Securing investment to deliver research goals

This has been an exciting and successful year for the Manchester Cancer Research Centre (MCRC) with evolution of our strategic partnership coming to fruition.

Our overarching goal is to establish a research centre ideally placed to capitalise on the unique opportunities in cancer research and to translate these into patient benefit in order to drive a more personalised treatment approach – Manchester is at the vanguard to deliver this goal.

Over the last six years, we have demonstrated an impressive track record of partnership and fostering of laboratory-clinical collaboration, established a robust infrastructure and facilities for high quality research, and brought together outstanding leaders. The new MCRC building is due for completion in summer 2014 and is testament to the commitment of our partners. The state-of-the-art laboratories will provide the means to expand our research capacity and build strengths in key priority areas, enabling us to proceed apace and deliver our research vision.

This year we agreed an exciting plan to attract and recruit 20 internationally outstanding investigators to Manchester focusing on six identified priority areas: personalised medicine and experimental therapeutics, radiotherapy-related research, lung cancer, melanoma, women’s cancers and haematological malignancies. This £30 million investment underpins our long-term strategy in personalised medicine.

In the past 12 months, we have also been very successful in securing funding through a number of major competitive bids. We became a national Cancer Research UK and Engineering and Physical Sciences Research Council Cancer Imaging Centre in partnership with the University of Cambridge. This represents a tremendous boost for imaging and builds on previous investment in the Wolfson Molecular Imaging Centre. In addition, we have been awarded £12.8 million from the Higher Education Funding Council for England (HEFCE) UK Research Partnership Investment Fund to part fund the construction and equipping of the new MCRC research building.

The MCRC will continue to build for the future and we have already developed plans for a research biopsy suite, which will facilitate the acquisition of pre- and post-treatment repeat biopsies. There are also plans for a genomic biomarker laboratory to complement our world-class blood borne biomarker capabilities. In addition, we will enhance our informatics capability and further build strengths in cancer screening and prevention. The highlights featured in this Progress Report demonstrate our progress on an exciting and continuing journey in cancer research.
Countdown to completion of new research laboratories

Construction of the new MCRC building has achieved key project milestones over the past 12 months and is on target for completion in summer 2014.

The first milestone was marked by a special breaking the ground event in November 2012, where cancer survivors Stan Parker, aged 73, and nine-year-old Amber Irvine, joined MCRC partner representatives to dig the first piece of ground and signal the start of construction. Amber was also invited to open the “Networks” garden for Cancer Research UK at RHS Tatton, which was inspired by plans for the new centre.

Within two months of the first piece of ground being excavated on site, the access road had been completed and an on-site Visitor Centre had been opened, providing the local community and visitors with the chance to find out more about the MCRC and the progress of the project. Within four months, the structural walls of the new building were emerging from the foundations. Over the summer, work on site focussed on completing construction of the structural steel frame and the installation of the concrete floors. During the autumn, work on the external façade will continue as the striking elevations take shape.

The new research building will accommodate 250 staff - providing space for an additional 150 University researchers on site and relocating around 100 of The Christie’s clinical trials support staff. With less than a year until the building is complete and ready for use, work on site is progressing well. The ‘More Tomorrows’ campaign was launched by MCRC partner organisations – Cancer Research UK, The Christie NHS Foundation Trust and The University of Manchester – to deliver the remaining funding commitment needed for the new building and other awards have also been received towards the target. The University of Manchester received £12.8 million funding from the HEFCE UK Research Partnership Investment Fund (UKRPIF), which will go towards construction of the building and vital specialist research equipment.

“Cancer research has come a long way in the last 40 years but there are still advances to be made in early diagnosis and treatment. The new research building brings together expertise in cancer biology, drug discovery and clinical trials on one site and provides a state-of-the-art environment essential for future breakthroughs that have the potential to improve patient treatment and outcomes,” said MCRC Director Professor Nic Jones.
New recruits will strengthen expertise base

Strategic recruitment aligned to priority research themes across the Manchester Cancer Research Centre partnership continues to strengthen the expertise base and leadership essential for advances in cancer research.

This year saw the launch of a £30 million global recruitment drive to bring 20 of the world’s best cancer experts and their teams to Manchester. Jointly funded by The University of Manchester and The Christie NHS Foundation Trust, the recruitment bid will attract around 100 new staff with clinical, research and teaching expertise in personalised cancer therapy, radiotherapy lung cancer, melanoma, women’s cancers and haematological oncology. Around 13 of the academic posts and their associated teams will have a clinical base at The Christie as well as a University role. The remaining positions will be based within the University’s Institute of Cancer Sciences and the CR-UK Manchester Institute.

“This investment will add to the high-calibre scientists who form part of the MCRC – many of whom will be based at our new state-of-the-art research building due to open in summer 2014. It will bring even more researchers and specialists together in Manchester enhancing our range of expertise and helping to translate research into treatments which can benefit patients,” said MCRC Director Professor Nic Jones.
Professor Kostas Kostarelos, a world-leading academic in nanomedicine, joined The University of Manchester this year bringing with him his Nanomedicine Laboratory. Along with his 15-strong team of scientists, he will explore the medical potential and applications of graphene, the world’s thinnest, strongest and most conductive material, which was first isolated by Manchester scientists. With research interests focussed on neurodegenerative disorders and cancer, Professor Kostarelos’ team will help drive the development of nano-technology and applications in both disease areas. The Nanomedicine Lab he founded is investigating novel gene therapies, clinical use of stem cells, advanced delivery systems for radio- and chemo-therapeutic agents against cancer and engineering smart vector systems for imaging and therapeutics.

Professor Belinda Borrelli is a leading clinical and health psychologist who specialises in motivating health behaviour change, including treatments to help smokers give up. She is working in the University’s School of Psychological Sciences as a Visiting Professor. Her work includes developing and testing treatments that motivate smoking cessation, encourage patients to take their medication and follow medical plans and treatments in chronic diseases such as asthma and cystic fibrosis. Professor Borrelli is also known for conducting high quality, longitudinal research in inner city, low income and understudied populations. As a Visiting Professor, she will give lectures and work with researchers on a part-time basis in addition to her current roles in the US.
Biomarker research thrives on collaboration and clinical contribution

Research in Manchester continues to focus on driving the translation of laboratory findings into the clinic, as exemplified by the collaborative achievements of the CR-UK Manchester Institute's Clinical and Experimental Pharmacology (CEP) Group and The Christie's early phase Clinical Trials Unit.

