The Institute has come to the end of an incredible era of leadership from Professor Chris Boshoff. Since opening in 2007, the Institute has more than tripled in size and is now widely recognised as one of the foremost institutions in the UK for basic, translational and clinical cancer research. Chris has worked relentlessly for the past six years in steering the growth and prosperity of the Institute with his clear vision, wisdom and charisma. He has done a fabulous job as Director and will no doubt continue to inspire and provide exceptional leadership in his new appointment as Vice President for Translational Oncology at Pfizer. We wish him all the very best in his new job.

Tariq Enver, Interim Director
Cancer Institute Research Trust Success

The UCL Cancer Institute Research Trust (CIoRT) has had a successful year’s fundraising and would like to take this opportunity to thank all of our funders for their generosity in helping with the funding towards our priority projects.

In 2012-2013, our priority projects have been to raise funds towards: the new Bill Lyons Informatics Centre (only £300,000 funding still required out of the original £2.21 million project target); a new DepArray liquid biopsy platform (total cost £350,000, of which we are now seeking the remaining £125,000); a TALENs Library within the Institute (total cost £100,000); and the purchase of a Confocal Microscope (total cost c.£500,000).

We continue to work closely with our dedicated supporters from a variety of Trusts and Foundations, as well as key individuals who are interested in supporting the work of the Institute. We are also very grateful to all those individuals who have chosen to support CIoRT by running, or sponsoring runners, in the Virgin London Marathon, or by helping us to raise funds for the Debbie Fund research, led by Professor Kerry Chester, into cervical cancer or Chordoma UK research, led by Professor Adrienne Flanagan, into chordoma, a rare spinal cancer.

Finally, we would like to take this opportunity to welcome Lisa McCarthy and Damian Hamill to the CIoRT team, covering Helen Quirke’s maternity leave. Lisa will be working to develop the support of major individual donors, whilst Damian will be focusing more on the admin/donor support side.

If you (or anyone you know) would like to support the research being undertaken at the Institute in any way, please contact our Head of Fundraising, Anna Roche, at a.roche@ucl.ac.uk or call 020 7679 6325.

CRUK UCL Centre

The CRUK UCL Centre was established in 2009 with Professor David Linch as the first director. Its major function has been to provide critical infrastructure to facilitate the consolidation of the UCL/UCLH axis in translational research. The first period of funding has been one of great success, with recruitments into key areas such as Professor Charles Swanton to a Chair in Personalised Cancer Medicine. Additional key appointments to positions within the Clinical Research Facility, Haematology and Pathology have aided the major international presence of UCL/UCLH cancer research over this time-frame. Most importantly, the Centre has provided graduate studentships and clinical fellowship funding to allow recruitment of a cadre of excellent scientists and clinician-scientists, many of whom have obtained external peer-reviewed funding.

This year Daniel Hochhauser and Henning Walczak were appointed as Co-Directors for the new programme of the Centre. The application submitted this summer will allow for major expansion of core infrastructural support with the formation of major cross-cutting multidisciplinary groups (in cancer biology, gene therapy/immunotherapy, cell death/inflammation/immunity, behavioural sciences, imaging) which will act across specialised cancer programmes such as lung, brain and haematological malignancies. The award would also further reinforce the emerging core resources in areas such as biobanking and clinical trial design. Our vision is to integrate the unique strengths of UCL with that of our main partner hospitals, UCLH, Great Ormond Street Children’s Hospital and the Royal Free, to develop an internationally competitive translational research focus.

Cancer Institute NEWSLETTER
Cancer Research UK Manchester UCL Lung Cancer Centre of Excellence

Lung cancer is the most common and lethal cancer in the UK, with > 40,000 new cases and ~35,000 lung cancer deaths p.a. Most patients present with metastatic disease so 5-year survival is < 10%, and despite the introduction of targeted therapies there have been only marginal improvements in overall survival over the past decade.

