

Manuel's diagnostic and research interest over the last 25 years has been in the integration of phenotype and genotype, and the discovery, validation and adoption of new biomarkers in cancer.

Conference Abstract

Digital Pathology, Artificial Intelligence and Multimodal Analysis

Manuel Salto-Tellez

The adoption of digital pathology (DP) by traditional histopathologists is transforming the way we practice diagnostics [1]. The evaluation of in-silico images (instead of the usual microscopic views) is opening diagnostic images to be analysed by computational science and, thus, bringing a new dimension to morphological interpretation. Indeed, the application of artificial intelligence (AI) architectures to simple and complex pathological images can help delivering existing biomarkers better or generate new predictive or prognostic biomarkers [2]. The first part of this talk will illustrate two key examples of this, namely the analysis of microsatellite instability in routine H&E images, or the scoring of PD-L1 in NSCLC by DP/AI. [3, 4], and stress the importance of applying these new paradigms to clinical trial materials [2, 5].

While pathologists make the most of a new paradigm, we wonder: after the revolution in diagnostics created by the adoption of immunohistochemistry (1980's), genomic testing (2000's) and digital analysis (2020's), what new disruptive technology will transform the way we deliver diagnosis yet again? In the second part of this presentation, we will discuss the concept of integrated diagnostics, or the Amalgamation of multiple analytical modalities, with evolved information technology, applied to a single patient cohort, and resulting in a synergistic effect in the clinical value of the diagnostic parts [6]. We will present examples of multi-modal analysis, explain how this would need to be developed in the context of hospitals, and finally make a case for the need of a new complexity in biomarkers as the new frontier in diagnostics.

Selected Publications

Arends MJ, Salto-Tellez M. Low-contact and high-interconnectivity pathology (LC&HI Path): post-COVID19-pandemic practice of pathology. Histopathology. 2020 Oct;77(4):518-524. doi: 10.1111/his.14174.

Geaney A, *et al*. Translation of tissue-based artificial intelligence into clinical practice: from discovery to adoption. Oncogene. 2023 Nov;42(48):3545-3555. doi: 10.1038/s41388-023-02857-6.

Saldanha OL, *et al*. Swarm learning for decentralized artificial intelligence in cancer histopathology. Nat Med. 2022 Jun;28(6):1232-1239. doi: 10.1038/s41591-022-01768-5.

Salto-Tellez M, Reis-Filho JS. Clinical Trials and Digital Pathology-Toward Quantitative Therapeutic Immunohistochemistry and Tissue Hybridization. JAMA Oncol. 2023 Feb 1;9(2):168-169. doi: 10.1001/jamaoncol.2022.5826.

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Biosketch

Professor Chris Scott is Dean of Research, Faculty of Medicine, Health and Life Sciences, Queen's University Belfast. Following a primary degree in Biochemistry he undertook a PhD and post-doctoral training at Queen's in molecular enzymology. Chris is internationally renowned for his work in development of antibody and nanomedicine-based therapies for the treatment of cancer and other conditions. Chris was Director of the Patrick J Johnston Centre for Cancer Research from 2018-2023. Work in his laboratory is funded by agencies such as Medical Research Council, HSCNI, and various industrial sources such as AstraZeneca and Immunocore. He also held a Royal Society Industrial Fellowship with GSK (2012-15), and won the Vice Chancellor's Prize for Innovation in 2015 with his group's work on developing a novel nanomedicine for the treatment of sepsis and other inflammatory conditions. Chris is actively involved in nanomedicine across the UK and is a Trustee of the British Society of Nanomedicine, and is scientific co-founder of Boston-based Aviceda Therapeutics Inc. and QUB-TCD spinout AilseVax Ltd.

Conference Abstract

Novel approaches to developing antibody targeted chemotherapies

Chris Scott

Antibody drug conjugates (ADCs) have become a major class of therapy for cancer treatment, overcoming manyof the typical issues associated with chemotherapy. The upward trend in ADC approvals clearly demonstrates the role that targeted chemotoxic agents will continue to have in the treatment of many cancers. Our group has developed an avenue of research at QUB investigating new ways to make ADC-like molecules. Our group has also been at the forefront of targeted nanomedicines for the last 15 years. In this presentation I will highlight some of the seminal work that we have done, lessons learned and current work that we are now undertaking to develop new precision therapeutic strategies and optimization of these molecules for future developability for the treatment of tumours.

Selected Publications

DR5-targeted, chemotherapeutic drug-loaded nanoparticles induce apoptosis and tumor regression in pancreatic cancer in vivo models. (2020). Johnston MC, Nicoll JA, Redmond KM, Smyth P, Greene MK, McDaid WJ, Chan DKW, Crawford N, Stott KJ, Fox JP, Straubinger NL, Roche S, Clynes M, Straubinger RM, Longley DB, Scott CJ. J Control Release. 324:610-619.