This year, research within CEP, lead by Professor Caroline Dive, has focussed on the expansion of clinical trials in lung cancer patients incorporating circulating biomarkers and the enumeration and molecular analysis of circulating tumour cells (CTCs), in close collaboration with medical oncologist Dr Fiona Blackhall from the University’s Institute of Cancer Sciences.

CEP’s lung cancer trial portfolio has been expanded to evaluate newly validated biomarker assays and in particular has seen the initiation of new collaborations within the Cancer Research UK Experimental Cancer Medicine Centre (ECMC) network. In collaboration with University researcher Dr Corinne Faivre-Finn, CEP is examining the impact of radiotherapy on CTC numbers in the CONVERT and MEKRT trials in patients.
with non-small cell (NSCLC) or small cell lung cancer (SCLC). A significant highlight for CEP this year was the development of a unique patient CTC-derived mouse model of SCLC that will allow MCRC researchers to test new treatments and better understand the biology of this disease. Exciting data are also emerging in collaboration with Dr Phil Crosbie, from the University’s Institute of Cancer Sciences, on the detection of CTCs in the pulmonary vein of patients with resectable NSCLC.

The CEP biomarker portfolio has expanded to include a Nucleic Acids Biomarkers (NAB) team led by CEP Deputy Dr Ged Brady. Over the last year, the NAB team has established a range of circulating biomarker assays optimised to address the processing needs of upcoming multi-site clinical trials. A major focus of the NAB team has been to establish routine molecular analysis of CTCs that complements and expands on CEP’s CTC analytical approaches. They have recently established a single cell isolation and whole genome amplification approach applicable to individual CTCs. “The single cell isolation approach has led to the identification of mutations found in CTCs and not in healthy white blood cells from the same patient. This approach is now being adapted to allow next generation sequencing of a large number of clinically relevant tumour ‘driver’ genes,” said Dr Brady.

Working with the Translational Angiogenesis Group led by Professor Gordon Jayson from the University, CEP aims to develop biomarkers that can predict which patients are most likely to benefit from anti-angiogenic therapies, such as Avastin. This year, analysis of data from ovarian cancer patients in the ICON7 phase III trial has identified Ang1 and Tie2 as candidate predictive biomarkers for Avastin. “These results translate to a clinical decision strategy that Avastin should be added to conventional chemotherapy for patients presenting with high Ang1 and low Tie2 levels and also suggests that patients with high levels of both should not be given Avastin,” explained Professor Dive. Further prospective trials are now under discussion to confirm these findings along with research to investigate the molecular mechanisms responsible.

Strong links with industry continue with the CEP/AstraZeneca Serological Alliance and, following renewal
of the Alliance in September 2012 with £3.1 million of funding secured, a more diverse range of biomarkers will be investigated. The highlight of 2012 was the award to Professor Dive of the prestigious Pasteur-Weizmann/Servier International Research Prize for her laboratory’s research on non-invasive biomarkers to aid the treatment of cancer patients. “The award will support our translational cancer research into specific markers of CTCs and also our work in clinical trials to monitor disease and response to novel drugs,” said Professor Dive.

Over the past year, the early phase Clinical Trials Unit at The Christie NHS Foundation Trust has continued to work closely with CEP to drive biomarkers into clinical evaluation and has also refined processes to facilitate the ongoing expansion of its trials portfolio.

Following the successful award of £4.5 million funding from the National Institute for Health Research (NIHR) in 2012, The Christie NIHR Clinical Research Facilities Showcase was held in April 2013 to celebrate successes and share highlights from ongoing work. It was attended by the NIHR Chief Executive Dr Jonathan Sheffield, collaborators from all the Manchester Clinical Research Facilities as well as academic and commercial partners. “Identifying opportunities to build integrated clinical research programmes through collaboration is key to making advances in cancer treatment.” said Dr Andrew Wardley, Clinical Director of The Christie’s early phase Clinical Trials Unit.

This year saw a major achievement in adoptive cell transfer (ACT) immunotherapy for melanoma with the first patient being treated in the summer by the Clinical and Experimental Immunotherapy Group, led by Professor Robert Hawkins from the Institute of Cancer Sciences at The University of Manchester. During ACT, lymphocytes from the patient’s tumour samples (tumour infiltrating lymphocytes - TILs) are collected and analysed to identify the ones with the most antitumour activity – ‘young’ TILs. These are then grown in the laboratory before being infused back to the patient. “We plan to offer Young TIL therapy to suitable patients and will be carefully monitoring
outcomes to help make this a routine treatment for melanoma patients. Once established here, we aim to refine the process to improve tolerability, so it can be offered to more patients, and potentially improve its effectiveness,” said Dr Wardley.

In the past 3 years, over 1,300 patients have participated in early phase clinical trials at The Christie, which generates, and requires co-ordination of, a vast amount of data from various sources. This year saw the launch of ResearchTools – a web-based application that provides a central ‘one-stop’ resource for all non-clinical study related information, which will reduce administration and expedite data-sharing and collaboration. A new out-of-hours system has also been introduced to ensure patients on clinical trials are managed safely by having all appropriate information readily available to facilitate medical decisions. The early phase working group has produced valuable data on referral patterns for patients entering early phase clinical trials, which will enhance targeting of relevant geographical areas. In addition, patient pathways are being developed for fresh tissue biopsies across the MCRC, led by ECMC Project Manager Charlotte Minter, which will enable faster and more streamlined recruitment.
Two early projects within the DDU have now progressed into the next phase of drug discovery, lead optimisation, which is a major achievement. “We have surpassed the initial target set in our five-year plan of having one project in lead optimisation phase within five years. Now, with 6 months of that plan remaining we already have two projects in this phase, which is very encouraging and a good indication of our progress,” explained Dr Donald Ogilvie who heads the DDU. As a result of that progress, the team are currently looking to partner these projects to accelerate potential clinical development and are filing patents to protect their intellectual property rights. Other projects within the portfolio are also progressing well, ensuring a sustained pipeline of potentially active compounds for investigation.

