Cancer Drug Discovery Day

At

Trinity Biomedical Sciences Institute

15th September 2015
Welcome to the 2015 Cancer Drug Discovery Day!

The Cancer Problem
While many new amazing anti-cancer drugs have come online in the last decade there is still an overwhelming need for new cellular targets to be discovered and new drugs to be synthesised. The need for basic science discovery in the cancer area has never been greater and both patient groups and the pharmaceutical industry are in urgent need of new targets for anti-cancer drug development. It is imperative that Ireland’s scientists respond to this demand. Today we are showcasing a series of novel research findings by some of Trinity’s best scientists, including up and coming postgraduate and postdoctoral researchers.

The Trinity Cancer Institute
A major new initiative in Trinity is the development of the Trinity Cancer Institute. This new Institute will be directly focused on the needs of cancer patients and will strive to integrate best patient treatment regimes with the latest clinical trials available. Fundamental to this exciting new Institute is the driving force of basic science research located in TBSI. It is here that some of Trinity’s best research scientists and research infrastructure are located and also where multidisciplinary research practices are being taught to early-stage cancer scientists.

In addition to today’s events information is provided on the cancer research groups currently working in the Trinity Biomedical Sciences Institute. We hope that you enjoy the day and are stimulated to engage with our researchers further.

Best wishes

Prof Gavin Davey
Co-ordinator TBSI Cancer Drug Discovery Theme
Trinity Biomedical Sciences Institute
Cancer Drug Discovery Day  
Tuesday, 15th September 2015  
Trinity Biomedical Sciences Institute  
STANLEY QUEK LECTURE THEATRE

The cancer-immune axis and druggable targets – Chair Prof Gavin Davey
9.30 Jerrard Hayes (PI) Sugars at the interface between cancer and the immune system - new therapeutic targets!
10.00 Chris Cluxton (PD) Platelet cloaked tumour cells suppress natural killer cell immune surveillance
10.20 Roisin Loftus (PG) Metabolic control of natural killer cell function
10.40 Brian Flood (PG) Inflammatory caspases during colorectal cancer

11-11.15 Coffee: foyer on level -1

Cancer metabolism and cell death signalling targets – Chair Prof Clive Williams
11.15 James Murray (PI) Targeting autophagy in solid tumours
11.45 Fintan Geoghegan (PG) The effect of resveratrol and SIRT3 overexpression on the metabolism of cisplatin resistance in non small cell lung cancer
12.05 Ryan McGarrigle (PG) Mitochondrial fusion/fission dynamics in cancer cells
12.25 Nicoleta Sinevici (PG) The novel potential of BAMLET in the treatment of oral cancer

12.45-2: Lunch: foyer on level -1

Cancer biomarker and target discovery – Chair Prof Eoin Scanlan
2.00 Adrian Bracken (PI) Targeting the epigenetic enzyme EZH2 in cancer
2.30 Vanesa Martinez (PD) Neuromedin U in breast cancer
2.50 Radka Fahey (PD) Epigenetic regulation of glycomic markers in cancer
3.10 Claire Fergus (PG) Queuosine in cancer and immunity

3.30-3.45: Coffee: foyer on level -1

Novel cancer therapeutics – Chair Prof Daniela Zisterer
3.45 Clive Williams (PI) Targeting cancer cells with supramolecular nanotechnology: The use of luminescent Ru(II)-polypyridyl complexes and gold nanoparticles
4.05 Eoin Scanlan (PI) The development of glycosidase activated anticancer prodrugs
4.25 Seema Nathwani (PD) Novel microtubule targeting agent, PBOX-15, sensitises acute lymphoblastic leukaemia cells to TRAIL-induced apoptosis
4.45 Niamh O’Boyle (PD) Novel cancer therapeutics: dual targeting of tubulin and reactive oxygen species

5.10 – 5.15: Prizes to best PG & PD speakers

Lecture by the Recipient of the 2015 Denis Burkitt Medal
5.30-6.30: Prof Riccardo Dalla Favera, Columbia University - Molecular genetics of aggressive B cell lymphoma: from the Burkitt translocation to genome sequencing

6.30 – 7.30: Reception: Foyer, Stanley Quek Lecture Theatre

PI = Principal Investigator; PD = postdoctoral researcher; PG = postgraduate researcher
2015 Burkitt Medal Awardee

Professor RICCARDO DALLA-FAVERA  M.D.
Professor of Pathology & Cell Biology
Director, Institute for Cancer Genetics
Columbia University
New York, New York, USA

Riccardo Dalla-Favera, M.D. holds the Joanne and Percy Uris Chair of Clinical Medicine, he is Professor of Pathology, and Professor of Genetics & Development at the College of Physicians & Surgeons of Columbia University. He is also the Director of the Institute for Cancer Genetics. He is the Director of the Specialized Center for Research on Lymphoma at Columbia University. He is the author of 200 publications and the co-editor of the textbook “Non Hodgkin Lymphoma” (Lippincott, Williams & Wilkins publishers).