In July 2013 CR-UK awarded UCL the Lung Cancer Centre of Excellence in partnership with Manchester, the Christie Hospital and the Paterson. The Centre combines expertise in early detection (Sam Janes), clinical trials (Ming Lee and Martin Forster) with research excellence within the UCL Cancer Institute (Sergio Quezada, Henning Walczak, Charles Swanton). The synergy with Manchester will enable the Centre to combine our unique and complementary strengths in clinical and translational cancer research to create an environment in which basic lung cancer research will flourish. This will catalyse high profile recruitments and provide the infrastructure for new groups to work on lung cancer in the UK.

A unifying theme of the Centre will be the application of evolutionary biology techniques to cancer medicine. Intra-tumour heterogeneity is emerging as a key theme in lung cancer and the Centre is applying Darwinian principles of evolution to develop a deeper understanding of the mechanisms shaping lung cancer genomes over space and time. The Lung Cancer Centre will investigate how intra-tumour heterogeneity limits tumour responses to targeted therapies and conversely whether it offers opportunities for immuno-modulatory therapies.

The CR-UK/Rosetrees Trust funded £13 million TRACERx (TRAcking lung Cancer Evolution through therapy/Rx) study will form a major focal point for the Centre’s lung cancer evolutionary research strategy. TRACERx is the first longitudinal cancer evolution study that will form a central component of joint efforts between UCL Cancer Institute, Manchester and the Crick institute. TRACERx will involve multi-region sequence analyses of lung cancers through the disease course from pre-invasive through to primary and metastatic disease, in order to understand cancer evolutionary life histories in this disease. This work will be supported by the excellent bioinformatics already available in our Centre together with substantial investment in bioinformatics staff, data storage and computer processing power. Newly discovered driver events will be functionally analysed in preclinical models and validated for drug discovery initiatives as part of the Centre’s program. Taken together, the CRUK Lung Centre and TRACERx will offer unprecedented opportunities to understand lung cancer biology in order to develop novel therapeutic approaches of the future.
The Cancer Institute welcomes Bart Vanhaesebroeck

In January 2013, Prof. Bart Vanhaesebroeck and his Group will join the UCL Cancer Institute. Following his PhD from the Laboratory of Molecular Biology (with Walter Fiers) at Ghent University, Belgium, Bart carried out postdoctoral studies at the UCL Ludwig Institute for Cancer Research (with Mike Waterfield) and became Professor at UCL. In 2007, he moved to Barts Cancer Institute, Queen Mary University of London, to set up the Centre for Cell Signalling. Research in Bart’s team focuses on PI 3-kinase (PI3K) enzymes, which regulate intracellular signal transduction. PI3K signalling is overactive in cancer, inflammation and auto-immunity, and many PI3K inhibitors are now in clinical development.

Bart’s laboratory has made key discoveries about the functions of PI3K in biology and disease, with work published in Science, Nature, PNAS and forefront journals. Through basic research of the PI3K system, his laboratory aims to understand the specific roles of the different PI3K family members and to explore their potential as new drug targets for cancer and other diseases, including inflammation and diabetes.

A key success was in the cloning and identification of the p110delta PI3K as a new target in immunity, inflammation and cancer, work that was incorporated into the drug development programmes of Plamed UK (acquired in 2007 by Roche) and other major pharmaceutical companies. It is anticipated that p110delta inhibitors will soon be approved for therapy in specific human haematological malignancies. They are also being evaluated for treatment of airway inflammation and arthritis. New discoveries in Bart’s laboratory are currently being explored for drug development and clinical trials.

Bart’s team has pioneered improved mouse models of signalling and disease, with significant advantages over classical gene knockout approaches, to model drug action. These mice are ideal for preclinical studies as they have proven to be excellent physiological models to study the effects of PI3K inhibitors.

Bart is an elected member of EMBO and the UK Academy of Medical Sciences. In 2010, together with Pedro Cutillas, he set up Activomics Ltd, a company to develop biomarkers in disease. The main funders of Bart’s research are CR-UK, BBSRC, EU and the UCLH/UCL Biomedical Research Centre (BRC).

Bart’s team is looking forward to collaborating with colleagues at UCL in basic and translational research applied to human disease.
The Cancer Institute has a strong commitment to the advancement of women’s careers in science and the principles of the Athena Scientific Women’s Academic Network (SWAN) Charter, launched in 2005 with UCL as one of the founder members [http://www.athenaswan.org.uk/](http://www.athenaswan.org.uk/).