This year, two ground-breaking agreements have been signed with AstraZeneca allowing DDU scientists unprecedented access to a massive library of chemical structures with the potential to yield active anticancer agents for further development. “To our best knowledge, this is the first time that a pharmaceutical company has given an external partner direct access to their high-throughput screening collection. The agreements demonstrate that the value of the work we are doing is being recognised by external organisations and is yielding new opportunities for collaboration,” said Dr Ian Waddell, Head of Bioscience at the DDU.

In the first agreement, AstraZeneca will provide access to chemical starting points, which DDU scientists will then develop to a defined stage. In the second agreement, the team will develop compounds that target a key protein involved in DNA damage response using preliminary compounds provided by AstraZeneca. In return, AstraZeneca will have first rights of refusal on any promising drug leads that are identified, while Cancer Research Technology – the commercial arm of Cancer Research UK – will receive royalty payments when the project reaches certain milestones.

Deals with other partners are also in progress to ensure that projects can be taken forward into clinical development and eventually to cancer patients.

Over the past 12 months, there has been an increased focus on building a wider portfolio of drug discovery targets. This has led to the development of a collaborative project with a National Institutes of Health (NIH) group in the US, working on validation of DNA repair targets. Internal collaborations with local groups continue to drive a drug-hunting culture within the MCRC and ongoing projects include work with Dr Tim Somervaille who leads the Leukaemia Biology Group, and Dr John Brognard, leader of the Signalling Networks in Cancer Group at the CR-UK Manchester Institute. Working with Dr Somervaille, DDU identified and synthesised chemical analogues able to target LSD1, an essential regulator of leukaemic stem cells, which prevents differentiation and programmed cell death and therefore represents a rational therapeutic target. This year, they identified the cell surface marker CD86 as a sensitive surrogate biomarker of LSD1 inhibition and have now developed a new rapid assay for LSD1 inhibition.

In July, the DDU successfully completed Cancer Research UK’s first five-yearly review of its activities. “This is a comprehensive review over two days of site...
visits by a panel of internationally-recognised experts. We received very positive feedback on our progress to date and future plans, which validates our strategy for driving drug discovery and development,” says Dr Ogilvie.

Several research highlights have been featured in peer-reviewed publications this year, one of which exemplifies the nature of DDU research where, despite encouraging initial data, the approach was not validated and the project was closed. Tyrosyl-DNA phosphodiesterase 2 (TDP2) is an enzyme involved in topoisomerase-mediated repair of DNA damage and may be involved in resistance to anticancer drugs, such as etoposide, that work through topoisomerase inhibition by etoposide.

"From a clinical perspective, developing selective agents that work through TDP2 to overcome drug resistance may be valuable. Using a high-throughput screening programme, we successfully identified two series of chemical compounds as the first reported sub-micromolar and selective inhibitors of TDP2,” explained Dr Ogilvie. However, further testing showed that these inhibitors had shortcomings that made them unsuitable for progression to clinical use.

With 29 scientists now in the group, there has also been a major investment in bioinformatics in the past year. DDU’s Phil Chapman is based within the Bioinformatics group at the CR-UK Manchester Institute in an infrastructure that supports his work. “Dr Chapman provides the ideal bridge within DDU by combining his skills in bioinformatics, including coding and programme development, with scientific understanding of the drug discovery process. Having him on board has transformed the way we undertake target validation,” explained Dr Waddell. DDU are now able to undertake more comprehensive mining of existing large datasets to identify new targets - a tactic that is already yielding results.

One approach is to identify naturally mutated genes within a pathway essential for cell survival and then find a homologue of that gene which has a similar function. Deliberately targeting the homologue makes the cell vulnerable to being killed by anticancer agents – collateral vulnerability. Target validation studies with Dr John Brognard are now underway using genes identified through a collateral vulnerability sweep in non-small cell and small cell lung cancer.

“As the DDU has matured, we have developed a way of working and a simple infrastructure that facilitates our research. This allows us to be very proactive and quickly take advantage of new opportunities as they arise. The past 12 months have produced encouraging results which we will build on over the next year,” said Dr Ogilvie.
A year of results for radiotherapy-related research

Radiotherapy-related research (RRR) continues to be an area of priority for the Manchester Cancer Research Centre and several important studies have reached key milestones this year.

This includes a trial of whole brain radiotherapy in combination with erlotinib, in patients with advanced non-small cell lung cancer (NSCLC) that has spread to the brain. Erlotinib targets epidermal growth factor receptors (EGFR) on cancer cells and blocks the signals that promote cancer growth and division, and may increase tumour sensitivity to radiotherapy.

"Whole brain radiotherapy is the current treatment standard for patients with NSCLC and brain metastases, so it was important to assess whether combining the two approaches could improve the effectiveness of treatment without increasing toxicity," explained Dr Corinne Faivre-Finn, one of the trial investigators from the University’s Institute of Cancer Sciences. Although the TACTIC study showed that there was no advantage for the combination in unselected patients, it paves the way for future studies focussing on evaluating the role of radiotherapy combined with erlotinib in patients with EGFR mutations.

Recruitment to academic trials in limited-stage small cell lung cancer (LS-SCLC) is a challenge due to the decrease in incidence of this disease and the lack of widespread adoption in the UK of concurrent...
chemo-radiotherapy, the gold standard treatment in good performance status SCLC. Dr Faivre-Finn is Chief Investigator for the CONVERT trial to establish the optimal chemo-radiotherapy regimen in this patient population. Thanks to international participation, the trial successfully completed accrual this year with a total of 540 patients recruited from 96 sites in nine countries.

Final results of the international, multicentre FIZZ study – one of the first trials run and sponsored by The Christie’s Clinical Trials Unit – were published this year. “We knew that radioimmunotherapy can achieve high response rates and prolonged remission in previously treated lymphoma patients but we had very little data about its effectiveness in untreated patients. The FIZZ study validates radioimmunotherapy as an effective and well-tolerated regimen for both previously treated and untreated follicular lymphoma,” said trial lead Professor Tim Illidge from The University of Manchester, who leads RRR at the Manchester Cancer Research Centre.

Another highlight over the last 12 months is the completion of the DREAM study, which used a pioneering study design to evaluate two biological therapies for rectal cancer in combination with radiotherapy. The innovative design was based on an idea developed by Dr Mark Saunders from The Christie, Chief Investigator for the study. The DREAM study has also provided a valuable opportunity for associated translational research with Professor Caroline Dive’s Clinical and Experimental Pharmacology Group at the CR-UK Manchester Institute.