Controlled coupling of an ultrapotent auristatin warhead to cetuximab yields a next-generation antibody-drug conjugate for EGFR-targeted therapy of KRAS mutant pancreatic cancer. (2020). Greene MK, Chen T, Robinson E, Straubinger NL, Minx C, Chan DKW, Wang J, Burrows JF, Van Schaeybroeck S, Baker JR, Caddick S, Longley DB, Mager DE, Straubinger RM, Chudasama V, Scott CJ. Br J Cancer. 123:1502-1512.

Antibody-mediated inhibition of Cathepsin S blocks colorectal tumour invasion and angiogenesis (2009). Burden RE, Gormley JA, Jaquin TJ, Small DM, Quinn DJ, Hegarty SM, Ward C, Walker B, Johnston JA, Olwill SA, Scott CJ. Clin Cancer Res. 15(19):6042-51.

Targeting Siglecs with a sialic acid-decorated nanoparticle abrogates inflammation (2015). Spence S, Greene MK, Fay F, Hams E, Saunders SP, Hamid U, Fitzgerald M, Beck J, Bains BK, Smyth P, Themistou E, Small DM, Schmid D, O'Kane CM, Fitzgerald DC, Abdelghany SM, Johnston JA, Fallon PG, Burrows JF, McAuley DF, Kissenpfennig A, Scott CJ. Sci Transl Med. 2015 Sep 2;7(303):303ra140. doi: 10.1126/scitranslmed.aab3459.

Repurposing of Cetuximab in antibody-directed chemotherapy-loaded nanoparticles in EGFR therapy-resistant pancreatic tumours. (2019). McDaid WJ, Greene MK, Johnston MC, Pollheimer E, Smyth P, McLaughlin K, Van Schaeybroeck S, Straubinger RM, Longley DB, Scott CJ. Nanoscale:20261-20273.

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Biosketch

Prof. Kienan Savage is the Professor of Molecular Oncology in the Patrick G Johnston Centre for Cancer Research – Queen's University Belfast and is the Scientific Lead of the Belfast Experimental Cancer Medicine Centre.

Kienan originally obtained his Bachelors degree in Biomedical Science from Griffith University in Australia, followed by an MD/PhD at the University of Queensland and The Queensland Institute of Medical Research in Australia. Kienan then undertook a post-doctoral research fellowship in Prof. Paul Harkin's group at Queen's University Belfast in 2007 before being awarded a career development fellowship from Cancer Focus Northern Ireland and forming the DNA damage response group at Queen's in 2012.

Kienan's basic and translational research interests focus on understanding the cellular DNA damage response/repair systems with a particular emphasis on the DNA damage driven immune response in breast cancer. In line with this, Kienan's group was involved in the identification of the DNA damage induced activation of the cGAS/STING pathway and its role in innate immune activation. More recent work from the Savage lab has focused on harnessing this knowledge to enhance responses to immune checkpoint blockade therapies by identifying rational chemotherapeutic combinations.

Conference Abstract

Optimizing chemo-immunotherapeutic combinations in breast cancer

Barros, E.M., Wilkinson, R. D. A, Zagnoli-Viera G., McIntosh, S. A., Lappin, K.M.1, Barker, O., Morgan, I. L., Parkes, E. E., McCabe, N., Greenberg, R.A., Harrison, T., Caldecott, K.W., Kennedy, R. D. and Savage, K. I.

There is currently increased interest in the use of immune checkpoint blockade (ICB) in the treatment of breast cancer, with trials demonstrating benefit in the neoadjuvant and adjuvant settings, in combination with cytotoxic chemotherapy. However, there remains debate as to optimal drug regimens and schedules in this setting. Certain breast cancers with genomic instability, appear to demonstrate enhanced immunogenicity and thus presumably potential for response to immune checkpoint blockade (ICB). We previously demonstrated activation of the cGAS-STING pathway following loss of DNA repair, resulting in cytokine induction, lymphocytic infiltration and immune checkpoint activation. Here we explore the role of different chemotherapies used clinically in breast cancer treatment in inducing this innate immune response, identifying topoisomerase II (TOP2) poisons, such as anthracyclines, as potent inducers of a cGAS-STING dependent interferon response. Mechanistically, anthracyclines result in significant induction of cytoplasmic DNA fragments that are resistant to nuclease degradation and are thus encapsulated within micronuclei, which are required for efficient cGAS-STING activation, and consequent cytokine and immune checkpoint gene induction. Intriguingly, the induction of micronuclei following anthracycline-mediated DNA damage, requires progression through mitosis, which can be blocked with anti-microtubule agents such as taxanes. In line with this, increased cytokine and immune checkpoint gene expression, as well as increased immune cell infiltration, is observed in breast tumour biopsies following anthracycline-based treatment, but is then supressed following taxane treatment. Taken together with existing clinical data, this study indicates that taxanes may not be the optimal drugs for combination with ICB in breast cancer and that anthracyclines may in fact be best placed to induce immunogenic inflammation, thus increasing responses to ICB therapies.