Dr. Dalla-Favera has been recognized with several national awards, including the Stohlman Award from The Leukaemia Society of America, two NIH MERIT Awards (1989, 2005), and the 2006 William Dameshek Prize for Outstanding Contribution to Haematology from The American Society of Haematology. In 2011 he has been elected to the Institute of Medicine of the National Academy of Sciences, USA. In 2015 he has been elected to The National Academy of Sciences, USA.

Dr. Dalla-Favera has been an active researcher in the field of lymphoma research for more than 30 years. His career started with his pioneering work on the cloning and chromosomal mapping of human proto-oncogenes, including c-MYC (1). This work established the basis for the seminal work on the involvement of c-MYC in chromosomal translocations in Burkitt’s lymphoma (2-4). Then, his research has continued to yield new insights into the pathogenesis of human B cell lymphomas, and, in particular, on the identification of the genetic lesions and biological mechanisms responsible for the development of these diseases (5-9).
Cancer Research in the Trinity Biomedical Sciences Institute (TBSI)

Introduction: TBSI has 24 groups in the area of cancer research. The main aims of these groups are to discover the biochemical mechanisms that drive cancer development, to identify new targets in cancer, to identify new biomarkers and imaging agents for cancer diagnostics and to develop new drugs (small molecules and biotherapeutics) for cancer treatments.

Research focus & impact: The cancer research programme is focused on four key areas.

1. Cancer-specific cell metabolism
2. Survival/death signalling mechanisms
3. The cancer-immune axis
4. Target discovery and novel therapeutics

Research into cancer cell metabolism helps us to understand how cancer cells fuel themselves and are able to successfully form primary tumours and eventually metastasise into disseminated disease. By investigating the control mechanisms that control cancer cell survival or death decisions, TBSI researchers are also looking at ways of understanding how normal and cancer cells are different. These two basic research themes are mechanistically linked and research in these areas is helping to define new therapeutic targets that can feed into a translational drug discovery programme. The third focus is on controlling the immune system to effect removal of cancer cells and our fourth focus is in the area of next generation therapeutics, both small molecules and biotherapeutics. Within TBSI we are developing new strategies for impacting on the success rates of pharmacological agents through computational chemistry approaches and developing cancer vaccines that trigger the immune system to detect and eradicate cancer cells. We partner with major pharmaceutical companies to bioengineer and glycoengineer novel anti-cancer biotherapeutics.
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Cancer research investigators

Dr. Emma Creagh
Cell signalling in cancer & inflammation

Our cancer-based research focuses on the link between persistent inflammation and an increased risk of cancer development. One such example is the increased risk of inflammatory bowel disease (IBD) development into colorectal cancer (CRC). A group of enzymes, termed caspases, are important in triggering inflammation during IBD and other inflammatory diseases. Using disease models and IBD/CRC patient biopsy samples, we are currently establishing whether these enzymes also have a mechanistic role in the development of inflammatory-mediated tumourigenesis.

Dr. Gavin Davey
Cancer cell metabolism & antibody biotherapeutics design

We focus on (1) mitochondrial energetics and fusion/fission dynamics specific to cancer cells (2) identification of metabolic control points as new targets for anti-cancer therapeutics (3) understanding control of N-linked and O-linked glycosylation pathways in cancer cells and effects on metastasis (4) glycoengineering IgG biotherapeutics for enhanced ADCC, CDC and enhanced immunomodulatory properties (5) Antibody drug conjugate (ADC) development (6) identification of glycosylation-based biomarkers for cancers.

Dr. David Finlay
Immunometabolism and anti-tumour immune responses

The immune system has a key role to detect and eliminate malignant transformed cells and cancer only arises when tumour cells develop the capacity to evade the anti-tumour immune response. Our research is investigating a new regulatory axis that controls the function of key anti-tumour immune subsets, notably Cytotoxic T cells (CTL) and Natural Killer (NK) cells. Our data shows that NK/CTL cell metabolism is integrally linked to the expression of key anti-tumour molecules IFNγ and granzyme B. We are investigating whether immune cell metabolism can be manipulated to promote enhanced anti-tumour T and NK cells responses.