Viruses are important in the aetiology of many cancers and there has been a dramatic rise in human papillomavirus (HPV)-associated head and neck cancers. There are different types of HPV and some are thought to have a poorer outcome following radiotherapy than others. Work over the past year by University researcher Professor Catharine West and colleagues indicates that the poor prognosis associated with some HPV genotypes in cervical carcinoma are not due to differences in radiosensitivity.

This year has also seen the implementation of a new model of working for research radiographers using three state-of-the-art linear accelerators rather than having one research-dedicated machine within the Wade Radiotherapy Research Centre at The Christie. “Carrying out research across different accelerators provides distinct advantages. The new model allows more department members to become involved in research and facilitates a more fertile research environment,” said Professor Tim Illidge.

The MCRC’s RRR group is one of only seven places in the UK to have secured National Institute for Health Research (NIHR) funding for an Academic Clinical Fellow. These prestigious NIHR Fellowships are only awarded to medically-qualified candidates who show outstanding promise for a career in academic medicine. In a joint agreement between the University and The Christie, support has also been secured to fund an additional post.

“Being able to attract the brightest and most promising doctors and scientists is key to being internationally competitive and is an important signal of our growing success within RRR. Over the past 12 months, we have seen some major trials come to fruition that have already yielded clinically important results. We are looking forward to seeing the results from the DREAM, CONVERT and other studies over the next year. The breadth and quality of RRR in Manchester is gaining growing recognition – evidenced by our ability to recruit and retain an increasingly high standard of researchers and scientists and to attract additional research funding,” said Professor Illidge.
Two sites, one strategy for imaging

A major achievement this year was the successful bid to establish a national cancer imaging research centre that formally links Manchester with the University of Cambridge.

The success of the joint bid secures £8.8 million funding for the Cancer Imaging Centre in Cambridge and Manchester (CMCIC) from Cancer Research UK and the Engineering and Physical Sciences Research Council (EPSRC).

Manchester and Cambridge will work as a single centre across two sites in a landmark collaborative venture that combines the expertise of both partners to strategically enhance cancer imaging research. “Cambridge has strengths in the development of new agents and preclinical imaging in cancer – particularly in magnetic resonance (MR) and hyperpolarised MR. Manchester has extensive experience in clinical trials and the development of clinical imaging techniques, such as imaging biomarkers. Combining these complementary skills creates one of the strongest imaging centres in the UK,” said Professor Alan Jackson from The University of Manchester, who leads clinical imaging at the Manchester Cancer Research Centre (MCRC).

The CMCIC will have a combined management structure with representation from both organisations and joint activities, including an annual summer school and scientific meetings. Many of the researchers...
will also spend time at both centres and most clinical trials will be run across the two sites, driving patient recruitment. Novel imaging methods developed in Cambridge are already being used at the MCRC on models developed at the Cancer Research UK Manchester Institute. “This is a mutually beneficial approach where we can use our models to validate their methods and their methods to investigate our models. Work on apoptosis tracers and death switch imaging has already begun,” said Professor Jackson.

A strategic decision has been made to focus on selected cancer types in order to develop and refine techniques that can be taken into clinical trials. Manchester is leading on brain and lung cancer, while Cambridge will focus primarily on breast and oesophageal cancer. Planned studies include those evaluating expression of cholesterol transporters in low grade brain tumours, as a potential early marker of tumourigenesis, and there will be a range of investigations in lung cancer. Around 50% of the work on the Manchester site will be on the development of markers for lung research and clinical trials.

As a result of the award, more resource is being channelled into the development of novel imaging methods to identify imaging signatures of tissue – tissue characteristics either in individual patients or within a single tumour that predict response, or failure to respond, to a particular treatment. “Our aim is to improve imaging technology to prospectively detect tumour-specific signatures and to correlate imaging signatures to tissue type, tissue subtype and histology. Assessment of these signatures in clinical trials will tell us whether they can be used to better tailor treatment to specific tumour characteristics that reflect the heterogeneity of tumours,” said Professor Jackson.

A major challenge in interpretation of imaging data is accuracy - different regions within each image have varying degrees of error. Current techniques use data averages to account for this variation but CMCIC will be taking a different approach by first identifying and selecting accurate parts of the image, and only using these areas for tumour classification. This will improve reproducibility and robustness of predictions of response. “We aim to use corrected measurements and multiple biomarkers along with evaluations of biomarker quality to fully interrogate the tumour tissue. Data from these studies will then be applied to standard imaging techniques to perform modelling,” said Professor Jackson.

Working with Cambridge will also open new opportunities in the development of innovative biomarkers using novel MR techniques, which employ
Hyperpolarised carbon. This allows detection of individual molecules and tracking of metabolic pathways in various cancer-related processes, such as apoptosis. Research themes include mechanisms of cancer (focusing on the use of imaging to measure cell death), hypoxia measurement and response to radiotherapy through development of agents that measure radiotherapy-induced damage. Preliminary data indicates that a tracer that appears to be taken up in areas of radiotherapy or chemotherapy-induced damage may be an indicator of early cellular response to treatment. “Combining this with hypoxia markers and tissue signatures will allow us to begin to build phenotypic risk maps for chemotherapy, radiotherapy and novel agents. It all goes towards advancing the development of personalised medicine but also our ability to apply imaging to mechanisms of cancer,” said Professor Jackson.

Preclinical imaging research continues to thrive within the MCR, with advances in both positron emission tomography (PET) and magnetic resonance (MR)-based approaches. PET imaging generates three-dimensional images of an injected PET radiotracer in the body. Biological molecules labelled with radioisotopes, such as 18-fluorine (18F), are widely used radiotracers and in the preclinical setting the use of PET imaging to study tumour biology and drug activity is growing. The need for more effective, robust radiotracers is developing, and this year, the radiochemistry group have developed a number of PET radiotracers for preclinical use. These include [11C]-temozolomide, which has previously proven difficult to manufacture in routinely usable yields. This new method generates radiochemical yields of approximately 26%, significantly higher than the 17% yield previously reported.

Other tracers recently developed for preclinical application are an [18F] tracer to image free radical damage to tissues during radiotherapy, [18F]-FAZA for hypoxia imaging, [18F]-FTHA for lipid metabolism studies and GE-180 an [18F]-labelled translocator protein tracer for modelling inflammation. The [11C]-temozolomide, GE180, free radical and [18F]-FAZA tracers have now been taken forward into initial validation studies for analysis of metabolites and uptake into tumours. “The ability to readily undertake metabolite analysis is a new initiative that is very important for our novel tracer development...”
pipeline. Over the past six months, we have set up the laboratory to enable us to carry out this research,” explained Professor Kaye Williams from The University of Manchester, who leads preclinical imaging at the MCRC.