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Biosketch

Dr. Arul Veerappan's academic and research career includes an appointment as an Assistant Professor in NYU Grossman School of Medicine at NewYork University New York, starting in 2018. He earned his MSc and PhD in Pharmacology and Environmental Toxicology degrees from the University of Madras, Chennai, India. Subsequently, he was awarded a prestigious Japan Science and Technology Agenecy (STA) fellowship and continued his research on PM2.5 and health effects at the National Institute for Environmental Studies, Tsukuba Science City, Japan. Further Dr. Veerappan moved to United States and he has completed his postdocotoral fellowship at the Weill Cornell Medical College of Cornell Univesity, an Ivy League University in New York. His notable discoveries at the Silver Laboratory in Cornell University include the lung mast cell secretes renin, a rate limiting enzyme locally apart from the kidney source (PNAS 2008). Dr. Veerappan has published his research work in high impact journals such as PNAS, Nature Medicine, Translational Science etc. He has also presented his work in various national and international conferences. His major areas of research at NYU are environmental toxicants such as endocrine disruptors, heavy metals and air pollution including World Trade Center Particulate Matter and cardiopulmonary health effects, and carcinogenesis.

Conference Abstract

Polyadenylation of canonical histone H3.1 in bisphenol associated carcinogenesis

Arul Veerappan[1*], Zhuo Zhang[1], Shan Liu[1], Aikaterini Stavrou[1] and Max Costa1

Bisphenol A (BPA) is a pervasive chemical exposure that may cause cancers including breast, lung, and ovarian cancers in humans. In recent days, structurally similar bisphenol S (BPS) and bisphenol F (BPF) are replacing BPA are, and already being used as BPA alternatives. Unfortunately, these three compounds are the leading bisphenols present in humans. Despite the vast information available for BPA, much remains to be known regarding these emerging BPA analogues. Notwithstanding some preliminary evidence of these bisphenol compounds' carcinogenicity in humans, the specific underlying molecular mechanisms remain unclear.

Therefore, in this study, we investigated the carcinogenicity of BPA and its analogues using human bronchial epithelial (BEAS-2B) and embryonic kidney (HEK293) cells. To determine whether these three bisphenol analogues alter canonical histone mRNA processing in vitro, we measured levels of polyadenylation (polyA) of canonical histone (H)3.1 mRNA as well as protein expression of Stem-loop binding protein (SLBP), and H3 protein in BEAS-2B exposed to various concentrations of bisphenols for 96 h. Furthermore, BEAS-2B and HEK-293 cells were chronically exposed to low doses of bisphenols, and cell transformation assay was performed using anchorage-independent growth and colony formation to assess carcinogenicity. Our results showed that not only the exposure of BPA exhibits carcinogenic properties but also chemicals substituted for BPA in consumer products such as BPS and BPF also exhibit similar carcinogenic properties in human BEAS-2B/HEK293 cells either following depletion of SLBP and H3.1 mRNA upregulation, elevation of H3.1 protein or cell transformation and carcinogenesis as judged by growth in soft agar assays.

Selected Publications

Veerappan A, Stavrou A, Costa M. Polyadenylation of canonical histone H3.1 in carcinogenesis. Adv Pharmacol. 2023;96:267-282. doi: 10.1016/bs.apha.2022.08. 003. Epub 2022 Sep 30.PMID: 36858776.

Veerappan A, Zhang Z, Costa, M. A Chronic Exposure of Endocrine Disruptors Cause the Cell Transformation in Human Lung Epithelial Cells. Am J Respir Crit Care Med. 2023 DOI: 10.1164/ajrccm-conference.2023.207.1.

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Biosketch

Richard Wilson completed his medical degree at the Queen's University Belfast and then worked in Northern Ireland and Scotland as a junior doctor. He undertook basic science research in colorectal cancer resulting in his doctoral degree. He subsequently trained in oncology in Northern Ireland and in the National Cancer Institute in the USA. He worked as a Senior Lecturer, Reader and Professor in Queen's and as an Honorary Consultant Oncologist in the Belfast Health and Social Care Trust. He set up the first early phase cancer clinical trials programme on the island of Ireland, and also set up the regional Northern Ireland Cancer Trials Network. He was Clinical Director of this regional network and Clinical Lead of the Belfast Experimental Cancer Medicine Centre. Richard moved in 2019 to the University of Glasgow where he is Professor of Gastrointestinal Oncology and an Honorary Consultant in the Beatson West of Scotland Cancer Centre. He works as a medical oncologist in experimental cancer medicine and in lower gastrointestinal cancer (mainly in colorectal cancer but also in small bowel cancer and peritoneal malignancies) and conducts clinical and translational research in these diseases. He has been Chief Investigator on many local, national and international cancer clinical trials in both early and late phase settings. He is passionate about improving outcomes for cancer patients through research and bringing discovery science into the clinic, and in training the next generation of cancer researchers and clinicians.

