Focussed investment to drive progress

Increasingly these days, to carry out meaningful and successful research you need to be associated with a centre that can facilitate and stimulate collaboration between different groups of researchers spanning the entire spectrum from basic through to translational and clinical research in different disciplines.

The integration of multidisciplinary working is going to be key to making real progress with translation of laboratory findings into the clinic, and ultimately patient benefit. Within the Manchester Cancer Research Centre (MCRC) we strive to create the environment that will facilitate that interaction and partnership. It is satisfying that we see that happening and the many examples of progress through collaboration featured in this Progress Report.

That whole ethos of multidisciplinary interaction will be enhanced with the development of the new MCRC building, which has been designed to promote interaction between the different research groups. Looking forward over the next one to three years, the partners of the MCRC have committed to significant additional investment in people to complement the investment and development of new research facilities. In depth discussions have taken place, resulting in a plan to recruit at least 20 senior academic researchers to the MCRC. This investment will be focused in areas we have already identified as critical in realising our research potential, increasing our strengths and allowing us to become internationally-recognised in those areas. These are: experimental therapeutics/personalised medicine; lung cancer; radiation-related research; women’s cancers; melanoma; and haemat-o-oncology. Within each of these areas we will endeavour to ensure that we have not only strength but depth across the basic and clinical research spectrum and in so doing be able to facilitate interaction between researchers that are trying to understand the basis of cancer and those that are translating that insight into patient benefit.

The MCRC is not standing still – it is constantly evolving and developing. The new building will be a fantastic stimulus for this increased development. But a building in itself is not sufficient: there needs to be matched investment in people. By focussing on identified priority areas we can ensure that we are getting the most value from these investments and are well placed to continue to make progress in the diagnosis, therapy and management of cancer and to drive the development of personalised treatment approaches.

Autumn marks the start of construction work on new research building

Construction work on the new Manchester Cancer Research Centre (MCRC) research building has now started marking a new phase for cancer research in Manchester.

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Professor Lisanti graduated with a degree in chemistry from New York University and obtained his PhD at Cornell University Medical School in Cell Biology and Genetics. From 1992–1996, he was a Skeggs Fellow at the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology (MIT), followed by several distinguished appointments at the Albert Einstein College of Medicine and the Kimmel Cancer Center in Philadelphia, USA. He is currently listed amongst the top 100 most–cited researchers in biochemistry and biology and has published over 440 papers. He is also the Editor–in–Chief of the American Journal of Pathology, one of the top pathology research journals.

Professor Lisanti’s research in Manchester focuses on the role of Caveolin-1 (Cav-1) in the pathogenesis of human breast cancer, with a strong emphasis its role in signalling, cancer, and stem cell biology. Recent advances have highlighted the important role of the stroma in breast cancer development; Cav-1 status in the stroma may provide important information about the aggressiveness of the cancer and be a valuable and accessible biomarker predictive of breast cancer recurrence and metastasis. “My work in the USA involved overseeing the translational research aspects of the Kimmel Cancer Center, while my work here will be more focused on breast cancer. With the discovery and validation of biomarkers that allow us to identify patients most likely to have poor prognosis, we have the tools with which to drive the continued development of personalised medicine approaches. These biomarkers will also play a role in informing patient selection for clinical trials, allowing new treatments to be tested in patient populations likely to derive the most benefit.

This is an exciting time for breast cancer research and Manchester is ideally placed to lead real progress in this field. I feel both humbled and honoured to be selected as the new Director for the Breakthrough Unit,” said Professor Lisanti.

Dr Wardley, a Consultant Medical Oncologist in breast cancer at The Christie since 2001, is also Chair of the newly formed Early Phase Trials Group, which aims to promote the rapid development of new targeted therapies and innovative treatments in cancer care, and to advance personalised medicine. A major achievement has been the improved coordination of early phase trials across Manchester, with strong working links established between laboratory-based research and services (such as genetic analysis of samples) and the clinic to streamline the patient treatment pathway. With the early phase trials research infrastructure in place there is a core of researchers to undertake important early phase trials work and activity at The Christie.

Dr Wardley was involved in the formation of the Manchester Breast Centre (MBC), and leads the Breast Clinical Trials Group, whose key goal is to introduce new agents and treatment approaches into the clinic, whilst continuing to develop other phase I to III trials in systemic therapy and radiotherapy in the context of industry and national and international groups. Most breast cancer patients referred to medical oncology at The Christie are now entered into clinical trials and the Unit is currently involved in over 60 trials.

"Being appointed Clinical Director of the Clinical Trials Unit is a very exciting opportunity and gives me the chance to facilitate the work of others. There is a wealth of expertise and experience in Manchester and a key part of my role is to bring people together and to foster increased cross-collaboration so that we work even more effectively as a team. By optimising the way in which clinical trials and the clinical service are run and coordinated, there will be additional opportunities to maximise research potential for patient benefit," said Dr Wardley.

Dr Wardley brings a varied research portfolio to his new post and has led many projects, including several pivotal clinical studies that have changed the way we currently treat early and advanced breast cancer. He also has strong links with numerous research partners in industry and academia, and is frequently involved in trial development and advising on trial programmes for new agents. The range of his experience adds to and complements the expertise within the Unit.
Funding successes ensure continued progress for Experimental Cancer Medicine Centre and early phase Clinical Trials Unit

This year Manchester has successfully renewed funding for their Experimental Cancer Medicine Centre (ECMC) and will receive £500,000 per annum for five years.

Manchester is one of only three ECMCs in the network that will receive the maximum level of funding. The application, led by ECMC Principal Investigators Professor Malcolm Ranson, Professor of Medical Oncology and Pharmacy at The University of Manchester and Honorary Consultant in Medical Oncology at The Christie, and Professor Caroline Dive, leader of the Clinical and Experimental Pharmacology Group (CEP) at the Paterson Institute for Cancer Research, secures funding from Cancer Research UK and the National Institute for Health Research (NIHR) from April 2012 following a successful site visit.

The early phase Clinical Trials Unit at The Christie has also been awarded £4.5 million infrastructure funding over five years from the NIHR funding scheme for Clinical Research Facilities in a bid led by Dr Andrew Wardley, the new Clinical Director of the Unit. “This funding will support the running of the unit with continuity of staffing levels to ensure that new and existing projects can be effectively delivered,” said Dr Wardley. Two advanced nurse practitioners have been appointed this year to the Unit. One of these, Lorraine Turner, was recruited from Liverpool where she was involved in establishing a phase I Unit and has extensive experience in setting up early phase clinical trials. The other advanced nurse practitioner, Michelle Davis, will start her training in October 2012. “The logistics of running clinical trials is substantial. Having the trained staff in place will help to ensure that we are able to reach our research potential and to increase our trials portfolio knowing we have secured the funding for staff to handle an increased demand,” said Dr Wardley.