Within the area of monitoring drug activity, studies have focused on the phosphoinositide 3-kinase (PI3K) pathway. Deregulation of the PI3K pathway is observed in a range of cancers and there are now several targeted inhibitors of the pathway being evaluated in the clinical setting, including the novel PI3K inhibitor GDC-0941. “Developing and validating radiotracers that can be used as imaging markers of drug activity is an increasingly important area of research. This year we have completed imaging studies with GDC-0941 that suggest the utility of 18F-FLT as an early response biomarker of inhibition of the PI3K pathway in tumours,” said Professor Williams.

Several novel anticancer drugs work by promoting apoptosis - tumour cell death. Studies have also been completed, in collaboration with Professor Dive’s group at the CR-UK Manchester Institute, that demonstrate integrated imaging and minimally invasive biomarker evaluation for analysing cell death. The preclinical ‘death-switch’ model that has been developed allowed the evaluation of a PET-based biomarker of apoptosis (18F-ML10) alongside a discovery programme for novel circulating biomarkers. “Our results showed increased tracer uptake in tumours undergoing apoptosis, compared with matched tumour controls and confirms the death-switch model as a robust and versatile tool for the discovery and validation of apoptosis biomarkers” said Professor Williams. Studies to similarly assess MR-based biomarkers of cell death in using this model system are ongoing.

An additional focus of work within preclinical MR-imaging this year has been on establishing a novel technique for measuring hypoxia in tumours. This will be used alongside established and validated techniques to assess tumour tissue integrity and perfusion using diffusion weighted and dynamic-contrast enhanced techniques respectively. “With the expanding portfolio of preclinical imaging-biomarkers being used within the MCRC across a range of studies coupled with the award of the imaging centre bid, there are exciting prospects for taking forward our research over the next 12 months,” said Professor Williams.
Lung cancer research takes a personal approach

Lung cancer is the most common and lethal cancer in the UK, with over 40,000 new cases and around 35,000 lung cancer deaths every year.

Improvement in patient outcome requires increased understanding of lung cancer biology driven by focussed and strategic investment. This year saw the launch of a nine year, £14 million, UK wide study - TRACERx (Tracking Cancer Evolution through Therapy) - involving MCRC researchers from The University of Manchester, The Christie and University Hospital South Manchester. Collaboration is a core element of TRACERx and CR-UK Manchester Institute Deputy Director Professor Caroline Dive will be working in tandem with Dr Fiona Blackhall from the University’s Institute of Cancer Sciences. The study will track how lung tumours develop and evolve as patients receive treatment to help determine how lung cancers mutate, adapt and become resistant to treatments.

Around 850 patients with non-small cell lung cancer (NSCLC) will be recruited with tumour samples collected before surgery, following surgery and subsequently if the disease recurs. Biopsies will be taken from different parts of each patient’s tumour and analysed along with DNA from circulating tumour cells in the blood to give a comprehensive genetic profile. The aim is to compare genetic changes within and between patients - recording how the treatment modifies the genetic profile of their disease and how this ultimately affects patients’ chances of survival. “TRACERx will provide an unprecedented insight into lung cancer and allow researchers to identify and understand the precise genetic makeup of lung cancers. The results will also lay the foundations for being able to offer patients treatment that is tailored to the specific genetic makeup of their cancer,” said Professor Dive.

Development of targeted therapies requires detailed knowledge of the underlying genetic alterations responsible for causing disease, however, the genetic basis is unknown for around half of NSCLC. Scientists at the CR-UK Manchester Institute were the first to use a new screening strategy to identify gene defects in tumour cells that represent possible drug targets. Using a targeted genetic dependency screen, they identified three kinases with gain-of-function mutations in lung cancer - FGFR4, MAP3K9, and PAK5. Targeted depletion of the mutated kinases prevented proliferation and inhibited downstream signalling pathways, leading to specific killing of the lung cancer cells. “Our study provides a new approach that can be personalised to an individual patient’s tumour and can identify potential drug targets. It enables us to begin mapping the most likely gene faults that encourage these cancers to grow,” said Dr John Brognard, lead author of the study published this year.

Dr Corinne Faivre-Finn, from the Institute of Cancer Sciences at The University of Manchester, is leading the CONVERT trial in patients with limited-stage small cell lung cancer (LS-SCLC), which aims to establish a standard chemo-radiotherapy regimen. The study successfully completed accrual of 540 patients from sites across Europe and Canada. Blood samples and tissue blocks have been collected as part of the study and will be analysed by Professor Dive and Dr Blackhall. “CONVERT is one of only two international phase III studies in the LS-SCLC setting worldwide linked to a biobank of blood and tissue samples. Results from the trial will give a more comprehensive insight into the effectiveness of treatment and facilitate optimisation of therapy for patients,” said Dr Blackhall.
With Manchester having the highest rates of smoking related deaths and amongst the highest rates of lung cancer incidence and mortality in the UK, early detection is pivotal to the MCRC’s lung cancer strategy. This focuses on identifying and stratifying those at highest risk using an integrated primary care electronic record, for the introduction of computed tomography (CT) screening and evaluating newer imaging methods, such as digital chest tomosynthesis, and is aligned to innovative smoking cessation programmes.

“This builds on an existing portfolio of high risk surveillance using autofluorescence bronchoscopy – a method used to detect cancerous cells that may not be visible using conventional bronchoscopy – and identifying primary lung cancer. We are also extending our work examining the full range of genes that are expressed and transcribed into RNA (the transcriptome) in early squamous cell carcinoma,” said Dr Richard Booton from the University’s Institute of Inflammation and Repair. In addition, there are plans to explore the basic mechanisms of lung cancer development in damaged lung via a multidisciplinary collaboration with colleagues in London, Cambridge and Bath. This will be facilitated by the expansion of the MCRC’s lung biobanking expertise to ensure a robust supply of linked benign respiratory samples in partnership with the Manchester Collaborative Centre for Inflammation Research.
New insight into the molecular biology of melanoma and potential therapeutic strategies

Developing realistic models of melanoma that accurately reflect the clinical situation is an essential step in improving understanding of melanoma and identifying targets for therapeutic intervention. Acral melanoma is a rare subtype of melanoma with distinct genetic and clinical features. Research this year using whole-exome sequencing and array comparative genomic hybridisation, which allows analysis of complex DNA variations, has identified two cell lines that share important characteristics with acral melanoma.