Conference Abstract

A Modular, First-in-Human Study of the dUTPase Inhibitor CV6-168 in Combination with 5-Fluorouracil

CV6-168 is a first-in-class (FIC) DNA uracilation agent that selectively inhibits dUTPase, a key enzyme in maintaining genomic integrity. By inducing the misincorporation of uracil into DNA when co-administered with thymidylate synthase (TS) inhibitors, CV6-168 leads to enhanced DNA damage and cancer cell death. The drug's mechanism also activates immune-stimulatory pathways. Notably, CV6-168 does not inhibit dihydropyrimidine dehydrogenase (DPD), the enzyme responsible for the catabolism of 5-fluorouracil (5-FU), thereby minimizing risks of drug-drug interactions and complex dosing modifications.

This study, the first in humans, is designed to assess the pharmacokinetics (PK), safety, and tolerability of CV6-168 in combination with bolus and infusional 5-FU and folinic acid (FA) in patients with advanced malignancies.

The primary objective of this modular Phase I/IIa study is to evaluate the safety and tolerability of CV6-168 in combination with 5-FU and FA. Secondary objectives include characterizing the PK profiles of CV6-168 and 5-FU both as single agents and in combination, as well as assessing their antitumor efficacy. Exploratory objectives aim to investigate multiple pharmacodynamic assays related to the drug's mechanism of action, including potential predictive biomarkers for CV6-168 activity.

The study's modular design enables adaptive testing based on emerging data. In Module 1, Part A (dose-escalation), up to 51 patients with incurable advanced solid tumours will be enrolled using a "3 + 3" design to determine the maximum tolerated dose (MTD).

Part B will expand on this cohort to establish proof of concept (PoC) and determine the recommended Phase II dose and schedule. Optional Parts C and D may involve further dose optimization and cohort expansions, respectively. The expansion cohorts in Part B will include patients with various tumour types to assess response rates compared to historical data.

The modular design provides flexibility to adapt the study protocol based on real-time data, reducing the time between emerging preclinical/clinical findings and clinical implementation. By minimizing the number of patients exposed to suboptimal doses, the trial efficiently balances patient safety with the need for timely data generation. This approach addresses the inherent challenges of oncology drug development, where rapid adaptation is necessary due to the evolving therapeutic landscape.

Trial Registration: ISRCTN12434145.

Early Career Showcase

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Can metabolic reprogramming alter T cell ability to kill lung tumour cells?

Matilda L Downs, Ellen Montgomery, Ciara Cunningham, Nikita Lewis, Niamh Doherty, Connor Brown, Róisín Morelli, Beckie Ingram, Donna Small and Emma M Kerr

Immunotherapy (IO) has revolutionised the treatment of lung cancers, with long term survival now possible in patients. However, predicting who will not respond and understanding drivers of resistance are vital to capitalise on the effectiveness of IO treatment. Advanced lung cancers have distinct reprogramming of glucose metabolism, driven by Krasmutant specific copy gains. We postulate that the changes this imposes on the metabolic tumour microenvironment (TME) will alter T cell activation and function, resulting in poor response to IO. The goal of this project is to define how metabolic reprogramming might do this, and if targeting enhanced glucose metabolism in tumour cells has potential to enhance efficacy of IO in advanced tumours.

Using a combination of in vitro and in vivo approaches, we profile the impact of metabolic reprogramming on TME using multiomic methodologies. We define the subsequent impact on the functional T cell landscape by high-parameter flow cytometry, immunohistochemical and metabolic analyses, and evaluate the impact this has to IO response in advanced GEMM models in vivo.

Here, we confirm that advanced lung tumours with enhanced glucose metabolism display poor response to anti-PD1 treatment. Mechanistically, we can demonstrate that increased glucose metabolism in advanced tumour cells significantly alters the metabolic and cytokine profiles of the TME that can actively block T cell proliferation. Inhibition of this metabolic axis, both genetically and pharmacologically, reverts this phenotype. Furthermore, by comprehensively analysing the T cell landscape we see changes in recruitment, localisation, co-stimulation, and activation of distinct T cell subtypes that together promote a more immunosuppressive, "pro-tumour" landscape. We are currently evaluating metabolic strategies to revert this TME stress, switching back on a cytotoxic response to IO therapy in advanced lung cancer models.

Reprogramming of the TME by glucose-addicted lung cancer cells has a dramatic impact on T cell subsets at multiple levels – recruitment, infiltration, metabolic requirements, activation, co-stimulation, and checkpoint expression – ultimately driving a tolerant TME that in turn dampens response to IO treatment. Reverting this metabolic change in cancer cells has the potential to restore T cell function and enhance IO response, therefore our work now focuses on defining best therapeutic approaches to deliver this.

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STEALTH: Silent Technology to deliver Engineered Antigens for a Lethal TH1 response against mutant p53 in TNBC.

