Trinity St James's Cancer Institute

SCIENTIFIC REPORT 2018-2022

Institiúid Ailse Choláiste na Tríonóide/San Séamas
Trinity St James's Cancer Institute

ECI CANCER CENTRE

Welcome to the Trinity St James's Cancer Institute's Scientific Report 2018-2022

TSJCI was established in 2014 as a collaborative project between St James's Hospital, Ireland's largest hospital, with St. Luke's Radiation Oncology Network, and Trinity College Dublin, its premier university. TSJCI is formally constituted under a memorandum of understanding between the institutions. In 2019, TSJCI was designated as a Cancer Centre by the Organisation of European Cancer Institutes (OECI), the first of its kind in Ireland. OECI accreditation is important as it helps to ensure that cancer patients in Ireland receive the same high standard of treatment and care as in lead Cancer Institutes in other countries.

Research is a critical component of TSJCI, spanning cancer prevention and early diagnosis; optimal treatment selection, based on specific information –at a molecular level- of a given patient's tumour; ways of helping the body's immune system to fight cancer; and living with and beyond cancer. Our goal is to advance all research findings from across the Institute (whether they are fundamental, translational, or clinical research findings) to the benefit of cancer patients, ensuring that -if cancer cannot be prevented- patients achieve the best possible quality of life and best possible outcome from their cancer diagnosis. While this report does not claim to summarise all of our research at TSJCI, it introduces many of our key researchers and, I hope, it offers a flavour of our many exciting collaborative cancer research studies.

Overall, this report aims to showcase research at TSJCI, to increase awareness of our research to patients and other members of the public and to foster further local, national and international research collaborations. I am hugely grateful to our excellent patient representative group who help with optimal design of our research and give advice throughout, helping to ensure our studies are addressing the most important and timely questions. This research would not be possible without the support of many funding authorities, philanthropic donors, and industry partners; to whom we are very grateful.

On a personal note, it is my honour and privilege to direct TSJCI research. I am indebted to TSJCI's Prof. Maeve Lowery (Academic Director), Prof. John Kennedy (Clinical Director), and our Research Theme Leaders Profs. John O'Leary, Karen Cadoo, Cara Martin, Adrian Bracken, Clair Gardiner, Joanne Lysaght, and Juliette Hussey for their unwavering support.

A particular word of thanks is due to Dr Patricia Doherty, Senior Research Programme Officer and TSJCI OECI Coordinator who, also drawing on her expertise as a former senior research scientist in Ireland and Canada, worked tirelessly to collate all the information included in this report; ably helped by Ms Eppie Ní Dhiarmada, TSJCI Executive Officer.

I very much hope you enjoy this report and find it informative. For further information please do not hesitate to get in touch: **thecancerinstitute@tcd.ie** and visit **stjames.ie/cancer/research**.

Sincerely,
Prof. Lorraine O'Driscoll PhD, FTCD, FRSB, MRIA

Overview of the Trinity St James's Cancer Institute

The research **vision** of the TSJCI is to advance cancer care through internationally recognised fundamental, translational, and clinical research in cancer prevention; molecular and precision oncology; cancer immunology; and cancer survivorship and supportive care, leading to improvements in health status and quality of life for people in Ireland and beyond. More specifically our **goals** are to:

1. Decrease the burden of cancer by conducting focused, impactful fundamental, translational, and clinical **research** into cancer prevention, causes, multi-modal therapies and survivorship.
2. Provide sustainable, long-term support to cancer research within the Trinity St. James's Cancer Institute, by **building and maintaining a community** of highly skilled world class researchers and attracting internationally competitive scientists and clinicians to the Institute.
3. Position TCD and its constituent hospitals and institutions as a nationally and internationally recognised hub for cancer research; ultimately
4. Enhance the quality and value of our **patient care**.

TSJCI aims to develop an internationally recognised comprehensive cancer center. TSJCI is committed to collaborations (e.g., between oncology, social and behavioural science, epidemiology, genetics/genomics, pharmacology, and allied health sciences, law, and the arts) that can lead to new discoveries, conceptual models, and strategies to reduce the burden of cancer in diverse populations and across the cancer continuum.

Our research strategy **builds on existing strengths** and integrates **key research areas** across four main themes. Discovery, translational, and clinical research, encompassing cancer clinical trials, radiation oncology research, nursing research and a broad spectrum of allied health professional research fields, spans the breadth of these four themes and results in a horizontally and vertically interwoven, multidisciplinary, vibrant cancer research network (**Figure 1**).

TSJCI RESEARCH METRICS 2018-2022

€65.5m
New contracts signed

€46.8m
Research expenditure

1,867
Publications

~20,000
Citations

12
Invention Disclosures

3 Patents

> 100
Clinical Trials

102 PhD
10 MSc research
7 MD

Figure 1. Research theme structures at TSJCI

Research at TSJCI is overseen by a Research Lead, supported by a Research Themes Leadership Group of scientists and clinicians representing the spectrum from fundamental, translational, and clinical research, including allied health professionals. The purpose of the Research Theme Leadership Group is to provide appropriate governance of research conducted at TSJCI Current Research Theme Leadership is outlined in **Table 1** below and **Figure 2** overleaf.

THEME	LEADER(S)		
Cancer Prevention	Prof. John O'Leary	Prof. Karen Cadoo	Dr. Cara Martin
Molecular and Precision Oncology	Prof. Lorraine O'Driscoll	Prof. Adrian Bracken	
Cancer Immunology	Prof. Clair Gardiner	Prof. Joanne Lysaght	
Cancer Survivorship and Supportive Care	Prof. Juliette Hussey		

Table 1. TSJCI Research Team leadership

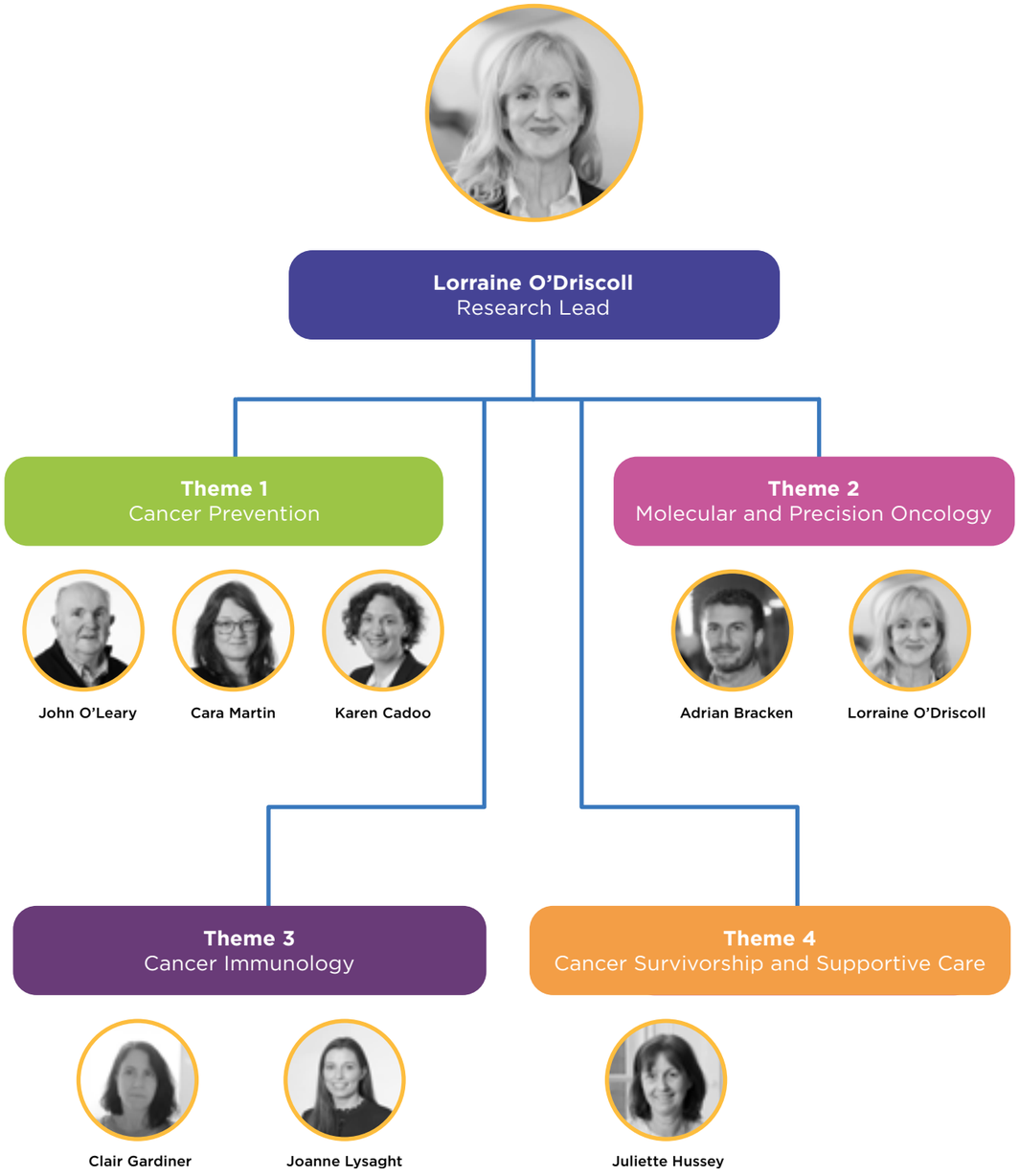


Figure 2. Organogram of TSJCI Research leadership (2023)

Research Highlights

The Trinity Academic Cancer Trials Group (TACC)

(Funder: Health Research Board; 2022-2026)

The Trinity Academic Cancer Trials Group (TACC) is a Health Research Board (HRB) partnership initiated in 2022 supporting cancer clinical trials to improve health and care – comprised of the Trinity St James's Cancer Institute at St James's Hospital, Tallaght University Hospital and the Midlands Regional Hospital Tullamore, with academic partner Trinity College Dublin – was awarded over €2m from the HRB.

Working together, the TACC hospitals provide care to an immediate local population of 800,000 people and the three cancer-treating hospitals collectively provide care to 7000 patients with cancers annually.

The TACC, led by Prof. Maeve Lowery, was one of six cancer trials groups awarded funding from the HRB. The funding is tackling childhood and adult cancers, making a real difference to the lives of cancer patients, allowing them more access to cancer trials by increasing the resources and expertise required to conduct them.

The Irish Research Radiation Oncology Group (IRROG)

(Funder: Health Research Board; 2022-2026)

Prof Sinead Brennan,
Consultant Radiation Oncologist at St. Luke's Radiation Oncology Network & St. James Hospital; Clinical Associate Professor, TCD

The Irish Research Radiation Oncology Group (IRROG) is a collaborative group which aims to unite the five Health Service Executive (HSE) radiotherapy centres under a common research function.

Led by Prof. Sinead Brennan, IRROG was initiated in January 2022 from a Health Research Board grant and co-investment from a number of collaborators. IRROG comprises of Cork University Hospital Radiotherapy Department, Galway University Hospital Radiotherapy Department, St Luke's Radiation Oncology Network (SLRON) at St. Luke's Hospital, Rathgar, SLRON at St James's Hospital and SLRON at Beaumont Hospital.

IRROG is undertaking several activities in order to elevate radiation oncology research in Ireland and, ultimately, position Ireland as an international leader in Radiation Oncology Research and Clinical Trials. Through IRROG, a co-ordinated strategic infrastructure is being established with the aim of ensuring uniform standards of excellence in clinical trials and creating a national portfolio of radiotherapy clinical trials. IRROG brings together a critical group of skilled multidisciplinary personnel with significant experience in clinical research and complex radiotherapy.
IRROG activities include national and international radiotherapy trials; investigating new technologies and combinations of drug therapy with radiotherapy; quality assurance, education and training; and co-ordination with national and public-patient groups to ensure that relevant important trials are performed for the benefit of Irish patients.

IRROG's vision is to improve cancer outcomes by providing all patients in Ireland with equal access to a portfolio of high-quality radiotherapy clinical trials. IRROG's mission is to build and support a national radiotherapy trials group and streamline work practices to ensure safe delivery of novel radiotherapy interventions through excellent research.

Through the "Irish Research Radiation Oncology Group National Conference" (Jan 2023), IRROG collaborated and interacted with key players in the Irish cancer research community in order to provide support, disseminate ideas and to ultimately enhance the research environment and experience for Irish cancer patients.

HEALED Consortium (The Personalised Active Cell Therapy Paradigm)

(Funder: Enterprise Ireland Disruptive Technologies Innovation Fund; 2021-2024)

The Personalised Active Cell Therapy Paradigm (HEALED) received €6.8m government funding as part of a 3-year programme, beginning in 2021, to develop next generation cell therapies for cancer. This consortium (TCD PIs: Prof. Aideen Long, Prof. Jacintha O'Sullivan and Prof. Maeve Lowery) will generate a pre-clinical tumour infiltrating lymphocytes (TIL) package and enable a new kind of revolutionary immunotherapy. HEALED combines the use of Remedy Biologics' nanoreactor technology, aCGT Vector's experience creating Good Cell Manufacturing Hubs, the patient-focused translational cancer research in TSJCI (TTMI) and University of Galway's experience in bioinformatics (SFI Centre for Research Training in Genomics Data Science), to create a pre-clinical package on TIL therapies.

TCD are specifically looking at the effects of energy metabolism, hypoxia and inflammation on the number, phenotype and migration potential of TILs in solid tumours of the ovary, breast, lung, colon, rectum, stomach, and oesophagus, and match this information with their TIL cell phenotype. This will help us understand the role of these biological processes in the tumour microenvironment and how this influences the TIL cell biology. We also aim to understand genetic changes in tumour tissues by conducting whole exome sequencing and RNA sequencing.

This will be used by University of Galway to predict appropriate neoantigens in the tumours, to aid in finding the most effective TILs. With the National Centre for Pharmacoeconomics (NCPE), we will investigate the expected cost effectiveness of TIL therapies from health-payers' perspective globally.

This group brings together deep capabilities in mass-scale functional biology, GMP clinical deployment, clinical and tumour microenvironment expertise in cancer, and molecular data analytics to create a world first in near-patient, personalised, functional cancer therapeutics. HEALED brings together an inter-disciplinary approach to generate awareness regarding the potential for TIL therapy to cure currently incurable cancers.

Deciphering the most clinically and biologically relevant circulating tumour cells (CTCs) in cancer metastasis

(Funder: Enterprise Ireland Innovation Partnership Award; 2018-2021)

Partnership: Prof John O'Leary and Becton Dickinson Circulating tumour cells (CTCs) are silent precursors of metastatic disease, that utilise various mechanisms to survive in the circulation and metastasise to distal sites. CTCs are believed to be responsible for metastatic seeding and tumour dissemination.

These cells originate in the primary tumour, before extravasating and entering the peripheral circulation where they circulate amongst immune cells and erythrocytes. CTCs are highly heterogeneous (existing as single, double or clusters) and often undergo EMT, resulting in a loss of the classical epithelial detection marker, EpCAM. The biology and clinical significance of non-classical CTCs such as those lacking EpCam expression or possessing the leucocyte marker CD45 is poorly understood. In addition, CTCs are also able to aggregate forming clusters, termed circulating tumour microemboli, whose size and concentration have been found to influence the development of metastases.

It is now accepted that CTC clusters have a survival advantage in the circulation, since the aggregation of the CTCs protects the tumour cells. CTCs have significant potential as clinical biomarkers in diagnosis, stratification and treatment, by facilitating early cancer detection, therapeutic target selection, real-time disease progression monitoring and real-time treatment response prediction. CTC enumeration is now considered a prognostic factor in breast, colorectal, and lung cancers.

This study, awarded over €800,000, focussed on evaluation of a number of CTC isolation devices to enable the full repertoire of CTC forms to be isolated and characterised by single cell sequencing using the BD precise assay technology.

The research group significantly gained from the technology transfer and support from BD, underpinning the research efforts of scientists and clinicians working in the cancer ecosystem and contributing directly to TSJCI, a key priority for the college. Direct links between BD and the university have been established and the group is proceeding with further single cell sequencing projects using the BD Rhapsody and is currently exploring further opportunities.

This research has advanced our understanding of the molecular basis of cancer metastasis and enabled us to move a step closer to the clinic to address the unmet need that exists in cancer metastasis. The research has also allowed us to develop ex-vivo models for CTC culture, propagation, and treatment testing. Our ability to grow CTCs in hypoxic conditions represents a significant step forward in technology development (TRL 3-5).

From the company perspective, it gave BD an opportunity to collaborate with world class clinical oncology researchers in order to apply the tools and methodology to CTCs. TCD and BD have built capacity around this work programme and had 2 SFI industrial fellowship grants.

As a leading global supplier, innovator and research focussed company, Becton Dickinson has a proven track record in working in collaboration with globally leading universities in the development and commercialisation of new products and processes. Interacting with high calibre scientists like the O'Leary group helped BD to drive their innovation and research forward, ensuring they are building the right products for customers.

The All-Ireland Cancer Liquid Biopsies Consortium (CLuB)

(Funder: HEA/North-South Research Programme; 2022-2027)

Founder and Lead Investigator: Prof. Lorraine O'Driscoll, TCD
Lead Investigator Northern Ireland: Prof. Paul Mullan, QUB
TCD Co-PIs: Dr. Kathy Gately, Dr. Sharon O'Toole, Prof. John O'Leary, Dr. James Beirne

The ambition and focus of the €4m All-Ireland Cancer Liquid Biopsies Consortium (**CLuB; Clubcancer.ie**) Emerging Hub of Excellence are on identifying and developing minimally invasive, cost effective, blood tests to complement or where possible replace surgical biopsies for cancer diagnosis and optimal treatment selection. CLuB will also use excised tumours as "avatars" to better understand the specific origin of important components of the liquid biopsy and to test the optimal drug treatment regime for a given patient.

CLuB aims to bring cohesive leadership, insights, novel approaches, excellence in research, training, and teaching collectively and on the individual components of liquid biopsies, feeding back into teaching North and South.

In collaboration with Queen's University Belfast and University of Galway, Club will deliver new knowledge on the importance and potential clinical relevance of various components of the liquid biopsies -individually and combined- including extracellular vesicles (EVs), tumour DNA (ct-DNA) and methylated DNA and circulating tumour cells (CTCs).

CLuB will also foster innovation, research, and development in the diagnostics industry by providing access to research infrastructure, know-how, and trained personnel. CLuB continues to unify and synergise current research on separate components of potential liquid biopsies while undertaking the cross-border multi-disciplinary training of six post-doctoral fellows and four PhD students, supported also by two funded nurses and a technician. Additionally, they have also

hosted many transition year (TY) students, held patient and public involvement and engagement (PPIE) events, and presented at events such as the Balmoral Show and European Researchers Night in addition to numerous national and international conferences.

NEO-adjuvant trial in adenocarcinoma of the oesophagus and oesophagogastric junction international study (Neo-AEGIS)

(Funders: Health Research Board, Cancer Research UK, Irish Cancer Society, Oesophageal Cancer Fund and French National Cancer Institute; 2013-2022)

Prof John Reynolds,
Head of Surgery, TCD;
Consultant GI surgeon,
St James's Hospital;
Clinical Lead, TSJCI

Adenocarcinomas of the oesophagus and oesophagastric junction (OGJ) have increased in incidence in the West over the last quarter century. In recent years, there has been a notable increase in the occurrence of adenocarcinoma, a type of cancer affecting the oesophagus and the junction between the oesophagus and stomach (OGJ), particularly in Western countries. To address this concerning trend, researchers conducted a large-scale clinical trial called Neo-AEGIS (CTRIAL-IE 10-14) across 24 medical centers in Europe. This international trial was led by TSJCI Clinical Lead, Prof. John Reynolds.

The study enrolled adults aged 18 and above diagnosed with adenocarcinoma at specific stages. Participants were randomly assigned to receive either perioperative chemotherapy or trimodality therapy. Perioperative chemotherapy involved cycles of various chemotherapy drugs given before and after surgery, while trimodality therapy combined chemotherapy with radiation before surgery. The main goal of the study was to compare overall survival between the two treatment approaches. Additionally, researchers assessed other factors such as disease-free survival, treatment complications, side effects, and quality of life.

The study found that both treatment approaches yielded similar results in terms of overall survival and other key outcomes like operative complications and quality of life after three years. However, the study was not large enough to draw definitive conclusions, and some data were incomplete.

Overall, Neo-AEGIS represents a significant effort to understand the best treatment options for adenocarcinoma of the oesophagus and OGJ. While the results suggest that both perioperative chemotherapy and trimodality therapy are viable options, further research is needed to confirm these findings and guide clinical practice effectively.

Personalised exercise rehabilitation in cancer survivorship: The PERCS Programme (PERCS)

(Funder: Irish Cancer Society; 2022- 2023)

Patients who undergo cancer treatments can experience side-effects including reduced fitness, muscle weakness, fatigue, depression, anxiety, which negatively impact survivorship. There is strong scientific evidence that exercise can positively impact many cancers, specific side-effects, and physical and mental wellbeing.

The COVID-19 pandemic has had a profound effect on the physical and mental wellbeing of the general population and of people diagnosed with cancer since March 2020. Therefore, there is an urgent need to make exercise accessible to as many cancer survivors as possible, particularly those impacted by COVID-19. This needs to be done in a way that considers the resources that are available in both the hospital and the community and refers people to appropriate services based on their own individual needs.

The PERCS project was an exercise triage and referral system, i.e., a system of patient assessment and onward referral to a suitable exercise resource, which resulted in improvements in physical and mental wellbeing and was applicable in a real-world setting. This model investigated an exercise triage and referral system for managing exercise and rehabilitation needs in cancer survivors which may be extended to other cancer centres or underpin a national model of care for cancer rehabilitation.

The research has contributed to a website that was co-designed by patients for patients with input from multiple disciplines including physiotherapy, occupational therapy, nursing, dietetics and psychology. Additionally, PERCS PI Dr Emer Guinan and PPI representative Ted Hennebry were featured in a video by Irish Cancer Society about PERCS study and the role of exercise during and after cancer and PERCS Project Manager Dr Louise Brennan and PPI representative Kay McKeon were featured in an article in the Irish Independent in February of 2023 to promote the study and the associated website.

This study developed a dedicated website cancerrehabilitation.ie (**Figure 3**) co-designed with patients for patients with input from multiple disciplines including physiotherapy, occupational therapy, nursing, dietetics, and psychology.

Figure 3. Personalised Exercise Rehabilitation in Cancer Survivorship dedicated website

The All-Ireland Cancer Network (AllCaN) Oesophageal Programme

(Funder: Breakthrough Cancer Research, Oesophageal Cancer Fund and CROSS - Cancer Research of the Oesophagus and Stomach - charity)

Director: Prof. Jacintha O'Sullivan, TCD
Co-Directors: Prof. Helen Coleman, Queens University Belfast and Prof. Juliette Hussey, TCD

The €1m AllCaN Programme represents a new, focused effort to implement advances in oesophageal cancer research as rapidly as possible through the creation of a collaborative, translational cancer research network.

Funded by Breakthrough Cancer Research with co-funding from the Oesophageal Cancer Fund (OCF), and CROSS the most talented and promising researchers across Irish institutions will be assembled into AllCaN forming an optimal configuration of expertise needed to solve key problems in Barrett's oesophagus and oesophageal cancer research with the aim to positively impact patient outcomes. AllCaN will establish for the first time an all-Ireland oesophageal consortium, bringing together experienced scientific, clinical and industry teams with internationally recognised experience in BO and OAC research and will work across four different work packages to achieve this: Improved Detection and Prevention, Co-Created Interventions, Targeted Diagnostics and Novel Therapeutics.

In addition to generating new knowledge, AllCaN will support the development of Ireland's oesophageal cancer community and will strive to advance evidence-based policy making and clinical guidelines. The programme is carried out with collaboration from Queen's University Belfast, University College Dublin, University of Galway, and University College Cork. Each element of this programme will significantly advance knowledge in designing new cancer prevention strategies, implementing lifestyle intervention changes, stratify those who are at risk of disease progression and finally identify new strategies to increase treatment response.

This will result in improved outcomes for BO and OAC patients. The programme is also in the process of launching a brand-new website in the coming months **(allcan.ie)**. Any new scholarly and/or societal outputs/outcomes will be communicated on this website.