An Early Phase Trials Group has been set up this year as a new collaboration between researchers involved in early phase research. The aim is to form links between researchers on The Christie site and other relevant groups within The University of Manchester, such as the Medical Genetics Unit, which is located at Central Manchester NHS Foundation Trust, to facilitate regular access to relevant clinical samples from patients with the ultimate goal of improving the speed of development of personalised medicine approaches. Discussions to develop a research-orientated biopsy service are also underway. Over the next year and beyond, the aim is to attract more trials funded by the pharmaceutical industry and Clinical Research Organisations and to foster collaborations between researchers through the new group. “With the research infrastructure secured, the Unit will be able to attract increased trials activity and increased recruitment to trials,” said Dr Wardley.

CEP has established a team that focuses on nucleic acid biomarkers, led by Senior Translational Scientist Dr Ged Brady, and over the past 12 months has built a team of eight scientists focussed on optimal analysis of blood samples for clinical and genetic information. “The work of the team aims to get the maximum information from blood samples we routinely collect from patients. At the simplest level this may involve identification of mutations in important genes that impact outcome with specific anticancer agents, such as epidermal growth factor receptor (EGFR) mutations to direct lung cancer treatment with EGFR inhibitors, or BRAF mutations to inform treatment with BRAF inhibitors,” said Professor Dive. The development of assays to detect and measure blood-borne biomarkers related to treatment outcome with specific anticancer agents is of particular value in tumours where access to biopsy material may be difficult, such as brain tumours. Work is ongoing to develop and validate reliable blood tests that can be used to inform treatment decisions.

In CEP, new technologies are being applied to extract the maximum information from circulating nucleic acids in blood samples with a view to minimally invasive tests for cancer patient monitoring. Towards this end, the nucleic acid biomarkers team are assessing the ability of a DEPArray™ platform newly installed in the Good Clinical Practice laboratory. This system allows purification of single circulating tumour cells (CTCs) from blood samples for downstream genetic analysis. “We can take blood samples from patients who initially present with sensitive disease and follow the patient with blood test monitoring to assess any changes in their CTCs as they relapse with drug resistance. This will allow us to identify molecular alterations that may be linked to relapse and inform further treatment strategy,” said Professor Dive.

The AstraZeneca CEP Biomarker Alliance, which was established in 2006, has been renewed for a second time with £3.1 million investment over the next three years. The renewal is recognition of the benefits that the academia-industry collaboration has brought to both partners and comes under the auspices of Dr Carl Barrett, the recently appointed Translational Science Lead in the Oncology Innovative Medicines Unit at AstraZeneca Pharmaceuticals in Boston, USA.

Work in CEP continues to be crucially important with regard to early phase clinical trials. The early phase clinical research team within the Clinical Trials Unit at The Christie has been strengthened with the recruitment of Dr Emma Dean – who undertook her PhD with Professor Dive and Professor Ranson – as a Senior Clinical Lecturer, where she will be working alongside Professor Ranson to develop the phase I trials portfolio.
New opportunities for radiation-related research

Manchester is set to become home to one of only two high energy Proton Beam Therapy (PBT) Centres in the UK following an investment of up to £1.25 million from the Department of Health, which was announced in April 2012.

PBT is a specialised form of radiotherapy, which uses a precision high-energy beam of particles to destroy cancer cells and is particularly suitable for complex childhood cancers. Currently patients requiring PBT have to travel abroad for long periods of time to receive this state-of-the-art treatment, as the service is not available in the UK. One of the PBT facilities will be built at The Christie NHS Foundation Trust and the other at University College London Hospitals NHS Foundation Trust.

Manchester was selected following a successful bid that involved a team of radiation-related researchers from the Manchester Cancer Research Centre (MCRC), which included Professor Nick Slevin, Director of Clinical Oncology at The Christie, Dr Ranald Mackay, Director of North West Medical Physics, and Dr Ed Smith, Consultant in Clinical Oncology at The Christie. The funding will provide a much-needed clinical facility to deliver PBT to patients, but also has longer-term opportunities in terms of PBT research.

Proton therapy provides improved treatments for some patients’ tumours and is particularly suitable for paediatrics and young adolescents, where long term toxicity is critical to long term outcome. However, PBT technology in treatment planning and delivery is not yet as well developed as photon therapy. Radiation-related research has led to advances in radiotherapy delivery to optimise treatment and improve patient outcomes – the same principles can be applied to PBT to enhance this treatment approach through PBT-focused research.

“We have an opportunity for many experienced groups to contribute to technological advances in PBT and now have the platform and facilities to do this in the UK. As well as treating patients, we will be able to collect data and monitor outcomes to identify the populations deriving most benefit from this treatment helping us to develop a more individualised treatment approach in the future,” said Dr Mackay. Though the PBT will be located in Manchester, it is a national facility and part of a national initiative. “Having a PBT Centre in Manchester will help to attract and recruit internationally leading researchers, build local research infrastructure and allow Manchester to host national research programmes, driving the future development of a centre of PBT research excellence within the MCRC,” said Professor Tim Illidge, lead for radiation-related research at the MCRC. The aim is that The Christie will start treating patients with PBT towards the end of 2017.

Professor Illidge also chairs the National Cancer Research Institute (NCRI) Clinical and Translational Radiotherapy Research Working Group (CTRAd), which had their first meeting on proton research in September 2012. Four core research themes have been established, three of which are chaired by MCRC researchers: Dr Mackay for the physics theme, Professor Catharine West for basic and scientific radiation biology, and Dr Susan Davidson for patient outcomes and late effects. This representation within the CTRAd will help to ensure that radiation-related research at the MCRC continues to be strategic and aligned with initiatives at both the local and national level.

Another major achievement in 2012 has been the approval of plans, led by Professor Kaye Williams, for a small animal radiation research platform (X-ray) to be located at the Wolfson Molecular Imaging Centre. The platform will allow for delivery of complex radiotherapy treatments.
to small animals and will enable the development of model systems, which are more informative than simple xenografts and more closely resemble the real clinical situation. Four other institutions in the UK have this facility and securing support for the plans will ensure that the MCRC remains competitive in this area.

Plans to build academic physics research are also being developed and, along with proton therapy, three other physics research themes are being established: individualised radiotherapy, functional imaging for therapy and motion. Rather than giving the same dose of radiotherapy to each patient, individualised or isotoxic radiotherapy aims to deliver a dose adjusted to the specific characteristics of the individual’s tumour and surrounding normal tissue tolerance. The dose of radiotherapy that can be given is currently limited by the dose that can be tolerated by normal tissue surrounding the tumour. Along with improved techniques to better target the tumour, isotoxic radiotherapy provides a means of safely increasing the dose for some patients and potentially decreasing the dose for others. Successful isotoxic radiotherapy requires high-quality imaging to provide accurate information about the location of the tumour to deliver accurately targeted radiation. It also requires information about the radiosensitivity of the tumour and surrounding normal tissue. Some patients may experience late effects from radiotherapy if they are genetically more susceptible to radiotherapy. Radiogenomics research, led by Professor West, aims to identify the factors and processes that mediate genetic susceptibility in order to facilitate the development of individualised radiotherapy. “The goal is to develop algorithms using clinical data which will provide a risk profile to identify patients likely to tolerate higher doses of radiotherapy and those for whom such an approach would be poorly tolerated,” said Professor Illidge. Using clinical data to individualise patient treatment is imminent – the longer-term goal of incorporating molecular and genetic information is still some way off. Investment in theragnostics, the process of delivering diagnostic therapy for individual patients, is actively being planned and developed in the near future.