Cory Fines, Helen McCarthy, Niamh Buckley

While Triple Negative Breast Cancer (TNBC) accounts for 15-20% of BC, it is associated with a disproportionately high number of deaths. This is underpinned by its aggressive nature, heterogeneity, and lack of targeted treatments. Breast cancer was historically seen as a "cold" tumour and thus many immunotherapies would be ineffective. However, TNBC has been shown to have immune cell infiltration and are responsive to immunotherapies such as the clinically approved PD-1/PD-L1 inhibitors. While these are effective, only a small proportion of TNBC patients are PD-1/PD-L1+. There is therefore an unmet clinical need to develop alternate treatment options.

Therapeutic cancer vaccines have been studied for immune "hot" cancers and are used to stimulate the patients' adaptive immune system to fight against specific cancer antigens. While the identification of cancer- specific antigens for individual patients would likely elicit the best therapeutic effect, this is labour and time intensive leading to the use of antigens that has shared expression over the patient population.

Up to 90% of TNBC harbour a p53 mutation with the vast majority resulting in protein stabilisation and overexpression. This results in de novo expression of formerly cryptic self p53-determinants and provides a window of discrimination from normal cells which maintain very low basal levels of p53.

Together this makes mutant p53 an attractive therapeutic vaccine target. To date over 20 clinical trials using p53 as a vaccine target have been carried out, but with limited immune response and/or therapeutic impact. The most promising to date has combined a DNA viral based vaccine with Gemcitabine (GEM), which unlike most other chemotherapies, is thought not to deplete all immune cells and in fact has been shown by a few studies to selectively modulate immune responses. Our aim was to build on this clinical observation to investigate the immunomodulatory role of GEM in TNBC and combine this with a novel mRNA vaccine which allows for sequence modification to ensure a more robust and prolonged TH1 response. Using a range of in vitro and in vivo assays we have shown GEM can decrease macrophage and monocyte derived suppressor cells (MDSCs) recruitment into the tumour microenvironment. Furthermore, GEM can promote M1 macrophage polarisation and increase tumour T-cell abundance. In all, GEM reduces pro-tumorigenic and increases anti-tumorigenic immune cells in the tumour. Our studies also showed that GEM's immune impact decreases over time post treatment, and the optimal therapeutic window for combination with the p53 vaccine is 24hrs. We now aim to combine our optimised GEM regimen with our novel p53 mRNA vaccine to maximise therapeutic responses and ultimately improve outcome for TNBC.

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Characterisation of quantitative imaging biomarkers for inflammatory and fibrotic radiation-induced lung injuries using preclinical radiomics

Kathryn H Brown, Mihaela Ghita-Pettigrew, Brianna N Kerr, Letitia Mohamed-Smith, Gerard M Walls , Conor K McGarry, Karl T Butterworth

Background and purpose: Radiation-induced lung injury (RILI) a major dose limiting factor that occurs in 15-40 % of lung cancer patients treated with chemoradiation. Current diagnostic models are only capable of identifying RILI when it is well established and are limited in differentiating acute inflammatory and late fibrotic disease. In this study, we used a rapidly evolving area of research that uses medical images to develop imaging biomarkers in preclinical models correlated with longitudinal biological biomarkers of inflammatory and fibrotic phenotypes.

Materials and methods: Female C3H/HeN and C57BL6 mice were irradiated with 20 Gy targeting the upper lobe of the right lung under cone-beam computed tomography (CBCT) image-guidance. Blood samples and lung tissue were collected at baseline, weeks 1, 10 & 30 to assess changes in serum cytokines and histological biomarkers. The right lung was segmented on longitudinal CBCT scans (ITK-SNAP) and radiomics features (n = 842) were extracted using PyRadiomics. Longitudinal changes were assessed by delta radiomics analysis and principal component analysis (PCA) was used to remove redundancy and identify clustering. Prediction of acute (week 1) and late responses (weeks 20 & 30) was performed through deep learning using the Random Forest Classifier (RFC) model.

Radiomics image analysis identified features that correlated with inflammatory and fibrotic phenotypes. Predictive features for fibrosis were detected from PCA at 10 weeks yet overt tissue density was not detectable until 30 weeks. RFC prediction models trained on 5 features were created for inflammation (AUC 0.88), early-detection of fibrosis (AUC 0.79) and established fibrosis (AUC 0.96).

This study demonstrates the application of deep learning radiomics to establish predictive models of acute and late RILI applicable to lung cancer patients. This approach also supports the wider application of radiomics as a non-invasive tool for detection of radiation-induced lung complications.

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Epigenetic Reprogramming in Drug-Tolerant Persistent Colorectal Cancer Cells

Fatemeh Mirzadeh Azad, Axelle Larue, Yaser Atlasi

The development of drug-tolerant persister (DTP) cells poses a significant challenge in colorectal cancer (CRC) treatment, particularly with 5-fluorouracil (5-FU)-based chemotherapy that is the standard-of-care treatment in CRC. However the epigenetic adaptation underlying DTP formation remains less understood. Here, we establish an in vitro model for DTP formation, showing that DTPs' resistance to 5-FU is reversible and that 5-FU-tolerant cells exhibit multidrug resistance. This underscores the need to identify novel therapeutic targets in DTPs.