Research Theme: Cancer Prevention

Theme Leadership

Prof John O'Leary,
Chair of Pathology and Consultant Histopathologist; Cancer Prevention Theme Lead,TSJCI

Dr. Cara Martin
Assistant Professor in Molecular Pathology, Tumour, Biology and Cancer Screening, Cancer Prevention Theme Lead,TSJCI

Dr. Karen Cadoo
Consultant Medical Oncologist and Cancer Geneticist, St James's Hospital; Clinical Associate Professor, TCD Cancer Prevention Theme Lead, TSJCI

Cancer is now the most common chronic disease in developed countries worldwide. In Ireland alone, excluding non-melanoma skin cancer, it is estimated that by 2040 cancer cases will increase by 81% for females and 108% for males. In addition, Ireland is following the global trend towards an ageing demographic that will result in a corresponding increase in the incidence of cancer.

There are increasing opportunities to improve our approach to cancer prevention. It is now also possible for some patients to identify the best approach to cancer treatment based on either their own genetic status or the genetic profile of their tumour. Fully characterising a person's genetic makeup and understanding their environmental exposures over time will enable us to tailor personalised measures to screen for and prevent cancer.

The Cancer Prevention Research Theme **(Figure 4)** within TSJCI comprises a broad spectrum of research areas, from molecular epidemiology, molecular diagnostics, cancer, genetics, translational research, cancer screening, disease modelling, behavioural science, and medical gerontology. They have several well-established research consortia, working around cancer prevention of ageing population **(www.tilda.tcd.ie)** and the cervical screening population **(www.cerviva.ie)**.

This theme's overall vision is to reduce morbidity and mortality from cancer through prevention and earlier detection of the disease, accomplished through the following strategic goals:

High level goals: TSJCI cancer prevention

Evaluating current screening protocols/programme and developing new approaches, technologies including molecular diagnostic approaches for cancer screening to support both prevention, early detection, and chemoprevention of cancers.

1. Developing new approaches to reducing susceptibility or exposure, to common modifiable risk factors (primary prevention). Examples of modifiable risk factors include smoking, alcohol, diet, insufficient physical activity, and obesity. Other modifiable risk factors include environmental risk factors such as occupational hazards, chemical agents, and infectious diseases such as Human Papillomavirus (HPV), Hepatitis B and C virus, (HBV, HCV) and Human Immunodeficiency Virus (HIV).
2. Understanding the genetic variants that predispose to cancer and using this knowledge to build a world-class cancer genetics service at TSJCI, which will be vital towards implementing preventative measures to reduce cancer incidence and mortality.
3. Conducting high quality research that informs the decisions and actions of knowledge users in the Irish health and social care system.
4. Focusing research on the implementation of interventions and adherence to recommendations on cancer prevention.

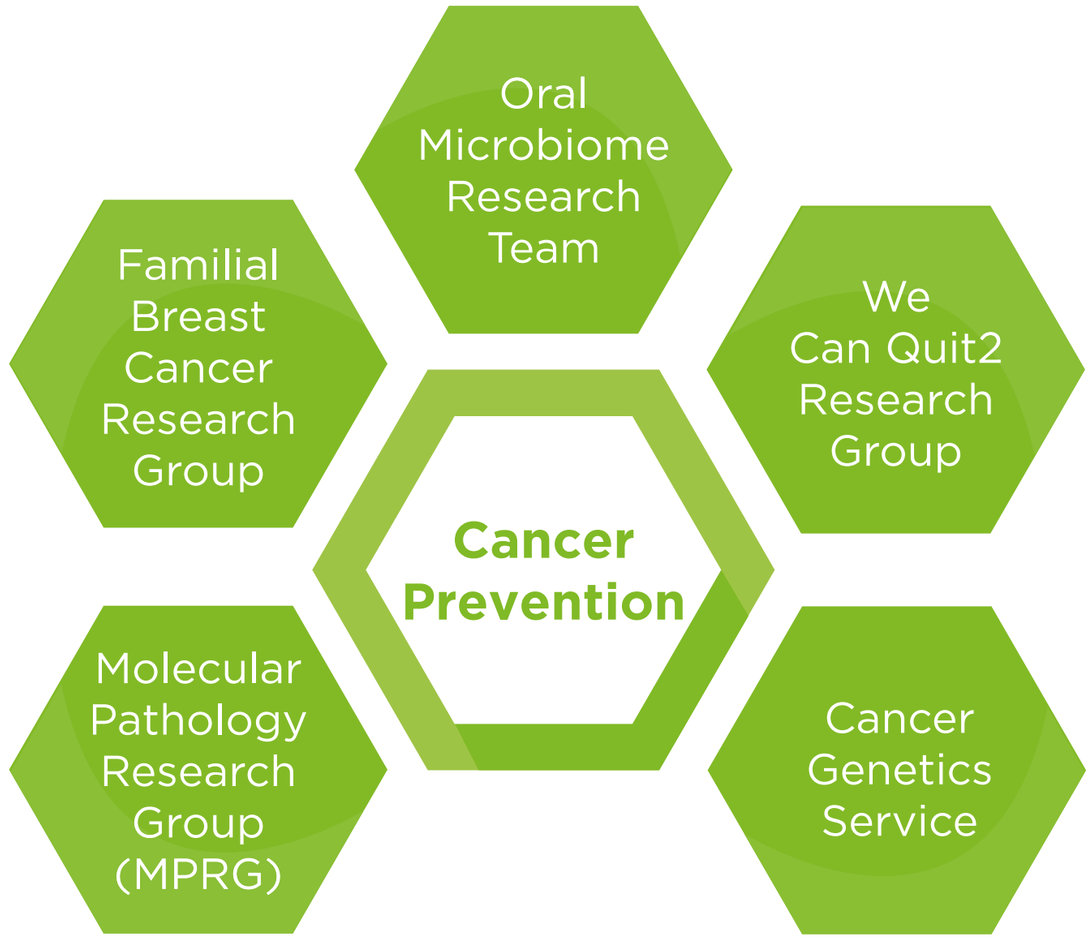


Figure 4. Cancer Prevention Research Theme at TSJCI

Oral Microbiome Research Team

Dr Gary Moran, Associate Professor in Dental Science, Head of the Oral Microbiome Research Group, School of Dental Science, TCD

Dr Claire Healy, Professor/ Consultant in Oral Medicine, School of Dental Science, TCD

Professor Moran's research focuses on the pathogenicity of oral microorganisms, specifically the fungal pathogen Candida albicans and the oral bacterium *Fusobacterium nucleatum*. His research involves a combination of molecular genetics, genomics and transcriptomics. The team has also carried out 16S profiling of the oral microbiome to better understand oral disease. The Oral Microbiome Research group is based at the Microbiology laboratory in the Dublin Dental University Hospital **(Figure 5)**.

Analysis of the oral metagenome of potentially malignant Oral Leukoplakia

(Funder: Health Research Board)

Oral squamous cell carcinoma (OSCC) accounts for 90% of oral cancers. According to the National Cancer Registry, the rate of OSCC in Ireland is increasing annually by 3.3% and early diagnosis and treatment is crucial if patients are to survive beyond 5 years. OSCCs can arise *de novo* or from preneoplasis such as Oral Leukoplakia (OLK). Our recent data show that these lesions are colonised with an altered microbiome which have been associated with malignant progression at other sites in the gastrointestinal tract. This study, in collaboration with King's College London, will examine a large cohort of OLK patients to determine if these bacteria are associated with high-risk lesions exhibiting severe dysplasia and will therefore allow us to design tests to identify those patients most at risk of developing oral cancer.

Interaction of *F. nucleatum* and oral keratinocytes

(Funder: Provosts Scholarship Award)

Among microbial species that have frequently been identified in association with OSCC and demonstrated to promote oral carcinogenesis, both *in vitro* and in animal models, include the bacterium *Fusobacterium nucleatum*. Infection of oral keratinocytes with *F. nucleatum* increased metastatic phenotypes such as cell migration, invasion, and angiogenesis. We hypothesise that colonisation of oral malignancies with *F. nucleatum* may result in poorer outcomes for oral cancer patients. This work is carried out in collaboration with Temple University and Virginia Tech and is expected to provide evidence for the role of *F. nucleatum* in worsening outcomes for oral malignancies.

Retrospective analysis of clinical and lifestyle factors linked to malignant progression of Oral Leukoplakia

(Funder: The Dublin Dental Hospital and the Health Research Board)

The goal of this retrospective review is to establish the clinical and histological characteristics and malignant transformation rates (MTRs) of oral leukoplakia and erythroplakia (OLK/OE) in an Irish cohort. Oral potentially malignant disorders (OPMDs) include a variety of conditions characterised by an increased risk for malignant transformation (MT) to oral squamous cell carcinoma (OSCC). The factors influencing rates of MT are not well understood, but associations with gender, clinical appearance, size, site, and degree of dysplasia have been reported. A retrospective chart review of all patients who have attended this clinic between 2007-2022 is being carried out. A database including data on age, gender, alcohol and tobacco consumption, site and histology of OLK/OE, duration of follow-up and change in degree of dysplasia or development of OSCC, is being compiled. This project will allow for the characterisation of the behavioural and clinical factors that increase risk of malignant transformation of oral leukoplakia and erythroplakia (OLK/OE) in an Irish cohort.

Figure 5. Oral Microbiome Research Team, 2024. L-R: Sviatlana Anishchuk, Claire Crowley, Gary Moran, Sheila Galvin, and Claire Healy.

Cancer Genetics Service

Dr Karen Cadoo, Consultant Medical Oncologist and Cancer Geneticist, St James's Hospital; Clinical Associate Professor, TCD Cancer Prevention Theme Lead. TSJCI

Dr David Gallagher, Medical Oncologist and Geneticist, St James's Hospital; Clinical Professor, TCD; National Clinical Lead in Cancer Genetics, National Cancer Control Programme

Dr Niamh Coleman, Consultant Medical Oncologist, St James's Hospital, Medical Oncology Academic Lead, TCD

Dr Rosie O'Shea, Principal Genetic Counsellor, St James's Hospital; Adjunct Assistant Professor, Genetic Counselling, School of Medicine, TCD

The Cancer Genetics service at St James's Hospital provides support for individuals and their families whilst undergoing investigations for hereditary cancer syndromes. The aim of the service is to identify individuals with a genetic predisposition to cancer through risk assessment and genetic testing, and to promote early detection of cancer and/or prevention strategies and inform medical management. The service works closely with other departments in the hospital, genetic testing laboratories, the NTPF and the NCCP to provide quality patient care and advance service development.

Our clinical team facilitates virtual and in-person genetic counselling consultations along with remote testing options. The service receives referrals nationwide and therefore the availability of virtual appointments has enabled remote patients to receive genetic counselling services without compromising patient care. The emerging availability of therapeutics on the basis of genetic testing has led to rapidly increasing demand for cancer genetics services. The service is facing significant challenges in meeting the increased demand for genetic testing and assessment in a timely manner.

An alternative pathway to improve access to cascade genetic testing for people with a high risk of hereditary cancer predisposition

(Funder: Irish Cancer Society)

With collaboration from the Gesinger Institute, the Royal Marsden Hospital, the Lynch Syndrome Ireland Patient Support Group, and GeneLinx, this research aims to improve access to cascade genetic testing in the cancer genetic service in St James's Hospital. Cascade genetic testing occurs in families where a known cancer predisposition gene is found and is associated with a high lifetime cancer risk.

A two-year wait exists for family members to access genetic counselling for cascade genetic testing in the service. Innovate service delivery solutions are required to overcome the access delay and the downstream effect of delayed cancer prevention and screening. This research project will develop and evaluate an alternative pilot digital cascade genetic testing pathway for those at high risk of inheriting a cancer pre-disposition gene. The findings of the research will also inform the implementation of the HSE - NCCP Hereditary Cancer Model of Care and can be leveraged to inform the future scale up of genomics into population-based cancer screening programs.

Clinician Research Leadership Award

(Funder: Irish Cancer Society)

Dr Karen Cadoo secured dedicated research time via the Irish Cancer Society Clinician Research Leadership award to focus on critical research in the inherited genetic cancer space. The ultimate aim is to ensure as many people as possible are aware of their own genetic risk of cancer. This project will establish a comprehensive database, biobank and inherited cancer risk registry from adult patients attending the cancer genetics service at SJH.

GENPROS

(Funder: Cancer Research UK, The Ronald and Rita McAulay Foundation, and the National Institute for Health Research, UK)

This observational study is designed to examine the difference in outcomes of two groups of people diagnosed with prostate cancer. GENPROS aims to evaluate the outcomes of patients with rare germline genetic variants including BRCA1, BRCA2, genes and other prostate cancer (PCa) predisposition gene mutations following PCa diagnosis and treatment.

The aim of this study is to follow up a group of people who have prostate cancer and who have a mutation in a gene that normally protects people against developing prostate cancer. The information collected will be used to work out whether there are differences in the aggressiveness of the disease between one group and another. This research study is taking place to help improve our understanding and allow us to give better treatment advice to people who get a prostate cancer diagnosis. This work is a collaboration with the Institute of Cancer Research and the Royal Marsden Hospital.

Molecular Pathology Research Group (MPRG)

Prof John O'Leary, Chair of Pathology and consultant histopathologist; Cancer Prevention Theme Lead,TSJCI

Dr Sharon O'Toole, Dept. Obstetrics and Gynaecology, PI with MPRG-Gynaecological Oncology Research

Dr Cara Martin, Assistant Professor in Molecular Pathology, Tumour Biology and Cancer Screening, Cancer Prevention Theme Lead,TSJCI

Clinical Collaborators: Prof. Colm Bergin (Consultant Physician in Infectious Diseases, SJH), Dr. Colm Kerr (Consultant in Infectious Diseases and General Medicine, Prof. Tom D'Arcy (Consultant Obstetrician and Gynaecologist, SJH and The Coombe Hospital), Dr. Gunther vun Bunau (Consultant Obstetrician and Gynaecologist, TUH and The Coombe Hospital), Dr. Roisin O'Connor (Consultant Histopathologist, SJH), Dr. Mary Toner (Consultant Histopathologist, SJH), Dr. Esther O'Regan (Consultant Histopathologist, SJH), Prof. Conrad Timon (Consultant Otolaryngologist, SJH)

The Molecular Pathology Research Group works in the areas of preventative medicine, precision medicine, basic scientific research, translational research and clinical trials and development of new diagnostics in clinical medicine (human and animal). The group's research work is focussed in the following areas: Cervical pre-cancer and cancer, Ovarian cancer, Prostate cancer, Head and Neck Cancer, Melanoma, Colorectal cancer, Cancer metastasis, the Cancer inflammasome, the cancer Immune Proteasome, Viruses and Cancer, Immune processing in cancer.

The Molecular Pathology Research Group hosts/ collaborates with several important international research consortia including **CERVIVA:** a consortium dedicated to research in HPV related cancers (cervix, anal, head and neck) and **PCRC (Prostate Cancer Research Consortium)**: a consortium dedicated to basic and translational research in prostate cancer **(tcd.ie/news)**

CERVIVA-Vax: Monitoring the impact of HPV vaccination in Ireland

(Funder: Health Research Board)

The introduction of primary prevention [vaccination] and changes to screening protocols [HPV testing], raise important clinical challenges for cervical screening programmes, most notably with regard to impact of HPV vaccination on screening as it is currently organised and how this will affect the disease landscape and sub-type of human papilloma virus (HPV), present in the Irish population.

Monitoring the impact of vaccination on screening is hugely important. CERVIVA-Vax led by Dr Cara Martin will generate, for the first time, Irish data relating to the early impact of HPV vaccination on cervical screening.

CERVIVA-Vax will assess the prevalence of HPV, HPV genotype diversity, abnormal cytology, and histology outcomes in vaccinated girls compared to age-matched unvaccinated women. We will investigate the impact of vaccination on screening uptake.

By investigating the early impact of HPV vaccination on screening in Ireland, CERVIVA-Vax will be able to inform policy and practice in relation to the best cervical screening approaches for vaccinated and unvaccinated women.

Molecular Pathology Research Group.

What influences cervical screening uptake in older women and how can screening programmes translate this knowledge into behaviour changing strategies? A CERVIVA-Cervical Check co-production project

(Funder: Health Research Board and the HSE National Screening Service)

Well-organised cervical screening is effective in reducing cervical cancer incidence and mortality. To achieve these benefits, high coverage is essential. In Ireland, the coverage target is 80%. While overall coverage has risen (from 61% to 79%) since the programme started in 2008, it has consistently been lower in older (50-60years) than younger (25-49years) women. This distinctive pattern is not seen in other countries with organised programmes and the reasons for it are unknown. This CERVIVA-Cervical Check co-production project is generating evidence on the influences on cervical screening participation among older women in Ireland, to inform development and implementation of evidence-based strategies to increase screening coverage in this group.

CERVIVA HPV Primary Screening Study – Molecular triage strategies for HPV positive women

(Funder: Health Research Board)

The CERVIVA- HPV Primary Screening Pilot Study is an observational cohort study which commenced in 2016 and has recruited over 13,000 women (aged 25-60years) who attended primary care for their routine cervical smear.

The study led by TCD was established in partnership with Cervical Check the National Cervical Screening Programme in Ireland, to evaluate a range of different HPV and novel biomarker tests and technologies for use in cervical screening, specifically in the context of HPV based primary screening. Our study is assessing a range of different triage options to help stratify those women at risk of developing cervical cancer.

The study is the first of its kind internationally that is looking at this range of molecular triage tests and their performance longitudinally. The study is ongoing they will continue to collect data on their cervical screening events for 10 years following their initial enrolment in the study.

ECHO: The epidemiology of HPV infection in oropharyngeal, oral cavity, and laryngeal cancer in Ireland (Funder: Health Research Board, Ireland)

Human papillomavirus (HPV) infection has been identified as a significant etiological agent in the development of head and neck squamous cell carcinoma (HNSCC). HPV's involvement has been linked to improved survival and prognosis in patients, indicating that they may benefit from different treatment strategies..

Only some data on the epidemiology of HPV infection in the oropharyngeal, oral cavity, and laryngeal SCC exists in Europe. Thus, this CERVIVA based study was carried out to investigate HPV's impact on HNSCC patient outcomes in the Irish population, one of the largest studies of its kind using consistent HPV testing techniques.

A total of 861 primary oropharyngeal, oral cavity, and laryngeal SCC cases diagnosed between 1994 and 2013, identified through the National Cancer Registry of Ireland (NCRI), were obtained from hospitals across Ireland and tested for HPV DNA).

Both overall and cancer-specific survival were significantly improved amongst all HPV-positive patients together, though HPV status was the only significant predictor of survival in the oropharynx. Amongst HPV-positive patients in the oropharynx, surgery alone was associated with prolonged survival, alluding to the potential for de-escalation of treatment in HPV-related OPSCC in particular.

Cumulatively, these findings highlight the need for continued investigation into treatment pathways for HPV-related OPSCC, the relevance of introducing boys into national HPV vaccination programs, and the relevance of the nona-valent Gardasil-9 vaccine to HNSCC prevention.

Anal cancer prevention in HIV-Positive and HIV-Negative men who have sex with men (Funder: TTMI Seed funding and internal funding)

Almost 90% of anal cancers globally are attributable to HPV infection. While anal cancer is rare among the general population (2/100,000), men who have sex with men (MSM) and particularly HIV positive MSM are particularly affected.

The rates of anal cancer among HIV negative men who have sex with men (MSM) (37/100,000) is as high as the rate of cervical cancer was in the general female population before the advent of widespread cervical screening (40-50/100,000). HPV vaccination combined with anal cancer screening for high-risk populations could dramatically reduce the morbidity and mortality associated with anal cancers in certain high-risk populations.

This collaborative research led by TCD researchers Dr Colm Kerr, Prof Colm Bergin, Prof John O'Leary and Dr Cara Martin is focused on developing new ways for screening and prevention of anal pre-cancer/cancer in a cohort of HIV-Positive and HIV-Negative men who have sex with men.

The study assesses the prevalence and genotype distribution, including seroprevalence of HPV in MSM with and without HIV in Ireland. This will provide a reference to help them understand **(a)** the impact of HPV vaccination on future HPV associated disease burden within this high-risk group and **(b)** the burden of hrHPV infection among this high-risk cohort.

Developing diagnostic, prognostic and therapeutic biomarkers in prostate cancer (Funder: University of South Australia and Envision Sciences)

An international team of scientists led by Professor John O'Leary, and Professor Doug Brooks at the University of South Australia (UniSA) has made a landmark breakthrough which will assist pathologists when visualising prostate cancer in patient tissue samples. The team has identified three new biomarkers which will allow pathologists to determine which patients require immediate, radical treatment compared to those who need close monitoring.

With more than one million men diagnosed with prostate cancer worldwide each year, the research breakthrough is significant. Prostate cancer incidence in Ireland is currently the highest in Europe (GLOBOCAN, 2020) causing to 12% of male cancer deaths (NCRI, 2021).

These markers are diagnostic and prognostic and define the metabolic state of the disease. The markers are being used in tissue, blood and urine. Their use is now being extended to other cancers: ovary, colorectal, melanoma, pancreas and head and neck cancers. The tests have been licensed by Quest Diagnostics as laboratory developed tests (LDTs) in the US.

RAMAN spectroscopy for cervical screening (Funder: Health Research Board)

Research underway within CERVIVA, in partnership with TUDublin has been developing a novel tool for cervical cancer screening based on Raman spectroscopy. Raman spectroscopy is a powerful tool that can generate a biochemical fingerprint of a sample in a rapid and non-destructive manner. Raman spectroscopy can be used as a diagnostic tool to identify spectral changes in malignant and premalignant cells.

In our ongoing work, the technology is being developed into 'the molecular Pap test' which can potentially identify biochemical changes related to cervical pre-cancer and high-risk HPV infection. We have conducted the largest clinical study conducted to date on over 1,000 cervical cytology samples using RAMAN spectroscopy to classify risk of disease.

Development of a comprehensive next generation sequencing facility at TSJCI: an industrial-academic co-production between TCD and Eurofins (Funder: Eurofins)

The aim of this project is to create a comprehensive genomic centre in TTMI in the areas: of cancer genomics, nutrigenetics and nutrigenomics, metabolomics, spatial transcriptomics and proteomic profiling, non-invasive testing and viral genomics.

This project is expected to result in the creation of a state-of-the-art genomic facility with robotics to drive genomic cancer research as well as develop new technologies and tests in cancer diagnostics and viral genomics.

Familial Breast Cancer Research Group

Prof Liz Connolly,
Consultant Breast Surgeon, St James's Hospital
Associate Professor, TCD

Dr Sarah McGarrigle,
Breast Research Programme Manager, St James's Hospital
Adjunct Assistant Professor, TCD

Yvonne Hanhauser,
Advanced Nurse Practitioner and Family Risk Service, St James's Hospital

Our group's major research interest is in the field of familial and hereditary breast cancer. The majority of breast cancers occur by chance. These are known as 'sporadic' cancers. However, breast cancer occurs more often than usual in some families due to their genetic make-up. This type of breast cancer is known as 'familial' or 'hereditary 'breast cancer.

Within this space, we have ongoing projects aimed at investigating risk prediction, risk modifiers and shared decision-making in this high-risk group with a view to improving risk-management and ultimately reducing breast cancer risk in these women.

Risk prediction models for familial breast cancer

(Funder: Health Research Board)

Women suspected of being at higher risk of breast-cancer than the general-population based on their family-history are frequently referred to a 'family-risk' clinic for risk assessment and management. Reliable estimation of an individual's risk is important so that they can be appropriately stratified for breast-cancer prevention strategies according to their estimated-risk.

A risk-prediction model is a statistical-tool for estimating the probability that an individual with specific risk factors (eg. strong family-history) will develop a future-condition such as breast cancer. It is unclear which of the currently available breast cancer risk-prediction models is most accurate for use in the family-risk setting. Working with collaborators from Royal College of Surgeons in Ireland, this study aims to answer the following question: Which breast cancer risk prediction model or models are reliable and appropriate for use in the breast cancer family risk setting? The objectives are to identify, describe and appraise all available breast cancer risk prediction models that have been developed or validated in women with a family history of breast cancer and meta-analyse their predictive performances across studies.

Furthermore, the ability to accurately predict risk in this 'family-risk' population can provide information about future disease burdens and future numbers of individuals that will require risk-reducing interventions.

Modifiable lifestyle factors in women with a BRCA pathogenic variant

(Funder: SJH Foundation BRAVE appeal)

Women who carry pathogenic variants (PVs) in the *BRCA1* or *BRCA2* genes have up to a 70-80% lifetime risk of developing breast cancer and up to approximately 44% risk of developing ovarian cancer. Identifying ways to reduce this cancer risk in women with *BRCA1/2* PVs, is therefore crucial.