Functional therapy for imaging is linked to individualised therapy and currently the most frequently used functional imaging technique is fluorodeoxyglucose positron emission tomography (FDG-PET), which provides information on tumour metabolism. Following radiotherapy, FDG-avid areas of the tumour (where FDG uptake continues) may persist, which identifies regions that may benefit from further radiotherapy. An open question is whether patient outcomes following radiotherapy can be improved by providing a higher dose of radiotherapy to the residual region around FDG-avid tumours. Preliminary data from ongoing studies indicate that this approach is feasible and radiation-related research within the MCRC is focusing on developing capability and expertise in this area. Research on motion during radiotherapy delivery and the development of tools to compensate for patient movement is ongoing. This research is led by Professor Chris Moore.

Over the past 12 months, further funding has been secured from AstraZeneca for a third MCRC/AstraZeneca Clinical Research Training Fellow in radiation-related research, and a proposal is now being developed for a preclinical PhD project focusing on DNA damage response. In addition, The Christie Charitable Funds Committee has approved part funding for two new senior positions for radiotherapy research and Dr Paul Roxby has joined to help drive increased trials activity. A key goal over the coming year is to increase the number of patients entering radiotherapy clinical trials to secure the MCRC’s position as a leading national centre for clinical trial development and recruitment. “The North West has the biggest cancer population in the UK and we are uniquely placed to ensure that patients are entering clinical trials to develop cancer treatments further,” said Professor Illidge.

The past 12 months have also seen MCRC radiation-related researchers recognised for their significant contributions to research. Professor Illidge was named “Researcher of the Year” within the Faculty of Medicine and Human Sciences at The University of Manchester’s annual Distinguished Achievement Awards, while Kaye Williams, Nick Slevin and Richard Cowan have all received honorary professorships. Professor Slevin has also been appointed as the Chair of a new national advisory group on radiotherapy. The group is part of the new clinical advisory system set up to advise the National Commissioning Board on clinical matters. This will be an important position as new technology for radiotherapy is developed and as a national tariff for radiotherapy is implemented. In addition, Dr Carl Rowbottom has received the Chief Scientific Officer’s Award for Leadership in the prestigious Advancing Healthcare Awards. The awards recognise healthcare science staff that have shown determination when driving up the quality of patient care, both cost efficiently and sustainably. He received the award, following his introduction of intensity modulated radiotherapy (IMRT) to patients at the specialist cancer centre. IMRT maximises the radiation dose to tumours while minimising damage to the surrounding tissue. Having worked in the USA, where IMRT is more commonly used, Dr Rowbottom was convinced that The Christie’s patients could benefit further if IMRT was offered as part of their treatment. Last year, 865 patients were treated with IMRT at The Christie, achieving the 30% target set in 2008. The service is now routine and sustainable. “These awards and appointments are an indication of the productivity of the group and the quality of research being done. Having three Chairs appointed within the group is a major and well deserved achievement, which highlights the progress that is being made in radiation related research within the MCRC,” said Professor Illidge.
Melanoma focus for Clinical Fellow

Dr Andrew Hudson has been appointed as an Manchester Cancer Research Centre (MCRC) Clinical Research Training Fellow to work with Dr John Brognard, leader of the Signalling Networks in Cancer Group at the Paterson Institute for Cancer Research and Dr Paul Lorigan, a Medical Oncologist specialising in melanoma treatment and research at The Christie NHS Foundation Trust.

The aim of Dr Hudson’s research is to understand why resistance to melanoma treatment occurs, and to identify alternative targets for intervention that can potentially overcome this resistance.

Dr Hudson has been an oncology registrar at The Christie for around five years and is training to become a Consultant in Clinical Oncology. Having completed a valuable and enjoyable research project while he was a medical student, he was keen to do further advanced research at the MCRC. “Oncology is a very research-driven field of medicine so an ideal speciality for those interested in research. Some projects undertaken by clinical fellows focus on more clinical aspects, such as optimisation of radiotherapy delivery, while others, like mine, are more laboratory-based. Melanoma research appealed to me with the recent treatment advances that have raised intriguing research questions and the promising work already carried out by John Brognard’s group,” explained Dr Hudson.

Vemurafenib is a new agent for the treatment of metastatic melanoma that carries a particular genetic mutation (the BRAF V600E mutation). Prior to vemurafenib, treatment options for these patients were limited with only a minority of patients responding to treatment and with significant treatment-associated toxicity. It provides an effective treatment in around 50% of patients eligible for therapy, but most patients become resistant to the agent and the average patient will experience progression of their melanoma within 6 months. Dr Hudson’s project aims to improve understanding of mechanisms of resistance and why patients become unresponsive to therapy.

Professor Richard Marais, Director of the Paterson Institute for Cancer Research, and colleagues at the Institute of Cancer Research in London discovered that when BRAF is mutated it becomes ‘hyperactivated’ and turns on a switch that tells the cells to constantly grow and divide. This uncontrolled cell proliferation leads to tumour formation.

Vemurafenib works by blocking mutated BRAF protein in the RAF/MEK/ERK cellular growth pathway. Blocking the abnormal BRAF protein with vemurafenib stops the cell from growing out of control by turning ‘off’ the switch. However after some time, other proteins reactivate the pathway further downstream, circumventing the vemurafenib brake and leading to resistance. “Some of these reactivating proteins have been identified, but we believe there are several more and want to identify them. My project involves collecting pre-treatment and post-relapse samples from patients and identifying potential genetic changes and mutations or differences in protein kinase profiles before treatment, compared to when resistance develops and relapse occurs,” explained Dr Hudson.

He will be based in Dr Brognard’s laboratory and working with Dr Lorigan’s patients and hopes to identify kinases that are potential targets for inhibition and therefore therapeutic intervention. Dr Hudson also aims to collaborate with MCRC researchers working on circulating tumour cells to evaluate whether the genetic profile of these cells, which can be obtained from a simple blood sample rather than a more invasive biopsy, correlates with that from biopsy material. “The eventual aim is to undertake research that can lead to a more personalised medicine approach where, if one treatment stops working, there are a range of downstream alternatives that can provide prolonged and durable disease control for patients,” says Dr Hudson.
Collaborations that are beginning to yield results.

Over the past year, there has been a significant growth in collaborations within clinical and preclinical imaging research both with internal and external partners — collaborations that are beginning to yield results.

A research agreement has been established with Bruker, which provides the Manchester Cancer Research Centre (MCRC) with a low-field animal magnetic resonance imaging (MRI) system for a trial period. The system will be based at the Wolfson Molecular Imaging Centre (WMIC) and allows combined MRI-position emission tomography (PET).

“Having access to an animal MRI facility on The Christie site is a first for us. The research agreement means that our investigators can have an important test period of this equipment before we decide whether its something we should invest in for the longer term,” said Professor Alan Jackson, who leads clinical imaging at the MCRC.