The beliefs underpinning the Charter are that:
- The advancement of science, technology, engineering, maths and medicine is fundamental to quality of life across the globe.
- It is vitally important that women are adequately represented in what has traditionally been, and is still, a male-dominated area.
- Science cannot reach its full potential unless it can benefit from the talents of the whole population, and until women and men can benefit equally from the opportunities it affords.

In the Cancer Institute we have a dedicated Athena SWAN self-assessment team (SAT) of senior and junior members that meet monthly to assess challenges for our female scientists and implement change. Since its formation in July 2012, the SAT have been active in variety of areas such as: raising awareness of Athena SWAN in a dedicated ‘SWAN week’, communicating with Institute staff to canvass opinion, collecting and analysing employment statistics, scrutinising the numbers of women on decision-making committees and improving the percentage of women giving high profile seminars.

We are also exploring the key issues supporting retention of women. Some of these are known to be providing personal and professional support (career development, networks and mentoring), having a supportive Head of Department, providing encouragement to apply for research fellowships and senior roles, including women in decision making process, creating a departmental culture supporting work-life balance and developing networking opportunities. Prof. Kerry Chester, SAT Chairperson commented “We know that we recruit equal numbers of women and men to academic posts in the Cancer Institute but we still have less women in senior and decision-making roles, this has to change!”

Some of our exciting new SWAN initiatives are: The training of dedicated mentors to support women’s career development led by Prof. Paolo Salomoni, an Academic Careers Day organised by Dr Julie Olszewski and a forthcoming series of inspirational seminars on the theme of “Inspiring Excellence Stories from Successful Women” led by Dr Sue Hadjur see below for details.

**Nicola Horlick,** Chairman of Rockpool Investments LLP
10am, Thursday November 14, 2013
Wilkins Old Refectory Room Main Campus

**Francesca Dow,** MD of Penguin Publishing, Children s
2pm, Friday December 13, 2013
Wilkins Old Refectory Room Main Campus, 2pm

**Helena Morrissey CBE,** CEO of Newton Investment Management and Founder of the
30 Percent Club
2pm, Wednesday January 15, 2014
Gustave Tuck Lecture Theatre

**Professor Kathy Sykes,** Bristol University and Founder of the Cheltenham Science Festival
Date and venue TBD

**Professor Dame Wendy Hall,** Dean of the Faculty of Physical & Applied Sciences, Southampton University
12pm, Thursday April 3, 2014
Darwin Lecture Theatre

Please visit our website [http://www.ucl.ac.uk/cancer/athena](http://www.ucl.ac.uk/cancer/athena)
or contact us [athenaswan-ci@ucl.ac.uk](mailto:athenaswan-ci@ucl.ac.uk) (@uclicancer) for more information.

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**Dr Sue Hadjur**
Richard Jenner Promoted to Reader

All of the cells in the human body contain the same set of instructions encoded in their DNA. But each cell must only follow a subset of these instructions, for example instructions to become a neuron or a white blood cell. Mistakes that arise from reading the wrong set of instructions can lead to developmental defects, cancer and immune disorders. Richard Jenner’s lab is working to understand how each cell “knows” which specific set of instructions in the DNA they should follow. They have identified novel ways in which regulatory proteins compete to dictate cell identity and discovered new forms of regulatory RNA that suggest new roles for DNA’s sister nucleic acid in the cell.

**Key references:**

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Dr Chakraverty promoted to Professor

Ron Chakraverty is a leading bone marrow transplant clinician scientist. His research group focuses upon the mechanisms underlying donor immune responses that occur following bone marrow transplantation and that lead to either to beneficial anti-tumour responses (‘graft-versus-leukaemia’ effects, GVL) or to host injury (graft-versus-host disease, GVHD). This information will be used to drive future clinical innovations with the aim of separating GVL from GV. His group has shown that bone-marrow derived antigen-presenting cells within tissues are key protagonists in driving GVHD through their capacity to activate or ‘license’ donor T cells in situ. In contrast, non-bone marrow-derived cells have the opposite effect and diminish donor immune cell reactivity by inducing a state of cellular ‘exhaustion’. A key focus now is to define molecular mechanisms underlying both licensing and exhaustion, with the intention of identifying targets for therapeutic intervention.