“We found mutations in oncogenes that have already been linked to melanoma, including BRAF and NRAS, but have also found mutations in cancer genes involved in DNA repair, not previously linked to melanoma, and in genes such as BRCA1 and BRCA2. Our study suggests that these cell lines may represent valuable tools to investigate the biology of this aggressive melanoma subtype,” explained Professor Richard Marais, Director of the Cancer Research UK Manchester Institute and head of the Molecular Oncology Group.

Whole genome and whole exome sequencing has also been applied to characterise the range of genetic alterations found in mucosal melanoma and results obtained in the last year indicate that mucosal and cutaneous melanomas are distinct diseases with discrete genetic features. The research also
suggests that different mechanisms are responsible for the development of these two diseases and that structural variations play a more important role in the development of mucosal compared with cutaneous melanoma. Similar genetic analysis techniques have been used to study uveal melanoma, the most common eye malignancy, which is fatal in around half of patients diagnosed. This has led to the identification of novel mutations and further insight into the genetics and biology of this disease.

The BRAF gene is mutated in about half of melanoma cases and drives tumour growth through activation of the MAP-kinase pathway. BRAF inhibitors, such as vemurafenib, have proven effective in tumours with mutated BRAF but development of resistance is common. “Our studies have identified a key pathway – the EGFR/SFK pathway – that mediates BRAF inhibitor resistance. Importantly, blocking BRAF in combination with EGFR or SFK prevented proliferation and invasion of resistant tumours, providing potentially effective therapeutic options for patients with drug-resistant BRAF-mutant melanoma,” explained Professor Marais.

Other studies have led to the discovery of a rare form of melanoma in children, primary melanoma of the central nervous system (CNS), and suggest that acquisition of mutations in the NRAS oncogene in CNS melanocytes is a predisposing risk factor for this disease. “Though rare, this childhood disease is devastating and we have developed powerful genetic models to gain further insight into the disease and to help develop therapeutic strategies for its treatment,” said Professor Marais.

The recent discovery of deregulations in the MAP-kinase pathway in melanoma has led to the development of new exciting therapy approaches. Dr Claudia Wellbrock’s laboratory at The University of Manchester is investigating how melanoma-specific faulty genes and proteins that are part of the MAP-kinase pathway control the growth and survival of melanoma cells in the body. Overall, the work in her laboratory aims to make existing treatments more effective.

Currently inhibitors targeting the MEK protein, a component of the pathway, are being evaluated in the clinic. However, the MAP-kinase pathway is important for all cells in the body, not only for melanoma cells. As a consequence, the high doses of MEK-targeting drugs that are required for a good response in melanoma cells lead to strong side effects in patients. Therefore, in order to improve therapies using MEK inhibitors the effectiveness of these drugs needs to be increased. This can be achieved by using MEK inhibitors in combination with other drugs whose action blocks vital survival factors specific to melanoma cells.

“An important step in the development of these combination therapies is the identification of such melanoma-specific survival factors. We identified the protein MITF as a crucial melanoma-specific survival factor and also discovered that targeting a protein called SMURF2 leads to the loss of MITF. As MITF is vital for melanoma cells, targeting SMURF2 makes melanoma cells more susceptible to the cancer-cell killing effects of MEK inhibitors such as selumetinib,” explained Dr Wellbrock. Removing SMURF2 from melanoma cells allowed selumetinib to kill melanoma cells more rapidly and at around 100-fold lower concentrations without affecting normal cells.

One of the reasons why melanoma is such an aggressive cancer is its early tendency to invade surrounding tissue. “We have made the striking discovery that MEK inhibition, although potently suppressing melanoma cell growth, induces increased invasiveness of melanoma cells. This is because a side effect of selumetinib is that it stimulates the production of enzymes that modify the extracellular matrix. It also changes the shape of the melanoma cells, enhancing their adhesion to the extracellular matrix. This makes the melanoma cells better at invading surrounding tissue,” said Dr Wellbrock.

Most importantly, this type of invasion is dependent on the activity of SRC kinases, which can be inhibited by a drug called saracatinib. When selumetinib and saracatinib were used in combination, thereby inhibiting both MEK and SRC, they not only stopped melanoma cell growth, but also completely abolished the unwanted side effects. “Our findings highlight the importance of fully understanding the multiple effects that interference of one particular pathway can produce and they reveal the potential for MEK and SRC inhibitors to be used in future combination therapies,” said Dr Wellbrock.
Research into women’s cancers continues to evolve with advances in screening, risk prediction and new insight on factors that can impact tumour risk and outcomes in the UK and beyond.

The Ugandan Women’s Health Initiative (UWHI) runs a range of projects in women’s health ranging from obstetrics to cancer and has a major focus on prevention of cervical cancer through screening. Launched in 2005, UWHI is a partnership between Makerere University, Mulago Hospital, Hospice Africa Uganda, University College London and most recently The University of Manchester. This year marked a major milestone as the number of women screened reached 20,000, of whom around 10–15% had precancerous lesions and received immediate treatment. Approximately one-third of these women would have developed cancer, so an estimated 1,000 lives have been saved.

"Cancer of the cervix is the biggest cause of death from cancer among women in Uganda with over 2,400 women dying from the disease each year, but it is an entirely preventable disease. The UWHI runs a one-stop ‘screen and treat’ programme using acetic acid for visual inspection followed by immediate cryotherapy in women requiring treatment," said Professor Ian Jacobs, co-chair and founder of UWHI. The programme has also identified further research opportunities including assessment of optimal testing regimens and health economics research. Following a visit to Uganda in August 2013, the aim is to work with the Ministry of Health to roll out testing across the country. “With a population of 35 million this is a
massive undertaking but the infrastructure to achieve this is already in place. This is a real opportunity to link with colleagues and experts in Uganda and to add value in terms of our expertise here in Manchester,” said Professor Jacobs.