Another research agreement with General Electric (GE) Healthcare provides the MCRC with FASTlab™, an automated system for producing the radioactive ligands (tracers) used in PET imaging. In order to be used in the clinical setting, materials produced for clinical research have to meet Good Manufacturing Practice (GMP) standards, which can be demanding as well as time and resource consuming. The new clinical FASTlab™ provides GMP-quality tracers, allows researchers access to new ligands and local production of fluorothymidine (FLT) and other new tracers. This faster ‘click radiochemistry’ technique allows researchers access to new ligands and local production of fluorothymidine (FLT) and other new tracers. This faster ‘click radiochemistry’ technique allows researchers access to new ligands and local production of fluorothymidine (FLT) and other new tracers.

A major achievement this year was the publication of research on advanced imaging reconstruction using a system that takes a series of images over time to improve image resolution, quality and the quantitative data that can be obtained from the images. The work, led by Dr Julian Matthews, a Senior Lecturer at the WMIC, is the basis of an ongoing research programme and is likely to have widespread use and to generate commercial interest. In the past 12 months imaging research has also focussed on developing imaging techniques to study tumour invasion initially in central nervous system (CNS) tumours. Methods to identify the edge of the tumour and to measure the density of tumour invasion in surrounding tumours are being developed. “We have found that we can estimate the density of malignant cells around the brain tumour and can classify their ‘invasiveness’,” said Professor Jackson. The award is also a significant boost for preclinical MRI and will enable Dr O’Connor to develop his advanced MRI techniques in both the preclinical and clinical setting.

Dr James O’Connor, who trained at the WMIC, has been awarded a Cancer Research UK Clinician Scientist Fellowship. This is a very prestigious award with no more than three given annually. Currently there are only two such Fellowships in imaging in the UK, the other being in Cambridge. Dr O’Connor’s work focuses on developing imaging methods to study different parts of the tumour that are biologically or genetically different, for example resistant to or more responsive to particular therapies, and that may benefit from tailored treatment approaches. “Tumours are heterogeneous — the aim is to identify imaging signatures that reflect and quantify this heterogeneity. We can then begin to link signature type with response to specific interventions in order to guide treatment decisions and to develop a personalised treatment plan that is tailored to the specific signature,” said Professor Jackson. The award also represents a significant boost for preclinical MRI and will enable Dr O’Connor to develop his advanced MRI techniques in both the preclinical and clinical setting.

“We are now able to provide investigators with a far better portfolio of compounds they can use to investigate disease processes, especially inflammation and tumour hypoxia,” said Professor Jackson. Over the past 12 months, Dr Adam McMahon, Associate Director for Radiochemistry at the University’s WMIC, has reorganised basement operations to the point where radiochemistry production within the imaging Centre has a success rate currently in excess of 95%: this is at the upper end of the success rates reported in similar UK and European centres. With the reliability of radiochemistry at the MCRC established, there is now an undertaking to start providing radioligands externally. Collaborations have been set up with other academic centres including University College London and Imperial College, London, to develop this further. This year has also seen investment in a new research-dedicated 3-tesla MRI system, which uses a more powerful magnet to provide images of higher resolution and image clarity compared with lower power systems. A major benefit is that the system is based at the Wellcome Trust Clinical Research Facility, close to the main University of Manchester Campus, giving patients local and convenient outpatient access.

“In the past patients were sent to a facility in Salford which restricted the type of tumours we could image. We focussed on brain tumours for which high-power MRI is particularly valuable, but can now undertake imaging projects on more common cancers such as colorectal and ovarian cancer,” said Professor Jackson.

A major achievement this year was the publication of research on advanced imaging reconstruction using a system that takes a series of images over time to improve image resolution, quality and the quantitative data that can be obtained from the images. The work, led by Dr Julian Matthews, a Senior Lecturer at the WMIC, is the basis of an ongoing research programme and is likely to have widespread use and to generate commercial interest. In the past 12 months imaging research has also focussed on developing imaging techniques to study tumour invasion initially in central nervous system (CNS) tumours. Methods to identify the edge of the tumour and to measure the density of tumour invasion in surrounding tumours are being developed. “We have found that we can estimate the density of malignant cells around the brain tumour and can classify their ‘invasiveness’,” said Professor Jackson. The award is also a significant boost for preclinical MRI and will enable Dr O’Connor to develop his advanced MRI techniques in both the preclinical and clinical setting.

Dr James O’Connor, who trained at the WMIC, has been awarded a Cancer Research UK Clinician Scientist Fellowship. This is a very prestigious award with no more than three given annually. Currently there are only two such Fellowships in imaging in the UK, the other being in Cambridge. Dr O’Connor’s work focuses on developing imaging methods to study different parts of the tumour that are biologically or genetically different, for example resistant to or more responsive to particular therapies, and that may benefit from tailored treatment approaches. “Tumours are heterogeneous — the aim is to identify imaging signatures that reflect and quantify this heterogeneity. We can then begin to link signature type with response to specific interventions in order to guide treatment decisions and to develop a personalised treatment plan that is tailored to the specific signature,” said Professor Jackson. The award also represents a significant boost for preclinical MRI and will enable Dr O’Connor to develop his advanced MRI techniques in both the preclinical and clinical setting.
Dr McMahon has been developing a new method to directly image the amount of energy deposition into tissues using PET as a means of imaging tissue damage due to radiation. He has secured investment funding and produced preliminary data to suggest that radioligands can be developed to monitor damage induced by radiotherapy or cytotoxic therapy and can act as biomarkers. “Like the work on identifying imaging signatures to account for tumour heterogeneity, this impacts progress towards more personalised therapy. The overarching aim is to develop improved monitoring of treatment response and treatment impact, allowing modification of treatment as relevant for individual patients and tumours,” said Professor Jackson.

The past year has also seen progress towards developing formal academic collaborations that bring together UK-based centres with complementary strengths in cancer imaging, such as Cambridge. Partnerships with centres outside the UK have also been forged and a formal collaboration with Professor Markus Schwager at the Technical University of Munich, a national centre of excellence in cancer imaging, has been established. The MCRC will provide MR expertise and in return will benefit from PET expertise within the Munich centre, which has a combined PET-MR system that has only recently been available for research. These collaborations add value to the MCRC’s imaging research and will provide additional opportunities for investigators. For example, within the PET-MR system the resolution of PET images is relatively low. Work within the MCRC on image reconstruction can be used to improve these images and quality of data that can be obtained from them. “There is a clear strategy for clinical imaging research at the MCRC with complementary streams of work that are designed to overlap and inform each other. Collaborating will facilitate this strategy leading us towards more sophisticated and tailored imaging approaches that match the complexity of the tumours we study and treat,” said Professor Jackson.

Preclinical imaging within the MCRC has continued to grow over the last 12 months. Through collaboration with the preclinical team, an increasing number of researchers within the MCRC have been able to develop and apply non-invasive imaging-based techniques to address a broad range of questions in tumour biology and therapeutic response. “Our aim is to provide the infrastructure and know-how to facilitate the development of any preclinical PET and/or MR based study that could have relevance for our understanding of cancer as a disease and/or a therapeutic target. We are particularly excited about research that has the potential for rapid translation into the clinical setting to aid patient management,” said Professor Kaye Williams from the School of Pharmacy at The University of Manchester, who leads preclinical imaging research at the MCRC.