Recently, there are increasing data to suggest that additional modifying factors influence cancer phenotype in women with *BRCA1/2* PVs; for example, exposure to environmental factors and unhealthy modifiable lifestyle factors, such as smoking, obesity, increased BMI, alcohol intake and physical inactivity, have all been suggested to increase the risk of breast cancer in this group.

To date, there are no data regarding the prevalence of such lifestyle factors among Irish women with *BRCA* PVs. This study aims to define the incidence of modifiable risk factors, such as body-composition, metabolic-profiles, and physical activity levels in our population of Irish women with germline *BRCA* PVs to gauge the potential for risk-modifying lifestyle interventions in this population.

Development of a web-based decision aid for BRCA mutation carriers

(Funder: Irish Cancer Society)

Women with a PV in the *BRCA1* or *BRCA2* genes have an elevated lifetime risk of developing breast and ovarian cancer. To address this risk, women are managed with surveillance and/or risk-reduction strategies. Decisions about risk management strategies can be complex and women often struggle with the decision-making process.

The aim of this project, conducted in collaboration with Dublin City University, was to develop a web-based patient decision aid (DA) for women with a *BRCA* PV to support decision-making. Development of the patient DA was guided by the International Patient Decision Aid Standards (IPDAS). This DA will provide support for women with a *BRCA* PV, in their decision-making process about which risk-reducing or risk management strategies to choose.

The use of this DA will enable the patient and clinician to have more focused and meaningful discussions regarding risk-reducing strategies based on trusted evidence, facilitating more in-depth shared decision-making (**brcadecisionaid.ie**).

Inherited cancer risk disclosure in families (Funder: N/A)

This study is a collaboration with the University of South Florida, USA. Clinicians recommend that families with an individual who has a known inherited cancer-predisposing gene mutation should be informed of their personal genetic risk.

The disclosure of genetic risk to family members can have a significant impact on the risk management decisions the members make concerning their own health. Thus, better understanding of whether and how individuals are likely to discuss genetic risk with their families is important for lowering cancer risk through prevention and management decisions.

The purpose of this study is to explore the motivations and goals of probands (the first individual to undergo genetic testing in the family) when disclosing their inherited cancer risk to a family member. It is hoped that the information gained through this study will enable health care professionals to better advise and support patients in disclosing their inherited cancer-predisposing mutation to family members.

We Can Quit2 Research Group

Prof Catherine Hayes, Professor in Public Health, TCD

Dr Catherine Darker, Associate Professor in Health Services Research, TCD

The We Can Quit2 group's research addresses the development, implementation, and evaluation of targeted interventions to address lifestyle determinants of cancer and chronic diseases in particular tobacco and obesity across the life course.

Their particular expertise lies in population health trials, implementation science methodologies in translation of research evidence into policy and practice to achieve maximum impact for health improvement. Much of their research is focused on vulnerable groups who are difficult to reach in terms of prevention.

Major collaborators of this TCD research group include Prof. Linda Bruce (University of Edinburgh), Prof. Nadine Dougall (Edinburgh Napier University) and Joanne Vance (Community Development and Health Network, Newry).

Online Dissemination Workshop

An online dissemination workshop with stakeholders included the active participation of PPI and members of the public including the community facilitators who delivered the We Can Quit programme[2]; representatives from the community pharmacies and community organisations who participated in trial; and representatives from the Irish Cancer Society, the Health Service Executive, the National Cancer Control programme and the Think Tank for Action on Social Change (TASC) Ireland. A policy brief was designed in consultation with our PPIs collaborators and NGO (Action on Smoking and Health (ASH); practitioners from the Health Service Executive Tobacco Control Programme, and collaborators from the Irish Cancer Society.

[2]www2.hse.ie

Research Theme: Molecular and Precision Oncology

Theme Leadership

Prof Adrian Bracken, Professor in Medical Molecular Genetics, School of Genetics and Microbiology, TCD Molecular and Precision Oncology Theme lead, TSJCI

Prof Lorraine O'Driscoll, Professor of Pharmacology and Biomedicine, School of Pharmacy and Pharmaceutical Sciences, TCD Research Lead, TSJCI.

Molecular Oncology aims to treat cancer based on knowledge of the molecular make-up of the cancer cells, tumour heterogeneity, and its microenvironment. This involves identifying, characterising, and targeting altered genes, cellular processes, and pathways that initiate and drive cancer. It also involves understanding and so aiming to prevent or treat metastasis, immune suppression, and anti-cancer drug-resistance.

Molecular oncology is an interdisciplinary field that juxtaposes the interface between target discovery, medicinal chemistry, drug development and/or drug re-purposing, pharmacology, predictive tissue and blood-based biomarker identification and utilisation -spanning fundamental, translational, and clinical research- to deliver optimal oncology treatment in the form of molecularly targeted therapies, often in combination with classical chemotherapy.

By identifying key molecular drivers and mechanisms of cancer development and progression using techniques including transcriptomics, functional genomics, proteomics, glycomics, metabolomics, computational biology, tumour imaging, *in vitro* and *in vivo* functional models, Molecular Oncology aims to discover novel targets as diagnostics and for therapeutic intervention. Thus, it fits in the realm of interdisciplinary research (genetics, immunology, chemistry, biochemistry, pharmacology, pharmacy, and medicine; to name a few) and service development, with the intent of improving patients' quality of life and outcome following a cancer diagnosis.

Successful examples arising from molecular oncology research include drugs developed to treat the ~20% of breast cancer patients (and also some gastric cancer patients) whose tumour cells expressed high amounts of HER2 oncogene. Drugs developed to target HER2 include trastuzumab; its antibody drug conjugate TDM1, and small molecules such as neratinib.

Others include the area of immunotherapy, in which a patient's own immune system is primed and manipulated to cells to produce an anti-tumour response. Rarely, if ever, are such targeted therapies sufficient as monotherapies, and so determining the most beneficial combinations of drugs - and the optimal order in which they should be administered - is also important, to ultimately provide optimal treatment for a given cancer patient.

Being mindful and considerate of comorbidities and so other pharmacological treatments that may be used in parallel with anti-cancer drugs is also an important consideration. Importantly, in addition to being central to the development of new anti-cancer treatments or combinations of treatments, Molecular Oncology research is also vital for developing companion diagnostics/biomarkers for predicting treatment response. Minimally invasive biomarkers, that can be evaluated on an on-going basis, are of substantial interest.

Precision Oncology is an innovative approach to cancer treatment that ensures an individual patient's treatment is specifically designed and targeted to their unique form of cancer. It's the science of using each patient's individual genomic profile – the genes that are mutated, causing their cancer to grow – to design a treatment protocol just for them, based on those genetic mutations that are driving their disease.

The premise of this strategy is that molecular diagnostic testing is employed to triage patients and to select optimal therapies based on the genetic content of an individual patient's tumour or their innate genetic complement.

They recognise that the interpretation of molecular data to facilitate best practice remains a significant barrier to precision oncology, therefore this theme integrates a functional genomics bench-side approach with clinical/molecular correlation and biomarker selected clinical trials. The key synergistic partnership, between our cancer genetics consultants in SJH and our experimental cancer biologists, has the potential to yield many new therapeutic opportunities.

High level goal: TSJCI Molecular and Precision Oncology

The primary goal of the Molecular and Precision Oncology theme (**Figure 6**) within TSJCI is to contribute vital molecular insights that facilitate a better understanding of cancer biology and may be translated into optimised treatments for patients with cancer and more refined diagnostics for early detection. This theme is also key to support the application of rational, disease and patient focused approaches to cancer therapy.

Ultimately, this is the goal of 'bench to beside', to feed discoveries from basic and translational researchers into new cancer clinical trials.

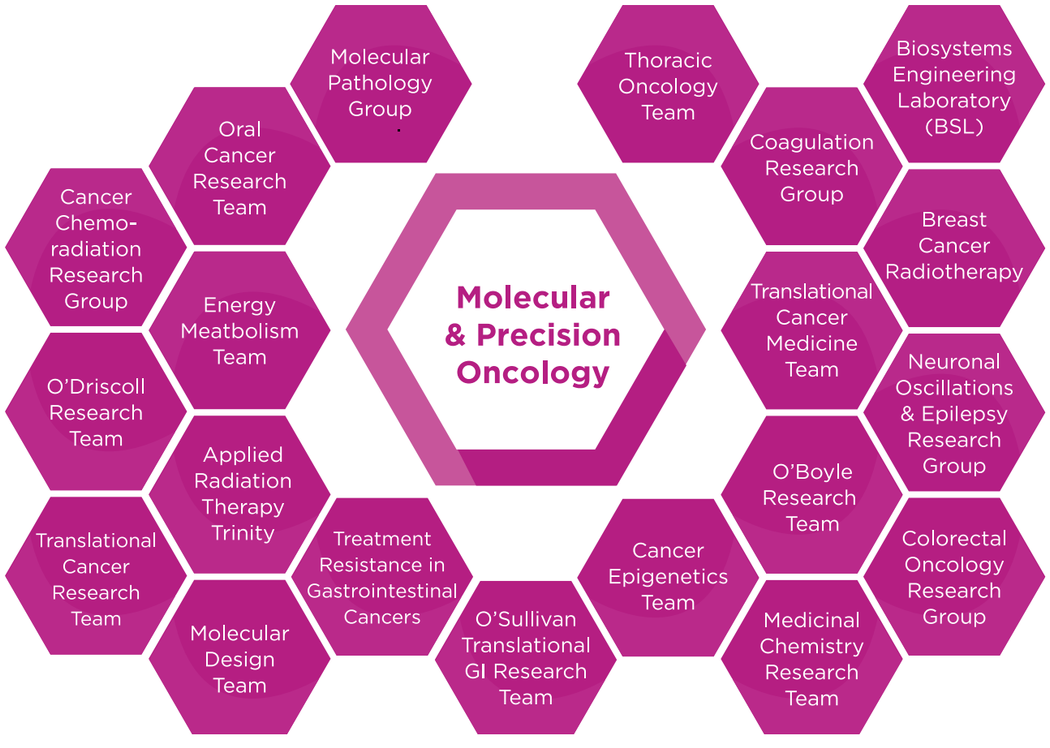


Figure 6. Molecular and Precision Oncology Research Teams at TSJCI

O'Driscoll Research Team

Prof Lorraine O'Driscoll, Professor of Pharmacology and Biomedicine, School of Pharmacy and Pharmaceutical Sciences, TCD
Research Lead, TSJCI.

The overall objectives of the O'Driscoll research group include understanding why anti-cancer drug-resistance, immune suppression, and metastasis occur in cancer -including, but not limited to- the role of extracellular vesicles (EV) in these processes; investigating the co-use of all components in blood, including EVs, circulating tumour cells, and ct-DNA as diagnostic, prognostic and predictive biomarkers to maximise the use of every drop of blood donated by both people who have cancer and those who are cancer-free, in order to achieve the best possible cancer liquid biopsies and determining smarter ways of delivering anti-cancer drugs singly and in combination, in order to maximise benefit and minimise side-effects. Professor O'Driscoll leads the All-Ireland Cancer Liquid Biopsies Consortium (CLuB) Emerging Hub of Excellence (See Research highlight on page 11).

AICRIStart (Funder: HEA/ North-South Research Programme 2021-2026)

The AICRIStart[3] programme is a Foundation Stone for the All-Island Cancer Research Institute (AICRI, a virtual cancer network co-led by University College Dublin, TSJCI/Trinity College Dublin, and Queen's University Belfast)). In March 2022, the AICRIstart programme -including ten third-level institutes- was awarded funding under the HEA North South Research Programme. This work is a collaboration with University College Dublin, Royal College of Surgeons in Ireland, Technological University Dublin, Queen's University Belfast, Ulster University, National University of Galway, University of Limerick, and University College Cork. The long term expected impact of this is to create a collaborative cancer research network across the island of Ireland in:

1. Immuno-Oncology and the Microbiome, and
2. Functional Cancer Genomics. AICRIstart supports a 4 year PhD student and 2 year Post-Doctoral Fellows in each of the ten institutes.

[3]aicri.org/aicristart

Irish Research Council Advanced Laureate Award, Extracellular Vesicles in Cancer (EVIC)

(Funder: Irish Research Council)

The aim of this €1m project is to understand and exploit the hypoxic environment of tumours/the tumour micro-environment. It is expected that the results of this project will contribute to selective treatment of cancer to targeted delivery of anti-cancer drugs to site of cancer thus minimising side-effects. To date, the team has had three Keynote talk invites, eight invites for speaker talks, multiple oral and poster presentations, a PPIE event, had more than thirty students work in the laboratory on research, and have published twelve peer-reviewed articles.

Milking Extracellular Vesicles for Health Benefit (MilkEV)

(Funder: Department of Agriculture, Food, and Marine (DAFM))

This project is vital for cancer research as a focus of the research is to investigate milk EVs as safe, affordable, easy, and accessible natural drug delivery vehicles for anti-cancer drugs. A goal of this project, supporting a Post-Doctoral Fellows and two PhD students, is to contribute to selective treatment of cancer and targeted delivery of anti-cancer drugs to site of cancer thus minimising side-effects.

Extracellular Vesicles Promoted Regenerative Osseointegration (EVPRO) (Funder: European Commission)

The focus of this work, a €6m programme, is the development of gels loaded with extracellular vesicles for enhanced osseointegration, and as a result should contribute to better success of treatments that need to be delivered to bones. The group has published several peer-review articles related to this work, presented at European Researchers Nights, had four invited talks, and one keynote talk.

Training in Extracellular Vesicles: for benefit in Health and Disease (TRAIN-EV) (Funder: European Commission)

Led by Prof. Lorraine O'Driscoll, TRAIN-EV is a €4m Innovative Training Network (ITN) supporting 15 PhD students and a Project Manager. In addition to TCD, TRAIN-EV includes five academic and clinical institutes and four industry partners throughout Europe.

Translational Cancer Research Team

Prof Orla Sheils,
Vice-Provost/Chief Academic Officer, and Professor of Pathology, TCD

Dr Anne-Marie Baird,
Senior Research Fellow, TCD

Dr Stephen Finn,
Consultant Histoathologist, St James' Hospital;
Associate Professor, TCD

The broad research area of the Translational Cancer Research Group relates to novel cancer diagnostics, with a particular emphasis on the molecular mechanisms of disease and drug resistance, liquid biopsy, metastatic cascade and the use of Artificial intelligence (AI).

Our objective is to identify new ways to diagnose, treat and monitor solid cancers (HPV-related, gastroesophageal, lung, prostate and ovarian) to improve outcomes for people impacted by cancer.

Novel mechanisms of disease and drug resistance in prostate cancer

(Funders: Irish Cancer Society/Prostate Cancer Foundation/World Cancer Research Fund)

The aim of this research was to identify novel mechanisms of disease as well as markers, in particular circRNAs, of drug resistance in prostate cancer. The data sought to identify predictive biomarkers to therapy and potential therapeutic targets for patients, as well as the impact of exercise in the metastatic setting.

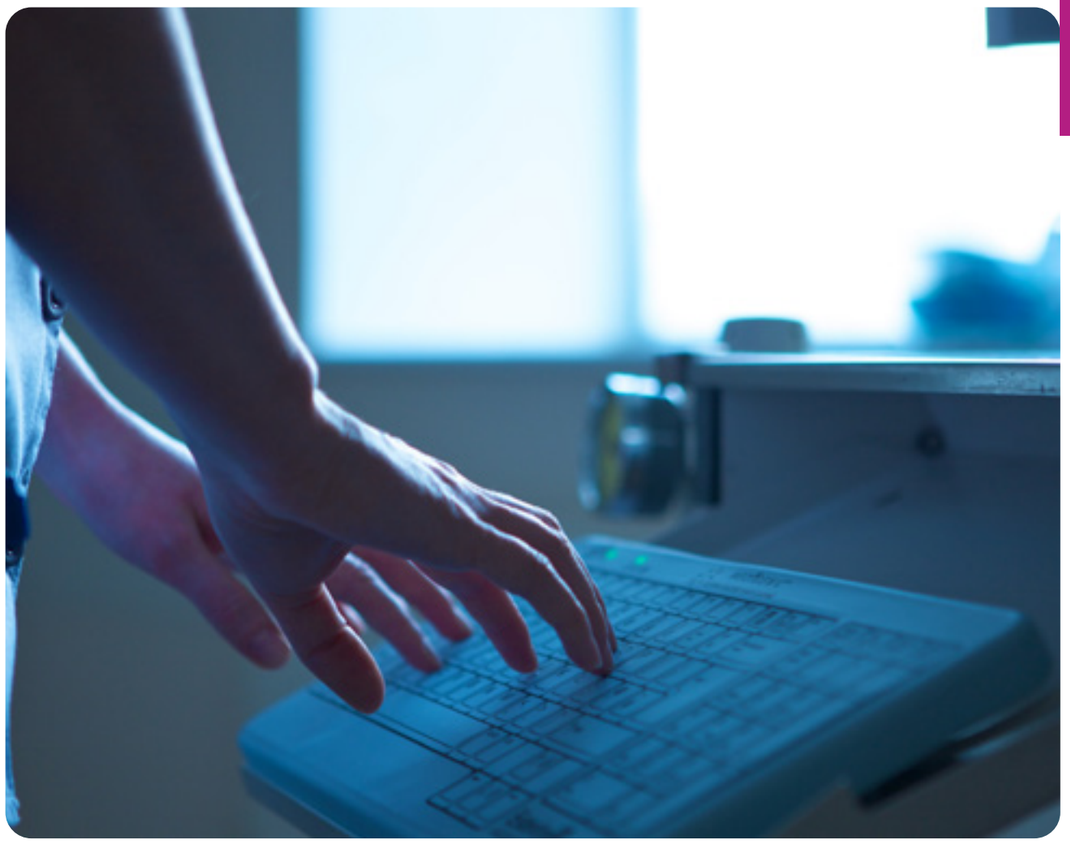
This project was performed in collaboration with the University of Galway, Queen's University Belfast, the Harvard School of Public Health, and the Dana Farber Cancer Institute. The result of the project provides beneficial groundwork for further exploration of RNA and DNA markers as potential biomarkers and therapeutic targets for prostate cancer, as well as exercise intervention in the metastatic setting. Additionally, this collection of work sets the foundation for identifying new biomarkers and targets for therapy, which could ultimately improve outcomes for people impacted by this disease.

Chronic obstruction pulmonary disorder (COPD), lung cancer and the microbiome

(Funder: Irish Research Council)

This project endeavours to comprehend the relationship between the lung microbiome profile and the risk of lung cancer development in individuals with COPD. The underlying belief is that the lung microbiome might be directly oncogenic, fostering oncogenic mucosal inflammation or promoting immune dysregulation. In addition, the project aims to evaluate the efficacy of metal-based drug complexes, especially silver(I) and copper(I) compounds.

The ultimate objective is to offer novel therapeutic strategies, potentially mitigating lung cancer risks in COPD patients. This project is executed with joint work of Tallaght University Hospital and Technological University Dublin. With the culmination of this research, the team aims to have a clearer understanding of the potential role of the lung microbiome in lung cancer progression among COPD patients. The findings may pave the way for innovative therapeutic strategies, centred on metal-based drugs, offering a more nuanced approach to managing microbial balance and, in turn, potentially mitigating lung cancer risks. Thus far the project has received IRC postdoctoral funding and internal Trinity College Dublin Seed funding.



Computational pathology and genomics in cancer diagnostics

(Funder: Science Foundation Ireland)

This work aims to investigate the use of AI methodology and bioinformatics to

1. assess deep feature batch correction for artificial intelligence applications in computational pathology,
2. genomically profile an Irish Upper Gastrointestinal Cancer Cohort and
3. evaluate the predictability of actionable lung cancer biomarkers from histology images.

Distinct subtypes of cancer based on molecular profiles are recognised and appear to correlate with prognosis. Defining the genomic alterations in these cancers using AI driven methodologies may allow the classification of these cancers and explore treatment options based on their molecular profile and thus assist in personalised medicine approaches. Working alongside University of Galway, Memorial Sloan Kettering Cancer Centre, and Tallaght University Hospital, the successful outcome of this research may enable safer translation of AI-based computational pathology systems to the clinic.

Platelets and the metastatic cascade in small cell lung cancer (Funder: Dr Joan McCormick PhD Scholarship)

Small cell lung cancer (SCLC) is a poor prognosis cancer, with only 10% of people surviving 5 years after their diagnosis. This is mainly due to the pro-metastatic nature of the disease, with most people diagnosed with extensive disease and limited treatment options.

The metastatic process is complex and recent research has indicated an important role for platelets. Under normal haemostatic conditions, platelets have key roles in clotting and the immune response. However, altered behaviour is linked to several conditions and lung cancer. Platelets can interact with and 'cloak' circulating tumour cells, thus protecting them from immune cells. Understanding these interactions and how platelets contribute to disease spread may help identify novel ways to target these interactions and prevent disease spread.

This feasibility study (in collaboration with UMC Amsterdam) will improve our understanding of the role of platelets in the metastatic cascade

by identifying targets from clinical samples. This project aims to identify potential targets for therapy for those impacted by SCLC, which is a cancer with poor outcomes and limited treatment options. In addition to this, the study will generate a valuable model of a pro-metastatic cancer that may be used by others examining this hallmark of cancer.

Modelling and exploring the resistance phenotype in ovarian cancer (Funder: Welcome Trust / Health Research Board)

In collaboration with University of Galway, this project focuses on investigating mechanisms which result in Ovarian cancers becoming resistant to Poly-(ADP)-ribose polymerase Inhibitors (PARPi) with a particular emphasis on circular RNA profile switching. The hypothesis is that acquired resistance mechanisms exist in Ovarian cancers with Homologous Recombination Deficiency (HRD) treated with PARPi.

This study will examine if circulating circular RNA (circRNA) as a predictive biomarker to define such resistance based on BRCA status. This work focuses on translational research which will investigate the profile of resistance mechanisms and how they differ depending on BRCA status in Ovarian cancer.

Human Papillomavirus associated oropharyngeal squamous cell carcinoma: Genetic aberrations associated with local and distant recurrence (Funder: Trinity Technicon Research Grant and BEHR Grant)

HPV driven cancers within the oropharynx have marked pathogenic differences in contrast to HPV driven cervical cancers. HPV proffers a favourable prognosis for HPV positive Oropharyngeal Squamous Cell Carcinoma (OPSCC) in contrast to its HPV negative counterparts. The main aims of this study were to determine

1. prevalence of various HPV DNA genotypes in HPV positive OPSCC alongside a panel of somatic mutations,
2. establish if these genotypes correlated with any clinico-pathological data and
3. establish the feasibility of molecular interrogation of drivers of disease progression on archival FFPE tumour tissue in head and neck squamous cell carcinoma (HNSCC).

A collaborator on this work is the Royal Victoria Eye and Ear Hospital. This study identified significant correlations between excessive alcohol consumption and a higher clinical stage at diagnosis with local recurrence and/or distant metastasis. In view of the largest research investment in de-intensifying therapeutic regimens for HPV positive OPSCC, upfront recognition of patients at greater risk of LR and/or DM is vital.

Biological characteristics of Gastroesophageal Junction Adenocarcinomas (GEJA) and their clinical correlates (Funder: Pathological Society of Great Britain and Ireland Research Award and BEHR Grant)

Gastroesophageal junction adenocarcinomas (GEJA) have increased in incidence in the Western world over the last 50 years. Their prognosis is poor, and treatment is often complicated by resistance to conventional anti-cancer therapies. However, a growing school of thought exists which believes that GEJAs have a distinct molecular profile.

Investigation of the molecular biology of these tumours may therefore provide novel targets for drug therapies, in addition to potential prognostic biomarkers for use in the clinical setting. This work investigated the presence of Cancer Stem Cell (CSC)-like cells in GEJA by analysing the expression patterns of mRNAs, miRNAs and proteins which have previously been described as CSC markers. This work resulted in the improved understanding of miRNA and CSC in GEJA.

Energy Metabolism Team

Dr Richard K. Porter,
Associate Professor,
School of Biochemistry
and Immunology, TCD

The overall aim of the Energy Metabolism team is to investigate the metabolic features of cancer and how they relate to phenotype, with view to finding anti-cancer target proteins.

An assessment of the efficacious role of ART27.13 (NEO1940) in a human *in vitro* cell model of cachexia

(Funder: Artelo Biosciences plc)

Working with Artelo Biosciences, this project established an *in vitro* model of cachexia in cultured primary human skeletal muscle cells. We optimised conditions to grow primary human myotubes.

We used conditioned media from human colon and human lung cancer cells to induce cachexia in the mature human myotubes as indexed by a significant decrease in myotube diameter.