Ovarian cancer has one of the highest mortality rates amongst women’s cancers, primarily due to late presentation with the disease often being advanced at diagnosis, and a poor understanding of risk factors. PROMISE 2016 (Predicting Risk of Ovarian Malignancies, Improved Screening and Early detection) is a five-year international research project that aims to halve deaths from ovarian cancer and is led by Professor Jacobs, who is also Vice-President and Dean of the Faculty of Medical and Human Sciences at The University of Manchester. With access to data from the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), the MCRC has a powerful research resource that can feed into the PROMISE project.

“We have information and tissue samples from over 200,000 women aged over 50 who have been studied for 10 years. As a subset of these women have developed ovarian cancer, we now have a discovery set of material from women pre-diagnosis which we are evaluating,” explained Dr Robert Graham from the University’s Institute of Cancer Sciences, who leads the proteomics biomarker discovery arm of the project. Using serum samples from women who developed ovarian cancer, along with samples from matched controls who did not get cancer, they are comparing the proteomic profiles - the full range of proteins present in one sample - of these two groups over time to see if there are any biomarkers that predict ovarian cancer development.

Over the past 12 months, a proteomic biomarker workflow has been established to analyse the samples using advanced techniques such as qualitative proteomics to identify and characterise the proteins isolated. Protein depletion is being used to remove the most abundant proteins in the samples that could mask any proteomic profile changes. Researchers in Manchester have now analysed around 150 samples and have data up to 36 months pre-diagnosis from women who later developed ovarian cancer. This approach, in combination with a complementary statistical and bioinformatics workflow, has already identified initial proteomic biomarker leads for further investigation. “The aim is to correlate our findings with
other results from PROMISE 2016 in order to develop more comprehensive algorithms for risk prediction that include robust genetic information,” said Dr Graham.

The role of human papilloma virus (HPV) in cervical cancer continues to be a major focus of investigation in Manchester. Research indicates that HIV protease inhibitors may have an anti-HPV effect and Drs Ian and Lynne Hampson, from the University’s Institute of Cancer Sciences, have initiated a new clinical trial of self-applied non-surgical treatment for HPV-related pre-cancer of the cervix in Kenya.

HPV also plays a role in the development of anal cancer and this year marked the start of another new study funded by the NHS, ANALOGY, which is assessing the feasibility, acceptability and effectiveness of screening for anal cancer in high-risk groups. “People whose immune system has been compromised, such as HIV-positive groups and women undergoing organ transplant who are on immunosuppressive therapy, are at increased risk of getting anal HPV, which increases their risk of developing anal cancer. We want to know whether screening is a beneficial and cost-effective option in these high-risk groups,” explained Professor Henry Kitchener, Chief Investigator of the study and Director of the Institute of Cancer Sciences at The University of Manchester. Participants will have an anoscopy examination, HPV testing and cytological analysis of collected samples to identify early asymptomatic disease.

Another study led by Professor Kitchener and funded by the National Institute for Health Research-Health Technology Assessment (NIHR-HTA) programme aims to develop strategies for improving the uptake of cervical screening by young women. Women in England are first invited for cervical screening aged 25 years and in Scotland aged 20 years. “In England, only around 60% of women aged 25–29 accept their invitation for cervical screening. We are designing and evaluating different strategies targeted specifically to this age group and will also be considering the impact of the national HPV vaccination programme,” said Professor Kitchener.

The STRATEGIC study was launched this year and includes General Practices in Greater Manchester and
Aberdeenshire. It will assess a range of interventions including internet booking and HPV self-testing, which would mean further screening can be offered to women who test positive. “This way of allowing the majority of women to determine that they are HPV-negative and therefore not at increased risk of developing cervical cancer may appeal to many women,” said Professor Kitchener.

Women with a Body Mass Index (BMI) over 40 have a ten-fold increased risk of developing cancer of the womb (endometrium). The overall incidence of endometrial cancer has increased by 40% in the UK since 1995 as a result of the obesity epidemic and it has overtaken ovarian cancer as the most common gynaecological cancer in the developed world. A new study led by University researcher Dr Emma Crosbie, who has recently received a prestigious NIHR Intermediate Clinician Scientist award of around £1 million, aims to better understand the link between obesity and endometrial cancer in order to develop strategies to reduce the risk in obese women. Two clinical research fellows are working on the study, one funded by Wellbeing for Women and the Wellcome Trust and the other by Central Manchester University Hospitals NHS Foundation Trust.
Breast cancer studies focus on risk prediction and the tumour microenvironment

Launched in October 2009 and due to complete recruitment of around 55,000 women this year, PROCAS (Predicting the Risk of Cancer at Screening) is now recruiting first time attendees. The aim of the study is to assess whether personalised breast cancer risk prediction can be introduced into the existing NHS Breast Screening Programme. Around 52,000 women attending breast screening in Greater Manchester have so far taken part in the study to evaluate their personal breast cancer risk using information on family history along with hormonal and lifestyle risk factors. Researchers have also been assessing mammographic breast density and collecting saliva DNA samples for genetic analysis, which will enable more accurate risk prediction.

“We have now had around 500 prospective cases of breast cancer in the cohort, which is the number required for statistically robust calculations of risk. We have been able to calculate the prevalence of moderate and high-risk breast cancer in PROCAS and are now calibrating our data using the Tyrer-Cusick
breast cancer risk assessment model to enhance predictive power,” said Professor Gareth Evans, Director of the Manchester Breast Centre.

The Family History Risk (FHRisk) study aims to improve breast cancer risk prediction amongst women with a family history of breast cancer, using risk information from individuals, mammographic breast density, and DNA from blood samples. Women with mutations in BRCA1/2 genes have an increased risk of developing breast and ovarian cancer. Data has now been collected from over 8,000 women from 895 families who have attended the Family History Clinic in Manchester. The data has been used to examine the risk of developing ovarian cancer in families with mutations in BRCA1/2 and to assess whether this risk is extended to families with no mutations in these genes.

Results published this year revealed that women from BRCA2 mutation families had a 17-fold increased risk of invasive ovarian cancer, which increased to 50-fold in women from families with BRCA1 mutations. Importantly, no association was found for women in families who tested negative for BRCA1/2 mutations. “These data will help counselling women from BRCA1/2 negative families with breast cancer that their risk of invasive ovarian cancer is not higher than the general population,” said Professor Evans. The group is now using the FHRisk data to evaluate a range of risk assessment tools in order to optimise their predictive value in the clinical setting.