**Key references:**
Flutter B. et al., Nonhematopoietic antigen blocks memory programming of alloreactive CD8+ T cells and drives their eventual exhaustion in mouse models of bone marrow transplantation. The Journal of Clinical Investigation 120, 3855 (Nov 1, 2010).

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Tim Meyer promoted to Professor

Over the past 10 years at UCL, Tim Meyer has established a nationally recognised research based clinical practice in Hepatocellular and Neuroendocrine Cancer at the Royal Free Hospital. He has led national trials in both diseases and integrated translational research into clinical practice. His laboratory work in the Cancer Institute has focussed on the analysis of circulating tumour cells (CTCs) and his group was the first to demonstrate the presence and prognostic utility of CTCs in Neuroendocrine Cancer. He is now exploring the potential of CTCs as pharmacodynamic markers in the context of drug development and the extent to which CTCs can direct therapy and anticipate the emergence of drug resistance.
He is currently the Cancer Director for the NIHR UCLH Clinical Research Facility and joint lead for the UCL Experimental Cancer Medicine Centre.

**Key references:**
UK-Japan Workshop
Neural Epigenetics: From Mechanisms to Disease
26-27 February 2013

Prof Paolo Salomoni was one of the invited speakers at the UK-Japan workshop “Neural epigenetics: from Mechanisms to Disease”, organised in Tokyo by the British Embassy and the RIKEN Brain Science Institute (BSI). The neural epigenetics field is a very exciting area of research spanning from basic to clinical research. In this respect, it is becoming clear that epigenetic mechanisms are involved in the pathogenesis of neurological/neurodevelopmental syndromes and brain cancer, hence the growing interest of the pharmaceutical industry in epigenetic drug discovery. The British Embassy/RIKEN BSI workshop was a forum for researchers to increase interactions between UK- and Japan-based institutions in the area of neural epigenetics. The scientific programme included leading experts in the field, such as Adrian Bird (Edinburgh, co-organiser), Antonella Riccio (LMCB), Andrea Brand (Cambridge), Anthony Isles (Cardiff), Yukiko Gotoh (Tokyo), Adrian Moore (organiser, RIKEN BSI), Tadafumi Kato (RIKEN BSI), and others. The two-day meeting included an open seminar and a visit to the RIKEN campus. Furthermore, visits to other RIKEN centres throughout Japan were arranged for Salomoni (RIKEN-Kobe) and other UK-based speakers. Finally, a group of junior researchers from the UK participated in a tour through RIKEN Institutes in Japan, which provided them with a flavour of research at this leading Japanese research institution. A follow-up meeting is being planned for 2014 at a UK-based institution. Exciting times lie ahead for UK-Japan cooperation in this area of research.

Glioma Club meeting

Prof Paolo Salomoni (Samantha Dickson Brain Cancer Unit, UCL Cancer Institute) jointly with Prof Silvia Marino (Queen Mary University) are organizing the 4th Glioma Club, a one-day meeting that will be held at the National Hospital for Neurology and Neurosurgery, 33 Queen Square, London WC1N 3BG on 14th October 2013. The Glioma Club is sponsored by The Brain Tumour Charity, the British Neuro-oncology Society (BNOS), UCL IQPath and Abcam.

The main objective of this meeting is to bring together researchers and clinical scientists working on various aspects of the origin, genetics, neuropathology, diagnosis, imaging and treatment of these tumours. As in the previous years, the meeting will be a mix of update talks on exciting on-going projects and two keynote international speakers, Rainer Glass (University of Munich, Germany) and Jacques Grill (Institut Gustav Roussy, Paris, France). This year’s meeting will also include a Junior Forum, where PhD students will present their research in short talks and the best presentation will be awarded a prize, sponsored by BNOS.