We also discovered a family of drugs that prevent myotube diameter reduction i.e., prevent cachexia, one of which is in human trials Phase 2a CAReS Trial Evaluating ART27.13 for the Treatment of Cancer-Related Anorexia. The model established during this work has been used to discover a potential new anti-cachexic drug.

Characterisation of triple negative breast cancer cell line Hs578T and its more invasive isogenic subclone, Hs578Ts(i)8 (Funder: Internal)

This project is characterising components of the cancer phenotype, transcriptome, and related with metabolism of triple negative breast cancer cell line Hs578T and its more invasive isogenic subclone, Hs578Ts(i)$_8$. It is expected that this research will lead to the identification of proteinaceous anti-cancer targets that cause metastasis in breast cancer.

Truxillic acid based (ART26.12) drug efficacy on human glioblastoma multiforme phenotype *in vitro*.

(Funder: Artelo Biosciences plc)

A collaboration with Artelo Biosciences and University of Indiana, this project focused on quantifying the efficacy of truxillic acid based (ART26.12) drug on human glioblastoma Multiforme Phenotype *in vitro*, and the role played by intracellular Fatty Acid Binding Proteins (FABPs) 3, 5 and 7.

Evidence of a Role for Inteleukin-6 (IL-6) in *anoikis* resistance and bioenergetic programming in Oral Squamous Cell Carcinoma (Funder: European Commission - Marie Curie)

This project, a collaboration with the University of Innsbruck, worked on establishing that oral squamous (tongue) cancer cells SCC4 produce Il-6 which drives *anoikis* resistance. We have also established that SCC4 reduced oxidative metabolism compared to pre-cancerous DOK (dysplastic oral (tongue) keratinocytes. The results of this work will provide insight into the mechanism behind metastasis in oral cancer plus identification of an anti-cancer target (*i.e.*, the Il-6 receptor).

The potential of Nicotinamide N-Methyltransferase (NNMT) as an anti-cancer target in cultured human Oral Squamous Cell Carcinoma (OSCC) (Funder: Internal and School of Dental Science)

The enzyme *N*-Nicotinamide Methyltransferase (NNMT) is over expressed in a variety of human cancers and has recently been investigated as a potential anti-cancer target by several laboratories. NNMT regulates NAD+ biosynthesis thus altering protein methylation profiles which promotes oncogenesis (3,4).

We have recently identified two small molecule inhibitors of NNMT (AG-670 and AO-022) based on a pharmacophore of the *in-silico* nicotinamide binding site. The effect of these modulators of NNMT on OSCC cell viability and energy metabolism was evaluated, in collaboration with Technological University Dublin. The long-term expected impact is that it will deliver pre-clinical evidence of a novel drug treatment for tongue cancer.

Applied Radiation Therapy Trinity

Prof Laure Marignol,
Professor in Radiation Biology,
School of Medicine, TCD

Prof Michelle Leech,
Professor in Radiation Therapy,
School of Medicine, TCD

Radiation therapy is a life-saving cancer treatment modality that is offered to millions of patients with cancer each year across all ages, sexes, and age groups.

However, this treatment remains associated with limited outcomes in subgroups of patients. Research at the Applied Radiation Therapy Trinity[4] aims at improving radiotherapy cancer patients' health, care and health service delivery. Our research is framed around three interlinked strands focusing on Translational Radiobiology and Oncology, Radiation Therapy in Practice and Health Care services research (**Figure 7**).

[4]www.tcd.ie/medicine/radiation-therapy/research

Figure 7. Applied Radiation Therapy Group interlinked strands focusing on Translational Radiobiology and Oncology, Radiation Therapy in Practice and Health Care services research

Applied Radiation Therapy Trinity

The objectives of our research are to improve patient stratification, to optimise treatment delivery and to address the unmet needs of patients treated with radiation therapy.

Tumours have a sex: impact of the response of cancer to therapy

(Funder: TCD Provost Award)

This project investigates the impact of sex as a biological variable in the response of bladder and lung cancer to radiotherapy. Specifically, this project (in collaboration with the University of Birmingham and the University of Manchester) tests the hypothesis that the genes located on the X and Y sex chromosomes can impact the rest of genome and alter the radiation response.

This work involves the generation of *in vitro* radiation survival curves using both female and male cancer cell lines, the review of published and recorded male and female clinical data, and a solid evaluation of the potential sex-specific differences in the molecular radiation response of cancer cells. This project has the potential to advance our ability to define biological sex beyond self-identification and open new opportunities to optimise cancer treatment.

ACORN- Advancing care of osteoradionecrosis (Funder: Irish Cancer Society)

The aims of this project are two-fold. First, to determine a more optimal dose volume constraint to the mandible when planning radiation therapy for patients with head and neck cancer, than the point dose that is currently used with a review to reduce the incidence of osteoradionecrosis. Osteoradionecrosis is a debilitating condition experienced by 2-9% of patients who receive radiation therapy for head and neck cancer where the mandible (jawbone) becomes necrotic (decayed) and impacts on patient ability to speak, eat and swallow.

The second aim of the project is to develop international consensus guidelines on the prevention and management of osteoradionecrosis using a Delphi consensus methodology. The long term expected impact is the publication and implementation of our consensus guidelines for the prevention and management of osteoradionecrosis for patients with head and neck cancer.

IMPORT-Interactive Monitoring of Paediatric Outcome Reporting for Radiation and Chemo Therapies

(Funder: The Irish Research Council)

Interactive Monitoring of Paediatric Outcome Reporting for Radiation and Chemo Therapies (IMPORT) hypothesises that merging the motivational benefit of gamification with the clinical benefit of side effect assessment of patient reported outcome measures (PROMS) can improve side effects reporting in paediatric cancer patients aged 8-12 years undergoing treatment. This will be achieved by transforming the most appropriate PROMS questionnaire for oncology into a child-friendly game and carer educational platform shared with their treating clinician (in collaboration with Childrens' Health Ireland).

IMPORT aims to prove the concept that the introduction of gamified PROMS during the clinical management of 8-12 years old paediatric cancer patients addresses their side-effect communication needs, supports their families and assists treating clinicians in best managing their symptoms. The long-term impact of this project is to produce a prototype patient reported outcome measure (PROM) integrated into video game system/ gamified featuring paediatric patients' area to rate side effects, parents' area to rate the side effects of their child and a clinicians' area to track these reported side effects.

Periprostatic adipose fat and advanced prostate cancer risk - a prospective study (Funder: World Cancer Research Fund)

Obesity is associated with increased risk of advanced and fatal prostate cancer, but mechanisms are incompletely understood. Periprostatic adipose tissue (PPAT) is a visceral fat depot in direct proximity to the prostate that may promote tumourigenesis through local metabolic effects.

Clinical studies of prostate cancer patients have shown that increased quantity of PPAT positively correlates with higher tumour aggressiveness defined by Gleason grade and pathological characteristics. Population-based prospective studies are needed to understand the association of PPAT with advanced/fatal prostate cancer risk.

We hypothesise that PPAT is a potentially modifiable fat depot associated with increased risk of advanced/fatal prostate cancer and will examine the association between PPAT and risk of advanced prostate cancer through radiomics as well as through a genome wide association (GWAS) and two sample Mendelian randomisation analysis. This study is a collaboration with Queen's University Belfast, University of Bristol, Oxford University, University of Iceland, and Cedars-Sinai Medical Centre.

The study will be the first prospective population-based analysis of the association between PPAT adiposity and advanced/fatal prostate cancer risk. The overall outcome will be an important first step towards understanding the role of PPAT adiposity in advanced/ fatal prostate cancer aetiology which, in turn, will inform future prostate cancer prevention efforts.

Oral Cancer Research Team

Dr Jeff O'Sullivan,
Assistant Professor in Biological Sciences, Dublin Dental University Hospital, TCD

Our research is focused on furthering the understanding of the biochemical and carcinogenic mechanisms in oral cancer and dysplasia, as well as examining the synergistic effects of oral epithelia metabolism and key oral microbial species. Another key focus is the identification of novel biomarkers aiding the rapid detection of oral cancer. The team also aims to establish long-term key collaborations to develop the next generation of chemotherapeutic alternatives to expedite patient treatment and resolution and develop novel analytical tools with potential for chair-side diagnoses.

Investigation of autophagic degradative pathways through Raman spectroscopy for early detection of oral cancer

(Funder: Irish Research Council)

This study aims to investigate the mechanism of the autophagic degradative pathway and identify autophagic Raman spectral markers for early detection of oral cancer/precancer. The study is a collaborative effort with Technological University Dublin. Our objectives are to

1. investigate the autophagic pathway in cell line models and identify Raman spectral markers,
2. to correlate the identified autophagic spectral markers in cell lines with the Raman spectral markers of precancer in patient samples,
3. establish autophagic pathways as Raman spectral markers for early detection of oral cancer and
4. to correlate bioassays and Raman data with Soft X ray microscopic images.

It is known that lipids such as ceramides are unregulated by autophagy inhibition in precancer and OSCC tumours.

To date, the autophagy degradative pathway has never been studied in detail for early detection of oral cancer using Raman spectroscopy. Hence this project has proposed an interface between Raman spectroscopic applications and biochemistry, in order to understand the role and in-depth mechanisms of autophagy in oral pre-cancer development and progression.

The effect of ethanol exposure on malignant transformation and progression of oral cancer (Funder: TCD Ussher Fellowship/DDUH Matched Funding)

This project has four main aims which are as follows:

1. Utilise stable oral mucosal cell lines to develop in vitro models of alcohol/inflammatory induced oral cancer progression,
2. Examine the interplay between alcohol and a number of oral microbial species,
3. Determine the cellular mechanisms responsible for this progression of oral cancer and
4. Examine potential avenues of disruption that may have anti metastatic potential.

Oral cancer has been predominantly perceived as an older person's disease but there is now an increasing trend with younger people and many new occurrences are presenting and are predominately related to personal habits including the use of alcohol.

Of interest is the potential for synergism between an individual's microbiome and the potential exacerbation of a transformative event leading to tumour formation. It is therefore imperative that the biochemical mechanisms behind this trend are identified and understood. This study will provide insight into these mechanisms in OSCC while opening the possibility of novel treatment targets or the identification of potential susceptibility markers.

Treatment Resistance in Gastrointestinal Cancers

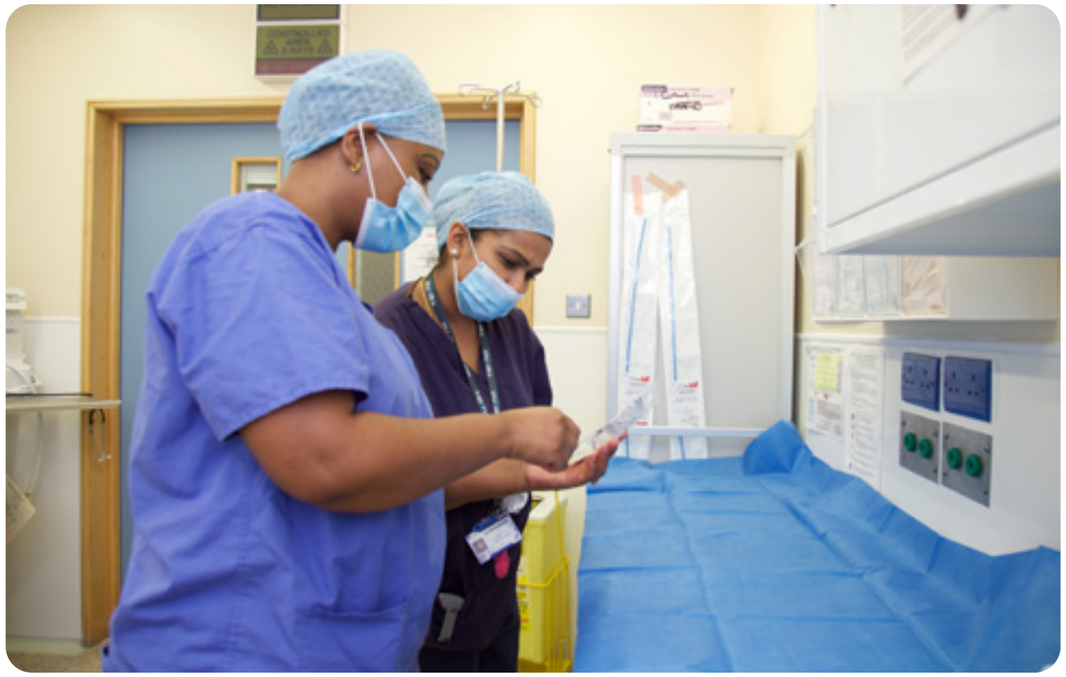
Dr Niamh Lynam-Lennon,
Research Assistant Professor,
Department of Surgery,
School of Medicine, TCD.

Dr Lynam-Lennon's research is focused on investigating mechanisms of chemoradiation therapy resistance in gastrointestinal cancers. She leads a research team focused on two main areas; prediction of response to therapy and identification of novel treatment strategies to enhance the tumour response to therapy, with the goal of improving treatment and survival for patients. The research spans several topical areas including miRNA and gene expression profiling, altered mitochondrial function and energy metabolism, and alterations in the complement system, the relationship between these processes and the role they play in treatment resistance.

Investigating the role of microRNA in the resistance of oesophago-gastric cancer to chemoradiation therapy

(Funder: TCD Provost Award)

This project is investigating the functional role of microRNA (miRNA) in modulating the resistance of oesophageal and gastric cancer to therapy (chemoradiation and chemotherapy). Utilising novel cell line models of treatment resistant oesophago-gastric cancer and blood and tumour samples from patients, this project aims to identify novel miRNA biomarkers predictive of response to treatment for improved patient stratification and novel therapeutic targets to boost treatment response to improve treatment and survival for patients. This project builds on previous work that identified a novel panel of 38 miRNA markers that are predictive of response to neoadjuvant chemoradiation therapy in pre-treatment oesophageal adenocarcinoma biopsies from patients.



Thoracic Oncology Team

Dr Stephen Finn,
Consultant Histopathologist,
St James's Hospital;
Associate Professor, TCD

Dr Martin Barr,
Clinical Scientist,
St James's Hospital,
Clinical Senior
Lecturer, TCD

Dr Kathy Gately,
Clinical Scientist,
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Clinical Senior
Lecturer, TCD

Dr Sinead Cuffe,
Consultant Medical Oncologist,
St James's Hospital

Dr Steven Gray,
Clinical Scientist,
St James's Hospital;
Clinical Senior
Lecturer, TCD

The Thoracic Oncology team bridges multidisciplinary clinical and translational research across a number of cancer types, including lung cancer. The programme within the group comprises of three main research themes – Biomarker Discovery (prognostic/predictive), Targeted Therapies and Liquid Biopsy. The group have several ongoing studies in lung, prostate and ovarian cancer:

1. Non-coding RNA signatures as diagnostic and prognostic tools in prostate cancer: The use of blood and tissue-based miRNA (microRNA), lncRNA (long non-coding RNA) and circRNA (circularRNA) signatures as markers for guiding clinical decision making and stratifying people for therapy.
2. Exploring and modelling the resistance phenotype in PARPi treated ovarian cancer: Identifying novel mechanisms of acquired resistance in ovarian cancer, with a specific interest in assessing the circRNA-mRNA-miRNA network.
3. Real world application of liquid biopsies as a means to track the natural evolution of cancer and identify mechanisms of drug resistance: Detecting blood based molecular markers in cell free DNA (cfDNA) and circulating tumour cells (CTCs), to further our understanding of the development of drug resistance at a genomic level using next generation sequencing (NGS).
4. Digital Pathology and AI in Cancer Genomics: This project applies machine and deep learning to histopathological, genomic and clinical data to identify specific cancer subtypes and assess their utility to inform personalised treatment strategies for people with cancer.

Developing novel inhaled bio-engineered extracellular vesicle RNA based advanced therapeutics, delivered by tailored aerosol delivery technology for the treatment of lung cancer

(Funder: European Commission)

Lung cancer is a complex heterogeneous disease. Despite treatment improvements with targeted and immune therapies, overall survival remains poor. OmniSpirant, coordinator of the INSPIRE project along with consortium partners, will work to drive significant progress of the development of a novel, effective and affordable gene therapy treatment, which will improve drug access and better outcomes for people with lung cancer.

This project will help in placing Europe as a leader in the fight against lung cancer and in the development of treatments for other debilitating lung diseases. The company's new gene therapies are based on its proprietary OmniSome™ platform technology, which utilises tiny particles, known as extracellular vesicles (EVs). These will be used to deliver RNA based therapeutics to lung tumours. This project is a collaboration with OmniSpirant Ltd, RemedyBio, Aerogen Ltd, EverZom, Pharmalex, and DKFZ. It is expected that this project will be impactful by providing a new breakthrough in the use of ATMPs for the treatment of lung cancer.

ETOP Lungscope

(Funder: ETOP IBCSG Partners Foundation)

This study explores the prevalence, biological significance and heterogeneity of biomarkers in primary NSCLC tumours and matched metastases. The research team is made up of a pan-European consortium comprising of collaborative group of physicians and scientists will expertise in lung cancer research and treatment, ETOP IBCSG Partners Foundation. In the long term, findings from this study will help expedite the rapid translation of biomarkers into the clinic and provide new knowledge on the expression and prevalence of specific biomarkers between matched primary tumours and metastases from NSCLC patients.

ETOP Smallscape

(Funder: ETOP IBCSG Partners Foundation)

Smallscope is a multi-centre, retrospective study which aims to establish a small cell lung cancer (SCLC) biobank with tumour tissue samples and annotated clinical data as a resource for translational research projects, generating hypotheses for future diagnostic platforms and biomarker-driven clinical trials. This infrastructure will provide a framework for conducting future Smallscope sub-projects, to address the challenges of studying the molecular epidemiology of small cell lung cancer (SCLC) and to expedite our knowledge of current and evolving clinical and molecular biomarkers on tumour tissue.

This research team is also made up of a Pan-European consortium comprising a collaborative group of physicians and scientists with expertise in lung cancer research & treatment, ETOP IBCSG Partners Foundation. Smallscope will deepen the knowledge of SCLC biology.. In the long-term, this study will add further knowledge to the use of new prognostic IHC markers in this poor prognosis cancer, create a framework for future analysis of emerging predictive biomarkers & overcome challenges of studying the molecular epidemiology of SCLC by coordinating and harmonising procedures among lung cancer specialists working in translational research across Europe and facilitate analysis of larger series of cases.

ETOP Mesoscape

(Funder: ETOP IBCSG Partners Foundation)

Mesoscape is a multi-centre, retrospective study which aims to establish a pleural mesothelioma (PM) biobank with tumour tissue samples and annotated clinical data as a resource for translational research projects, generating hypotheses for future diagnostic platforms and biomarker-driven clinical trials.

This infrastructure will provide a framework for conducting future Mesoscape sub-projects, to address the challenges of studying the molecular epidemiology of small cell lung cancer (PM) and to expedite our knowledge of current and evolving clinical and molecular biomarkers on tumour tissue.
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Generation of Organoid 3D tumor models for screening and testing of candidate CAR-T/TCR-T

(Funder: Legend Biotech)

Generation of Organoid 3D tumor models from colorectal cancer (CRC), non-small cell lung cancer (NSCLC) and gastric cancer (GC) human tissues to use as a platform biomarker discovery and drug screening and testing including candidate CAR-T/TCR-T.

Profiling the perioperative immune response, tumour immune microenvironment and efficacy of immunotherapy in patient-derived organoids following surgery for lung cancer

(Funder: Royal City of Dublin Hospital Trust)

This research proposes to profile systemic anti-tumour immunity prior to surgery and post-operatively to identify predictive biomarkers of disease relapse. Differences in immune profiles following open and minimally invasive thoracic surgery will also be determined. In addition, the tumour immune microenvironment will be examined in a cohort of patients with early recurrence (<2 years) and those who remain disease free at two years post-surgery. The long term expected impact of this study is that the identification of patients who are more likely to relapse after surgery will become easier and will allow for more of them to access frequent follow-up surveillance.

O'Sullivan Translational GI Research Team

Prof Jacintha O'Sullivan, Professor in Translational Oncology, School of Medicine, TCD; Education Lead, TSJCI

Clinical collaborators: Prof. John Reynolds, Prof. Narayanasamy Ravi, Ms. Claire O'Donohoe Mr Michael Kelly, Mr. Brian Mehigan, Mr. Paul Larkin, Dr. Ciara Ryan, Dr. Cian Muldoon.

Currently, Prof O'Sullivan directs a translational gastrointestinal (GI) research team in the Trinity Translational Medicine Institute (TTMI) in collaboration with clinical and surgical colleagues. She utilises well established bio-banking structures to drive this GI translational research program. Prof. O'Sullivan's current translational research themes include

1. Development of diagnostic platforms to stratify cancer risk and response to targeted therapies for gastrointestinal diseases.
2. Development of novel patented therapeutics to be used in the neoadjuvant and adjuvant treatment setting for gastrointestinal cancer patients (Colorectal and Oesophageal cancers).
3. Elucidating how the tumour microenvironment cross talks to the immune system in GI patients.
4. Importance of metabolism, inflammation, and obesity in driving disease progression and in regulating treatment response in GI diseases.

The outputs of these translational themes will benefit patient care, treatment and management for gastrointestinal diseased patients.

Endoscopic outpatient cancer treatment platform (ENACT)

(Funder: DTIF- Enterprise Ireland)

Electroporation is the application of electric pulses to cause transient permeabilisation of the cell membrane, termed reversible electroporation (rEP), allowing ions and molecules to enter the cell. Electroporation can be used for the treatment of tumours since increased membrane permeability causes chemotherapeutic drugs to enter cells, a method termed electrochemotherapy (ECT). ECT allows local cancer treatment, lowering drug dose and reducing side-effects of systemic chemotherapy. Irreversible electroporation (iEP) is an emerging cancer therapy that uses high intensity electrical pulses to ablate solid tumours. Both forms of electroporation are in use clinically. In collaboration with Mirai Medical which provides the technology (ePORE electroporator) the aim of this project is to investigate the immune response elicited by this treatment. They aim to look at the immune response in Pan GI cancer using ex vivo explants from patients in SJH. Post treatment conditioned media will be used to determine the effects of the proteomic secretome on immune cell responsiveness. This proteome will be analysed by Multiplex ELISA to determine the inflammatory profile. They will investigate the effects of electroporation on our cell line isogenic models of chemo/radio resistance to oesophageal cancer, to establish whether EP can reverse this resistance and to optimise the settings for treatment. The goal of this project is to evaluate if electroporation can be used as a combination treatment to boost treatment response in GI cancer patients.

The All-Ireland Cancer Network (AllCaN) Programme
See research highlight on page 14.

Translational Cancer Medicine Team

Professor Maeve Lowery, Professor of Translational Cancer Medicine, TCD; Consultant Medical Oncologist, St James's Hospital; Academic Lead, TSJCI

Professor Lowery's clinical and translational research is focused on the development of a personalised approach to management of gastrointestinal cancers, particularly oesophageal, gastric and pancreaticobiliary cancers. Through better understanding of the molecular mechanisms underlying these diseases, her team hope to develop more effective strategies for prevention and treatment of gastrointestinal cancers and improve outcomes for patients while also maintaining quality of life.

HEALED Consortium (The personalised active cell therapy paradigm) (Funder: Enterprise Ireland)
See research highlight on page 10

Identification of coding and novel regulatory mutations in DNA Damage Response (DDR) pathway genes as personalised targets for the treatment of patients with pancreatic cancer (Funder: The Pancreatic Cancer Research Fund)

Performed with collaboration from Dublin City University, this study aims to identify and functionally characterise coding and non-coding mutations that are associated with the DNA damage repair pathway in pancreatic cancer patients. Long term this work aims to develop new and more effective combination treatment strategies for patients with pancreatic cancer.

The PRECODE Network (Pancreatic cancer organoids research) (Funder: European Commission)

This network is focused on genomic analysis and functional profiling of DNA repair in pancreatic cancer organoids for identification of targetable DNA damage repair defects. PRECODE will

generate organoid models of pancreatic cancer for patient tumours and use these models to identify mechanisms of sensitivity and resistance to agents targeting the DNA damage response pathway. Long term they hope to develop new and better systemic therapies targeting that DDR pathway.

Elucidating the immunometabolic and genomic characteristics in young onset gastroesophageal cancers (Funder: Health Research Board)

This project investigates the genetic, tumour and host factors accounting for the epidemiologic observations of increasing incidence of gastroesophageal cancer in young patients. Early-onset gastric cancer presents more frequently with metastatic disease and is associated with chemoresistance, and an overall worse prognosis compared to gastric cancer in older adults.