Dr John Gilmer
Cancer chemical biology approaches

Our work is directed at optimizing the effects of established compounds, both drugs and endogenous compounds. Our strategies include the design and synthesis of analogues with improved targeting to cancer tissue or increased biochemical selectivity. We also develop new tools for investigating biomedical problems. We are interested in bile acids, their role in tumour development in oesophagus and colon and in the design of bile acid analogues with chemotherapeutic properties. We are interested in the interactions between bile acids, matrix metalloproteinases and aspirin in oesophageal disease. We have developed novel compounds related to aspirin that have little or no GI toxicity but with greatly increased ability to reduce interactions between platelets and cancer cells and improved ability to block bile acid induced signalling. We are interested in developing clinical pathways for these.
Dr. Clair Gardiner  
Natural Killer Cells & cancer

Neuroblastoma is the most common extra-cranial tumour in children. Despite intensive treatment, the prognosis for patients with 'high risk' neuroblastoma is very poor. The advent of immunotherapy, which targets tumour cells coated with antibody for cytotoxicity by Natural Killer (NK) cells of the immune system, has been a significant breakthrough. We are investigating a role for NK cell genetic diversity in the development, progression and treatment response to neuroblastoma.

Dr Jerrard Hayes  
Therapeutic antibodies, Fcγ Receptors and antibody drug conjugate design.

Fc gamma receptors (FcγR) play a critical role in the immune response following recognition of invading particles and tumour associated antigens by circulating antibodies. Effector responses such as natural killer cell dependent ADCC toward tumourigenic material rely on engagement of IgG antibodies with the cell surface FcγRs. Our research is directed towards the development of an FcγR based analytical platform based on surface plasmon resonance to determine the binding of therapeutic antibodies to the range of FcγRs (FcγRI, FcγRIIa H131/Arg131, FcγRIIa Phe158/Val158, FcγRIIIb. From this affinity and kinetic analysis it is possible to predict the potential biological response of anti-cancer and other therapeutic antibodies. We also research antibody drug conjugates and tumour imaging antibodies.

Dr. Vincent Kelly  
Transfer RNA (tRNA) modifications in cancer

The metabolism of a cancer cell is intimately linked to its differentiation and proliferative status. Therefore, agents that alter metabolism can profoundly affect the degree and severity of cancer progression. Our group is focused on understanding the metabolic changes that occur in breast cancer and on how metabolism is influenced by naturally derived chemicals. Our work will hopefully lead to new strategies to invoke anti-proliferative effects in cancer, either as standalone therapy or combined with current therapeutic strategies.

Dr Andrew Knox  
Polypharmacological targeting & drug repositioning in cancer

In silico drug design group with interests in nuclear receptors, HSPs and tubulin chemistry. Computational screening and binding site off-target effects of drugs. 1) Identification of other targets of known anti-cancer compounds. 2) Repositioning of approved drugs, old drugs, generic drugs, drugs that failed to achieve their primary endpoint in the oncology space.

Prof. Mary J Meegan  
Discovery and development of new anti-cancer drugs

Our cancer-based research focuses on the design, chemical synthesis and biochemical evaluation of novel molecules with anticancer activity as potential clinical agents. We are
currently developing novel microtubule targeting agents; we also utilize in silico high-throughput screening methods for the identification of small molecule modulators of nuclear receptors relevant in the development of multiple cancers. Our research also includes a study of the structural optimization of amphetamines and related compounds with cytotoxic effects for the treatment of Burkitt’s lymphoma.

Dr. Andrew McDonald & Prof Keith Tipton
Computational modelling of glycosylation for therapeutic development

Our research is interested in mathematical modelling of glycosylation and its applications to cancer research. In particular, we are modelling mucin-type O-glycans, which are altered in adenocarcinomas such as breast, colon and pancreatic cancers. From a knowledge of the enzymes of glycosylation, and their expression levels, possible O-glycan structures can be predicted and the likelihood of their appearance estimated. Such modelling will reveal new insights into the regulation of flux through the O-glycosylation pathways, leading to possible new drug targets or vaccination therapies.

Prof. Kingston Mills
Anti-tumour vaccines

We study the role of the immune response in controlling tumours and how tumours subvert and evade the immune response. As a direct result of our basic research programme, we are developing novel therapeutics for cancer based on enhancing anti-tumour immunity and suppression of regulatory immune responses. Translation of these novel therapeutics to the clinic is being led by a start-up company, TriMod therapeutics.