SPOTLIGHT

Dr May Elbanna, a clinical oncologist who is intrigued by the science behind her daily profession, has come from Egypt to enroll in the MSc Cancer programme at the UCL Cancer Institute. She says “It will not only provide me with knowledge about the science that is shaping my specialty, but it will also provide me with hands on lab experience in an amazing research hub where the knowledge we are embracing in the clinic is being created. I believe this experience will qualify me to do a PhD within a translational research context that is focused on drug development. This will help me evolve into the clinician scientist I want to be, who can confidently move between the bench and the clinic and get the most of the two worlds.” May has recently won a Fulbright Scholarship to begin her PhD studies in the USA upon completion of the MSc Cancer Programme.
Improving the outcome for patients with Cervical Cancer

The standard treatment for cervical cancer (not amenable to surgery) is daily radiotherapy and concurrent weekly cisplatin chemotherapy. However despite this treatment almost 50% of the patients will experience a relapse and most will die from their disease. Dr Mary McCormack (UCLH and UCL Cancer Institute) conducted a small trial of weekly chemotherapy with carboplatin and paclitaxel for 6 weeks followed immediately by the standard chemotherapy and radiotherapy. This new treatment was very well tolerated and the results are promising. Cancer Research UK has therefore funded a large international randomised trial, led by Dr McCormack, to test whether this new longer course of treatment will improve the cure rate for women with cervical cancer. The trial is currently open to recruitment at UCLH and other centres in the UK. Meanwhile the scientists in the Cancer Institute working for the Debbie Fund continue to make headway in developing antibody therapy to offer hope to those women who experience a recurrence of their cervical cancer.

Key reference:

Sugar makes cancer light-up in MRI scanners

Dr Simon Walker-Samuel of the UCL Centre for Advanced Biomedical Imaging (CABI), in collaboration with researchers at the Cancer Institute, reports on a new technique for detecting cancer by imaging sugar consumption with magnetic resonance imaging (MRI). This technique, ‘glucose chemical exchange saturation transfer’ (glucoCEST), is based on the fact that tumours consume more glucose than normal tissues for sustained growth. GlucoCEST uses radio waves to magnetically label glucose in the body, causing tumours to appear bright on MRI images. The breakthrough could provide a cheaper, safer and simpler alternative to standard radioactive techniques, enabling tumours to be imaged in greater detail.

Image: The uptake of glucose in a colorectal tumour xenograft model. ‘Hot’ colours at the outside of the tumour show increased uptake of glucose, compared with ‘cold’ regions in the centre.

Key reference:
Biological therapy with cediranib improves survival in women with recurrent ovarian cancer

Women with ovarian cancer that has recurred after chemotherapy have survived for longer after treatment with a biological therapy called cediranib, according to new results to be presented by Prof Ledermann at the 2013 European Cancer Congress (ECC2013).

Cediranib, which is taken in pill form, is a tyrosine kinase inhibitor, blocking the activity of vascular endothelial growth factor (VEGF) receptors, involved in formation of tumour blood vessels, essential for tumour growth. Professor Jonathan Ledermann, Professor of Medical Oncology at UCL Cancer Institute, presented first results from ICON6, an international randomised, double-blind, academic clinical phase III trial of cediranib.

“In women whose ovarian cancer had been treated with platinum-based chemotherapy together with cediranib given during and after the chemotherapy, we found that the time before the tumour started to grow again was extended by an average of 3.2 months. This sounds like a modest increase but represents about a 30% improvement, with overall survival also increased by a similar amount, to an average of 2.7 months over a two-year period of follow-up,” he said.

These latest results show that cediranib in addition to chemotherapy increased the time before the disease progressed from 9.4 to 12.6 months over a period of two years, and it extended overall survival from 17.6 to 20.3 months.

“These are ground-breaking data,” said Prof Ledermann. “Cediranib is the first oral VEGF tyrosine kinase inhibitor that has been shown to delay tumour progression and improve overall survival in recurrent ovarian cancer. It is simple to give for a prolonged period and in most patients it is well-tolerated.” Adverse side-effects included high blood pressure, diarrhoea and fatigue.