We do not fully understand the genomic and immunological reasons for this, currently an acute unmet clinical need with current projection expecting incidence of early gastric cancer cases to increase significantly over the next decade. We hope to identify better strategies for prevention, early detection and treatment of OGJ cancer.

Genotype matched therapies in intrahepatic cholangiocarcinoma: A multipronged strategy for improving efficacy and combating resistance

(Funder: ERA-NET TRANSCAN)

The project uses annotated clinical samples and genetically defined murine models to undertake a multipronged approach to the discovery of mechanisms causing resistance to oral targeted agents in cholangiocarcinoma. We will build on established methods, including multiplex immunohistochemistry and computational modelling of gene expression networks, to investigate how oncodrivers to shape the iCCA TME and, consequently, whether oral targeted agents can modulate TME components contributing to immunotherapy drug sensitivity/resistance. This research is a collaboration with University College Dublin, Hannover University, University of Rennes, and Istituti Fisioterapici Ospitalieri, Rome. The long- term aim of the project is to design rational combination therapies (e.g., combinations of molecularly targeted strategies and/or immunotherapies) and test them in our pre-clinical models and ultimately in clinical trials of patients with advanced cholangiocarcinoma. Prof. Adrian Bracken (Cancer Genetics Team) is co-investigator on this award.

TACC (see research highlight page 9)

Cancer Epigenetics Team

Prof Adrian Bracken, Professor in Medical Molecular Genetics, School of Genetics and Microbiology, TCD Molecular and Precision Oncology Theme lead, TSJCI

Our team is focused on understanding the molecular mechanisms of how epigenetic factors regulate cell-fate decisions in stem cells and in cancer. We have several exciting ongoing projects in the lab studying the roles of epigenetic regulators in development disorders and cancer. We are also studying genetic predisposition to cancer and using our expertise in chromatin biology and epigenetics to explore the contribution of regulatory elements in the 'non-coding genome'.

Genotype matched therapies in intrahepatic cholangiocarcinoma: A mutli-pronged strategy for improving efficacy and combating resistance

(Funder: ERA-NET TRANSCAN) (see page 47)

Circumventing resistance to EZH2 inhibition in cancer: A role for the H3K36me2 Methyltransferases NSD1/2 (Funder: Worldwide Cancer Research)

Driven by numerous ground-breaking studies demonstrating that the regulation of chromatin is frequently disrupted in cancer, a new generation of potent and specific inhibitors for several chromatin associated proteins such as EZH2, a member of the Polycomb Repressive Complex 2 (PRC2), have been developed. EZH2 has 'change-of function' missense mutations in B-Cell Lymphomas.

EZH2 inhibitors have recently been approved for the treatment of patients with these mutations. However, the discovery of additional mutations conferring resistance to EZH2 inhibitors in lymphomas and other forms of EZH2-dependent cancers highlight the pressing need to address the challenge of resistance to EZH2 inhibitors. This project aims to address this unmet need. The team anticipates that this research will develop proof of principle data supporting strategies for the better treatment of a wider spectrum of cancers which are also dependent on deregulated EZH2 function.

BioSystems Engineering Laboratory (BSEL)

Prof Athanasios (Sakis) Mantalaris, Don Panoz Chair, Professor of Pharmaceutical Biology, School of Pharmacy and Pharmaceutical Sciences, TCD; Principal Investigator, National Institute for Bioprocessing Research and Training (NIBRT)

Prof Nicki Panoskaltsis, Professor in Personalised Therapeutics, School of Pharmacy and Pharmaceutical Sciences, TCD; Consultant in Haematology, St James's Hospital

In 2021, Professors Anthanasios (Sakis) Mantalaris (Bioprocess Engineer) and Nicki Panoskaltsis (Haemato-Oncologist) were recruited by the School of Pharmacy and Pharmaceutical Sciences to Trinity College Dublin. Together they co-lead the BioSystems Engineering Laboratory (BSEL) an inter-disciplinary lab which focuses on providing integrated *in vitro/in silico* platforms for clinical translational biomedical applications. The research laboratory delivers an interdisciplinary program on precision and personalised medicine employing engineering methods and solutions for healthcare applications with research focus is in the following areas:

1. precision personalised anti-cancer (leukaemia) in *silico/in vitro (organoid) /in vivo* treatment platforms,
2. biomanufacturing technologies for cellular therapeutics (blood, bone, lung),
3. monoclonal antibody production technologies,
4. understanding and modulating cellular metabolism, and
5. understanding the immune pathogenesis of leukaemia and related conditions. The research ethos of the lab is not limited to mechanistic science and discovery but places importance on translational applications.

An example of this interdisciplinary approach is the "Making Blood" programme: Blood supply to meet demand (through donor registries) is the primary challenge for Blood Banks internationally and requires significant resources to avoid shortages and ensure safety.

An alternative, practical and cost-effective solution to conventional allogeneic donated blood is essential to reduce patient morbidity and mortality, stabilise and guarantee the donor supply, limit multiple donor exposures, reduce risk of infection of known or as yet unidentified pathogens, and ensure a robust and safe turn-around for blood supply management, all important factors to consider for patients undergoing treatment for Blood cancers and other bone marrow failure disorders.

BSEL has developed an ex vivo perfusion organoid for blood production without the use of serum or other unnecessary cytokines/proteins to produce continuously harvested enucleated red blood cells and is engaging with the Irish Blood Transfusion Service to continue the research and development of the application.

Establishing 3D tumour platforms for validation of pipeline programs

(Funder: Enterprise Ireland (Innovation Partnership Project)

Using BSEL's Leukaemia organoid platform, they have a collaborative project with Legend Biotech Ireland Ltd, led by Dr Tony McElligott (TTMI).

Metabolism-driven precision biomanufacturing of cellular therapeutics

(Funder: SFI Research Professorship)

The overall research aim is to characterise and direct cellular heterogeneity through the understanding and control of metabolism from input to bioprocess to output to develop improved ACTs that can result in improved clinical outcomes. The research programme is addresses the following aims:

1. Develop a comprehensive cloud-based metabolism database for bioprocess development,
2. Characterise and direct cellular heterogeneity as a function of metabolism,
3. Model-based precision culture media and feeding strategy design for optimal point-of-care cell manipulation for the production of high-quality allogeneic & autologous ACTs,
4. Metabolic biomarker identification for high-throughput, rapid QA and for real-time QC,
5. Metabolism-centered precision biomanufacturing of ACTs,
6. Deliver impact on knowledge, training, communication, and commercialisation and
7. Execute effective management, dissemination, and outreach.

O'Boyle Research Team

Dr Niamh O'Boyle,
Associate Professor in Pharmaceutical Chemistry, School of Pharmacy and Pharmaceutical Sciences, TCD.

The O'Boyle research group is fascinated by the interaction of chemicals, both drugs and toxins, with the body. This inspires our research in the development of novel drugs for hard-to-treat cancers. Targets of interest include tubulin and cysteinyl leukotrienes.

From chemistry to clinic: increasing the solubility and stability of promising drugs for gastrointestinal cancers

(Funder: Trinity College Dublin)

Successful drugs must overcome many hurdles on their journey to clinical use, and it is essential to have a favourable solubility and stability profile. This project aims to increase the solubility and stability of the radio sensitising molecule pyrazinib, which is under development as treatment for oesophageal adenocarcinoma. Drug development options for pyrazinib are limited due to poor water solubility. This research aims to overcome these limitations by chemical synthesis of stable, water-soluble versions of pyrazinib called prodrugs. Prodrugs are compounds with little or no inherent pharmacological activity that are enzymatically converted to the active drug in vivo.

Prodrug formation is an excellent option for improving the solubility and stability of drugs. We have synthesised a series of prodrugs, including phosphate esters and amino acids to optimise the physiochemical profile of pyrazinib and enable further progression along the drug delivery pipeline into clinical studies.

Anti-proliferative enantiomeric beta-lactams targeting tubulin

(Funder: Wellcome Trust, Royal Society of Chemistry, Trinity College Dublin)

Triple-negative breast cancer (TNBC) is the most lethal form of breast cancer which is unresponsive to endocrine therapies. Our family of 3-hydroxy β-lactam *cis*-restricted combretastatin A-4 analogues are amongst the most potent tubulin-targeting agents ever reported as colchicine binding site inhibitors. The long-term expected impact of this research is the identification of clinically relevant tubulin-targeting beta-lactams for hard-to-treat cancers.

Medicinal Chemistry Research Team

Prof Mathias Senge,
Chair of Organic Chemistry, School of Chemistry, TCD;
Hans Fischer Senior Fellow, Institute for Advanced Study, Technical University of Munich.

The Medicinal Chemistry team (**Figure 8**) focuses on photomedicine; particularly photodynamic therapy (PDT). Traditional therapies typically used to treat cancer and microbial infections are often insufficient to the demands of modern medicine.

Current therapies have significant side effects and infections with total resistance to hospital antibiotics exist, with few new antibiotic strategies in development pipelines to combat this danger.

PDT is an alternative approach to therapy which can alleviate some of the above concerns.

PDT involves three key components: a photosensitiser, a light source, and the oxygen present in the tissue - these combine to form highly toxic reactive oxygen species (ROS) inside the biological mass. This approach is used for the treatment of malignancies and bacterial and viral infections. The group's main interests are

1. the development of novel photosensitisers,
2. nano formulations for cancer treatment,
3. using 'molecular shape' as a drug design principle for cell internalisation,
4. endoperoxides as slow-release singlet oxygen generators and oxygen transport molecules,
5. immune-stimulation via PDT and
6. treatment of glioblastoma with sonodynamic therapy.

Figure 8. The Medicinal Chemistry Research team

Medicinal Chemistry Research Team

POLYTHEA - Design and photo-optimisation of photosensitiser for human health and food security applications or "how light can save lives" (Funder: European Commission)

The development of active compounds that can efficiently fight microbial infections and cancer are of utmost importance for food security and human health, two main challenges for Europe. Tetrapyrrolic photosensitisers (PS) are good candidates to meet these expectations.

These photo-excitable molecules induce cell death via the formation of oxygen reactive species (ROS) and present very low toxicity in the absence of light. They are already used in photodynamic therapy (PDT) for cancer or skin disease treatments or in photo-antimicrobial chemotherapy (PACT). Unfortunately, research and training are still largely fragmented in this field in Europe. Some scientific barriers have to be overcome to increase their efficacy, e.g., improvement of the excitation pathways, ROS production, specific cell targeting, Gram (-) bactericidal effect and prevention and/or eradication of biofilms. That is why the EJD Polythea project aims to develop an integrated and multidisciplinary approach of PDT through the implementation of 10 PhD research projects.

With collaboration from University of Limoges, University of Amsterdam, University of Coimbra, Wroclaw University of Science and Technology, and Biolitec AG, POLYTHEA will result in the development of new photosensitisers and formulations for cancer therapy and as antimicrobial agents.

Atropisomerism in medicinal chemistry (Funder: Irish Research Council)

'Atropisomerism in Medicinal Chemistry' encompasses interdisciplinary thinking to investigate the implications of axial chirality on both drug delivery and efficiency. Atropisomerism occurs when the rotation of a single bond can lead to a non-superimposable mirror image of the molecule. Depending on the number of such bonds present in a molecule, there will be an equivalent possibility of different orientations. Whilst this project will examine the implications of atropisomerism specifically in porphyrin-based systems, the fundamental pillar of chirality in drugs means that these findings would translate to a broad range of therapeutics, including cancer. The long-term expected outcome is that it will lead to the development of a new concept for general drug delivery based on molecular shape.

Dyes with switchable intersystem crossing for photonics

(Funder: Science Foundation Ireland)

Functional dyes which interact with light in a predictable manner are essential for photonic technologies and biomedical research. Controlling the processes that take place in molecules after light absorption is challenging and development of dyes for target application relies on trial-and-error approach.

The DyeSICPhoto project aims to address this fundamental problem by developing a general approach to dyes with programmed excited state behaviour and to set up a technological background for its application in biophotonics and solar energy conversion. With collaboration from Technological University Dublin, this project is expected to lead to the development of a new concept for activation of photosensitisers for biomedical applications.

Re-engineering porphyrins - From shape to function (PORPHYSHAPE)

(Funder: Science Foundation Ireland)

Porphyrins are the red (blood) and green (plants) 'pigments of life', which constitute some of the most important cofactors found in nature and crucial for oxygen transport, electron transfer, catalysis, and photosynthesis. By making our own versions of these molecules, with a dramatically changed shape, they can re-engineer for new chemical functions in catalysis and sensing beyond what can be accomplished by the natural versions.

Being able to incorporate these 'building blocks' into the construction of nanoscale systems, they can make molecule-scale factories, designed for purpose at the atom scale for use as catalysts and as key components of nanomaterials.

Working alongside collaborators from Technical University of Munich, King Abdullah University of Science and Technology, and University of Salento, this project will develop a new concept for molecular engineering of functional organic materials.

Neuronal Oscillations and Epilepsy Research Group

Prof Mark Cunningham, Head of Discipline of Physiology, Ellen Mayston Bates Professor of Neurophysiology of Epilepsy, Discipline of Physiology, School of Medicine, TCD

The Cunningham research group aims to understand the basis of neurological and psychiatric disease at the level of the neuronal microcircuit. Our research seeks to understand physiological and pathological electrical activity generated in various disease states. In the brain tumour related epilepsy (BTRE) context, our research aims to employ chemo genetic approaches to prevent seizure generation and propagation.

Gene therapy approaches for brain tumour related epilepsy

(Funder: Science Foundation Ireland)

Seizures are a frequent and severe symptom for patients with brain tumours. Seizures are poorly controlled with current medical and surgical treatments. The neurotransmitter glutamate, present in the peritumoral microenvironment, contributes to both tumour growth and seizure generation. They aim to use a modified glutamate-gated chloride channel to limit the capacity of neurons to fire excessively by opening an inhibitory channel in response to elevated glutamate. The project uses a variety of animal and human models to develop this gene therapy approach for clinical translation. This project is a collaboration with Beaumont Hospital, University College London, and Royal College of Surgeons in Ireland.

Colorectal Oncology Research Group

Mr Michael Kelly,
Consultant Colorectal Surgeon,
St James's Hospital;
Clinical Senior Lecturer, TCD

Prof Paul McCormick,
Consultant Colorectal Surgeon,
St James's Hospital;
Clinical Associate Professor, TCD

Prof Brian Mehigan,
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Mr John Larkin
Consultant Colorectal Surgeon,
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Dr Alison Corr,
Consultant Radiologist,
St James's Hospital

Prof Jim Meaney,
Consultant Radiologist,
St James's Hospital;
Clinical Professor, TCD

The application of radiomics within the field of anal cancer to predict response to primary treatment, recurrence, and overall survival

(Funder: Supported by the Joly Leadership Fund, TSJCI awarded to Mr. Michael Kelly)

To develop a radiomic nomogram that will allow them to identify poor prognostic factors on pre-treatment imaging and subsequently predict, with accuracy, those who will have poor outcomes, in patients with anal cancer. This work will have two separate phases.

1. Retrospective, multi-centre cohort study. Nomograms will be constructed based on clinical variables, radiomic, and genomic data to predict the probability of disease recurrence and poor survival outcomes.
2. Prospective, multi-centre cohort study. Radiomic and radiogenomic nomograms developed in phase 1 will be applied to patients with locally advanced or recurrent anal cancer in a prospective setting to predict oncological outcomes and suitability for minimally invasive surgery. Patients will be followed up for a period to determine success of applied nomograms in prediction of primary and secondary outcomes.

Our hypothesis is that radiomic and radiogenomic nomograms can be developed to help select patients, based on pre-treatment imaging, of those likely to respond poorly to primary treatment, recur or have poor survival outcomes.

The development of an MRI based radiomics nomogram to predict oncological outcomes in patients with locally advanced rectal cancer (LARC).

(Funder: Supported by the Joly Leadership Fund, TSJCI awarded to Mr. Michael Kelly).

Data on radiomics and radiogenomics in the field of rectal cancer remains limited by small, retrospective studies. Studies have shown good individual efficacy yet poor reproducibility. Using data from multiple international centres, they aim to develop radiomic and radiogenomic nomograms to identify patients with locally advanced rectal malignancies who are at high risk of recurrence or early treatment failure, in an attempt to avoid exposure to highly morbid exenterative procedures and preserve quality of life.

They aim to develop MRI-based radiomic signatures predictive of poor oncological outcomes. Exenterative surgery is highly morbid and has a profound effect on patient quality of life. Reducing the unnecessary exposure of patients with poor prognostic factors to such procedures will provide these patients with a superior quality of life in the time they have remaining.

Predictors for those having complete clinical response following neoadjuvant treatment for locally-advanced rectal cancer (Funder: N/A).

A propensity-matched study will investigate differences in patients with locally-advanced rectal cancer (LARC) who achieved complete clinical response (cCR) following nCRT/TnT (Neoadjuvant chemoradiotherapy / Total neoadjuvant therapy) and are on a watch-and-wait (WW) program versus those that don't have a cCR.

Predicting patient response to nCRT or TnT will help guide more personalised treatment strategies for LARC. There is currently no international consensus regarding the WW protocol, and optimal patient selection criteria is essential in establishing this. This research will add to the evidence base that may inform treatment planning systems for rectal cancer, underpinning the practice of surgeons, oncologists, radiation oncologists, and radiologists.

Functional, economic, surgical, and histopathological outcomes in robot-assisted colorectal cancer surgery (Funder: N/A)

This is a survivorship-based project because it has a patient-centred approach that will primarily explore economic and functional outcomes such as postoperative length of stay, the return to normal bodily functions (defecation, full mobilisation, etc), reasons for extended stays, and the measurement of patient satisfaction for robotic vs traditional surgeries.

The primary aim is to carry out a comparative analysis of patient outcomes between robotic-assisted surgeries, laparoscopic, and open approaches in TSJCI.

The long-term expected impact is that ultimately it will evaluate the role of robotic surgery as part of the colorectal speciality. They hypothesise that robotic cancer surgeries in colorectal surgery will demonstrate improved patient outcomes compared to traditional techniques, especially regarding functional outcomes.

Coagulation Research Group

Dr Lucy Norris,
Senior Experimental Officer, TCD

Prof Feras Abu Saadeh,
Clinical Associate Professor, TCD;
Gynaecology Oncology Consultant,
St James's Hospital.

Dr. Mark Ward,
Medical Scientist, TCD

Gynaecological cancers have been associated with high rates of Venous thromboembolism (VTE) which is exacerbated by pelvic surgery and chemotherapy. Current risk models perform poorly and development of specific risk models for gynaecological cancers has been a focus of this research program. In addition, the coagulation system appears to play a role in the aetiology of ovarian cancer. The coagulation research group comprises of basic scientists, gynaecologists and oncologists working in the area of thrombosis in cancer.

The main focus of the group is the development of risk models for predicting and preventing thrombosis in gynaecological and other cancers. Using a combination of clinical risk factors and haemostatic biomarkers, they have developed a risk model for the prediction of venous thrombosis in gynaecological cancer patients. More recently they are developing biomarkers to predict thrombosis in patients undergoing chemotherapy which may be used to tailor prophylaxis in high-risk patients.

The group also works with patient organisations to increase awareness of thrombosis risk in cancer patients and to identify key priorities for patients in relation to VTE prophylaxis leading to the development of better decision aids.

Lymph node status and coagulation biomarkers as predictors of venous thromboembolism in gynaecological cancer patients post-surgery

(Funder: Leo Pharma)

Gynaecological cancer is associated with an increased incidence of (VTE) even with appropriate thromboprophylaxis. The risk is greatest following surgery and can persist for up to 6-12 months post surgery. Lymph node dissection (LND) is a common procedure in gynaecological cancer surgery and increases the complications and complexity of the surgery.

In prostate cancer, lymph node dissection during radical prostatectomy increased the incidence of deep venous thrombosis and pulmonary embolism. In addition, lymph node metastasis is a strong risk factor for VTE and that early metastasis is associated with an activation of haemostatic system in the early stages of metastasis.

The role of LND as a predictor of metastasis is unknown. Thrombin generation is useful as a biomarker for VTE in gynaecological cancer and can improve the predictive ability of the thrombogyn risk score (a risk model for VTE in gynaecological cancer recently developed by our group).

Pilot work has shown that FVIII, Free protein S and Factor V are important contributors to increased thrombin generation in gynaecological cancer patients. The aims of our study are:

1. to investigate the role of lymph node dissection and lymph node metastasis in VTE following both open and laparoscopic surgery for gynaecological cancer,
2. to evaluate the ability of pre-operative FVIII, free Protein S and Factor V levels to predict VTE in gynaecological cancer patients post surgery and
3. to determine whether addition of lymph node status or biomarker levels can improve the accuracy and predictive strength of the Thrombogyn score.

Thrombomodulin as a predictor for chemotherapy associated venous thromboembolism (Funder: TCD Dean of Health Sciences Research award)

Recent guidelines recommend that primary prophylaxis should be considered in intermediate/high risk patients undergoing chemotherapy following risk assessment with a validated risk score (Khorana score). However, the Khorana score performs poorly in cancers of a single type particularly lung and ovarian cancer.

The development of VTE is a dynamic ongoing process which cannot be determined by a single risk assessment prior to therapy. Biomarkers measured serially during chemotherapy may provide a more effective method of identifying patients at risk of VTE. Our previous work has suggested that a key regulatory pathway involved in thrombus formation, the activated protein C pathway(aPC) is dysregulated during chemotherapy and may be implicated in VTE risk. Recent novel data from our group suggests that thrombomodulin, a key protein in the aPC pathway, could act as a biomarker for VTE. The aims of this study are to:

1. Determine whether plasma thrombomodulin levels measured serially during chemotherapy can act as a novel dynamic predictive marker for chemotherapy associated VTE,
2. Investigate the prothrombotic mechanisms involved in chemotherapy associated VTE using *in vivo* and *in vitro* studies.

Activated protein C pathway in ovarian cancer - a novel prognostic marker?

(Funder: TCD Research Boost Award)

Coagulation activation also plays a key role in the growth and spread of ovarian and other cancers and markers of coagulation activation may serves as predictors of prognosis and treatment response. Our group have discovered that a major anticoagulant pathway (aPC pathway) is dysregulated in ovarian cancer and may play a role in the pathogenesis of the disease. The aim of this study is to measure plasma and tissue expression EPCR, THBD, protein C, protein S and Factor V and correlate them with overall survival and treatment response. This will determine their potential as novel prognostic biomarkers.

Molecular Pathology Group-Gynaecological Oncology

Dr Sharon O'Toole,
Senior Research Fellow (Obstetrics) & Senior Experimental Officer (Histopathology), TCD

Prof John O'Leary,
Chair of Pathology and Consultant Histopathologist; Cancer Prevention Theme Lead, TSJCI

Dr Cara Martin,
Assistant Professor in Molecular Pathology, Tumour Biology and Cancer Screening, Cancer Prevention Theme Lead, TSJCI

Clinical Team: Prof Feras AbuSaadeh (Consultant Obstetrician and Gynaecologist, SJH), Prof Karen Cadoo (Cancer Geneticist and Medical Oncologist, SJH), Dr Waseem Kamran (Consultant Gynaecological Oncologist, SJH), Prof. Tom D'Arcy (Consultant Obstetrician and Gynaecologist, SJH and the Coombe Hospital), Dr Paddy Maguire (Consultant Gynaecological Oncologist, SJH), Dr Dearbhaile O'Donnell (Consultant Medical Oncologist, SJH), Dr Ciaran O'Riain (Consultant Histopathologist, SJH), Dr. Niamh Coleman (Consultant Medical Oncologist, SJH), Dr. Niall Sheehy (Consultant Radiologist, SJH), Dr. Ciara O'Hanlon Brown (Consultant Medical Oncologist, SJH), Prof. Michelle Leech (Prof. in Radiation Therapy, TCD), Dr Catherine O'Gorman, Consultant Gynaecological Oncologist, St James's Hospital

Gynaecological cancers are on the increase in Ireland with over 2000 cases presenting each year across the island of Ireland. Ovarian cancer outcomes, in particular, are one of the poorest in Europe due to late presentation and lack of screening.

Our research focuses on ways to improve diagnosis and outcomes for patients by incorporating new biomarkers into the patient pathway. Biomarkers present in blood or other liquid biopsies from patients, tissue and also the routine imaging a patient will have as part of the diagnosis. We aim to develop a more personalised treatment for patients which will ultimately improve outcomes. The Gynaecology Oncology Research Group hosts DISCOVARY/INNOVATION, a consortium dedicated to research in ovarian cancer and cancer metastasis.