Dr Carlos Medina
New therapeutic strategies in Intestinal inflammation and Cancer

Our primary research objective is the identification and characterization of different molecular targets involved in inflammatory bowel disease (IBD) and cancer. Preliminary results indicate that matrix metalloproteinase-9 (mmp-9), different isoforms of protein kinase c (PKC) and mitogen- activated protein kinase (MAPk) may be among targets to be considered. The secondary research objective is to design new effective therapeutic strategies for both diseases including selective MMP-9 inhibitors. Our work is also focused on novel nanoparticle-based therapeutics of IBD and colonic cancer.

Dr. Ken Mok
Peptide based anti-cancer therapeutics

We investigate the anti-tumour properties of a protein-fatty acid nanoparticle called HAMLET that selectively kills tumour cell while leaving healthy, differentiated cells intact. We are studying the mechanism of action of HAMLET and mechanisms by which it selectively kills tumour cells. Pilot clinical studies of HAMLET and its analogues have shown proven clinical efficacies against bladder cancer, HPV-induced lesions, and glioblastoma cancers and we are filing a new biological entity patent in this area. We also employ state-of-the-art NMR metabolomics, using the TBSI 800 MHz NMR to profile the metabolomes of blood sera, CSF & urine of cancer patients. Data generated from these analyses is linked to potentially thousands of samples from genome-wide and/or longitudinal studies and will serve as a fully-retrievable, archived repository of high-resolution metabolomics data ready for mining.
Dr. James Murray
Cell survival mechanisms in cancer

My research focuses on growth, nutrient and energy signalling pathways that control cell survival and death pathways to identify and develop novel molecularly targeted therapies that will cripple the ability of cancers to survive and proliferate. In particular we concentrate on protein and lipid kinase-dependent signalling pathways that control cellular autophagy, a survival pathway that promotes cell survival during periods of physiological stress, which is dysregulated in almost all cancers. Autophagy is a rapidly emerging therapeutic target area that could provide an Achilles heel for therapy-resistant cancers.

Dr. Lorraine O’Driscoll
Towards earlier diagnosis & personalised treatment for cancer patients

My group’s cancer research includes (1) identification and validation of biomarkers (in vitro diagnostics) for earlier diagnosis, prognosis and predicting response to drug treatment (companion biomarkers for drugs); (2) new therapeutic target identification; (3) understanding and circumventing resistance to targeted anti-cancer agents and classical chemotherapy; and (4) translating our findings to the clinic. Our studies include analysis of an extensive range of both commercially available and novel cancer cell lines, including drug resistant variants that we established and characterised; studies on patients’ specimens (tissue serum, urine, saliva --- circulating tumour cells, exosomes and microvesicles involved in cancer metastasis and spread of drug resistance); pre-clinical in vivo studies; and translational phase I & Phase II clinical trials.

Dr. Jeff O’Sullivan
Risk factors in the development of oral cancer

Our current studies are focused on determining glycomic and metabolomic profile of cells undergoing this transition with the goal of identifying possible therapeutic targets and biomarkers. Additional studies within the group examine the disruption in oxidative stress response enzymes observed in oral squamous cell carcinoma cells harbouring p53 mutations. Our research on the role of p53 in oral cancer suggests that it may be responsible for the variations in therapeutic sensitivity and response that will help stratify patients that will respond to specific therapies and therefore inform personalised treatment plans for patients.

Dr. Richard Porter
Mitochondrial energy metabolism in haematological malignancy

We investigate the role of mitochondrial uncoupling proteins (UCPs) in energy metabolism by analysing the regulation and function of UCPs 1, 2 and 3. By comparing cell profiles in thymus and spleen of wild-type and UCP 1 knock-out mice we are learning new insights into the role of mitochondrial UCP 1 in thymocyte function and determining T-cell population selection in mice. UCP 2 is also an area of research both in immune cells and pancreatic beta-cells. Understanding UCP function and regulation has direct implications for mitochondrial function and the development of haematological malignancies.
Prof Pauline Rudd  
**Glycoanalytics and biomarker discovery for cancer**  

My group specialises in cutting edge detailed glycan analysis. Our cancer programme makes use of the workflow we have established for a clinical marker discovery platform. This involves an automated glycan release platform (364 well plates), separations technologies including LC-MS and bioinformatics programmes to enable rapid data interpretation. This workflow has recently been commercialised by Waters (UNIFI 1.7) who gave us a global innovator award. We have identified dozens of markers in the serum glycomes of patients that individually or in panels discriminate between different stages, including metastasis, of some 10 cancers more effectively than the current markers. We aim to provide an instrument that could be used in routine diagnostics. We also have the technical capability to link glycans in the serum glycome to the proteins that carry them and, using a novel technology, with an individual’s genomic profile, thus giving an insight into risk factors for some diseases. This could also be an interesting way to look at the aggressiveness of individual tumours.