Our research revealed that DTPs undergo a profound epigenetic reprogramming, suggesting that targeting epigenetic vulnerabilities may provide a promising strategy to eliminate DTP cells. Using time resolved epigenetic profiling, we show that DTPs gain activity at cis-regulatory elements that are enriched with TEAD and AP-1 motifs and upregulate revival stem cell and inflammation transcriptional programs. Accordingly, we demonstrate that inhibiting TEAD transcription factors significantly impairs DTP formation, supporting their potential as therapeutic targets. In line with the observed reprogramming of transcriptional enhancers, we noted a significant change in YAP1-TAZ signalling associated with DTP formation.

Our research on characterizing the epigenetic landscape in DTPs provides a foundation for developing effective strategies to prevent or overcome chemotherapy resistance and tumour relapse in CRC.

Timothy O'Brien, MD
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Enhancing the neoadjuvant treatment of rectal cancer by targeting Inhibitor of Apoptosis Proteins

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Of the ~50,000 cases of bowel cancer diagnosed in Ireland and the UK annually, one third occur in the rectum. Total Neoadjuvant Therapy (TNT) is a standard of care option for locally advanced rectal cancer and involves a sequence of (chemo)radiotherapy and systemic chemotherapy prior to surgery. Multiple benefits of TNT have been reported including a greater chance of avoiding an operation in the event of a complete response as well as improvements in rates of local and distant disease recurrence. However, despite TNT, most patients will still require significant surgery and approximately 25% will relapse within 3 years leading to death in most cases.

A potential strategy to improve the effectiveness of TNT is to increase the rate of cell death (apoptosis) induced by radiation and chemotherapy. Inhibitor of Apoptosis Proteins (IAPs) are frequently upregulated in rectal tumours and correlate with poorer responses to neoadjuvant therapy and a worse prognosis overall. Interestingly, intra-tumoral bacteria such as Fusobacterium nucleatum can also increase IAP expression and convey therapy resistance. Therefore, incorporating a small molecule IAP antagonist into the TNT paradigm might improve tumour regression and survival rates, at least in a subset of patients.

The clinically relevant dual antagonist of cIAP1/2 and XIAP, tolinapant, was combined with different radiation and chemotherapy schedules in two- and three-dimensional in vitro models including the APC, KRAS and p53 mutant rectal cancer-specific cell lines, SW837 and SW1463. Live cell imaging (Incucyte), viability assays (CellTiterGlo), Annexin V Propidium Iodide flow cytometry and Western Blotting were performed to investigate the impact of IAP inhibition on proliferation and apoptosis. Several subspecies of F.nucleatum were grown anaerobically and cocultured with cancer cell lines and THP1 monocytes.

Tolinapant enhanced apoptosis in all radiation schedules explored including single fraction (5 Gy), short-course (5 x 5 Gy) and chemo-radiation (5 x 2 Gy plus 5-fluorouracil). These effects were more pronounced in the presence of exogenous Tumour Necrosis Factor alpha (TNFa). Tolinapant/TNFa increased the cytotoxicity of chemotherapy and reduced the formation of 5FU drug-tolerant persister cells. Finally, F.nucleatum infection increased the proliferation of colorectal cancer cells and elevated cIAP2 expression whilst supernatant from F.nucleatum-infected monocytes enhanced the effect of tolinapant in a TNFa-dependent manner.

This preclinical work suggests that antagonizing IAPs with tolinapant could enhance radiation- and chemotherapy-induced apoptosis in the total neoadjuvant management of rectal cancer. Tumours that are rich in TNFa, for example, those with abundant F.nucleatum may be more susceptible to this approach. An in vivo efficacy study is ongoing.

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Understanding Barrett's oesophagus: Insights from a population-based Barrett's oesophagus register

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Oesophageal adenocarcinoma has been highlighted as a cancer of unmet need as diagnosis often occurs at late-stage disease with poor survival outcomes. Barrett's oesophagus, the precursor to oesophageal adenocarcinoma, offers an opportunity for early detection and diagnosis. Previous work from the Northern Ireland Barrett's register (NIBR) has shown an increasing trend in Barrett's oesophagus incidence and also that the risk of progression to oesophageal is not uniform across all Barrett's oesophagus patients. Work is currently ongoing to: 1. update the incidence and progression trends now that the register contains >28,000 patients and longer follow-up is available and 2. better establish which patients are at increased risk of progression to adenocarcinoma. Preliminary unpublished findings of this work will be presented.