Integrating radiomics into ovarian cancer management (Funder: Royal City of Dublin Hospital Trust)

This study aims to incorporate data from radiological imaging and pathological features to improve on the current prognostic and predictive markers. According to the radiomics principles, images are more than pictures, they are data, and as such they contain a huge amount of information that cannot be analysed visually but need a deep level of analysis.

Radiomic features can be used to obtain information about heterogeneity and have the potential to uncover disease characteristics. This project aims to build a model to identify predictive and prognostic features of High grade serous ovarian cancer and to correlate with clinical outcomes. The long-term expected impact of this project is that will lead to the improvement of prognostic and predictive markers in ovarian cancer.

All-Ireland Cancer Liquid Biopsies Consortium (CLuB) (Funder: HEA)

See research highlight (page 11)

MISSION: Monitoring response to treatment in ovarian cancer

(Funder: Royal City of Dublin Hospital Trust)

Surgery is the cornerstone of treatment in ovarian cancer and remains one of the prognostic indicators for the disease. An important criterion for entry into clinical trials in ovarian cancer is often the degree of residual disease post cytoreductive surgery. However, given the considerable variability in definition and assessment of de-bulked disease, such predictors have not been particularly reliable. Hence, a surrogate marker for successful surgery is an emerging area of interest in ovarian cancer. No single marker has proved useful to date.

We are proposing to use a combination of serum-based biomarkers in conjunction with circulating tumour cell enumeration and characterisation. In addition, we will assess the value of routine biochemical markers to evaluate their prognostic role.

As well as establishing prognostic ability, the identification of novel markers expressed on the surface of circulating tumour cells may lead to future targeted therapies in ovarian cancer specifically targeting the metastatic phase of the disease.

It is expected that this work will help identify a surrogate marker for successful surgery in high grade serous ovarian cancer and the inclusion of CTCs may aid identification of novel therapeutic targets for future studies.

Advancing ovarian cancer diagnostics and prognostics (ADAPT) (Funder: Royal City of Dublin Hospital Trust)

Ovarian cancer has long suffered from lack of new therapies but is slowly moving into the arena of targeted therapies with the introduction of anti-angiogenic agents and more recently PARP inhibitors.

There are significant limitations to the full implementation and exploitation of novel targeted precision therapies, most notably the standard use of tissue biopsies to diagnose and monitor treatment. Blood as a personalised medicine approach and in particular as a 'Liquid Biopsy' is a highly promising alternative approach to tissue biopsies.

This study asks whether a liquid biopsy can direct targeted therapy in ovarian cancer and can we monitor response to targeted therapies using the liquid biopsy? This work will aid with the incorporation of ctDNA from a liquid biopsy into ovarian cancer management.

Cancer Chemoradiation Research Group

Dr Stephen Maher,
Associate Professor in Translational Oncology, School of Medicine, TCD.

The group's current research focuses on

1. Understanding the molecular genetic regulation of chemotherapy trafficking within cancer cells, focusing on GI cancers.
2. Understanding the molecular genetic regulation of radiosensitivity in cancer cells, focusing on GI cancers.
3. Developing a new, personalised risk stratification algorithm for managing patients with pancreatic cystic lesions in a less invasive capacity than the current clinical standard.
4. Leading frontier research in understanding the molecular role of pancreatic cyst fluid in driving the evolution of pancreatic disease.
5. Understanding the role of pancreatic cyst microenvironmental biology in altering T cell function.
6. Developing oxygen-carrying nanoemulsion technology for radiosensitising hypoxic pancreatic cancer cells.

Understanding the role of microRNA-31 in regulating cellular sensitivity to chemoradiotherapy in pancreatic ductal adenocarcinoma

(Funder: TCD Provost's PhD Project Award)

This project established that loss of miR-31 on chromosome 9p21.3 in pancreatic tumours impacts on cellular sensitivity to platinum-based chemotherapy and radiotherapy. Using genetically engineered cell models in the lab, the project also determined that miR-31 loss results in dysfunctional regulation of both the ATOX1 and GPx8 pathways simultaneously, which drives altered chemotherapy and radiotherapy sensitivity, respectively. We have identified miR-31, ATOX1 and GPx8 as potential targets for therapeutic intervention. It is expected that this work will result in synthetic RNA-based treatment co-administered with conventional chemotherapy and radiation which enhances tumour sensitivity.

Cancer Chemoradiation Research Team

Integrative multi-omic analytics for the early detection of pancreatic cancer

(Funder: Meath Foundation and Viatris Ireland)

Pancreatic cystic lesions (PCLs) are fluid-filled structures found within or on the pancreas. Most PCLs are detected incidentally during routine investigations. While many PCLs are benign, others have the ability to undergo malignant transformation and are regarded as precursor lesions of pancreatic cancer.

PCLs represent a unique opportunity to identify and monitor patients with a high-risk of developing pancreatic cancer. Unfortunately, the ideal strategy for managing patients with PCLs is very unclear. In this study we developed a high-performance cross-biofluid (cyst fluid and blood serum), multi-omic (transcriptomic and proteomic) biomarker algorithm that strategies PCL patients into high-risk and low risk groups with excellent accuracy. Our team also determined that PCL fluid itself drives hallmarks of cancer, and likely contributes to the progression of disease within the pancreas. This is expected to lead to the further refinement of the PCL risk stratification algorithm, independent validation and development for routine clinical implementation.

Immunophenotyping of pancreatic cystic lesions

(Funder: TCD Provost's PhD Project Award, see page 69)

Development of miR-31 mimics/ inhibitors for altering chemoradiation responses in pancreatic tumours

(Funder: Musgrave Breakthrough Cancer Research)

Using genetically engineered cell models in the lab, this project is examining how miR-31 loss results in dysfunctional regulation of both the ATOX1 and GPx8 pathways simultaneously, which drives altered chemotherapy and radiotherapy sensitivity, respectively.
We examine if nanoparticles loaded with synthetic miR-31 mimics or inhibitors can re-establish chemosensitivity and radiosensitivity in pancreatic tumour spheroid and organoid models. The long term expected impact is that this work will contribute to synthetic RNA-based treatment co-administered with conventional chemotherapy and radiation which enhances pancreatic tumour sensitivity.

Development of a series of clinically relevant radio sensitising agents for cancer (Funder: Science Foundation Ireland)

Ireland has one of the highest incidences of oesophageal adenocarcinoma (OAC) in Europe and rates are predicted to continue rising. For patients diagnosed with OAC, chemoradiotherapy (CRT) prior to surgery is increasingly becoming that standard of care for treatment.

Yet, resistance to treatment, radiotherapy in particular, remains a substantial clinical problem. Through patient cohort tumour analysis and complementary in vitro cell models we have identified a number of novel microRNA that regulate cellular sensitivity to radiation.

We have optimised the release and uptake of these radio sensitising microRNAs to tumour cells, using a combination of natural collagen-based hydrogel scaffolds loaded with liposomes containing microRNAs.

These radiosensitiser-loaded scaffolds are tested in pre-clinical tumour models for efficacy, with the downstream metric being enhanced tumour regression in response to clinically-relevant radiotherapy. This study provides the first step in the feasibility of moving these innovative radio sensitising agents into commercial development, larger scale pre-clinical evaluation and assessment in clinical trials on-site.

The group's work will result in synthetic RNA-based treatment co-administered with conventional chemotherapy and radiation which enhances oesophageal tumour sensitivity.

Breast Cancer Radiotherapy

Prof Frances Duane,
Consultant Radiation Oncologist, St Luke's Radiation Oncology Network, St Luke's Hospital and St James's Hospital; Clinical Associate Professor, Discipline of Radiation Therapy, TCD.

Professor Duane is involved in clinical research aiming to investigate the benefits and risks of radiotherapy for breast cancer, the development of dose-response relationships for the effects of radiotherapy, as well as projects focused on breast cancer radiotherapy optimisation.

She is currently leading Ireland's participation in international breast radiotherapy clinical studies on the Irish Radiation Research Oncology Group and Cancer Trials Ireland Breast Disease Specific Site Group portfolio including a number of phase III clinical trials and prospective registry studies.

Radiotherapy related adverse effects

(Funder: N/A)

Dose response relationships for radiotherapy-related adverse effects depend on dosimetry of past regimens in conjunction with long-term clinical follow-up data. Breast cancer radiotherapy can cause various types of heart disease, lung cancer and oesophageal cancer, with risks increasing with incidental radiation dose.

Prof Duane has published studies describing heart and cardiac substructure, lung and oesophageal dosimetry and collaborating with international research groups she has published epidemiology studies predicting risks of late effects in breast cancer survivors.

Other collaborative works include studies of central endocrine complications in childhood cancer survivors, cardiovascular and second cancer risks for survivors of Hodgkin lymphoma in Ireland, and studies of heart disease in lung cancer survivors.

Recent published work on heart exposure in lung cancer led at TCD was awarded Editor-in-Chief Emeritus Pick of Papers in Radiotherapy and Oncology in 2022 showing that heart radiation dose in lung cancer radiotherapy may be reduced in the clinic by using more stringent optimisation objectives during rotational intensity modulated radiotherapy planning than are currently used in many centres.

This work is a collaborative effort with the University of Oxford, The National Cancer Institute in the Netherlands, University of Manchester, the Peter MacCallum Cancer Centre, and the Northern Ireland Cancer Centre.

Breast cancer radiotherapy optimisation (Funder: N/A)

Professor Duane is a member of the Early Breast Cancer Trialists Collaborative Group secretariat. This international group publishes individual patient data meta-analyses on the benefits and risks of treatment for breast cancer, reliably assessing moderate differences in long-term survival, differences that may not be identified in individual randomised control trials.

For example, regional nodal irradiation has been shown to significantly reduce breast cancer mortality and overall mortality. As breast cancer is very common moderate effects on survival could result in the avoidance of many thousands of deaths each year worldwide.

Prof Duane has highlighted the benefits of regional nodal radiotherapy by leading the development of breast radiotherapy guidelines at the St. Luke's Radiation Oncology Network and nationally through the National Cancer Control Programme.

Research Theme: Cancer Immunology

Theme Leadership

Prof Clair Gardiner,
Professor in Biochemistry
and Immunology, TCD;
Research Theme Lead, TSJCI

Prof Joanne Lysaght,
Professor in Cancer Immunology
and Immunotherapy,
School of Medicine, TCD;
Research Team Lead, TSJCI

Cancer Immunology and immunotherapy is a major research and clinical strength within TCD and is an area that has potential to make substantial contributions of global impact. The last decade has witnessed a watershed in cancer therapy in which the immune system has been targeted in a myriad of new ways to treat cancers.

For example, the scientific discovery that resulted in immune check-point blockade therapies resulted in a Nobel Prize for its revolutionary impact in the clinic. There is a lot more potential for new and combination therapies including cell therapies such as CAR-T cells, allogeneic and autologous cell therapies. Improved immune biomarkers in this new era will ensure that more patients benefit from these treatments.

A full spectrum of fundamental, translational, and pre-clinical immunology research, together with immunotherapy clinical trials covering a range of malignancies is ongoing on TCD and St. James's Hospital sites (**Figure 9**).

Immunology has been a key strength of TCD's research portfolio for over two decades, with many experts in fundamental and translational immunology based in TCD. Research areas include anti-tumour immune cells, immunometabolism, mechanisms of tumours evasion, identification of new immunotherapeutic targets and improved prediction of treatment responsiveness.

Clinical trials at St. James's Hospital are testing cutting edge immunotherapies in patients with solid and hematological malignancies including lung, colorectal, head and neck and breast cancer, and these trials importantly allow patients access to new immunotherapies, with many additional trials in the pipeline.

Why focus on immune-oncology?

- We now know that our immune systems protect most of us from cancer for most of our lives. Learning how will help us develop new therapies for correcting the system when it fails.
- For some cancer patients, immunotherapy has already made previously incurable cancer a chronic illness
- We recognise that immunotherapy will be a key pillar of therapy for advanced cancer in the long term.
- It is likely that combination therapies e.g., combining immunotherapy with radiation strategies +/- tyrosine kinase inhibition, +/-chemotherapy may be powerful against difficult to treat cancers
- Immunotherapies currently established in clinical practice exploit only a limited proportion of known anti-tumour or immune-activating mechanisms
- The co-location of immune scientific expertise with research-active clinicians in a high- volume Cancer Institute with excellent research facilities has unique potential to deliver transformative research in this field
- Developments in cancer immunology have a high likelihood of being transferable to other immune-related disease groups including inflammatory disease, autoimmune disease, and infectious disease.

High Level Goal: TSJCI Cancer Immunology

To harness the outstanding immunology and oncology expertise at TCD and St. James's Hospital to rapidly translate immunotherapy research into clinical benefits for cancer patients.

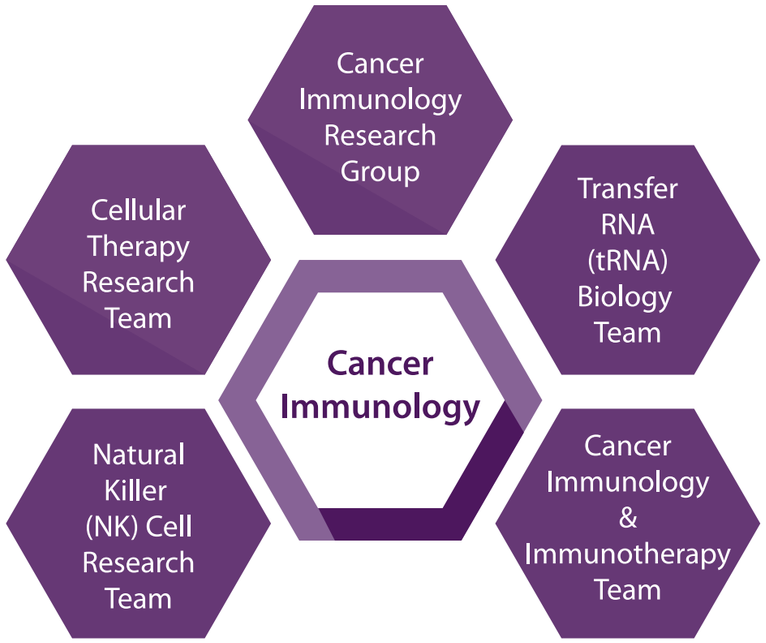

Figure 9. Cancer Immunology research teams at TSJCI

Cellular Therapy Research Team

Dr Nicola Gardiner, (Group Lead), Chief Medical Scientist, Cryobiology Laboratory, St James's Hospital

Prof Derek Doherty, (Group Co-Lead), Professor in Immunology (Head of Immunology), School of Medicine, TCD

Prof Joanne Lysaght, Professor in Cancer Immunology and immunotherapy, School of Medicine, TCD; Research Theme Lead, TSJCI

Dr Tony McElligott, Assistant Professor in Molecular Haematology, TCD

Dr Nina Orfali, Consultant Medical Oncologist, St James's Hospital; Clinical Senior Lecturer, TCD

Dr Aoife Marie Kilgallon, Research Fellow, School of Medicine, TCD

Dr Allison Waters, Research Facilitator, Irish Blood Transfusion Service

Dr Richard Hagan, Chief Medical Scientist, NIHRL, Irish Blood Transfusion Service

Dr Chris Armstrong, Specialist Registrar, MD Candidate, St James's Hospital

Hayley Foy Stones; Medical Scientist, St James's Hospital; PhD candidate, TCD

Prof Tor Hervig, Medical and Scientific Director, Irish Blood Transfusion Service

Prof Larry Bacon, (Group Co-Lead), Consultant Haematologist, CAR-T Clinical Lead, St James's Hospital; Clinical Professor, TCD

Dr Diarmuid O'Donghaile, Consultant Haematologist, Irish Blood Transfusion Service and St James's Hospital

Dr Rob Henderson, Consultant Haematologist, Irish Blood Transfusion and St James's Hospital

Cellular Therapy Research Team

The function of the Cellular Therapy Research Team is to establish research collaborations and projects in the field of cellular therapy to develop novel and improved immunotherapies for cancer. This group brings together multiple disciplines to harness substantial institutional knowledge: Irish Blood Transfusion Service (IBTS) donor HLA profiling, component collection and processing at Cryobiology Stem Cell facility with the clinical input and knowledge at the National Stem Cell Transplant and CAR-T programme and the extensive immunology and cancer biology experience at TTMI.

There are active projects ongoing in the field of CAR-T monitoring and immunosuppression post Stem Cell Transplantation (SCT) investigating in detail immune function and the impact of treatment and immune status on patient outcome. The aim of these projects is the development of state-of-the-art bioassays, monitoring outcome of current and new cellular therapy products. The group objective is to build up research capacity in this crucial area for further development and innovation, build collaborations, and develop submissions for further large-scale funding to expand the research portfolio to include the potential development of on-site cellular therapy manufacturing, up-skilling staff, and developing enhanced treatment options for patient.

Development of an immunobiology platform to monitor immune reconstitution after allogeneic haematopoietic stem cell transplantation and CAR T cell therapy

(Funder: Irish Blood Transfusion Service)

To prospectively characterise early immune reconstitution through the serial measurement and investigation of the roles of the individual immune cell subsets and of the cytokine secretome in the early post-transplant phase and during the development and treatment of graft versus host disease (GvHD) or disease relapse post stem cell transplant.

The group is also investigating the impact of graft content on immune reconstitution and outcomes of transplantation. We will assess the impact of HLA matching and KIR profile on immune reconstitution, GvHD, chimerism, measurable residual disease and outcome post-transplant. In a CAR T patient cohort, we are prospectively characterising early immune reconstitution, CAR T cell persistence, T cell exhaustion marker profile and cytokine levels by serial measurement in the early post CAR T therapy phase and during the development and treatment of the cytokine release syndrome and disease relapse post treatment.

Determinants of immune reconstitution after allogenic haematopoietic stem cell transplantation performed with Anti-T-Lymphocyte Globulin (ATG)

(Funder: CREST Award) (See page 89)

Design of an assay to efficiently measure levels of CAR (chimeric antigen receptor) T cells in the peripheral blood of recipient patients at St James's Hospital

(Funder: CREST Award) (See page 90)

Evaluation of cell engineering technology potential using patient-derived cells (Funder: Avectas)

The streamlining and optimisation of the CAR T-cell manufacture processes to create a safe and universally available product is critical to cellular therapy. This study, with collaboration of Maynooth University and Technological University Dublin, aims to establish an in-vitro protocol for the thawing and preparation of cryopreserved cell units to optimise transfection with mRNA via electroporation.

A T-cell flow cytometry panel will be established to identify and enumerate T-cell phenotypes which have the best transfection efficiency. The panel will be used to compare cell expansion rates and transfection efficiencies in patient cells versus normal donor cells.

This will provide proof of principle that cryopreserved patient T-cells can be successfully transfected with mRNA using electroporation and identify the T cell subset with best uptake. The study should yield proof of principle that cryopreserved patient PBSC cells can be used to create viable CAR T-cell products.

Natural Killer (NK) Cell Research Team

Prof Clair Gardiner,
Professor in Biochemistry and Immunology, TCD;
Research Theme Lead, TSJCI

Immunotherapy offers huge potential in terms of hard-to-treat cancers including metastatic breast cancer, metastatic melanoma, glioblastoma and high-risk neuroblastoma, all of which we investigate.

Natural Killer (NK) cells are a target for immunotherapy using several different strategies including antibody mediated immunotherapy, check-point inhibitors and a variety of autologous and allogeneic NK cell therapy options. The group's work focuses on understanding NK cell metabolism and how it becomes dysregulated in cancer patients.

Understanding the cancer environment in which NK cells have to work is also important. This information can be integrated together to improve NK cell therapies for their optimal deployment.

Metabolically optimised NK cell therapies for glioblastoma

(Funder: ERA-NET TRANSCAN)

This research seeks to define specific factors e.g., metabolites in GBM tumours which inhibit NK cells. Understanding both intrinsic and extrinsic NK cells dysregulation in GBM patients will help design new NK cell therapies for GBM.

This project, in collaboration with Beaumont Hospital, University of Oslo, University of Louvain, University of Regensberg, and University of Dundee, aims to have an NK cell therapy designed to specifically overcome immunosuppression by GBM and thereby improve patient outcome.

Correlation of restoration of Natural Killer (NK) cell function with response to pembrolizumab in metastatic melanoma patients

(Funder: Meath Foundation)

The group will analyse NK cell responses to pembrolizumab in vitro from patients, prior to their starting its use as an immunotherapy. Additionally, we will investigate if these in vitro data predict clinical response. As a result, the group the projects aim to stratify patients based on tests to identify patients likely to respond to immunotherapy.

HDACi in Natural Killer (NK) cell immunotherapy

(Funder: Health Research Board)

There is evidence that normal acetylation is impaired in NK cells from patients with cancer. Therefore, HDACi which are being used as a cancer therapy, have the potential to also interact with the immune system. The project investigates how different HDACi impact on NK cell function and metabolism.

As a result of this research, it is expected that the group will be able to strategically design HDACi that is optimal to maintain immune function and therapeutic effect.

Transfer RNA (tRNA) Biology Team

Dr. Vincent P. Kelly,
Associate Professor,
School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, TCD.

The team's research is directed towards improving the imaging and detection strategies for cancer and the discovery of novel cancer therapeutic approaches which include protein and RNA methodologies.

Turning up the voltage on anti-cancer immunity (Funder: Irish Cancer Society)

In collaboration with University of Galway, this project studies the immune stimulatory effect of electroporation therapy and investigating ways that RNA therapies can be used to enhance the anti-cancer immune response. It is expected that this project will establish a clearer understanding of why electroporation can, on occasion, lead to complete eradication of cancer at distal sites to the primary turn. Additionally in the long term, it is expected to deliver an improved approach to cancer treatment by electroporation therapy with potential curative effects of immune clearance of metastatic cancer.

Endoscopic outpatient cancer treatment platform (ENACT)

(Funder: DTIF) (See page 45)

Cancer Immunology and Immunotherapy Team

Prof Joanne Lysaght,
Professor in Cancer Immunology and Immunotherapy,
School of Medicine, TCD;
Research Team Lead, TSJCI.

Currently, a major focus of the group is investigating the impact of chemotherapy and radiotherapy on anti-tumour immunity, when used in combination with immunotherapies, namely immune checkpoint inhibitors.

Most of the research in the cancer immunology and immunotherapy group is focused on upper gastrointestinal cancer, particularly obesity-associated oesophageal cancer but also gastric and pancreatic cancer. Research into how the regulation and trafficking of lymphocytes can be targeted to enhance immune responses following treatment is another area of focus. It also aims to identify novel immunotherapeutic targets in the pre-malignant setting such as Barrett's oesophagus and pancreatic cysts, which can be used to slow or prevent progression to malignancy. The group also has a keen interest in the role of adaptive immunity and obesity in the debilitating cancer-associated wasting disease cachexia and sarcopenia.

Identifying novel aspects of immune checkpoint pathways to improve response rates in upper gastrointestinal cancer

(Funder: Science Foundation Ireland)

Cancer immunotherapy has offered new therapeutic options for countless cancer patients. Immune checkpoint inhibitors (ICI), arguably the most successful form of immunotherapy, aim to restore T cell function by blocking

immunosuppressive signals through immune checkpoint receptors (ICR), predominantly PD-1 and CTLA-4. However, there is a lack of accurate biomarkers of response or basis for patient selection for ICI therapy. Currently PD-L1 expression, immune cell infiltrate or mutational burden are used as indicators of response but are all focused on the immunological response.

We will investigate in detail the functional redundancy of immune checkpoint pathways to identify better combination treatments for upper gastrointestinal cancer patients. We will also assess the pro-tumourigenic roles of tumour cell intrinsic ICR signalling. Understanding these pro-tumour roles of ICR signalling will lead to the identification of pathways essential for tumour cell survival and ultimately expand the cohort of patients who will benefit from these treatments.

The pro-tumourigenic role of ICR opens avenues for potential new targets and therapeutic benefits for patients who would be excluded based on immune-based criteria. This will allow for the greater inclusion of patients who are likely to respond to ICI.

Immunophenotyping pancreatic cystic lesions for cancer risk stratification

(Funder: TCD PhD Provost Award)

Pancreatic cancer is amongst the most lethal of all cancers worldwide, with a dismal 5-year survival rate of just 9%. Most pancreatic cancer patients have advanced disease at first diagnosis, as the symptoms are generally nonspecific and commonly arise only at late stages in disease development. A proportion of pancreatic cancers arise from a pre-cancerous lesion. These pre-cancerous lesions are a type of fluid filled cyst. Some of these fluid-filled cysts are high-risk for pancreatic cancer development, while some are low-risk. It is very difficult to determine which cysts are high-risk and which are low-risk. Thus, the ability to identify which patients are at high-risk of developing pancreatic cancer from these cysts would allow for early treatment intervention and better outcomes.