A total of 456 patients whose ovarian cancer had recurred were enrolled in the trial in 63 centres from the UK, Canada, Australasia and Spain.

“ICON6 has a three-arm design in which the effect of cediranib given with chemotherapy and continued as maintenance can be compared with standard chemotherapy. This is the first trial to have demonstrated a benefit of concurrent cediranib with chemotherapy, as well as demonstrating an additional benefit with maintenance cediranib,” he said.

An increased survival time of nearly three months is significant in this group of patients. Prof Ledermann explained: “In previous ovarian cancer trials any improvement seen with each new treatment has been incremental. Survival has improved through sequential use of drugs. Trials showing an improvement in overall survival are uncommon. Cediranib produces an incremental improvement in progression-free survival and an incremental improvement in overall survival. Although the average improvement in overall survival is 2.7 months, some patients will see a much more substantial benefit.”

Key references:
Abstract no: LBA10. “Randomised double-blind phase III trial of cediranib (AZD 2171) in relapsed platinum sensitive ovarian cancer: Results of the ICON6 trial”.
ICON6 is an academic trial run by the UK Medical Research Council’s Clinical Trials Unit, funded by Cancer Research UK, and supported by AstraZeneca. Cediranib is an investigational compound manufactured by AstraZeneca and is not currently approved for use in the European Union or United States.

Elucidating the Genetic Basis of Chondrosarcoma

The UCL Cancer Institute Sarcoma Research Group in collaboration with the Sanger Institute performed exome sequencing of 50 chondrosarcoma, the second most common primary bone cancer. They report that the Indian Hedgehog pathway is activated through mutations in 20% of chondrosarcoma. Drugs that target this pathway are already used to treat other cancer types, and could be candidate treatments for patients with chondrosarcoma.

The team also discovered that COL2A1, a gene central to the production of cartilage, is mutated in nearly 40% of chondrosarcoma. This discovery may act as an important way to diagnose this type of rare cancer, thereby improving patient care.

Key reference:
Haemophilia A gene therapy treatment licensed to BioMarin Pharmaceutical Inc.

BioMarin Pharmaceutical Inc. licensed the novel technology for gene therapy of haemophilia A developed in the laboratory of Prof Amit Nathwani, of the UCL Cancer Institute and the Katharine Dormandy Haemophilia Centre. This technology show great promise as it uses the same vector platform that proved to be successful in patients with severe haemophilia B, a related condition. In the ground-breaking haemophilia B trial, pioneered by the Nathwani group, long term correction (> 3 years) of the bleeding diathesis was achieved following a single administration of vector.

Haemophilia is an attractive target for gene therapy as factors levels in the blood serve as good biomarkers, relatively low factors levels are required for a clinically important benefit in severely affected patients and the current standard of care of intravenous infusions three times a week is highly demanding, associated with significant complications and prohibitively expensive (£170,000/patient/year). The new technology developed for haemophilia A is highly potent; enabling high level expression of coagulation factor VIII (FVIII) without any toxicity in preclinical studies. Therefore, this technology has the potential to change the treatment paradigm for Haemophilia A, the most common inherited bleeding disorder, resulting in significant improvement in the quality of life. Savings resulting from the reduction in the need for factor concentrates amount to >£1.5M so far in the haemophilia B trial.

UCL Cancer Institute and Biomarin each bring distinct strengths to the partnership to fully explore the potential of gene therapy as a life-saving treatment for people with haemophilia. Continued success with haemophilia will have wider impact, leading ultimately to the development of gene therapy for both metabolic disorders and application to cancers. BioMarin, a global biotech, has a strong focus on developing first-to-market or best-in-class therapies, making a real difference to the lives of individuals with rare conditions.