Over the last year research within the preclinical PET team has identified biomarkers that can be used to mark the response of tumours to therapeutic agents that target key oncogenic pathways in cancer. Such an approach would enable clinicians to make early decisions as to whether a patient is receiving benefit from treatment or not, and to rapidly switch those who are not onto an alternative therapy. “Through this expanding portfolio of imaging projects and increased interaction with multidisciplinary imaging scientists across The University of Manchester we have been able to increase the research training opportunities within preclinical imaging and have welcomed both Masters and PhD students across a broad range of subjects from image reconstruction, through imaging proteomics to novel tracer development,” said Professor Williams. The models developed by CEP have also supported further expansion of collaborations with GE Healthcare within novel apoptotic tracer development. This work conducted between the WMIC, CEP and GE was recently awarded the best preclinical study at the World Molecular Imaging Congress.

To support an expanding programme of novel PET tracer development within the WMIC, investments have been made within analytical chemistry enabling on site metabolite analysis. An exciting new programme of work will be initiated in 2013 using the small animal radiation research platform (X-ray) within the WMIC. There is already a strong background of preclinical radiotherapy research within the MCRC that has formed the basis of clinical studies within The Christie. As of 2013, researchers will be able to integrate preclinical imaging within this framework to assess both therapeutic response and normal tissue damage, which are critical elements guiding the success of clinical radiotherapy. “Through this expanding portfolio of imaging projects and increased interaction with multidisciplinary imaging scientists across The University of Manchester we have been able to increase the research training opportunities within preclinical imaging and have welcomed both Masters and PhD students across a broad range of subjects from image reconstruction, through imaging proteomics to novel tracer development,” said Professor Williams. The preclinical and clinical imaging research undertaken at the MCRC over the past 12 months demonstrates the degree of progress that can be made through strategic collaboration.
Collaboration drives progress at Drug Discovery Unit

The past 12 months has seen the Cancer Research UK-funded Drug Discovery Unit (DDU) make significant progress in several core areas including target validation, hit-finding and portfolio development.

This progress has been driven by the close interaction with group leaders at the Paterson Institute for Cancer Research and elsewhere across the Manchester Cancer Research Centre (MCRC), to identify and begin early work on new targets.

A successful target validation project undertaken this year demonstrates the importance and benefits of working closely with researchers and clinical colleagues within the MCRC. Dr Tim Somervaille is a clinician scientist and leader of the Leukaemia Biology Group at the Paterson Institute, focusing his research on identifying genes and cellular pathways in human leukaemia stem cells (LSCs) that are critical for their function and which could be targeted by novel therapies. As a clinician, Dr Somervaille is also an Honorary Consultant in Haematology at The Christie, treating patients with leukaemia. Acute myeloid leukaemia (AML) is an aggressive leukaemia with generally poor prognosis. Research in Dr Somervaille’s laboratory led to identification of an essential LSC regulator, LSD1 (also known as KDM1A), which sustains the cancer phenotype by preventing differentiation and programmed cell death. The DDU was approached and worked with Dr Somervaille to identify and synthesise chemical analogues able to target LSD1 selectively. Evaluation of these tool compounds in the laboratory yielded promising results and led to further evaluation in patient samples collected in the clinic, again with promising results. Data from this collaborative project, which have been recently published (Cancer Cell 2012;21:473-87), indicate that LSD1 targeting may be a rational therapeutic approach and work is ongoing to further evaluate its therapeutic potential.

“Within the DDU we have a specific and complementary expertise in chemistry, and one of our key strengths is to be able to offer this to researchers. Part of our mission is to source compounds using our chemical knowledge to identify substances that may be potentially biologically active and therefore attractive options for testing in the laboratory,” said Dr Donald Ogilvie who heads the Unit. Once shown to be active, the DDU are able to produce and supply the test compound, possibly with alterations to increase activity, which can then be used for high-quality research. “Helping basic researchers source the best compounds to evaluate in the laboratory and then aligning this with clinical testing in patient samples is a real-life demonstration of the benefits of the MCRC,” Dr Ogilvie added.

This year, the DDU have also begun collaborative projects with other Paterson Institute researchers, Dr John Brognard, leader of the Signalling Networks in Cancer Group, and Dr Karim Labib, leader of the Cell Cycle Group. Both have identified novel targets through their basic research and, through collaborative projects, the DDU have been given access to early proprietary data to carry out druggability assessments to review opportunities for drug discovery. Another druggability assessment project has also begun with Dr Ivan Ahel, leader of the DNA Damage Response Group at the Paterson Institute. These projects have been facilitated with strategic investment in automated technology over the past 12 months; the acoustic dispenser (used to transfer minute amounts of test compounds) has been upgraded and automated to allow screening of 2,000 to 20,000 compounds in a week.

Working with basic scientists, the DDU are developing assays suitable for automation to allow high-throughput screening. Screening begins with a diversity of compounds in each assay—the aim is to identify a subset of compounds (prototype small molecules, or ‘hits’) that interact and interfere with the activity of a particular target. Each target will give a different ‘fingerprint’ of hits. DDU scientists assess the uniqueness of the fingerprint (which gives a measure of its specificity to the target) and how many compounds contribute to the fingerprint—enough to ensure diversity and optimise therapeutic opportunities while remaining logistically manageable. “We are gaining considerable experience and improving our assessment of potentially attractive compounds. Again, co-location and close collaboration have been essential in this process and ensure that we can provide an early and rapid assessment that allows us to decide whether further investment in a particular target is likely to be valuable or whether another approach may be more viable. Prioritising use of research resources and research focus is vitally important and our work facilitates this,” said Dr Ogilvie.

The past 12 months have also seen the maturation of the DDU’s project portfolio into a product pipeline with several promising projects at different stages of development and novel inhibitor compound series are being discovered and optimised, often in collaboration with basic research scientists. The Unit now has its first project in lead identification phase, where they have successfully developed and validated chemicals that inhibit the target biochemically, but are also able to penetrate and inhibit the target in whole cancer cells. They are now working to improve the potency of these chemicals and to optimise their drug-like properties. Another project is expected to enter the lead identification phase shortly.

The inherent risk of DDU projects, with only a minority of early lead compounds being worthy of further investment, means that many potential cancer targets enter the project portfolio and are then stopped to ensure that resources are deployed on potentially more attractive projects. “The maturation of the DDU workstream from portfolio to pipeline indicates that we are on track to deliver our five-year goals, which were set out over three years ago. After a recruitment drive in 2011, the team is now at full strength with around 28 full-time members ensuring that we can maintain and build on the progress we have already made,” said Dr Ogilvie. The development and embedding of a drug-hunting culture within the MCRC was a major rationale for the establishment of the Unit. In the past year, several projects demonstrate that this culture is being cultivated and is flourishing.

This year demonstrates the importance and benefits of working closely with researchers and clinical colleagues within the MCRC. The development and embedding of a drug-hunting culture within the MCRC was a major rationale for the establishment of the Unit. In the past year, several projects demonstrate that this culture is being cultivated and is flourishing.
MRes in Oncology sets the bar high

Since the first intake of just four students in September 2010, 19 high-calibre students have now completed the one-year course, which equips them with the specialist knowledge and research skills to pursue a research career in oncology with the potential to become leaders in their field.