A recent breakthrough in cancer treatment uses the patient's own immune system to fight cancer. Only one immunotherapy has been approved for pancreatic cancer to date. The immune response to pancreatic cancer is weak and often the immune cells within and around the tumour are corrupted to help the tumour rather than destroy it.

This project aims to investigate the immune cells present within low- and high-risk pancreatic cyst fluid. This will provide important information on the role of the immune system in fighting this cancer and potentially identify unique immune features associated with high-risk cysts. We will investigate what molecules are present in the cyst fluid that may alter the ability of the immune cells to gain entry into the tumour and also how they may help tumour cells become more aggressive and spread to other organs.

Lastly, we will look at the direct effect of the cyst fluid on the function of .T cells, which are key for killing tumour cells. We will examine if the cyst fluid is killing T cells, changing their characteristics to be more supportive of tumour growth and if the cyst fluid can prevent these T cells from killing tumour cells. Overall, this project will significantly add to the knowledge around the role of the immune system in pancreatic cysts and cancer risk. The data generated will hold significant potential to impact patient outcomes as a result of a greater understanding of where the immune system is failing in pancreatic cancer and through the identification of potential new therapeutic targets which could boost the immune response against this lethal cancer.

Cancer Immunology Research Group

Dr Melissa Conroy,
Assistant Professor (Anatomy),
School of Medicine, TCD.

Therapeutically remodelling the immune profile of 'cold' tumours in obesity-associated cancer

(Funder: Breakthrough Cancer Research)

This project focuses on the development of new and urgently needed treatments for the poor prognosis and obesity-associated malignancy oesophageal adenocarcinoma (OAC). The team are utilising *in vitro* and *in vivo* pre-clinical models to test the efficacy of two novel immunotherapeutic approaches in OAC. The ultimate aim is to bring new treatment options to patients with oesophageal adenocarcinoma and improve survival rates for this poor prognosis cancer.

Identifying the therapeutic potential of novel compounds in glioblastoma multiforme

(Funder: Deans Research Initiative, TCD)

This project is testing the therapeutic utility of 2 novel drugs and 1 existing anti-cancer drug in glioblastoma multiforme (GBM) alone and in combination with NK cell therapy. We hope to generate new treatment options for patients with glioblastoma multiforme and improve survival rates for this poor prognosis cancer.

Research Theme: Cancer Survivorship and Supportive Care

Theme Leadership

Prof. Juliette Hussey
Professor of Cancer Rehabilitation and Survivorship, School of Medicine, TCD; Cancer Survivorship and Supportive Care Research Theme Lead

In Ireland, it is estimated that the number of cancer survivors is set to double over the next 25 years. A cancer survivor is described as someone living with and beyond cancer.

Cancer survivorship commences at diagnosis and continues through to the balance of life, encompassing prevention and surveillance for new and recurrent cancers, health promotion, surveillance and management of physical, psychological, and social effects, coordination and management of chronic conditions, psycho-oncology, self-management, supportive care, and social prescribing.

Multiple domains of health-related quality of life, including physical wellbeing, psychological wellbeing, spiritual wellbeing, and social wellbeing, can be impacted by cancer and its treatment. In addition to this, given the typical older age profile of individuals with cancer, many individuals have or will be at risk of other chronic conditions. Addressing the prevention of other chronic disease is an important aspect of survivorship management.

Caregivers, family members and friends of loved ones affected by cancer also play an important role in cancer survivorship. Consequently, survivorship care and research in cancer survivorship involves multiple disciplines addressing patient needs and concerns throughout the survivorship continuum and into palliative care.

This theme also includes the impact of cancer diagnosis on the family members – spouse, partner, and children. Over the past 25 years, cancer survival rates have improved significantly in Ireland and internationally as a result of enhanced clinical care and emerging treatment modalities.

In late 2019, a National Cancer Survivorship Needs Assessment was launched, '*Living with and beyond cancer in Ireland*'. Its Priority Action 6.3 recommends supporting research into all aspects of cancer survivorship, through collaboration between stakeholders, including cancer survivors themselves.

Broadly, improved physical function (cardiopulmonary exercise testing capacity, muscle strength, and physical activity participation) has a protective effect across the cancer continuum. Consistently in the literature mid-life cardiorespiratory fitness, the gold standard measure of physical function, is associated with lower risk of cancer development and cancer-related mortality.

Furthermore, cardiorespiratory fitness and functional performance measures are strongly associated with cancer treatment outcomes. Higher physical function is associated with lower rates of surgical morbidity and mortality, and higher completion rates of neoadjuvant and adjuvant therapies. A positive feature of physical function is its amenability to change by intervention, and accordingly pre-habilitative and rehabilitative programs which aim to improve physical function in cancer cohorts have become important topics of study by their group.

Given the ever-growing older population, it is timely to consider the impact of this projected change, not only on the oncology infrastructure required to effectively manage additional patients, but also the demands of an ageing population and the health service planning changes that may be required to respond to their needs. Ireland's National Cancer Strategy 2017–2026, launched in July 2017, has recognised for the first time that geriatric oncology (also referred to as onco-geriatrics), or care of the older person with cancer, is a priority area for development in Ireland.

Figure 10. Cancer Survivorship and Supportive Care Research teams at TSJCI

The strategy focuses on three main areas to prioritise – education, clinical practice, and research. It states that "formalised geriatric input needs to be built into the multidisciplinary assessment of the care of older patients with solid and haematological malignancies". It also calls for more research evidence to underpin clinical care. Of particular significance to research, clinical care, and management of the aging-related consequences of cancer are malnutrition, sarcopenia, frailty, and disability. In addition to addressing survivorship issues in children with cancer along with the transition to surveillance and lifelong survivorship care TSJCI Cancer Survivorship will focus on the needs of Adolescents and Young Adult (AYA) oncology. The location of the new Children's Hospital on the same campus as TSJCI, along with joint medical appointments, will assist in greater research collaboration.

High Level Goals: TSJCI Cancer Survivorship and Supportive Care

1. To deliver world class healthcare and support to cancer survivors, which supports optimal functional recovery, through the provision of appropriate supportive care services at the right time and in the right place.
2. To reduce the impact of physical, psychological, and social difficulties for cancer survivors and their families and improve quality of life (including palliative care).
3. To provide leadership in post graduate education and research in this field
4. To generate new evidence to inform and enhance prognostication and personalised clinical management in older people living with cancer, young people with cancer and those with more complex cancers leading to significant symptom burden.
5. To expand the evidence, base to inform education, clinical and public health strategies to optimise healthy aging of cancer survivors.

Academic Department of Palliative Medicine

Prof Andrew Davies, Professor Consultant of Palliative Medicine, Head of Academic Department of Palliative Medicine, TCD, University College Dublin, and Our Lady's Hospice, Dublin.

The Academic Department of Palliative Medicine is a multi-professional collaboration between Trinity College Dublin, University College Dublin, and Our Lady's Hospice and Care Services (**Figure 11**). The research team includes physicians, nurses, and allied healthcare professionals, and is based in the Education and Research Centre at Our Lady's Hospice in Harold's Cross. Studies are undertaken within local teaching hospitals, hospices, and the community.

The focus of the research is clinical research involving patients with cancer: research projects span supportive care, palliative care, end-of-life care, and cancer survivorship. Current areas of research include clinically assisted hydration, circadian rhythm disorders, sleep disturbance, remote monitoring, oral problems, opioid-induced constipation, cancer-associated anorexia and cachexia, cognitive impairment, and models of specialist palliative care.

EU-Navigate study

(Funder: European Commission)

The project works with Vrije Universiteit Brussel and is an international, multicentre, RCT of "navigators" (trained volunteers) which support older cancer patients during and beyond anticancer treatment. The aim of the programme is that navigators will improve patients' and their carers' quality of life by supporting them through their treatment, as well as helping them to access the available health and social services.

Cancer Appetite Recovery Study (CAReS) (Funder: Artelo Biosciences Ltd.)

With the collaboration of the University of Edinburgh, the project is examining the impact and use of synthetic cannabinoid for cancer-associated anorexia (and weight loss). As of yet, there are no recommended pharmacological interventions to manage cancer-associated anorexia/cachexia. Cannabinoids are known to stimulate appetite, and this product has been shown to cause weight gain in cancer patients when used to treat cancer pain. As a result, this may be useful in the management of cancer-associated anorexia.

E-STOIC (European Study of Opiod-Induced Constipation)

(Funder: Kyowa Kirin)

This is an international, multicentre, observational study of opioid-induced constipation in patients with cancer to determine clinical impact and management. This project is being carried out in collaboration with Our Lady's Hospice in Harold's Cross. The impact of this study is expected to show that currently opioid-induced constipation is under diagnosed and undertreated (and often mismanaged), in patients with cancer. Thus far, the study has presented two posters at the 2023 EAPC annual conference in Rotterdam, the Netherlands, and an additional two posters at the 2023 MASCC annual conference in Nara, Japan.

Figure 11. The Academic Department of Palliative Medicine

Oral Cavity Cancer Survivorship Research Team

Mr John Edward O'Connell, Consultant Maxillofacial/Head and Neck Surgeon, St James Hospital: Clinical Senior Lecturer, TCD

Assessment of usability of eAltra conversation agent web application for patient concerns inventory

(Funder: N/A)

Health-related quality of life (HRQOL) is a key outcome in cancer care. In Head and Neck Cancer (HNC), patients have a wide range of unmet needs. The Patient Concerns Inventory (PCI) is a prompt list completed by patients in clinic prior to consultations, which allows them to choose topics they would like to raise at their consultation from a range of common concerns.

Conversational Artificial Intelligence (CAI) provides to tool to improve the quality and quantity of information flow between patients and professionals remote from the consultation. A conversational AI system, eAltra, has been created in Trinity College Dublin to facilitate communication between clinicians and patients on patients' devices (phone, tablet, computer).

The current study will investigate the usability and performance of the eAltra system, based on the PCI, with patients from SJH. This work is also being carried out in collaboration with the Liverpool Head and Neck Unit in the United Kingdom.

Feasibility and acceptability of a targeted intervention to improve functional outcomes and treatment related side-effects in patients with head and neck cancer in the early survivorship phase'

(See CREST Section; page 88)

Optimising Quality of Life in Cancer Survivorship Team

Prof Deirdre Connolly, Professor in Occupational Therapy, School of Medicine, TCD

Professor Connolly's current research focuses on the prevention and management of chronic diseases including cancer survivorship. She has led multidisciplinary research teams in developing and testing occupational therapy interventions in the prevention and management of chronic diseases.

Her research also includes examining social prescribing and how it can address social determinants of health and reduce health inequalities.

Examining the effectiveness of work and cancer for women with breast cancer

(Funder: Health Research Board)

Professor Connolly and Dr. Naomi Algeo (Clinical Specialist Occupational Therapist -Oncology/ Haematology - at St. James' Hospital Dublin; adjunct Assistant Professor at TCD) developed a six-week programme, *Work and Cancer*, to support women with breast cancer to return to work following completion of cancer treatment. The aim of this project is to test the effectiveness of *Work and Cancer* to increase return to work and improve management of cancer-related symptoms affecting work performance.

People with cancer experience significant difficulties going back to work that are often not acknowledged. They are told by health professionals you can go back to work now, but many struggle with the how, where and when of doing that.

This research will provide a programme that people with cancer can avail themselves of when the time comes for them to think about going back to work.

If *Work and Cancer* is effective in increasing work rates of people with cancer it is expected that it will be offered as routine cancer survivorship care in Ireland.

Identifying support needs of adolescents and young adult cancer survivors for successful return to education and/or work

(Funder: Irish Cancer Society)

There is increasing recognition that Adolescent and Young Adult (AYA) cancer survivors have difficulty returning to education and work due to ongoing difficulties with their physical, mental and social health following completion of cancer treatment.

As a result, research is recommended to identify survivorship interventions and services needed for this population. The purpose of this study therefore is to examine health difficulties impacting on return to education and/or work for AYA cancer survivors and to identify services required to meet the unique support needs of AYA cancer survivors in Ireland.

This work is carried out in collaboration with Crumlin Hospital and the National Cancer Control Programme. The findings from this study will inform the design of age-appropriate interventions and services to support AYA cancer survivors to successfully manage their return to education and/or work.

Exploration of suitability and acceptability of social prescribing for men with prostate cancer

(Funder: CREST)(See CREST Section, page 90)

Upper Gastrointestinal (GI) Surgical Research

Dr Jessie Elliot, Clinical Lecturer, Trinity St. James's Cancer Institute and European Minimally Invasive Esophagectomy Fellow, UMC Utrecht

Recent advances in multimodal therapy, surgery, and perioperative care have produced significant improvements in oncologic and operative outcomes for patients with oesophageal and gastric cancer who can be treated with curative intent. Nevertheless, oesophageal, and gastric cancer surgery is associated with significant morbidity, and with short, medium, and long-term challenges to functional recovery and health-related quality of life.

Furthermore, when local or systemic disease recurrence occurs, where therapeutic nihilism may have once prevailed, a menu of therapeutic options can now be considered. In the context of this changing landscape and expanded armamentarium, a key question, yet unresolved, is how patients should be optimally followed-up after completion of curative intent cancer treatment.

The focus of our work is to develop postoperative follow-up strategies to support functional recovery, and facilitate early detection and management of recurrent disease, to preserve quality of life after curative intent surgery for oesophageal and gastric cancer.

Open label international multicentre randomised controlled trial of intensive surveillance Vs standard postoperative follow-up in patients undergoing surgical resection for oesophageal and gastric cancer

(Funder: National Surgical Research Support Centre, Royal College of Surgeons in Ireland, Irish Cancer Society)

This international multicentre randomised controlled trial will assess the impact of intensive postoperative surveillance as compared with clinical follow-up on oncologic outcomes and health-related quality of life among patients who have completed curative intent treatment for oesophageal and gastric cancer.

A programme of complimentary translational research will assess the clinical utility of novel biomarkers of molecular residual disease such as circulating tumour DNA, and the use of radiomics for the prediction of cancer recurrence. The trial will be embedded within a dedicated follow-up infrastructure, allowing development and optimization of investigational and treatment pathways for the management of survivorship issues after oesophagogastric cancer surgery.

This trial will determine the efficacy of an intensive surveillance strategy for the detection of cancer recurrence among patients following curative intent surgery for oesophageal and gastric cancer. It is envisaged that this research will inform clinical guidelines for the management of oesophageal and gastric cancer. Furthermore, the translational work embedded within the project will provide hypothesis generating data for future clinical trials of personalised approaches to adjuvant therapies.

An international multicentre study exploring whether surveillance after oesophageal cancer surgery impacts oncological and quality of life outcomes (ENSURE)

(Funder: Society of Research and Surgery)

Although therapies for recurrent oesophageal cancer may impact survival and HRQL, surveillance protocols after primary curative treatment are varied and inconsistent, reflecting a lack of evidence. The aim of this study was to determine the impact of surveillance on recurrence pattern, treatment, survival and health-related quality-of-life (HRQL) following curative-intent resection for oesophageal cancer.

European Investigation of Surveillance after Resection for Esophageal cancer (ENSURE) was an international multicentre observational study of consecutive patients undergoing surgery for oesophageal and esophagogastric junction cancers (2009–2015) across 20 centres (NCT03461341). Intensive surveillance was defined as annual computed tomography for 3 years postoperatively.

The primary outcome measure was overall survival, secondary outcomes included treatment, disease-specific survival, recurrence pattern, and HRQL. This project is comprised of work from the University of Oxford and the Karolinska Institutet. This study resulted in the first major evidence-based publication on the use of intensive surveillance for patients following surgery for esophagogastric cancer. It also led to the development of the SARONG-I and II RCTs which will be led by the University of Oxford in the UK and Trinity St. James's Cancer Institute in the EU.

Trinity Exercise Oncology Team

Prof Juliette Hussey,
Prof. of Physiotherapy.
Discipline of Physiotherapy,
School of Medicine, TCD.

Dr Emer Guinan, Assoc.
Prof. Cancer Survivorship,
Discipline of Physiotherapy,
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Dr Linda O Neill,
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Dr Louise Brennan,
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Discipline of Physiotherapy,
School of Medicine, TCD.

Dr Grainne Sheill,
Physiotherapy Dept, St
James's Hospital;
Adjunct Assistant Professor
Discipline of Physiotherapy,
School of Medicine, TCD.

Dr Suzanne Doyle,
Assistant Lecturer
in Dietetics,
Technological
University Dublin.

Over the last 10 years there has been considerable growth in research in cancer survivorship in Trinity, primarily from Physiotherapy and Nutrition/ Dietetics with an increase in collaboration with many other disciplines. These include Surgery, Medical Oncology, Psychology, Occupational Therapy, Nursing etc. The research is multidisciplinary (**Figure 12**) and has been focused on exercise and lifestyle interventions addressing symptoms in various patient groups but particularly those with more complex needs.

While much of the initial and continuing focus has been pre and post-surgical exercise interventions in more complex cancers such as GI, the wider team have collaborated in many aspects of cancer care and with multiple cancer types. The wider survivorship agenda is continually appearing as a priority as more and more survivors, their families and health care providers identify the need for services, interventions and research in this growing area.

The broad area of focus is exercise rehabilitation in patients with cancer. This currently includes evaluating means of improving physical capacity preoperatively to reduce postoperative morbidity for patients undergoing complex cancer surgery, developing rehabilitation strategies in oesophageal, hepatopancreatic biliary cancer and in understanding the rehabilitation needs of adolescents and young adult cancer survivors.

Figure 12. The Trinity Exercise Oncology team

PRE-HIIT: Preoperative exercise to improve fitness in patients undergoing complex surgery for cancer of the lung or oesophagus (Funder: Irish Cancer Society HRB/MRCG)

Exercise pre-habilitation is a preoperative intervention targeting fitness to reduce risk. Delivery of an effective intervention within the preoperative period faces challenges: limited time frames; patients' physical and mental ability to participate; and the acceptability of the service. HIIT may represent an efficient an effective approach to optimising patients within the short timeframes. However, there is a need to clarify the role of exercise pre-habilitation to identify the most meaningful and effective approaches for patients. It is envisioned that this project will help to determine the impact of high intensity exercise training on preoperative cardiopulmonary fitness in patients scheduled for oesophageal or thoracic resection.

Restore II: Rehabilitation strategies following oesophagogastric and hepatopancreaticobiliary cancer

(Funder: Health Research Board)

The Rehabilitation Strategies following Oesophagogastric and Hepatopancreaticobiliary Cancer (Restore II) trial funded by a Health Research Board (HRB) Definitive Intervention and Feasibility Award (DIFA). Along with increasing survival rates after treatment for upper GI cancers, survivors experience significant physical, nutritional, and psychosocial challenges which persist long term into survivorship.

Restore II randomised controlled trial is a definitive intervention examining whether a 12-week multidisciplinary rehabilitation can improve functional capacity and health related quality of life in a cohort of 120 survivors of oesophagogastric and hepatopancreaticobiliary cancer. This project is carried out in collaboration with Technological University Dublin. It is expected that the research will help with the evaluation of a 12-week multidisciplinary rehabilitation intervention.

Head and neck cancer rehabilitation: identifying and addressing patient needs (The Care Study)

(Funder: Irish Cancer Society)

In 2019 St James's Hospital was responsible for 40% of national cases of head and neck cancer, with 3 and 5 year survival rates of 70% and 58% respectively. People living with HNC share many of the same side effects and survivorship needs as those treated for other cancers (eg. fear of recurrence and early mortality), but also unique biopsychosocial issues. Side-effects such as fatigue, shortness of breath, muscle weakness and shoulder weakness and pain can affect people's

ability to engage in physical activity. Despite the well documented benefits of engaging with physical activity during and after cancer treatment, it is estimated that only between 8-40% of HNC survivors participate in regular exercise.

Early signposting and development of supportive interventions of patients in the acute phase post treatment is needed. Specifically, qualitative work with patients with head and neck cancer has indicated that personalised exercise interventions tailored towards the specific needs of the patient are needed.

There is no clear post discharge physiotherapy pathway for head and neck patients experiencing physical impairments in St James's Hospital at present. The Trinity Exercise Oncology Research Group developed Restore, a 12-week, multi-component rehabilitation programme comprising exercise prescription, dietary advice and patient education as an intervention in a number of research studies. Restore was developed and evaluated in patients with upper gastrointestinal (UGI) cancer. However, many of the components are suitable and adaptable for additional populations such as those with HNC. This study will identify the rehabilitation priorities of patients with HNC in Ireland and test the adaptation of the ReStOre programme for a population of patients following treatment.

PERCS Study (see highlight page 12)

Developing and feasibility testing of a pragmatic, patient-centred exercise intervention during chemotherapy: A mixed-methods approach (2021-2025, Irish Cancer Society/Provost's PhD Award) (Funder: Provost's PhD Project, Leveraged Funding, Irish Cancer Society PPI Award 2022)

While the benefits of exercise training during chemotherapy are becoming clear, there are issues with how acceptable these interventions are to most patients. Often patients decline to participate due to feeling unable to complete the amount of exercise being prescribed, experiencing too many side-effects from their chemotherapy or due to practical issues such as travel or transport burden. Exercise is known to be safe and can be tailored to individual patient presentations, and therefore overcoming these barriers to enrolment is important.
Involving key stakeholders including patients with the lived experience of a condition, in intervention development and evaluation, can positively impact trial enrolment and retention, however, to date this approach has not been applied in exercise trials in patients with cancer.

Using an established framework for developing and evaluating complex interventions such as exercise trials, this study will focus on the development and feasibility testing of an exercise intervention for patients with cancer undergoing chemotherapy. Designing an intervention that improves exercise participation during chemotherapy will help to reduce the side effects of treatment and will ultimately be of great benefit to cancer patients.

Evaluation of a pilot early-detection lymphoedema service for high-risk gynecological cancers (Funder: CREST Funding) (See CREST Section, page 88)

Childhood Cancer Survivorship Team

Dr Michael Capra,
Clinical Professor
Consultant (Paediatrics),
School of Medicine, TCD;
Consultant Paediatric
Oncologist, CHI Crumlin

Survival rates are now approaching 80% for childhood cancers overall, however survivors of childhood cancer carry a substantial burden of morbidity and are at increased risk of premature death. Early detection and intervention of side-effects/long term effects of disease and treatment may improve patient outcomes. No population-based data exists on the numbers of childhood cancer survivors in Ireland or the incidence and range of direct cancer and/or cancer treatment-related effects experienced. There is no comprehensive survivorship service for survivors of childhood cancer in Ireland.

The project's objectives are to establish a longitudinal survivorship research infrastructure through the development of a national childhood cancer survivorship database and to develop of a world class national survivorship service for all survivors of childhood cancer with survivors, parents/guardians/carers at the centre.

Childhood cancer survivorship project
(Funder: CHI at Crumlin Hospital)

Phase 1 and 2 of the **childhood cancer survivorship** project were concerned with a needs assessment to inform service development from the perspectives of patients, parent/guardian/carers and healthcare providers respectively. This will ensure survivors and parents/guardians/carers are at the core of future service development. The current focus is on establishing a comprehensive national population-based database to provide each survivors with a detailed medical treatment summary on discharge from childhood services together with an algorithm generated Survivorship Care Plan to guide future surveillance according to international best practice guidelines.

The Medical Treatment Summary and Survivorship Care Plan will facilitate transfer of care from childhood services to community or adult care. Survivors will be empowered to take responsibility for their ongoing care. Care of childhood cancer may be improved through database research. The needs assessment will inform service development.

Cancer Data Team

Dr Claire Donohoe,
Consultant Gastrointestinal and General Surgeon,
St James's Hospital;
Clinical Senior Lecturer, TCD

Dr Donohoe's research interests from a digital perspective include using OMOP to contribute to federated real world evidence data sets within a trusted research environment and digitising information acquisition from patients including patient reported outcome measures in clinical oncology.

EU Quality of Life in Oncology: Measuring what matters for cancer patients and survivors in Europe (EUonQoL) (Funder: European Commission)

This study is part of a larger, EU-funded project aimed to develop and validate a toolkit of three questionnaires (EUonQoL-kit) designed to assess the QoL of European patients across the continuum of oncology care, through patient-reported outcomes measures (PROMs).

The present study consists of a multicentre pilot survey, which aims to evaluate the validity and reliability of the new toolkit in an European sample of cancer patients at different stages of their disease (in active treatment, survivors, and in palliative care). The study involves 46 centres, each recruiting 100 patients for a total sample of 4,600 patients.