Last year, funding for the Breakthrough Breast Cancer Research Unit was secured following a successful application for renewal. Professor Michael Lisanti, who became the Director of the Unit, led the bid with Dr Rob Clarke, both from the Institute of Cancer Sciences at The University of Manchester. The new funding commenced on 1 October 2013.

Gaining a better understanding of the role played by the tumour microenvironment in breast cancer development continues to be a major focus of research within the Unit. “Determining how tumours interact with their microenvironment is key to improving patient response to therapy and the tolerability of treatments. It will also help to identify novel targets for drug discovery and inform approaches that aim to overcome acquired resistance to anticancer agents,” said Professor Lisanti.

A growing number of studies suggest that it may be possible to manipulate the microenvironment to turn on and off drug resistance. If so, use of companion drugs that modify the microenvironment may be able to overcome resistance. “Our aim is to discover whether by elucidating the interaction between the tumour and its microenvironment we can tackle drug resistance and also identify new diagnostics to predict the patients most likely to fail conventional therapies. Improved understanding of this relationship will help us to achieve the goals of personalised medicine, with more effective individualised patient-based diagnostics and therapeutics,” said Professor Lisanti.

Over the last year, the Breakthrough Unit has published a series of new studies showing that cancer behaves more as a systemic disease, with oncogenes acting at a distance, and metabolically reprogramming the tumour microenvironment. As a consequence, catabolic fibroblasts transfer energy and biomass to anabolic cancer cells, fuelling tumour growth and metastasis. This has important implications for new drug discovery, by therapeutically targeting mitochondria and oxidative metabolism in breast cancer cells.

Interactive laboratory meetings have been established with breast cancer investigators presenting their work in order to generate greater collaboration between the Breakthrough Unit and other parts of the University. “Collaborations, both internally in Manchester and internationally with expert colleagues, will play a key role in driving enhanced understanding of breast cancer. This is an exciting time in breast cancer research with new paradigms that have the potential to change the way we think about cancer treatment and ultimately deliver more effective therapies for cancer patients,” said Professor Lisanti.
Biobank service streamlined for improved efficiency

With its five-year ethics approval successfully renewed, the Manchester Cancer Research Centre (MCRC) Biobank has put into place a more streamlined service to improve the capability of this essential research resource.

The Biobank provides a single simplified access point for research material and currently has over 4,500 samples available for MCRC researchers with around 100 new samples added every month.

This year, the Biobank applied for and received Section 251 support, which is granted by the Health Research Authority Confidentiality Advisory Group. The approval means that the Biobank can interact directly with patient identifiable information to select cases from the pathology archive. This is particularly valuable where the cohort may be too large to feasibly gain retrospective consent and where only a limited amount of information is needed to perform linkage analysis. “With this Section 251 support, we have a streamlined process that allows us to better meet research needs. We can now provide Biobank users with samples from a cohort of patients together with information on treatments received and outcomes,” explained MCRC Biobank Business Manager, Jane Rogan.

The improved service put into place this year also allows the Biobank to access clinical data from these
retrospective cohorts, for example information on treatments and outcomes, which can be linked to each sample. “Being able to correlate information from the samples with clinical outcomes is increasingly important. Until now, the onus has been on clinical teams to go back through consented patient records to find information on treatment and outcomes,” said Jane Rogan.

The renewed ethics approval has been revised to make the most of every patient interaction by allowing researchers to collect additional material during biopsy with clinician and patient consent. The service also now collects a range of sample types along with the standard tissue, blood and urine collections.

July 2013 marked the completion of phase one of Cancer Research UK’s Stratified Medicine Programme, for which the Biobank was chosen as the collecting centre for lung cancer, colorectal cancer, melanoma and prostate cancer. The Biobank is now looking to deliver samples for phase two of the programme focussing on collection of lung biopsy samples. “Working on the Programme has proven that we are able to routinely collect, store and distribute high quality samples for detailed analysis. So far, we have received around 70 applications from teams throughout the MCRC and across a range of cancer types – this is a reflection of the value of the Biobank as an accessible research resource,” said Professor Noel Clarke, Chair of the MCRC Biobank Management Board.
Training the next generation of clinician scientists

The recruitment, development and retention of outstanding clinical scientists continues to be an essential component of the MCRC’s goals and the Cancer Research UK-funded Clinical Research Training Fellowship scheme plays an important role in this strategy.

This year, Dr Ed Britton, a gastroenterology registrar in training at the Mersey Deanery, has been appointed to work with Professor Andrew Sharrocks from The University of Manchester and Dr Yeng Ang from Salford Royal NHS Foundation Trust. His research is focussed on investigating the role of the transcription factor ETV4 in the development of oesophageal cancer.

“The ETV4 transcription factor plays a key role in cell proliferation and invasion in oesophageal adenocarcinoma cell lines and tumour samples, though its target gene networks remain to be fully identified. ETV4 is overexpressed in tumour samples compared to normal oesophageal tissue, furthermore expression correlates with late stage disease, suggesting that it may also play a role in
metastasis,” said Dr Britton. ETV4 has also been implicated in other malignancies including Ewing’s sarcoma and prostate cancer.

Dr Britton’s research will involve mapping of ETV4 binding sites using chromatin immunoprecipitation and deep sequencing (ChIP-seq). ChIP-seq is a method used to study interactions between specific proteins and a region of DNA within the genome and can be used to assess whether a transcription factor associates with a candidate target gene. He will also be exploring pathways that may be involved in ETV4-mediated signalling to drive tumour development.

Part of his clinical work focuses on managing oesophageal cancer and Barrett’s oesophagus, a condition that causes a change in cells lining the oesophagus that may be a precursor to malignancy. Oesophageal cancer is associated with poor prognosis with five-year survival of only around 13 percent where improvements have been achieved mainly through earlier diagnosis rather than advances in treatment.

“The fellowship is an ideal opportunity to link my clinical interests with research that aims to elucidate the molecular mechanisms involved in oesophageal cancer tumourigenesis in order to identify potential treatment targets and prognostic markers,” said Dr Britton.

As the fourth gastroenterologist in the team, his research will build on previous studies, which suggest that ETV4 may interact with genes important in cell cycle progression. Dr Britton’s focus will be on identifying the target gene network for ETV4 in oesophageal cancer cells, studying the regulation of this network and then determining the relevance of the regulatory network to tumourigenesis.