“The MRes in Oncology is a practical programme that focuses on providing successful applicants to the course with applicable and clinically relevant skills. Although we also provide a grounding in biology, the focus is on therapy and this differentiates the Manchester course from other programmes,” said Professor Catharine West, Postgraduate Director at The University of Manchester’s Institute of Cancer Sciences. Last year’s intake of 15 students have just graduated and included nine undergraduate medical students who had completed year 4 of their degree and were taking the MRes as an intercalated element, four science graduates and two qualified medics from overseas. Having completed the course, one of the four science graduates is now in medical school while the remaining three hope to undertake PhDs.

“It was particularly encouraging to attract the qualified medics who were able to benefit from the excellent facilities and training from Manchester experts, which they may not have access to in their own countries. They will now return home equipped with the knowledge, skills and practical experience from the MRes course to make a real difference in their own countries,” said Professor West. The MRes students benefit from lectures, tutorials and master classes delivered by internationally renowned researchers and clinicians drawing on the expertise that exists across the Manchester Cancer Research Centre (MCRC) partnership to provide an exceptional learning opportunity. “The high level of engagement and willingness of busy MCRC staff to get involved and take part has been outstanding and is a real strength of the course,” said Professor West.

Feedback from students who have completed the MRes training has been overwhelmingly positive. Intercalating medical student, Chris Mansbridge, who completed the course last year prior to his final medical exams said: “The experience has enriched my knowledge of the basic sciences and enabled me to apply and translate this knowledge to clinical medicine, which I hope will make me a better doctor and help me provide a higher quality of care for my patients. The course has stimulated me to think critically and gain a wealth of experience and enthusiasm in medical research, which I did not have the opportunity to do in my undergraduate medical studies.” Chris also highlighted the excellent organisation, inclusion of stimulating material and the two-week Fellowship of the Royal College of Radiologists (FRCR) course, and felt that the research component of the MRes allowed him to go into depth in a particular component of oncology. “It was inspiring to be involved in the forefront of that aspect of cancer research and work with leaders in the UK and internationally. I wasn’t sure about a career in oncology, but the course lectures were so interesting and seeing how the basic science connects to clinical pathology and therapeutics was amazing. Having completed the MRes I know that oncology is the area I want to focus on,” said Chris.

Chris and other past MRes graduates will be meeting the eight new recruits who have started the programme this year, and the aim is to attract more intercalated medical undergraduates from other universities and further afield. The MRes course accepts only the most promising students and the bar for entry has been set high to attract the right calibre of student. “We want to attract and stimulate the best medical students to become interested in oncology. Our aim is to inspire and train future leaders in oncology – the clinical, medical and surgical oncologists who will drive progress in future cancer research,” said Professor West.
Funding secured for Breakthrough Unit: More good news for the Manchester Breast Centre

Continued funding for the Breakthrough Breast Cancer Research Unit has been secured following a successful application for renewal submitted in January 2012.

Professor Michael Lisanti, who became the Director of the Unit in September 2011, was nominated as Principal Investigator and led the successful bid with Dr Rob Clarke from the Institute of Cancer Sciences at The University of Manchester.

This year, the focus and structure of the Breakthrough Unit has been streamlined, allowing optimisation of resource use. Research will now focus on the prevention of breast cancer recurrence and metastasis; understanding the role of ageing, oxidative stress, and the tumour microenvironment. “We were delighted with the success of the application in what is a very competitive funding environment. Our renewal is a reflection and acknowledgement of the quality of research within the Unit. The reorganisation and streamlining of the Unit will allow strategic investment in priority areas of research,” said Professor Gareth Evans, Director of the Manchester Breast Centre. The new structure will also facilitate fundraising activities by providing one comprehensive stream of work and one identified Principal Investigator to co-ordinate delivery of the research.

As well as being Director of the Breakthrough Unit, Professor Lisanti also holds the Muriel Edith Rickman Chair of Breast Biology within the Institute of Cancer Sciences at The University of Manchester and his research focuses on the role of Caveolin-1 (Cav-1) in the pathogenesis of human breast cancer. Studies indicate that Cav-1 may have a more important role in the stroma – the connective tissue in the breast – rather than in the cancer cells themselves. Loss of Cav-1 is associated with poor prognosis in breast cancer and it has now been implicated in a range of other cancer types, including prostate cancer and melanoma. These findings suggest that Cav-1 may be able to identify high-risk patients and may be a valuable diagnostic biomarker for therapeutic outcomes. More recently, a revised model for cancer metabolism has been proposed to account for the role of oxidative stress in driving tumour growth and metastasis. In this model, cancer cells produce and secrete hydrogen peroxide as well as promoting manufacture and release of L-lactate by fibroblasts in the stroma. The cancer cells then use L-lactate as an energy source to grow and metastasise, repeating the process in each new metastatic region and further promoting cancer growth and spread.

“We now know that oxidative stress is a driving force behind cancer – identifying ways of ‘starving’ the cancer cells of fuel by targeting the cells and machinery responsible for producing essential nutrients may be a more promising approach than traditional anticancer treatments, which often have the effect of increasing oxidative stress,” said Professor Lisanti. A major focus of work over the last year has been in improving understanding of the metabolic coupling and interactions between breast cancer cells and fibroblasts. “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.

In the past 12 months, research activity at the Manchester Breast Centre has been strengthened with the appointment of new investigators, including Dr Cliona Kirwan, a Breast Surgeon at the University Hospital of South Manchester and Dr Paul Shore, a Senior Lecturer within the Faculty of Life Sciences at The University of Manchester. The Manchester Breast Centre, an umbrella organisation that brings together researchers, research groups and units active in breast cancer research, including the Breakthrough Unit, now has 15 investigators active in breast cancer research.

Following the success of the 28th IABCR/Breakthrough Breast Cancer Conference hosted by Manchester and organised by Dr Clarke in April 2012, a symposium is being held in November 2012 at the Paterson Institute for Cancer Research with invited lectures from internationally leading breast cancer researchers. Professor Andrew Tutt, Director of the Breakthrough Breast Cancer Research Unit at Kings College London, will be delivering the symposium’s Breakthrough Lecture, while Professor Charles Coombes, Head of the Division of Cancer at Imperial College, London, will focus on new therapies for breast cancer. The meeting will also showcase some of the highlights of Manchester Breast Centre research and will have representation from major funders such as Breast Cancer Campaign, Genesis Breast Cancer Prevention Appeal and Breakthrough Breast Cancer.

Over the coming year, the Manchester Breast Centre aims to continue to be more collaborative and interactive, and to secure increased funding. “Our aim is to make Manchester an increasingly renowned and attractive centre for breast cancer research by showcasing the range and quality of our research and the benefits of the Centre as a strategic umbrella organisation. From the funders’ perspective, the strength of the collaboration means that we are ideally placed to deliver a return on research investment and to carry out research that has clinical relevance and aims to improve patient outcomes,” said Professor Evans.
In four years, the Manchester Cancer Research Centre (MCRC) Biobank has become an established resource for cancer researchers in Manchester.