Dr. Eoin Scanlan  
**Synthetic glycoconjugates as anticancer therapeutics**  

Our research is focused on the design, synthesis and biological screening of oligosaccharides and glycoconjugates as potential anticancer therapeutics. We have developed new methodologies for the preparation of glycosylated porphyrins as targeted and water soluble PDT reagents. We have also developed new methodologies for the preparation of glycopeptides and glycosylated nanomaterials for targeted drug delivery and tumour imaging. The group is also involved in the design and synthesis of small molecule glycosidase inhibitors as anticancer therapeutics.

Prof. Dr. Mathias O. Senge  
**Photodynamic cancer therapy and imaging**  

The group focuses on (1) chemical synthesis, QSAR studies, and drug development of porphyrin-based photosensitizers for use in photodynamic therapy, (2) high content screening methods, (3) light-activatable dual-modality anti-cancer agents with bioconjugate targeting groups, and (4) new anti-angiogenesis treatment modalities for oesophageal cancer.

Prof. Marek W. Radomski  
**(Nano)Pharmacology of platelet-cancer cell interactions**  

We investigate the biological and pharmacological significance of platelet activation for carcinogenesis using combination of nanofluidics, nanopharmacology, molecular, flow cytometry and classical pharmacological methods. The key objective of this research is to develop selective inhibitors of cancer cell-induced thrombosis and platelet-stimulated carcinogenesis.
Prof Isabel Rozas  
**Towards new cancer therapies: a drug discovery approach**

With the help of Molecular modelling techniques, organic synthesis and medicinal chemistry methodologies we design, prepare and biologically test new cancer therapies. Thus, we aim at two different targets: i) different families of compounds that target DNA as minor-groove binders have been prepared showing good cytotoxicity in HL-60, MCF-7 and neuroblastoma cell lines; now a Platinum moiety (similar to that present in cisplatin) is being attached to these binders to achieve a double DNA attack; ii) new guanidine-base derivatives that inhibit the RAF/MEK pathway have been developed (with good cytotoxicity in HL-60, MCF-7, Tam-resistant-MCF7 and RKO cell lines) and kinases assays plus modelling studies indicate that they are allosteric MEK inhibitors. Now, we are optimizing their activity and looking at the impact of these compounds in mTOR.

Dr. John J. Walsh  
**Targeting tumour vasculature**

Our research is focused on the design, synthesis, *in vitro, ex vivo* and *in vivo* evaluation of small molecule inhibitors of tumour angiogenesis and vasculature. While the principal target is tubulin dynamics, we have also prepared hybrids, designed multiple ligands, pH and controlled release agents as well as adapted our most potent vasculature disrupting agents with suitable linker units for the preparation of antibody drug conjugates. Studies are ongoing on the optimization of the molecular scaffolds generated to date.

Profs. Clive Williams & Thorri Gunnlaugsson  
**Advanced approaches to cancer drug discovery**

Our research is focused on the identification or development and subsequent improvement of chemical small molecules with potential for triggering cancer cell death. We are also developing photo-activatable compounds for use as therapeutics and imaging agents and higher order complexes with nanoparticles to kill cancer cells. Preliminary studies in our laboratories have shown activity of some of these compounds towards lymphoma and lung cancer lines. We are also exploring amphetamine compounds as anti-cancer agents, where their induction of programmed cell death provides a novel mechanism for cancer therapy.

Dr. Daniela Zisterer  
**Pharmacological inducers of apoptotic cell death in cancer**

Our research programme studies molecular mechanisms underlying apoptotic cell death and how deregulated apoptosis leads to cancer and the mechanisms that underlie drug resistance, potentially through autophagy-dependent cell survival signalling. We aim to develop novel therapies that target the apoptotic pathway. Currently developing novel microtubule targeting agents and novel tyrosine kinase inhibitors. Focusing on drug-resistant cancers including neuroblastoma, gastrointestinal stromal tumours, colorectal cancers and TRAIL resistant acute lymphoblastic leukaemia.