A Public and Patient Involvement (PPI) group was established in June 2020 to inform the development of future Barrett's oesophagus research projects, and the group quickly identified an area of unmet need for the standardisation of the information provided to patients at the time of their Barrett's oesophagus diagnosis. Together with the PPI group, we co-designed an evidence-based patient information leaflet using a six-step co-design model involving rounds of iterative feedback and pilot testing with lived experience and clinical reference groups. The co-design process identified several important areas for inclusion in the leaflet including what Barrett's oesophagus is, what causes it and how it is managed. Balancing risk communication of a pre-malignant condition with a relatively low lifetime risk of cancer progression, was a key focus of discussions and feedback at the co-design meetings. Overall, the leaflet and in particular how it communicates the risk of developing cancer has received positive feedback from both Barrett's oesophagus patients and clinical staff and has been disseminated to endoscopy clinics across Northern Ireland.

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The majority of DNA repair deficiencies do not alter the correlation between relative biological effectiveness (RBE) and linear energy transfer (LET) in CRISPR-edited cells

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Cancer is driven by genetic alterations which affect radiosensitivity. Radiotherapy is typically given with a standard dose. As a result, a proportion of patients are under- or over-dosed.

Biological optimization would not only allow individual dose prescription but also a more efficient allocation of limited resources (particle therapy). Despite dosimetric benefits, particle therapies also induce greater levels of complex damage than X-rays. Despite significant interest in optimizing LET by tailoring radiotherapy plans, RBE's genetic dependence remains unclear. This study aims to better define the RBE/LET relationship in a panel of cells with defects in DSB repair pathways.

CRISPR-Cas9 was used to generate defects in different DNA repair genes (ATM, BRCA1, DCLRE1C, LIG4, PRKDC, TP53 and FANCD2) in normal RPE-1 cells. Survival and DNA damage repair were evaluated post-exposure to photons, protons (LET 1 and 12 keV/µm), carbon-ions (LET 34 and 73 keV/µm) and alpha-particles (129 keV/µm).

Key NHEJ notably affected photon sensitivity (Lig4-/- SER = 1.8 and ATM-/- SER = 2), with genes associated with HR and complex damage had minor effects (BRCA1-/- SER = 1.2). Wild-type cells exhibited RBEs of 1.1, 1.3, 2.6, 3,2 and 5.0 for low- and high-LET protons low- and high- LET carbon-ions and alpha-particles respectively.

53BP1 foci data revealed reduced detectable DSBs with increasing LET due to lesion clustering, resulting in larger and brighter foci compared to X-rays. This clustered damage is also hard to revolve as seen by the percentage of persistent damage 24 hours after exposure, 6% X-ray, 11% Low-LET carbon, 22% High-LET carbon and 50% alpha-particles in WT cells. Mechanistic modelling suggests these results are consistent with there being no repair pathway dependence for survival which is specific to high-LET irradiation, and that as with X-rays, NHEJ has the biggest impact on the repair of high-LET damage and consequent decisions regarding cell fate.

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Using Organoids as a Patient Avatar to support the development of liquid biopsy-based assays

Syed Umbreen, Yu Sun, Alex McIntyre, Micheal Ryan, Charity Hall, Paul Mullan, and Niamh Buckley

Liquid biopsy offers a non-invasive method for detecting tumour-derived biomarkers, such as extracellular vesicles (EVs), circulating tumor DNA (ctDNA), and circulating tumour cells (CTCs) in the blood. However, tumour heterogeneity and limited patient samples present challenges for the development and optimisation of these assays. Patient-derived organoids (PDOs), which replicate the structure and function of primary tumours, provide a novel platform for use as ex vivo tumour models. We hypothesise that PDOs release similar biomolecules in their secretome as tumours do in the bloodstream. This study explores the potential of PDOs as "patient avatars" to improve the development of liquid biopsy assays, aiming to enhance their accuracy and clinical application for personalized cancer diagnostics.

Patient-derived organoids (PDOs) were established from biopsies and ascitic fluid of pancreatic, breast, and ovarian cancer patients. The nucleosomal profile, cfDNA quantity and DNA methylation markers were compared between the PDO secretome and patient plasma or FFPE samples to assess biomarker correlation.

PDOs derived from tissues exhibited robust growth, particularly pancreatic organoids. Factors influencing organoid establishment included cell viability, the live-to-dead cell ratio, tissue integrity and matrigel dome formation. PDO-derived cfDNA nucleosome profiles closely match patient blood profiles, with higher fractions of methylated DNA in the organoid secretome compared to FFPE samples. Organoids from ascites were more difficult to establish, exhibiting smaller, rounder morphology than tissue organoids, and ascites cultured in 2D were more resistant to standard chemotherapy.

PDOs offer a valuable model for developing liquid biopsy assays, acting as patient avatars to refine diagnostics and improve early cancer detection and monitoring. The next steps include expanding the PDO sample size to increase diversity, conducting longitudinal analysis of PDO secretomes to track biomarker changes over time, and evaluating therapeutic responses to correlate secreted biomarkers with treatment outcomes, aiming to establish predictive liquid biopsy assays for personalised cancer treatment.