Ultimately, the study hopes to develop a patient reported outcome measure to easily and routinely capture health related quality of life during clinical encounters. The measure can then be used to assess patient outcomes, help clinicians better understand their patient's quality of life and for research purposes – to better understand the influence of treatment on quality of life.

Digitising cancer data acquisition for real world data studies

(Funder: Higher Education Authority and European Commission)

Despite having an electronic healthcare record, curation of cancer registries is manual and highly labour intensive. Recognising that harnessing the potential of the digital patient information for operational as well as research purposes will enable their patients to benefit from involvement in research, we have been heavily involved in activities to improve the digital capture and curation of patient healthcare data.

We are collaborating on a HEA grant that aims to train the next generation of data scientists in federated cancer data analysis via the lead site in University of Limerick. We have also obtained funding via the European Commission to work in a public-private partnership called DigiOne to help them transform clinically held data such that it can be used for real world evidence generation including *in silico* synthetic trials and clinical trial matching.

Conversational agents for patient reported outcome measures

(Funder: Health Innovation Hub Ireland/ Enterprise Ireland)

Conversational agents are computer programmes that use natural language processing (NLP) and machine learning to stimulate conversation with human users. The use of conversational agents has been explored in various healthcare settings to monitor health and check for symptoms by provision of an independent app to patients. However, there has been almost no research about how conversational agents might be integrated in clinical work practices to enhance person-centred care.

The aim of this work is to integrate data from conversational agents to individual patient electronic health records and provide an automated system to identify patients safe to progress to treatment. Additionally, other goals include co-producing with health care practitioners and patients, an automated system to safely identify patients fit to process with chemotherapy and to assess feasibility and acceptability of a conversational agent for patients receiving chemotherapy. This work is a collaboration with eAltra and ADAPT.

Cross Cutting Research Teams

A number of TSJCI research teams cut across a number of thematic areas as outlined below (Figure 13).

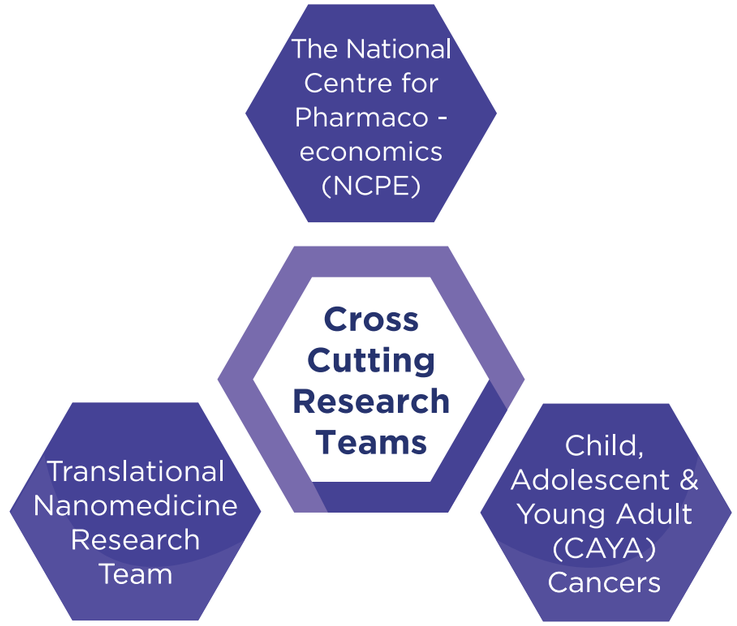


Figure 13. TSJCI Cross Cutting Research Teams

The National Centre for Pharmacoeconomics (NCPE)

Dr Laura McCullagh,
Clinical Senior Lecturer, Pharmacology and Therapeutics, TCD;
Chief I Pharmacist, Head of Research,
National Centre for Pharmacoeconomics,
Trinity Centre for Health Sciences, St James's Hospital.

The National Centre for Pharmacoeconomics (NCPE) is a national Health Technology Assessment (HTA) Agency. The NCPE evaluates evidence for comparative effectiveness, cost-effectiveness and budget impact of technologies, for all indications, for use by patients in Ireland and Europe. During HTA evacuations they seek advice from clinical experts and patient organisation groups. The multidisciplinary NCPE team includes individuals with backgrounds in medicine, pharmacy, pharmacoepidemiology, statistics and health economics.

Health Technology Assessment of next generation cell therapies for cancer for the HEALED Consortium

(Funder: Enterprise Ireland (EI) (See highlight page 10)

Translational nanomedicine research team and Laboratory for Biological Characterisation of Advanced Materials (LBCAM)

Dr Adriele Prina-Mello,
Ussher Assistant Professor
School of Medicine, TCD

This group focuses on the translation of nanomedicine, nanotechnology-tools, or nanotechnology-enabled products (NEPs), for improving diagnosis, treatment, monitoring and follow-up on chronic diseases (such as cancer).

Expanding platforms for efficacious mRNA therapeutics (EXPERT)

(Funder: European Commission)

Working with 13 collaborators across Europe, EXPERT will create an off-the-shelf mRNA-delivering nanomedicine platform that is manufactured via a quality-by-design (QbD) approach with precise nanoparticle characterisation and specifications that meet the requirements for GMP scaling up and clinical translation. EXPERT will create an off-the-shelf mRNA-delivering nanomedicine platform to meet GMP and clinical translation requirements. As proof-of-concept the project will perform a first-in-man clinical study for an intratumorally administered immunostimulatory mRNA-nanomedicine in cancer patients.

Safety testing in the life cycle of nanotechnology-enabled medical technologies for health (Safe-n-Medtech) (Funder: European Union- Industrial Leadership)

The EU-funded SAFE-N-MEDTECH project will develop an open access platform to provide the know-how, networks and services required for the development of nanotechnology-based medical and diagnostic devices. This project is made up of 34 collaborators across Europe on the development of nanotechnology-based medical and diagnostic devices. The SAFE-N-MEDTECH platform will be directed to companies and laboratories and offer an integrated approach for assessing qualification, regulation, biocompatibility and the properties of nanomaterials. Implementation of the platform will expedite the transition of nanotechnology-based medical technologies to the market. Safe-N-Medtech project has created a sustainability plan where an OITB Pathway association has been set up to carry forward the OITB work to further assist medical technologies or medical devices companies.

Child, Adolescent, and Young Adult (CAYA) Cancers

Prof Owen Smith,
Professor of Adolescent, and Young Adult Oncology, TCD;
Professor of Haematology, TCD;
National Clinic Lead for Children, Adolescent, and Young Adult (CAYA Cancers,
National Cancer Control Program Academic Lead, Children's Health Ireland

Adolescent and young adult (AYA) patients with cancer are a diverse group as defined not simply by their age and distinct biology of their cancer, but in terms of the challenges they face with regards to adequate access to age-appropriate oncological care, representation on clinical trials, short and long-term health and psychosocial issues, that include, fertility considerations, transition to survivorship care, psychosocial support, adherence to treatment difficulties and other dilemmas and problems exclusive to this group of patients.

The recently published, *Framework for the Care and Support of Adolescent and Young Adults (AYA) in Ireland [2021-2026]* Report succinctly outlines strategies to coordinate state-of-the- art integrated AYA care to be delivered locally when possible but centralised, when necessary, by providing separate facilities and specialist care teams for these patients. It then goes on to say that once this has been achieved the challenge will then be to secure the future through education, research/ innovation and future service developments. The aim of the framework is to improve the standards and quality of cancer care provided to AYAs and at the same time define outcome measures of high-quality care for AYA patients across the proposed AYA cancer network as outlined in the Cancer Strategy (2016-2026). This network construct which consists of the Adolescent Young Adult Cancer Services Partnership (AYACSP – Children's Health Ireland and St. James's Hospital) and its two network partners at Cork and Galway has now been approved by the National Cancer Control Programme.

The CAYA group's 5-year research priorities are as follows:

1. Creation of a Trinity Centre for CAYA Cancer Survivorship Research.

Survival of CAYA cancer has considerably improved with advances in cancer-directed therapies and new approaches hold promise for decreasing treatment-related toxicities, improving the likelihood of survival, and enhancing long-term quality of life for survivors. Yet, this population is at very high risk of late occurring health problems, including significant morbidity and early mortality.

Current models of cancer care, with a focus on the acute, active phase of treatment fail to address the many unmet needs of CAYA survivors of cancer. The creation of a Centre for CAYA Cancer Survivorship Research, comprised of an interdisciplinary collaborative working group of healthcare professionals from Trinity College Dublin (MSc Cancer Survivorship course), Children's Health Ireland, St. James's Hospital, trainees, community health professionals and patient advocates will address the unique barriers to high quality care for this group.

2. AYA Cancer Clinical Trials and Research

For AYA with cancer, a multifaceted strategy is needed to modify traditional approaches to clinical trial regulation and improve drug development. Since no legal or regulatory barriers exclude adolescents from participating in adult phase I and II clinical trials, AYA accrual in such trials must be increased. In line with the proposal made by the ACCELERATE Fostering Age Inclusive Research (FAIR) trial, the AYA Cancer Clinical Trials & Research Programme within the AYACSP and its network partners will support some of their suggested solutions.

3. Implementation of Genomic Testing in AYA Cancer

As recently as a decade ago, the genetic aberrations that cause cancer, oncogenic drivers, remained elusive especially in children and adolescents. Genomic sequencing projects that were underway focused on adult cancers. At the same time, major advances were being made in sequencing technologies that resulted in lower costs and faster results.

Ireland has significantly lagged behind in introducing genomics into the clinic. Therefore, the aim of this study will be to implement genomic diagnostics in AYA cancer care across the Adolescent Young Adult Cancer Service Network (AYACSN) comprising St. James's Hospital, Galway and Cork University Hospitals. The study will attempt to show that whole genome sequencing (WGS) and gene expression / fusion analysis (RNAseq) for AYA cancer patients can be integrated as an effective first-tier diagnostic in the Irish frontline healthcare system, that is scalable in terms of capacity, and future proof.

4. Down Syndrome Leukaemia

Ireland has the highest rate of Down syndrome (DS) in the EU. Compared to the non-DS population, individuals with DS are 500 times more likely to be diagnosed with acute myeloid leukaemia (ML-DS) and 20 times more likely to be diagnosed with acute lymphoblastic leukaemia (DS-ALL). The risk for DS-leukemia is greatest during early childhood (ages 1 – 4), a critical neurodevelopmental period. Treatment for DS-leukemia (DS-ALL in particular) involves central nervous system (CNS) - directed chemotherapy.

Treatment for DS-ALL is 2.5 – 3 years in duration with extended periods of immunocompromise resulting in missed opportunities for social interaction, early intervention and education services that support developmental gains throughout childhood.

It has been well- established that survivors of childhood ALL without DS have a higher risk of neurocognitive deficits. Given the preexisting cognitive vulnerability in DS, the cumulative impact of CNS- directed treatment and missed community participation may add to neurocognitive deficits. Compared to survivors of leukaemia without DS, survivors of DS-leukemia may be at increased risk for treatment late effects and poorer quality of life.

A better understanding of DS-leukemia genomics may have implications for surveillance and diagnosis – all children, adolescents and young adults with DS will be offered genomic testing (somatic and germline). Evidence-based approaches to supportive care, improved assessment and management of side effects and toxicities in DS leukaemia will be developed.

Longitudinal studies of neurodevelopmental, health, and quality of life outcomes in cancer survivors beginning during therapy, to inform supportive care and interventions to ameliorate problems will also be developed members of the Trinity Centre for CAYA Cancer Survivorship Research.

Feasibility of a national program for fertility preservation in CAYA across Merrion Fertility Centre and Children's Health Ireland at Crumlin- Co lead applicant
(Funder: The Irish Cancer Society)

Each year in Ireland around 200 children are diagnosed with cancer, the treatments for which can cause lifelong damage to fertility, seriously impacting their future chances of ever starting a family of their own. A new partnership between the Irish Cancer Society and Merrion Fertility Clinic aims to ensure that, where possible, lifesaving treatment for children does not come at the cost of their future dreams of parenthood.

The three-year project aims to develop new supports and services across a number of phases to address a current significant gap in care and improve the long-term quality of life for children with cancer in Ireland. The first of its kind in Ireland, the Childhood Cancer Fertility Project will develop cutting-edge methods to preserve fertility for certain children who do not have access to such a service here. More than four in five children now survive their cancer diagnosis, and it is known that having the ability to start their own family is incredibly important to survivors in later life.

Ireland currently lags behind the UK and other European countries in fertility services for children, adolescents and young adults who go through cancer despite this increasing need, leaving some families resorting to travelling abroad for help amid the stress of cancer treatment, with others receiving no help at all. The Childhood Cancer Fertility Project looks at life beyond treatment for these groups, ensuring that where possible survivors are given the precious opportunity of having their own family in future.

TSJCI Cancer Research Stimulus Awards 2022

In 2022 TSJCI was delighted to announce the inaugural Cancer Research Stimulus Awards (CREST). The CREST awards are a research funding scheme providing seed funding to foster and develop new research collaborations between clinicians and scientists across the Cancer Institute, *supported by a philanthropic gift from The Dr Margaret Sau Sheung Ip and Dr Jonathan Chiu Fund,* and by donations to *support cancer research at TSJCI*.

The CREST scheme was designed by TSJCI's *Research Pillar*, led by Prof. Lorraine O'Driscoll and managed by Dr. Patricia Doherty, to enable short-term (up to 12 months) new, innovative research projects that will enhance the ability of TSJCI researchers to foster new avenues of cancer research and generate impactful data to leverage significant external funding.

Following a peer-review process including external reviewers and TSJCI's Research Theme Leaders, 10 projects were awarded funding (see below). All awardees must engage with the TSJCI Patient Representative Group early in their project, ensuring the research is patient-centric and relevant.

Knowledge Support for Adolescents and Young Adult Cancer Survivors in Ireland (KAYAC).
Dr. Scheryll Alken (Consultant in Adolescent and Young Adult Cancer, Children's Health Ireland) and Dr. Maeve Kearney (Assistant Professor, School of Medicine, Discipline of Radiation Therapy)
There is currently a lack of Adolescent and Young Adult (AYA) focused late effect information resources to support this unique group after completing cancer treatment. This research will address this by co-creating an information hub with AYA cancer survivors providing age-appropriate late effect information to support this group during the survivorship period.

Evaluation of a pilot early-detection lymphoedema service for high-risk gynaecological cancers.
Dr Emer Guinan (Assistant Professor, School of Medicine, Discipline of Physiotherapy) and Dr Catherine O'Gorman (Gynaecological oncology Fellow, St James's Hospital)
Lymphoedema is a well-known and very debilitating side-effect of cancer treatments, such as surgery and radiotherapy. At St James's Hospital, the physiotherapists run an early detection lymphoedema service to allow early intervention, and good quality advice and resources about lymphoedema prevention and management. This service is established for patients who have had breast cancer but not for patients who have gynaecological cancers. This project will examine the implementation of a pilot pathway that is being set up for the early detection and management of lymphoedema in patients with gynaecological cancer.

Improving pneumonia detection in oesophageal cancer patients to reduce sepsis and multi-organ failure following surgery.
Prof. Joanne Lysaght (Associate Professor, School of Medicine, Discipline of Surgery) and Ann-Marie Duff (CNM2 SACC Directorate, St James's Hospital)
The main objective of this study is to examine in more detail how defining pneumonia and the severity of pneumonia after oesophageal surgery will enhance patient outcomes & survivorship. This will be systemically investigated through a multi-faceted approach - involving clinical, radiological, microbiological and immunological expertise. We hypothesise that improving pneumonia detection and early clinical management of pneumonia in oesophageal cancer patients will reduce the incidence of sepsis and multi-organ failure following surgery.

Feasibility and acceptability of a targeted intervention to improve functional outcomes and treatment related side-effects in patients with head and neck cancer in the early survivorship phase'.
Dr. Julie Broderick (Assistant Professor, School of Medicine, Discipline of Physiotherapy) and Mr John O'Connell (Consultant Oral and Maxillofacial/Head and Neck Surgeon, St James's Hospital)
The early intervention piece is often missing in the cancer care continuum, which is an opportune time to intervene to mitigate against the development of late effects and long-term dysfunction. This study will initiate a physiotherapy intervention in the early survivorship phase assessing the effect of a single, individualised, standardised treatment session during the early survivorship phase pre-radiotherapy.

In this session, the research physiotherapist will go through a bespoke booklet, which targets movement/strengthening as well as graded return to activity, education on early signs/prevention of lymphoedema, managing pain/posture, self-monitoring and self-management and general healthy lifestyle behaviours. Patients will be assessed pre-operatively and 14-16 weeks post-operatively.

Role of endosomal biomarkers in defining the head and neck cancer metabolome: Implications for risk-stratification and therapeutic intervention.
Dr. Prerna Tewari (Senior Research Fellow, School of Medicine, Discipline of Histopathology) and Prof Sinead Brennan (Consultant Radiation Oncologist, St James's Hospital and St Luke's Radiation Oncology Network)
Head and neck cancers (HNC) affect the mouth, tongue and tonsils. Most of these cancers occur in heavy smokers and alcohol drinkers. Recently a new type of HNC has been observed which is related to Human Papillomavirus (HPV) infections. The majority of HPV-positive HNC patients are relatively young (~50 years) at diagnosis and are expected to carry the burden of treatment-related toxicity for life.

Quality of life considerations and superior clinical outcomes associated with these patients have prompted treatment de-intensification trials which unfortunately have had disappointing outcomes due to failure to accurately select patients.
The investigators propose to employ novel biomarkers to stratify HNC patients into clinically relevant metabolic phenotypes, define tumour pathology in tissue samples and select patients correctly for therapeutic management with dose-deintensification protocols and novel therapies. Ultimately, we believe that study findings will have significant implications for clinical management of not only HNCs but other HPV related cancers and find translation in clinical space.

Immune Recovery After Allogeneic Stem Cell Transplantation for Blood Cancers.
Prof. Derek G. Doherty (Professor in Immunology, School of Medicine, Discipline of Immunology) and Dr. Nina Orfali (Consultant Haematologist, St James's Hospital)
Stem cell transplantation is a potentially life-saving treatment for patients with aggressive blood cancers. To ensure acceptance of a new blood system and immune system, patients receive chemotherapy and immunosuppression to prepare or 'condition' their body before they receive the new cells.

They also remain on immunosuppression for some time after the transplant to prevent a unique complication called 'Graft versus host disease' – where the new immune system attacks the patient's normal organs. Too much immunosuppression however can increase a patient's risk of infection after their transplant and can compromise the ability of the donor immune cells to recognize and kill their cancer cells. Our research aims to identify the factors that influence immune recovery after a stem cell transplant. We hope our findings ultimately will be used to personalise the dosing of conditioning and immunosuppression treatments for patients to ensure the best possible transplant outcomes for future patients.

The role of SESN1 and SESN2 genes in the regulation of mTORC1 and STAT3 signalling pathways in lung tumours.
Dr. Andrei Budanov (Ussher Assistant Professor, School of Biochemistry and Immunology) and Mr. Gerard Fitzmaurice (Consultant Cardiothoracic Surgeon, St James's Hospital)
The major purpose of our study is to understand the role of the Sestrin family proteins in lung carcinogenesis. According to their previous work, Sestrins are major regulators of cell growth, and these proteins are often down regulated in cancer cells. In the proposed work, we will determine the role of Sestrins in prevention of tumour growth and will study the regulation of pro-carcinogenic mTOR and STAT proteins by Sestrins in human lung tumours.

Selection of cold tumor phenotype (Cell) specific aptamers.
Dr. Brian Henderson (Postdoctoral Researcher, School of Medicine, Discipline of Clinical Medicine) and Mr Gerard Fitzmaurice (Consultant Cardiothoracic Surgeon, St James's Hospital)
Lung cancer has the highest mortality rate compared to other forms of cancer as it is often detected at an advanced stage. Cancer cells often have high levels of surface proteins that stop the patient's immune system detecting these cells. One of these proteins is called PD-L1 and novel drugs, called immunotherapies, can bind to it and cause the patient's own immune system to trigger a response and dramatically improved patient outcomes.

Unfortunately, not all patients respond to immunotherapies, and the majority eventually fail to respond due to drug resistance. Mechanisms of resistance remain largely unknown. In collaboration with partners in the Irish Lung Cancer Community (ILCC) and the TSJCI Patient Representative Group this project will develop novel tools which can be used to visualise cancer cells and better classify their qualities by Immunohistochemistry. The aim is to develop novel tools to insert into existing hospital protocols and improve patient outcomes.

Exploration of suitability and acceptability of social prescribing for men with Prostate Cancer
Prof. Deirdre Connolly (Associate Professor, School of Medicine, Discipline of Occupational Therapy) and Mr. Peter Lonergan (Consultant Urologist, St James's Hospital)
Many men with Prostate Cancer (PCa) experience a range of physical and psychological health difficulties during cancer treatment and research has identified a need for individualised support to improve the health of men with PCa. Social prescribing is a community-based support service that links individuals with health-promoting activities, and support services, in their local community. This study will examine the range and extent of health difficulties experienced by men with PCa during and after treatment and whether social prescribing is a suitable community-based support to improve physical and psychological health.

Design of an assay to efficiently measure levels of CAR (Chimeric Antigen Receptor) T cells in the peripheral blood of recipient Patients at St James's Hospital.
Dr. Aoife Marie Kilgallon (Research Fellow, School of Medicine, Discipline of Surgery) and Dr. Larry Bacon (Consultant Haematologist, St James's Hospital)
The National Adult Chimeric Antigen Receptor (CAR) T cell Centre is based at St James's Hospital and to date 17 patients with high grade B cell lymphomas have been treated with CAR T cell therapy since the programme opened in December 2021.

CAR T cell therapy is a new type of immunotherapy whereby live immune cells (T cells) are taken from the patient and modified before being re-introduced to the patient. These modified immune cells can recognise and target the patients' cancer cells. Overall, 40% of patients with B cell cancer who receive CAR T cell treatment no longer have detectable cancer.

Since CAR T cells are living cells, these can continue to survive in the patient's body for months and years following treatment. Levels of CAR T cells can be measured in a blood sample taken from a patient. This project aims to identify an effective way of measuring the levels of CAR T cells in the blood of patients treated with CAR T cells at St. James's hospital. This important clinical information will allow for more effective monitoring of patients following treatment to identify if any additional treatments are required and ultimately improve outcomes for these

Figure 13. CREST Awardees at the TSJCI 12th International Cancer Conference, 13th October 2022.
L-R: Prof. Joanne Lysaght Prof. Lorraine O'Driscoll, Dr. Julie Broderick and Dr. Patricia Doherty.

Figure 14. CREST Awardees at the TSJCI 12th International Cancer Conference, 13th October 2022.
L-R: Dr. Patricia Doherty, Dr. Brian Henderson, Dr. Andrei Budanov, Prof. Joanne Lysaght, Dr. Emer Guinan, Dr. Prerna Tewari, Dr. Maeve Kearney and Prof. Lorraine O'Driscoll.

Cancer Clinical Trials

The Cancer Clinical Trials Unit (CCTU) is comprised of a multi-disciplinary team of research nurses, clinical trial coordinators, research assistants, pharmacists and research registrars.

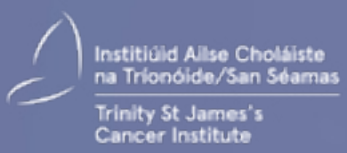
Our remit is to conduct solid oncology and haematology clinical trials to the highest international standards. We conduct both academic and industry sponsored trials in all trials phases from phase I to phase IV. The majority of the trials that we conduct are large phase III trials.

We provide an end-to-end service to Principal Investigators (PIs) from trial feasibility all the way through to trial closure. The Research Nursing team, led by a CNM3 Team Lead, are patient facing and they screen, treat and follow up patients throughout their clinical trial journey. The Clinical Trial Coordinators manage the data entry of all the clinical trial data, answer the associated queries and manage the day-to-day administration of the each and every clinical trial. The pharmacy team, led by a Chief II Cancer Trials Pharmacist ensure that all the trial drugs are receipted, stored, compounded and administered according to the clinical trial protocols.

The CCTU works with a diverse group of 17 PIs (nine Medical Oncologists and eight Haematologists) and has opened and recruited patients in the following disease areas: Breast, Lung, Head & Neck, Skin, Upper and Lower GI, Gynae, Lymphoid and Myeloid Haematology cancers.

Supplementary Information

A supplement to this Scientific Report is available which outlines Clinical Trials, Current and past doctoral students, COST Action involvement and publications for the period 2018-2022. Please contact **thecancerinstitute@tcd.ie** for further information.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