The Biobank is now evolving to provide more tailored collections to better meet the needs of the research community. With over 3,300 patient samples, growing at an average of 100 new samples every month, the MCRC Biobank aims to improve the usefulness of its collections by working with researchers to identify and provide samples for specific project needs. “We are beginning to craft collections, looking at what researchers want as well as the standard collections we do that form a valuable resource. Researchers can apply prospectively to the Biobank, telling us what their requirements are so that we can provide more tailored collections,” explained MCRC Biobank Business Manager, Jane Rogan. The specific funding streams for distinct cancer types such as male cancer also allows the Biobank team to prioritise what they collect and to provide a user and need led service.

The Biobank has reapplied for renewal of its five-year ethics approval and taken this opportunity to streamline the service. For example, the consent process is being refined so that patients are asked to provide enduring consent rather than being asked for consent for each individual procedure. The aim is to make the process more efficient and to use the knowledge gained over the past four years to predict likely requirements such as pre- and post-treatment samples as well as matched controls. Collaboration with AstraZeneca has secured funding for five full-time Biobank technicians in exchange for AstraZeneca tissue samples collected from patients with testicular cancer to identify pre- and post-treatment markers of response. Two collaborative large-scale projects have also been undertaken with AstraZeneca, University Hospital of South Manchester. The Christie and Salford Royal. The first of these involved screening around 11,500 slides from patients with bladder cancer who had undergone surgery in the past 35 years. Samples were matched with clinical information and tissue microarrays (TMAs) were developed to screen for possible markers of treatment response. “The bladder dataset we now have from this study is one of the largest in Europe and is a highly valuable resource. We have identified over 500 informative patients and also have matched controls in terms of non-cancerous tissue samples from patients undergoing bladder surgery for other reasons,” said Professor Noel Clarke, Chair of the MCRC Biobank Management Board.

In another study, TMAs have been developed from all prostate cancer samples collected from patients with prostate cancer, melanoma and prostate cancer. This work is in collaboration with the University Hospital of South Manchester NHS Foundation Trust, The Christie NHS Foundation Trust, Salford Royal NHS Foundation Trust and Pennine Acute Hospitals NHS Trust. Selection of the MCRC Biobank to deliver across four cancer types in this national two-year programme, highlights its effectiveness as a reliable research resource.

Last year, the Biobank was chosen as the collecting centre for lung cancer samples within Cancer Research UK’s Stratified Medicine Programme. Having successfully delivered on this programme, the Biobank is now collecting three additional cancer types and has expanded its activity to include colorectal cancer, melanoma and prostate cancer. This work is in collaboration with the University of Manchester, The Christie NHS Foundation Trust, The Christie NHS Foundation Trust, Salford Royal NHS Foundation Trust and Pennine Acute Hospitals NHS Trust. Selection of the MCRC Biobank to deliver across four cancer types in this national two-year programme, highlights its effectiveness as a reliable research resource.

From a research perspective, the value and flexibility of the Biobank has been demonstrated in both small- and large-scale projects over the past 12 months. One example is a small study on testicular cancer which will be undertaken by visiting researcher Dr Tanaka from Osaka, Japan. The study will involve correlation of molecular findings from laboratory-based research with Biobank tissue samples collected from patients with testicular cancer to identify pre- and post-treatment markers of response. Two collaborative large-scale projects have also been undertaken with AstraZeneca, University Hospital of South Manchester. The Christie and Salford Royal. The first of these involved screening around 11,500 slides from patients with bladder cancer who had undergone surgery in the past 35 years. Samples were matched with clinical information and tissue microarrays (TMAs) were developed to screen for possible markers of treatment response. “The bladder dataset we now have from this study is one of the largest in Europe and is a highly valuable resource. We have identified over 500 informative patients and also have matched controls in terms of non-cancerous tissue samples from patients undergoing bladder surgery for other reasons,” said Professor Noel Clarke, Chair of the MCRC Biobank Management Board.

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Manchester hosts a truly international gathering for breast cancer

With over 300 delegates and more than fifty percent of attendees from outside of the UK, the 28th IABCR/Breakthrough Breast Cancer Conference hosted by the Manchester Cancer Research Centre (MCRC) was a truly international meeting highlighting the unified global approach to breast cancer research.

The four-day IABCR (International Association for Breast Cancer Research) conference was held on 15-18 April 2012 and focussed on the stromal-epithelial interactions in breast cancer development and progression. It attracted leading speakers from around the world as well as researchers and clinicians at different stages of their career path, from highly experienced specialists to trainees and students. The conference included around 30 presentations, eight of which were delivered by selected promising young scientists, and around 100 posters. “The conference was very successful and allowed budding researchers an opportunity to share their work with the rest of the research community. The exchange of ideas and information was a major highlight of the conference – seeing how the next generation of research leaders are already making significant progress in their field is very encouraging,” said Dr Rob Clarke, IABCR President and conference organiser from The University of Manchester’s Institute of Cancer Sciences.

The conference opened with a keynote lecture from Professor Zena Werb at the University of California, USA, focusing on new insights into the stromal regulation of mammary development. Professor Werb’s laboratory is recognised internationally for discoveries on the molecular and cellular basis of extracellular matrix proteolysis and its role in the normal function and pathogenesis of tissues. The lecture set the scene for the conference, highlighting the role of the stroma (the supporting cells and connective tissue of the breast) in the development of breast tissue and the impact of disease.

The conference was organised into five complementary sessions: normal breast stromal-epithelial interactions; precursor lesion stromal-epithelial interactions; two sessions on stem cells and stroma in breast tumour biology; and a final session on stem cells and stroma in metastasis.

Professor Max Wicha of the University of Michigan, USA, is the founding and current Director of the University of Michigan’s Comprehensive Cancer Center, a post he has held for over 25 years. He gave the closing keynote lecture on targeting breast cancer stem cells. “The aim of our research is to better understand the role of stem cells and the stroma in breast cancer so that we can improve the treatments and outcomes for breast cancer patients in the clinic. Professor Wicha’s lecture provided an ideal end to the meeting and focused on the clinical impact of the interaction between stem cells and the stroma in breast cancer,” said Dr Clarke. The next IABCR conference will be held in September 2014 in Sydney, Australia.
Lung cancer research continues to thrive

Lung cancer research within the Manchester Cancer Research Centre (MCRC) has continued to thrive over the past 12 months with several key publications and grant awards for new projects.

Research aimed at improving supportive and palliative care for patients with lung cancer to improve quality of life has been strengthened with the award of a £175,000 project grant from the Marie Curie Cancer Care Research Programme. The grant will fund a pilot feasibility randomised trial of a novel non-pharmacological intervention for the management of the respiratory distress symptom cluster (breathlessness, cough, fatigue) in patients with advanced lung cancer. Principal Investigator Professor Alexander Molassiotis, Chair of Cancer and Supportive Care at The University of Manchester, will be testing the new intervention ‘package’, which has been developed through patient and caregiver input against current best supportive care in 100 patients recruited from four centres in the North West. If successful, the results will influence the provision of care for patients with lung cancer experiencing complex respiratory symptoms, an area that is currently suboptimally managed.