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The cancer-associated SF3B1^{K700E} spliceosome mutation confers enhanced susceptibility to SMAC mimetics

Lydia E Roets, Jaine K Blayney, Alex Mutch, Patrick Preston, Hayley McMillan, Ken I Mills, Kienan I Savage, Katrina M Lappin

Recurrent somatic mutations in the key spliceosome component, SF3B1, have been identified at various frequencies across several cancer types. The most common hotspot mutation is the K700E missense mutation and while its effects on splicing have been well characterised at the molecular level, the mis-spliced genes that contribute to cancer progression and/or dictate responses to therapy are still unclear. We used an isogenic K-562 cell model to assess the impact of the SF3B1^{K700E} mutation on the cellular response to various apoptosis-inducing agents. Further validation of 'hit' compounds was conducted with an additional isogenic NALM-6 cell model and two matched lung mesothelioma and pancreatic adenocarcinoma models. Combined, our data suggest that the SF3B1^{K700E} mutation alters the levels of key apoptotic and necroptotic effectors, causing a shift in the balance of pro-survival (i.e., cFLIP and BCL-2) and Programmed Cell Death-associated (i.e., RIP(K1) and RIPK3) proteins, that ultimately confers greater susceptibility to SMAC mimetic-induced cytotoxicity. As such, the SF3B1^{K700E} mutation could serve as a useful biomarker to stratify cancer patients for therapies with SMAC mimetics.

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Exploiting 5FU-Induced Vulnerabilities in Colorectal Cancer

Scott Monteith, Jamie Roberts, Cecilia McCluskey, Shauna Lambe, Emily Rogan, Melissa LaBonte Wilson, Daniel Longley, Simon McDade.

Standard of care for the majority of colorectal cancer (CRC) patients is 5-fluorouracil (5FU)-based chemotherapy. However, resistance is found in over half of patients with metastatic disease. This can emerge from a subpopulation of drug tolerant persister (DTP) cells which exit their normal proliferative state to survive. Upon removal of the stress, DTP cells can resume normal growth, clinically mimicking tumour relapse. Understanding DTP biology may provide insight to prevent their emergence or target them for treatment. To identify mediators of increased sensitivity and resistance to 5FU, a genome-wide CRISPR-knockout screen was performed on SW620 cells in combination with 5FU. Gene hits were identified using two computational methods – MAGeCK RRA and DrugZ. Across four biologically relevant comparisons of drug-treated samples (2.5μM or 5μM) versus a matched control, DrugZ identified 66 sensitiser and 266 resistance genes (FDR<0.1).

Many of these hits were common across multiple comparisons, while others revealed time course progression and provided insight to the uncoupling of intrinsic resistance versus DTP biology. To prioritise gene hits, we performed gene set analysis on CRISPR hits and integrated muti-omic datasets. Sensitiser biology included DNA repair pathways, epithelial-to-mesenchymal transition (EMT) and cell cycle checkpoints. Some of these genes were also induced by 5FU in RNAseq data, making them attractive targets to inhibit in combination with 5FU. Resistance biology included acetylation, mTOR signalling, metabolic changes and transcriptional regulation. While in vitro validation is required of both sensitiser and resistance hits, this data-driven approach has identified promising targets for increasing patient response to 5FU and provided insight to resistance biology, which may be possible to reverse or prevent.

Thank You

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Organizing Committees

A heartfelt thank you to the International Organizing Committee and the Local Organizing Committee, whose dedication and commitment to advancing cancer research have been instrumental in shaping this symposium. Your tireless efforts in curating a comprehensive and diverse scientific program have ensured a platform for meaningful discussions and collaborations.

Sponsors

We gratefully acknowledge the generous contributions from our sponsors, whose support has been vital to the success of this event:

- *The Charles and Patricia Heidelberger Foundation for Cancer Research* - for its continued sponsorship and unwavering commitment to the legacy of Charles Heidelberger.
- *Sponsors* - for their generous sponsorship, enabling the symposium to bring together leading experts and emerging voices in cancer research from around the world.

Queen's University Belfast

We extend special thanks to Queen's University Belfast and the Patrick G. Johnston Centre for Cancer Research for hosting this year's symposium and providing an inspiring venue that embodies the spirit of scientific excellence.

Volunteers and Support Staff

We would also like to express our gratitude to the numerous volunteers, administrative staff, and support teams who have worked behind the scenes to ensure the seamless execution of the symposium. Your efforts have been invaluable and greatly appreciated.

Participants and Speakers

Finally, we wish to thank the distinguished speakers and participants whose contributions to the symposium have enriched the discussions and broadened the scope of our shared knowledge. Your expertise and passion for cancer research continue to inspire and drive progress toward a future free of cancer.

Thank you all for your support, collaboration, and participation in this year's symposium. Together, we move closer to achieving our common goal of transforming cancer treatment and improving patient outcomes worldwide.

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