Discovering a potential therapeutic target for Ewing’s sarcoma

Ewing’s sarcoma (ES) is the second most common bone tumour in children and adolescents. Most patients with EW have a poor outcome with five-year survival rates of only 20-25%. Thus, there is an urgent need to identify the drivers of metastasis in ES and novel therapies that will specifically target metastases in these patients. Ariadna Mendoza-Naranjo, collaborating with Poul Sorensen in Vancouver, have found that high expression of ERBB4, a member of the epidermal growth factor receptor family, is directly linked to metastasis and reduced survival of patients with ES. Inhibition of ERBB4 decreases tumour cell growth, migration and invasion, sensitisizes metastatic/chemoresistant ES cells to chemotherapy and reduces metastasis formation in experimental models of the disease. This finding that ERBB4 drives cancer progression and chemo-resistance in ES, and that inhibition of ERBB4 is linked to reduction of metastasis suggest that therapeutic targeting of ERBB4, alone or in combination with other agents, could suppress ES metastatic potential.

Ariadna is currently investigating effects of ERBB4 targeted therapies alone, or combined with other drugs. For children with high-risk ES, intensive combination chemotherapy is currently given, which can have significant long-term toxicities. Since anti-ERBB4 inhibitors are specific agents, they are less toxic than chemotherapy, potentially reducing side effects and allowing for lower doses of chemotherapeutic agents to be used.

Key reference:
New insights into the mechanism of action of immune-modulatory antibodies in cancer; expanding effectors whilst killing the regulators.

Immune-modulatory antibodies are a new class of potent anti-cancer therapy. Targeting inhibitory receptors on T cells, such as CTLA-4 and PD-1, acts to release the brakes on immune cells, promoting tumour regression and durable responses in patients with advanced cancer.

Work led by the Sergio Quezada and Kari Peggs groups at UCL Cancer Institute, in collaboration with the Allison lab at MD Anderson Cancer Center, recently demonstrated a new mechanism of action for antibodies targeting the immune modulatory receptor CTLA-4. The work demonstrates that the activity of anti-CTLA-4 antibodies relies not only on potentiating effector lymphocyte (Teff) function, but also on the selective depletion of regulatory T cells (Treg) within the tumour. Remarkably, Treg depletion is driven by a particular subset of tumour infiltrating macrophages expressing a specific receptor (FcgRIV) on their surface.

These data have significant translational implications as it suggests that tumours infiltrated by these cellular subsets are likely to be good targets for anti-CTLA-4 therapy, illustrating the importance of specific features of the tumour microenvironment in dictating the final outcome of immune modulatory therapies.

Key reference:

Small but mighty: a crucial role for microRNAs in the origin of blood stem cells

Haematopoietic stem cells (HSCs) are required to maintain the blood and immune systems throughout life. However, HSCs are first generated in the embryo by budding from a specialized endothelium lining the wall of some arteries. Understanding how this blood-forming endothelium is generated during embryogenesis will inform efforts to produce patient-specific HSCs for stem cell replacement therapies. It has long been proposed that blood and endothelial cells have a common cellular ancestor, termed a hemangioblast, although these cells have proven elusive in mammals. However, lineage-tracing studies on the more tractable frog embryo have enabled the identification of a population of hemangioblasts that give rise to HSCs. Using this model system Rachel Nimmo in the laboratory of Tariq Enver discovered an essential role for small regulatory RNAs, called microRNAs in the development of blood stem cells and identified a single microRNA, miR-142-3p, that is required for the formation of hemangioblasts. This microRNA was found to have a crucial role at the top of the hierarchy of genes responsible for switching on the blood and endothelial cell fates during development. These findings illustrate that though they may be small, microRNAs are mighty players in the formation of blood stem cells.

Key reference:
Discovering new cancer-specific Epigenetic and Genetic Alterations

Cancer is a disease of the genome caused predominantly by mutations and epimutations. While mutations result in changes to the DNA sequence of the cancer genome, epimutations only result in changes to chemical marking of the cancer genome (e.g. through DNA methylation). Both changes are known to contribute to the activation of cancer promoting processes. By comparing such epimutations in cancers with and without specific mutations, Cancer Institute PhD student Paul Guilhamon (supervisor Stephan Beck) and colleagues discovered a novel targeting mechanism that explains why certain genes acquire more epimutations in cancers with the specific mutation. As epimutations are reversible and druggable, the new mechanism provides a novel target for cancer therapy.

Key reference:

Selected recent Funding awarded

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