Cough is a common and distressing lung cancer symptom, with a significant impact on quality of life (QoL). Dr Amélie Harle, a Medical Oncology Specialist Registrar at The Christie, has been conducting research on lung cancer-related cough via an observational study to characterise cough in lung cancer patients (CLiC Study) using subjective and objective cough assessment tools, including the recently developed Manchester Cough in Lung Cancer Scale (MCLCS). “At present there is no validated scale to assess the complex cough experience in lung cancer patients: objective tools to measure patient reported outcomes are increasingly required for evaluation of significant benefit from novel therapies in selected populations,” said Dr Fiona Blackhall, Senior Clinical Lecturer in the Institute of Cancer Sciences at The University of Manchester and Consultant Medical Oncologist at The Christie, who leads lung cancer research at the MCRC. “The MCLCS has undergone preliminary evaluation, the results of which were published this year,” she said. An interventional study assessing aprepitant for treatment of cough in lung cancer patients (CALC Study) is also ongoing.

Dr Blackhall is a global steering committee member for development of crizotinib, a dual ALK/MET inhibitor. Results of patient reported outcomes and efficacy of crizotinib were presented at the ESMO 2012 Congress of the European Society for Medical Oncology in September. Data from the phase III study indicate improved efficacy and also patient reported improvement in QoL compared with chemotherapy. “Results from our research on supportive and palliative care has been published in five peer-reviewed papers this year and highlights the importance of not only striving for improved treatments but also for improved QoL for lung cancer patients,” said Dr Blackhall.

The continued high quality of lung cancer research in Manchester has been highlighted with three key publications in the Journal of Clinical Oncology this year, demonstrating that MCRC researchers are recruiting to priority studies worldwide through their international network of collaborators. All three studies compared novel mechanism-based therapies with standard chemotherapy and are potentially practice-changing. In the first study, the MONET1 pivotal phase III trial, addition of motesanib to standard chemotherapy failed to show an overall survival benefit over chemotherapy alone. The second study compared dacomitinib, an irreversible inhibitor of human epidermal growth factor receptors (EGFRs) with erlotinib, a reversible EGFR inhibitor in patients with advanced non-small-cell lung cancer (NSCLC). A progression-free survival benefit was observed for dacomitinib in this phase II trial, providing a rationale for larger trials of this agent. A second phase II study demonstrated that addition of dulaneerin (which induces apoptosis, programmed cell death) to bevacizumab-based therapy does not provide
additional benefit to patients with advanced NSCLC. “Participating in these large multicentre studies evaluating novel agents is hugely important to identify promising new treatment approaches. Negative results are also important and highlight the role of both preclinical studies and clinical trials in patients. It’s essential to determine which combinations of therapies should not be evaluated further in order to direct its resources to the treatments with most potential,” said Dr Blackhall. This year has also seen significant progress in translational research, including in small cell lung cancer (SCLC), an area of huge unmet need. Results from circulating tumour cell (CTC) studies in patients have highlighted the utility of CTC evaluation in this patient population. “The potential to use CTCs rather than biopsy material to get information about the activity and status of the tumour is very attractive – especially in tumours like lung cancer where access to biopsy material may be challenging. Work published this year demonstrates that pre-treatment CTC levels and change in CTC levels after just one cycle of chemotherapy are independent prognostic factors for SCLC,” said Dr Blackhall. On the basis of these findings, a number of international clinical trials now plan to incorporate CTC analysis (in collaboration with Professor Caroline Dive, Dr Paul Lorigan and other researchers at the Paterson Institute). Ongoing work aims to molecularly characterise CTCs in patients at various time points before and after treatment with a focus on resistance mechanisms.

Encouraging progress has also been made in early detection research over the past 12 months. Principal Investigator Dr Philip Crosbie, Senior Clinical Lecturer at The University of Manchester has secured an award from The Roy Castle Lung Cancer Foundation for a pilot study to look for a lung cancer specific signal using plasma proteomics. He will be working with Professor Tony Whetton, who leads the Stem Cell and Leukaemia Proteomics Laboratory within the University’s Institute of Cancer Sciences, Dr Richard Booth, Senior Clinical Lecturer and Consultant Respiratory Physician, and Mr Rajesh Shah, a Consultant Thoracic Surgeon and Honorary Senior Lecturer. Given the large number of proteins in the plasma, detection of those specific to the cancer is problematic. The study aims to overcome this challenge by comparing blood plasma sampled from the pulmonary vein directly draining a cancer-bearing lobe with plasma from the pulmonary artery just prior to re-entry into the lung and a pulmonary vein draining a non-cancerous lobe. “We hypothesise that plasma from a vein draining a non-cancerous lobe will have much lower levels of cancer proteins. By comparing the plasma samples we hope to maximise the chance of detecting a cancer specific signal,” said Dr Crosbie. These signals would then be evaluated as potentially valuable blood-borne markers for early disease detection.

Led by Dr Corinne Faivre-Finn, a consultant Clinical Oncologist and an Honorary Senior Clinical Lecturer at The Christie, radiotherapy research continues to be a focus area within the lung cancer strategy and has had notable achievements this year. As well as publication of 12 research papers, the team has secured grants worth almost £350,000 for three studies of radiotherapy in patients with lung cancer. The first of these is from the National Institute for Health Research (NIHR) Research for Patient Benefit Programme (RfPB), and provides around £250,000 over three years. Patients with mesothelioma (a type of cancer invariably caused by asbestos exposure) often have invasive procedures to allow access to biopsy and fluid samples, but these can cause the development of skin nodules where tubes have been inserted into the chest wall. The phase II PIT trial will recruit around 370 patients and aims to assess whether prophylactic irradiation of the tracts can prevent skin nodule formation and whether this type of treatment should be routinely offered to all patients after invasive chest wall intervention. A second grant of £85,000 has been awarded by Cancer Research UK for the LungART trial. This is an international phase III study comparing post-operative conformal radiotherapy to no post-operative radiotherapy in patients with completely resected NSCLC and mediastinal node involvement. The study will assess whether delivery of modern 3-dimensional radiotherapy to the chest after surgery in this patient population can improve disease-free survival. The Christie is the lead centre for the UK. The third grant of just over £48,000 awarded by Cancer Research UK will fund a multicentre feasibility study of isotopic intensity modulated radiotherapy (IMRT) for stage III NSCLC. The gold standard for this disease is concurrent chemotherapy and radiotherapy (both treatment modalities given at the same time) but the majority of patients are unable to receive this treatment due to their level of fitness. The alternative treatment option is sequential chemo-radiotherapy (chemotherapy followed by radiotherapy). The study aims to assess whether sequential therapy with IMRT, a more targeted method of delivering high-dose radiotherapy that spares surrounding normal tissue, can facilitate the escalation of radiotherapy dose, tailored for each individual patient and improve local control and subsequent long-term outcomes. The study will also develop a robust Quality Assurance system for lung IMRT in the UK ensuring thorough validation of the delivery as well as providing a framework for implementation in new centres. ‘At The Christie we treat around 900 patients every year with radiotherapy which is an important backbone of treatment for patients with lung cancer. Our research aims to continue to drive advances and improvements in how this radiotherapy is delivered in order to optimise treatment for improved patient outcome,” said Dr Faivre-Finn.